NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 402

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF FURAN

(CAS NO. 110-00-9)

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

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements, and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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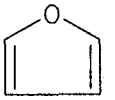
ABSTRACT



FURAN

CAS No. 110-00-9

C_4H_4O Molecular Weight: 68.08

Synonyms: Divinylene oxide, tetrole, furfuran, oxole, 1,4-epoxy-1,3-butadiene, axole, oxacyclopentadiene

Furan serves as an intermediate in the synthesis and preparation of numerous linear polymers used to prepare temperature-resistant structural laminates and to prepare copolymers used in machine dishwashing products as alternatives to phosphorus- and nitrogen-containing detergents. Toxicology and carcinogenesis studies were conducted by administering furan (purity > 99%) in corn oil by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex for 16 days, 13 weeks, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, *Drosophila melanogaster*, mouse bone marrow cells, mouse L5178Y lymphoma cells, and Chinese hamster ovary cells.

16-Day Studies

Groups of five male rats received doses of 0, 5, 10, 20, 40, or 80 mg of furan per kg of body weight and groups of five female rats and five mice of each sex received doses of 0, 10, 20, 40, 80, and 160 mg/kg in corn oil by gavage. All male and female mice and female rats that received 160 mg/kg, all male and female rats and all male and four female mice that received 80 mg/kg, and three male mice that received 40 mg/kg died by day 8. Final mean body weights of male rats that received 20 mg/kg and of male and female rats that received 40 mg/kg were significantly lower than controls. Final mean body weights of male mice that received 10 or 20 mg/kg were significantly greater than controls. Mottled and enlarged livers were observed at necropsy in male rats that received 20, 40, or 80 mg/kg and in females that received 40, 80, or 160 mg/kg. No lesions were observed at necropsy that were considered related to furan administration in mice.

13-Week Studies

Groups of 10 rats of each sex and groups of 10 female mice received doses of 0, 4, 8, 15, 30, or 60 mg of furan per kg of body weight, and groups of 10 male mice received doses of 0, 2, 4, 8, 15, or 30 mg/kg in corn oil by gavage. Nine male and four female rats that received 60 mg/kg died before the end of the studies. There were no chemical-related deaths in mice. Final mean body weights of male rats that received 15 or 30 mg/kg and female rats that received 60 mg/kg were significantly lower than controls. Final mean body weights of male mice that received 60 mg/kg were significantly lower than controls. Relative and absolute liver weights in both sexes of rats and mice were increased in groups that received furan, as were relative and absolute kidney weights in female rats that received furan. Thymus weights were decreased in all groups of rats that received furan.

Toxic lesions of the liver (bile duct hyperplasia, cholangiofibrosis, cytomegaly and degeneration of hepatocytes, and nodular hyperplasia of hepatocytes) were associated with furan administration in all dose groups of rats; the severity of the lesions increased with dose. Kidney lesions (tubule dilatation and necrosis of tubule epithelium) were present in rats that received 30 or 60 mg/kg. Thymic atrophy and testicular or ovarian atrophy were also observed in rats exposed to 60 mg/kg furan. Toxic liver lesions (cytomegaly, degeneration, and necrosis of hepato-

cytes) were also present in all groups of furan-exposed mice. Bile duct hyperplasia and cholangiofibrosis were observed in groups of mice receiving 30 or 60 mg/kg.

Doses selected for the 2-year studies of rats and mice were based on the hepatotoxicity associated with exposure to furan.

2-Year Studies

Groups of 70 rats of each sex were administered 2, 4, or 8 mg furan per kg body weight in corn oil by gavage 5 days per week for 2 years. After 9 and 15 months of chemical exposure, 10 rats per group were evaluated for the presence of treatment-associated lesions. Groups of 50 mice of each sex received doses of 8 or 15 mg/kg furan 5 days per week for 2 years.

Body Weight and Survival. Mean body weights of male rats that received 8 mg/kg furan were lower than controls from approximately week 73 to the end of the study. Survival of male and female rats that received 8 mg/kg was lower than controls from approximately week 85 to the end of the studies as a result of moribund condition associated with liver and biliary tract neoplasms and mononuclear cell leukemia.

Mean body weights of male and female mice that received 15 mg/kg furan were lower than controls during the studies. Survival of low- and high-dose male and high-dose female mice was lower than controls from approximately week 80 to the end of the studies as a result of moribund condition associated with liver neoplasms.

Neoplastic and Nonneoplastic Lesions. Cholangiocarcinoma of the liver occurred in all groups of dosed rats (males: control, 0/50; low dose, 43/50; mid dose, 48/50; high dose, 49/50; females: 0/50; 49/50; 50/50; 48/50) and was present in many rats of each sex at the 9- and 15-month interim evaluations (9-month: males - 0/10, 5/10, 7/10, 10/10; females - 0/10, 4/10, 9/10, 10/10; 15-month: males - 0/10, 7/10, 9/10, 6/10; females - 0/10, 9/10, 9/10, 7/10). Hepatocellular adenomas or carcinomas (combined) were significantly increased in male rats after 2 years of chemical administration (1/50, 5/50, 22/50, 35/50) and hepatocellular adenomas were significantly increased in female rats (0/50, 2/50, 4/50, 7/50); hepatocellular neoplasms were not observed at the 9- or 15-month interim evaluations. Increased incidences of numerous nonneoplastic liver lesions were present in rats administered furan. These lesions included biliary tract fibrosis, hyperplasia, chronic inflammation, and proliferation and hepatocyte cytomegaly, cytoplasmic vacuolization, degeneration, nodular hyperplasia, and necrosis.

The incidence of mononuclear cell leukemia was increased in male and female rats that received 4 or 8 mg/kg furan (males: 8/50, 11/50, 17/50, 25/50; females: 8/50, 9/50, 17/50, 21/50); the incidence in the 8 mg/kg groups of each sex exceeded the historical control ranges for corn oil gavage studies.

The severity of nephropathy increased with dose and the incidence was significantly increased in all groups of dosed rats; this increased severity was accompanied by an associated increased incidence of parathyroid hyperplasia (renal secondary hyperparathyroidism).

The incidence of forestomach hyperplasia was increased in male and female rats (males: 1/50, 4/49, 7/50, 6/50; females: 0/50, 2/50, 5/50, 5/50) and the incidence of subacute inflammation of the forestomach was increased in female rats (0/50, 1/50, 5/50, 6/50). No forestomach neoplasms were observed in males; a squamous papilloma was present in one low-dose female.

The incidences of hepatocellular adenomas and carcinomas were significantly increased in mice receiving furan (males: adenoma - 20/50, 33/50, 42/50; carcinoma - 7/50, 32/50, 34/50; females: adenoma - 5/50, 31/50, 48/50; carcinoma - 2/50, 7/50, 27/50). The incidences of numerous nonneoplastic hepatocellular lesions were increased in dosed mice. These lesions included hepatocyte cytomegaly, degeneration, necrosis, multifocal hyperplasia, and cytoplasmic vacuolization and biliary tract dilatation, fibrosis, hyperplasia, and inflammation.

The incidences of benign pheochromocytoma and focal hyperplasia of the adrenal medulla were increased in low- and high-dose male and in high-dose female mice (benign pheochromocytoma: males - 1/49, 6/50, 10/50; females - 2/50, 1/50, 6/50).

The incidences of squamous papilloma, focal inflammation, and papillary hyperplasia of the forestomach were increased in male mice (squamous papilloma:

0/49, 1/50, 3/50; focal inflammation: 9/49, 13/50, 21/50; papillary hyperplasia: 7/49, 14/50, 22/50).

Stop-Exposure Study

A separate 2-year study was conducted in which 50 male rats were administered 30 mg/kg furan in corn oil by gavage 5 days per week for 13 weeks and then maintained for the remainder of the 2 years without additional furan administration. Groups of 10 animals were evaluated for the presence of treatment-related lesions at the end of the 13-week period of furan administration and at 9 and 15 months.

Neoplastic and Nonneoplastic Lesions. Cholangiocarcinoma of the liver occurred with an overall incidence of 100% (40/40) and hepatocellular carcinoma occurred with an overall incidence of 15% (6/40) in stop-exposure male rats that survived at least 9 months. Cholangiocarcinoma was observed in all 10 males at both the 9-month and 15-month interim evaluations. Hepatocellular carcinoma was first observed in 2 males at the 15-month interim evaluation.

Genetic Toxicology

Furan was negative for induction of gene mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 in the presence and the absence of exogenous metabolic activation (S9). Furan was negative for the induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* when administered either by feeding or by injection. *In vitro* tests for genotoxicity in mammalian cells, however, were positive. Furan induced trifluorothymidine resistance in mouse L5178Y lymphoma cells in the absence of S9, and sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, with and without S9. Furan administered to male $B6C3F_1$ mice by intraperitoneal injection induced chromosomal aberrations but not sister chromatid exchanges in bone marrow cells.

Conclusions

Under the conditions of these 2-year gavage studies there was *clear evidence of carcinogenic activity** of furan in male and female F344/N rats based on increased incidences of cholangiocarcinoma and hepatocellular neoplasms of the liver and on increased incidences of mononuclear cell leukemia. There was *clear evidence of carcinogenic activity* of furan in male and female $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms of the liver and benign pheochromocytomas of the adrenal gland.

Nonneoplastic liver lesions associated with furan administration in rats and mice included biliary tract fibrosis, hyperplasia, inflammation, and proliferation, as well as hepatocellular cytomegaly, degeneration, hyperplasia, necrosis, and vacuolization. In rats, increased severity of nephropathy with an associated increased incidence of parathyroid hyperplasia was associated with exposure to furan.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of peer review comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and the Genetic Toxicology Studies of Furan

Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses			
0, 2, 4, or 8 mg/kg of furan in corn oil by gavage 5 days per week	0, 2, 4, or 8 mg/kg of furan in corn oil by gavage 5 days per week	0, 8, or 15 mg/kg of furan in corn oil by gavage 5 days per week	0, 8, or 15 mg/kg of furan in corn oil by gavage 5 days per week
Body weights			
High-dose less than control	Dosed similar to control	Dosed less than control	High-dose less than control
2-Year survival rates			
33/50; 28/50; 26/50; 16/50	34/50; 32/50; 28/50; 19/50	33/50; 17/50; 16/50	29/50; 25/50; 2/50
Nonneoplastic effects			
Kidney: nephropathy Liver: biliary tract - dilatation, chronic inflammation, fibrosis, and hyperplasia; hepatocyte - cytomegaly, degeneration, and necrosis Parathyroid: hyperplasia	Kidney: nephropathy Liver: biliary tract - chronic focal inflammation, cyst, focal fibrosis, focal hyperplasia, and metaplasia; hepatocyte - cytomegaly, cytoplasmic vacuolization, focal degeneration, focal hyperplasia, and focal necrosis Parathyroid: hyperplasia	Liver: biliary tract - chronic focal inflammation, cyst, focal fibrosis, focal hyperplasia, and metaplasia; hepatocyte - cytomegaly, cytoplasmic vacuolization, focal degeneration, focal hyperplasia, and focal necrosis	Liver: biliary tract - dilatation, chronic inflammation, fibrosis, and hyperplasia; hepatocyte - cytomegaly, degeneration, and necrosis
Neoplastic effects			
Liver: cholangiocarcinoma - 0/50; 43/50; 48/50; 49/50 hepatocellular adenoma or carcinoma - 1/50; 5/50; 22/50; 35/50 Mononuclear cell leukemia: 8/50; 11/50; 17/50; 25/50	Liver: cholangiocarcinoma - 0/50; 49/50; 50/50; 48/50 hepatocellular adenoma or carcinoma - 0/50; 2/50; 4/50; 8/50 Mononuclear cell leukemia: 8/50; 9/50; 17/50; 21/50	Liver: hepatocellular adenoma or carcinoma - 26/50; 44/50; 50/50 Adrenal gland: benign pheochromocytoma - 1/49; 6/50; 10/50	Liver: hepatocellular adenoma or carcinoma - 7/50; 34/50; 50/50 Adrenal gland: benign pheochromocytoma - 2/50; 1/50; 6/50
Level of evidence of carcinogenic activity			
Clear evidence	Clear evidence	Clear evidence	Clear evidence
Genetic toxicology			
Gene Mutations			
Salmonella typhimurium in vitro:	Negative with and without S9 in strains TA98, TA100, TA1535, TA1537		
L5178Y/TK$^{+/-}$ mouse lymphoma *in vitro*:	Positive without S9		
Sister Chromatid Exchanges			
Chinese hamster ovary cells *in vitro*:	Positive with and without S9		
$B6C3F_1$ mouse bone marrow cells *in vivo*:	Negative when administered by injection		
Chromosomal Aberrations			
Chinese hamster ovary cells *in vitro*:	Positive with and without S9		
$B6C3F_1$ mouse bone marrow cells *in vivo*:	Positive when administered by injection		
Sex-linked Recessive Lethal Mutations			
Drosophila melanogaster:	Negative when administered in feed or by injection		

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 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 chemical-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** describes studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence of carcinogenic activity** is demonstrated by studies that are interpreted as showing no chemical-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 is selected for a particular experiment, 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:

- 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);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- 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.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the NTP draft Technical Report on furan on 11 March 1991, 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:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS

On March 11, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of furan received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Committee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of furan by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and reviewing the neoplastic and nonneoplastic lesions in rats and mice. The proposed conclusions were *clear evidence of carcinogenic activity* for furan for male and female F344/N rats and for male and female B6C3F$_1$ mice.

Dr. Goodman, a principal reviewer, agreed with the proposed conclusions. He commented on the four widely used *in vitro* tests for genetic toxicity and noted the inability of three of the assays, mutagenesis in mouse lymphoma cells and chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells, to improve on the ability of mutagenesis in *Salmonella typhimurium* for predicting carcinogenicity of chemicals in long-term rodent studies. He thought presentation of data from these assays should be very limited in the report. Further, he said the possibility should be considered that sister chromatid exchanges and chromosomal aberrations might be artifacts resulting from lysosome breakdown secondary to cytotoxicity and not from direct chemical action on DNA.

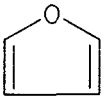
Mr. Beliczky, the second principal reviewer, agreed with the proposed conclusions. He said the discussion and comparison of furan and furan compounds was excellent, and the presence of uncommon mutations in cellular genes suggested they were chemical related.

Dr. Hayden, the third principal reviewer, agreed with the proposed conclusions. He suggested more illustration of differentiation between cholangiofibrosis and cholangiocellular carcinoma. Dr. Irwin said photomicrographs would be added. Dr. Hayden commented on the frequent discrepancies in furan dose formulations between the study laboratory and the analytical chemistry laboratory and asked whether the animals had received the proper doses. Dr. Irwin responded that this was an analytical problem due to the high volatility of furan. Considerable care was taken with the dosing solutions in the animal rooms to minimize potential loss.

Dr. Davis commented on the variable incidence of mononuclear cell leukemia with time. Dr. J.K. Haseman, NIEHS, said the NTP database is updated at least yearly with data from older studies being dropped and from newer studies added so as to maintain about a 5-year window. Dr. Hayden and Dr. Zeise thought increased incidences of urinary bladder papillomas in female rats and squamous cell papillomas of the forestomach in male mice deserved more discussion. Mr. Beliczky said that, based on the carcinogenicity of furan and the wide industrial use, there should be information included on potential worker exposure. Dr. J.C. Haartz, NIOSH, said the most recent exposure data indicated only 14 plants with 35 workers potentially exposed.

Dr. Goodman moved that the Technical Report on furan be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *clear evidence of carcinogenic activity.* Mr. Beliczky seconded the motion, which was accepted unanimously with 10 votes.

INTRODUCTION



FURAN

CAS No. 110-00-9

C_4H_4O Molecular Weight: 68.08

Synonyms: Divinylene oxide, tetrole, furfuran, oxole, 1,4-epoxy-1,3-butadiene, axole, oxacyclopentadiene

Physical and Chemical Properties, Production, and Use

Furan, a clear, colorless liquid, has an ethereal odor, boils at 320° C, freezes at -85.60° C, and has a specific gravity of 0.9371 at 758 mm mercury. Furan is insoluble in water but is soluble in alcohol, ether, and most common organic solvents (*Merck Index*, 1983). Chemically, furan is classified as a cyclic, dienic ether. Spectroscopic and diffraction data confirm that the furan ring is planar and possesses an aromatic character resulting from interaction of the lone pair of oxygen electrons with neighboring carbon *p* orbitals (Acheson, 1976). Based on energy calculations using various methods, the resonance stabilization energy for furan is 25 ± 1 kcal/mole. This is less than that for benzene (36 ± 1 kcal/ mole); therefore, furan and furan-containing compounds are more reactive than the corresponding benzene analogues (Acheson, 1976; *Kirk-Othmer*, 1978). The introduction of substituents into the furan ring may significantly alter its reactivity, depending on the strength of interaction with the π-electron system. Strong electron-withdrawing substituents such as $-NO_2$ make the furan ring more resistant to oxidation, whereas alkyl substituents may enhance oxidation (*Kirk-Othmer*, 1978). Therefore, ring substitutions may influence the metabolic fate of compounds containing substituted furans and their potential for conversion to biologically reactive species such as electrophiles.

Commercial production of furan is performed by the decarbonylation of furfural, which can be accomplished by a number of processes. Steam distillation of furfural over catalysts such as lime or mixed chromite of zinc/manganese provides high yields of furan. Furan can also be produced from butadiene in a high-temperature process in the presence of a molybdenum-bismuth catalyst, or by the oxidation of butadiene (*Kirk-Othmer*, 1978).

Furan is used primarily as an intermediate in the synthesis and preparation of other organic compounds. Hydrogenation of furan over a nickel catalyst produces high yields of tetrahydrofuran (THF) and serves as a source of commercial THF. Reaction with hydrogen sulfide at 4,000° C over an alumina catalyst produces thiophene. Furan is also used in the preparation of numerous polymeric compounds; linear polymers prepared in a Diels-Adler reaction with bis(furfuryl)imide are used for preparation of temperature-resistant structural laminates. Copolymers of maleic acid and furan form complexes with alkaline earth ions and are used in metals, foodstuffs, and machine dishwashing products as alternatives to phosphorus- and nitrogen-containing detergents (*Kirk-Othmer*, 1978).

Human Exposure

Because the industrial processes in which furan is used are conducted in closed systems, and because its volatility requires that furan be handled in closed containers, occupational exposure is limited. Moreover, the pattern of commercial use suggests that minimal exposure to the general public would be expected through contact with products contaminated with furan. Potential furan exposure was observed in two 1972 Standard Industrial Classifications (SIC) in

the National Institute of Occupational Safety and Health Exposure Survey (NIOSH, 1981-1983), SIC 73 (Business Services) and SIC 37 (Transportation Equipment). Potential exposure was observed at an estimated 14 plants, 7 in each classification. Thirty-five employees were potentially exposed to furan, 28 males in SIC 37 and 7 females in SIC 73.

Compounds containing the furan ring, however, are common. Numerous terpenoids and other plant products have been identified which contain the furan ring as part of their structure. Furan-containing compounds occur naturally in foodstuffs (Maga, 1979). Furfural and other substituted furans can also form during heating or cooking through the cyclodehydration of simple sugars such as pentoses, especially when heated under weakly acidic conditions (Toverud and Karlsen, 1974; Ulbricht *et al.*, 1984). The urine of normal healthy individuals contains many furan compounds, which are present in common foodstuffs containing furan or which form during the digestion of carbohydrates.

METABOLISM

The metabolites of furan and the specific pathways involved in its elimination have not yet been identified. Because furan is insoluble in water, its metabolism may involve the introduction of substituents such as hydroxyl groups into the furan ring, which can be conjugated or further biotransformed to more polar groups such as carboxylic acids. Alternatively, furan may be disrupted to simpler carbon compounds and degraded. However, numerous studies show that one of the initial steps involves the bioactivation of furan by cytochrome P_{450}-containing mixed-function oxidase(s). The resulting reactive intermediate correlates with the toxicity of furan and certain furan-containing compounds. The experimental evidence upon which these conclusions are based has been reviewed by Burka and Boyd (1985) and is summarized below.

TOXICITY AND CARCINOGENICITY OF FURAN-CONTAINING COMPOUNDS

Toxicity

Furan and many furan compounds are cytotoxic and cause necrosis in their respective target organs, most frequently the liver, kidney, and lung. These target organs contain cells (hepatocytes, tubule epithelial cells, and Clara cells) which express high levels of cytochrome P_{450}-mixed-function oxidase activity (Burka and Boyd, 1985).

Prior administration of compounds that induce mixed-function oxidase activity, such as phenobarbital, markedly increases the severity of target organ necrosis associated with exposure to furan. Conversely, compounds which inhibit mixed-function oxidase activity, such as piperonyl butoxide, decrease the severity of target organ necrosis (Boyd, 1977; McMurty and Mitchell, 1977; Boyd *et al.*, 1978a,b).

In experiments with various furan compounds labeled in the ring with ^{14}C, severity of target organ necrosis correlates with the extent of covalent incorporation of radioactivity into cellular protein (Mitchell *et al.*, 1976; Dutcher and Boyd, 1979). Although the reactive intermediate has not been identified, activation seems to involve the furan ring, because covalent attachment to cellular protein occurs through the ring moiety (Wirth *et al.*, 1975). The reactive intermediate also exhibits properties of an electrophile. For example, adding glutathione, cysteine, or cysteamine to incubation mixtures containing furosemide and mouse liver microsomes significantly reduces the amount of radioactivity incorporated into microsomal protein (Mitchell *et al.*, 1976; Boyd *et al.*, 1978a). Similarly, administering cysteine or cysteamine to rats increases the LD_{50} of the lung toxin, 4-ipomeanol, and decreases the extent of covalent incorporation into liver and lung protein (Boyd *et al.*, 1982). Conversely, administering 4-ipomeanol with diethyl maleate, a compound that lowers tissue glutathione levels, reduces the LD_{50} of 4-ipomeanol in rats, and causes a twofold to threefold increase in covalent incorporation of radioactivity into liver and lung protein (Statham and Boyd, 1982).

Furan compounds exhibit individual target organ specificities. In acute and short-term studies, 100 to 300 mg/kg doses of furan administered intraperitoneally to mice were equally toxic to the liver and kidney, based on the development of necrosis over a 48-hour period after administration. In the same experimental system, furosemide was more toxic to the liver than to the kidney, while 2-ethyl furan was significantly more toxic to the kidney than to the liver (McMurty and Mitchell, 1977). Other alkyl-substituted furans exhibit a spectrum of toxicities; doses of 3-methyl furan administered intraperitoneally to mice were toxic to the lung but were not toxic to the liver or the kidney, whereas 3-ethyl furan and 3-pentyl furan caused marked nephrotoxicity but

were not toxic to the liver or the lung (Gammal *et al.*, 1984; Wiley *et al.*, 1984). 4-Ipomeanol and perilla ketone are primarily lung toxins, even when administered by noninhalation routes, but also produce mild liver and kidney toxicity (Buckpitt and Boyd, 1980; Wolf *et al.*, 1982; Durham *et al.*, 1985).

Carcinogenicity

No long-term studies of furan have been reported in the literature. However, five furan compounds (furfural, benzofuran, furosemide, nitrofurantoin, and nitrofurazone) have been evaluated for carcinogenicity in 2-year studies conducted by the National Toxicology Program.

The carcinogenic potential of furfural was evaluated by administering doses of 0, 30, or 60 mg/kg to male and female F344/N rats and doses of 0, 50, 100, or 175 mg/kg to male and female B6C3F$_1$ mice in corn oil by gavage for 2 years. Exposure to furfural induced cholangiocarcinomas in two high-dose male rats, and dysplasia with fibrosis, a nonneoplastic precursor lesion to cholangiocarcinoma, in two other high-dose male rats, but did not induce carcinomas in female rats. In both male and female mice, exposure to furfural was associated with a dose-related increase in the incidence of hepatocellular neoplasms (NTP, 1990).

Benzofuran was administered in corn oil by gavage to male and female F344/N rats and B6C3F$_1$ mice for 2 years. No evidence of carcinogenicity was found in male rats. However, renal tubule cell adenocarcinomas occurred in one low-dose and four high-dose female rats. Mice showed a marked dose-related increase in the incidence of hepatocellular adenomas and hepatocellular carcinomas (NTP, 1989a).

Dietary administration of furosemide to F344/N rats and B6C3F$_1$ mice for 2 years was associated with a minimal carcinogenic response in male rats and female mice, but produced no response in female rats or male mice. Renal tubule cell neoplasms were slightly increased in low-dose but not in high-dose male rats (1/50, 4/50, 2/50), and meningiomas of the brain were present in three low-dose male rats but not in the control or high-dose animals. Malignant mammary gland neoplasms occurred in two low-dose and five high-dose female mice (NTP, 1989b).

Dietary administration of nitrofurantoin to F344/N rats and B6C3F$_1$ mice for 2 years was associated with increased incidences of ovarian neoplasms in female mice, including tubular adenomas, benign mixed neoplasms, and granulosa cell neoplasms, but did not induce a carcinogenic response in male mice or in female rats (NTP, 1989c).

Dietary administration of nitrofurazone produced sebaceous gland adenomas, trichoepitheliomas of the skin, mesotheliomas of the tunica vaginalis, and preputial gland neoplasms in male F344/N rats. Female F344/N rats showed a markedly increased incidence of fibroadenomas of the mammary gland. Female B6C3F$_1$ mice showed increased incidences of benign mixed neoplasms and granulosa cell neoplasms of the ovary. Administration of nitrofurazone was associated with decreased incidences of mononuclear cell leukemia in rats, testicular interstitial cell neoplasms in male rats, and pituitary gland neoplasms in female mice. Convulsive seizures in mice, ovarian atrophy in female mice, testicular degeneration in male rats, and degeneration of the articular cartilage in rats were associated with the administration of nitrofurazone (NTP, 1988a).

Genetic Toxicity

Few genetic toxicity studies of furan have been reported. The chemical was negative for induction of gene mutations in *Salmonella typhimurium* (Table E1; Mortelmans *et al.*, 1986) but positive for induction of trifluorothymidine resistance in mouse L5178Y lymphoma cells (Table E2; McGregor *et al.*, 1988). An *in vitro* study tested for induction of chromosomal aberrations in Chinese hamster ovary cells treated with 0 to 200 mM furan (Stich *et al.*, 1981). In the 100- to 200-mM furan treatment range, a dose-related increase in chromosomal aberrations, primarily chromatid exchanges, occurred only in the presence of S9. At the highest dose level, approximately 25% of the cells contained aberrations. Another study describes the *in vivo* induction of micronuclei by 400 mg/kg furan (micronucleated PCE, 1.4%) and two structural analogues, 5-methylfurfural and 2-methylfuran, but no data were provided (Kong *et al.*, 1988).

Genetic toxicity tests of three furan analogues (tetrahydrofuran [THF], furfural, and furfuryl alcohol) were negative in a variety of *S. typhimurium* strains, with and without S9 (Marshall *et al.*, 1983; Marnett *et al.*, 1985; Mortelmans *et al.*, 1986; Nakamura *et al.*, 1987). Exceptions are the mutagenic activity (1.1 revertants/μg) reported in a preincubation assay for furfural (5 to 500 μg/plate) in strain TA104 with

S9 (Shane *et al.*, 1988) and the positive results reported in strain TA100 with and without S9 (Zdzienicka *et al.*, 1978). The mutagenicity of furfural was reviewed by the NTP (1990). Furfural was negative for induction of gene mutations in *S. typhimurium*, but positive for the induction of *Drosophila melanogaster* germ cell mutations when administered by injection (Woodruff *et al.*, 1985), trifluorothymidine resistance in L5178Y cells, and Chinese hamster ovary cell sister chromatid exchanges and chromosomal aberrations. Two other structural analogues, THF and 2-furanmethanol, were negative in the *D. melanogaster* sex-linked recessive lethal assay (Valencia *et al.*, 1985; Rodriques-Arnais *et al.*, 1989). Thus, the available data suggest that furan and furan-containing compounds have little or no activity in bacterial gene mutation assays, but do have clastogenic potential in mammalian cells.

STUDY RATIONALE

Furan was nominated by the National Cancer Institute for evaluation of carcinogenic potential because of its large production volume and use and the potential for widespread human exposure to a variety of furan-containing compounds. Corn oil was chosen as the vehicle for these studies because furan is lipophilic, highly volatile, and does not mix with water.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF FURAN

Furan was obtained from the Quaker Oats Company (Chicago, IL) in one lot (Lot No. OF20-M) which was not stabilized with butylated hydroxytoluene. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and confirmed by the study laboratory (Appendix H). The study chemical, a clear, colorless liquid with an ethereal odor, was identified as furan by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Purity was determined to be greater than 99% by Karl Fischer water analysis, elemental analyses, and two gas chromatographic systems. A gas chromatographic analysis for butylated hydroxytoluene confirmed that no stabilizer was present. Stability studies performed with gas chromatography found that the bulk chemical was stable for 2 weeks when stored at temperatures up to 25° C in amber vials under a nitrogen atmosphere. Throughout the studies, the bulk chemical was stored in sealed containers protected from light under a nitrogen atmosphere at -20° C. Stability of the bulk chemical was monitored by the study laboratory using gas chromatography and infrared spectroscopy during all phases of the studies. No change in the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Throughout the studies, the dose formulations were prepared weekly by mixing appropriate amounts of furan with corn oil (Table H1). Stability studies conducted by the analytical chemistry laboratory and the study laboratory using gas chromatography confirmed the stability of the furan solutions for at least 14 days when stored in sealed containers, in the dark, under a nitrogen atmosphere at room temperature (20° to 24° C). However, under simulated dosing conditions (exposed to air and light for 3 hours), 6% of the chemical was lost due to evaporation and even greater losses occurred as the ratio of the volume of dosed corn oil to volume of flask decreased. Thus, rapid and careful handling of gavage solutions during dose administration was required during the studies. In addition, the dose formulations were decanted into daily dosing containers, and each day any residual dosed corn oil was discarded. During the studies, dose formulations were stored in the dark, in amber bottles, under a nitrogen atmosphere at 5° C for no longer than 2 weeks.

The study laboratory periodically analyzed the furan dose formulations using the gas chromatographic procedures described in Appendix H. During the 2-year studies, 76% (32/42) of the dose formulations for rats and 92% (24/26) of the dose formulations for mice were within 10% of the target concentrations (Table H3). As expected, all of the dose formulations that were out of specifications were low, ranging from -11% to -18%. Results of periodic referee analyses of the dose formulations performed by the analytical chemistry laboratory were not always in agreement with the results from the study laboratory (Table H4). The results from a special study to evaluate reasons for the frequent discrepancies suggested that the differences in values obtained by the study laboratory and the analytical chemistry laboratory were due to the high volatility of furan, and that the animals had received the proper doses.

16-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Kingston, NY) and observed for 14 days before the studies began. The rats averaged 47 days old and the mice averaged 51 days old when placed on study. Groups of five male rats received 0, 5, 10, 20, 40, or 80 mg of furan per kg body weight in corn oil by gavage. Groups of five female rats and groups of five mice of each sex received 0, 10, 20, 40, 80, or 160 mg of furan per kg body weight in corn oil by gavage. All groups received the doses for 12 days (days 1 through 5, 8 through 12, and at least two consecutive

dosing days before the terminal sacrifice). Animals were housed five per cage, and water and feed were available *ad libitum*. Clinical and toxicological observations were conducted twice daily. The animals were weighed at the start of the study and on days 8 and 16. Complete necropsies were performed on all animals. Further experimental details are presented in Table 1.

13-WEEK STUDIES

The 13-week studies were conducted to determine the cumulative toxic effects of repeated exposure to furan and to determine appropriate chemical concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratory (Kingston, NY) and were observed for 19 days before the studies began. The average age of the rats and mice at the beginning of the studies was 51 days. Groups of 10 rats of each sex and groups of 10 female mice received 0, 4, 8, 15, 30, or 60 mg of furan per kg body weight in corn oil by gavage 5 days per week for 13 weeks. Groups of 10 male mice received 0, 2, 4, 8, 15, or 30 mg of furan per kg body weight in corn oil by gavage 5 days per week for 13 weeks. Animals were housed five per cage, and water and feed were available *ad libitum*. Animals were observed twice daily, and clinical observations recorded weekly. The animals were weighed at the start of the studies and weekly thereafter.

Survivors were killed at the end of the 13-week studies. Necropsies were performed on all animals. The brain, heart, right kidney, liver, lungs, and thymus of survivors were weighed at necropsy. Complete histopathologic examinations were performed on all animals in the control group, all rats that received 30 mg/kg or 60 mg/kg, all female mice that received 60 mg/kg, and all male mice that received 30 mg/kg. Livers were histopathologically examined for all remaining animals except male mice that received 2 mg/kg and female mice that received 4 mg/kg. Additional details of the experimental design are presented in Table 1.

2-YEAR STUDIES

Study Design

Groups of 70 rats of each sex were administered 0, 2, 4, or 8 mg of furan per kg body weight in corn oil by gavage 5 days per week for up to 104 weeks. Groups of 50 mice of each sex were administered 0, 8, or 15 mg of furan per kg body weight. Groups of 10 rats per dose group were evaluated (necropsy and histopathology) after 9 and 15 months of chemical administration. Hematology and clinical chemistry tests were performed on blood collected from rats at the 9-month interim evaluation. Organ and body weights of the rats from the 15-month interim evaluation were also measured. Experimental details for the 2-year studies are also presented in Table 1.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Kingston, NY) for use in the 2-year studies. Rats were quarantined for 19 days, and mice were quarantined for 18 days. Five rats and five mice of each sex were randomly selected and killed for parasite evaluation and gross observation of disease. Serology samples were collected for viral screens. Rats were 51 days old and mice averaged 58 days old at the start of the studies. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix J).

Animal Maintenance

Five rats or mice were housed per cage. Feed (Appendix I) and water were available *ad libitum*. Cages were rotated every 2 weeks during the studies.

Clinical Examinations and Pathology

All animals were observed twice daily. Animals were weighed at study initiation, weekly for 13 weeks, and monthly thereafter. Clinical findings were recorded monthly.

All males received a complete gross examination. Body weights and kidney, liver, lung, and spleen weights were recorded for all rats at the 15-month evaluation.

Histopathologic evaluation was performed on livers and kidneys from all 9-month interim males and on livers, kidneys, and lungs from all 15-month interim males.

Animals found moribund or surviving to the end of the studies were killed. Necropsy was performed on

all animals, including those found dead. At necropsy, all organs and tissues were examined for gross lesions. All major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination.

After the microscopic evaluation was completed by the study laboratory pathologist, the pathology data were entered into the Toxicology Data Management System (TDMS). The microscope slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The microscope 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 by the quality assessment laboratory. All livers and spleens from male and female rats, all livers, adrenal medullae, and kidneys from male and female mice, and all forestomachs from male mice were evaluated microscopically by a quality assessment pathologist for neoplasms and nonneoplastic lesions. In addition, all kidneys from male and female rats were examined to confirm the presence of nephropathy and all lungs from male mice were examined for alveolar epithelial hyperplasia. All neoplastic diagnoses in all tissues in all rats and mice, and all diagnoses in all tissues from a randomly selected 10% of the control and high-dose animals of each sex and species were also examined by the quality assessment pathologist.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the aforementioned tissues and any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of liver and kidney lesions from rats, urinary bladder lesions from female rats, liver, adrenal medulla and forestomach lesions from mice, and lesions of general interest were selected by the chair for review by the PWG. The PWG consisted of the quality assessment pathologist and others experienced in rodent toxicologic pathology, who examined the tissues without knowledge of dose group or previously rendered diagnoses. Whenever 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 PWG. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type were combined according to the guidelines of McConnell *et al.* (1986).

2-YEAR STOP-EXPOSURE STUDY

Study Design

The stop-exposure study consisted of 50 male F344/N rats that received 30 mg furan per kg of body weight in corn oil by gavage five days per week for 13 weeks and then were held up to 90 additional weeks without further treatment. Groups of 10 animals were evaluated (necropsy and selected histopathology) after 13 weeks, 9 months, and 15 months on study. Experimental details are presented in Table 1.

Source and Specification of Animals

Male F344/N rats were obtained from Charles River Breeding Laboratories (Kingston, NY) for use in the stop-exposure study. Rats were quarantined for 18 to 25 days. Rats were between 47 and 61 days old at the start of the study. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix J).

Animal Maintenance

Five rats were housed per cage. Feed (Appendix I) and water were available *ad libitum*. Cages were rotated every 2 weeks during the studies.

Clinical Examinations and Pathology

All animals were observed twice daily. Animals were weighed at study initiation, weekly for 13 weeks, and monthly thereafter. Clinical findings were recorded weekly for 13 weeks and monthly thereafter.

All males received a complete gross examination. Body weights and kidney, liver, lung, and spleen weights were recorded for all rats at the 15-month evaluation.

Histopathologic evaluation was performed on the livers from all 13-week interim rats, on livers and kidneys from all 9-month interim rats; on livers, kidneys, and lungs from all 15-month interim rats.

Animals found moribund or surviving to the end of the studies were killed. Necropsy was performed on all animals, including those found dead. At necropsy, all organs and tissues were examined for gross lesions. All major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination.

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 dead from other than natural causes. Animals dying from natural causes were not censored. Statistical analysis 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 to identify dose-related trends. All reported P values for the survival analysis are two sided.

Calculation of Incidence

Tables A1, B1, C1, and D1 in the appendixes to this report present the incidences of neoplasms in male and female rats and mice. Tables A5, B5, C5, and D5 summarize the incidences of nonneoplastic lesions in male and female rats and mice. The incidence of neoplasms 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 the 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., oral cavity, skin) prior to histologic sampling, or when lesions had multiple potential sites of occurrence (e.g., mononuclear cell leukemia), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidence

The majority of neoplasms in this study were considered to be incidental to the cause of death or not rapidly fatal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalence also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

In addition to logistic regression, 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), a survival-adjusted procedure appropriate for rapidly lethal neoplasms, and the Fisher exact and Cochran-Armitage trend tests (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals.

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

Historical Control Data

Although the concurrent control group is 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 neoplasm incidence. Consequently, neoplasm incidences from the NTP historical control database for 2-year studies (Haseman *et al.*, 1984, 1985) are included for neoplasms that appear to show compound-related effects.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and body weight data, which have approx-

imately normal distributions, were analyzed using the parametric multiple comparison procedures of Williams (1971, 1972) and Dunnett (1955). Clinical chemistry and hematology data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-response trend (Dunnett's or Dunn's test). Average nephropathy severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

GENETIC TOXICITY

The genetic toxicity of furan was assessed by testing the ability of the chemical to induce mutations in *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, sex-linked recessive lethal mutations in *Drosophila melanogaster*, trifluorothymidine resistance in mouse L5178Y lymphoma cells, and sister chromatid exchanges and chromosomal aberrations in mouse bone marrow cells. The protocols and results for these studies are in Appendix E.

QUALITY ASSURANCE METHODS

The 13-week and 2-year studies were conducted in compliance with FDA Good Laboratory Practice Regulations (21 CFR Part 58). In addition, as study records were submitted to the NTP Archives, they were audited retrospectively by an independent quality assurance contractor. Separate audits were conducted covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of the NTP Technical Report. Audit procedures are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by NTP staff so that all had been resolved or were otherwise addressed during the preparation of this Technical Report.

TABLE 1
Experimental Design and Materials and Methods in the Corn Oil Gavage Studies of Furan

16-Day Studies	13-Week Studies	Stop-Exposure Study	2-Year Studies
Study Laboratory			
Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)
Strain and Species			
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N	Rats: F344/N Mice: $B6C3F_1$
Animal Source			
Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)
Time Held Before Study			
14 days	19 days	18-25 days	Rats: 19 days Mice: 18 days
Age When Placed on Study			
Rats: 47 days Mice: 51 days	Rats: 51 days Mice: 51 days	47-61 days	Rats: 51 days Mice: 58 days
Date of First Dose			
4 December 1980	3 March 1981	5 July 1982	Rats: 29 June 1982; 5 July 1982 for interim evaluation animals Mice: 31 May 1982
Duration of Dosing			
Days 1-5, 8-12, 15, 16	13 weeks (5 days/week)	13 weeks (5 days/week); no gavage treatments for remaining 90 weeks	Rats: 103 weeks (5 days/week) Mice: 104 weeks (5 days/week)
Necropsy Dates			
20-23 December 1980	2-10 June 1981	13-week interim evaluation: 1 October 1982; 9-month interim evaluation: 15 April 1983; 15-month interim evaluation: 6 October 1983; 2-year: 29 June 1984	Rats: 9-month interim evaluations, 13-15 April 1982; 15-month interim evaluations, 4-6 October 1983; 2-year studies, 26 June - 2 July 1984 Mice: 4-6 June 1984
Average Age at Necropsy			
Rats: 65 days Mice: 72 days	Rats: 146 days Mice: 153 days	548 days	Rats: 783 days Mice: 795 days

TABLE 1
Experimental Design and Materials and Methods in the Corn Oil Gavage Studies of Furan (continued)

16-Day Studies	13-Week Studies	Stop-Exposure Study	2-Year Studies
Size of Study Groups			
5 males and 5 females	10 males and 10 females	50 males	Rats: 70 males and 70 females Mice: 50 males and 50 females
Method of Animal Distribution			
Animals grouped by weight intervals. Animals assigned to cages, then cages assigned to treatment groups using appropriate table of random numbers.	Same as 16-day studies	Same as 16-day studies	Same as 16-day studies
Animals per Cage			
5	5	5	5
Method of Animal Identification			
Ear punch	Ear punch	Ear punch and toe clip	Ear punch and toe clip
Diet			
NIH-07 Rat and Mouse Ration, Open formula, pellets (Zeigler Bros., Inc., Gardners, PA); available *ad libitum*	Same as 16-day studies	Same as 16-day studies	Same as 16-day studies
Water			
Tap water (City of Birmingham Public Water Supply) via outside-the-cage automatic watering system (Edstrom Industries, Inc., Waterford, WI); available *ad libitum*	Same as 16-day studies	Same as 16-day studies	Same as 16-day studies
Cages			
Solid-bottom polycarbonate (Lab Products, Inc., Garfield, NJ)	Same as 16-day studies	Same as 16-day studies	Same as 16-day studies
Bedding			
Heat-treated hardwood chips (Northeastern Products Corp., Warrensburg, NY); changed twice weekly	Same as 16-day studies	Same as 16-day studies	Same as 16-day studies

TABLE 1
Experimental Design and Materials and Methods in the Corn Oil Gavage Studies of Furan (continued)

16-Day Studies	13-Week Studies	Stop-Exposure Study	2-Year Studies
Cage Filters			
Spun-bonded polyester (Snow Filtration, Cincinnati, OH)	Same as 16-day studies	Same as 16-day studies	Same as 16-day studies
Animal Room Environment			
Temperature: 23°-24° C Relative humidity: 43%-62% Fluorescent light: 12 hours/day Room air changes: minimum 15/hour	Temperature: 22°-26° C Relative humidity: 36%-65% Fluorescent light: 12 hours/day Room air changes: minimum 15/hour	Temperature: Average 22° C Relative humidity: Average 50% Fluorescent light: 12 hours/day Room air changes: minimum 15/hour	Temperature: Average 22° C Relative humidity: Average 50% (rats), 51% (mice) Fluorescent light: 12 hours/day Room air changes: minimum 15/hour
Doses			
Rats: 0, 5 (males only), 10, 20, 40, 80, or 160 (females only) mg/kg furan in corn oil by gavage Mice: 0, 10, 20, 40, 80, or 160 mg/kg furan in corn oil by gavage	Rats: 0, 4, 8, 15, 30, or 60 mg/kg furan in corn oil by gavage Mice: 0, 2 (males only), 4, 8, 15, 30, or 60 (females only) mg/kg furan in corn oil by gavage	30 mg/kg furan in corn oil by gavage	Rats: 0, 2, 4, or 8 mg/kg furan in corn oil by gavage Mice: 0, 8, or 15 mg/kg furan in corn oil by gavage
Type and Frequency of Observation			
Observed twice/day; body weight initially and once/week; clinical observations twice/day	Observed twice/day; body weight initially and once/week; clinical observations once/week	Observed twice/day; body weight initially, once/week for 13 weeks, once/month thereafter; clinical observations once/week for 13 weeks, once/month thereafter	Observed twice/day; body weight initially, once/week for 13 weeks, once/month thereafter; clinical observations once/month
Clinical Pathology			
None	None	None	Hematology and clinical chemistry tests were conducted on blood collected from 10 rats from each dose group at 9 months. Parameters measured included: hematocrit, hemoglobin, erythrocyte count, leukocyte count and differential, lactate dehydrogenase, sorbitol dehydrogenase, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, and blood urea nitrogen.

TABLE 1
Experimental Design and Materials and Methods in the Corn Oil Gavage Studies of Furan (continued)

16-Day Studies	13-Week Studies	Stop-Exposure Study	2-Year Studies
Necropsy Examinations			
All animals necropsied and examined for gross lesions.	Necropsy performed on all animals. Organs weighed were: brain, heart, right kidney, liver, lungs, thymus; in addition, livers of four interim-death male rats were weighed.	Necropsy performed on all animals. Organs weighed for rats at the 15-month interim evaluations: kidney, liver, lung, and spleen.	Necropsy performed on all animals. Organs weighed for rats at 15-month interim evaluations: liver, lung, and kidney.
Histopathologic Examinations			
No histopathologic examinations were conducted.	Complete histopathology on all controls, 30 and 60 mg/kg rats, 30 mg/kg male mice and 60 mg/kg female mice. Tissues examined included: adrenal gland, bone and marrow (femur), brain, clitoral or preputial gland (rats), colon, esophagus, gallbladder (mice), heart, kidney, liver, lung, lymph nodes (mandibular, mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, small intestine, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, uterus, and gross lesions. The liver was examined from 4, 8, and 15 mg/kg rats, male 4 mg/kg mice, all 8 and 15 mg/kg mice, and female 30 mg/kg mice.	At the 13-week evaluation only livers were examined. Histopathology on all males from the 9- and 15-month interim evaluations and all males found dead or killed moribund during study. Tissues examined: kidney, liver, lung (15-month only), and gross lesions.	Selected histopathology on all 2 or 4 mg/kg rats from the 9- and 15-month interim evaluations. Tissues examined: liver, kidney, and gross lesions. Complete histopathology on all 0 or 8 mg/kg rats from the 9- and 15-month interim studies, all animals that died, and all killed moribund or at study termination. Tissues examined: adrenal gland, bone and marrow (femur), brain, cecum, clitoral or preputial gland (rats), colon, duodenum, epididymis, esophagus, gallbladder (mice), heart, ileum, jejunum, kidney, liver, lung, lymph nodes (mandibular, mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, rectum, salivary gland, skin, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, uterus, and gross lesions.

RESULTS

RATS

16-Day Studies

All five male rats that received 80 mg/kg died by day 8. All females that received 160 mg/kg died by the second day and all females that received 80 mg/kg died by the fourth day (Table 2). There were no other deaths during the studies. The final mean body weights of males in the 20 and 40 mg/kg dose groups and of females in the 40 mg/kg group were significantly lower than the control groups (Table 2). The only clinical findings consistently observed in furan-dosed groups were inactivity or reduced activity. At necropsy, mottled and often enlarged livers were observed in the 20, 40, and 80 mg/kg male dose groups and in the 40, 80, and 160 mg/kg female dose groups.

TABLE 2
Survival and Mean Body Weights of Rats in the 16-Day Gavage Studies of Furan

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b] Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	5/5	127 ± 2	207 ± 5	79 ± 3	
5	5/5	135 ± 3	213 ± 5	78 ± 3	103
10	5/5	131 ± 3	203 ± 6	71 ± 4	98
20	5/5	125 ± 3	189 ± 3*	64 ± 1**	92
40	5/5	131 ± 2	171 ± 8**	40 ± 7**	83
80	0/5[c]	128 ± 2	–	–	–
Female					
0	5/5	100 ± 3	137 ± 3	38 ± 1	
10	5/5	103 ± 2	138 ± 1	35 ± 1	101
20	5/5	100 ± 2	136 ± 3	37 ± 2	99
40	5/5	95 ± 1	113 ± 6**	19 ± 5**	83
80	0/5[d]	99 ± 3	–	–	–
160	0/5[e]	100 ± 2	–	–	–

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. No final group mean body weight is calculated in groups with 100% mortality.
[c] Day of death: 4, 4, 4, 5, 8
[d] Day of death: 3, 3, 3, 4, 4
[e] Day of death: 2, 2, 2, 2, 2

13-Week Studies

Nine males and four females from the 60 mg/kg groups died before the end of the studies (Table 3). Final mean body weights of male rats in the 15 and 30 mg/kg groups and of female rats in the 60 mg/kg group were significantly lower than controls. Final mean body weights of all other dose groups were similar to controls. Reduced activity and occasional irregular breathing were observed in the 60 mg/kg male and female dose groups.

Relative and absolute liver weights were significantly greater than controls in males administered 30 mg/kg and in females administered 8, 15, 30, or 60 mg/kg of furan (Table F1). Absolute thymus weights were significantly decreased in male rats administered 30 mg/kg and in females administered 60 mg/kg. Relative and absolute kidney weights were significantly increased in females administered 15, 30, and 60 mg/kg furan. There was a significant increase in the relative kidney weights in the 15 and 30 mg/kg male dose groups as well as significant differences in relative and/or absolute weights of the brain, heart, and lungs in groups of treated males and 60 mg/kg females; these differences were considered secondary to the decreased body weights in rats administered furan. At necropsy, the livers of rats in the 15, 30, and 60 mg/kg dose groups had pronounced lobular patterns, raised areas, and nodules.

Lesions associated with administration of furan were observed in the liver, kidney, thymus, testes, and ovaries (Table 4). The most prominent liver change was bile duct hyperplasia, which occurred in all

TABLE 3
Survival and Mean Body Weights of Rats in the 13-Week Gavage Studies of Furan

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b] Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	10/10	156 ± 3	378 ± 5	222 ± 4	
4	10/10	149 ± 4	375 ± 6	226 ± 5	99
8	10/10	144 ± 3	370 ± 6	226 ± 5	98
15	10/10	153 ± 4	353 ± 7**	201 ± 5**	93
30	10/10	155 ± 5	309 ± 6**	154 ± 5**	82
60	1/10[c]	148 ± 3	134	–	35
Female					
0	10/10	124 ± 1	207 ± 3	83 ± 3	
4	10/10	116 ± 2*	207 ± 4	91 ± 4	100
8	10/10	122 ± 2	211 ± 3	89 ± 4	102
15	10/10	125 ± 2	209 ± 3	84 ± 3	101
30	10/10	123 ± 2	201 ± 5	78 ± 5	97
60	6/10[d]	118 ± 1	169 ± 5**	51 ± 3**	82

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Number surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. No group mean body weight is calculated in groups with high mortality.
[c] Week of death: 2, 2, 3, 3, 3, 9, 10, 11, 11
[d] Week of death: 1, 11, 11, 12

TABLE 4
Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Gavage Studies of Furan

	Vehicle Control	4 mg/kg	8 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
Male						
Number of animals examined	10	10	10	10	10	10
Liver						
Biliary tract						
Cholangiofibrosis	0	4*	7**	10**	10**	10**
Hyperplasia	0	4*	9**	10**	10**	10**
Hepatocytes						
Cytomegaly	0	0	0	8**	10**	10**
Degeneration	0	0	7**	9**	10**	10**
Necrosis	0	0	0	9**	10**	10**
Hyperplasia, nodular	0	0	0	0	10**	10**
Kupffer cells						
Pigmentation	0	4*	6**	10**	10**	9**
Kidney						
Renal tubule						
Dilatation	0	–[a]	–	–	2	9**
Necrosis	0	–	–	–	0	10**
Thymus						
Atrophy	0	–	–	–	0	7**
Testes						
Atrophy	0	–	–	–	0	9**
Female						
Number of animals examined	10	10	10	10	10	10
Liver						
Biliary tract						
Cholangiofibrosis	0	1	7**	10**	10**	9**
Hyperplasia	0	7**	10**	10**	10**	9**
Hepatocytes						
Cytomegaly	0	0	0	10**	10**	9**
Degeneration	0	0	1	10**	10**	10**
Necrosis	0	0	0	8**	10**	10**
Hyperplasia, nodular	0	0	0	0	8**	9**
Kupffer cells						
Pigmentation	0	2	8**	10**	10**	9**
Kidney						
Renal tubule						
Dilatation	0	–	–	–	0	8**
Necrosis, epithelium	0	–	–	–	0	7**
Thymus						
Atrophy	0	–	–	–	0	3
Ovaries						
Atrophy	0	–	–	–	0	9**

° Significantly different (P≤0.05) from the control group by the Fisher exact test
°° P≤0.01
[a] Not examined in this dose group

furan dose groups examined. The severity grade increased with dose from minimal in the 4 mg/kg groups to marked in the 60 mg/kg groups. Minimally severe lesions consisted of multiple scattered small foci of periportal fibrosis containing proliferating bile ducts. In the markedly severe liver lesions, all portal areas were involved. The fibrous tissue and proliferating bile ducts extended between adjacent portal areas (Plate 1), which resulted in the pronounced lobular pattern seen at necropsy. In most affected livers, a few to many hepatic lobules were totally replaced by fibrous tissue containing proliferating bile ducts composed of large atypical basophilic epithelial cells (cholangiofibrosis) (Plate 2). Cholangiofibrosis was also seen in livers with minimally severe bile duct hyperplasia. Hepatocytes usually were enlarged with abundant eosinophilic cytoplasm (cytomegaly). Scattered individual or clusters of hepatocytes were characterized by mildly to markedly vacuolated cytoplasm (degeneration) or were necrotic. Livers in the 30 and 60 mg/kg furan dose groups contained one or more foci of nodular hepatocyte hyperplasia (Plates 3 and 4). These large nodules were usually several hepatic lobules in diameter and sometimes bulged above the capsular surface. The nodules consisted of large densely packed hepatocytes arranged in a recognizable lobular pattern. In some individuals from each furan dose group, scattered Kupffer cells in the liver contained greenish brown pigment (presumably bile).

Kidneys of nearly all 60 mg/kg males and females and of two 30 mg/kg males had dilatated renal tubules up to approximately twice normal diameter. In many tubules the epithelium was necrotic or lost from the basement membrane, while in other tubules the epithelial cells were enlarged. Most tubular lumina contained eosinophilic granular material or cell debris.

Atrophy of the thymus, testes, or ovaries was seen in several male and female rats administered 60 mg/kg furan. Thymic atrophy was characterized by a partial to nearly complete loss of cortical lymphocytes. Testicular atrophy consisted of varying degrees of loss of spermatogenic cells within seminiferous tubules. Atrophic ovaries were smaller than normal and contained a few small corpora lutea. These changes are probably the result of debilitation associated with furan toxicity.

Dose selection rationale: The selection of doses for the 2-year studies in rats was based on liver toxicity. The severity of the liver lesions at 15 mg/kg and above and the fact that a no-effect level was not achieved suggested that continued exposure to even low doses of furan could result in cumulative hepatotoxicity which might eventually be life threatening. The lesions observed at 8 mg/kg involved primarily the bile duct epithelium and, although clearly resulting from exposure to furan, were not considered the type that would become life threatening in 2-year studies. Therefore, 8 mg/kg was selected as the high dose. Although furan-related hepatotoxicity was apparent at 4 mg/kg, evaluation of the response between 8 and 4 mg/kg indicated a considerable reduction in the incidence and severity of furan-induced lesions. This suggested that a dose lower than 4 mg/kg would be close to a no-effect level. Based on this reasoning, 2 mg/kg was selected as the low dose and 4 mg/kg as the mid dose for the 2-year studies.

2-Year Studies

Survival

Survival of high-dose males and females was significantly lower than controls as a result of moribund conditions associated with the presence of liver neoplasms (Table 5 and Figure 1). Survival of other groups of dosed rats was similar to controls.

Body Weights and Clinical Findings

Mean body weights of male rats that received 2 or 4 mg/kg and of all dose groups of female rats were similar to controls; however, mean body weights of male rats that received 8 mg/kg were 6% to 8% lower than controls from week 73 to the end of the studies (Figure 2 and Tables 6 and 7). No clinical findings related to furan administration were observed.

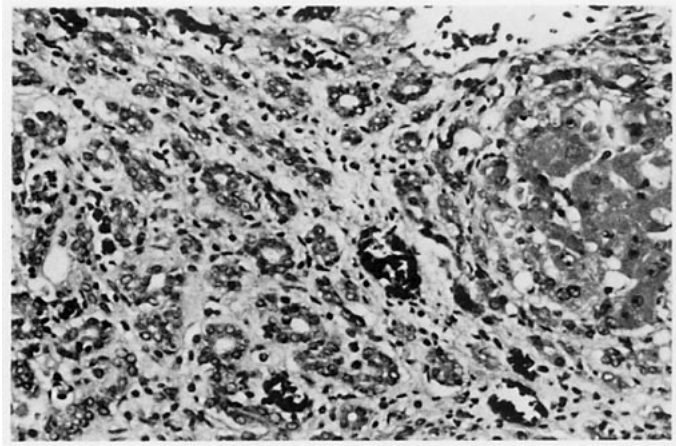


PLATE 1
Biliary hyperplasia in a male F344 rat receiving 60mg/kg furan in the 13-week gavage study. Note the many bile ductules surrounded by a loose connective tissue stroma. H&E, Magnification 80×

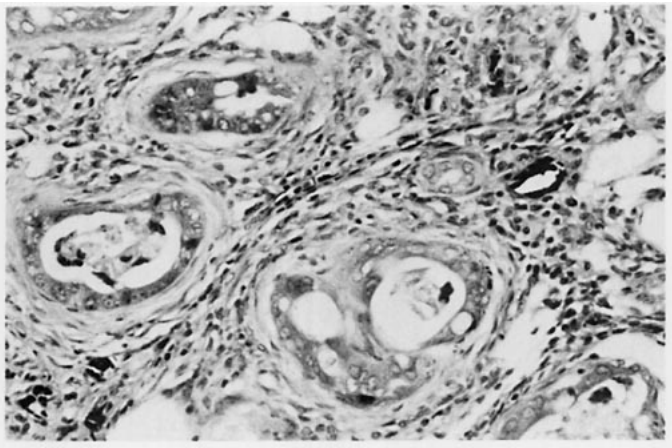


PLATE 2
Cholangiofibrosis in a male F344 rat receiving 30 mg/kg furan in the 13-week gavage study. Note the irregular ducts lined by pleomorphic epithelium and the surrounding immature fibrous connective tissue containing scattered mononuclear inflammatory cells. Compare with Plate 1. H&E, Magnification 80×

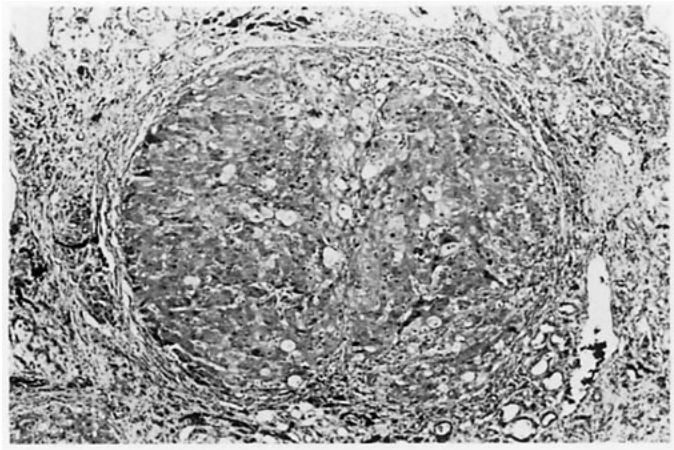


PLATE 3
Focal hepatocellular hyperplasia in a male F344 rat receiving 60 mg/kg furan in the 13-week gavage study. The focus of hepatocellular hyperplasia is delineated by fibrous connective tissue representing collapsed hepatic stroma and fibrosis. H&E, Magnification 20×

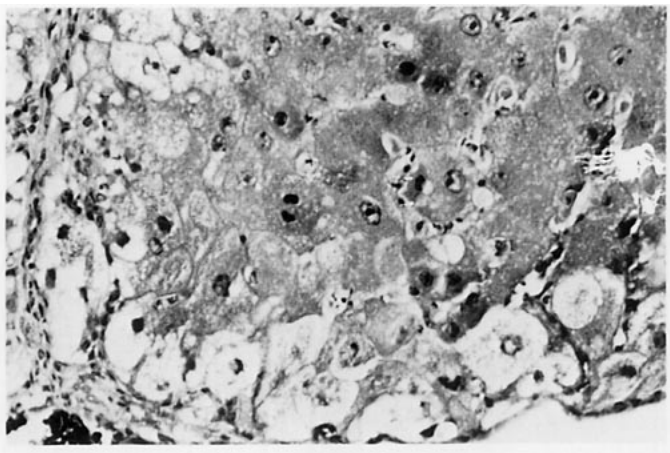


PLATE 4
High magnification of hepatocytes in a focus of hyperplasia from a male F344 rat receiving 60 mg/kg furan in the 13-week gavage study. The hyperplastic hepatocytes are enlarged and some have granular eosinophilic cytoplasm while other hepatocytes have clear cytoplasm. H&E, Magnification 80×

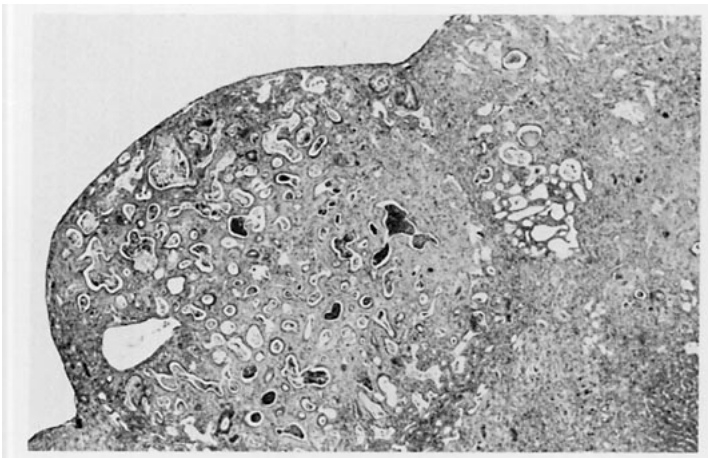


PLATE 5
Cholangiocarcinoma in a female F344 rat receiving 8 mg/kg furan in the 2-year gavage study. H&E, Magnification 10×

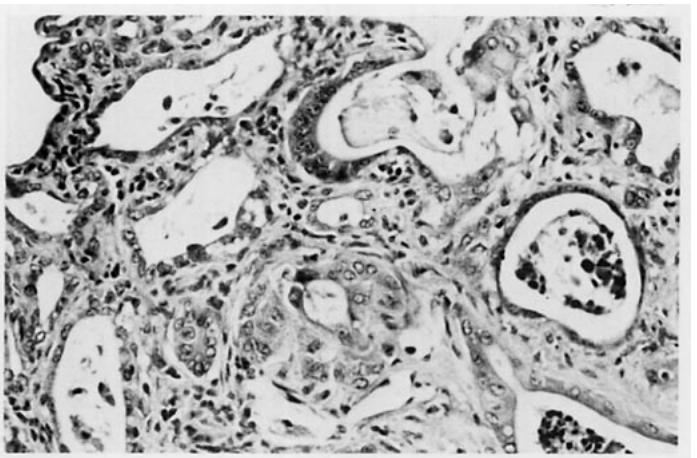


PLATE 6
High magnification of cholangiocarcinoma shown in Plate 5. The neoplastic epithelial cells are pleomorphic and are arranged in irregular ducts. H&E, Magnification 80×

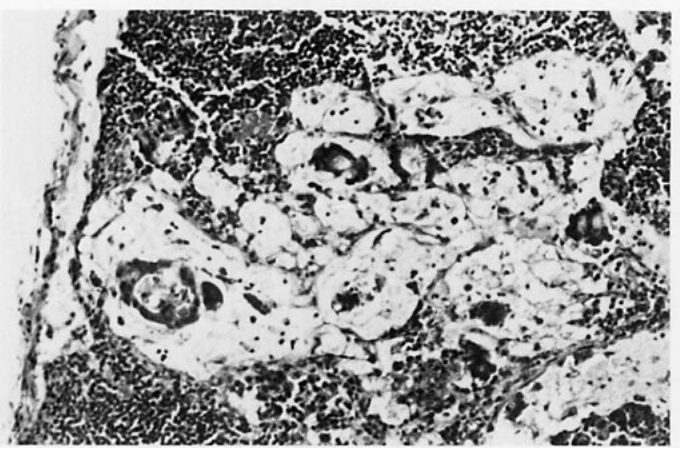


PLATE 7
Metastasis of cholangiocarcinoma in a lymph node from a female F344 rat receiving 8 mg/kg furan in the 2-year gavage study. H&E, Magnification 50×

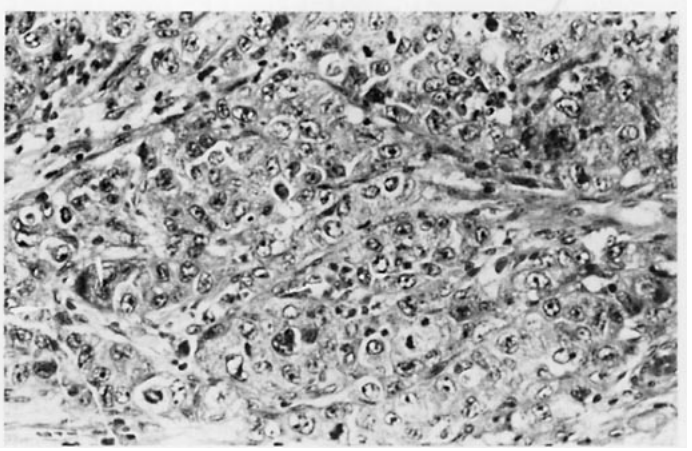


PLATE 8
Hepatocellular carcinoma in a female F344 rat receiving 8 mg/kg furan in the 2-year gavage study. Note the neoplastic hepatocytes arranged in thick trabeculae. H&E, Magnification 80×

TABLE 5
Survival of Rats in the 2-Year Gavage Studies of Furan[a]

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Male				
Animals initially in study	70	70	70	70
9-Month interim evaluation[b]	10	10	10	10
15-Month interim evaluation[b]	10	10	10	10
Natural deaths	1	4	3	5
Moribund kills	10	13	17	28
Accidental deaths[b]	6	5	4	1
Animals surviving until study termination	33	28	26	16
Percent probability of survival at end of study[c]	75	62	57	33
Mean survival days[d]	654	618	644	648
Survival analyses[e]	P<0.001	P=0.245	P=0.086	P<0.001
Female				
Animals initially in study	70	70	70	70
9-Month interim evaluation[b]	10	10	10	10
15-Month interim evaluation[b]	10	10	10	10
Natural deaths	4	1	5	10
Moribund kills	12	17	17	19
Accidental deaths[b]				2
Animals surviving until study termination	34	32	28	19
Percent probability of survival at end of study[c]	68	64	56	40
Mean survival days[d]	698	683	673	634
Survival analyses[e]	P=0.002	P=0.732	P=0.263	P=0.006

[a] First day of terminal sacrifice: 729
[b] Censored from survival analyses
[c] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths.
[d] Mean of all deaths (uncensored, censored, terminal sacrifice)
[e] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns.

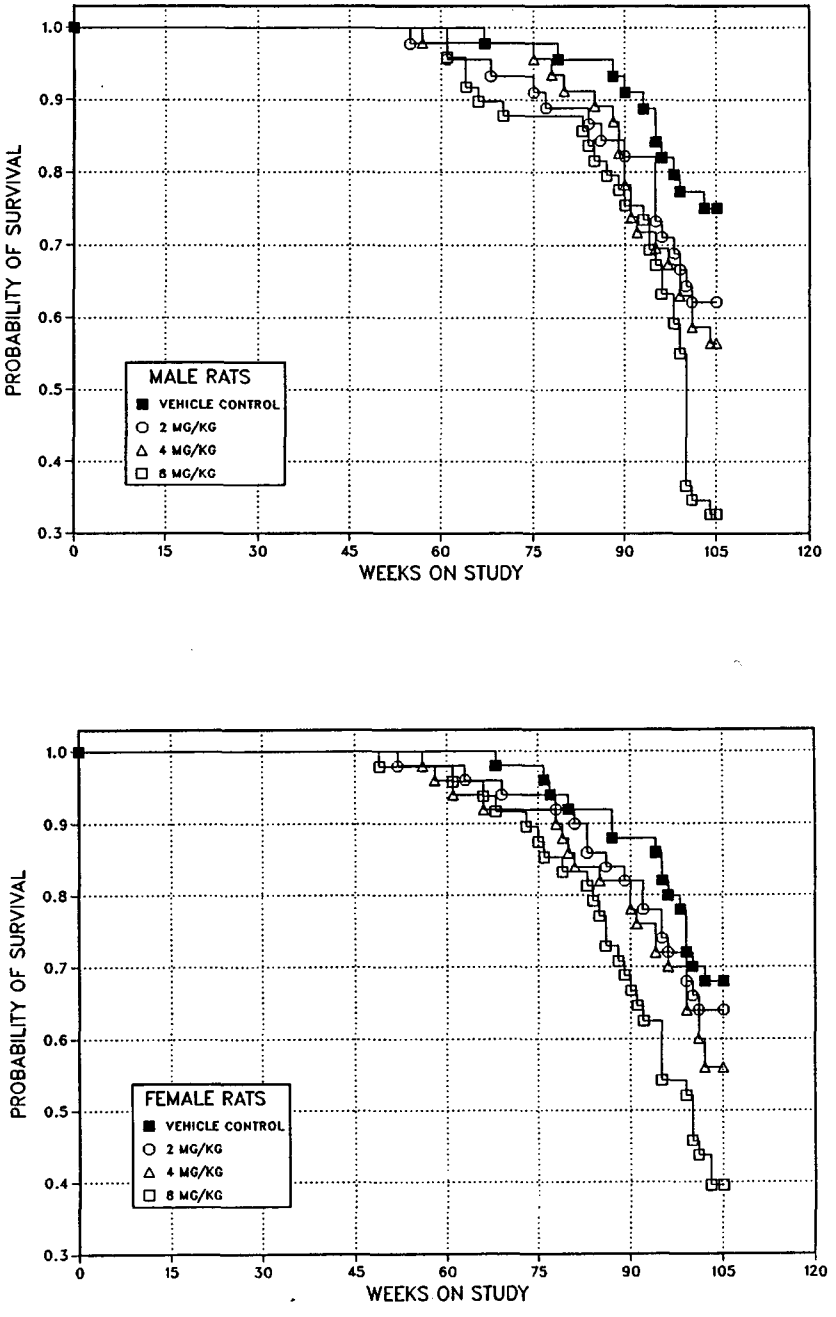


FIGURE 1
Kaplan-Meier Survival Curves for Rats Administered Furan by Gavage for 2 Years

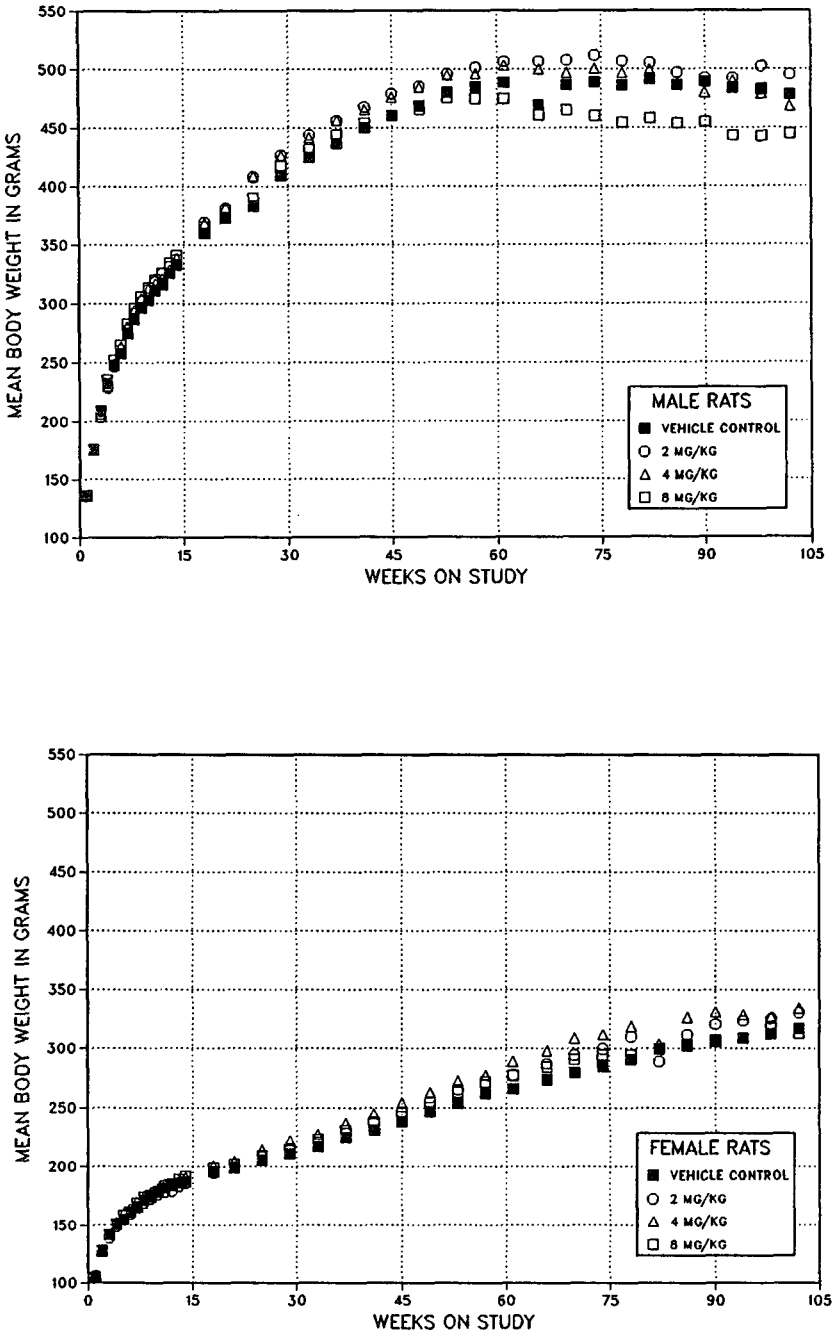


FIGURE 2
Growth Curves for Rats Administered Furan by Gavage for 2 Years

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Furan

Weeks on Study	Vehicle Control		2 mg/kg			4 mg/kg			8 mg/kg		
	Av.Wt. (g)	No. of Survivors	Av.Wt. (g)	Wt. (% of controls)	No. of Survivors	Av.Wt. (g)	Wt. (% of controls)	No. of Survivors	Av.Wt. (g)	Wt. (% of controls)	No. of Survivors
1	136	50	136	100	50	136	100	50	136	100	50
2	175	50	176	101	50	176	100	50	176	100	50
3	208	50	204	98	50	207	99	50	209	100	50
4	232	50	229	99	50	230	99	50	236	101	50
5	248	50	246	99	48	250	101	50	252	102	50
6	258	50	261	101	48	264	102	50	265	103	50
7	275	50	278	101	48	281	102	50	283	103	50
8	287	50	292	102	48	295	103	49	296	103	50
9	297	49	303	102	47	305	103	49	306	103	49
10	304	49	312	103	46	313	103	49	314	104	49
11	311	49	319	102	46	317	102	48	320	103	49
12	316	49	325	103	46	321	102	48	326	103	49
13	326	49	332	102	46	329	101	48	335	103	49
14	333	49	338	101	45	339	102	48	341	102	49
18	360	48	369	103	45	369	102	48	365	102	49
21	373	48	381	102	45	382	102	48	379	102	49
25	383	48	408	106	45	409	107	48	390	102	49
29	409	47	427	104	45	426	104	48	418	102	49
33	425	47	444	105	45	442	104	48	432	102	49
37	437	47	456	105	45	456	105	48	444	102	49
41	450	47	467	104	45	465	103	47	454	101	49
45	460	47	479	104	45	476	104	47	461	100	49
49	469	46	485	104	45	485	103	47	466	99	49
53	480	46	496	103	45	495	103	47	476	99	49
57	485	46	502	103	44	496	102	47	475	98	49
61	488	45	506	104	44	503	103	45	475	97	49
66	469	45	507	108	43	500	107	45	461	98	44
70	486	44	508	104	42	497	102	45	465	96	44
73	489	44	512	105	42	500	102	45	460	94	43
78	486	44	507	104	40	497	102	44	455	94	43
82	492	43	505	103	40	500	102	42	458	93	43
86	486	43	497	102	39	489	100	41	454	93	40
90	489	41	492	101	38	480	98	38	455	93	38
94	484	39	492	102	37	490	101	33	443	92	36
98	483	35	502	104	31	479	99	31	442	92	30
102	478	34	495	104	28	469	98	27	445	93	17
Terminal sacrifice		33			28			26			16
Mean for weeks											
1-13	259		263	101		263	101		266	102	
14-52	410		425	104		425	104		415	101	
53-102	484		502	104		492	101		459	95	

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of Furan

Weeks on Study	Vehicle Control Av.Wt. (g)	Vehicle Control No. of Survivors	2 mg/kg Av.Wt. (g)	2 mg/kg Wt. (% of controls)	2 mg/kg No. of Survivors	4 mg/kg Av.Wt. (g)	4 mg/kg Wt. (% of controls)	4 mg/kg No. of Survivors	8 mg/kg Av.Wt. (g)	8 mg/kg Wt. (% of controls)	8 mg/kg No. of Survivors
1	105	50	106	101	50	105	101	50	105	100	50
2	127	50	127	100	50	129	102	50	128	101	50
3	142	50	139	98	50	142	100	50	142	100	50
4	150	50	149	99	50	153	102	50	152	101	50
5	155	50	155	100	50	161	104	50	159	102	50
6	162	50	160	99	50	165	102	50	162	100	50
7	166	50	165	99	50	171	103	50	169	102	50
8	172	50	170	99	50	175	102	50	174	101	50
9	175	50	173	99	50	179	102	50	176	101	50
10	179	50	177	99	50	182	102	50	179	100	50
11	182	50	179	98	50	185	102	50	184	101	50
12	184	50	180	98	50	186	101	50	185	101	50
13	186	50	183	99	50	189	101	50	189	102	50
14	187	50	186	100	50	191	102	50	192	103	50
18	196	50	195	100	50	201	103	50	199	102	50
21	199	50	199	100	50	204	103	50	202	102	50
25	205	50	208	102	50	214	105	50	209	102	49
29	211	50	216	102	50	223	105	50	215	102	49
33	217	50	221	102	50	228	105	50	223	103	49
37	225	50	229	102	50	237	105	50	231	103	48
41	231	50	238	103	50	245	106	50	237	103	48
45	238	50	246	103	50	254	107	50	243	102	48
49	247	50	255	103	50	263	106	50	250	101	48
53	254	50	265	105	49	272	107	50	263	104	47
57	262	50	270	103	49	278	106	49	272	104	47
61	266	50	278	105	49	289	109	47	277	104	47
66	274	50	287	105	48	298	109	47	285	104	46
70	280	49	295	105	47	309	110	46	291	104	44
73	285	49	300	105	47	312	110	46	295	103	44
78	291	47	310	107	47	319	110	46	295	101	41
82	300	46	289	97	45	304	101	42	300	100	40
86	303	46	312	103	43	327	108	41	304	100	36
90	306	44	321	105	41	331	108	41	307	100	33
94	309	44	324	105	39	329	107	38	309	100	30
98	312	40	325	104	36	327	105	35	318	102	26
102	317	35	331	104	32	335	106	30	313	99	21
Terminal sacrifice		34			32			28			19
Mean for weeks											
1-13	160		159	99		163	102		162	101	
14-52	216		219	102		226	105		220	102	
53-102	289		301	104		310	107		295	102	

Clinical Chemistry and Hematology

Significantly increased serum sorbitol dehydrogenase levels in animals of both sexes in the 4 and 8 mg/kg dose groups were consistent with mild liver damage (Table G1). No other biologically significant clinical chemistry changes were noted at the 9-month interim evaluation. Hematocrit, hemoglobin, and erythrocyte count were significantly reduced in the high-dose male group compared to controls (Table G1). These findings were consistent with a slight anemia due to chronic inflammation, and may have been secondary to inflammatory lesions in the liver.

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions in the liver, hematopoietic system, urinary bladder, kidney, parathyroid gland, heart, and forestomach.

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

Liver: Absolute and relative weights of the liver in the mid- and high-dose male and female groups were significantly greater than controls at the 15-month interim evaluations (Table F3).

Lesions related to furan administration were seen in the livers of some 9-month interim evaluation rats and in all 15-month interim evaluation rats (Tables 8 and 9); the incidence of cholangiocarcinomas and the severity of a variety of nonneoplastic liver changes were dose-related at the interim evaluations.

Neoplasms and nonneoplastic lesions occurred at markedly increased incidences in rats administered furan for 2 years. The incidences of cholangiocarcinoma, hepatocellular adenoma, and hepatocellular carcinoma were significantly increased in rats administered furan (Table 10).

Cholangiocarcinomas consisted of numerous duct-like structures and irregular, variably sized cystic spaces that were lined by pleomorphic epithelial cells and imbedded within a prominent dense fibrous tissue stroma (Plates 5 and 6). Many neoplasms were so extensive that they appeared to replace entire liver lobes. Epithelial cells varied from flattened to cuboidal or columnar. Some cells were very large, with deeply basophilic nuclei. Mucus-secreting epithelial cells were present within some cysts, and the lumens of these cysts were filled with mucinous material, sometimes mixed with cell debris. Proliferating blood vessels (neovascularization) were observed near cystic spaces in many neoplasms. In some areas, cells piled up in multiple layers or invaded the fibrous tissue stroma. Cholangiocarcinomas often invaded locally into the adjacent liver parenchyma, and metastases were found in two high-dose males and in two high-dose females (Plate 7).

Hepatocellular adenomas were discrete collections of hepatocytes that compressed adjacent hepatic tissue. The hepatic plates in the adenomas were not arranged in the normal lobular structure and often intersected the plates in adjacent normal liver at right angles. The normal cord structure was not usually apparent and the cells appeared to form solid sheets. Staining characteristics of the neoplastic hepatocytes sometimes differed from that of normal cells. Hepatocellular carcinomas were distinguished from adenomas by the presence of atypical, highly disorganized cells that formed broad trabeculae several cell layers thick and, occasionally, glandular structures (Plate 8).

Various nonneoplastic lesions involving the biliary tract and the hepatocytes were observed in most male and female rats administered furan (Table 11). Changes in the biliary tract were observed in most portal areas and sometimes extended between adjacent portal areas. A prominent change was hyperplasia of bile ducts, which was usually accompanied by varying degrees of fibrosis that encompassed many of the hyperplastic ducts. Affected portal areas often contained an infiltration of varying numbers of mononuclear inflammatory cells (inflammation, chronic). Some hyperplastic ducts trapped within the fibrous tissue were variably dilated (cyst, multiple) and often contained large cuboidal to tall columnar epithelial cells that resembled small intestinal epithelium more than biliary epithelium (metaplasia).

PLATE 5

Cholangiocarcinoma in a female F344 rat receiving 8 mg/kg furan in the 2-year gavage study. H&E, Magnification 10×

PLATE 6

High magnification of cholangiocarcinoma shown in Plate 5. The neoplastic epithelial cells are pleomorphic and are arranged in irregular ducts. H&E, Magnification 80×

PLATE 7

Metastasis of cholangiocarcinoma in a lymph node from a female F344 rat receiving 8 mg/kg furan in the 2-year gavage study. H&E, Magnification 50×

PLATE 8

Hepatocellular carcinoma in a female F344 rat receiving 8 mg/kg furan in the 2-year gavage study. Note the neoplastic hepatocytes arranged in thick trabeculae. H&E, Magnification 80×

TABLE 8
Incidences of Selected Lesions in Rats at the 9-Month Interim Evaluations in the 2-Year Gavage Studies of Furan

	Incidence (Average Severity)[a]			
	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
n	10	10	10	10
Male				
Neoplasms				
Liver				
Cholangiocarcinoma	0	5*	7**	10**
Nonneoplastic Lesions				
Liver				
Biliary tract				
Fibrosis, multifocal	0	10** (1.1)	10** (1.7)	10** (2.8)
Hyperplasia, multifocal	0	10** (1.0)	10** (1.8)	10** (2.8)
Inflammation, chronic, multifocal	0	10** (1.0)	10** (1.7)	10** (2.8)
Cysts, multiple	0	6** (1.0)	7** (1.4)	10** (2.2)
Hepatocytes				
Cytomegaly	0	10** (1.0)	10** (1.3)	10** (2.8)
Degeneration, multifocal	0	10** (1.0)	10** (1.2)	10** (2.8)
Hyperplasia, nodular, multifocal	0	3 (1.0)	10** (1.7)	10** (2.9)
Necrosis, multifocal	3 (1.3)	10** (1.0)	10** (1.1)	10** (2.0)
Vacuolization, cytoplasmic	0	10** (1.0)	10** (1.4)	10** (2.7)
Kupffer cells				
Pigmentation, multifocal	0	10** (1.0)	10** (1.9)	10** (2.5)
Kidney				
Casts, protein	2 (1.5)	6 (1.1)	7* (1.1)	8** (1.4)
Mineralization, multifocal	0	0	0	4* (1.5)
Female				
Neoplasms				
Liver				
Cholangiocarcinoma	0	4*	9**	10**
Nonneoplastic Lesions				
Liver				
Biliary tract				
Fibrosis, multifocal	0	10** (1.0)	10** (1.8)	10** (2.8)
Hyperplasia, multifocal	0	10** (1.0)	10** (1.6)	10** (2.9)
Inflammation, chronic, multifocal	0	10** (1.0)	10** (1.7)	10** (2.9)
Cysts, multiple	0	4* (1.0)	8** (1.5)	10** (2.3)
Hepatocytes				
Cytomegaly	0	10** (1.0)	10** (1.1)	10** (2.4)
Degeneration, multifocal	0	7** (1.0)	10** (1.0)	10** (2.0)
Hyperplasia, nodular, multifocal	0	2 (1.0)	6** (1.1)	10** (2.4)
Necrosis, multifocal	0	6** (1.0)	10** (1.1)	10** (1.9)
Vacuolization, cytoplasmic	0	3 (1.0)	8** (1.0)	10** (2.3)
Kupffer cells				
Pigmentation, multifocal	0	10** (1.0)	10** (2.0)	10** (2.8)
Kidney				
Casts, protein	0	0	0	4* (1.0)
Mineralization, multifocal	0	1 (2.0)	2 (1.5)	6** (1.5)

* Significantly different ($P \leq 0.05$) from the controls by the Fisher exact test
** $P \leq 0.01$
[a] Average severity grade of lesions in affected animals. Severity grade of 1 = minimal; 2 = mild; 3 = moderate; 4 = marked.

TABLE 9
Incidences of Selected Lesions in Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Furan

	Incidence (Average Severity)[a]			
	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Male				
n	9	9	9	6
Neoplasms				
Cholangiocarcinoma	0	7**	9**	6**
Nonneoplastic Lesions				
Liver				
Biliary tract				
Fibrosis, multifocal	0	9** (1.7)	9** (2.9)	6** (3.7)
Hyperplasia, multifocal	0	9** (1.7)	9** (3.0)	6** (3.3)
Inflammation, chronic, multifocal	0	9** (1.7)	9** (2.3)	6** (3.0)
Cysts, multiple	0	8** (1.3)	9** (2.7)	6** (2.8)
Metaplasia	0	8** (1.3)	9** (2.2)	6** (2.5)
Hepatocytes				
Cytomegaly	0	9** (1.6)	9** (2.6)	6** (3.2)
Degeneration, multifocal	0	9** (1.4)	9** (2.0)	6** (2.7)
Hyperplasia, nodular, multifocal	0	9** (1.3)	9** (2.4)	6** (3.2)
Necrosis, multifocal	0	9** (1.2)	9** (2.0)	6** (2.0)
Vacuolization, cytoplasmic	0	9** (1.8)	9** (2.7)	6** (3.2)
Kupffer cells				
Pigmentation, multifocal	0	9** (1.7)	9** (2.1)	6** (3.0)
Kidney				
Nephropathy, chronic	8 (1.1)	5 (1.0)	9 (1.2)	6 (1.5)
Female				
n	9	10	9	7
Neoplasms				
Cholangiocarcinoma	0	9**	9**	7**
Nonneoplastic Lesions				
Liver				
Biliary tract				
Fibrosis, multifocal	0	10** (1.8)	9** (2.9)	7** (3.7)
Hyperplasia, multifocal	0	10** (1.8)	9** (2.7)	7** (3.7)
Inflammation, chronic, multifocal	0	10** (1.5)	9** (2.9)	7** (3.4)
Cysts, multiple	0	10** (1.4)	9** (2.4)	7** (3.4)
Metaplasia	0	10** (1.2)	9** (2.4)	7** (3.0)
Hepatocytes				
Cytomegaly	0	10** (1.2)	9** (2.0)	7** (3.0)
Degeneration, multifocal	0	10** (1.0)	9** (2.0)	7** (2.4)
Hyperplasia, nodular, multifocal	0	10** (1.0)	9** (2.4)	7** (3.0)
Necrosis, multifocal	0	10** (1.0)	9** (2.0)	7** (2.0)
Vacuolization, cytoplasmic	0	10** (1.2)	9** (2.2)	7** (3.0)
Kupffer cells				
Pigmentation, multifocal	0	10** (1.7)	9** (2.2)	7** (3.1)
Kidney				
Nephropathy, chronic	0	0	3 (1.0)	6** (1.3)

** Significantly different ($P \leq 0.01$) from the controls by the Fisher exact test
[a] Average severity grade of lesions in affected animals. Severity grade of 1 = minimal; 2 = mild; 3 = moderate; 4 = marked.

TABLE 10
Liver Neoplasms in Rats in the 2-Year Gavage Studies of Furan

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Male				
Cholangiocarcinoma[a]				
Overall rates[b]	0/50 (0%)	43/50 (86%)	48/50 (96%)	49/50 (98%)
Adjusted rates[c]	0.0%	100.0%	100.0%	100.0%
Terminal rates[d]	0/33 (0%)	28/28 (100%)	26/26 (100%)	16/16 (100%)
First incidence (days)	–[e]	470	254	421
Logistic regression tests[f]	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocellular Adenoma				
Overall rates	1/50 (2%)	4/50 (8%)	18/50 (36%)	27/50 (54%)
Adjusted rates	2.6%	14.3%	56.9%	74.0%
Terminal rates	0/33 (0%)	4/28 (14%)	13/26 (50%)	8/16 (50%)
First incidence (days)	660	729 (T)	613	490
Logistic regression tests	P<0.001	P=0.149	P<0.001	P<0.001
Hepatocellular Carcinoma				
Overall rates	0/50 (0%)	1/50 (2%)	6/50 (12%)	18/50 (36%)
Adjusted rates	0.0%	3.6%	22.0%	58.5%
Terminal rates	0/33 (0%)	1/28 (4%)	5/26 (19%)	5/16 (31%)
First incidence (days)	–	729 (T)	703	624
Logistic regression tests	P<0.001	P=0.467	P=0.009	P<0.001
Hepatocellular Adenoma or Hepatocellular Carcinoma[g]				
Overall rates	1/50 (2%)	5/50 (10%)	22/50 (44%)	35/50 (70%)
Adjusted rates	2.6%	17.9%	68.0%	84.5%
Terminal rates	0/33 (0%)	5/28 (18%)	16/26 (62%)	10/16 (63%)
First incidence (days)	660	729 (T)	613	490
Logistic regression tests	P<0.001	P=0.079	P<0.001	P<0.001
Female				
Cholangiocarcinoma				
Overall rates	0/50 (0%)	49/50 (98%)	50/50 (100%)	48/50 (96%)
Adjusted rates	0.0%	100.0%	100.0%	100.0%
Terminal rates	0/34 (0%)	32/32 (100%)	28/28 (100%)	19/19 (100%)
First incidence (days)	–	436	388	143
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocellular Adenoma				
Overall rates	0/50 (0%)	2/50 (4%)	4/50 (8%)	7/50 (14%)
Adjusted rates	0.0%	6.0%	13.3%	33.8%
Terminal rates	0/34 (0%)	1/32 (3%)	3/28 (11%)	6/19 (32%)
First incidence (days)	–	697	688	644
Logistic regression tests	P<0.001	P=0.224	P=0.048	P=0.002

(continued)

TABLE 10
Liver Neoplasms in Rats in the 2-Year Gavage Studies of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Female (continued)				
Hepatocellular Carcinoma				
Overall rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Hepatocellular Adenoma or Hepatocellular Carcinoma[h]				
Overall rates	0/50 (0%)	2/50 (4%)	4/50 (8%)	8/50 (16%)
Adjusted rates	0.0%	6.0%	13.3%	36.1%
Terminal rates	0/34 (0%)	1/32 (3%)	3/28 (11%)	6/19 (32%)
First incidence (days)	–	697	688	644
Logistic regression tests	P<0.001	P=0.224	P=0.048	P<0.001

[a] No historical data available
[b] Number of tumor-bearing animals/number of animals necropsied
[c] Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at first occurrence of this tumor type in any of the groups
[d] Observed incidence at terminal kill
[e] Not applicable; no neoplasms in animal group
[f] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard neoplasms in animals dying prior to terminal kill as nonfatal.
[g] Historical incidence for 2-year NTP corn oil gavage studies for vehicle control groups (mean ± standard deviation): 19/770 (2.5% ± 2.8%), range 0%–10%
[h] Historical incidence: 9/770 (1.2% ± 2.7%), range 0%–10%

A change commonly involving hepatocytes was the presence of multiple foci of nodular hyperplasia. These were discrete foci composed of enlarged hepatocytes with abundant eosinophilic cytoplasm. The hepatocytes were arranged in a lobular pattern, although the pattern was somewhat distorted due to the enlargement of the hepatocytes. Nodular hyperplasias were distinguished from adenomas by the fact that hepatocytes in hyperplasias were arranged in recognizable lobular patterns, hyperplasias did not cause distinct compression, and hepatic plates in hyperplastic nodules were parallel rather than perpendicular to the plates in adjacent parenchyma. Hepatocytes adjacent to some portal areas were enlarged with abundant, lightly eosinophilic cytoplasm (cytomegaly), while other hepatocytes appeared shrunken and contained basophilic nuclei (degeneration) or one or more large, clear, intracytoplasmic vacuoles (cytoplasmic vacuolation). Scattered individual or small clusters of hepatocytes were necrotic. Multilocular cysts were observed in many rats of both sexes administered furan but not in controls. These cysts consisted of empty spaces usually larger than a hepatic lobule, and were divided by incomplete and complete partitions and lined by low cuboidal to flattened epithelium. Brown to green pigment (presumably bile) was present in Kupffer cells in the livers of nearly all rats administered furan.

Some liver lesions commonly found in both sexes of aging F344/N rats occurred with decreased incidences (basophilic foci in males and females; multiple granulomas in females) or were not observed (eosinophilic foci and biliary tract proliferation in males and females) in animals administered furan (Tables A5 and B5). The decreased incidences of these lesions were considered secondary to the hepatic damage caused by furan administration.

TABLE 11
Incidences of Nonneoplastic Liver Lesions in Rats in the 2-Year Gavage Studies of Furan

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Male				
Multilocular Cyst				
Overall rates[a]	0/50 (0%)	1/50 (2%)	17/50 (34%)	24/50 (48%)
Logistic regression tests[b]	P<0.001	P=0.467	P<0.001	P<0.001
Biliary Tract: Chronic Focal Inflammation				
Overall rates	0/50 (0%)	44/50 (88%)	48/50 (96%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Biliary Tract: Cyst				
Overall rates	0/50 (0%)	44/50 (88%)	47/50 (94%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Biliary Tract: Focal Fibrosis				
Overall rates	0/50 (0%)	44/50 (88%)	48/50 (96%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Biliary Tract: Focal Hyperplasia				
Overall rates	0/50 (0%)	44/50 (88%)	48/50 (96%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Biliary Tract: Metaplasia				
Overall rates	0/50 (0%)	44/50 (88%)	48/50 (96%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocyte: Cytomegaly				
Overall rates	0/50 (0%)	35/50 (70%)	46/50 (92%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocyte: Cytoplasmic Vacuolization				
Overall rates	1/50 (2%)	39/50 (78%)	45/50 (90%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocyte: Focal Degeneration				
Overall rates	0/50 (0%)	33/50 (66%)	46/50 (92%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocyte: Focal Hyperplasia				
Overall rates	0/50 (0%)	30/50 (60%)	46/50 (92%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocyte: Focal Necrosis				
Overall rates	0/50 (0%)	32/50 (64%)	46/50 (92%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Kupffer Cell: Focal Pigmentation				
Overall rates	0/50 (0%)	44/50 (88%)	48/50 (96%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001

(continued)

TABLE 11
Incidences of Nonneoplastic Liver Lesions in Rats in the 2-Year Gavage Studies of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Female				
Multilocular Cyst				
Overall rates	0/50 (0%)	6/50 (12%)	2/50 (4%)	12/50 (24%)
Logistic regression tests	P<0.001	P=0.017	P=0.256	P<0.001
Biliary Tract: Chronic Focal Inflammation				
Overall rates	0/50 (0%)	49/50 (98%)	50/50 (100%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Biliary Tract: Cyst				
Overall rates	0/50 (0%)	49/50 (98%)	50/50 (100%)	46/50 (92%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Biliary Tract: Focal Fibrosis				
Overall rates	0/50 (0%)	49/50 (98%)	50/50 (100%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Biliary Tract: Focal Hyperplasia				
Overall rates	0/50 (0%)	49/50 (98%)	50/50 (100%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Biliary Tract: Metaplasia				
Overall rates	0/50 (0%)	49/50 (98%)	50/50 (100%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocyte: Cytomegaly				
Overall rates	0/50 (0%)	44/50 (88%)	50/50 (100%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocyte: Cytoplasmic Vacuolization				
Overall rates	0/50 (0%)	43/50 (86%)	49/50 (98%)	47/50 (94%)
Logistic regression tests	P<0.001	P<0.001	"P<0.001	P<0.001
Hepatocyte: Focal Degeneration				
Overall rates	0/50 (0%)	35/50 (70%)	49/50 (98%)	47/50 (94%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocyte: Focal Hyperplasia				
Overall rates	0/50 (0%)	32/50 (64%)	47/50 (94%)	46/50 (92%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocyte: Focal Necrosis				
Overall rates	0/50 (0%)	18/50 (36%)	46/50 (92%)	47/50 (94%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Kupffer Cell: Focal Pigmentation				
Overall rates	0/50 (0%)	49/50 (98%)	50/50 (100%)	48/50 (96%)
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001

[a] Number of lesion-bearing animals/number of animals necropsied
[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard lesions in animals dying prior to terminal kill as nonfatal.

Hematopoietic System: The incidence of mononuclear cell leukemia in male and female rats administered furan followed a dose-related positive trend and was significantly increased in rats that received 4 or 8 mg/kg furan (Table 12). The incidence of mononuclear cell leukemia in high-dose males (25/50) and high-dose females (21/50) exceeds the NTP historical ranges for control F344/N rats from 2-year NTP corn oil gavage studies (males: 164/770, mean 21.3%, range 4%-38%; females: 206/770, mean 26.8%, range 16%-38%) (Tables A4b and B4b).

The incidences of several nonneoplastic lesions of the hematopoietic system were increased in male and female rats administered furan (Table 13). Bone marrow hyperplasia and congestion and proliferation of hematopoietic cells in the spleen occurred with significantly increased incidences. These increased incidences were considered secondary to the inflammatory liver lesions present in furan-exposed rats. Dilatation of medullary sinuses (ectasia) was observed in the mediastinal and pancreatic lymph nodes in a number of dosed males and females. The ectasia may have been due to an altered flow of lymph fluid secondary to the extensive liver damage found in animals administered furan. Hyperplasia of the pancreatic and mediastinal lymph nodes occurred with increased incidences in dosed males.

TABLE 12
Mononuclear Cell Leukemia in Rats in the 2-Year Gavage Studies of Furan

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Male				
Mononuclear Cell Leukemia[a]				
Overall rates[b]	8/50 (16%)	11/50 (22%)	17/50 (34%)	25/50 (50%)
Adjusted rates[c]	21.0%	31.7%	46.5%	70.6%
Terminal rates[d]	4/33 (12%)	6/28 (21%)	8/26 (31%)	8/16 (50%)
First incidence (days)	645	384	520	421
Life table tests[e]	P<0.001	P=0.227	P=0.016	P<0.001
Logistic regression tests[e]	P<0.001	P=0.267	P=0.027	P<0.001
Female				
Mononuclear Cell Leukemia[f]				
Overall rates	8/50 (16%)	9/50 (18%)	17/50 (34%)	21/50 (42%)
Adjusted rates	18.6%	24.1%	45.4%	59.9%
Terminal rates	1/34 (3%)	5/32 (16%)	9/28 (32%)	7/19 (37%)
First incidence (days)	556	602	557	238
Life table tests	P<0.001	P=0.441	P=0.022	P<0.001
Logistic regression tests	P<0.001	P=0.526	P=0.034	P=0.008

[a] Historical incidence for 2-year NTP corn oil gavage studies for vehicle control groups (mean ± standard deviation): 164/770 (21.3% ± 8.9%), range 4%–38%
[b] Number of lesion-bearing animals/number of animals necropsied
[c] Number of lesion-bearing animals/effective number of animals, i.e., number of animals alive at first occurrence of this tumor type in any of the groups
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal.
[f] Historical incidence: 206/770 (26.8% ± 7.0%), range 16%–38%

TABLE 13
Incidences of Selected Nonneoplastic Lesions of the Hematopoietic System in Rats in the 2-Year Gavage Studies of Furan

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Male				
Bone Marrow: Hyperplasia				
Overall rates[a]	0/50 (0%)	8/50 (16%)	9/50 (18%)	28/50 (56%)
Logistic regression tests[b]	P<0.001	P=0.003	P=0.002	P<0.001
Mediastinal Lymph Node: Ectasia				
Overall rates	0/48 (0%)	5/45 (11%)	7/48 (15%)	16/45 (36%)
Logistic regression tests	P<0.001	P=0.024	P=0.007	P<0.001
Mediastinal Lymph Node: Hyperplasia				
Overall rates	0/48 (0%)	1/45 (2%)	0/48 (0%)	9/45 (20%)
Logistic regression tests	P<0.001	P=0.480	–[c]	P<0.001
Pancreatic Lymph Node: Ectasia				
Overall rates	0/50 (0%)	4/50 (8%)	12/50 (24%)	24/50 (48%)
Logistic regression tests	P<0.001	P=0.034	P<0.001	P<0.001
Pancreatic Lymph Node: Hyperplasia				
Overall rates	0/50 (0%)	3/50 (6%)	2/50 (4%)	10/50 (20%)
Logistic regression tests	P<0.001	P=0.079	P=0.216	P<0.001
Spleen: Congestion				
Overall rates	5/50 (10%)	16/50 (32%)	25/50 (50%)	25/50 (50%)
Logistic regression tests	P<0.001	P=0.004	P<0.001	P<0.001
Spleen: Hematopoietic Cell Proliferation				
Overall rates	9/50 (18%)	23/50 (46%)	27/50 (54%)	30/50 (60%)
Logistic regression tests	P<0.001	P=0.001	P<0.001	P<0.001
Female				
Bone Marrow: Hyperplasia				
Overall rates	0/50 (0%)	8/50 (16%)	11/50 (22%)	24/50 (48%)
Logistic regression tests	P<0.001	P=0.006	P=0.001	P<0.001
Mediastinal Lymph Node: Ectasia				
Overall rates	0/48 (0%)	3/48 (6%)	4/49 (8%)	10/49 (20%)
Logistic regression tests	P<0.001	P=0.125	P=0.053	P<0.001
Pancreatic Lymph Node: Ectasia				
Overall rates	0/50 (0%)	6/50 (12%)	16/50 (32%)	23/50 (46%)
Logistic regression tests	P<0.001	P=0.020	P<0.001	P<0.001
Spleen: Congestion				
Overall rates	2/50 (4%)	6/50 (12%)	17/50 (34%)	23/50 (46%)
Logistic regression tests	P<0.001	P=0.161	P<0.001	P<0.001
Spleen: Hematopoietic Cell Proliferation				
Overall rates	8/50 (16%)	14/50 (28%)	27/50 (54%)	25/50 (50%)
Logistic regression tests	P<0.001	P=0.109	P<0.001	P<0.001

[a] Number of lesion-bearing animals/number of animals necropsied
[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard lesions in animals dying prior to terminal kill as nonfatal.
[c] Not applicable; no lesions in animal group

Urinary Bladder: Papillomas of the urinary bladder were found in three high-dose female rats; none were found in the other groups (Table B1). These are uncommon neoplasms in female rats and have been observed in 4/751 (0.5%) vehicle control females from the most recent NTP corn-oil gavage studies, with no more than one in any control group. Hyperplasia of the urinary bladder transitional epithelium, a lesion generally considered to be a precursor to neoplasia, occurred in one mid-dose male and one mid-dose female (Tables A5 and B5). The mid-dose female had a urinary calculus in its bladder and the hyperplasia was secondary to the presence of the calculus.

Kidney: Kidney lesions at the 9-month interim evaluations consisted of increased incidences of protein casts and/or multiple small foci of mineralization within renal tubules. Absolute and relative weights of the kidney were significantly greater in high-dose females than in controls at the 15-month evaluation. Kidney lesions at the 15-month interim evaluations consisted of an increased severity of nephropathy in males administered furan and an increased incidence and severity of nephropathy in females administered furan.

The severity of nephropathy in male rats administered furan and the incidence and severity of nephropathy in female rats administered furan were increased compared to controls (Table 14). Nephropathy was typical of that seen in aging F344/N rats and consisted of multiple changes including tubule dilatation with occasional cyst formation; atrophy, regeneration, and hypertrophy of tubule epithelial cells; proteinaceous tubule casts; thickened tubular and glomerular basement membranes; interstitial fibrosis; and scattered foci or suppurative and/or chronic inflammation. No primary renal neoplasms or renal tubule cell hyperplasias were seen in any control or dosed rats.

Parathyroid Gland: The incidence of parathyroid hyperplasia was increased in male rats at all dose levels (control, 0/46; 2 mg/kg, 2/47; 4 mg/kg, 10/49; 8 mg/kg, 6/43; Table A5) and in female rats that received 4 or 8 mg/kg (0/48, 0/50, 2/49, 9/46; Table B5). These increased incidences were considered secondary to the increased severity of nephropathy in rats administered furan.

Heart: The incidence of cardiomyopathy in dosed rats was increased compared with controls (males: 29/50, 30/50, 38/50, 39/50; females: 17/50, 25/50, 11/50, 32/50; Tables A5 and B5). This increased incidence may have been secondary to the increased severity of nephropathy.

Forestomach: The incidence of forestomach hyperplasia was slightly increased in male and female rats that received furan (males: 1/50, 4/49, 7/50, 6/50; females: 0/50, 2/50, 5/50, 5/50; Tables A5 and B5). The incidence of subacute inflammation in females administered furan was also increased (0/50, 1/50, 5/50, 6/50).

TABLE 14
Incidences and Severity of Nephropathy in Rats in the 2-Year Gavage Studies of Furan

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Male				
Number of animals examined	50	50	50	50
None	5	6	2	2
Minimal	19	2	2	0
Mild	21	15	3	5
Moderate	3	21	22	24
Marked	2	6	21	19
Average severity grade[a]	1.56	2.38**	3.16**	3.16**
Female				
Number of animals examined	50	50	50	50
None	34	3	3	4
Minimal	10	11	2	1
Mild	4	27	17	5
Moderate	2	9	21	16
Marked	0	0	7	24
Average severity grade	0.48	1.84**	2.54**	3.10**

** Significantly different ($P \leq 0.01$) from the controls by the Mann-Whitney U test.
[a] Average severity grade of lesions for all animals. Severity grade was based on percent renal parenchyma involved: minimal - usually less than 25% of cortex; mild - 25% to 50% of cortex; moderate - 50% to 75% of cortex; marked - greater than 75% of cortex.

Stop-Exposure Study

Survival

Six male rats died between the 9- and 15-month interim evaluations, and 14 males died in a moribund condition between the 15-month interim evaluation and the end of the 2-year study.

Body Weights and Clinical Findings

Relative and absolute organ weights for the kidney, liver, and spleen were significantly increased compared to controls at the 15-month interim evaluation (Table F2).

Pathology and Statistical Evaluation

Exposure to furan was associated with extensive hepatotoxicity as evidenced by the presence of numerous nonneoplastic liver lesions in males evaluated after 13 weeks of exposure (Table 15). Moreover, the lesions did not regress after cessation of furan exposure, but continued to progress and develop into neoplasms (Tables 15 and 16).

Cholangiocarcinoma was present in all males evaluated at 9 and 15 months and occurred with an overall incidence of 100% in those males examined between the 9- and 15-month interim evaluations or after the 15-month interim evaluation. Hepatocellular carcinoma was first observed in males from the 15-month interim evaluation. Detailed histopathologic descriptions of these lesions are provided in the sections of the report describing the results of the 2-year studies.

TABLE 15
Incidences of Selected Liver Lesions in Male Rats at the Interim Evaluations of the Stop-Exposure Gavage Study of Furan[a]

	Incidence (Average Severity)[b]		
	13-Week	9 Month	15 Month
Number of animals examined	10	10	10
Neoplasms			
Cholangiocarcinoma	0	10	10
Hepatocellular carcinoma	0	0	2
Nonneoplastic Lesions			
Biliary tract			
Fibrosis, multifocal	10 (4.0)	10 (4.0)	10 (4.0)
Hyperplasia, multifocal	10 (4.0)	10 (4.0)	10 (4.0)
Inflammation, chronic, multifocal	0	10 (4.0)	10 (4.0)
Cysts, multiple	0	10 (4.0)	10 (4.0)
Hepatocytes			
Cytomegaly	10 (3.3)	10 (2.8)	10 (2.9)
Degeneration, multifocal	10 (3.1)	10 (2.7)	10 (2.5)
Hyperplasia, nodular, multifocal	10 (4.0)	10 (4.0)	10 (3.1)
Necrosis, multifocal	10 (2.4)	10 (2.0)	10 (2.0)
Vacuolization, cytoplasmic	10 (3.1)	10 (2.7)	10 (2.5)
Kupffer cells			
Pigmentation, multifocal	10 (1.6)	10 (2.1)	10 (2.0)

[a] All animals received 30 mg/kg. Vehicle control animals were examined at the 9- and 15-month interim evaluations; no liver lesions were found; a single control male had cytoplasmic vacuolization of hepatocytes.
[b] Average severity grade of lesions in affected animals. Severity grade of 1 = minimal; 2 = mild; 3 = moderate; 4 = marked.

TABLE 16
Incidences of Selected Liver Lesions in Male Rats Evaluated between the 9- and 15-Month Interim Evaluations of the Stop-Exposure Gavage Study of Furan

	Incidence (Average Severity)[a]	
	9 to 15 Months	After 15 Months
Number of animals examined	6	14
Neoplasms		
Cholangiocarcinoma	6	14
Hepatocellular carcinoma	0	4
Nonneoplastic Lesions		
Biliary tract		
Fibrosis, multifocal	6 (3.7)	14 (4.0)
Hyperplasia, multifocal	6 (3.7)	14 (4.0)
Inflammation, chronic, multifocal	6 (4.0)	14 (4.0)
Cysts, multiple	4 (2.3)	14 (4.0)
Hepatocytes		
Cytomegaly	6 (3.0)	14 (3.9)
Degeneration, multifocal	6 (2.7)	14 (3.0)
Hyperplasia, nodular, multifocal	6 (3.7)	14 (4.0)
Necrosis, multifocal	6 (2.3)	14 (2.5)
Vacuolization, cytoplasmic	6 (2.7)	14 (3.0)
Kupffer cells		
Pigmentation, multifocal	6 (2.1)	14 (2.0)

[a] Average severity grade of lesions in affected animals. Severity grade of 1 = minimal; 2 = mild; 3 = moderate; 4 = marked.

MICE

16-Day Studies

Three males that received 40 mg/kg, all males and four females that received 80 mg/kg, and all mice that received 160 mg/kg furan died by day 6 (Table 17). Final mean body weights of males receiving 10 and 20 mg/kg were significantly greater than controls; final mean body weights of other dose groups were similar to controls (Table 17). Inactivity was the most consistently observed clinical finding among furan-exposed mice. No observations noted at necropsy were clearly associated with exposure to furan.

TABLE 17
Survival and Mean Body Weights of Mice in the 16-Day Gavage Studies of Furan

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b] Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	5/5	22.2 ± 0.4	25.0 ± 0.6	2.8 ± 0.4	
10	5/5	23.8 ± 0.6	27.2 ± 0.6*	3.4 ± 0.4	109
20	5/5	23.2 ± 0.2	27.4 ± 0.5*	4.2 ± 0.5	110
40	2/5[c]	21.2 ± 0.6	25.5 ± 0.5	3.5 ± 0.5	102
80	0/5[d]	23.0 ± 0.3	–	–	–
160	0/5[e]	22.0 ± 0.5	–	–	–
Female					
0	5/5	18.6 ± 0.4	21.8 ± 0.4	3.2 ± 0.2	
10	5/5	18.8 ± 0.4	21.6 ± 0.2	2.8 ± 0.2	99
20	5/5	19.0 ± 0.3	22.0 ± 0.5	3.0 ± 0.3	101
40	5/5	17.6 ± 0.4	21.0 ± 0.3	3.4 ± 0.2	96
80	1/5[f]	19.0 ± 0.3	19.0	–	87
160	0/5[g]	18.2 ± 0.4	–	–	–

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
[a] Number surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. No final mean body weight is calculated for groups with 100% mortality.
[c] Day of death: 3, 5, 6
[d] Day of death: 2, 2, 3, 3, 3
[e] Day of death: 2, 2, 2, 2, 3
[f] Day of death: 3, 4, 4, 4
[g] Day of death: 2, 2, 2, 3, 3

13-Week Studies

One male from the 4 mg/kg furan group and one 30 mg/kg female died before the end of the studies. Final mean body weights of 30 mg/kg males were significantly lower than controls; final mean body weights of the other dose groups of males and females were similar to controls (Table 18). Clinical findings associated with furan administration were observed only in the high-dose females and consisted of reduced activity or of inactivity.

The absolute and relative liver weights of males that received 15 or 30 mg/kg furan and females that received 30 or 60 mg/kg furan were significantly increased compared to controls; changes observed in the weights of other organs were not considered related to furan exposure (Table F4).

The incidences of liver lesions increased with dose in male mice that received 8, 15, or 30 mg/kg and in females that received 15, 30, or 60 mg/kg (Table 19). Lesions in males and females administered 30 mg/kg furan or less were of minimal to mild severity, while lesions in the 60 mg/kg female group were generally of moderate to marked severity. Hepatocyte lesions (cytomegaly, degeneration, and necrosis) usually involved periportal hepatocytes, but in more severe cases other areas of the lobules were affected. Cytomegaly was characterized by enlargement of hepatocytes due to an increase in the amount of cytoplasm, sometimes accompanied by nuclear enlargement. Hepatocyte degeneration consisted of varying degrees of clear cytoplasmic vacuolization. Coagulation necrosis was observed in multiple scattered individual or small clusters of hepatocytes. Bile duct lesions included hyperplasia and cholangiofibrosis. Minimal to mild bile duct hyperplasia, which occurred in the 30 mg/kg male and female dose groups, consisted of proliferation of small numbers of normal appearing bile ducts in few to several portal areas. Moderate to marked hyperplasia seen in the 60 mg/kg group females involved essentially all portal areas, and the proliferating bile ducts extended

TABLE 18
Survival and Mean Body Weights of Mice in the 13-Week Gavage Studies of Furan

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b] Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	10/10	25.1 ± 0.3	38.1 ± 1.1	13.0 ± 1.0	
2	10/10	24.5 ± 0.3	39.1 ± 0.8	14.6 ± 0.6	103
4	9/10[c]	24.6 ± 0.3	38.4 ± 0.9	13.8 ± 1.0	101
8	10/10	24.8 ± 0.3	39.2 ± 0.8	14.4 ± 0.7	103
15	10/10	24.5 ± 0.4	37.5 ± 0.9	13.0 ± 0.8	98
30	10/10	24.6 ± 0.4	35.3 ± 0.8*	10.7 ± 0.6*	93
Female					
0	10/10	18.6 ± 0.2	27.3 ± 0.7	8.7 ± 0.6	
4	10/10	18.2 ± 0.2	26.5 ± 0.7	8.3 ± 0.6	97
8	10/10	18.1 ± 0.3	27.0 ± 0.8	8.9 ± 0.6	99
15	10/10	18.6 ± 0.2	27.4 ± 0.5	8.8 ± 0.5	100
30	9/10[d]	17.9 ± 0.2	26.6 ± 0.5	8.6 ± 0.4	97
60	10/10	18.2 ± 0.3	26.1 ± 0.5	7.9 ± 0.4	96

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
[a] Number surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Week of death: 7
[d] Week of death: 2

TABLE 19
Incidences of Nonneoplastic Liver Lesions in Mice in the 13-Week Gavage Studies of Furan

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
Male							
Number of animals examined	10	10	10	10	10	10	0
Biliary tract							
Hyperplasia	0	–[a]	0	0	0	2	–
Hepatocytes							
Cytomegaly	0	–	0	0	0	10**	–
Degeneration	0	–	0	0	1	10**	–
Necrosis	0	–	0	1	1	8**	–
Kupffer cells							
Pigmentation	0	–	0	0	0	3	–
Female							
Number of animals examined	10	0	10	10	10	10	10
Biliary tract							
Hyperplasia	0	–	–	0	0	8**	10**
Hepatocytes							
Cytomegaly	0	–	–	0	0	10**	10**
Degeneration	0	–	–	0	3	10**	10**
Necrosis	0	–	–	0	0	9**	10**
Kupffer cells							
Pigmentation	0	–	–	0	0	9**	10**
Cholangiofibrosis	0	–	–	0	0	4*	10**

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Not examined

between adjacent portal areas, giving the liver parenchyma a marked lobular appearance. In some areas of affected livers in females the hyperplastic bile ducts were surrounded by fibrous tissue (cholangiofibrosis). Greenish yellow to brown pigment (presumably bile) was observed in scattered Kupffer cells in both male and female mice administered furan.

Dose selection rationale: Dose selection for mice in the 2-year studies was based on hepatotoxicity. Examination of the response of both males and females indicated a substantial decrease in the incidence and severity of hepatotoxicity between mice that received 30 and 15 mg/kg furan, and indicated that the lesions occurring at 15 mg/kg would not become life threatening in the 2-year studies. Therefore, 15 mg/kg furan was selected as the high dose and 8 mg/kg as the low dose. In the 13-week studies, 8 mg/kg was a no-effect level for female mice, and minimal focal necrosis of hepatocytes was observed in a single male at this dose level.

2-Year Studies

Survival

Survival of both dose groups of male mice and of high-dose female mice was significantly lower than control (Table 20 and Figure 3). Survival of low-dose female mice was similar to control.

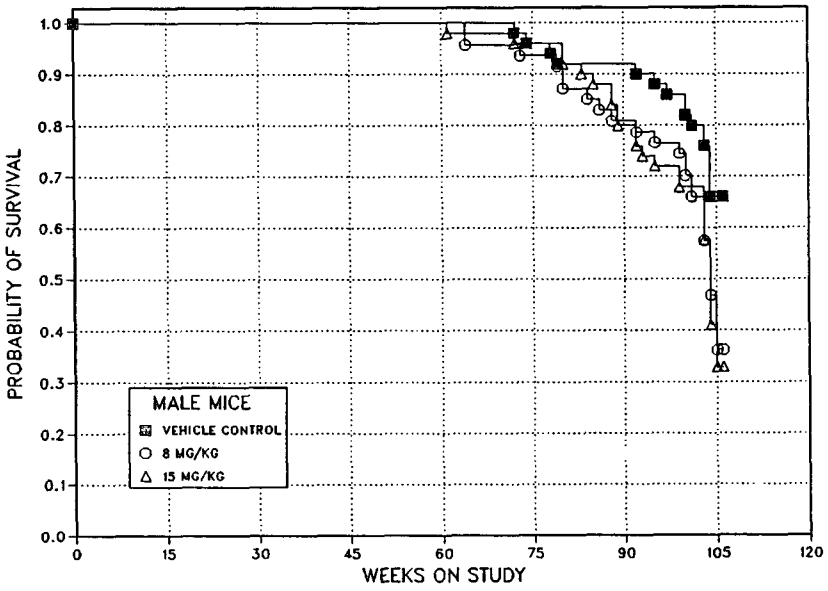
Body Weights and Clinical Findings

Mean body weights of male mice that received 15 mg/kg furan remained 5% to 21% less than mean body weights of controls from week 11 to the end of the studies; mean body weights of males that received 8 mg/kg remained 5% to 14% less than controls from week 76 to the end of the studies. Female mice that received 15 mg/kg had mean body weights that were 6% to 19% less than controls from week 36 to the end of the study; mean body weights of low-dose female mice were similar to controls (Tables 21 and 22 and Figure 4). No clinical findings were associated with furan administration.

TABLE 20
Survival of Mice in the 2-Year Gavage Studies of Furan[a]

	Vehicle Control	8 mg/kg	15 mg/kg
Male			
Animals initially in study	50	50	50
Natural deaths		1	1
Accidental deaths[b]	1	8	8
Moribund kills	16	24	25
Animals surviving until study termination	33	17	16
Percent probability of survival at end of study[c]	66	36	32
Mean survival days[d]	710	652	688
Survival analyses[e]	P=0.002	P=0.009	P=0.002
Female			
Animals initially in study	50	50	50
Natural deaths	1	1	
Accidental deaths[b]	4	8	11
Moribund kills	16	16	37
Animals surviving until study termination	29[f]	25	2
Percent probability of survival at end of study[c]	58	50	4
Mean survival days[d]	690	691	642
Survival analyses[e]	P<0.001	P=0.622	P<0.001

[a] First day of terminal sacrifice: 736
[b] Censored from survival analyses
[c] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths.
[d] Mean of all deaths (uncensored, censored, terminal sacrifice)
[e] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns.
[f] One animal was found dead at terminal sacrifice



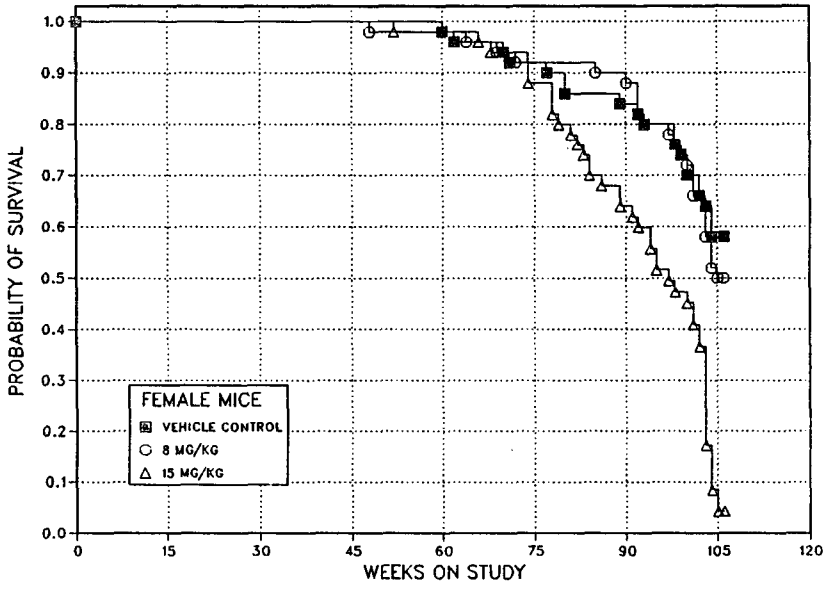


FIGURE 3
Kaplan-Meier Survival Curves for Mice Administered Furan by Gavage for 2 Years

TABLE 21
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of Furan

Weeks on Study	Vehicle Control Av.Wt. (g)	Vehicle Control Number of Survivors	8 mg/kg Av.Wt. (g)	8 mg/kg Wt. (% of controls)	8 mg/kg Number of Survivors	15 mg/kg Av.Wt. (g)	15 mg/kg Wt. (% of controls)	15 mg/kg Number of Survivors
1	26.7	50	26.9	101	50	26.5	99	50
2	28.4	50	28.6	101	50	28.3	100	50
3	28.7	50	30.0	105	49	29.4	102	50
4	31.2	50	30.7	98	48	29.7	95	50
5	31.9	50	32.2	101	48	31.1	98	50
6	31.5	50	33.5	106	48	31.5	100	50
7	33.6	50	33.9	101	48	31.8	95	50
8	34.3	50	34.7	101	48	33.3	97	50
9	34.9	50	35.1	101	48	33.6	96	50
10	34.5	50	36.1	105	48	33.7	98	50
11	36.3	50	36.8	101	48	34.0	94	50
12	36.3	50	36.9	102	48	34.5	95	50
13	37.0	50	38.2	103	48	35.1	95	50
17	39.9	50	39.0	98	48	36.2	91	50
21	41.8	50	40.6	97	48	37.0	89	50
24	42.8	50	41.8	98	48	37.8	88	50
28	44.3	50	42.2	95	48	38.2	86	50
32	44.6	50	44.1	99	48	39.2	88	50
36	46.2	50	45.2	98	48	40.3	87	50
40	47.0	50	45.9	98	47	40.4	86	50
44	46.6	50	45.3	97	47	40.5	87	50
48	48.2	50	46.4	96	47	41.4	86	50
52	49.6	50	47.7	96	47	41.5	84	50
56	49.6	50	47.9	97	47	42.4	86	50
60	50.5	50	47.7	95	47	42.0	83	50
64	50.8	50	48.9	96	45	42.3	83	49
68	50.6	50	48.8	96	45	41.8	83	49
72	49.5	49	47.5	96	45	41.6	84	48
76	50.1	48	47.8	95	44	41.7	83	48
80	50.8	46	47.5	94	41	41.6	82	46
84	49.3	46	46.4	94	40	40.4	82	45
88	50.0	46	46.0	92	38	39.7	79	42
92	46.9	45	43.1	92	37	37.4	80	38
96	48.5	44	43.5	90	36	39.4	81	35
100	48.2	41	41.6	86	33	38.6	80	33
104	47.9	33	42.7	89	22	37.9	79	20
Terminal sacrifice		33			17			16
Mean for weeks								
1-13	32.7		33.4	102		31.7	97	
14-52	45.1		43.8	97		39.3	87	
53-104	49.4		46.1	93		40.5	82	

TABLE 22
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of Furan

Weeks on Study	Vehicle Control Av.Wt. (g)	Vehicle Control Number of Survivors	8 mg/kg Av.Wt. (g)	8 mg/kg Wt. (% of controls)	8 mg/kg Number of Survivors	15 mg/kg Av.Wt. (g)	15 mg/kg Wt. (% of controls)	15 mg/kg Number of Survivors
1	20.3	50	20.2	100	50	20.1	99	50
2	21.5	50	21.3	99	50	21.2	99	50
3	22.6	50	22.2	98	50	21.5	95	50
4	23.0	50	23.6	103	50	22.9	100	50
5	23.5	50	24.8	106	50	24.1	103	50
6	24.5	50	24.9	102	50	24.7	101	50
7	24.8	50	24.8	100	50	25.0	101	50
8	25.1	50	25.8	103	50	25.3	101	50
9	25.2	50	26.0	103	50	25.5	101	50
10	26.1	50	26.2	100	50	26.0	100	50
11	26.5	50	27.0	102	50	26.2	99	50
12	26.2	50	26.9	103	50	26.4	101	50
13	27.3	50	28.1	103	50	26.9	99	50
17	28.1	50	28.9	103	50	28.1	100	50
21	28.6	50	30.1	105	50	28.9	101	50
24	29.8	50	29.9	100	50	29.0	97	50
28	31.6	50	32.0	101	50	30.4	96	50
32	32.4	50	33.0	102	50	31.1	96	50
36	34.2	50	34.1	100	50	32.2	94	50
40	35.8	50	35.5	99	50	33.5	94	50
44	36.1	50	36.6	101	50	34.0	94	50
48	37.6	50	38.1	101	49	34.9	93	50
52	39.7	50	40.4	102	49	36.2	91	49
56	40.6	50	41.1	101	49	36.6	90	49
60	41.3	49	42.3	102	49	37.1	90	49
64	43.4	48	43.2	100	49	37.7	87	49
68	43.5	48	43.3	100	48	37.5	86	48
72	42.2	46	42.9	102	46	37.4	89	47
76	43.0	46	42.8	100	46	37.3	87	44
80	43.2	43	44.6	103	46	37.2	86	40
84	43.9	43	45.0	103	46	37.9	86	37
88	43.7	43	47.1	108	45	37.4	86	34
92	42.9	41	45.9	107	41	37.3	87	29
96	44.5	40	44.2	99	40	36.6	82	24
100	44.3	35	43.4	98	36	36.6	83	21
104	45.8	29	45.7	100	27	36.9	81	4
Terminal sacrifice		29			25			2
Mean for weeks								
1-13	24.4		24.8	102		24.3	100	
14-52	33.4		33.9	101		31.8	96	
53-104	43.3		44.0	102		37.2	86	

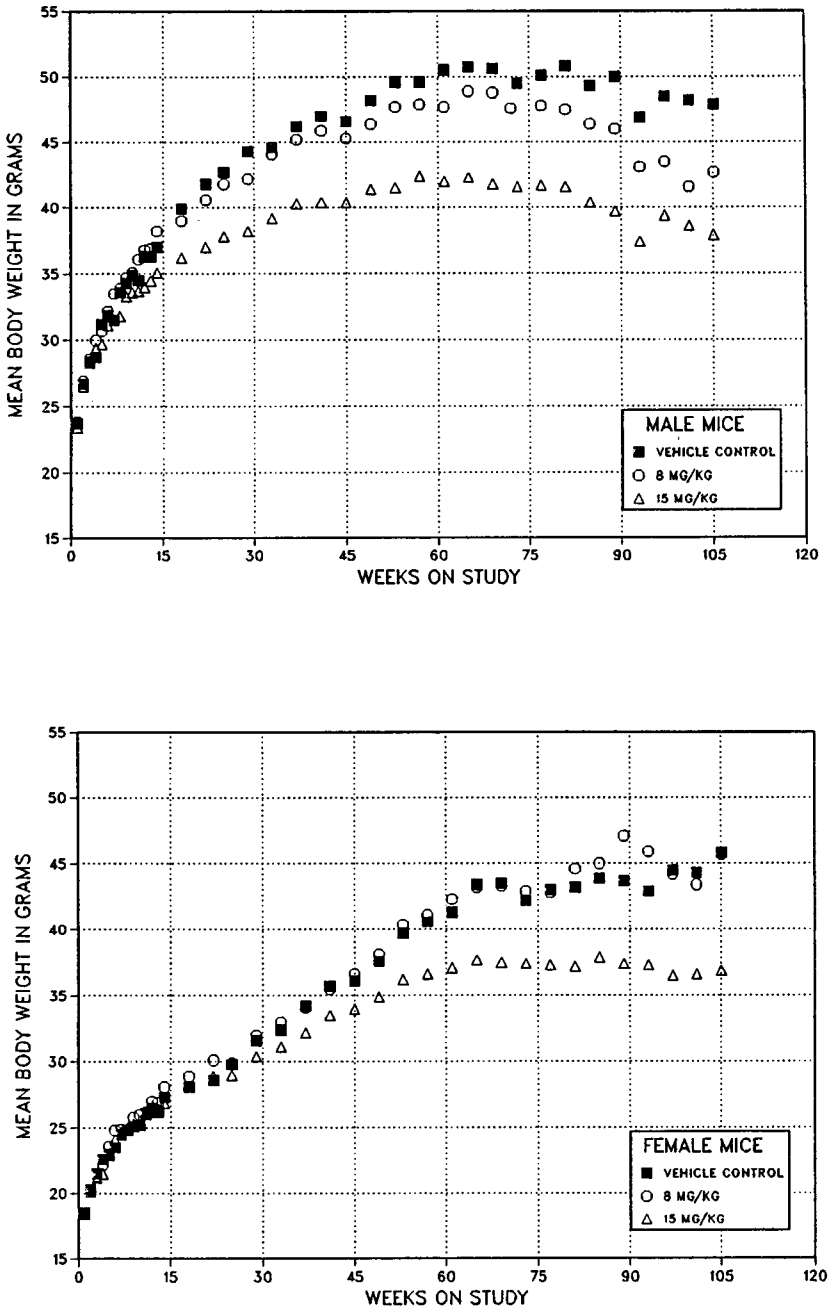


FIGURE 4
Growth Curves for Mice Administered Furan by Gavage for 2 Years

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions in the liver, adrenal medulla, forestomach, spleen, and pituitary gland.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal neoplasm 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 of neoplasms related to furan administration mentioned in this section are presented in Appendixes C and D for male and female mice.

Liver: Neoplasms and nonneoplastic lesions occurred with significantly greater incidences in both male and female mice exposed to furan than in controls. The incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) were markedly increased in both sexes of mice (Table 23) and large numbers of male and female mice administered furan had multiple adenomas (Tables C1 and D1). In addition, two low-dose and two high-dose male mice had biliary tract adenocarcinomas, and two low-dose males had hepatocholangiocarcinomas. Hepatocellular adenomas were circumscribed expansile masses that compressed adjacent parenchyma. The adenomas lacked a well-defined lobular pattern and were composed of hepatocytes that appeared well differentiated. These hepatocytes sometimes had different staining characteristics than normal hepatocytes and were arranged into irregular cords or solid clusters. Hepatocellular carcinomas differed from adenomas in that the neoplastic hepatocytes in carcinomas exhibited greater cellular atypia and formed broad (more than three cell layers thick) trabeculae or glandular structures. A few carcinomas metastasized, principally to the lung. The biliary tract adenocarcinomas consisted of areas of proliferating bile ducts surrounded by dense fibrous tissue. Neoplastic bile duct epithelial cells usually were well differentiated but in some areas these cells appeared anaplastic. The hepatocholangiocarcinomas contained elements of both hepatocellular carcinoma and biliary tract adenocarcinoma within the same neoplasm.

Incidences of numerous nonneoplastic degenerative and regenerative lesions involving hepatocytes or the biliary tract were also increased in both sexes of mice administered furan (Table 24). Degenerative hepatocyte lesions included cytoplasmic vacuolization, characterized by multiple clear vacuoles in the cytoplasm of scattered clusters of cells, degeneration and necrosis of individual or groups of hepatocytes, and multifocal atrophy of the liver parenchyma secondary to necrosis and loss of hepatocytes. There was a diffuse infiltrate of small to moderate numbers of mixed inflammatory cells (infiltration, cellular, mixed cell) within the livers of many animals administered furan, which was presumably secondary to the degenerative changes. Small aggregates of lymphoid cells within portal areas (lymphoid hyperplasia) occurred with increased incidence in females administered furan. Infarcts, large areas of coagulative necrosis of hepatocytes, occurred at moderately increased incidences in mice of both sexes administered furan (Tables C5 and D5) and were considered to be secondary to the presence of hepatocellular neoplasms. Regenerative hepatocellular changes included enlargement of hepatocytes (cytomegaly), and multifocal hyperplasia. Hyperplasias were discrete lesions, usually larger than a lobule, that sometimes compressed adjacent parenchyma. They were composed of normal or enlarged hepatocytes arranged in normal lobular patterns, with recognizable portal areas and central veins, although the pattern was sometimes distorted due to enlargement of hepatocytes.

Biliary tract lesions were most noticeable in portal areas and consisted of proliferation of bile ducts (hyperplasia), accompanied by slight proliferation of fibrous tissue (fibrosis), infiltration by small numbers of mononuclear inflammatory cells (chronic inflammation), and in some mice, dilatation of bile duct lumens (bile duct dilatation). Kupffer cells in the livers of nearly all mice administered furan contained greenish brown pigment (presumably bile).

TABLE 23
Liver Neoplasms in Mice in the 2-Year Gavage Studies of Furan

	Vehicle Control	8 mg/kg	15 mg/kg
Male			
Hepatocellular Adenoma			
Overall rates[a]	20/50 (40%)	33/50 (66%)	42/50 (84%)
Adjusted rates[b]	51.7%	86.4%	100.0%
Terminal rates[c]	15/33 (45%)	12/17 (71%)	16/16 (100%)
First incidence (days)	550	444	498
Logistic regression tests[d]	P<0.001	P=0.001	P<0.001
Hepatocellular Carcinoma			
Overall rates	7/50 (14%)	32/50 (64%)	34/50 (68%)
Adjusted rates	17.1%	74.8%	77.9%
Terminal rates	0/33 (0%)	7/17 (41%)	7/16 (44%)
First incidence (days)	514	444	423
Logistic regression tests	P<0.001	P<0.001	P<0.001
Hepatocellular Adenoma or Hepatocellular Carcinoma[e]			
Overall rates	26/50 (52%)	44/50 (88%)	50/50 (100%)
Adjusted rates	58.9%	97.8%	100.0%
Terminal rates	15/33 (45%)	16/17 (94%)	16/16 (100%)
First incidence (days)	514	444	423
Logistic regression tests	P<0.001	P<0.001	P<0.001
Female			
Hepatocellular Adenoma			
Overall rates	5/50 (10%)	31/50 (62%)	48/50 (96%)
Adjusted rates	17.2%	78.5%	100.0%
Terminal rates	5/29 (17%)	17/25 (68%)	2/2 (100%)
First incidence (days)	736 (T)	446	360
Logistic regression tests	P<0.001	P<0.001	P<0.001
Hepatocellular Carcinoma			
Overall rates	2/50 (4%)	7/50 (14%)	27/50 (54%)
Adjusted rates	5.8%	21.8%	94.7%
Terminal rates	1/29 (3%)	3/25 (12%)	1/2 (50%)
First incidence (days)	646	499	475
Logistic regression tests	P<0.001	P=0.081	P<0.001
Hepatocellular Adenoma or Hepatocellular Carcinoma[f]			
Overall rates	7/50 (14%)	34/50 (68%)	50/50 (100%)
Adjusted rates	22.6%	82.3%	100.0%
Terminal rates	6/29 (21%)	18/25 (72%)	2/2 (100%)
First incidence (days)	646	446	360
Logistic regression tests	P<0.001	P<0.001	P<0.001

[a] Number of tumor-bearing animals/number of animals necropsied
[b] Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at first occurrence of this tumor type in any of the groups
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard neoplasms in animals dying prior to terminal kill as nonfatal.
[e] Historical incidence in 2-year NTP corn oil gavage studies for vehicle control groups (mean ± standard deviation): 210/599 (35.1% ± 11.0%), range 14%–52%
[f] Historical incidence: 60/597 (10.1% ± 4.3%), range 2%–16%

TABLE 24
Incidences of Nonneoplastic Liver Lesions in Mice in the 2-Year Gavage Studies of Furan

	Vehicle Control	8 mg/kg	15 mg/kg
Male			
Cytoplasmic Vacuolization			
Overall rates[a]	8/50 (16%)	24/50 (48%)	36/50 (72%)
Logistic regression tests[b]	P<0.001	P<0.001	P<0.001
Focal Hyperplasia			
Overall rates	1/50 (2%)	44/50 (88%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Mixed Cell Cellular Infiltration			
Overall rates	2/50 (4%)	23/50 (46%)	29/50 (58%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Bile Duct: Dilatation			
Overall rates	0/50 (0%)	0/50 (0%)	6/50 (12%)
Logistic regression tests	P=0.002	–[c]	P=0.012
Biliary Tract: Chronic Inflammation			
Overall rates	0/50 (0%)	44/50 (88%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Biliary Tract: Fibrosis			
Overall rates	0/50 (0%)	45/50 (90%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Biliary Tract: Hyperplasia			
Overall rates	0/50 (0%)	46/50 (92%)	49/50 (98%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Hepatocyte: Cytomegaly			
Overall rates	8/50 (16%)	45/50 (90%)	50/50 (100%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Hepatocyte: Degeneration			
Overall rates	0/50 (0%)	43/50 (86%)	43/50 (86%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Hepatocyte: Necrosis			
Overall rates	2/50 (4%)	39/50 (78%)	41/50 (82%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Kupffer Cell: Pigmentation			
Overall rates	2/50 (4%)	43/50 (86%)	50/50 (100%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Parenchyma: Focal Atrophy			
Overall rates	1/50 (2%)	45/50 (90%)	50/50 (100%)
Logistic regression tests	P<0.001	P<0.001	P<0.001

(continued)

TABLE 24
Incidences of Nonneoplastic Liver Lesions in Mice in the 2-Year Gavage Studies of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Female			
Cytoplasmic Vacuolization			
Overall rates	6/50 (12%)	29/50 (58%)	36/50 (72%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Focal Hyperplasia			
Overall rates	0/50 (0%)	48/50 (96%)	48/50 (96%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Lymphoid Hyperplasia			
Overall rates	27/50 (54%)	33/50 (66%)	42/50 (84%)
Logistic regression tests	P<0.001	P=0.155	P<0.001
Mixed Cell Cellular Infiltration			
Overall rates	8/50 (16%)	23/50 (46%)	32/50 (64%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Bile Duct: Dilatation			
Overall rates	0/50 (0%)	1/50 (2%)	11/50 (22%)
Logistic regression tests	P<0.001	P=0.470	P<0.001
Biliary Tract: Chronic Inflammation			
Overall rates	2/50 (4%)	48/50 (96%)	50/50 (100%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Biliary Tract: Fibrosis			
Overall rates	0/50 (0%)	47/50 (94%)	50/50 (100%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Biliary Tract: Hyperplasia			
Overall rates	0/50 (0%)	47/50 (94%)	50/50 (100%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Hepatocyte: Cytomegaly			
Overall rates	0/50 (0%)	48/50 (96%)	50/50 (100%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Hepatocyte: Degeneration			
Overall rates	0/50 (0%)	47/50 (94%)	48/50 (96%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Hepatocyte: Necrosis			
Overall rates	0/50 (0%)	44/50 (88%)	47/50 (94%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Kupffer Cell: Pigmentation			
Overall rates	5/50 (10%)	48/50 (96%)	50/50 (100%)
Logistic regression tests	P<0.001	P<0.001	P<0.001
Parenchyma: Focal Atrophy			
Overall rates	0/50 (0%)	48/50 (96%)	50/50 (100%)
Logistic regression tests	P<0.001	P<0.001	P<0.001

[a] Number the lesion-bearing animals/number of animals examined at site
[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard lesions in animals dying prior to terminal kill as nonfatal.
[c] Not applicable; no lesions in animal group.

Adrenal Medulla: The incidence of benign pheochromocytoma increased with dose and was significantly increased in both dose groups of male mice and in high-dose female mice (Table 25). The incidence of focal hyperplasia was increased in low- and high-dose male mice and in high-dose female mice. The incidences of benign pheochromocytoma in male and female mice exceed the historical ranges for control B6C3F$_1$ mice from 2-year NTP corn oil gavage studies (males: 16/582, mean 2.7%, range 0%-4%; females: 9/584, mean 1.5%, range 0%-8%) (Tables C4a and D4a). There is a morphologic continuum from adrenal medullary hyperplasia to benign pheochromocytoma. Hyperplasias are focal lesions causing little or no compression of adjacent tissue and consisting of increased numbers of normal-appearing cells. Benign pheochromocytomas are expansile nodules which displace and compress the medulla and overlying cortex; they consist of densely packed atypical cells with basophilic cytoplasm.

TABLE 25
Lesions of the Adrenal Medulla in Mice in the 2-Year Gavage Studies of Furan

	Vehicle Control	8 mg/kg	15 mg/kg
Male			
Focal Hyperplasia			
Overall rates[a]	0/49 (0%)	3/50 (6%)	9/50 (18%)
Logistic regression tests[b]	P<0.001	P=0.090	P=0.002
Benign Pheochromocytoma[c]			
Overall rates	1/49 (2%)	6/50 (12%)	10/50 (20%)
Adjusted rates[d]	2.6%	24.6%	32.9%
Terminal rates[e]	0/33 (0%)	2/17 (12%)	2/16 (13%)
First incidence (days)	723	701	423
Logistic regression tests	P=0.004	P=0.032	P=0.009
Female			
Focal Hyperplasia			
Overall rates	2/50 (4%)	1/50 (2%)	8/50 (16%)
Logistic regression tests	P=0.020	P=0.500N	P=0.033
Benign Pheochromocytoma[f]			
Overall rates	2/50 (4%)	1/50 (2%)	6/50 (12%)
Adjusted rates	5.9%	4.0%	47.1%
Terminal rates	1/29 (3%)	1/25 (4%)	0/2 (0%)
First incidence (days)	680	736 (T)	642
Logistic regression tests	P=0.028	P=0.499N	P=0.040

[a] Number of lesion-bearing animals/number of animals necropsied
[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard lesions in animals dying prior to terminal kill as nonfatal. A lower incidence in a dose group is indicated by N.
[c] Historical incidence for NTP corn oil gavage studies of vehicle control groups (mean ± standard deviation): 16/582 (2.7% ± 1.6%), range 0%–4%
[d] Number of lesion-bearing animals/effective number of animals, i.e., number of animals alive at first occurrence of this tumor type in any of the groups
[e] Observed incidence at terminal kill
[f] Historical incidence: 9/584 (1.5% ± 2.4%), range 0%–8%

Forestomach: Squamous papilloma of the forestomach occurred in one low-dose and three high-dose male mice; none occurred in controls. Squamous papillomas occurred with a positive trend, but the increase was not statistically significant (Table C3). In addition, the incidence in the high-dose group falls within the range of historical control incidences for control male B6C3F$_1$ mice from NTP 2-year corn oil gavage studies (16/600, mean 2.7%, range 0%-14%) (Table C4c). Consequently, the marginal increase in forestomach papillomas was not considered related to furan administration. The incidences of focal inflammation of the forestomach and papillary hyperplasia of the forestomach mucosa were also increased in male mice (focal inflammation: control, 9/49; low-dose, 13/50; high-dose, 21/50; papillary hyperplasia: 7/49, 14/50, 22/50; Table C5). Squamous papillomas were focal pedunculated lesions consisting of a highly branched, fibrous tissue core covered by thickened stratified squamous epithelium. Papillary hyperplasias were broad lesions characterized by thickening and folding of the forestomach epithelium. Hyperplasias lacked the fibrous tissue cores and complex structure that characterized papillomas.

Spleen: The incidence of hematopoietic cell proliferation was increased in low- and high-dose males, and in high-dose females (male: 5/50, 11/50, 15/49; female: 17/50, 17/50, 34/50; Tables C5 and D5). This increase was considered secondary to the inflammation associated with degenerative and neoplastic liver lesions in mice administered furan.

Pituitary Gland: The incidence of adenoma or carcinoma of the pituitary gland was decreased in high-dose female mice (26/49, 19/47, 9/46; Table D1). This decrease may be due in part to the reduced survival of high-dose female mice and may also be associated with the reduced body weights that occurred in the high-dose group.

GENETIC TOXICOLOGY

Furan was tested for mutagenicity in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; no mutagenic activity was observed in any of the strain/activation combinations (Table E1; Mortelmans *et al.*, 1986). The maximum concentration tested was 10,000 μg/plate; a precipitate was observed in several of the trials at concentrations of 1,000 μg/plate or higher. Furan induced trifluorothymidine resistance in mouse L5178Y lymphoma cells at concentrations of 1,139 to 3,800 μg/mL in the absence of S9 activation; it was not tested with S9 (Table E2; McGregor *et al.*, 1988).

In cytogenetic tests with Chinese hamster ovary cells, furan induced both sister chromatid exchanges (Table E3) and chromosomal aberrations (Table E4) in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9. Concentrations of 1.6 to 160 μg/mL furan produced significant responses in the sister chromatid exchange test without S9; with S9, a significant induction of sister chromatid exchanges was observed only at the highest dose tested, 500 μg/mL. Positive responses in the chromosomal aberration test were seen at furan concentrations of 100 to 500 μg/mL without S9 and at 500 and 1,000 μg/mL with S9. Furan did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* when administered in feed (10,000 ppm) or by abdominal injection (25,000 ppm) (Table E5). No increase in sister chromatid exchanges was observed in bone marrow cells of male B6C3F$_1$ mice administered furan by intraperitoneal injection (Table E6). Two sampling times were used to maximize the chance of detecting an effect: mice treated with 87.5 to 350 mg/kg furan were sampled 23 hours after injection, and mice treated with 25 to 100 mg/kg furan were sampled 42 hours after injection. Due to furan toxicity, lower doses were used with the longer exposure time. Significantly increased frequencies of chromosomal aberrations were observed in bone marrow cells of male B6C3F$_1$ mice treated with furan (Table E7). An extended harvest protocol was necessary to detect this increase, which was observed only at the highest dose tested (250 mg/kg) in both trials. The magnitude of the response was similar to that seen with the positive control.

DISCUSSION AND CONCLUSIONS

Furan is the parent structure for a group of oxygen-containing heterocyclic compounds that includes furfural, furfuryl alcohol, and tetrahydrofuran. These compounds are produced in large quantities and have numerous industrial uses. Compounds containing the furan ring are common and occur in numerous edible plants and foodstuffs. Furan-containing compounds are also readily formed from carbohydrates during cooking. Because of the large volume of production and the potential for human exposure, furan, furfural, and furfuryl alcohol were selected by the NTP for evaluation of carcinogenic potential.

Toxicity studies found in the literature and other information available prior to initiation of the 16-day studies indicated that male rats are more sensitive to the acute toxic effects of furan than are female rats or mice. However, in these 16-day studies rats and female mice responded similarly to furan exposure while male mice were somewhat less tolerant. Therefore, rats and female mice received doses up to 60 mg of furan per kg of body weight in the 13-week studies, while male mice received doses up to 30 mg/kg.

Among groups of rats administered furan for 13 weeks, exposure to 60 mg/kg was associated with mortality and low final mean body weights; absolute and relative liver and kidney weights were increased at doses between 15 to 60 mg/kg. Proliferative lesions involving the bile ducts as well as parenchymal cells (hepatocytes) were present in the livers of rats from all dose groups. Minimally severe lesions of the bile duct occurred in four males and six females that received 4 mg/kg. The severity of the bile duct lesions at 8 mg/kg was minimal and the incidence decreased between 8 and 4 mg/kg.

During the 13-week studies no deaths were related to furan administration among male or female mice. Final mean body weights of males that received 30 mg/kg were somewhat lower than controls; however, the final mean body weights in other furan-exposed groups were similar to controls. Absolute and relative liver weights were increased in males given 15 or 30 mg/kg and in females given 30 or 60 mg/kg furan. Histopathologic evaluation revealed liver lesions in males that received 30 mg/kg and in females that received 30 or 60 mg/kg, but the incidence and severity of these lesions decreased sharply at doses less than 30 mg/kg; minimal lesions were observed in one male and three female mice that received 15 mg/kg.

Because the biological potential of the bile duct lesions observed in the 13-week rat studies was uncertain, 20 additional rats per group were incorporated into the 2-year studies for interim evaluations of the possible progression of proliferative lesions of the liver and bile ducts. In addition, a special stop-exposure study was designed to monitor the progression of the proliferative liver lesions.

In the 2-year rat studies, survival of males and females that received 8 mg/kg was lower than controls as a result of moribund sacrifices associated with neoplasms of the liver and biliary tract and possibly mononuclear cell leukemia. Mean body weights of male rats administered 8 mg/kg furan were lower than controls.

A high incidence of cholangiocarcinoma occurred in all dosed rat groups during the 2-year studies, but this neoplasm was not present in any controls. Moreover, cholangiocarcinoma was diagnosed in the livers of male and female rats evaluated after 9 months of furan administration and was present in the livers of essentially all rats evaluated after 15 months of exposure. Cholangiocarcinoma was also present in the livers of rats from the stop-exposure study: all rats evaluated after 9 or more months on study had cholangiocarcinomas.

In an effort to determine the biological potential of furan-induced cholangiocarcinomas, samples of neoplastic tissue from both the 2-year study and the stop-exposure study rats were transplanted subcutaneously into the inguinal region of 6-week-old male and female F344/N rats. The transplanted neoplasms

grew rapidly into large subcutaneous masses; several of these masses metastasized (Montgomery *et al.*, 1986; Maronpot *et al.*, 1991). In addition, metastases were found in several 2-year study animals, confirming the malignant character of these neoplasms.

The terminology reported in the literature for benign and malignant lesions of the bile duct epithelium is confusing and reflects uncertainty about the more benign-appearing lesions. Cholangiofibrosis, cholangiofibroma, cystic cholangioma, and cholangiocarcinoma are closely related lesions that are distinguished on the basis of degree of proliferation and anaplasia of the biliary epithelium, evidence of invasive behavior, and quantity of fibrous connective tissue stroma. An important result of the stop-exposure study is the finding that the benign-appearing lesions of the bile duct epithelium present after 13 weeks of furan exposure frequently progressed into cholangiocarcinomas. Because progression continued in the absence of continued furan exposure, the precursor lesions apparently became neoplastic within the 13-week exposure period. The observations that cholangiocarcinomas can be transplanted and will metastasize confirm the malignant potential of these lesions.

In addition to the increased incidence of cholangiocarcinoma, the incidence of hepatocellular neoplasms was significantly increased in groups of rats administered 2, 4, or 8 mg/kg furan. There was a dose-related increase in hepatocellular adenomas and hepatocellular carcinomas in male rats, and there was a dose-related increase in hepatocellular adenomas and hepatocellular adenomas or carcinomas (combined) in female rats. The striking neoplastic response observed in the livers of male and female rats administered furan was interpreted as clear evidence of carcinogenic activity.

Exposure to furan produced a spectrum of nonneoplastic liver lesions including fibrosis, hyperplasia, chronic inflammation, and metaplasia of the biliary tract; cytomegaly, degeneration, necrosis, nodular hyperplasia, and cytoplasmic vacuolization of hepatocytes; and pigmentation of Kupffer cells. These lesions occurred with high incidence in dosed animals but were essentially absent from control rats.

The incidence of mononuclear cell leukemia increased with a significant dose-related trend among groups of male and female rats administered furan. In both the 4 and 8 mg/kg groups, the incidence in both sexes was significantly increased. The incidences of 25/50 (50%) in the 8 mg/kg male group and 21/50 (42%) in the 8 mg/kg female group exceed the historical control ranges for 2-year NTP corn oil gavage studies (males, 4% to 38%; females, 16% to 38%). The incidence of mononuclear cell leukemia in concurrent controls (16%) was lower than the historical control rates (males, 21.3%; females, 26.8%); however, the incidences in the 8 mg/kg male and female groups are significantly increased even when compared to the historical control incidences. Moreover, the proportion of early death rats with mononuclear cell leukemia was increased in the 8 mg/kg male and female groups compared to both the control and lower dose groups. This suggests that mononuclear cell leukemia appeared earlier in high-dose rats than in other dose groups. Therefore, because of the clear dose response in both sexes, the significant increase in both the 4 and 8 mg/kg groups, and the earlier observation of mononuclear cell leukemia in the high-dose groups, the increased incidence of mononuclear cell leukemia was considered to be related to furan administration.

Papillomas of the urinary bladder occurred in three high-dose female rats. These are uncommon neoplasms in female rats and have occurred in only 4/751 control females from the most recent NTP corn oil gavage studies; the highest incidence occurring in a control group is 1/50. While the presence of these neoplasms in high-dose females is suggestive of an association to furan administration, the low incidence and the absence of supporting nonneoplastic lesions argue against a clear association.

The survival of both groups of furan-exposed male mice and of high-dose female mice was lower than control survival as a result of moribund sacrifices associated with liver neoplasms. Mean body weights of furan-exposed males and of females administered 15 mg/kg were significantly lower than controls.

Male and female mice administered furan for 2 years had significant dose-related increased incidences of hepatocellular adenomas, hepatocellular carcinomas, and hepatocellular adenomas or carcinomas (combined). A variety of nonneoplastic liver lesions occurred with significantly increased incidences in male and female mice exposed to furan. These lesions included hepatocyte cytomegaly, degeneration, and necrosis; multifocal hyperplasia; cytoplasmic vacuolation; Kupffer cell pigmentation; and dilatation, fibrosis, hyperplasia, and bile duct inflammation.

The incidence of benign pheochromocytoma increased with dose in mice exposed to furan and was significantly increased in males that received 15 mg/kg. Benign pheochromocytoma has a relatively low historical control incidence of 16/582 (2.7%, range 0%-4%) in male mice and 9/584 (1.5%, range 0%-8%) in female mice. The incidence in both dose groups of males and in high-dose females exceeds the historical control range for these neoplasms. The rates in the concurrent controls (males, 2%; females, 4%) are well within the historical ranges; therefore, the significance of the increase is not the result of an aberrant control rate. The incidence of focal hyperplasia of the adrenal medulla was also increased in male and female mice exposed to furan. Medullary hyperplasia and pheochromocytoma represent a morphologic continuum, although the frequency with which they develop into malignant neoplasms is unknown. The significant dose-related increased incidences of these lesions in the present studies are considered related to furan exposure.

Increased incidences of pheochromocytoma associated with chemical exposure have been observed in mice in six previous NTP 2-year studies: C.I. Basic Red 9 monohydrochloride in female mice (NTP, 1986), 1,4-dichlorobenzene in male mice (NTP, 1987a), 4-hexylresorcinol in male mice (NTP, 1988b), 4,4′-methylenedianiline dihydrochloride in male mice (NTP, 1983), pentachlorophenol in male mice (NTP, 1989d), and 1,1,2-trichloroethane in both sexes of mice (NCI, 1978). In four of these studies, increased incidences of pheochromocytomas occurred along with significantly increased incidences of liver neoplasms; the occurrence of liver neoplasms served as a basis for the interpretation of clear evidence of carcinogenic activity in mice. For 4-hexylresorcinol, the response in mice was judged equivocal.

Six compounds containing the furan ring have now been evaluated in NTP 2-year toxicology and carcinogenesis studies: furan, furfural (NTP, 1990), benzofuran (NTP, 1989a), nitrofurantoin (NTP, 1989c), nitrofurazone (NTP, 1988a), and furosemide (NTP, 1989b). For the purposes of discussion, the results of the completed studies have been briefly summarized in Tables 26 and 27. The chemical structures of these compounds are shown in Figure 5.

The toxicity of furan-containing compounds is associated with cytotoxicity resulting from the formation of reactive intermediates during metabolic reactions occurring on the furan ring. Because two of the compounds in Figure 5 are nitrofurans, it is possible to note the influence of the nitro group on metabolism. The formation of reactive metabolites from nitrofurans, and hence their potential cytotoxicity, appears to be dominated by reactions leading to reduction of the nitro group (Josephy and Mason, 1985; Nelson and Harrison, 1987). One-electron reduction of the nitro group yields the nitro anion radical, which will reduce molecular oxygen to superoxide anion; this reaction leads to the formation of other activated oxygen species and to the initiation of lipid peroxidation. More complete reduction could, in theory, result in the formation of nitroso-, hydroxylamine-, or amino-substituted furans, all of which are capable of further biotransformation.

By contrast, the formation of reactive intermediates from furan or simple alkyl-substituted furans appears to be dominated by reactions involving oxidation of the furan ring (Burka and Boyd, 1985; Nelson and Harrison, 1987). Current evidence is consistent with a cytochrome P_{450}-catalyzed one-electron oxidation of the furan ring resulting in the formation of a highly reactive furan radical cation that may react directly with cellular nucleophiles or form a furan epoxide. Identification of the putative reactive intermediate for furan-containing compounds has been an area of active investigation. In the case of aflatoxin B_1, there is now considerable evidence suggesting that the dihydrofuran moiety is oxidized to an epoxide which subsequently reacts with cellular protein and DNA (Wogan, 1992). For other furans the nature of the reactive intermediate does not seem compatible with epoxide formation. Simple alkyl furans are oxidized by rat liver microsomes to enedials, which are unsaturated dialdehydes capable of reacting with cellular macromolecules either by cross-linking through the dialdehyde functions or by Michael addition of a nucleophile, such as a protein sulfhydryl, to the -ene double bond (Ravindranath *et al.*, 1984).

Virtually nothing is known about the metabolism of benzofuran; however, hydroxylation of either the benzene or the furan portion of the molecule (or of both), possibly by way of an epoxide, followed by glucuronide or sulfate formation would be a likely possibility. This would be consistent with the reaction observed on furan rings fused to other ring systems such as in the case of aflatoxin B_1.

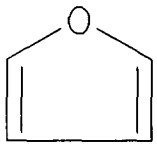
TABLE 26
Target Organs in 2-Year Studies of Furan Compounds

Compound	Lesions (Level of Evidence[a], Sex, Species)			Genetic Toxicology[b]
	Liver	Kidney	Other	
Furan	Cholangiocarcinoma (CE, ♂ & ♀ rats) Hepatocellular neoplasms (CE, ♂ & ♀ mice)	Increased severity of nephropathy (♂ & ♀ rats)	Mononuclear cell leukemia (♂ & ♀ rats) Adrenal medulla lesions (♂ & ♀ mice)	*S. typhimurium* (–) *D. melanogaster* (–) Mouse lymphoma (+) SCE (+) Abs (+)
Furfural	Cholangiocarcinoma (SE, ♂ rats) Hepatocellular neoplasms (CE, ♂ mice; SE, ♀ mice)	Renal cortical neoplasms (EE, ♂ mice)	Forestomach squamous papilloma (EE, ♀ mice)	*S. typhimurium* (–) *D. melanogaster* (+/-)[c] Mouse lymphoma (+) SCE (+) Abs (+)
Benzofuran	Hepatocellular adenoma (CE, ♂ & ♀ mice)	Tubule cell neoplasms (SE, ♀ rats) Increased severity of nephropathy (♂ rats) Increased incidence of nephropathy (♀ rats)	Forestomach and lung lesions (♂ & ♀ mice)	*S. typhimurium* (–) Mouse lymphoma (+) SCE (+) Abs (–)
Nitrofurantoin	None	Tubule cell neoplasms (SE, ♂ rats) Increased severity of nephropathy (♂ rats)	Ovarian neoplasms (CE, ♀ mice)	*S. typhimurium* (+) *D. melanogaster* (–) Mouse lymphoma (+) SCE (+) Abs (+)
Nitrofurazone	None	None	Mammary fibroadenomas (CE, ♀ rats) Ovarian neoplasms (CE, ♀ mice)	*S. typhimurium* (+) Mouse lymphoma (+) SCE (+) Abs (+)
Furosemide	None	Tubule cell neoplasms (EE, ♂ rats) Increased severity of nephropathy (♂ rats) Increased nephropathy (♂ & ♀ mice)	Mammary neoplasms (SE, ♀ mice)	*S. typhimurium* (–) Mouse lymphoma (+/-)[d] SCE (+) Abs (+)

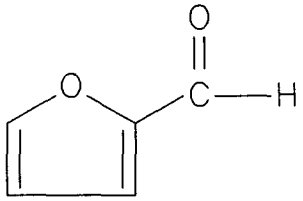
[a] Levels of evidence of carcinogenic activity: CE = clear evidence, SE = some evidence, EE = equivocal evidence
[b] SCE = sister chromatid exchanges; Abs = chromosomal aberrations
[c] Positive for sex-linked recessive lethal mutations; negative for reciprocal translations
[d] Positive with S9; negative without S9

TABLE 27
Comparison of Chronic Studies of Furan Compounds

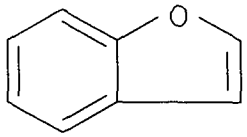
Compound	Route	13-Week Doses	2-Year Doses
Furan	Gavage	Rats: 0, 4, 8, 25, 30, or 60 mg/kg Mice: 0, 2, 4, 8, 15, or 30 mg/kg ♂; 0, 4, 8, 15,30, or 60 mg/kg ♀	Rats: 0, 2, 4, or 8 mg/kg Mice: 0, 8, or 15 mg/kg
Furfural	Gavage	Rats: 0, 11, 22, 44, 88, or 180 mg/kg Mice: 0, 75, 150, 300, 600, or 1,200 mg/kg	Rats: 0, 30, or 60 mg/kg Mice: 0, 50, 100, or 175 mg/kg
Benzofuran	Gavage	Rats: 0, 31, 62, 124, 250, or 500 mg/kg Mice: 0, 31, 62, 125, 250, or 500 mg/kg	Rats: 0, 30, or 60 mg/kg ♂; 0, 60, or 120 mg/kg ♀ Mice: 0, 60, or 120 mg/kg ♂; 0, 120, or 240 mg/kg ♀
Nitrofurantoin	Feed	Rats: 0, 600, 1,200, 2,400, 5,000, or 10,000 ppm Mice: 0, 300, 600, 1,300, 2,500, or 5,000 ppm	Rats: 0, 1,300, or 2,500 ppm (0, 60, or 110 mg/kg) ♂; 0, 600, or 1,300 ppm (0, 30, or 60 mg/kg) ♀ Mice: 0, 1,300, or 2,500 ppm (0, 300, or 570 mg/kg) ♂; (0, 280, or 580 mg/kg) ♀
Nitrofurazone	Feed	Rats: 0, 150, 310, 620, 1,250, or 2,500 ppm Mice: 0, 70, 150, 310, 620, or 1,250 ppm	Rats: 0, 310, or 620 ppm (0, 11, or 24 mg/kg ♂; 0, 12, or 26 mg/kg ♀) Mice: 0, 150, or 310 ppm (0, 16, or 33 mg/kg ♂; 0, 14, or 29 mg/kg ♀)
Furosemide	Feed	Rats: 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm ♂; 0, 938, 1,875, 3,750, 7,500, or 15,000 ppm ♀ Mice: 0, 938, 1,875, 3,750, 7,500, or 15,000 ppm ♂; 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm ♀	Rats: 0, 360, or 700 ppm (0, 14, or 29 mg/kg ♂; 0, 16, or 31 mg/kg ♀) Mice: 0, 700, or 1,400 ppm (0, 90, or 190 mg/kg ♂; 0, 100, or 215 mg/kg ♀)



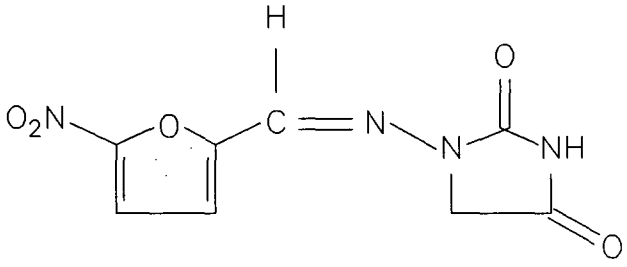
Furan



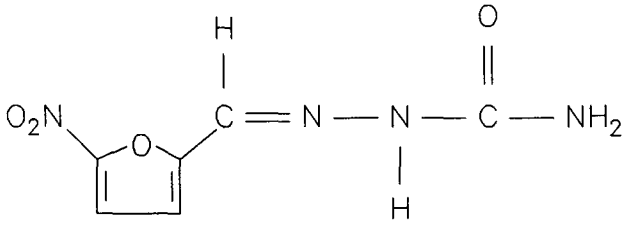
Furfural



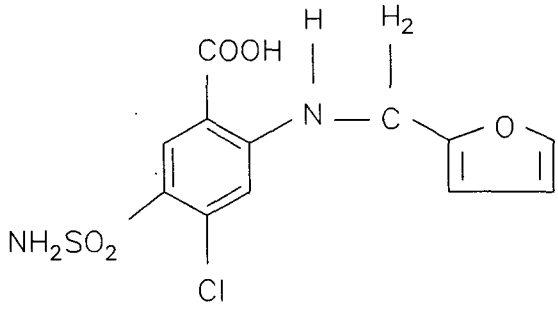
Benzofuran



Nitrofurantoin



Nitrofurazone



Furosemide

FIGURE 5
Chemical Structures of Furan and Furan-Containing Compounds

Table 26 presents similarities and differences in response among the six furan compounds. Only two of the six compounds are bacterial mutagens; both of these are nitrofurans. The four remaining compounds, which are not bacterial mutagens, do not possess substituents with the electron-withdrawing strength of the nitro group. The lack of mutagenic activity of furan, furfural, benzofuran, and furosemide and the ability of bacteria to carry out nitroreduction suggest that the mutagenicity of nitrofurantoin and nitrofurazone is associated with the presence of the nitro group.

The tumor responses observed for nitrofurantoin and nitrofurazone were also quite different from those of the other furan-containing compounds. Although the incidence of renal tubule cell neoplasms was increased in male rats exposed to nitrofurantoin, the most significant response was the increase in ovarian neoplasms in female mice exposed to nitrofurantoin. Exposure to nitrofurazone was associated with a significant increase in mammary fibroadenomas in female rats and of granulosa cell neoplasms in female mice. Moreover, both compounds were toxic to the gonads of female mice. Neither nitrofuran was a hepatocarcinogen; however furan, furfural, and benzofuran were hepatocarcinogens in at least one species. Moreover, furan and furfural were relatively specific hepatocarcinogens in both rats and mice and were the only compounds that produced uncommon cholangiocarcinomas in rats.

Furan was clearly much more toxic and a more potent carcinogen than furfural. Although very similar in structure, furan and furfural are metabolized quite differently by F344/N rats (Irwin *et al.*, 1985; NTP, 1987b; Burka *et al.*, 1991). The disposition of ^{14}C-furan or ^{14}C-furfural radioactivity 24 hours after oral administration of comparable doses to F344/N rats is shown in Table 28. Furfural is metabolized predominantly by oxidation of the aldehyde function to give furoic acid followed by conjugation with glycine and urinary excretion; thus the major urinary metabolites of furfural in F344/N rats are furoic acid and furoyl-glycine. Retention of radioactivity in tissues was minimal 24 hours after administration of furfural. By contrast, 24 hours after administration of an oral dose of furan, nearly 25% of the administered radioactivity had been eliminated as CO_2, 20% was eliminated in feces, while 20% still remained in tissues, mostly in an unextractable form in the liver. Only 25% had been eliminated in the urine after 24 hours, and examination of a radiochromatogram of the urinary metabolites from rats administered furan revealed a complex multicomponent mixture of metabolites containing a large proportion of mercapturates.

Cytochrome P_{450}-catalyzed oxidation of furan to an enedial would yield 2-butene-1,4-dial, a dialdehyde which could be easily oxidized to fumaric acid, a tricarboxylic acid cycle intermediate that is efficiently metabolized to CO_2. This could account for the significant conversion of furan-derived ^{14}C into CO_2. In addition, since the enedial is derived directly from the reactive intermediate, CO_2 formation should serve as an indication of the yield of reactive intermediate formed and should be proportional to the observed cytotoxicity if the latter is indeed associated with reactive intermediate formation. Direct reaction of the reactive intermediate with glutathione or with protein sulfhydryl groups would result in the ultimate formation and urinary excretion of mercapturates, as would Michael addition of protein sulfhydryl groups to the 2,3-double bond of 2-butene-1,4-dial. The ability of protein sulfhydryl groups to undergo Michael addition to the 2,3-double bond of N-ethyl maleimide is a well-known and often-used reaction for group-specific modification of proteins and is analogous to the reaction with 2-butene-1,4-dial.

It is unclear whether furfural would be oxidized in the same manner as furan; however, 24 hours after administration, approximately 6.5% of furfural-derived radioactivity appears as CO_2 (Table 28). To the extent that CO_2 formation can be considered representative of reactive intermediate formation, the data in Table 28 clearly show that the yield of reactive intermediate from furan is much greater than that obtained from furfural. Moreover, the presence of significant quantities of ^{14}C-containing mercapturates in the urine of rats administered furan is consistent with extensive reaction of the intermediate with glutathione and/or protein sulfhydryl groups, events usually associated with cytotoxicity. Therefore, the markedly lower hepatotoxicity and hepatocarcinogenic potency of furfural compared to furan in F344/N rats may be due to the presence of a metabolic pathway that does not involve cleavage of the furan ring or formation of a reactive intermediate, but that rapidly and efficiently removes furfural from the liver in the form of a soluble metabolite that is readily excreted in urine. By contrast, furan undergoes oxidative ring cleavage and in the process is

TABLE 28
Disposition of Radioactivity 24 Hours after Oral Administration to F344/N Rats[a]

Site	Compound	
	Furan	Furfural
Tissues	19.4 ± 1.7	0.6 ± 0.1
Urine	25.3 ± 1.6	79.3 ± 5.4
Feces	20.4 ± 0.3	1.41 ± 0.28
CO_2	24.8 ± 1.1	6.47
Volatiles	14.3 ± 2.0	– [b]
Total	104%	88%

[a] Percent recovery, given as mean ± standard error
[b] None detected

converted to a highly reactive metabolite that has the potential of reacting with DNA or wreaking intracellular havoc that may result in cell death.

In the genetic toxicology studies reported here, furan was not a bacterial mutagen and did not induce sex-linked recessive lethal mutations in the germ cells of male *Drosophila melanogaster*. Furan did induce chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells, chromosomal aberrations in $B6C3F_1$ mouse bone marrow cells, and trifluorothymidine resistance in mouse L5178Y lymphoma cells. However, furan exhibited no activity as an initiator of hepatocarcinogenesis when administered to F344/N rats 6 or 18 hours after partial hepatectomy, followed by 52 weeks of promotion with phenobarbital in the drinking water (R.R. Maronpot, unpublished data). Furthermore, no evidence of unscheduled DNA synthesis was found in primary cultures of F344/N rat or $B6C3F_1$ mouse hepatocytes exposed to furan *in vitro* or in hepatocytes isolated from F344/N rats or $B6C3F_1$ mice administered a single oral dose of furan.

Other evidence, however, suggests that furan and furfural may be capable of inducing mutations in certain cellular genes. A high percentage of transforming DNA isolated from spontaneously occurring hepatocellular adenomas or carcinomas of $B6C3F_1$ mice contains Ha-*ras* with activating mutations in the 61st codon (Reynolds *et al.*, 1987). DNA isolated from hepatocellular adenomas or carcinomas present in the livers of furan-exposed mice in the present studies, or from the furfural 2-year studies, also contained Ha-*ras* with codon-61 activating mutations; however, K-*ras*, *raf*, and an unidentified transforming gene were also detected in chemically induced neoplasms. Analysis of Ha-*ras* from furan- or furfural-induced neoplasms revealed mutations not only in codon 61 but also in codons 13 and 117. Mutations in these latter codons of Ha-*ras* as well as the activation of K-*ras* and *raf* appear to be rare events in spontaneous rodent neoplasms. Therefore, the presence of these uncommon mutations in neoplasms from furan- or furfural-exposed animals suggests that they were caused by exposure to these compounds.

There are alternative interpretations. Ames and Gold (1990) recently suggested that increased rates of cell proliferation associated with chemically related cytotoxicity could significantly amplify background mutation rates, thus leading to increased incidences of neoplasms in animals exposed to chemicals which are cytotoxic but not genotoxic. In theory, such amplification would increase the probability of observing rare or uncommon "spontaneous" events. A high incidence of proliferative lesions occurred in the livers of both rats and mice in the 13-week studies of furan. Moreover, examination of the hepatocyte labeling index (as measured by incorporation of ^{3}H-thymidine into hepatocyte nuclei) during continuous oral administration of furan at the highest doses used in the present study (8 mg/kg to F344/N rats or 15 mg/kg to $B6C3F_1$ mice) indicated a marked increase in labeling index after one week of exposure (B.F. Butterworth, personal communication).

Although the values at weeks 3 and 6 declined somewhat compared to week 1, the labeling index at week 6 was still fivefold greater than controls for male mice, eighteenfold greater than controls for male rats, and twelvefold greater than controls for female rats.

These results indicate that exposure to furan 5 days per week at the highest doses used in the present 2-year studies induces a strong proliferative response in hepatocytes. However, while male rats and mice exposed to furan had exceptionally high incidences of hepatocellular neoplasms, the incidence of hepatocellular neoplasms in female rats was not as dramatically affected by administration of furan, even though female rats had a significant increase in hepatocyte labeling index and a high incidence of cholangiocarcinomas. It is also noteworthy that male rats in the stop-exposure group developed hepatocellular neoplasms as well as cholangiocarcinomas. Because chemical exposure, and presumably the cytotoxicity necessary for continued proliferative stimulation, did not continue beyond the initial 13-week exposure period, all events necessary and sufficient for the subsequent development of neoplasms must have occurred before the end of the period of chemical exposure.

Conclusions

Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity** of furan in male and female F344/N rats based on increased incidences of cholangiocarcinoma and hepatocellular neoplasms of the liver and on increased incidences of mononuclear cell leukemia. There was *clear evidence of carcinogenic activity* of furan in male and female $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms of the liver and benign pheochromocytoma of the adrenal gland.

Nonneoplastic liver lesions associated with furan administration in rats and mice included biliary tract fibrosis, hyperplasia, inflammation, and proliferation, as well as hepatocellular cytomegaly, degeneration, hyperplasia, necrosis, and vacuolization. In rats, increased severity of nephropathy with an associated increased incidence in parathyroid hyperplasia was associated with exposure to furan.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the peer review comments and the public discussion on this Technical Report appears on page 11.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF FURAN

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TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Furan

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Natural deaths	1	4	3	5
Moribund kills	10	13	17	28
Accidental deaths	6	5	4	1
Survivors				
Terminal sacrifice	33	28	26	16
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(49)	(50)	(50)	(50)
Liver	(50)	(50)	(50)	(50)
Cholangiocarcinoma, multiple		43 (86%)	48 (96%)	49 (98%)
Hepatocellular carcinoma		1 (2%)	6 (12%)	17 (34%)
Hepatocellular carcinoma, multiple				1 (2%)
Hepatocellular adenoma	1 (2%)	3 (6%)	16 (32%)	17 (34%)
Hepatocellular adenoma, multiple		1 (2%)	2 (4%)	10 (20%)
Mesentery	(5)	(12)	(12)	(14)
Cholangiocarcinoma, metastatic, liver				2 (14%)
Pancreas	(50)	(50)	(50)	(49)
Adenocarcinoma			1 (2%)	
Adenoma	4 (8%)	6 (12%)	9 (18%)	4 (8%)
Adenoma, multiple	2 (4%)	3 (6%)	1 (2%)	2 (4%)
Mixed neoplasm benign		1 (2%)		
Pharynx		(1)	(1)	
Papilloma squamous		1 (100%)		
Salivary glands	(49)	(50)	(50)	(49)
Stomach, forestomach	(50)	(49)	(50)	(50)
Stomach, glandular	(50)	(49)	(50)	(50)
Tongue	(1)		(2)	
Papilloma squamous	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Adrenal gland, medulla	(50)	(47)	(48)	(49)
Pheochromocytoma malignant	1 (2%)		3 (6%)	
Pheochromocytoma benign	7 (14%)	4 (9%)	8 (17%)	8 (16%)
Pheochromocytoma benign, multiple	1 (2%)		1 (2%)	2 (4%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Adenoma, multiple	3 (6%)			
Carcinoma	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Endocrine System (continued)				
Parathyroid gland	(46)	(47)	(49)	(43)
Adenoma				1 (2%)
Pituitary gland	(49)	(50)	(49)	(49)
Pars distalis, adenoma	11 (22%)	11 (22%)	17 (35%)	11 (22%)
Pars distalis, carcinoma				1 (2%)
Thyroid gland	(48)	(50)	(50)	(48)
Adenoma		1 (2%)		
C-cell, adenoma	6 (13%)	5 (10%)	1 (2%)	4 (8%)
C-cell, carcinoma	1 (2%)	1 (2%)	2 (4%)	
Follicular cell, carcinoma				1 (2%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(49)	(50)	(46)	(48)
Adenoma	1 (2%)	2 (4%)	4 (9%)	3 (6%)
Carcinoma		4 (8%)		
Squamous cell carcinoma	1 (2%)			
Bilateral, adenoma				1 (2%)
Prostate	(50)	(50)	(50)	(49)
Seminal vesicle	(1)		(4)	(1)
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Interstitial cell, adenoma, multiple	41 (82%)	36 (72%)	39 (78%)	43 (86%)
Interstitial tissue, adenoma	1 (2%)			
Hematopoietic System				
Blood			(1)	(1)
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(50)	(50)	(50)	(50)
Lymph node, bronchial	(34)	(40)	(35)	(27)
Lymph node, mandibular	(48)	(45)	(48)	(48)
Lymph node, mediastinal	(48)	(45)	(48)	(45)
Lymph node, mesenteric	(46)	(50)	(49)	(49)
Spleen	(50)	(50)	(50)	(50)
Sarcoma				2 (4%)
Thymus	(48)	(49)	(46)	(42)
Mediastinum, schwannoma malignant		1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Integumentary System				
Mammary gland	(48)	(50)	(50)	(50)
Adenocarcinoma		1 (2%)		
Fibroadenoma	4 (8%)	3 (6%)	1 (2%)	1 (2%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)			
Basal cell carcinoma		1 (2%)		1 (2%)
Fibroma			1 (2%)	
Keratoacanthoma		3 (6%)	5 (10%)	2 (4%)
Papilloma squamous	1 (2%)	2 (4%)		1 (2%)
Squamous cell carcinoma		1 (2%)		
Subcutaneous tissue, fibroma		3 (6%)	4 (8%)	3 (6%)
Subcutaneous tissue, fibrosarcoma	1 (2%)		2 (4%)	
Subcutaneous tissue, fibrous histiocytoma		1 (2%)		
Subcutaneous tissue, lipoma	1 (2%)			
Musculoskeletal System				
Skeletal muscle		(1)		(1)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland				1 (2%)
Glioma malignant			1 (2%)	
Granular cell neoplasm benign	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma			2 (4%)	
Pheochromocytoma malignant, metastatic, adrenal gland			1 (2%)	
Squamous cell carcinoma, metastatic, preputial gland	1 (2%)			
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Nasolacrimal duct, squamous cell carcinoma			1 (2%)	
Special Senses System				
Zymbal's gland			(1)	(1)
Carcinoma				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Urinary bladder	(50)	(50)	(50)	(50)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Systemic Lesions				
Multiple organs[a]	(50)	(50)	(50)	(50)
Leukemia mononuclear	8 (16%)	11 (22%)	17 (34%)	25 (50%)
Mesothelioma malignant	1 (2%)	1 (2%)	3 (6%)	3 (6%)
Neoplasm Summary				
Total animals with primary neoplasms[b]	46	45	48	49
Total primary neoplasms	108	156	198	217
Total animals with benign neoplasms	46	42	46	47
Total benign neoplasms	94	90	112	116
Total animals with malignant neoplasms	14	44	48	49
Total malignant neoplasms	14	66	86	101
Total animals with metastatic neoplasms	1		3	3
Total metastatic neoplasms	1		3	3

[a] Number of animals with any tissue examined microscopically
[b] Primary tumors: all tumors except metastatic tumors

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: Vehicle Control

Number of Days on Study	0 5 3	1 1 5	1 8 8	3 1 9	4 0 7	4 6 4	5 4 9	6 1 1	6 1 3	6 2 9	6 4 5	6 5 9	6 6 0	6 6 6	6 8 0	6 8 9	7 1 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0
Carcass ID Number	0 8 1	0 1 1	0 4 1	0 1 2	0 4 2	0 6 1	0 8 2	0 5 1	0 5 2	0 1 3	0 1 4	0 7 1	0 9 1	1 0 1	0 9 2	1 0 2	0 5 3	0 1 5	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 3 1	0 3 2
Alimentary System																									
Esophagus	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma													X												
Mesentery								+			+					+									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X	X									
Adenoma, multiple																					X				
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue													+												
Papilloma squamous													X												
Tooth																									+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant										X															
Pheochromocytoma benign																			X			X			
Pheochromocytoma benign, multiple																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adenoma, multiple																									
Carcinoma																	X								

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 3 3	0 3 4	0 3 5	0 4 3	0 4 4	0 4 5	0 5 4	0 5 5	0 6 2	0 6 3	0 6 4	0 6 5	0 7 2	0 7 3	0 7 4	0 7 5	0 8 3	0 8 4	0 8 5	0 9 3	0 9 4	0 9 5	1 0 3	1 0 4	1 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery											+											+				5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X	X																	4
Adenoma, multiple						X																				2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Papilloma squamous																										1
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign									X			X	X	X			X									7
Pheochromocytoma benign, multiple								X																		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X				X						X													3
Adenoma, multiple				X					X								X									3
Carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	0 5 3	1 1 5	1 8 8	3 1 9	4 0 7	4 6 4	5 4 9	6 1 1	6 1 3	6 2 9	6 4 5	6 5 9	6 6 0	6 6 6	6 8 0	6 8 9	7 1 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0
Carcass ID Number	0 8 1	0 1 1	0 4 1	0 1 2	0 4 2	0 6 1	0 8 2	0 5 1	0 5 2	0 1 3	0 1 4	0 7 1	0 9 1	1 0 1	0 9 0	1 0 2	0 5 3	0 1 5	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 3 1	0 3 2
Endocrine System (continued)																									
Parathyroid gland	+	M	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X				X	X				X	X			X
Thyroid gland	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X		X							X								X		
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Squamous cell carcinoma								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle													+												
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma					X			X								X									
Interstitial cell, adenoma, multiple							X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Interstitial tissue, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	+	+	+	M	M	M	M	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Fibroadenoma															X								X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Papilloma squamous																									
Subcutaneous tissue, fibrosarcoma						X																			
Subcutaneous tissue, lipoma												X													

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	
Carcass ID Number	0 3 3	0 3 4	0 3 5	0 4 3	0 4 4	0 4 5	0 5 4	0 5 5	0 6 2	0 6 3	0 6 4	0 6 5	0 7 2	0 7 3	0 7 4	0 7 5	0 8 3	0 8 4	0 8 5	0 9 3	0 9 4	0 9 5	1 0 3	1 0 4	1 0 5		**Total Tissues/ Tumors**
Endocrine System (continued)																											
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pars distalis, adenoma		X		X									X							X	X						11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
C-cell, adenoma																X									X		6
C-cell, carcinoma																X											1
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenoma																				X							1
Squamous cell carcinoma																											1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Seminal vesicle																											1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Interstitial cell, adenoma																											3
Interstitial cell, adenoma, multiple	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
Interstitial tissue, adenoma				X																							1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node, bronchial	M	+	M	+	+	M	M	+	+	+	M	M	+	+	+	+	+	+	M	+	M	+	+	+	M		34
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+		48
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+		48
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Fibroadenoma		X										X															4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Basal cell adenoma							X																				1
Papilloma squamous																	X										1
Subcutaneous tissue, fibrosarcoma																											1
Subcutaneous tissue, lipoma																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	0 5 3	1 1 5	1 8 8	3 1 9	4 0 7	4 6 4	5 4 9	6 1 1	6 1 3	6 2 9	6 4 5	6 5 9	6 6 0	6 6 6	6 8 0	6 8 9	7 1 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0
Carcass ID Number	0 8 1	0 1 1	0 4 1	0 1 2	0 4 2	0 6 1	0 8 2	0 5 1	0 5 2	0 1 3	0 1 4	0 7 1	0 9 1	1 0 1	0 9 2	1 0 2	0 5 3	0 1 5	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 3 1	0 3 2
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign																			X						
Spinal cord																+									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, preputial gland								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X	X	X		X				X		X				
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2		
Carcass ID Number	0 3 3	0 3 4	0 3 5	0 4 3	0 4 4	0 4 5	0 5 4	0 5 5	0 6 2	0 6 3	0 6 4	0 6 5	0 7 2	0 7 3	0 7 4	0 7 5	0 8 3	0 8 4	0 8 5	0 9 3	0 9 4	0 9 5	1 0 3	1 0 4	1 0 5		**Total Tissues/ Tumors**
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Granular cell tumor benign																												1
Spinal cord																												1
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Squamous cell carcinoma, metastatic, preputial gland																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			48
Special Senses System																												
Eye								+																				1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Leukemia mononuclear							X		X																			8
Mesothelioma malignant											X																	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 2 mg/kg

Number of Days on Study	0 2 5	0 2 9	0 5 4	0 6 0	0 8 5	3 8 4	4 2 1	4 7 0	5 2 5	5 3 9	5 8 7	6 0 2	6 2 9	6 6 0	6 6 0	6 6 0	6 6 0	6 6 8	6 8 0	6 8 7	6 9 4	7 0 2	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 2 1	4 0 1	3 7 1	3 6 1	4 0 2	3 5 1	3 9 1	3 8 1	3 1 1	3 2 2	3 9 3	4 0 3	3 9 4	3 1 2	3 3 1	3 5 2	3 9 2	3 1 3	3 9 5	3 5 3	3 4 1	3 6 2	3 1 4	3 1 5	3 2 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, multiple								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatocellular carcinoma																									
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Mesentery						+			+			+		+		+			+	+			+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Adenoma, multiple																						X		X	
Mixed tumor benign																	X								
Pharynx																						+			
Papilloma squamous																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																			+						
Cardiovascular System																									
Blood vessel											+														
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 2 mg/kg (continued)

Number of Days on Study	729	729	732	732	732	732	732	732	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	32 4	32 5	33 2	33 3	33 4	33 5	34 2	34 3	34 4	34 5	35 4	35 5	36 3	36 4	36 5	37 2	37 3	37 4	37 5	38 2	38 3	38 4	38 5	40 4	40 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	43
Hepatocellular carcinoma						X																				1
Hepatocellular adenoma			X						X												X					3
Hepatocellular adenoma, multiple		X																								1
Mesentery	+																+					+			+	12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X						X				X			X								X				6
Adenoma, multiple															X											3
Mixed tumor benign																										1
Pharynx																										1
Papilloma squamous																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma benign		X	X				X						X													4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 2 mg/kg (continued)

Number of Days on Study	0 2 5	0 2 9	0 5 4	0 6 0	0 8 5	3 8 4	4 2 1	4 7 0	5 2 5	5 3 9	5 8 7	6 0 2	6 2 9	6 6 0	6 6 0	6 6 0	6 6 0	6 6 8	6 8 0	6 8 7	6 9 4	7 0 2	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 2 1	4 0 1	3 7 1	3 6 1	4 0 2	3 5 1	3 9 1	3 8 1	3 1 1	3 2 2	3 9 3	4 0 3	3 9 4	3 1 2	3 3 1	3 5 2	3 9 2	3 1 3	3 9 5	3 5 3	3 4 1	3 6 2	3 1 4	3 1 5	3 2 3
Endocrine System (continued)																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma													X		X	X		X	X		X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
C-cell, adenoma															X	X									
C-cell, carcinoma																			X						
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma															X		X				X				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Interstitial cell, adenoma, multiple											X	X	X	X			X	X	X	X	X	X	X	X	X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	M	M	M	+	+	M	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	M	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+			M	+	+		+	+	+	+	+
Mediastinum, schwannoma malignant																X									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma										X															
Fibroadenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 2 mg/kg (continued)

Number of Days on Study	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 2 4	3 2 5	3 3 2	3 3 3	3 3 4	3 3 5	3 4 2	3 4 3	3 4 4	3 4 5	3 5 4	3 5 5	3 5 6	3 6 4	3 6 5	3 7 2	3 7 3	3 7 4	3 7 5	3 8 2	3 8 3	3 8 4	3 8 5	4 0 4	4 0 5	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	50
Adenoma																		X								2
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma								X				X	X							X	X					11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
C-cell, adenoma			X													X							X			5
C-cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X													X						2
Carcinoma												X														4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma													X						X							2
Interstitial cell, adenoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	36
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	40
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mediastinum, schwannoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Fibroadenoma	X														X	X										3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 2 mg/kg (continued)

Number of Days on Study	0 2 5	0 2 9	0 5 4	0 6 0	0 8 5	3 8 4	4 2 1	4 7 0	5 2 5	5 3 9	5 8 7	6 0 2	6 2 9	6 6 0	6 6 0	6 6 0	6 6 0	6 6 8	6 8 0	6 8 7	6 9 4	7 0 2	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 2 1	4 0 1	3 7 1	3 6 1	4 0 2	3 5 1	3 9 1	3 8 1	3 1 1	3 1 2	3 2 3	4 0 3	3 9 4	3 3 2	3 1 1	3 5 2	3 9 2	3 1 3	3 9 5	3 5 3	3 4 1	3 6 2	3 1 4	3 1 5	3 2 3
Integumentary System (continued)																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma														X								X	X		
Papilloma squamous							X																		
Squamous cell carcinoma																									
Subcutaneous tissue, fibroma									X															X	
Subcutaneous tissue, fibrous histiocytoma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye								+					+											+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X			X					X						X	X			X	X
Mesothelioma malignant																								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 2 mg/kg (continued)

Number of Days on Study	729	729	732	732	732	732	732	732	733	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	32 4	32 5	33 2	33 3	33 4	33 5	34 2	44 3	44 4	44 5	55 4	55 5	63 3	64 4	65 5	67 2	73 3	74 4	75 5	82 2	83 3	84 4	85 5	04 4	05 5	**Total Tissues/ Tumors**
Integumentary System (continued)																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma						X																				1
Keratoacanthoma																										3
Papilloma squamous									X																	2
Squamous cell carcinoma							X																			1
Subcutaneous tissue, fibroma																X										3
Subcutaneous tissue, fibrous histiocytoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X														X					X		X			11
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 4 mg/kg

Number of Days on Study	0 4 6	0 7 0	2 5 4	3 9 4	4 1 0	5 2 0	5 4 1	5 5 6	5 8 9	6 1 3	6 1 8	6 1 8	6 2 7	6 2 7	6 3 3	6 3 4	6 3 9	6 6 5	6 7 8	6 8 8	6 8 8	7 0 3	7 0 7	7 2 5	7 2 9
Carcass ID Number	2 5 1	2 4 1	2 3 1	2 5 2	3 0 1	3 0 2	2 7 1	2 2 1	2 9 1	2 7 3	2 5 3	3 0 3	2 2 2	2 6 1	2 4 2	2 4 3	2 1 1	2 1 8	2 7 2	2 3 2	2 4 4	2 1 2	2 3 3	2 2 3	2 2 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, multiple			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatocellular carcinoma																						X			
Hepatocellular adenoma										X						X			X	X					X
Hepatocellular adenoma, multiple																		X							
Mesentery									+		+	+	+			+						+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma																		X		X		X			
Adenoma, multiple																									
Pharynx			+																						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue							+																		
Tooth							+																		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pheochromocytoma malignant						X																			
Pheochromocytoma benign															X					X					
Pheochromocytoma benign, multiple																							X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 4 mg/kg (continued)

Number of Days on Study	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 8 2	2 1 3	2 1 4	2 1 5	2 2 5	2 3 4	2 3 5	2 4 5	2 5 4	2 5 5	2 6 2	2 6 3	2 6 4	2 6 5	2 7 4	2 7 5	2 8 3	2 8 4	2 8 5	2 9 2	2 9 3	2 9 4	2 9 5	3 0 4	3 0 5	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+		49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Cholangiocarcinoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		48
Hepatocellular carcinoma					X					X				X	X					X							6
Hepatocellular adenoma		X	X		X	X		X	X				X	X					X			X			X		16
Hepatocellular adenoma, multiple										X																	2
Mesentery														+				+	+	+		+					12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenocarcinoma																					X						1
Adenoma			X			X			X		X		X						X								9
Adenoma, multiple														X													1
Pharynx																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Tongue																	+										2
Tooth																											1
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adrenal gland, medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Pheochromocytoma malignant						X								X													3
Pheochromocytoma benign		X				X							X							X		X	X				8
Pheochromocytoma benign, multiple																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 4 mg/kg (continued)

Number of Days on Study	0 4 6	0 7 0	2 5 4	3 9 4	4 1 0	5 2 0	5 4 1	5 5 6	5 8 9	6 1 3	6 1 8	6 1 8	6 2 7	6 2 7	6 3 3	6 3 4	6 3 9	6 6 5	6 7 8	6 8 8	6 8 8	7 0 3	7 0 7	7 2 5	7 2 9
Carcass ID Number	2 5 1	2 4 1	2 3 1	2 5 2	3 0 1	3 0 2	2 7 1	2 2 1	2 9 1	2 7 3	2 5 3	3 0 3	2 2 2	2 6 1	2 4 2	2 4 3	2 1 1	2 8 1	2 7 2	2 3 2	2 4 4	2 1 2	2 3 3	2 2 3	2 2 4
Endocrine System (continued)																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X				X	X			X		X	X				X		X		X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																			X						
C-cell, carcinoma																								X	
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X								X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle										+					+								+		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma														X											
Interstitial cell, adenoma, multiple						X	X		X	X	X		X			X	X		X	X	X	X	X	X	X
Hematopoietic System																									
Blood													+												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	+	M	+	M	M	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery										X															
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 4 mg/kg (continued)

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	28223	21343	21144	21255	22355	23444	23555	24455	25544	25552	26262	26363	26464	26565	27464	27555	28344	28445	28552	29223	29334	29445	29552	30443	30545	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma				X	X				X		X		X	X								X				17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										1
C-cell, carcinoma			X																							2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+		46
Adenoma	X																		X							4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Seminal vesicle															+											4
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Interstitial cell, adenoma																										1
Interstitial cell, adenoma, multiple	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		39
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node, bronchial	+	M	+	M	M	+	+	M	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+		35
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Mesothelioma malignant, metastatic, mesentery																										1
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+		46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Fibroadenoma																							X			1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 4 mg/kg (continued)

Number of Days on Study	0 4 6	0 7 0	2 5 4	3 9 4	4 1 0	5 2 0	5 4 1	5 5 6	5 8 9	6 1 3	6 1 8	6 1 8	6 2 7	6 2 7	6 3 3	6 3 4	6 3 9	6 6 5	6 7 8	6 8 8	6 8 8	7 0 3	7 0 7	7 2 5	7 2 9
Carcass ID Number	2 5 1	2 4 1	2 3 1	2 5 2	3 0 1	3 0 2	2 7 1	2 2 1	2 9 1	2 7 3	2 5 3	3 0 3	2 2 2	2 6 1	2 4 2	2 4 3	1 1 1	2 8 1	2 7 2	2 3 2	2 4 4	2 1 2	2 3 3	2 2 3	2 2 4
Integumentary System (continued)																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																X									
Keratoacanthoma																			X						
Subcutaneous tissue, fibroma							X											X				X			
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant				X																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																							X		
Pheochromocytoma malignant, metastatic, adrenal gland						X																			
Mediastinum, alveolar/ bronchiolar carcinoma, metastatic, lung																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasolacrimal duct, squamous cell carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye			+																						
Zymbal's gland							+																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X			X		X		X			X	X		X	X			X		X
Mesothelioma malignant								X		X			X												

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 4 mg/kg (continued)

Number of Days on Study	729	730	300	300	300	300	300	300	300	300	300	300	300	300	300	300	222	222	222	222	222	222	222	222	222	222	
Carcass ID Number	28 2	21 3	11 4	11 5	12 5	23 4	33 5	34 5	45 4	55 5	55 2	62 3	63 4	64 5	65 4	74 5	75 3	83 4	84 5	85 2	92 3	93 4	94 5	95 4	04 5	05 5	**Total Tissues/ Tumors**
Integumentary System (continued)																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																											1
Keratoacanthoma							X													X	X		X			5
Subcutaneous tissue, fibroma																	X										4
Subcutaneous tissue, fibrosarcoma			X																						X		2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																				X							2
Pheochromocytoma malignant, metastatic, adrenal gland																											1
Mediastinum, alveolar/ bronchiolar carcinoma, metastatic, lung																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasolacrimal duct, squamous cell carcinoma																								X			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																											1
Zymbal's gland																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X			X												X	X	X	X				17
Mesothelioma malignant																											3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 8 mg/kg

Number of Days on Study	0 5 2	4 2 1	4 2 1	4 4 3	4 4 8	4 5 6	4 9 0	5 7 5	5 8 3	5 9 1	6 0 9	6 1 7	6 2 4	6 4 5	6 5 5	6 5 6	6 6 5	6 6 6	6 6 7	6 8 0	6 8 6	6 8 8	6 8 8	6 9 4	6 9 4
Carcass ID Number	2 0 1	1 3 1	2 0 2	1 7 1	1 3 2	1 6 1	1 6 2	1 9 1	1 4 2	1 9 2	1 9 3	2 0 3	1 8 1	1 2 1	2 0 4	1 3 3	1 4 1	2 0 5	1 4 3	1 7 2	1 2 2	1 2 3	1 5 1	1 6 3	1 6 4
Alimentary System																									
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, multiple		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatocellular carcinoma													X		X		X	X					X	X	X
Hepatocellular carcinoma, multiple																					X				
Hepatocellular adenoma							X	X	X			X		X		X			X			X			
Hepatocellular adenoma, multiple											X						X	X		X	X				X
Mesentery				+			+	+			+				+					+					
Cholangiocarcinoma, metastatic, liver																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Adenoma, multiple																									
Salivary glands	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																					X	X		X	
Pheochromocytoma benign, multiple													X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+
Adenoma																									X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	6 9 4	6 9 5	6 9 5	6 9 5	6 9 5	6 9 6	6 9 8	7 0 7	7 2 3	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 8 2	1 3 4	1 4 4	1 5 2	1 9 4	1 5 3	1 7 3	1 9 5	1 7 4	1 1 1	1 1 2	1 7 5	1 1 3	1 1 4	1 1 5	1 2 4	1 2 5	1 3 5	1 4 5	1 5 4	1 5 5	1 6 5	1 8 3	1 8 4	1 8 5	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	49
Hepatocellular carcinoma	X		X		X			X	X			X					X			X		X	X		17
Hepatocellular carcinoma, multiple																									1
Hepatocellular adenoma		X						X	X	X				X	X					X		X	X		17
Hepatocellular adenoma, multiple	X			X												X								X	10
Mesentery		+			+	+				+	+	+	+										+		14
Cholangiocarcinoma, metastatic, liver										X													X		2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																		X	X					X	4
Adenoma, multiple																						X			2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign											X		X								X	X		X	8
Pheochromocytoma benign, multiple									X																2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																									1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	43
Adenoma																									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	0 5 2	4 2 1	4 2 1	4 4 3	4 4 8	4 5 6	4 9 0	5 7 5	5 8 3	5 9 1	6 0 9	6 1 7	6 2 4	6 4 5	6 5 5	6 5 6	6 6 5	6 6 6	6 6 7	6 8 0	6 8 6	6 8 8	6 8 8	6 9 4	6 9 4
Carcass ID Number	2 0 1	1 3 1	2 0 2	1 7 1	1 3 2	1 6 1	1 6 2	1 9 1	1 4 2	1 9 2	1 9 3	2 0 3	1 8 1	1 2 1	2 0 4	1 3 3	1 4 1	2 0 5	1 4 3	1 7 2	1 2 2	1 2 3	1 5 1	1 6 3	1 6 4
Endocrine System (continued)																									
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X											X	X	X		X							
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Adenoma														X											
Bilateral, adenoma								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Seminal vesicle			+																						
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma						X															X				
Interstitial cell, adenoma, multiple					X		X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	X
Hematopoietic System																									
Blood								+																	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	M	M	+	M	M	M	+	+	M	+	M	+	M	+	M	+	+	M	+	M	+	M	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mediastinal	M	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma											X														
Thymus	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																	X			X					
Papilloma squamous																			X						
Subcutaneous tissue, fibroma										X												X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	6 9 4	6 9 5	6 9 5	6 9 5	6 9 5	6 9 6	6 9 8	7 0 7	7 2 3	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 8 2	1 3 4	1 4 4	1 5 2	1 9 4	1 5 3	1 7 3	1 9 5	1 7 4	1 1 1	1 1 2	1 7 5	1 1 3	1 1 4	1 1 5	1 2 4	1 2 5	1 3 5	1 4 5	1 5 4	1 5 5	1 6 5	1 8 3	1 8 4	1 8 5	**Total Tissues/ Tumors**
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma									X				X		X	X					X			X	11
Pars distalis, carcinoma			X																						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
C-cell, adenoma								X		X						X		X							4
Follicular cell, carcinoma												X													1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	48
Adenoma				X																		X			3
Bilateral, adenoma																									1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle																									1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																									2
Interstitial cell, adenoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	43
Hematopoietic System																									
Blood																									1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	+	M	+	+	M	M	M	M	+	+	+	+	+	+	M	M	+	M	+	+	M	+	M	27
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma										X															2
Thymus	+	+	M	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma		X																							1
Keratoacanthoma																									2
Papilloma squamous																									1
Subcutaneous tissue, fibroma														X											3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	0 5 2	4 2 1	4 2 1	4 4 3	4 4 8	4 5 6	4 9 0	5 7 5	5 8 3	5 9 1	6 0 9	6 1 7	6 2 4	6 4 5	6 5 5	6 5 6	6 6 5	6 6 6	6 7 7	6 8 0	6 8 6	6 8 8	6 8 8	6 9 4	6 9 4
Carcass ID Number	2 0 1	1 3 1	2 0 2	1 7 1	1 3 2	1 6 1	1 6 2	1 9 1	1 4 2	1 9 2	1 9 3	2 0 3	1 8 1	1 2 1	1 0 4	2 3 3	1 4 1	1 0 5	2 4 3	1 7 2	1 2 2	1 2 3	1 5 1	1 6 3	1 6 4
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																			+						
Harderian gland																									
Zymbal's gland																		+							
Carcinoma																		X							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X					X	X	X			X	X		X	X	X	X	X	X	X		X
Mesothelioma malignant							X	X																	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	6 9 4	6 9 5	6 9 5	6 9 5	6 9 5	6 9 6	6 9 8	7 0 7	7 2 3	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 8 2	1 3 4	1 4 4	1 5 2	1 9 4	1 5 3	1 7 3	1 9 5	1 7 4	1 1 1	1 1 2	1 7 5	1 1 3	1 1 4	1 1 5	1 2 4	1 2 5	1 3 5	1 4 5	1 5 4	1 5 5	1 6 5	1 8 3	1 8 4	1 8 5	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland			X																							1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye		+																								2
Harderian gland																							+			1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X					X					X	X				X			X		X	X	X		X	25
Mesothelioma malignant											X															3

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Furan

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	8/50 (16%)	4/47 (9%)	9/48 (19%)	10/49 (20%)
Adjusted rates[b]	24.2%	14.3%	31.0%	45.1%
Terminal rates[c]	8/33 (24%)	4/28 (14%)	6/25 (24%)	5/15 (33%)
First incidence (days)	729 (T)	729 (T)	633	624
Life table tests[d]	P=0.009	P=0.259N	P=0.281	P=0.036
Logistic regression tests[d]	P=0.058	P=0.259N	P=0.335	P=0.155
Cochran-Armitage test[d]	P=0.184			
Fisher exact test[d]		P=0.210N	P=0.463	P=0.379
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rates	1/50 (2%)	0/47 (0%)	3/48 (6%)	0/49 (0%)
Adjusted rates	2.4%	0.0%	10.0%	0.0%
Terminal rates	0/33 (0%)	0/28 (0%)	2/25 (8%)	0/15 (0%)
First incidence (days)	629	–[e]	520	–
Life table tests	P=0.616N	P=0.515N	P=0.251	P=0.520N
Logistic regression tests	P=0.502N	P=0.511N	P=0.289	P=0.504N
Cochran-Armitage test	P=0.502N			
Fisher exact test		P=0.515N	P=0.293	P=0.505N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rates	9/50 (18%)	4/47 (9%)	11/48 (23%)	10/49 (20%)
Adjusted rates	26.1%	14.3%	36.1%	45.1%
Terminal rates	8/33 (24%)	4/28 (14%)	7/25 (28%)	5/15 (33%)
First incidence (days)	629	729 (T)	520	624
Life table tests	P=0.016	P=0.182N	P=0.203	P=0.070
Logistic regression tests	P=0.129	P=0.162N	P=0.294	P=0.284
Cochran-Armitage test	P=0.239			
Fisher exact test		P=0.142N	P=0.362	P=0.480
Liver: Cholangiocarcinoma				
Overall rates	0/50 (0%)	43/50 (86%)	48/50 (96%)	49/50 (98%)
Adjusted rates	0.0%	100.0%	100.0%	100.0%
Terminal rates	0/33 (0%)	28/28 (100%)	26/26 (100%)	16/16 (100%)
First incidence (days)	–	470	254	421
Life table tests	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma				
Overall rates	1/50 (2%)	4/50 (8%)	18/50 (36%)	27/50 (54%)
Adjusted rates	2.6%	14.3%	56.9%	74.0%
Terminal rates	0/33 (0%)	4/28 (14%)	13/26 (50%)	8/16 (50%)
First incidence (days)	660	729 (T)	613	490
Life table tests	P<0.001	P=0.142	P<0.001	P<0.001
Logistic regression tests	P<0.001	P=0.149	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.181	P<0.001	P<0.001

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Liver: Hepatocellular Carcinoma				
Overall rates	0/50 (0%)	1/50 (2%)	6/50 (12%)	18/50 (36%)
Adjusted rates	0.0%	3.6%	22.0%	58.5%
Terminal rates	0/33 (0%)	1/28 (4%)	5/26 (19%)	5/16 (31%)
First incidence (days)	–	729 (T)	703	624
Life table tests	P<0.001	P=0.467	P=0.008	P<0.001
Logistic regression tests	P<0.001	P=0.467	P=0.009	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.500	P=0.013	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	1/50 (2%)	5/50 (10%)	22/50 (44%)	35/50 (70%)
Adjusted rates	2.6%	17.9%	68.0%	84.5%
Terminal rates	0/33 (0%)	5/28 (18%)	16/26 (62%)	10/16 (63%)
First incidence (days)	660	729 (T)	613	490
Life table tests	P<0.001	P=0.075	P<0.001	P<0.001
Logistic regression tests	P<0.001	P=0.079	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.102	P<0.001	P<0.001
Mammary Gland: Fibroadenoma				
Overall rates	4/50 (8%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rates	11.6%	10.7%	3.8%	3.4%
Terminal rates	3/33 (9%)	3/28 (11%)	1/26 (4%)	0/16 (0%)
First incidence (days)	680	729 (T)	729 (T)	688
Life table tests	P=0.219N	P=0.586N	P=0.252N	P=0.355N
Logistic regression tests	P=0.141N	P=0.568N	P=0.216N	P=0.233N
Cochran-Armitage test	P=0.092N			
Fisher exact test		P=0.500N	P=0.181N	P=0.181N
Mammary Gland: Fibroadenoma or Adenocarcinoma				
Overall rates	4/50 (8%)	4/50 (8%)	1/50 (2%)	1/50 (2%)
Adjusted rates	11.6%	12.9%	3.8%	3.4%
Terminal rates	3/33 (9%)	3/28 (11%)	1/26 (4%)	0/16 (0%)
First incidence (days)	680	539	729 (T)	688
Life table tests	P=0.184N	P=0.560	P=0.252N	P=0.355N
Logistic regression tests	P=0.089N	P=0.606	P=0.216N	P=0.233N
Cochran-Armitage test	P=0.077N			
Fisher exact test		P=0.643N	P=0.181N	P=0.181N
Pancreas: Adenoma				
Overall rates	6/50 (12%)	9/50 (18%)	10/50 (20%)	6/49 (12%)
Adjusted rates	17.0%	29.8%	33.9%	35.3%
Terminal rates	4/33 (12%)	7/28 (25%)	7/26 (27%)	5/15 (33%)
First incidence (days)	680	668	665	665
Life table tests	P=0.142	P=0.191	P=0.105	P=0.196
Logistic regression tests	P=0.378	P=0.212	P=0.142	P=0.401
Cochran-Armitage test	P=0.506N			
Fisher exact test		P=0.288	P=0.207	P=0.606

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Pancreas: Adenoma or Adenocarcinoma				
Overall rates	6/50 (12%)	9/50 (18%)	11/50 (22%)	6/49 (12%)
Adjusted rates	17.0%	29.8%	37.4%	35.3%
Terminal rates	4/33 (12%)	7/28 (25%)	8/26 (31%)	5/15 (33%)
First incidence (days)	680	668	665	665
Life table tests	P=0.125	P=0.191	P=0.064	P=0.196
Logistic regression tests	P=0.353	P=0.212	P=0.088	P=0.401
Cochran-Armitage test	P=0.519N			
Fisher exact test		P=0.288	P=0.143	P=0.606
Pancreatic Islets: Adenoma				
Overall rates	6/50 (12%)	2/50 (4%)	1/50 (2%)	1/49 (2%)
Adjusted rates	18.2%	6.9%	3.8%	2.5%
Terminal rates	6/33 (18%)	1/28 (4%)	1/26 (4%)	0/15 (0%)
First incidence (days)	729 (T)	702	729 (T)	609
Life table tests	P=0.107N	P=0.192N	P=0.101N	P=0.235N
Logistic regression tests	P=0.048N	P=0.179N	P=0.101N	P=0.095N
Cochran-Armitage test	P=0.032N			
Fisher exact test		P=0.134N	P=0.056N	P=0.059N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rates	7/50 (14%)	2/50 (4%)	1/50 (2%)	1/49 (2%)
Adjusted rates	20.6%	6.9%	3.8%	2.5%
Terminal rates	6/33 (18%)	1/28 (4%)	1/26 (4%)	0/15 (0%)
First incidence (days)	716	702	729 (T)	609
Life table tests	P=0.066N	P=0.129N	P=0.065N	P=0.175N
Logistic regression tests	P=0.026N	P=0.112N	P=0.053N	P=0.058N
Cochran-Armitage test	P=0.017N			
Fisher exact test		P=0.080N	P=0.030N	P=0.032N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	11/49 (22%)	11/50 (22%)	17/49 (35%)	11/49 (22%)
Adjusted rates	30.4%	31.3%	45.2%	43.5%
Terminal rates	8/33 (24%)	5/28 (18%)	7/26 (27%)	5/16 (31%)
First incidence (days)	659	629	394	421
Life table tests	P=0.107	P=0.455	P=0.064	P=0.139
Logistic regression tests	P=0.446	P=0.519	P=0.110	P=0.528
Cochran-Armitage test	P=0.469			
Fisher exact test		P=0.574N	P=0.132	P=0.595N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	11/49 (22%)	11/50 (22%)	17/49 (35%)	12/49 (24%)
Adjusted rates	30.4%	31.3%	45.2%	45.9%
Terminal rates	8/33 (24%)	5/28 (18%)	7/26 (27%)	5/16 (31%)
First incidence (days)	659	629	394	421
Life table tests	P=0.069	P=0.455	P=0.064	P=0.092
Logistic regression tests	P=0.349	P=0.519	P=0.110	P=0.428
Cochran-Armitage test	P=0.372			
Fisher exact test		P=0.574N	P=0.132	P=0.500

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Preputial Gland: Adenoma				
Overall rates	1/49 (2%)	2/50 (4%)	4/46 (9%)	4/48 (8%)
Adjusted rates	3.1%	7.1%	14.1%	15.0%
Terminal rates	1/32 (3%)	2/28 (7%)	2/24 (8%)	1/15 (7%)
First incidence (days)	729 (T)	729 (T)	633	575
Life table tests	P=0.030	P=0.453	P=0.120	P=0.087
Logistic regression tests	P=0.092	P=0.453	P=0.146	P=0.166
Cochran-Armitage test	P=0.106			
Fisher exact test		P=0.508	P=0.162	P=0.175
Preputial Gland: Carcinoma				
Overall rates	0/49 (0%)	4/50 (8%)	0/46 (0%)	0/48 (0%)
Adjusted rates	0.0%	11.8%	0.0%	0.0%
Terminal rates	0/32 (0%)	1/28 (4%)	0/24 (0%)	0/15 (0%)
First incidence (days)	–	660	–	–
Life table tests	P=0.316N	P=0.056	–	–
Logistic regression tests	P=0.263N	P=0.059	–	–
Cochran-Armitage test	P=0.256N			
Fisher exact test		P=0.061	–	–
Preputial Gland: Adenoma or Carcinoma				
Overall rates	1/49 (2%)	6/50 (12%)	4/46 (9%)	4/48 (8%)
Adjusted rates	3.1%	18.4%	14.1%	15.0%
Terminal rates	1/32 (3%)	3/28 (11%)	2/24 (8%)	1/15 (7%)
First incidence (days)	729 (T)	660	633	575
Life table tests	P=0.125	P=0.047	P=0.120	P=0.087
Logistic regression tests	P=0.267	P=0.049	P=0.146	P=0.166
Cochran-Armitage test	P=0.290			
Fisher exact test		P=0.059	P=0.162	P=0.175
Skin: Keratoacanthoma				
Overall rates	0/50 (0%)	3/50 (6%)	5/50 (10%)	2/50 (4%)
Adjusted rates	0.0%	9.4%	18.0%	6.1%
Terminal rates	0/33 (0%)	1/28 (4%)	4/26 (15%)	0/16 (0%)
First incidence (days)	–	660	678	665
Life table tests	P=0.137	P=0.104	P=0.019	P=0.214
Logistic regression tests	P=0.251	P=0.108	P=0.023	P=0.233
Cochran-Armitage test	P=0.291			
Fisher exact test		P=0.121	P=0.028	P=0.247
Skin: Squamous Papilloma or Squamous Cell Carcinoma				
Overall rates	1/50 (2%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rates	3.0%	9.3%	0.0%	3.1%
Terminal rates	1/33 (3%)	2/28 (7%)	0/26 (0%)	0/16 (0%)
First incidence (days)	729 (T)	421	–	667
Life table tests	P=0.539N	P=0.262	P=0.548N	P=0.668
Logistic regression tests	P=0.409N	P=0.298	P=0.548N	P=0.746
Cochran-Armitage test	P=0.409N			
Fisher exact test		P=0.309	P=0.500N	P=0.753N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Skin (Subcutaneous Tissue): Fibroma				
Overall rates	0/50 (0%)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted rates	0.0%	9.4%	12.0%	11.7%
Terminal rates	0/33 (0%)	2/28 (7%)	1/26 (4%)	1/16 (6%)
First incidence (days)	–	525	541	591
Life table tests	P=0.078	P=0.102	P=0.051	P=0.073
Logistic regression tests	P=0.161	P=0.115	P=0.062	P=0.118
Cochran-Armitage test	P=0.162			
Fisher exact test		P=0.121	P=0.059	P=0.121
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	1/50 (2%)	3/50 (6%)	6/50 (12%)	3/50 (6%)
Adjusted rates	2.2%	9.4%	19.1%	11.7%
Terminal rates	0/33 (0%)	2/28 (7%)	3/26 (12%)	1/16 (6%)
First incidence (days)	464	525	541	591
Life table tests	P=0.125	P=0.271	P=0.043	P=0.227
Logistic regression tests	P=0.264	P=0.313	P=0.058	P=0.304
Cochran-Armitage test	P=0.264			
Fisher exact test		P=0.309	P=0.056	P=0.309
Testes: Adenoma				
Overall rates	45/50 (90%)	38/50 (76%)	40/50 (80%)	45/50 (90%)
Adjusted rates	100.0%	100.0%	97.5%	100.0%
Terminal rates	33/33 (100%)	28/28 (100%)	25/26 (96%)	16/16 (100%)
First incidence (days)	407	587	520	448
Life table tests	P<0.001	P=0.504N	P=0.331	P<0.001
Logistic regression tests	P=0.329	P=0.031N	P=0.054N	P=0.526N
Cochran-Armitage test	P=0.348			
Fisher exact test		P=0.054N	P=0.131N	P=0.630N
Thyroid Gland (C-cell): Adenoma				
Overall rates	6/48 (13%)	5/50 (10%)	1/50 (2%)	4/48 (8%)
Adjusted rates	15.6%	15.5%	3.1%	24.4%
Terminal rates	3/33 (9%)	3/28 (11%)	0/26 (0%)	3/15 (20%)
First incidence (days)	464	660	678	707
Life table tests	P=0.501N	P=0.581N	P=0.091N	P=0.542
Logistic regression tests	P=0.265N	P=0.510N	P=0.052N	P=0.395N
Cochran-Armitage test	P=0.242N			
Fisher exact test		P=0.471N	P=0.050N	P=0.370N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	6/48 (13%)	6/50 (12%)	3/50 (6%)	4/48 (8%)
Adjusted rates	15.6%	18.2%	10.3%	24.4%
Terminal rates	3/33 (9%)	3/28 (11%)	1/26 (4%)	3/15 (20%)
First incidence (days)	464	660	678	707
Life table tests	P=0.538N	P=0.533	P=0.334N	P=0.542
Logistic regression tests	P=0.277N	P=0.611	P=0.233N	P=0.395N
Cochran-Armitage test	P=0.247N			
Fisher exact test		P=0.591N	P=0.223N	P=0.370N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
All Organs: Mononuclear Cell Leukemia				
Overall rates	8/50 (16%)	11/50 (22%)	17/50 (34%)	25/50 (50%)
Adjusted rates	21.0%	31.7%	46.5%	70.6%
Terminal rates	4/33 (12%)	6/28 (21%)	8/26 (31%)	8/16 (50%)
First incidence (days)	645	384	520	421
Life table tests	P<0.001	P=0.227	P=0.016	P<0.001
Logistic regression tests	P<0.001	P=0.267	P=0.027	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.306	P=0.032	P<0.001
All Organs: Malignant Mesothelioma				
Overall rates	1/50 (2%)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted rates	3.0%	3.6%	7.2%	10.5%
Terminal rates	1/33 (3%)	1/28 (4%)	0/26 (0%)	1/16 (6%)
First incidence (days)	729 (T)	729 (T)	556	490
Life table tests	P=0.104	P=0.725	P=0.279	P=0.190
Logistic regression tests	P=0.163	P=0.725	P=0.307	P=0.306
Cochran-Armitage test	P=0.164			
Fisher exact test		P=0.753N	P=0.309	P=0.309
All Organs: Benign Neoplasms				
Overall rates	46/50 (92%)	42/50 (84%)	46/50 (92%)	47/50 (94%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	33/33 (100%)	28/28 (100%)	26/26 (100%)	16/16 (100%)
First incidence (days)	407	421	394	421
Life table tests	P<0.001	P=0.414	P=0.094	P<0.001
Logistic regression tests	P=0.609	P=0.200N	P=0.691N	P=0.417N
Cochran-Armitage test	P=0.244			
Fisher exact test		P=0.178N	P=0.643N	P=0.500
All Organs: Malignant Neoplasms				
Overall rates	14/50 (28%)	44/50 (88%)	48/50 (96%)	49/50 (98%)
Adjusted rates	33.5%	100.0%	100.0%	100.0%
Terminal rates	6/33 (18%)	28/28 (100%)	26/26 (100%)	16/16 (100%)
First incidence (days)	464	384	254	421
Life table tests	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rates	46/50 (92%)	45/50 (90%)	48/50 (96%)	49/50 (98%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	33/33 (100%)	28/28 (100%)	26/26 (100%)	16/16 (100%)
First incidence (days)	407	384	254	421
Life table tests	P<0.001	P=0.221	P=0.053	P<0.001
Logistic regression tests	P=0.241	–[f]	P=0.268	–[f]
Cochran-Armitage test	P=0.079			
Fisher exact test		P=0.500N	P=0.339	P=0.181

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Furan (continued)

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be calculated

TABLE A4a
Historical Incidence of Liver Neoplasms in Male F344/N Rats Receiving Corn Oil Vehicle by Gavage[a]

Study	Incidence in Controls		
	Hepatocellular Adenoma or Neoplastic Nodule	Hepatocellular Carcinoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Neoplastic Nodule
Historical Incidence at Southern Research Institute			
Benzaldehyde	2/50	0/50	2/50
Dichlorvos	0/50	1/50	1/50
Furan	1/50	0/50	1/50
Furfural	1/50	0/50	1/50
γ-Butyrolactone	0/50	0/50	0/50
Total	4/250 (1.6%)	1/250 (0.4%)	5/250 (2.0%)
Standard deviation	1.7%	0.9%	1.4%
Range	0%–4%	0%–2%	0%–4%
Overall Historical Incidence			
Total	15/770 (1.9%)	4/770 (0.5%)	19/770 (2.5%)
Standard deviation	2.5%	0.9%	2.8%
Range	0%–8%	0%–2%	0%–10%

[a] Data as of 17 September 1990

TABLE A4b
Historical Incidence of Mononuclear Cell Leukemia in Male F344/N Rats Receiving Corn Oil Vehicle by Gavage[a]

Study	Incidence of Leukemia in Controls
Historical Incidence at Southern Research Institute	
Benzaldehyde	10/50
Dichlorvos	11/50
Furan	8/50
Furfural	13/50
γ-Butyrolactone	16/50
Total	58/250 (23.2%)
Standard deviation	6.1%
Range	16%–32%
Overall Historical Incidence	
Total	164/770 (21.3%)
Standard deviation	8.9%
Range	4%–38%

[a] Data as of 17 September 1990 for lymphocytic, monocytic, mononuclear, or undifferentiated leukemia

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Furan[a]

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Natural deaths	1	4	3	5
Moribund kills	10	13	17	28
Accidental deaths	6	5	4	1
Survivors				
Terminal sacrifice	33	28	26	16
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(48)	(50)	(50)	(49)
Hemorrhage, focal		1 (2%)		
Intestine large, cecum	(49)	(50)	(50)	(50)
Parasite metazoan	2 (4%)	1 (2%)	4 (8%)	
Ulcer, multiple	1 (2%)			
Intestine large, colon	(49)	(49)	(50)	(50)
Diverticulum		1 (2%)		
Parasite metazoan	4 (8%)	2 (4%)	3 (6%)	6 (12%)
Intestine large, rectum	(50)	(49)	(48)	(50)
Fibrosis, focal			1 (2%)	
Parasite metazoan	5 (10%)	6 (12%)	6 (13%)	2 (4%)
Liver	(50)	(50)	(50)	(50)
Angiectasis, focal			1 (2%)	
Basophilic focus	32 (64%)	20 (40%)	2 (4%)	1 (2%)
Clear cell focus	8 (16%)			
Cyst multilocular		1 (2%)	17 (34%)	24 (48%)
Degeneration, cystic	2 (4%)			
Degeneration, cystic, focal	3 (6%)			
Degeneration, cystic, multifocal	1 (2%)			
Developmental malformation	3 (6%)	3 (6%)	3 (6%)	1 (2%)
Eosinophilic focus	14 (28%)			
Granuloma, multiple	1 (2%)	21 (42%)	10 (20%)	1 (2%)
Hematopoietic cell proliferation, multifocal	1 (2%)	3 (6%)	3 (6%)	
Hemorrhage, multifocal		1 (2%)	1 (2%)	5 (10%)
Leukocytosis		1 (2%)		
Necrosis, focal	1 (2%)		1 (2%)	
Neovascularization		6 (12%)	14 (28%)	15 (30%)
Thrombus			3 (6%)	4 (8%)
Biliary tract, cyst, multiple		44 (88%)	47 (94%)	49 (98%)
Biliary tract, ectasia, focal	1 (2%)			
Biliary tract, fibrosis, multifocal		44 (88%)	48 (96%)	49 (98%)
Biliary tract, hyperplasia, multifocal		44 (88%)	48 (96%)	49 (98%)
Biliary tract, inflammation, chronic, multifocal		44 (88%)	48 (96%)	49 (98%)
Biliary tract, metaplasia		44 (88%)	48 (96%)	49 (98%)
Biliary tract, proliferation	39 (78%)			
Centrilobular, necrosis	5 (10%)	7 (14%)	5 (10%)	9 (18%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Furan
(continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Alimentary System (continued)				
Liver (continued)				
Hepatocyte, cytomegaly		35 (70%)	46 (92%)	49 (98%)
Hepatocyte, degeneration, multifocal		33 (66%)	46 (92%)	49 (98%)
Hepatocyte, hyperplasia, nodular, multifocal		30 (60%)	46 (92%)	49 (98%)
Hepatocyte, necrosis, multifocal		32 (64%)	46 (92%)	49 (98%)
Hepatocyte, vacuolization cytoplasmic	1 (2%)	39 (78%)	45 (90%)	49 (98%)
Kupffer cell, pigmentation, multifocal		44 (88%)	48 (96%)	49 (98%)
Mesentery	(5)	(12)	(12)	(14)
Foreign body		1 (8%)		
Inflammation, suppurative, acute		1 (8%)		
Pigmentation, hemosiderin, multifocal			1 (8%)	3 (21%)
Fat, hemorrhage				1 (7%)
Fat, necrosis, focal	3 (60%)	7 (58%)	9 (75%)	6 (43%)
Fat, necrosis, multifocal				1 (7%)
Pancreas	(50)	(50)	(50)	(49)
Atrophy, focal	9 (18%)	2 (4%)	1 (2%)	6 (12%)
Atrophy, multifocal	6 (12%)	7 (14%)	3 (6%)	5 (10%)
Cyst multilocular			1 (2%)	
Hyperplasia	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	8 (16%)	12 (24%)	9 (18%)	12 (24%)
Hyperplasia, multifocal	13 (26%)	9 (18%)	6 (12%)	10 (20%)
Inflammation, chronic, focal	1 (2%)		2 (4%)	
Inflammation, subacute, focal	1 (2%)			
Pigmentation, hemosiderin			1 (2%)	
Artery, inflammation, subacute		1 (2%)		
Stomach, forestomach	(50)	(49)	(50)	(50)
Edema				3 (6%)
Hyperkeratosis			1 (2%)	
Hyperplasia	1 (2%)	4 (8%)	7 (14%)	6 (12%)
Hyperplasia, squamous				1 (2%)
Inflammation, subacute	1 (2%)	2 (4%)	6 (12%)	2 (4%)
Perforation		1 (2%)	3 (6%)	
Ulcer		1 (2%)	3 (6%)	3 (6%)
Ulcer, multiple			1 (2%)	3 (6%)
Artery, inflammation, subacute		2 (4%)		
Serosa, fibrosis, focal				1 (2%)
Stomach, glandular	(50)	(49)	(50)	(50)
Edema				2 (4%)
Erosion			2 (4%)	1 (2%)
Erosion, multiple	1 (2%)		1 (2%)	1 (2%)
Inflammation, subacute			1 (2%)	
Mineralization, multifocal			1 (2%)	2 (4%)
Ulcer			1 (2%)	2 (4%)
Tongue	(1)		(2)	
Foreign body	1 (100%)			
Hemorrhage			1 (50%)	
Inflammation, granulomatous	1 (100%)			
Tooth	(1)	(1)	(1)	
Dysplasia	1 (100%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Furan
(continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Cardiovascular System				
Blood vessel		(1)		
Aorta, mineralization		1 (100%)		
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	29 (58%)	30 (60%)	38 (76%)	39 (78%)
Fibrosis, focal			1 (2%)	
Inflammation, suppurative, acute, multifocal	1 (2%)			
Mineralization, multifocal		1 (2%)		1 (2%)
Thrombus	1 (2%)	1 (2%)		1 (2%)
Valve, embolus bacterial	1 (2%)			
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule				2 (4%)
Focal cellular change	2 (4%)	7 (14%)	7 (14%)	2 (4%)
Hematopoietic cell proliferation, multifocal		2 (4%)		
Hemorrhage		1 (2%)	1 (2%)	
Necrosis, diffuse			1 (2%)	
Vacuolization cytoplasmic, diffuse	1 (2%)			
Capsule, fibrosis, focal				1 (2%)
Left, atrophy			1 (2%)	
Adrenal gland, medulla	(50)	(47)	(48)	(49)
Hyperplasia			1 (2%)	
Hyperplasia, focal	2 (4%)	7 (15%)	1 (2%)	3 (6%)
Hyperplasia, multifocal			1 (2%)	1 (2%)
Necrosis, diffuse		1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Parathyroid gland	(46)	(47)	(49)	(43)
Hyperplasia		2 (4%)	10 (20%)	6 (14%)
Pituitary gland	(49)	(50)	(49)	(49)
Pars distalis, angiectasis	10 (20%)	18 (36%)	18 (37%)	8 (16%)
Pars distalis, cyst	2 (4%)	2 (4%)	4 (8%)	4 (8%)
Pars distalis, hyperplasia	1 (2%)		2 (4%)	2 (4%)
Pars distalis, hyperplasia, focal	10 (20%)	12 (24%)	5 (10%)	6 (12%)
Pars distalis, necrosis		1 (2%)		
Pars distalis, pigmentation, hemosiderin	7 (14%)	10 (20%)	3 (6%)	6 (12%)
Pars intermedia, cyst				1 (2%)
Thyroid gland	(48)	(50)	(50)	(48)
Hyperplasia, focal		1 (2%)		
Ultimobranchial cyst	1 (2%)			
C-cell, hyperplasia	2 (4%)	1 (2%)		1 (2%)
C-cell, hyperplasia, focal	3 (6%)	1 (2%)	1 (2%)	1 (2%)
C-cell, hyperplasia, multifocal	1 (2%)	1 (2%)	1 (2%)	
Follicle, cyst	2 (4%)		4 (8%)	6 (13%)
General Body System				
None				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Furan
(continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Genital System				
Preputial gland	(49)	(50)	(46)	(48)
Foreign body	1 (2%)			
Granuloma	1 (2%)			
Hyperplasia	1 (2%)			
Inflammation, chronic	1 (2%)			
Inflammation, subacute, focal	1 (2%)	1 (2%)	1 (2%)	
Inflammation, suppurative, acute, focal	3 (6%)	2 (4%)	1 (2%)	3 (6%)
Duct, cyst	1 (2%)	5 (10%)		4 (8%)
Prostate	(50)	(50)	(50)	(49)
Inflammation, subacute	8 (16%)	22 (44%)	26 (52%)	11 (22%)
Inflammation, suppurative, acute				1 (2%)
Seminal vesicle	(1)		(4)	(1)
Inflammation, subacute			3 (75%)	
Inflammation, suppurative, acute				1 (100%)
Testes	(50)	(50)	(50)	(50)
Atrophy	2 (4%)	5 (10%)	4 (8%)	3 (6%)
Interstitial cell, hyperplasia		4 (8%)	3 (6%)	1 (2%)
Hematopoietic System				
Blood			(1)	(1)
Polychromasia				1 (100%)
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia		8 (16%)	9 (18%)	28 (56%)
Necrosis	1 (2%)			
Lymph node	(50)	(50)	(50)	(50)
Inguinal, ectasia		1 (2%)		
Inguinal, hyperplasia		1 (2%)		
Inguinal, inflammation, granulomatous			1 (2%)	
Pancreatic, ectasia		4 (8%)	12 (24%)	24 (48%)
Pancreatic, hyperplasia		3 (6%)	2 (4%)	10 (20%)
Pancreatic, inflammation, granulomatous			1 (2%)	
Renal, ectasia				3 (6%)
Renal, hyperplasia				1 (2%)
Lymph node, bronchial	(34)	(40)	(35)	(27)
Congestion				1 (4%)
Ectasia	1 (3%)		2 (6%)	
Hyperplasia				2 (7%)
Inflammation, granulomatous			1 (3%)	
Lymph node, mandibular	(48)	(45)	(48)	(48)
Congestion				1 (2%)
Ectasia	10 (21%)	6 (13%)	7 (15%)	13 (27%)
Hyperplasia	1 (2%)	2 (4%)	1 (2%)	6 (13%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	
Inflammation, granulomatous			1 (2%)	
Lymph node, mediastinal	(48)	(45)	(48)	(45)
Congestion	1 (2%)			2 (4%)
Ectasia		5 (11%)	7 (15%)	16 (36%)
Hyperplasia		1 (2%)		9 (20%)
Inflammation, granulomatous			1 (2%)	
Pigmentation, hemosiderin			2 (4%)	1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Hematopoietic System (continued)				
Lymph node, mesenteric	(46)	(50)	(49)	(49)
Congestion		1 (2%)		
Ectasia	2 (4%)		2 (4%)	7 (14%)
Hyperplasia		1 (2%)		2 (4%)
Inflammation, granulomatous			1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Congestion	5 (10%)	16 (32%)	25 (50%)	25 (50%)
Degeneration, fatty, multifocal				1 (2%)
Fibrosis, focal	4 (8%)	4 (8%)	7 (14%)	7 (14%)
Hematopoietic cell proliferation	9 (18%)	23 (46%)	27 (54%)	30 (60%)
Inflammation, granulomatous			1 (2%)	
Necrosis, focal	1 (2%)			1 (2%)
Capsule, fibrosis, multifocal			1 (2%)	
Capsule, pigmentation, hemosiderin			1 (2%)	
Thymus	(48)	(49)	(46)	(42)
Cyst		2 (4%)		
Integumentary System				
Mammary gland	(48)	(50)	(50)	(50)
Duct, cyst	20 (42%)	24 (48%)	29 (58%)	20 (40%)
Duct, hemorrhage, focal				1 (2%)
Skin	(50)	(50)	(50)	(50)
Bacterium			1 (2%)	
Foreign body			1 (2%)	
Inflammation, subacute, focal			1 (2%)	
Inflammation, subacute, multifocal	1 (2%)			
Subcutaneous tissue, edema, focal		1 (2%)		3 (6%)
Subcutaneous tissue, inflammation, subacute, focal		1 (2%)		2 (4%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy		1 (2%)	1 (2%)	4 (8%)
Skeletal muscle		(1)		(1)
Inflammation, suppurative, acute		1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression		1 (2%)	2 (4%)	1 (2%)
Cyst	1 (2%)			
Hemorrhage, multifocal	1 (2%)	1 (2%)	3 (6%)	
Hydrocephalus		1 (2%)		
Inflammation, suppurative, acute, multifocal	1 (2%)			
Spinal cord	(1)			
Degeneration	1 (100%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Furan
(continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	6 (12%)	6 (12%)	3 (6%)	4 (8%)
Foreign body	5 (10%)	6 (12%)	4 (8%)	2 (4%)
Fungus				1 (2%)
Granuloma, multiple	9 (18%)	8 (16%)	4 (8%)	9 (18%)
Hemorrhage, focal				2 (4%)
Hemorrhage, multifocal		1 (2%)		1 (2%)
Hyperplasia	1 (2%)			
Infiltration cellular, histiocytic	1 (2%)			
Infiltration cellular, histiocytic, focal			1 (2%)	3 (6%)
Infiltration cellular, histiocytic, multifocal		2 (4%)		4 (8%)
Inflammation, granulomatous, focal				1 (2%)
Inflammation, subacute	1 (2%)			
Pigmentation, cholesterol, focal			1 (2%)	1 (2%)
Pigmentation, cholesterol, multifocal				1 (2%)
Thrombus				1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)			
Alveolar epithelium, hyperplasia, focal	2 (4%)	1 (2%)	3 (6%)	3 (6%)
Alveolar epithelium, hyperplasia, multifocal		1 (2%)		1 (2%)
Fat, mediastinum, necrosis, multifocal	1 (2%)	1 (2%)	1 (2%)	5 (10%)
Mediastinum, foreign body				1 (2%)
Mediastinum, inflammation, chronic				1 (2%)
Mediastinum, inflammation, chronic, multifocal	1 (2%)			
Pleura, fibrosis, focal	1 (2%)			
Smooth muscle, hyperplasia, focal		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Foreign body	16 (32%)	2 (4%)	6 (12%)	5 (10%)
Fungus	5 (10%)	5 (10%)	6 (12%)	4 (8%)
Hyperkeratosis, focal		1 (2%)		
Hyperplasia, squamous		1 (2%)		
Inflammation, suppurative, acute	11 (22%)	7 (14%)	8 (16%)	7 (14%)
Nasolacrimal duct, inflammation, subacute	1 (2%)	9 (18%)	2 (4%)	3 (6%)
Nasolacrimal duct, inflammation, suppurative, acute	4 (8%)	1 (2%)	1 (2%)	
Nasopharyngeal duct, cyst	1 (2%)		1 (2%)	
Nasopharyngeal duct, foreign body	1 (2%)			
Nasopharyngeal duct, fungus		1 (2%)		
Nasopharyngeal duct, hyperplasia		1 (2%)		
Nasopharyngeal duct, inflammation, subacute	1 (2%)			
Nasopharyngeal duct, inflammation, suppurative, acute		1 (2%)		
Submucosa, foreign body				1 (2%)
Submucosa, inflammation, chronic, focal				1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Furan
(continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Special Senses System				
Eye	(1)	(3)	(1)	(2)
Cataract	1 (100%)	2 (67%)		1 (50%)
Anterior chamber, inflammation, suppurative, acute		1 (33%)		
Cornea, cyst				1 (50%)
Retina, degeneration	1 (100%)	2 (67%)		2 (100%)
Harderian gland				(1)
Inflammation, chronic, focal				1 (100%)
Zymbal's gland			(1)	(1)
Inflammation, subacute				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Nephropathy, chronic	45 (90%)	44 (88%)	48 (96%)	48 (96%)
Cortex, cyst	1 (2%)	1 (2%)	2 (4%)	
Cortex, cyst, multiple				1 (2%)
Cortex, embolus bacterial	1 (2%)			
Cortex, fibrosis, focal	1 (2%)			1 (2%)
Cortex, inflammation, suppurative, acute, multifocal	1 (2%)			
Renal tubule, mineralization, multifocal		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Transitional epithelium, hyperplasia, focal			1 (2%)	

[a] Number of animals examined microscopically at site and number of animals with lesion.

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF FURAN

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TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Furan

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Natural deaths	4	1	5	10
Moribund kills	12	17	17	19
Accidental deaths				2
Survivors				
Terminal sacrifice	34	32	28	19
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(49)	(50)	(50)	(50)
Intestine large, rectum	(49)	(50)	(50)	(50)
Intestine small, duodenum	(49)	(50)	(50)	(50)
Serosa, fibrous histiocytoma				1 (2%)
Liver	(50)	(50)	(50)	(50)
Cholangiocarcinoma			2 (4%)	2 (4%)
Cholangiocarcinoma, multiple		49 (98%)	48 (96%)	46 (92%)
Fibrous histiocytoma				1 (2%)
Hepatocellular carcinoma				1 (2%)
Hepatocellular adenoma		1 (2%)	4 (8%)	6 (12%)
Hepatocellular adenoma, multiple		1 (2%)		1 (2%)
Sarcoma, metastatic, tissue NOS	1 (2%)			
Mesentery	(8)	(12)	(9)	(13)
Fibrous histiocytoma, multiple				1 (8%)
Hepatocellular carcinoma, metastatic, liver				1 (8%)
Pancreas	(50)	(49)	(50)	(50)
Adenoma			1 (2%)	
Cholangiocarcinoma, metastatic, liver				1 (2%)
Fibrous histiocytoma				1 (2%)
Pharynx	(1)			
Squamous cell carcinoma	1 (100%)			
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Papilloma squamous		1 (2%)		
Stomach, glandular	(50)	(50)	(50)	(50)
Tongue			(1)	(1)
Papilloma squamous			1 (100%)	
Cardiovascular System				
Blood vessel	(1)			(1)
Abdominal, cholangiocarcinoma, metastatic, liver				1 (100%)
Heart	(50)	(50)	(50)	(50)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Adrenal gland, medulla	(50)	(49)	(50)	(49)
Pheochromocytoma malignant		1 (2%)		2 (4%)
Pheochromocytoma complex	1 (2%)			
Pheochromocytoma benign	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Pheochromocytoma benign, multiple	1 (2%)			
Islets, pancreatic	(49)	(49)	(49)	(50)
Adenoma	1 (2%)			1 (2%)
Pituitary gland	(50)	(50)	(49)	(49)
Pars distalis, adenoma	26 (52%)	26 (52%)	25 (51%)	19 (39%)
Pars distalis, adenoma, multiple	2 (4%)			1 (2%)
Thyroid gland	(50)	(50)	(50)	(49)
C-cell, adenoma	8 (16%)	4 (8%)	5 (10%)	2 (4%)
C-cell, carcinoma	1 (2%)	1 (2%)		
Follicular cell, adenocarcinoma		1 (2%)	1 (2%)	
General Body System				
Tissue NOS	(1)			
Abdominal, sarcoma	1 (100%)			
Genital System				
Clitoral gland	(43)	(48)	(50)	(47)
Adenoma	3 (7%)	7 (15%)	5 (10%)	2 (4%)
Carcinoma			2 (4%)	1 (2%)
Papilloma squamous		1 (2%)		
Ovary	(50)	(50)	(50)	(50)
Fibrous histiocytoma				1 (2%)
Granulosa cell neoplasm malignant		2 (4%)		
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Adenocarcinoma	1 (2%)			1 (2%)
Adenoma		1 (2%)		2 (4%)
Polyp stromal	9 (18%)	12 (24%)	13 (26%)	7 (14%)
Polyp stromal, multiple	1 (2%)		1 (2%)	2 (4%)
Sarcoma stromal	1 (2%)	1 (2%)		
Cervix, sarcoma			1 (2%)	
Vagina	(2)	(1)	(2)	
Polyp	2 (100%)			
Sarcoma		1 (100%)	1 (50%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Hematopoietic System				
Blood	(2)		(2)	
Bone marrow	(50)	(50)	(50)	(50)
Fibrous histiocytoma				1 (2%)
Lymph node	(50)	(50)	(50)	(50)
Axillary, adenocarcinoma, metastatic, mammary gland		1 (2%)		
Lymph node, bronchial	(27)	(43)	(42)	(30)
Fibrous histiocytoma				1 (3%)
Lymph node, mandibular	(47)	(48)	(47)	(46)
Fibrous histiocytoma				1 (2%)
Lymph node, mediastinal	(48)	(48)	(49)	(49)
Fibrous histiocytoma				1 (2%)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Pancreatic, cholangiocarcinoma, metastatic, liver				1 (2%)
Lymph node, mesenteric	(48)	(50)	(50)	(48)
Fibrous histiocytoma				1 (2%)
Spleen	(50)	(50)	(50)	(50)
Fibrous histiocytoma				1 (2%)
Thymus	(47)	(46)	(47)	(43)
Fibrous histiocytoma				1 (2%)
Mediastinum, carcinoma, metastatic, Zymbal's gland			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(49)	(50)
Adenocarcinoma	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Adenocarcinoma, multiple		1 (2%)		
Adenoma			2 (4%)	1 (2%)
Fibroadenoma	14 (28%)	13 (26%)	16 (33%)	12 (24%)
Fibroadenoma, multiple	1 (2%)	4 (8%)	2 (4%)	2 (4%)
Skin	(50)	(50)	(50)	(50)
Fibroma		1 (2%)		
Keratoacanthoma			1 (2%)	
Papilloma squamous		1 (2%)		
Musculoskeletal System				
Skeletal muscle		(1)		(1)
Rhabdomyosarcoma		1 (100%)		
Diaphragm, hepatocellular carcinoma, metastatic, liver				1 (100%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant				1 (2%)
Fibrous histiocytoma				1 (2%)
Glioma malignant		1 (2%)		
Granular cell neoplasm malignant			1 (2%)	
Oligodendroglioma malignant		1 (2%)		
Spinal cord	(1)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma	1 (2%)			
Carcinoma, metastatic, Zymbal's gland			1 (2%)	
Fibrous histiocytoma				1 (2%)
Sarcoma, metastatic, tissue NOS	1 (2%)			
Sarcoma stromal, metastatic, uterus	1 (2%)			
Mediastinum, fibrous histiocytoma				1 (2%)
Venule, mediastinum, cholangiocarcinoma, metastatic, liver				1 (2%)
Nose	(50)	(50)	(50)	(50)
Papilloma squamous			1 (2%)	
Squamous cell carcinoma			1 (2%)	
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Ear		(2)		
Fibrosarcoma		1 (50%)		
Pinna, sarcoma		1 (50%)		
Harderian gland	(2)		(1)	(1)
Lacrimal gland	(1)		(1)	
Squamous cell carcinoma, metastatic, pharynx	1 (100%)			
Zymbal's gland	(1)		(1)	
Carcinoma	1 (100%)		1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Fibrous histiocytoma				1 (2%)
Sarcoma			1 (2%)	
Urinary bladder	(49)	(50)	(49)	(50)
Transitional epithelium, papilloma				3 (6%)
Systemic Lesions				
Multiple organs[a]	(50)	(50)	(50)	(50)
Leukemia mononuclear	8 (16%)	9 (18%)	17 (34%)	21 (42%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[b]	45	50	50	50
Total primary neoplasms	86	149	157	156
Total animals with benign neoplasms	42	41	41	37
Total benign neoplasms	69	76	78	64
Total animals with malignant neoplasms	16	50	50	50
Total malignant neoplasms	17	73	79	92
Total animals with metastatic neoplasms	3	1	1	3
Total metastatic neoplasms	4	1	2	9

[a] Number of animals with any tissue examined microscopically
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: Vehicle Control

Number of Days on Study	470	528	537	556	605	605	655	659	666	668	668	687	688	688	695	714	729	729	729	729	729	729	729	729	729
Carcass ID Number	44111	41112	48122	41222	43111	48111	49111	47112	49123	49123	42121	47122	43222	44222	45121	41133	41133	41144	42155	42223	42234	42245	43353	43383
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, tissue NOS											X														
Mesentery												+			+	+	+					+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx						+																			
Squamous cell carcinoma						X																			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex													X												
Pheochromocytoma benign																				X					
Pheochromocytoma benign, multiple												X													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X		X	X		X	X					X	X	X	X			X				X	X	
Pars distalis, adenoma, multiple						X														X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X								X							
C-cell, carcinoma																					X				

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 3 4	4 3 5	4 4 4	4 4 5	4 5 2	4 5 3	4 5 4	4 5 5	4 6 1	4 6 2	4 6 3	4 6 4	4 6 5	4 7 3	4 7 4	4 7 5	4 8 4	4 8 5	4 9 4	4 9 5	5 0 1	5 0 2	5 0 3	5 0 4	5 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, tissue NOS																										1
Mesentery				+					+						+											8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																										1
Squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel									+																	1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex																										1
Pheochromocytoma benign																										1
Pheochromocytoma benign, multiple																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X																			1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X					X	X		X	X			X						X	X	X	X	X		26
Pars distalis, adenoma, multiple																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X					X							X					X				X			X		8
C-cell, carcinoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	4 7 0	5 2 8	5 3 7	5 5 6	6 0 5	6 0 5	6 5 5	6 5 9	6 6 5	6 6 6	6 8 4	6 8 7	6 8 8	6 8 8	6 9 5	7 1 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	4 4 1	4 1 1	4 8 2	4 1 2	4 3 1	4 8 1	4 9 1	4 7 1	4 9 2	4 9 3	4 2 1	4 7 2	4 3 2	4 4 2	4 5 1	4 4 3	4 1 3	4 1 4	4 1 5	4 2 2	4 2 3	4 2 4	4 2 5	4 3 3	4 8 3
General Body System																									
Tissue NOS											+														
Abdominal, sarcoma											X														
Genital System																									
Clitoral gland	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+
Adenoma								X																	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																							X		
Polyp stromal		X					X				X		X		X				X						
Polyp stromal, multiple																									
Sarcoma stromal																			X						
Vagina																									
Polyp																									
Hematopoietic System																									
Blood				+											+										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	+	M	+	+	M	M	M	+	M	+	M	+	+	+	M	+	M	+	M	M	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma									X				X	X	X				X	X	X			X	
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord									+																

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 3 4	4 3 5	4 4 4	4 4 5	4 5 2	4 5 3	4 5 4	4 5 5	4 6 1	4 6 2	4 6 3	4 6 4	4 6 5	4 7 3	4 7 4	4 7 5	4 8 4	4 8 5	4 9 4	4 9 5	5 0 1	5 0 2	5 0 3	5 0 4	5 0 5	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										1
Abdominal, sarcoma																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	43
Adenoma								X														X				3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Polyp stromal					X					X						X										9
Polyp stromal, multiple																	X									1
Sarcoma stromal																										1
Vagina													+					+								2
Polyp													X					X								2
Hematopoietic System																										
Blood																										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	M	+	+	M	M	+	M	M	+	+	M	+	+	+	M	+	+	+	M	M	M	M	+	M	M	27
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	48
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																						X				1
Fibroadenoma												X		X			X		X			X	X		14
Fibroadenoma, multiple										X																1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	470	528	537	556	605	605	655	659	665	666	684	687	688	688	695	714	729	729	729	729	729	729	729	729	729
Carcass ID Number	4411	4411	4812	4822	4931	4881	4891	4971	4992	4993	4921	4972	4932	4942	4951	4913	4913	4941	4951	4922	4923	4924	4925	4933	4883
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																							X		
Sarcoma, metastatic, tissue NOS											X														
Sarcoma stromal, metastatic, uterus																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye		+				+																			
Harderian gland																		+			+				
Lacrimal gland						+																			
Squamous cell carcinoma, metastatic, pharynx						X																			
Zymbal's gland																									+
Carcinoma																									X
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X				X	X		X			X	X	X								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 3 4	4 3 5	4 4 4	4 4 5	4 5 2	4 5 3	4 5 4	4 5 5	4 6 1	4 6 2	4 6 3	4 6 4	4 6 5	4 7 3	4 7 4	4 7 5	4 8 4	4 8 5	4 9 4	4 9 5	5 0 1	5 0 2	5 0 3	5 0 4	5 0 5	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Sarcoma, metastatic, tissue NOS																										1
Sarcoma stromal, metastatic, uterus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Harderian gland																										2
Lacrimal gland																										1
Squamous cell carcinoma, metastatic, pharynx																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										8

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 2 mg/kg

Number of Days on Study	3 6 4	4 3 6	4 7 8	5 4 1	5 6 1	5 7 5	5 7 5	6 0 2	6 1 7	6 3 9	6 4 2	6 5 9	6 6 5	6 6 7	6 8 8	6 8 9	6 9 7	7 0 3	7 2 9	7 3 3	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	7 4 1	7 7 1	7 6 1	7 2 1	7 3 1	7 1 1	7 6 2	7 7 2	7 5 1	7 2 2	7 9 1	7 6 3	7 9 2	7 4 2	7 2 3	7 7 3	7 2 4	7 9 3	7 4 3	7 8 1	7 1 2	7 1 3	7 1 4	7 1 5	7 2 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, multiple		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																	X								
Mesentery							+			+					+	+			+	+		+	+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																							X		
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X							X			X	X	X	X	X				X		X	X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																						X			
C-cell, carcinoma							X																		
Follicular cell, adenocarcinoma											X														

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 2 mg/kg (continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	7 3 2	7 3 3	7 3 4	7 3 5	7 4 4	7 4 5	7 5 2	7 5 3	7 5 4	7 5 5	7 6 4	7 6 5	7 7 4	7 7 5	7 8 2	7 8 3	7 8 4	7 8 5	7 9 4	7 9 5	8 0 1	8 0 2	8 0 3	8 0 4	8 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	49
Hepatocellular adenoma																				X						1
Hepatocellular adenoma, multiple																										1
Mesentery							+									+				+			+			12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous					X																					1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										1
Pheochromocytoma benign															X					X				X		3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X				X	X		X	X	X	X			X	X			X	X	X	X		26
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma															X				X			X				4
C-cell, carcinoma																										1
Follicular cell, adenocarcinoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 2 mg/kg (continued)

Number of Days on Study	3 6 4	4 3 6	4 7 8	5 4 1	5 6 1	5 7 5	5 7 5	6 0 2	6 1 7	6 3 9	6 4 2	6 5 9	6 6 5	6 6 7	6 8 8	6 8 9	6 9 7	7 0 3	7 2 9	7 3 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	7 4 1	7 7 1	7 6 1	7 2 1	7 3 1	7 1 1	7 6 2	7 7 2	7 5 1	7 2 2	7 9 1	7 6 3	7 9 2	7 4 2	7 2 3	7 7 3	7 2 4	7 9 3	7 4 3	7 8 1	7 1 2	7 1 3	7 1 4	7 1 5	7 2 5
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenoma										X												X			
Papilloma squamous																		X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Polyp stromal														X										X	
Sarcoma stromal										X															
Vagina						+																			
Sarcoma						X																			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, adenocarcinoma, metastatic, mammary gland												X													
Lymph node, bronchial	M	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mediastinal	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																							X		X
Adenocarcinoma, multiple												X													
Fibroadenoma				X	X				X				X	X		X				X		X			
Fibroadenoma, multiple															X				X						X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma															X										
Papilloma squamous																			X						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 2 mg/kg (continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	7 3 2	7 3 3	7 3 4	7 3 5	7 4 4	7 4 5	7 5 2	7 5 3	7 5 4	7 5 5	7 6 4	7 6 5	7 7 4	7 7 5	7 8 2	7 8 3	7 8 4	7 8 5	7 9 4	7 9 5	8 0 1	8 0 2	8 0 3	8 0 4	8 0 5	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma		X	X					X													X			X		7
Papilloma squamous																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant																X									X	2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Polyp stromal				X	X			X						X	X	X						X	X	X	X	12
Sarcoma stromal																										1
Vagina																										1
Sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, adenocarcinoma, metastatic, mammary gland																										1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	43
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Lymph node, mesenteric																										50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										2
Adenocarcinoma, multiple																										1
Fibroadenoma		X	X			X				X						X										13
Fibroadenoma, multiple																			X							4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Papilloma squamous																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 2 mg/kg (continued)

Number of Days on Study	3 6 4	4 3 6	4 7 8	5 4 1	5 6 1	5 7 5	5 7 5	6 0 2	6 1 7	6 3 9	6 4 2	6 5 9	6 6 5	6 6 7	6 8 8	6 8 9	6 9 7	7 0 3	7 2 9	7 3 3	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	7 4 1	7 7 1	7 6 1	7 2 1	7 3 1	7 1 1	7 6 2	7 7 2	7 5 1	7 2 2	7 9 1	7 6 3	7 9 2	7 4 2	7 2 3	7 7 3	7 2 4	7 9 3	7 4 3	7 8 1	7 1 2	7 1 3	7 1 4	7 1 5	7 2 5
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																						
Rhabdomyosarcoma			X																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant																							X		
Oligodendroglioma malignant	X																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear			+																						
Fibrosarcoma			X																						
Pinna, sarcoma																									
Eye															+										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X		X		X				X									X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 2 mg/kg (continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	7 3 2	7 3 3	7 3 4	7 3 5	7 4 4	7 4 5	7 5 2	7 5 3	7 5 4	7 5 5	7 6 4	7 6 5	7 7 4	7 7 5	7 8 2	7 8 3	7 8 4	7 8 5	7 9 4	7 9 5	8 0 1	8 0 2	8 0 3	8 0 4	8 0 5	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																										1
Oligodendroglioma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear														+												2
Fibrosarcoma																										1
Pinna, sarcoma														X												1
Eye													+											+		3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X									X				X									X			9

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 4 mg/kg

Number of Days on Study	3 8 8	4 0 2	4 2 1	4 6 2	5 4 1	5 4 9	5 5 7	5 6 1	5 9 1	6 2 7	6 2 7	6 3 5	6 5 4	6 5 5	6 6 6	6 8 8	6 8 8	6 9 1	7 0 2	7 0 3	7 0 8	7 1 4	7 2 9	7 2 9	7 2 9
Carcass ID Number	6 5 1	6 9 1	6 3 1	6 8 1	6 2 1	6 5 2	6 2 2	6 2 3	6 8 2	6 1 1	7 0 1	6 6 1	6 1 2	6 3 2	7 0 2	6 5 3	6 7 1	6 9 2	6 3 3	6 3 4	6 5 4	6 9 3	6 3 5	6 4 1	6 7 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma	X		X																						
Cholangiocarcinoma, multiple		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatocellular adenoma																	X								
Mesentery					+		+	+			+				+								+	+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																								+	
Papilloma squamous																								X	
Tooth																			+						
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X						X					X	X	X	X	X	X			X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenocarcinoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 4 mg/kg (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	6 1 3	6 1 4	6 1 5	6 2 4	6 2 5	6 4 2	6 4 3	6 4 4	6 4 5	6 5 5	6 6 2	6 6 3	6 6 4	6 6 5	6 7 3	6 7 4	6 7 5	6 8 3	6 8 4	6 8 5	6 9 4	6 9 5	7 0 3	7 0 4	7 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																										2
Cholangiocarcinoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	48
Hepatocellular adenoma									X							X						X				4
Mesentery													+											+		9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Papilloma squamous																										1
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign									X																	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X				X	X		X	X	X	X		X	X		X	X	X				X	X		X	25
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma									X		X		X				X							X		5
Follicular cell, adenocarcinoma					X																					1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 4 mg/kg (continued)

Number of Days on Study	3 8 8	4 0 2	4 2 1	4 6 2	5 4 1	5 4 9	5 5 7	5 6 1	5 9 1	6 2 7	6 2 7	6 3 5	6 5 4	6 5 5	6 6 8	6 8 8	6 8 8	6 9 1	7 0 2	7 0 3	7 0 8	7 1 4	7 2 9	7 2 9
Carcass ID Number	6 5 1	6 9 1	6 3 1	6 8 1	6 2 1	6 5 2	6 2 2	6 2 3	6 8 2	6 1 1	7 0 1	6 6 1	6 1 2	6 3 2	7 0 2	6 5 3	6 7 1	6 9 2	6 3 3	6 3 4	6 5 4	6 9 3	6 3 5	6 4 1	6 7 2
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X					X											
Carcinoma	X																							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal							X		X		X	X					X	X		X				
Polyp stromal, multiple													X											
Cervix, sarcoma			X																					
Vagina																					+		+	
Sarcoma																					X			
Hematopoietic System																								
Blood							+		+															
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	M	M	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mediastinal	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Mediastinum, carcinoma, metastatic, Zymbal's gland																			X					
Integumentary System																								
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma					X																X			
Adenoma											X											X		
Fibroadenoma						X		X				X					X		X	X				
Fibroadenoma, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 4 mg/kg (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	6 1 3	6 1 4	6 1 5	6 2 4	6 2 5	6 4 2	6 4 3	6 4 4	6 4 5	6 5 5	6 6 2	6 6 3	6 6 4	6 6 5	6 7 3	6 7 4	6 7 5	6 8 3	6 8 4	6 8 5	6 9 4	6 9 5	7 0 3	7 0 4	7 0 5	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X		X												X											5
Carcinoma																									X	2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X	X		X			X										X		X			13
Polyp stromal, multiple																										1
Cervix, sarcoma																										1
Vagina																										2
Sarcoma																										1
Hematopoietic System																										
Blood																										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	42
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mediastinum, carcinoma, metastatic, Zymbal's gland																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																		X								3
Adenoma																										2
Fibroadenoma		X					X		X	X		X	X		X	X				X					X	16
Fibroadenoma, multiple																	X					X				2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma					X																					1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 4 mg/kg (continued)

Number of Days on Study	3 8 8	4 0 2	4 2 1	4 6 2	5 4 1	5 4 9	5 5 7	5 6 1	5 9 1	6 2 7	6 2 7	6 3 5	6 5 4	6 5 5	6 6 6	6 8 8	6 8 8	6 9 1	7 0 2	7 0 3	7 0 8	7 1 4	7 2 9	7 2 9
Carcass ID Number	6 5 1	6 9 1	6 3 1	6 8 1	6 2 1	6 5 2	6 2 2	6 2 3	6 8 2	6 1 1	7 0 1	6 6 1	6 1 2	6 3 2	7 0 2	6 5 3	6 7 1	6 9 2	6 3 3	6 3 4	6 5 4	6 9 3	6 3 5	6 4 1	6 7 2
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor malignant																								
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																			X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous				X																				
Squamous cell carcinoma						X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye						+																		
Harderian gland																	+							
Lacrimal gland						+																		
Zymbal's gland																			+					
Carcinoma																			X					
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma										X														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X		X		X	X			X	X		X	X			X	X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 4 mg/kg (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	6 1 3	6 1 4	6 1 5	6 2 4	6 2 5	6 4 2	6 4 3	6 4 4	6 4 5	6 5 5	6 6 2	6 6 3	6 6 4	6 6 5	6 7 3	6 7 4	6 7 5	6 8 3	6 8 4	6 8 5	6 9 4	6 9 5	7 0 3	7 0 4	7 0 5	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor malignant																	X									1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																										1
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye							+																			2
Harderian gland																										1
Lacrimal gland																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X					X			X	X										X		X			X	17

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 8 mg/kg

Number of Days on Study	1 4 3	2 3 8	3 3 9	4 2 4	4 5 7	4 7 1	5 1 1	5 2 1	5 3 2	5 4 9	5 7 5	5 8 3	5 9 2	5 9 6	5 9 8	6 1 3	6 2 3	6 2 7	6 3 3	6 4 4	6 6 3	6 6 4	6 6 5	6 6 5	6 8 9
Carcass ID Number	5 3 1	5 8 1	5 6 1	5 5 1	5 5 2	5 6 2	5 6 3	5 4 1	5 3 2	5 6 4	6 0 1	6 0 2	5 7 1	5 1 1	5 2 1	5 2 2	6 0 3	6 0 4	5 7 2	5 1 2	5 5 5	5 5 3	5 2 3	6 0 5	5 3 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, fibrous histiocytoma													X												
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma	X		X																						
Cholangiocarcinoma, multiple				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Fibrous histiocytoma													X												
Hepatocellular carcinoma																						X			
Hepatocellular adenoma																				X					
Hepatocellular adenoma, multiple																									
Mesentery				+									+						+	+		+			
Fibrous histiocytoma, multiple													X												
Hepatocellular carcinoma, metastatic, liver																						X			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver																									
Fibrous histiocytoma													X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue	+																								
Cardiovascular System																									
Blood vessel																									
Abdominal, cholangiocarcinoma, metastatic, liver																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																						X			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	6 9 3 6	6 9 3 7	6 9 3 8	7 0 1 1	7 1 1 6	7 1 1 8	7 2 2 9	7 3 3 0	7 3 3 0	7 3 3 0	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1	
Carcass ID Number	5 4 4 2	5 4 4 3	5 4 4 4	5 8 4 2	5 5 4 4	5 7 4 3	5 9 4 1	5 1 4 3	5 1 4 4	5 1 4 5	5 2 4 4	5 2 4 5	5 3 4 4	5 3 4 5	5 4 4 5	5 5 4 5	5 7 4 4	5 7 4 5	5 8 4 3	5 8 4 4	5 8 4 5	5 9 4 2	5 9 4 3	5 9 4 4	5 9 4 5	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Serosa, fibrous histiocytoma																									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																									2
Cholangiocarcinoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	46
Fibrous histiocytoma																									1
Hepatocellular carcinoma																									1
Hepatocellular adenoma											X			X		X							X	X	6
Hepatocellular adenoma, multiple								X																	1
Mesentery	+			+		+					+	+	+					+				+			13
Fibrous histiocytoma, multiple																									1
Hepatocellular carcinoma, metastatic, liver																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, metastatic, liver					X																				1
Fibrous histiocytoma																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																									1
Cardiovascular System																									
Blood vessel						+																			1
Abdominal, cholangiocarcinoma, metastatic, liver						X																			1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	1 4 3	2 3 8	3 3 9	4 2 4	4 5 7	4 7 1	5 1 1	5 2 1	5 3 2	5 4 9	5 7 5	5 8 3	5 9 2	5 9 6	5 9 8	6 1 3	6 2 3	6 2 7	6 3 3	6 4 4	6 6 3	6 6 4	6 6 5	6 6 5	6 8 9
Carcass ID Number	5 3 1	5 8 1	5 6 1	5 5 1	5 5 2	5 6 2	5 6 3	5 4 1	5 3 2	5 6 4	6 0 1	6 0 2	5 7 1	5 1 1	5 2 1	5 2 2	6 0 3	6 0 4	5 7 2	5 1 2	5 6 5	5 5 3	5 2 3	6 0 5	5 3 3
Endocrine System (continued)																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pheochromocytoma malignant									X						X										
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pars distalis, adenoma										X		X		X	X										X
Pars distalis, adenoma, multiple																					X				
Thyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+
Adenoma																									
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma													X												
Hepatocellular carcinoma, metastatic, liver																						X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma			X																						
Adenoma									X																
Polyp stromal					X									X						X		X	X		
Polyp stromal, multiple																		X							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma													X												
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	M	+	+	M	+	+	+	M
Fibrous histiocytoma													X												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Fibrous histiocytoma													X												
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma													X												
Hepatocellular carcinoma, metastatic, liver																						X			
Pancreatic, cholangiocarcinoma, metastatic, liver																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Fibrous histiocytoma													X												
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma													X												
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M
Fibrous histiocytoma													X												

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	6 9 6	6 9 7	6 9 8	7 0 1	7 1 6	7 1 8	7 2 9	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 4 2	5 4 3	5 4 4	5 8 2	5 5 4	5 7 3	5 9 1	5 1 3	5 1 4	5 1 5	5 2 4	5 2 5	5 3 4	5 3 5	5 4 5	5 5 5	5 7 4	5 7 5	5 8 3	5 8 4	5 8 5	5 9 2	5 9 3	5 9 4	5 9 5	Total Tissues/ Tumors
Endocrine System (continued)																										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										2
Pheochromocytoma benign	X																	X	X							3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Parathyroid gland	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X			X	X			X			X		X	X		X	X			X	X	X	X	19
Pars distalis, adenoma, multiple																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma				X																	X					2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Adenoma					X																			X		2
Carcinoma																						X				1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Hepatocellular carcinoma, metastatic, liver																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Adenoma													X													2
Polyp stromal								X																	X	7
Polyp stromal, multiple																					X					2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	M	M	+	+	M	+	+	M	M	+	+	+	+	M	+	M	M	M	M	M	M	M	+	M	+	+	30
Fibrous histiocytoma																										1
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibrous histiocytoma																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Fibrous histiocytoma																										1
Hepatocellular carcinoma, metastatic, liver																										1
Pancreatic, cholangio-carcinoma, metastatic, liver					X																					1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrous histiocytoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	M	M	+	43
Fibrous histiocytoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	1 4 3	2 3 8	3 3 9	4 2 4	4 5 7	4 7 1	5 1 1	5 2 1	5 3 2	5 4 9	5 7 5	5 8 3	5 9 2	5 9 6	5 9 8	6 1 3	6 2 3	6 2 7	6 3 3	6 4 4	6 6 3	6 6 4	6 6 5	6 6 5	6 8 9
Carcass ID Number	5 3 1	5 8 1	5 6 1	5 5 1	5 5 2	5 6 2	5 6 3	5 4 1	5 3 2	5 6 4	6 0 1	6 0 2	5 7 1	5 1 1	5 2 1	5 2 2	6 0 3	6 0 4	5 7 2	5 1 2	5 6 5	5 5 3	5 2 3	6 0 5	5 3 3
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma										X															
Fibroadenoma								X											X				X	X	X
Fibroadenoma, multiple															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																						+			
Diaphragm, hepatocellular carcinoma, metastatic, liver																						X			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant					X																				
Fibrous histiocytoma													X												
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma													X												
Mediastinum, fibrous histiocytoma													X												
Venule, mediastinum, cholangiocarcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																			+						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma													X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X		X	X					X		X					X	X				X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	6 9 6	6 9 7	6 9 8	7 0 1	7 1 6	7 1 8	7 2 9	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 4 2	5 4 3	5 4 4	5 8 2	5 5 4	5 7 3	5 9 1	5 1 3	5 1 4	5 1 5	5 2 4	5 2 5	5 3 4	5 3 5	5 4 5	5 5 5	5 7 4	5 7 5	5 8 3	5 8 4	5 8 5	5 9 2	5 9 3	5 9 4	5 9 5	**Total Tissues/ Tumors**
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma					X																					1
Adenoma																										1
Fibroadenoma					X		X	X					X						X		X			X		12
Fibroadenoma, multiple				X																						2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Diaphragm, hepatocellular carcinoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Fibrous histiocytoma																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Mediastinum, fibrous histiocytoma																										1
Venule, mediastinum, cholangiocarcinoma, metastatic, liver					X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma								X						X										X		3
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X				X			X			X	X							X	X	X		21

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Furan

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	2/50 (4%)	3/49 (6%)	1/50 (2%)	3/49 (6%)
Adjusted rates[b]	5.4%	9.4%	3.6%	14.1%
Terminal rates[c]	1/34 (3%)	3/32 (9%)	1/28 (4%)	2/19 (11%)
First incidence (days)	687	729 (T)	729 (T)	696
Life table tests[d]	P=0.250	P=0.471	P=0.557N	P=0.285
Logistic regression tests[d]	P=0.302	P=0.467	P=0.539N	P=0.344
Cochran-Armitage test[d]	P=0.471			
Fisher exact test[d]		P=0.490	P=0.500N	P=0.490
Adrenal Medulla: Pheochromocytoma (Benign, Complex, or Malignant)				
Overall rates	3/50 (6%)	4/49 (8%)	1/50 (2%)	5/49 (10%)
Adjusted rates	7.9%	12.5%	3.6%	18.5%
Terminal rates	1/34 (3%)	4/32 (13%)	1/28 (4%)	2/19 (11%)
First incidence (days)	687	729 (T)	729 (T)	532
Life table tests	P=0.135	P=0.466	P=0.360N	P=0.172
Logistic regression tests	P=0.246	P=0.463	P=0.335N	P=0.316
Cochran-Armitage test	P=0.324			
Fisher exact test		P=0.489	P=0.309N	P=0.346
Clitoral Gland: Adenoma				
Overall rates	3/43 (7%)	7/48 (15%)	5/50 (10%)	2/47 (4%)
Adjusted rates	9.1%	21.3%	15.1%	10.1%
Terminal rates	2/29 (7%)	6/31 (19%)	3/28 (11%)	1/18 (6%)
First incidence (days)	659	639	561	716
Life table tests	P=0.511N	P=0.174	P=0.321	P=0.659
Logistic regression tests	P=0.337N	P=0.178	P=0.429	P=0.607N
Cochran-Armitage test	P=0.222N			
Fisher exact test		P=0.207	P=0.445	P=0.457N
Clitoral Gland: Adenoma or Carcinoma				
Overall rates	3/43 (7%)	7/48 (15%)	7/50 (14%)	3/47 (6%)
Adjusted rates	9.1%	21.3%	20.1%	15.3%
Terminal rates	2/29 (7%)	6/31 (19%)	4/28 (14%)	2/18 (11%)
First incidence (days)	659	639	388	716
Life table tests	P=0.403	P=0.174	P=0.141	P=0.440
Logistic regression tests	P=0.478N	P=0.178	P=0.266	P=0.542
Cochran-Armitage test	P=0.389N			
Fisher exact test		P=0.207	P=0.227	P=0.618N
Liver: Cholangiocarcinoma				
Overall rates	0/50 (0%)	49/50 (98%)	50/50 (100%)	48/50 (96%)
Adjusted rates	0.0%	100.0%	100.0%	100.0%
Terminal rates	0/34 (0%)	32/32 (100%)	28/28 (100%)	19/19 (100%)
First incidence (days)	–[e]	436	388	143
Life table tests	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Liver: Hepatocellular Adenoma				
Overall rates	0/50 (0%)	2/50 (4%)	4/50 (8%)	7/50 (14%)
Adjusted rates	0.0%	6.0%	13.3%	33.8%
Terminal rates	0/34 (0%)	1/32 (3%)	3/28 (11%)	6/19 (32%)
First incidence (days)	–	697	688	644
Life table tests	P<0.001	P=0.230	P=0.045	P<0.001
Logistic regression tests	P<0.001	P=0.224	P=0.048	P=0.002
Cochran-Armitage test	P=0.003			
Fisher exact test		P=0.247	P=0.059	P=0.006
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	0/50 (0%)	2/50 (4%)	4/50 (8%)	8/50 (16%)
Adjusted rates	0.0%	6.0%	13.3%	36.1%
Terminal rates	0/34 (0%)	1/32 (3%)	3/28 (11%)	6/19 (32%)
First incidence (days)	–	697	688	644
Life table tests	P<0.001	P=0.230	P=0.045	P<0.001
Logistic regression tests	P<0.001	P=0.224	P=0.048	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.247	P=0.059	P=0.003
Mammary Gland: Fibroadenoma				
Overall rates	15/50 (30%)	17/50 (34%)	18/50 (36%)	14/50 (28%)
Adjusted rates	39.2%	42.5%	51.6%	48.9%
Terminal rates	11/34 (32%)	10/32 (31%)	12/28 (43%)	6/19 (32%)
First incidence (days)	665	541	549	521
Life table tests	P=0.112	P=0.351	P=0.171	P=0.148
Logistic regression tests	P=0.417	P=0.370	P=0.231	P=0.395
Cochran-Armitage test	P=0.419N			
Fisher exact test		P=0.415	P=0.335	P=0.500N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rates	15/50 (30%)	17/50 (34%)	20/50 (40%)	15/50 (30%)
Adjusted rates	39.2%	42.5%	55.7%	50.2%
Terminal rates	11/34 (32%)	10/32 (31%)	13/28 (46%)	6/19 (32%)
First incidence (days)	665	541	549	521
Life table tests	P=0.065	P=0.351	P=0.089	P=0.107
Logistic regression tests	P=0.325	P=0.370	P=0.125	P=0.347
Cochran-Armitage test	P=0.531N			
Fisher exact test		P=0.415	P=0.201	P=0.586N
Mammary Gland: Adenocarcinoma				
Overall rates	1/50 (2%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rates	2.9%	8.7%	8.9%	4.8%
Terminal rates	1/34 (3%)	2/32 (6%)	1/28 (4%)	0/19 (0%)
First incidence (days)	729 (T)	659	541	716
Life table tests	P=0.502	P=0.282	P=0.257	P=0.638
Logistic regression tests	P=0.564N	P=0.285	P=0.312	P=0.665
Cochran-Armitage test	P=0.500N			
Fisher exact test		P=0.309	P=0.309	P=0.753N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Mammary Gland: Fibroadenoma, Adenoma or Adenocarcinoma				
Overall rates	15/50 (30%)	18/50 (36%)	23/50 (46%)	15/50 (30%)
Adjusted rates	39.2%	44.0%	61.0%	50.2%
Terminal rates	11/34 (32%)	10/32 (31%)	14/28 (50%)	6/19 (32%)
First incidence (days)	665	541	541	521
Life table tests	P=0.061	P=0.282	P=0.029	P=0.107
Logistic regression tests	P=0.334	P=0.297	P=0.042	P=0.347
Cochran-Armitage test	P=0.530N			
Fisher exact test		P=0.335	P=0.074	P=0.586N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	28/50 (56%)	26/50 (52%)	25/49 (51%)	20/49 (41%)
Adjusted rates	61.6%	66.1%	68.7%	69.4%
Terminal rates	17/34 (50%)	19/32 (59%)	16/27 (59%)	11/19 (58%)
First incidence (days)	470	436	541	549
Life table tests	P=0.266	P=0.546N	P=0.441	P=0.365
Logistic regression tests	P=0.264N	P=0.449N	P=0.473N	P=0.241N
Cochran-Armitage test	P=0.075N			
Fisher exact test		P=0.421N	P=0.384N	P=0.095N
Thyroid Gland (C-cell): Adenoma				
Overall rates	8/50 (16%)	4/50 (8%)	5/50 (10%)	2/49 (4%)
Adjusted rates	22.5%	12.5%	17.9%	9.6%
Terminal rates	7/34 (21%)	4/32 (13%)	5/28 (18%)	1/19 (5%)
First incidence (days)	666	729 (T)	729 (T)	701
Life table tests	P=0.199N	P=0.208N	P=0.407N	P=0.213N
Logistic regression tests	P=0.148N	P=0.212N	P=0.373N	P=0.143N
Cochran-Armitage test	P=0.050N			
Fisher exact test		P=0.178N	P=0.277N	P=0.049N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	9/50 (18%)	5/50 (10%)	5/50 (10%)	2/49 (4%)
Adjusted rates	25.4%	14.4%	17.9%	9.6%
Terminal rates	8/34 (24%)	4/32 (13%)	5/28 (18%)	1/19 (5%)
First incidence (days)	666	575	729 (T)	701
Life table tests	P=0.122N	P=0.228N	P=0.309N	P=0.157N
Logistic regression tests	P=0.070N	P=0.225N	P=0.278N	P=0.100N
Cochran-Armitage test	P=0.025N			
Fisher exact test		P=0.194N	P=0.194N	P=0.028N
Urinary Bladder: Papilloma				
Overall rates	0/49 (0%)	0/50 (0%)	0/49 (0%)	3/50 (6%)
Adjusted rates	0.0%	0.0%	0.0%	15.8%
Terminal rates	0/34 (0%)	0/32 (0%)	0/27 (0%)	3/19 (16%)
First incidence (days)	–	–	–	729 (T)
Life table tests	P=0.002	–	–	P=0.040
Logistic regression tests	P=0.002	–	–	P=0.040
Cochran-Armitage test	P=0.012			
Fisher exact test		–	–	P=0.125

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Uterus: Stromal Polyp				
Overall rates	10/50 (20%)	12/50 (24%)	14/50 (28%)	9/50 (18%)
Adjusted rates	24.6%	36.1%	36.8%	30.0%
Terminal rates	5/34 (15%)	11/32 (34%)	6/28 (21%)	3/19 (16%)
First incidence (days)	528	667	557	457
Life table tests	P=0.211	P=0.344	P=0.157	P=0.318
Logistic regression tests	P=0.540N	P=0.356	P=0.243	P=0.526N
Cochran-Armitage test	P=0.421N			
Fisher exact test		P=0.405	P=0.241	P=0.500N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rates	10/50 (20%)	13/50 (26%)	14/50 (28%)	9/50 (18%)
Adjusted rates	24.6%	37.7%	36.8%	30.0%
Terminal rates	5/34 (15%)	11/32 (34%)	6/28 (21%)	3/19 (16%)
First incidence (days)	528	639	557	457
Life table tests	P=0.233	P=0.266	P=0.157	P=0.318
Logistic regression tests	P=0.499N	P=0.278	P=0.243	P=0.526N
Cochran-Armitage test	P=0.388N			
Fisher exact test		P=0.318	P=0.241	P=0.500N
All Organs: Mononuclear Cell Leukemia				
Overall rates	8/50 (16%)	9/50 (18%)	17/50 (34%)	21/50 (42%)
Adjusted rates	18.6%	24.1%	45.4%	59.9%
Terminal rates	1/34 (3%)	5/32 (16%)	9/28 (32%)	7/19 (37%)
First incidence (days)	556	602	557	238
Life table tests	P<0.001	P=0.441	P=0.022	P<0.001
Logistic regression tests	P<0.001	P=0.526	P=0.034	P=0.008
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.500	P=0.032	P=0.004
All Organs: Benign Neoplasms				
Overall rates	42/50 (84%)	41/50 (82%)	41/50 (82%)	37/50 (74%)
Adjusted rates	85.7%	93.1%	95.2%	92.4%
Terminal rates	27/34 (79%)	29/32 (91%)	26/28 (93%)	16/19 (84%)
First incidence (days)	470	436	462	457
Life table tests	P=0.012	P=0.462	P=0.221	P=0.034
Logistic regression tests	P=0.549N	P=0.609	P=0.561	P=0.549N
Cochran-Armitage test	P=0.120N			
Fisher exact test		P=0.500N	P=0.500N	P=0.163N
All Organs: Malignant Neoplasms				
Overall rates	16/50 (32%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rates	35.9%	100.0%	100.0%	100.0%
Terminal rates	6/34 (18%)	32/32 (100%)	28/28 (100%)	19/19 (100%)
First incidence (days)	556	364	388	143
Life table tests	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rates	45/50 (90%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rates	91.8%	100.0%	100.0%	100.0%
Terminal rates	30/34 (88%)	32/32 (100%)	28/28 (100%)	19/19 (100%)
First incidence (days)	470	364	388	143
Life table tests	P<0.001	P=0.129	P=0.036	P<0.001
Logistic regression tests	P=0.010	P=0.033	P=0.034	P=0.043
Cochran-Armitage test	P=0.009			
Fisher exact test		P=0.028	P=0.028	P=0.028

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Liver Neoplasms in Female F344/N Rats Receiving Corn Oil Vehicle by Gavage[a]

Study	Incidence in Controls		
	Hepatocellular Adenoma or Neoplastic Nodule	Hepatocellular Carcinoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Neoplastic Nodule
Historical Incidence at Southern Research Institute			
Benzaldehyde	5/50	0/50	5/50
Dichlorvos	0/50	0/50	0/50
Furan	0/50	0/50	0/50
Furfural	0/50	0/50	0/50
γ-Butyrolactone	0/50	0/50	0/50
Total	5/250 (2.0%)		5/250 (2.0%)
Standard deviation	4.5%		4.5%
Range	0%–10%		0%–10%
Overall Historical Incidence			
Total	9/770 (1.2%)	0/770 (0.0%)	9/770 (1.2%)
Standard deviation	2.7%		2.7%
Range	0%–10%		0%–10%

[a] Data as of 17 September 1990

TABLE B4b
Historical Incidence of Mononuclear Cell Leukemia in Female F344/N Rats Receiving Corn Oil Vehicle by Gavage[a]

Study	Incidence of Leukemia in Controls
Historical Incidence at Southern Research Institute	
Benzaldehyde	15/50
Dichlorvos	17/50
Furan	8/50
Furfural	18/50
γ-Butyrolactone	13/50
Total	71/250 (28.4%)
Standard deviation	7.9%
Range	16%–36%
Overall Historical Incidence	
Total	206/770 (26.8%)
Standard deviation	7.0%
Range	16%–38%

[a] Data as of 17 September 1990 for lymphocytic, monocytic, mononuclear, or undifferentiated leukemia

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Furan[a]

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Natural deaths	4	1	5	10
Moribund kills	12	17	17	19
Accidental deaths				2
Survivors				
Terminal sacrifice	34	32	28	19
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(49)	(50)	(50)	(49)
Parasite metazoan	3 (6%)	2 (4%)		1 (2%)
Intestine large, colon	(50)	(50)	(50)	(50)
Parasite metazoan	2 (4%)	6 (12%)		6 (12%)
Intestine large, rectum	(49)	(50)	(50)	(50)
Parasite metazoan	5 (10%)	12 (24%)	7 (14%)	4 (8%)
Liver	(50)	(50)	(50)	(50)
Basophilic focus	43 (86%)	38 (76%)	1 (2%)	
Clear cell focus	1 (2%)			
Cyst multilocular		6 (12%)	2 (4%)	12 (24%)
Developmental malformation	9 (18%)	1 (2%)	3 (6%)	3 (6%)
Eosinophilic focus	17 (34%)			
Granuloma, multiple	10 (20%)	19 (38%)	8 (16%)	
Hematopoietic cell proliferation, multifocal		7 (14%)	7 (14%)	
Hemorrhage, focal			1 (2%)	2 (4%)
Hemorrhage, multifocal			1 (2%)	3 (6%)
Hyperplasia, nodular, multifocal				1 (2%)
Necrosis, focal	1 (2%)			
Neovascularization			4 (8%)	8 (16%)
Pigmentation, hematoidin			1 (2%)	1 (2%)
Pigmentation, hemosiderin, multifocal			1 (2%)	
Thrombus			1 (2%)	1 (2%)
Biliary tract, cyst, multiple		49 (98%)	50 (100%)	46 (92%)
Biliary tract, fibrosis, multifocal		49 (98%)	50 (100%)	49 (98%)
Biliary tract, hyperplasia, multifocal		49 (98%)	50 (100%)	49 (98%)
Biliary tract, inflammation, chronic, multifocal		49 (98%)	50 (100%)	49 (98%)
Biliary tract, metaplasia		49 (98%)	50 (100%)	49 (98%)
Biliary tract, proliferation	11 (22%)			
Centrilobular, necrosis	8 (16%)	2 (4%)	10 (20%)	2 (4%)
Hepatocyte, cytomegaly		44 (88%)	50 (100%)	49 (98%)
Hepatocyte, degeneration, multifocal		35 (70%)	49 (98%)	47 (94%)
Hepatocyte, hyperplasia, nodular, multifocal		32 (64%)	47 (94%)	46 (92%)
Hepatocyte, necrosis, multifocal		18 (36%)	46 (92%)	47 (94%)
Hepatocyte, vacuolization cytoplasmic		43 (86%)	49 (98%)	47 (94%)
Kupffer cell, pigmentation, multifocal		49 (98%)	50 (100%)	48 (96%)
Serosa, inflammation, chronic	1 (2%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Alimentary System (continued)				
Mesentery	(8)	(12)	(9)	(13)
Inflammation, chronic, diffuse	1 (13%)			
Mineralization, focal			1 (11%)	2 (15%)
Fat, necrosis, focal	6 (75%)	11 (92%)	5 (56%)	7 (54%)
Fat, necrosis, multifocal	2 (25%)	1 (8%)	1 (11%)	2 (15%)
Pancreas	(50)	(49)	(50)	(50)
Atrophy, focal	4 (8%)	6 (12%)	6 (12%)	2 (4%)
Atrophy, multifocal	3 (6%)	5 (10%)	1 (2%)	1 (2%)
Hyperplasia, focal	4 (8%)	1 (2%)	2 (4%)	2 (4%)
Hyperplasia, multifocal	1 (2%)	1 (2%)	1 (2%)	
Acinus, atrophy	1 (2%)			
Acinus, hyperplasia	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Atrophy, multifocal			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema, diffuse	1 (2%)			
Erosion		1 (2%)	1 (2%)	2 (4%)
Hyperkeratosis				1 (2%)
Hyperplasia		2 (4%)	5 (10%)	5 (10%)
Hyperplasia, squamous				1 (2%)
Inflammation, subacute		1 (2%)	5 (10%)	6 (12%)
Perforation			2 (4%)	
Ulcer	2 (4%)		2 (4%)	3 (6%)
Ulcer, multiple			1 (2%)	
Artery, inflammation, subacute		1 (2%)		
Stomach, glandular	(50)	(50)	(50)	(50)
Edema, diffuse			2 (4%)	
Erosion		1 (2%)	2 (4%)	1 (2%)
Erosion, multiple			1 (2%)	1 (2%)
Inflammation, subacute		1 (2%)		
Mineralization	1 (2%)			
Mineralization, multifocal				1 (2%)
Ulcer		1 (2%)	1 (2%)	1 (2%)
Ulcer, multiple			1 (2%)	
Cardiovascular System				
Blood vessel	(1)			(1)
Abdominal, hypertrophy				1 (100%)
Abdominal, inflammation, subacute				1 (100%)
Abdominal, thrombus				1 (100%)
Aorta, inflammation, chronic	1 (100%)			
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	17 (34%)	25 (50%)	11 (22%)	32 (64%)
Granuloma		1 (2%)		
Mineralization, multifocal				1 (2%)
Thrombus				1 (2%)
Pericardium, fibrosis		1 (2%)		
Pericardium, necrosis, focal		1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Endocrine System				
Adrenal gland	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Angiectasis	3 (6%)			
Focal cellular change	9 (18%)	9 (18%)	7 (14%)	3 (6%)
Hematopoietic cell proliferation			1 (2%)	1 (2%)
Hypertrophy, focal	1 (2%)			
Necrosis, diffuse	1 (2%)		1 (2%)	
Necrosis, multifocal			2 (4%)	
Thrombus		1 (2%)		
Vacuolization cytoplasmic, diffuse	1 (2%)			1 (2%)
Vacuolization cytoplasmic, focal	1 (2%)			
Vacuolization cytoplasmic, multifocal	1 (2%)			
Adrenal gland, medulla	(50)	(49)	(50)	(49)
Cyst		1 (2%)		
Hyperplasia, focal	1 (2%)		1 (2%)	2 (4%)
Hyperplasia, multifocal		1 (2%)		1 (2%)
Necrosis, diffuse	1 (2%)			
Parathyroid gland	(48)	(50)	(49)	(46)
Hyperplasia			2 (4%)	9 (20%)
Pituitary gland	(50)	(50)	(49)	(49)
Pars distalis, angiectasis	31 (62%)	30 (60%)	29 (59%)	22 (45%)
Pars distalis, cyst	18 (36%)	9 (18%)	16 (33%)	20 (41%)
Pars distalis, hyperplasia	2 (4%)	2 (4%)	4 (8%)	2 (4%)
Pars distalis, hyperplasia, focal	9 (18%)	11 (22%)	12 (24%)	18 (37%)
Pars distalis, pigmentation, hemosiderin	11 (22%)	19 (38%)	17 (35%)	10 (20%)
Thyroid gland	(50)	(50)	(50)	(49)
Ultimobranchial cyst	1 (2%)			
C-cell, hyperplasia		1 (2%)	2 (4%)	
C-cell, hyperplasia, focal	7 (14%)	6 (12%)	4 (8%)	8 (16%)
C-cell, hyperplasia, multifocal	5 (10%)	2 (4%)	4 (8%)	
Follicle, cyst			1 (2%)	2 (4%)
General Body System				
None				
Genital System				
Clitoral gland	(43)	(48)	(50)	(47)
Hyperplasia	4 (9%)			2 (4%)
Hyperplasia, focal			1 (2%)	
Inflammation, chronic			1 (2%)	
Inflammation, subacute, focal			1 (2%)	
Inflammation, suppurative, acute, focal	2 (5%)	1 (2%)	1 (2%)	2 (4%)
Duct, cyst		5 (10%)	5 (10%)	5 (11%)
Ovary	(50)	(50)	(50)	(50)
Cyst	12 (24%)	3 (6%)	3 (6%)	6 (12%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Genital System (continued)				
Uterus	(50)	(50)	(50)	(50)
Abscess	1 (2%)			
Cyst	2 (4%)			2 (4%)
Hemorrhage			2 (4%)	1 (2%)
Hydrometra	2 (4%)	3 (6%)		
Hyperplasia, cystic	1 (2%)	4 (8%)	2 (4%)	
Inflammation, acute	1 (2%)			
Inflammation, chronic, focal			1 (2%)	
Inflammation, suppurative, acute	1 (2%)			
Prolapse		1 (2%)	1 (2%)	
Cervix, cyst	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Cervix, cyst, multiple	1 (2%)			
Cervix, hypertrophy	1 (2%)			
Vagina	(2)	(1)	(2)	
Inflammation, suppurative, acute			1 (50%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia		8 (16%)	11 (22%)	24 (48%)
Infiltration cellular, histiocytic		1 (2%)		
Myelofibrosis		1 (2%)	2 (4%)	
Lymph node	(50)	(50)	(50)	(50)
Pancreatic, ectasia		6 (12%)	16 (32%)	23 (46%)
Pancreatic, hyperplasia		2 (4%)	2 (4%)	1 (2%)
Pancreatic, inflammation, granulomatous			1 (2%)	
Pancreatic, necrosis				1 (2%)
Renal, ectasia			1 (2%)	1 (2%)
Lymph node, bronchial	(27)	(43)	(42)	(30)
Ectasia		1 (2%)		1 (3%)
Lymph node, mandibular	(47)	(48)	(47)	(46)
Ectasia	3 (6%)	4 (8%)	3 (6%)	2 (4%)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	3 (7%)
Inflammation, suppurative, acute	1 (2%)			
Lymph node, mediastinal	(48)	(48)	(49)	(49)
Congestion	1 (2%)			2 (4%)
Ectasia		3 (6%)	4 (8%)	10 (20%)
Hyperplasia				1 (2%)
Lymph node, mesenteric	(48)	(50)	(50)	(48)
Ectasia		1 (2%)	1 (2%)	
Hyperplasia				2 (4%)
Spleen	(50)	(50)	(50)	(50)
Congestion	2 (4%)	6 (12%)	17 (34%)	23 (46%)
Fibrosis, focal	3 (6%)		2 (4%)	1 (2%)
Hematopoietic cell proliferation	8 (16%)	14 (28%)	27 (54%)	25 (50%)
Inflammation, chronic, focal				1 (2%)
Necrosis, diffuse				1 (2%)
Necrosis, focal			2 (4%)	2 (4%)
Pigmentation, hemosiderin			1 (2%)	
Thrombus				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Hematopoietic System (continued)				
Thymus	(47)	(46)	(47)	(43)
Cyst	1 (2%)	3 (7%)	1 (2%)	
Hemorrhage				1 (2%)
Fat, mediastinum, inflammation, chronic	1 (2%)			
Integumentary System				
Mammary gland	(50)	(50)	(49)	(50)
Duct, cyst	43 (86%)	44 (88%)	45 (92%)	43 (86%)
Skin	(50)	(50)	(50)	(50)
Foreign body	1 (2%)			
Inflammation, granulomatous, focal	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, hypertrophy, focal	2 (4%)	4 (8%)	6 (12%)	2 (4%)
Femur, hypertrophy, focal	1 (2%)	5 (10%)	2 (4%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Degeneration, multifocal	1 (2%)			
Hemorrhage, focal		1 (2%)		1 (2%)
Hemorrhage, multifocal	1 (2%)	1 (2%)		3 (6%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Abscess		1 (2%)		
Congestion	1 (2%)			4 (8%)
Foreign body	1 (2%)			2 (4%)
Granuloma, multiple	12 (24%)	14 (28%)	14 (28%)	11 (22%)
Hemorrhage, multifocal			1 (2%)	3 (6%)
Infiltration cellular, histiocytic, focal	1 (2%)	5 (10%)	4 (8%)	2 (4%)
Infiltration cellular, histiocytic, multifocal	1 (2%)	4 (8%)	8 (16%)	3 (6%)
Pigmentation, cholesterol, focal	1 (2%)	3 (6%)	3 (6%)	3 (6%)
Pigmentation, cholesterol, multifocal		2 (4%)	2 (4%)	2 (4%)
Alveolar epithelium, hyperplasia, focal	4 (8%)	2 (4%)	1 (2%)	4 (8%)
Alveolar epithelium, hyperplasia, multifocal	1 (2%)	1 (2%)	1 (2%)	
Fat, mediastinum, necrosis, multifocal	2 (4%)	10 (20%)	11 (22%)	4 (8%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(50)
Foreign body		2 (4%)	2 (4%)	2 (4%)
Fungus		1 (2%)	3 (6%)	2 (4%)
Inflammation, suppurative, acute		4 (8%)	5 (10%)	2 (4%)
Mucosa, cyst			1 (2%)	
Nasolacrimal duct, foreign body		1 (2%)		
Nasolacrimal duct, hyperkeratosis			1 (2%)	
Nasolacrimal duct, inflammation, subacute	4 (8%)	3 (6%)	10 (20%)	3 (6%)
Nasolacrimal duct, inflammation, suppurative, acute	1 (2%)		3 (6%)	1 (2%)
Nasopharyngeal duct, foreign body		1 (2%)		
Nasopharyngeal duct, inflammation, subacute		2 (4%)		
Special Senses System				
Eye	(2)	(3)	(2)	
Cataract	1 (50%)	3 (100%)	1 (50%)	
Hemorrhage		1 (33%)	2 (100%)	
Inflammation, subacute	1 (50%)			
Retina, degeneration	1 (50%)	2 (67%)	1 (50%)	
Harderian gland	(2)		(1)	(1)
Inflammation, chronic, focal	2 (100%)		1 (100%)	
Lacrimal gland	(1)		(1)	
Inflammation, suppurative, chronic			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst multilocular	1 (2%)			
Developmental malformation				1 (2%)
Nephropathy, chronic	16 (32%)	47 (94%)	47 (94%)	46 (92%)
Cortex, fibrosis, focal		1 (2%)	1 (2%)	
Papilla, necrosis			1 (2%)	
Pelvis, inflammation, suppurative, acute			1 (2%)	
Renal tubule, mineralization, multifocal				1 (2%)
Renal tubule, necrosis, multifocal				1 (2%)
Transitional epithelium, hyperplasia			1 (2%)	
Urinary bladder	(49)	(50)	(49)	(50)
Calculus gross observation			1 (2%)	
Transitional epithelium, hyperplasia			1 (2%)	

[a] Number of animals examined microscopically at site and number of animals with lesion.

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF FURAN

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TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Furan

	Vehicle Control	8 mg/kg	15 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Natural deaths		1	1
Accidental deaths	1	8	8
Moribund kills	16	24	25
Survivors			
Terminal sacrifice	33	17	16
Animals examined microscopically	50	50	50
Alimentary System			
Gallbladder	(50)	(48)	(44)
Adenocarcinoma, metastatic, liver		1 (2%)	
Intestine small, duodenum	(49)	(49)	(48)
Adenocarcinoma, metastatic, uncertain primary site		1 (2%)	
Serosa, sarcoma, metastatic, uncertain primary site		1 (2%)	
Liver	(50)	(50)	(50)
Adenocarcinoma, metastatic, uncertain primary site		1 (2%)	
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Carcinoma, metastatic, multiple, harderian gland		1 (2%)	
Hemangiosarcoma	2 (4%)	1 (2%)	2 (4%)
Hemangiosarcoma, two, multiple		2 (4%)	
Hemangiosarcoma, three, multiple		1 (2%)	
Hepatoblastoma	1 (2%)		
Hepatocellular carcinoma	5 (10%)	26 (52%)	27 (54%)
Hepatocellular carcinoma, multiple		2 (4%)	
Hepatocellular carcinoma, two	1 (2%)		
Hepatocellular carcinoma, two, multiple	1 (2%)	3 (6%)	5 (10%)
Hepatocellular carcinoma, three, multiple		1 (2%)	1 (2%)
Hepatocellular carcinoma, four, multiple			1 (2%)
Hepatocellular adenoma	18 (36%)	16 (32%)	12 (24%)
Hepatocellular adenoma, two	1 (2%)		2 (4%)
Hepatocellular adenoma, two, multiple	1 (2%)	8 (16%)	11 (22%)
Hepatocellular adenoma, three, multiple		6 (12%)	8 (16%)
Hepatocellular adenoma, four, multiple		1 (2%)	4 (8%)
Hepatocellular adenoma, five, multiple		1 (2%)	2 (4%)
Hepatocellular adenoma, greater than five, multiple		1 (2%)	3 (6%)
Hepatocholangiocarcinoma		2 (4%)	
Ito cell neoplasm benign			1 (2%)
Sarcoma, metastatic, uncertain primary site		1 (2%)	
Biliary tract, adenocarcinoma		2 (4%)	2 (4%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Alimentary System (continued)			
Mesentery	(6)	(10)	(3)
Adenocarcinoma, metastatic, liver		2 (20%)	
Adenocarcinoma, metastatic, multiple, uncertain primary site		1 (10%)	
Adenocarcinoma, greater than five, metastatic, multiple, liver			1 (33%)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (10%)	
Carcinoma, metastatic, harderian gland		1 (10%)	
Hemangiosarcoma	1 (17%)		
Hepatocellular carcinoma, metastatic, liver		1 (10%)	
Hepatocholangiocarcinoma, metastatic, multiple, liver		1 (10%)	
Sarcoma, metastatic, uncertain primary site		1 (10%)	
Pancreas	(50)	(50)	(50)
Adenocarcinoma, metastatic, liver		1 (2%)	1 (2%)
Sarcoma, metastatic, uncertain primary site		1 (2%)	
Salivary glands	(50)	(50)	(48)
Stomach, forestomach	(49)	(50)	(50)
Mucosa, papilloma squamous		1 (2%)	3 (6%)
Stomach, glandular	(49)	(50)	(50)
Carcinoid neoplasm malignant		1 (2%)	1 (2%)
Sarcoma, metastatic, uncertain primary site		1 (2%)	
Tooth	(43)	(36)	(32)
Peridontal tissue, carcinoma, metastatic, harderian gland		1 (3%)	
Cardiovascular System			
Heart	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Carcinoma, metastatic, multiple, harderian gland		1 (2%)	
Hemangiosarcoma			1 (2%)
Hepatocellular carcinoma, metastatic, liver		3 (6%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Endocrine System			
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma	2 (4%)	1 (2%)	
Carcinoma, metastatic, harderian gland		1 (2%)	
Extra adrenal tissue, sarcoma, metastatic, uncertain primary site		1 (2%)	
Subcapsular, adenoma	3 (6%)	2 (4%)	
Subcapsular, adenoma, multiple	1 (2%)		
Adrenal gland, medulla	(49)	(50)	(50)
Pheochromocytoma benign		5 (10%)	7 (14%)
Pheochromocytoma benign, multiple	1 (2%)	1 (2%)	3 (6%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Endocrine System (continued)			
Pituitary gland	(50)	(44)	(48)
Pars distalis, adenoma			1 (2%)
Pars intermedia, adenoma		1 (2%)	
Thyroid gland	(50)	(50)	(50)
Follicular cell, adenoma	1 (2%)		
Follicular cell, carcinoma			1 (2%)
General Body System			
None			
Genital System			
Ductus deferens	(1)	(2)	
Epididymis	(50)	(50)	(50)
Preputial gland	(6)	(6)	(5)
Adenoma	1 (17%)		
Prostate	(49)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)
Adenocarcinoma, metastatic, liver		1 (2%)	
Sarcoma, metastatic, uncertain primary site		1 (2%)	
Testes	(50)	(50)	(50)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)		1 (2%)
Lymph node	(50)	(50)	(49)
Lymph node, bronchial	(14)	(27)	(26)
Lymph node, mandibular	(49)	(48)	(43)
Lymph node, mediastinal	(38)	(45)	(41)
Adenocarcinoma, metastatic, liver		1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Sarcoma, metastatic, uncertain primary site		1 (2%)	
Lymph node, mesenteric	(50)	(50)	(48)
Adenocarcinoma, metastatic, liver		1 (2%)	
Spleen	(50)	(50)	(49)
Adenocarcinoma, metastatic, liver		1 (2%)	
Hemangiosarcoma	3 (6%)		2 (4%)
Thymus	(42)	(44)	(42)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Integumentary System			
Skin	(50)	(50)	(50)
Fibrosarcoma	1 (2%)		
Papilloma squamous		1 (2%)	
Subcutaneous tissue, fibroma	3 (6%)		
Subcutaneous tissue, fibrosarcoma		3 (6%)	1 (2%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)		
Subcutaneous tissue, neurofibroma		1 (2%)	
Subcutaneous tissue, sarcoma		2 (4%)	2 (4%)
Subcutaneous tissue, sarcoma, multiple	1 (2%)		
Musculoskeletal System			
Bone	(50)	(50)	(50)
Cranium, carcinoma, metastatic, harderian gland		1 (2%)	
Cranium, hemangiosarcoma		1 (2%)	
Skeletal muscle	(2)	(3)	(1)
Hepatocholangiocarcinoma, metastatic, liver		1 (33%)	
Back, hemangiosarcoma	1 (50%)		
Diaphragm, intercostal, alveolar/bronchiolar carcinoma, metastatic, multiple, lung		1 (33%)	
Head, carcinoma, metastatic, harderian gland		1 (33%)	
Nervous System			
Brain	(50)	(50)	(49)
Adenocarcinoma, metastatic, liver		1 (2%)	
Carcinoma, metastatic, harderian gland		1 (2%)	
Meninges, hemangiosarcoma		1 (2%)	
Respiratory System			
Lung	(50)	(50)	(50)
Adenocarcinoma, metastatic, liver		1 (2%)	
Adenocarcinoma, metastatic, multiple, uncertain primary site		1 (2%)	
Adenocarcinoma, greater than five, metastatic, multiple, liver			1 (2%)
Alveolar/bronchiolar adenoma	7 (14%)	6 (12%)	12 (24%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)		
Alveolar/bronchiolar adenoma, two, multiple	1 (2%)	1 (2%)	4 (8%)
Alveolar/bronchiolar carcinoma	3 (6%)	2 (4%)	
Carcinoma	1 (2%)		
Hepatocellular carcinoma, metastatic		1 (2%)	
Hepatocellular carcinoma, metastatic, liver	2 (4%)	4 (8%)	2 (4%)
Hepatocellular carcinoma, metastatic, multiple, liver	1 (2%)	1 (2%)	
Hepatocellular carcinoma, three, metastatic, multiple, liver		1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Respiratory System (continued)			
Lung (continued)			
Hepatocellular carcinoma, greater than five, metastatic, multifocal, liver			1 (2%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Mediastinum, adenocarcinoma, metastatic, liver		1 (2%)	
Mediastinum, sarcoma, metastatic, uncertain primary site		1 (2%)	
Parenchyma, mediastinum, alveolar/bronchiolar carcinoma, multiple		1 (2%)	
Parenchyma, mediastinum, carcinoma, metastatic, multiple, harderian gland		1 (2%)	
Nose	(50)	(50)	(50)
Mucosa, carcinoma, metastatic, harderian gland		1 (2%)	
Mucosa, hemangiosarcoma		1 (2%)	
Special Senses System			
Ear			(1)
Glioma malignant, metastatic			1 (100%)
Eye		(1)	
Carcinoma, metastatic, harderian gland		1 (100%)	
Harderian gland	(3)	(5)	
Adenoma	3 (100%)	4 (80%)	
Carcinoma		1 (20%)	
Urinary System			
Kidney	(50)	(50)	(50)
Adenocarcinoma, metastatic, liver		1 (2%)	
Alveolar/bronchiolar carcinoma, metastatic, multiple, lung		1 (2%)	
Hepatocellular carcinoma, metastatic, multiple, liver		1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Adventitia, adenocarcinoma, metastatic, liver		1 (2%)	
Capsule, sarcoma, metastatic, uncertain primary site		1 (2%)	
Urinary bladder	(50)	(49)	(50)
Transitional epithelium, papilloma	1 (2%)		
Systemic Lesions			
Multiple organs[a]	(50)	(50)	(50)
Lymphoma malignant histiocytic		1 (2%)	1 (2%)
Lymphoma malignant mixed	5 (10%)	11 (22%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Neoplasm Summary			
Total animals with primary neoplasms[b]	43	45	50
Total primary neoplasms	74	122	121
Total animals with benign neoplasms	32	38	46
Total benign neoplasms	45	57	73
Total animals with malignant neoplasms	18	41	39
Total malignant neoplasms	29	65	48
Total animals with metastatic neoplasms	3	10	3
Total metastatic neoplasms	3	62	8
Total animals with malignant neoplasms of uncertain primary site		3	

[a] Number of animals with any tissue examined microscopically
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: Vehicle Control

Number of Days on Study	4 9 9	5 1 4	5 4 2	5 5 0	6 3 8	6 6 0	6 7 6	6 9 7	6 9 7	7 0 4	7 1 5	7 1 5	7 2 3	7 2 3	7 2 3	7 2 6	7 2 6	7 2 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7
Carcass ID Number	0 2 1	1 0 1	0 1 1	0 3 1	0 7 1	1 0 2	0 3 2	0 4 1	0 5 1	0 4 2	0 3 3	0 9 1	0 1 2	0 2 2	0 6 1	0 2 3	0 3 4	0 1 3	0 1 4	0 1 5	0 2 4	0 2 5	0 3 5	0 4 3	0 4 4
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X												X		
Hepatoblastoma																	X									
Hepatocellular carcinoma		X										X	X		X		X									
Hepatocellular carcinoma, two																X										
Hepatocellular carcinoma, two, multiple														X												
Hepatocellular adenoma				X				X		X	X			X				X		X		X				
Hepatocellular adenoma, two																										
Hepatocellular adenoma, two, multiple																										
Mesentery						+	+															+				
Hemangiosarcoma							X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth		+		+	+	+		+	+		+	+	+		+	+	+	+	+	+		+	+	,	+
Cardiovascular System																										
Blood vessel								+					+													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X							
Subcapsular, adenoma				X																						
Subcapsular, adenoma, multiple																										

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	0 4 5	0 5 2	0 5 3	0 5 4	0 5 5	0 5 2	0 6 3	0 6 4	0 6 5	0 7 2	0 7 3	0 7 4	0 7 5	0 7 8	0 8 1	0 8 2	0 8 3	0 8 4	0 8 5	0 9 2	0 9 3	0 9 4	0 9 5	1 0 3	1 0 4	1 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Hepatoblastoma																										1
Hepatocellular carcinoma																										5
Hepatocellular carcinoma, two																										1
Hepatocellular carcinoma, two, multiple																										1
Hepatocellular adenoma			X					X		X		X			X				X	X		X	X			X	18
Hepatocellular adenoma, two																		X								1
Hepatocellular adenoma, two, multiple																					X					1
Mesentery					+														+						+	6
Hemangiosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Cardiovascular System																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				2
Subcapsular, adenoma																						X			X	3
Subcapsular, adenoma, multiple																				X						1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	4 9 9	5 1 4	5 4 2	5 5 0	6 3 8	6 6 0	6 7 6	6 9 7	6 9 7	7 0 4	7 1 5	7 1 5	7 2 3	7 2 3	7 2 3	7 2 6	7 2 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7
Carcass ID Number	0 2 1	1 0 1	0 1 1	0 3 1	0 7 1	1 0 2	0 3 2	0 4 1	0 5 1	0 4 2	0 3 3	0 9 1	0 1 2	0 2 2	0 6 1	0 2 3	0 3 4	1 1 3	1 1 4	1 1 5	1 2 4	2 2 5	3 3 5	4 4 3	4 4 4
Endocrine System (continued)																									
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign, multiple													X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Coagulating gland																									
Ductus deferens																									+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+													+		+						+		+
Adenoma																									X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X						X													
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	M	M	M	M	M	+	+	M	M	M	M	+	M	M	M	+	+	+	M	M	M	+	+	M
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X						X				X									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma										X															
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, hemangiosarcoma						X																			
Subcutaneous tissue, sarcoma, multiple									X																

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	0 4 5	0 5 2	0 5 3	0 5 4	0 5 5	0 6 2	0 6 3	0 6 4	0 6 5	0 7 2	0 7 3	0 7 4	0 7 5	0 7 8	0 8 1	0 8 2	0 8 3	0 8 4	0 8 5	0 9 2	0 9 3	0 9 4	0 9 5	1 0 3	1 0 4	1 0 5	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign, multiple																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma												X														1
General Body System																										
None																										
Genital System																										
Coagulating gland					+																					1
Ductus deferens																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland													+													6
Adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	M	+	+	+	M	+	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	14
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	M	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	M	M	38
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										3
Thymus	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	M	+	+	M	+	42
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Subcutaneous tissue, fibroma				X							X									X						3
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, sarcoma, multiple																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	4 9 9	5 1 4	5 4 2	5 5 0	6 3 8	6 6 0	6 7 6	6 9 7	6 9 7	7 0 4	7 1 5	7 1 5	7 2 3	7 2 3	7 2 3	7 2 6	7 2 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7
Carcass ID Number	0 2 1	1 0 1	0 1 1	0 3 1	0 7 1	1 0 2	0 3 2	0 4 1	0 5 1	0 4 2	0 3 3	0 9 1	0 1 2	0 2 2	0 6 1	0 2 3	0 3 4	0 1 3	0 1 4	0 1 5	0 2 4	0 2 5	0 3 5	0 4 3	0 4 4
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+							+						
Back, hemangiosarcoma												X													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X			X			X														
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar adenoma, two, multiple																									
Alveolar/bronchiolar carcinoma			X																				X		
Carcinoma																									X
Hepatocellular carcinoma, metastatic, liver		X												X											
Hepatocellular carcinoma, metastatic, multiple, liver																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland											+	+													
Adenoma											X	X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter						+																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma										X															
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed							X								X										X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	0 4 5	0 5 2	0 5 3	0 5 4	0 5 5	0 6 2	0 6 3	0 6 4	0 6 5	0 7 2	0 7 3	0 7 4	0 7 5	0 8 1	0 8 2	0 8 3	0 8 4	0 8 5	0 9 2	0 9 3	0 9 4	0 9 5	1 0 3	1 0 4	1 0 5	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Back, hemangiosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X	X			X											X						7
Alveolar/bronchiolar adenoma, multiple				X																						1
Alveolar/bronchiolar adenoma, two, multiple													X													1
Alveolar/bronchiolar carcinoma		X																								3
Carcinoma																										1
Hepatocellular carcinoma, metastatic, liver																										2
Hepatocellular carcinoma, metastatic, multiple, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																							+			3
Adenoma																							X			3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																		X					X			5

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 8 mg/kg

Number of Days on Study	0 1 6	0 2 1	2 5 0	4 4 4	4 4 4	5 0 8	5 4 9	5 5 6	5 5 7	5 8 4	6 0 0	6 1 2	6 4 2	6 6 3	6 9 0	6 9 7	6 9 8	7 0 1	7 0 4	7 1 8	7 1 9	7 1 9	7 1 9	7 2 3	7 2 3
Carcass ID Number	2 2 8 1	2 6 1	2 7 1	2 9 1	3 0 1	2 6 2	2 6 3	2 8 2	2 3 1	2 5 1	2 5 2	2 9 2	2 3 2	3 0 2	3 0 3	2 3 3	2 9 3	2 1 1	2 4 1	3 0 4	2 1 2	2 1 3	2 3 4	2 7 2	2 9 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, liver													X												
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uncertain primary site								X																	
Serosa, sarcoma, metastatic, uncertain primary site														X											
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uncertain primary site													X												
Alveolar/bronchiolar carcinoma, metastatic, lung										X															
Carcinoma, metastatic, multiple, harderian gland								X																	
Hemangiosarcoma																									
Hemangiosarcoma, two, multiple																			X	X					
Hemangiosarcoma, three, multiple																									
Hepatocellular carcinoma					X	X	X	X	X	X	X	X	X		X	X		X	X			X	X		X
Hepatocellular carcinoma, multiple														X											
Hepatocellular carcinoma, two, multiple																								X	
Hepatocellular carcinoma, three, multiple																									
Hepatocellular adenoma					X			X	X					X		X							X	X	X
Hepatocellular adenoma, two, multiple																				X					
Hepatocellular adenoma, three, multiple						X															X				
Hepatocellular adenoma, four, multiple															X										
Hepatocellular adenoma, five, multiple																									
Hepatocellular adenoma, greater than five, multiple																			X						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	7 2 4	7 2 5	7 2 5	7 3 1	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 7 3	2 2 1	2 8 3	2 2 2	2 2 3	2 4 2	2 4 3	2 8 4	2 1 4	2 1 5	2 2 4	2 2 5	2 3 5	2 4 4	2 4 5	2 5 3	2 5 4	2 5 5	2 5 6	2 6 4	2 6 5	2 7 4	2 7 5	2 8 5	2 9 4	3 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, metastatic, liver																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Adenocarcinoma, metastatic, uncertain primary site																										1
Serosa, sarcoma, metastatic, uncertain primary site																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uncertain primary site																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Carcinoma, metastatic, multiple, harderian gland																										1
Hemangiosarcoma								X																		1
Hemangiosarcoma, two, multiple																										2
Hemangiosarcoma, three, multiple					X																					1
Hepatocellular carcinoma			X		X		X	X	X		X						X				X			X	X	26
Hepatocellular carcinoma, multiple		X																								2
Hepatocellular carcinoma, two, multiple	X																			X						3
Hepatocellular carcinoma, three, multiple						X																				1
Hepatocellular adenoma		X			X		X	X				X				X		X	X							16
Hepatocellular adenoma, two, multiple	X		X							X			X	X						X					X	8
Hepatocellular adenoma, three, multiple				X		X			X						X											6
Hepatocellular adenoma, four, multiple																										1
Hepatocellular adenoma, five, multiple											X															1
Hepatocellular adenoma, greater than five, multiple																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	0 1 6	0 2 1	2 5 0	4 4 4	4 4 4	5 0 8	5 4 9	5 5 6	5 5 7	5 8 4	6 0 0	6 1 2	6 4 2	6 6 3	6 9 0	6 9 7	6 9 8	7 0 1	7 0 4	7 1 8	7 1 9	7 1 9	7 1 9	7 2 3	7 2 3
Carcass ID Number	2 8 1	2 6 1	2 7 1	2 9 1	3 0 1	2 6 2	2 6 3	2 8 2	2 3 1	2 5 1	2 5 2	2 9 2	2 3 2	3 0 2	3 0 3	3 3 3	2 9 3	2 1 1	2 4 1	2 0 4	2 1 2	2 1 3	2 3 4	2 7 2	2 9 5
Alimentary System (continued)																									
Liver (continued)																									
Hepatocholangiocarcinoma									X												X				
Sarcoma, metastatic, uncertain primary site														X											
Biliary tract, adenocarcinoma							X																		
Mesentery							+	+	+	+			+	+					+	+	+				
Adenocarcinoma, metastatic, liver							X						X												
Adenocarcinoma, metastatic, multiple, uncertain primary site								X																	
Alveolar/bronchiolar carcinoma, metastatic, lung										X															
Carcinoma, metastatic, harderian gland								X																	
Hepatocellular carcinoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, multiple, liver									X																
Sarcoma, metastatic, uncertain primary site														X											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, liver							X																		
Sarcoma, metastatic, uncertain primary site														X											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucosa, papilloma squamous																				X					
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor malignant																									
Sarcoma, metastatic, uncertain primary site														X											
Tongue																									
Tooth				+				+	+		+	+	+		+		+		+	+	+	+	+	+	+
Peridontal tissue, carcinoma, metastatic, harderian gland								X																	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	7 2 4	7 2 5	7 2 5	7 3 1	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 7 3	2 2 1	2 8 3	2 2 2	2 2 3	2 4 2	2 4 3	2 8 4	2 1 4	2 1 5	2 2 4	2 2 5	2 3 5	2 4 4	2 4 5	2 5 3	2 5 4	2 5 5	2 6 4	2 6 5	2 6 4	2 7 5	2 7 5	2 8 5	2 9 4	3 0 5	**Total Tissues/ Tumors**
Alimentary System (continued)																										
Liver (continued)																										
Hepatocholangiocarcinoma																										2
Sarcoma, metastatic, uncertain primary site																										1
Biliary tract, adenocarcinoma																			X							2
Mesentery							+																			10
Adenocarcinoma, metastatic, liver																										2
Adenocarcinoma, metastatic, multiple, uncertain primary site																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver							X																			1
Hepatocholangiocarcinoma, metastatic, multiple, liver																										1
Sarcoma, metastatic, uncertain primary site																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, uncertain primary site																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucosa, papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoid tumor malignant																			X							1
Sarcoma, metastatic, uncertain primary site																										1
Tongue							+																			1
Tooth	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+		+	+	+		36
Peridontal tissue, carcinoma, metastatic, harderian gland																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	0161	0261	2510	4404	4408	5058	5459	5569	5577	5584	6600	6612	6642	6663	6690	6697	6698	7011	7014	7018	7119	7119	7199	7213	7223	7223
Carcass ID Number	2281	2661	2771	2991	3001	2062	2663	2682	2231	2551	2952	2922	2302	3002	3033	2933	2991	2211	2414	2401	2212	2113	2934	2725	2925	2925
Cardiovascular System																										
Blood vessel																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung										X																
Carcinoma, metastatic, multiple, harderian gland								X																		
Hepatocellular carcinoma, metastatic, liver										X			X			X										
Hepatocholangiocarcinoma, metastatic, liver									X																	
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X					
Carcinoma, metastatic, harderian gland								X																		
Extra adrenal tissue, sarcoma, metastatic, uncertain primary site													X													
Subcapsular, adenoma																										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																		X								
Pheochromocytoma benign, multiple																										X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	I	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M
Pars intermedia, adenoma																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																										
None																										
Genital System																										
Coagulating gland																										
Ductus deferens																					+					
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland													+					+				+				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, liver							X																			
Sarcoma, metastatic, uncertain primary site														X												
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	7 2 4	7 2 5	7 2 5	7 3 1	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 7 3	2 2 1	2 8 3	2 2 2	2 2 3	2 4 2	2 4 3	2 8 4	2 1 4	2 1 5	2 2 4	2 2 5	2 3 5	2 4 4	2 4 5	2 5 3	2 5 4	2 5 5	2 6 4	2 6 5	2 7 4	2 7 5	2 8 5	2 9 4	3 0 5	**Total Tissues/ Tumors**
Cardiovascular System																										
Blood vessel							+																+			2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Carcinoma, metastatic, multiple, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																										3
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma, metastatic, harderian gland																										1
Extra adrenal tissue, sarcoma, metastatic, uncertain primary site																										1
Subcapsular, adenoma				X											X											2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign		X		X												X							X			5
Pheochromocytoma benign, multiple																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+		48
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pars intermedia, adenoma																X										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Coagulating gland												+														1
Ductus deferens											+															2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland									+						+		+									6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, uncertain primary site																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	0 1 6	0 2 1	2 5 0	4 4 4	4 4 4	5 0 8	5 4 9	5 5 6	5 5 7	5 8 4	6 0 0	6 1 2	6 4 2	6 6 3	6 9 0	6 9 7	6 9 8	7 0 1	7 0 4	7 1 8	7 1 9	7 1 9	7 1 9	7 2 3	7 2 3
Carcass ID Number	2 8 1	2 6 1	2 7 1	2 9 1	3 0 1	2 6 2	2 6 3	2 8 2	2 3 1	2 5 1	2 5 2	2 9 2	2 3 2	3 0 2	3 0 3	2 3 3	2 9 3	2 1 1	2 4 1	3 0 4	2 1 2	2 1 3	2 3 4	2 7 2	2 9 5
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	M	+	+	+	M	M	M	M	M	M	+	M	M	M	M	M	M	+	+	M	M	M	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, liver													X												
Alveolar/bronchiolar carcinoma, metastatic, lung										X															
Hepatocholangiocarcinoma, metastatic, liver									X																
Sarcoma, metastatic, uncertain primary site														X											
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, liver							X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, liver							X																		
Thymus	+	M	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, fibrosarcoma																	X								
Subcutaneous tissue, neurofibroma																									
Subcutaneous tissue, sarcoma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, carcinoma, metastatic, harderian gland								X																	
Cranium, hemangiosarcoma																									
Skeletal muscle								+	+	+															
Hepatocholangiocarcinoma, metastatic, liver									X																
Diaphragm, intercostal, alveolar/bronchiolar carcinoma, metastatic, multiple, lung										X															
Head, carcinoma, metastatic, harderian gland								X																	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	7 2 4	7 2 5	7 2 5	7 3 1	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 7 3	2 2 1	2 8 3	2 2 2	2 2 3	2 4 2	2 4 3	2 8 4	2 1 4	2 1 5	2 2 4	2 2 5	2 3 5	2 4 4	2 4 5	2 5 3	2 5 4	2 5 5	2 6 4	2 6 5	2 7 4	2 7 5	2 8 5	2 9 4	3 0 5	**Total Tissues/ Tumors**
Hematopoietic System																										
Blood								+																+		2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	+	M	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	27
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenocarcinoma, metastatic, liver																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, uncertain primary site																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, liver																										1
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																							X			1
Subcutaneous tissue, fibrosarcoma		X						X																		3
Subcutaneous tissue, neurofibroma																								X		1
Subcutaneous tissue, sarcoma																							X			2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, carcinoma, metastatic, harderian gland																										1
Cranium, hemangiosarcoma				X																						1
Skeletal muscle																										3
Hepatocholangiocarcinoma, metastatic, liver																										1
Diaphragm, intercostal, alveolar/bronchiolar carcinoma, metastatic, multiple, lung																										1
Head, carcinoma, metastatic, harderian gland																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	0 1 6	0 2 1	2 5 0	4 4 4	4 4 4	5 0 8	5 4 9	5 5 6	5 5 7	5 8 4	6 0 0	6 1 2	6 4 2	6 6 3	6 9 0	6 9 7	6 9 8	7 0 1	7 0 4	7 1 8	7 1 9	7 1 9	7 2 3	7 2 3
Carcass ID Number	2 8 1	2 6 1	2 7 1	2 9 1	3 0 1	2 6 2	2 6 3	2 8 2	2 3 1	2 5 1	2 5 2	2 9 2	2 3 2	3 0 2	3 0 3	3 3 3	2 9 3	2 1 1	2 4 1	3 0 4	2 1 2	2 1 3	2 3 4	2 7 2	2 9 5
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, liver													X												
Carcinoma, metastatic, harderian gland								X																	
Meninges, hemangiosarcoma																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, liver													X												
Adenocarcinoma, metastatic, multiple, uncertain primary site								X																	
Alveolar/bronchiolar adenoma								X				X													
Alveolar/bronchiolar adenoma, two, multiple																									
Alveolar/bronchiolar carcinoma																								X	
Hepatocellular carcinoma, metastatic									X																
Hepatocellular carcinoma, metastatic, liver													X			X									
Hepatocellular carcinoma, metastatic, multiple, liver										X															
Hepatocellular carcinoma, three, metastatic, multiple, liver																									
Hepatocholangiocarcinoma, metastatic, liver									X																
Mediastinum, adenocarcinoma, metastatic, liver							X																		
Mediastinum, sarcoma, metastatic, uncertain primary site														X											
Parenchyma, mediastinum, alveolar/bronchiolar carcinoma, multiple										X															
Parenchyma, mediastinum, carcinoma, metastatic, multiple, harderian gland								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucosa, carcinoma, metastatic, harderian gland								X																	
Mucosa, hemangiosarcoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	7 2 4	7 2 5	7 2 5	7 3 1	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 7 3	2 2 1	2 8 3	2 2 2	2 2 3	2 4 2	2 4 3	2 8 4	2 1 4	2 1 5	2 2 4	2 2 5	2 3 5	2 4 4	2 4 5	2 5 3	2 5 4	2 5 5	2 6 4	2 6 5	2 7 4	2 7 5	2 8 5	2 9 4	3 0 5	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, liver																										1
Carcinoma, metastatic, harderian gland																										1
Meninges, hemangiosarcoma				X																						1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, liver																										1
Adenocarcinoma, metastatic, multiple, uncertain primary site																										1
Alveolar/bronchiolar adenoma			X														X		X				X		6
Alveolar/bronchiolar adenoma, two, multiple																		X								1
Alveolar/bronchiolar carcinoma													X													2
Hepatocellular carcinoma, metastatic																										1
Hepatocellular carcinoma, metastatic, liver							X		X																	4
Hepatocellular carcinoma, metastatic, multiple, liver																										1
Hepatocellular carcinoma, three, metastatic, multiple, liver																								X		1
Hepatocholangiocarcinoma, metastatic, liver																										1
Mediastinum, adenocarcinoma, metastatic, liver																										1
Mediastinum, sarcoma, metastatic, uncertain primary site																										1
Parenchyma, mediastinum, alveolar/bronchiolar carcinoma, multiple																										1
Parenchyma, mediastinum, carcinoma, metastatic, multiple, harderian gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucosa, carcinoma, metastatic, harderian gland																										1
Mucosa, hemangiosarcoma				X																						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	0 1 6	0 2 1	2 5 0	4 4 4	4 4 4	5 0 8	5 4 9	5 5 6	5 5 7	5 8 4	6 0 0	6 1 2	6 4 2	6 6 3	6 9 0	6 9 7	6 9 8	7 0 1	7 0 4	7 1 8	7 1 9	7 1 9	7 1 9	7 2 3	7 2 3
Carcass ID Number	2 8 1	2 6 1	2 7 1	2 9 1	3 0 1	2 6 2	2 6 3	2 8 2	2 3 1	2 5 1	2 5 2	2 9 2	3 3 2	3 0 2	3 0 3	2 3 3	2 9 3	2 1 1	2 4 1	3 0 4	2 1 2	2 1 3	3 3 4	2 7 2	2 9 5
Special Senses System																									
Eye								+																	
Carcinoma, metastatic, harderian gland								X																	
Harderian gland								+						+	+										
Adenoma														X	X										
Carcinoma								X																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, liver													X												
Alveolar/bronchiolar carcinoma, metastatic, multiple, lung										X															
Hepatocellular carcinoma, metastatic, multiple, liver										X															
Hepatocholangiocarcinoma, metastatic, liver									X																
Adventitia, adenocarcinoma, metastatic, liver							X																		
Capsule, sarcoma, metastatic, uncertain primary site														X											
Ureter																						+			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic											X														
Lymphoma malignant mixed															X				X	X	X		X		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	7 2 4	7 2 5	7 2 5	7 3 1	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 7 3	2 2 1	2 8 3	2 2 2	2 2 3	2 4 2	2 4 3	2 8 4	2 1 4	2 1 5	2 2 4	2 2 5	2 3 5	2 4 4	2 4 5	2 5 3	2 5 4	2 5 5	2 6 4	2 6 5	2 7 4	2 7 5	2 8 5	2 9 4	3 0 5	**Total Tissues/ Tumors**
Special Senses System																										
Eye																										1
Carcinoma, metastatic, harderian gland																										1
Harderian gland								+						+												5
Adenoma								X						X												4
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, liver																										1
Alveolar/bronchiolar carcinoma, metastatic, multiple, lung																										1
Hepatocellular carcinoma, metastatic, multiple, liver																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Adventitia, adenocarcinoma, metastatic, liver																										1
Capsule, sarcoma, metastatic, uncertain primary site																										1
Ureter							+																			2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed					X						X			X		X		X					X			11

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 15 mg/kg

Number of Days on Study	4 2 3	4 9 8	5 5 6	5 5 6	5 7 7	5 9 5	6 1 0	6 1 2	6 2 1	6 2 1	6 4 1	6 4 2	6 4 9	6 6 3	6 6 8	6 8 9	6 9 1	7 1 6	7 1 8	7 1 8	7 1 8	7 1 8	7 2 2	7 2 3	7 2 4
Carcass ID Number	1 1 1	1 9 1	1 1 2	1 7 1	1 7 3	1 9 2	1 6 1	1 7 2	1 8 1	2 0 1	1 4 1	1 2 1	1 4 2	1 9 3	2 0 2	1 5 1	1 4 3	2 2 2	2 5 2	1 6 2	6 6 3	1 8 2	1 1 3	1 0 3	1 5 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	+	M	+	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Hepatocellular carcinoma	X	X			X	X	X	X	X	X		X	X				X		X	X		X		X	X
Hepatocellular carcinoma, two, multiple																					X				
Hepatocellular carcinoma, three, multiple																		X							
Hepatocellular carcinoma, four, multiple														X											
Hepatocellular adenoma		X						X		X				X		X	X			X		X			
Hepatocellular adenoma, two																									
Hepatocellular adenoma, two, multiple				X	X						X				X			X	X						
Hepatocellular adenoma, three, multiple			X										X											X	X
Hepatocellular adenoma, four, multiple																									
Hepatocellular adenoma, five, multiple																									
Hepatocellular adenoma, greater than five, multiple																									
Ito cell tumor benign																									
Biliary tract, adenocarcinoma														X					X						
Mesentery										+				+	+										
Adenocarcinoma, greater than five, metastatic, multiple, liver														X											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, liver														X											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucosa, papilloma squamous																		X							
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 15 mg/kg (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 5	7 2 5	7 2 6	7 3 1	7 3 1	7 3 1	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 5 4	1 8 3	1 7 4	2 0 4	1 3 1	1 1 4	1 5 5	2 0 5	1 2 3	1 1 5	1 2 4	1 2 5	1 3 2	1 3 3	1 3 4	1 3 5	1 4 4	1 4 5	1 6 4	1 6 5	1 7 5	1 8 4	1 8 5	1 9 4	1 9 5	**Total Tissues/ Tumors**
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																		X									2
Hepatocellular carcinoma		X		X	X	X		X			X	X				X						X	X		X		27
Hepatocellular carcinoma, two, multiple			X				X		X				X														5
Hepatocellular carcinoma, three, multiple																											1
Hepatocellular carcinoma, four, multiple																											1
Hepatocellular adenoma					X				X							X		X									12
Hepatocellular adenoma, two	X										X																2
Hepatocellular adenoma, two, multiple				X		X						X									X	X				11
Hepatocellular adenoma, three, multiple							X	X		X										X							8
Hepatocellular adenoma, four, multiple																	X						X	X	X		4
Hepatocellular adenoma, five, multiple														X					X								2
Hepatocellular adenoma, greater than five, multiple		X											X		X												3
Ito cell tumor benign			X																								1
Biliary tract, adenocarcinoma																											2
Mesentery																											3
Adenocarcinoma, greater than five, metastatic, multiple, liver																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, liver																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucosa, papilloma squamous																		X								X	3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoid tumor malignant																		X									1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 15 mg/kg (continued)

Number of Days on Study	442	499	556	566	577	595	601	612	621	622	641	642	646	663	668	689	691	711	716	718	718	718	718	722	723	724
Carcass ID Number	11	19	12	17	73	92	61	72	81	80	41	21	42	93	02	51	43	22	52	22	63	62	82	13	03	53
Alimentary System (continued)																										
Tongue															+											
Tooth			+	+	+	+			+	+	+	+	+		+	+			+				+		+	
Cardiovascular System																										
Blood vessel									+	+					+			+								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X							
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign	X				X					X							X							X		
Pheochromocytoma benign, multiple																					X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma																										
General Body System																										
Tissue NOS												+														
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																			
Lymph node	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	M	+	M	M	M	M	M	M	+	+	M	M	+	M	+	M	+	+	+	M	+	M	M	+	
Lymph node, mandibular	M	M	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	
Lymph node, mediastinal	+	+	M	M	+	+	A	+	M	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	
Adenocarcinoma, metastatic, liver														X												

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 15 mg/kg (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 5	7 2 5	7 2 6	7 3 1	7 3 1	7 3 1	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 5 4	1 8 3	1 7 4	2 0 4	1 3 1	1 1 4	1 5 5	2 0 5	1 2 3	1 1 5	1 2 4	1 2 5	1 2 6	1 3 2	1 3 3	1 3 4	1 3 5	1 4 4	1 4 5	1 6 4	1 6 5	1 7 5	1 8 4	1 8 5	1 9 4	1 9 5	**Total Tissues/ Tumors**
Alimentary System (continued)																											
Tongue																											1
Tooth	+	+			+	+	+	+	+	+			+	+	+	+		+	+	+	+	+			+		32
Cardiovascular System																											
Blood vessel																											4
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																											1
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign						X							X														7
Pheochromocytoma benign, multiple					X											X											3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, carcinoma														X													1
General Body System																											
Tissue NOS																											1
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+							+			+					+											5
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																											1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, bronchial	+	M	+	+	+	M	+	M	+	+	M	+	+	+	+	+	M	+	+	+	M	M	M	+	+	M	26
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	43
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	41
Adenocarcinoma, metastatic, liver																											1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 15 mg/kg (continued)

Number of Days on Study	4 2 3	4 9 8	5 5 6	5 6 6	5 7 7	5 9 5	6 1 0	6 1 2	6 2 1	6 2 1	6 4 1	6 4 1	6 4 2	6 4 9	6 6 3	6 6 8	6 8 9	6 9 1	7 1 6	7 1 8	7 1 8	7 1 8	7 1 8	7 2 2	7 2 3	7 2 4
Carcass ID Number	1 1 1	1 9 1	1 1 2	1 7 1	1 7 3	1 9 2	1 6 1	1 7 2	1 8 1	2 0 1	1 4 1	1 2 1	1 4 2	1 9 3	2 0 2	2 5 1	1 4 3	1 2 2	1 5 2	1 6 2	1 6 3	1 8 2	1 1 3	2 0 3	1 5 3
Hematopoietic System (continued)																										
Lymph node, mesenteric	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X																
Thymus	+	+	+	+	+	+	A	+	+	M	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																							X			
Subcutaneous tissue, sarcoma			X																X							
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																			+							
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, greater than five, metastatic, multiple, liver														X												
Alveolar/bronchiolar adenoma					X					X									X	X			X		X	
Alveolar/bronchiolar adenoma, two, multiple																										
Hepatocellular carcinoma, metastatic, liver														X							X					
Hepatocellular carcinoma, greater than five, metastatic, multifocal, liver																						X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear																						+				
Glioma malignant, metastatic																						X				
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter														+												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic								X																		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Furan: 15 mg/kg (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 5	7 2 5	7 2 6	7 3 1	7 3 1	7 3 1	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 5 4	1 8 3	1 7 4	2 0 4	1 3 1	1 1 4	1 5 5	2 0 5	1 2 3	1 1 5	1 2 4	1 2 5	1 3 2	1 3 3	1 3 4	1 3 5	1 4 4	1 4 5	1 6 4	1 6 5	1 7 5	1 8 4	1 8 5	1 9 4	1 9 5	**Total Tissues/ Tumors**
Hematopoietic System (continued)																										
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma										X																2
Thymus	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	42
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, sarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, greater than five, metastatic, multiple, liver																										1
Alveolar/bronchiolar adenoma								X	X					X		X		X				X				12
Alveolar/bronchiolar adenoma, two, multiple						X	X								X						X					4
Hepatocellular carcinoma, metastatic, liver																										2
Hepatocellular carcinoma, greater than five, metastatic, multifocal, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Glioma malignant, metastatic																										1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter					+																					2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Furan

	Vehicle Control	8 mg/kg	15 mg/kg
Adrenal Cortex: Adenoma			
Overall rates[a]	6/50 (12%)	3/50 (6%)	0/50 (0%)
Adjusted rates[b]	17.0%	13.2%	0.0%
Terminal rates[c]	5/33 (15%)	1/17 (6%)	0/16 (0%)
First incidence (days)	550	719	–[e]
Life table tests[d]	P=0.068N	P=0.540N	P=0.072N
Logistic regression tests[d]	P=0.015N	P=0.308N	P=0.018N
Cochran-Armitage test[d]	P=0.011N		
Fisher exact test[d]		P=0.243N	P=0.013N
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates	1/49 (2%)	6/50 (12%)	10/50 (20%)
Adjusted rates	2.6%	24.6%	32.9%
Terminal rates	0/33 (0%)	2/17 (12%)	2/16 (13%)
First incidence (days)	723	701	423
Life table tests	P<0.001	P=0.016	P=0.001
Logistic regression tests	P=0.004	P=0.032	P=0.009
Cochran-Armitage test	P=0.004		
Fisher exact test		P=0.059	P=0.004
Harderian Gland: Adenoma			
Overall rates	3/50 (6%)	4/50 (8%)	0/50 (0%)
Adjusted rates	7.9%	15.2%	0.0%
Terminal rates	1/33 (3%)	1/17 (6%)	0/16 (0%)
First incidence (days)	715	663	–
Life table tests	P=0.273N	P=0.308	P=0.193N
Logistic regression tests	P=0.159N	P=0.429	P=0.146N
Cochran-Armitage test	P=0.132N		
Fisher exact test		P=0.500	P=0.121N
Harderian Gland: Adenoma or Carcinoma			
Overall rates	3/50 (6%)	5/50 (10%)	0/50 (0%)
Adjusted rates	7.9%	17.2%	0.0%
Terminal rates	1/33 (3%)	1/17 (6%)	0/16 (0%)
First incidence (days)	715	556	–
Life table tests	P=0.291N	P=0.200	P=0.193N
Logistic regression tests	P=0.159N	P=0.329	P=0.146N
Cochran-Armitage test	P=0.152N		
Fisher exact test		P=0.357	P=0.121N
Liver: Hepatocellular Adenoma			
Overall rates	20/50 (40%)	33/50 (66%)	42/50 (84%)
Adjusted rates	51.7%	86.4%	100.0%
Terminal rates	15/33 (45%)	12/17 (71%)	16/16 (100%)
First incidence (days)	550	444	498
Life table tests	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P=0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.008	P<0.001

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Liver: Hepatocellular Carcinoma			
Overall rates	7/50 (14%)	32/50 (64%)	34/50 (68%)
Adjusted rates	17.1%	74.8%	77.9%
Terminal rates	0/33 (0%)	7/17 (41%)	7/16 (44%)
First incidence (days)	514	444	423
Life table tests	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	26/50 (52%)	44/50 (88%)	50/50 (100%)
Adjusted rates	58.9%	97.8%	100.0%
Terminal rates	15/33 (45%)	16/17 (94%)	16/16 (100%)
First incidence (days)	514	444	423
Life table tests	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	9/50 (18%)	7/50 (14%)	16/50 (32%)
Adjusted rates	23.8%	30.3%	58.4%
Terminal rates	6/33 (18%)	4/17 (24%)	6/16 (38%)
First incidence (days)	638	556	577
Life table tests	P=0.003	P=0.410	P=0.004
Logistic regression tests	P=0.041	P=0.478N	P=0.044
Cochran-Armitage test	P=0.065		
Fisher exact test		P=0.393N	P=0.083
Lung: Alveolar/bronchiolar Carcinoma			
Overall rates	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rates	8.0%	11.6%	0.0%
Terminal rates	2/33 (6%)	1/17 (6%)	0/16 (0%)
First incidence (days)	542	584	–
Life table tests	P=0.232N	P=0.461	P=0.214N
Logistic regression tests	P=0.106N	P=0.659N	P=0.096N
Cochran-Armitage test	P=0.111N		
Fisher exact test		P=0.661N	P=0.121N
Lung: Alveolar/bronchiolar Carcinoma or Carcinoma (NOS)			
Overall rates	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted rates	11.0%	11.6%	0.0%
Terminal rates	3/33 (9%)	1/17 (6%)	0/16 (0%)
First incidence (days)	542	584	–
Life table tests	P=0.151N	P=0.571	P=0.148N
Logistic regression tests	P=0.052N	P=0.507N	P=0.053N
Cochran-Armitage test	P=0.053N		
Fisher exact test		P=0.500N	P=0.059N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Lung: Alveolar/bronchiolar Adenoma, Alveolar/bronchiolar Carcinoma, or Carcinoma (NOS)			
Overall rates	13/50 (26%)	10/50 (20%)	16/50 (32%)
Adjusted rates	33.7%	39.5%	58.4%
Terminal rates	9/33 (27%)	5/17 (29%)	6/16 (38%)
First incidence (days)	542	556	577
Life table tests	P=0.028	P=0.373	P=0.029
Logistic regression tests	P=0.241	P=0.387N	P=0.248
Cochran-Armitage test	P=0.303		
Fisher exact test		P=0.318N	P=0.330
Skin (Subcutaneous Tissue): Fibroma			
Overall rates	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rates	9.1%	0.0%	0.0%
Terminal rates	3/33 (9%)	0/17 (0%)	0/16 (0%)
First incidence (days)	736 (T)	–	–
Life table tests	P=0.108N	P=0.259N	P=0.273N
Logistic regression tests	P=0.108N	P=0.259N	P=0.273N
Cochran-Armitage test	P=0.035N		
Fisher exact test		P=0.121N	P=0.121N
Skin (Subcutaneous Tissue): Fibrosarcoma			
Overall rates	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rates	0.0%	11.4%	3.6%
Terminal rates	0/33 (0%)	0/17 (0%)	0/16 (0%)
First incidence (days)	–	698	722
Life table tests	P=0.245	P=0.071	P=0.439
Logistic regression tests	P=0.315	P=0.092	P=0.468
Cochran-Armitage test	P=0.360		
Fisher exact test		P=0.121	P=0.500
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma			
Overall rates	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rates	9.1%	11.4%	3.6%
Terminal rates	3/33 (9%)	0/17 (0%)	0/16 (0%)
First incidence (days)	736 (T)	698	722
Life table tests	P=0.487N	P=0.422	P=0.541N
Logistic regression tests	P=0.338N	P=0.557	P=0.429N
Cochran-Armitage test	P=0.250N		
Fisher exact test		P=0.661N	P=0.309N
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma			
Overall rates	1/50 (2%)	5/50 (10%)	3/50 (6%)
Adjusted rates	2.3%	18.7%	8.4%
Terminal rates	0/33 (0%)	1/17 (6%)	0/16 (0%)
First incidence (days)	697	600	556
Life table tests	P=0.150	P=0.048	P=0.251
Logistic regression tests	P=0.247	P=0.085	P=0.346
Cochran-Armitage test	P=0.250		
Fisher exact test		P=0.102	P=0.309

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma			
Overall rates	4/50 (8%)	5/50 (10%)	3/50 (6%)
Adjusted rates	11.2%	18.7%	8.4%
Terminal rates	3/33 (9%)	1/17 (6%)	0/16 (0%)
First incidence (days)	697	600	556
Life table tests	P=0.459	P=0.248	P=0.597
Logistic regression tests	P=0.466N	P=0.424	P=0.502N
Cochran-Armitage test	P=0.442N		
Fisher exact test		P=0.500	P=0.500N
Stomach (Forestomach): Squamous Papilloma			
Overall rates	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rates	0.0%	3.3%	15.2%
Terminal rates	0/33 (0%)	0/17 (0%)	2/16 (13%)
First incidence (days)	–	719	716
Life table tests	P=0.029	P=0.453	P=0.047
Logistic regression tests	P=0.045	P=0.467	P=0.077
Cochran-Armitage test	P=0.065		
Fisher exact test		P=0.500	P=0.121
All Organs: Hemangiosarcoma			
Overall rates	5/50 (10%)	5/50 (10%)	5/50 (10%)
Adjusted rates	12.2%	19.0%	19.1%
Terminal rates	1/33 (3%)	0/17 (0%)	2/16 (13%)
First incidence (days)	660	704	610
Life table tests	P=0.315	P=0.405	P=0.403
Logistic regression tests	P=0.533	P=0.546	P=0.614N
Cochran-Armitage test	P=0.571		
Fisher exact test		P=0.630N	P=0.630N
All Organs: Malignant Lymphoma (Mixed)			
Overall rates	5/50 (10%)	12/50 (24%)	1/50 (2%)
Adjusted rates	13.5%	44.2%	2.3%
Terminal rates	3/33 (9%)	5/17 (29%)	0/16 (0%)
First incidence (days)	676	600	612
Life table tests	P=0.493N	P=0.006	P=0.242N
Logistic regression tests	P=0.218N	P=0.025	P=0.105N
Cochran-Armitage test	P=0.173N		
Fisher exact test		P=0.054	P=0.102N
All Organs: Benign Neoplasms			
Overall rates	32/50 (64%)	38/50 (76%)	46/50 (92%)
Adjusted rates	77.6%	94.9%	100.0%
Terminal rates	24/33 (73%)	15/17 (88%)	16/16 (100%)
First incidence (days)	550	444	423
Life table tests	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P=0.017	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.138	P<0.001

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
All Organs: Malignant Neoplasms			
Overall rates	18/50 (36%)	41/50 (82%)	39/50 (78%)
Adjusted rates	39.5%	89.1%	86.1%
Terminal rates	6/33 (18%)	12/17 (71%)	10/16 (63%)
First incidence (days)	514	444	423
Life table tests	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms			
Overall rates	43/50 (86%)	45/50 (90%)	50/50 (100%)
Adjusted rates	87.8%	97.8%	100.0%
Terminal rates	27/33 (82%)	16/17 (94%)	16/16 (100%)
First incidence (days)	514	444	423
Life table tests	P<0.001	P=0.002	P<0.001
Logistic regression tests	P=0.001	P=0.066	P=0.009
Cochran-Armitage test	P=0.009		
Fisher exact test		P=0.380	P=0.006

(T)Terminal sacrifice

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

[e] Not applicable; no neoplasms in animal group

TABLE C4a
Historical Incidence of Benign Pheochromocytomas of the Adrenal Medulla in Male B6C3F$_1$ Mice Receiving Corn Oil Vehicle by Gavage[a]

Study	Incidence of Benign Pheochromocytoma in Controls
Historical Incidence at Southern Research Institute	
Benzaldehyde	2/49
Dichlorvos	2/48
Furan	1/49
Furfural	2/50
γ-Butyrolactone	1/48
Total	8/244 (3.3%)
Standard deviation	1.1%
Range	2%–4%
Overall Historical Incidence	
Total	16/582 (2.7%)
Standard deviation	1.6%
Range	0%–4%

[a] Data as of 17 September 1990

TABLE C4b
Historical Incidence of Liver Neoplasms in Male B6C3F$_1$ Mice Receiving Corn Oil Vehicle by Gavage[a]

Study	Incidence in Controls		
	Hepatocellular Adenoma or Neoplastic Nodule	Hepatocellular Carcinoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Neoplastic Nodule
Historical Incidence at Southern Research Institute			
Benzaldehyde	8/50	12/50	19/50
Dichlorvos	7/50	10/50	16/50
Furan	20/50	7/50	26/50
Furfural	9/50	7/50	16/50
γ-Butyrolactone	8/50	16/50	24/50
Total	52/250 (20.8%)	52/250 (20.8%)	101/250 (40.4%)
Standard deviation	10.8%	7.6%	9.2%
Range	14%–40%	14%–32%	32%–52%
Overall Historical Incidence			
Total	123/599 (20.5%)	103/599 (17.2%)	210/599 (35.1%)
Standard deviation	10.4%	6.2%	11.0%
Range	4%–40%	10%–32%	14%–52%

[a] Data as of 17 September 1990

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Furan[a]

	Vehicle Control	8 mg/kg	15 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Natural deaths		1	1
Accidental deaths	1	8	8
Moribund kills	16	24	25
Survivors			
Terminal sacrifice	33	17	16
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(50)	(50)	(50)
Perforation		2 (4%)	
Intestine large, cecum	(50)	(50)	(49)
Mucosa, epithelium, metaplasia, squamous			1 (2%)
Intestine large, colon	(50)	(50)	(49)
Mucosa, cyst	1 (2%)		
Intestine small, duodenum	(49)	(49)	(48)
Angiectasis		1 (2%)	
Inflammation, chronic			2 (4%)
Mucosa, hyperplasia, papillary		1 (2%)	
Mucosa, ulcer			1 (2%)
Intestine small, ileum	(50)	(49)	(48)
Lymphoid tissue, hyperplasia, lymphoid	1 (2%)	1 (2%)	
Intestine small, jejunum	(50)	(49)	(48)
Lymphoid tissue, hyperplasia, lymphoid			1 (2%)
Mucosa, hyperplasia, papillary			1 (2%)
Liver	(50)	(50)	(50)
Angiectasis		1 (2%)	3 (6%)
Basophilic focus		1 (2%)	
Basophilic focus, two, multiple			1 (2%)
Clear cell focus		1 (2%)	1 (2%)
Clear cell focus, three, multiple			1 (2%)
Congestion		1 (2%)	
Cyst	1 (2%)	1 (2%)	1 (2%)
Cyst, multiple		1 (2%)	
Cytoplasmic alteration, focal			1 (2%)
Degeneration, cystic		1 (2%)	
Depletion, glycogen	2 (4%)	1 (2%)	
Eosinophilic focus	1 (2%)	1 (2%)	1 (2%)
Fibrosis, focal	3 (6%)		
Hematopoietic cell proliferation	4 (8%)		2 (4%)
Hemorrhage			2 (4%)
Hyperplasia, lymphoid	26 (52%)	24 (48%)	22 (44%)
Hyperplasia, multifocal	1 (2%)	44 (88%)	49 (98%)
Infarct	1 (2%)	13 (26%)	11 (22%)
Infarct, two, multiple			1 (2%)
Infiltration cellular, mixed cell	2 (4%)	23 (46%)	29 (58%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Alimentary System (continued)			
Liver (continued)			
Inflammation, multifocal	17 (34%)	7 (14%)	2 (4%)
Mineralization			3 (6%)
Mixed cell focus		5 (10%)	1 (2%)
Necrosis, multifocal	1 (2%)	2 (4%)	3 (6%)
Thrombus		4 (8%)	1 (2%)
Vacuolization cytoplasmic	8 (16%)	24 (48%)	36 (72%)
Artery, inflammation, chronic			1 (2%)
Bile duct, dilatation			6 (12%)
Biliary tract, fibrosis		45 (90%)	49 (98%)
Biliary tract, hyperplasia		46 (92%)	49 (98%)
Biliary tract, inflammation, chronic		44 (88%)	49 (98%)
Centrilobular, necrosis	1 (2%)	3 (6%)	1 (2%)
Hepatocyte, cytomegaly	8 (16%)	45 (90%)	50 (100%)
Hepatocyte, degeneration		43 (86%)	43 (86%)
Hepatocyte, mitotic alteration	1 (2%)	1 (2%)	
Hepatocyte, necrosis	2 (4%)	39 (78%)	41 (82%)
Hepatocyte, pigmentation			1 (2%)
Kupffer cell, pigmentation	2 (4%)	43 (86%)	50 (100%)
Parenchyma, atrophy, focal	1 (2%)		
Parenchyma, atrophy, multifocal		45 (90%)	50 (100%)
Serosa, fibrosis, focal		1 (2%)	
Serosa, pigmentation, focal		1 (2%)	
Mesentery	(6)	(10)	(3)
Fibrosis	1 (17%)		1 (33%)
Hyperplasia, lymphoid		1 (10%)	
Infarct		1 (10%)	
Inflammation, chronic	1 (17%)		1 (33%)
Mineralization		1 (10%)	1 (33%)
Necrosis			1 (33%)
Fat, necrosis	3 (50%)		
Pancreas	(50)	(50)	(50)
Atrophy, focal		1 (2%)	
Atypical cells, focal			1 (2%)
Hyperplasia, lymphoid		3 (6%)	
Duct, dilatation			1 (2%)
Salivary glands	(50)	(50)	(48)
Depletion	1 (2%)		
Hyperplasia, lymphoid		4 (8%)	4 (8%)
Adventitia, inflammation, chronic		1 (2%)	
Stomach, forestomach	(49)	(50)	(50)
Cyst epithelial inclusion	1 (2%)		
Inflammation, focal	9 (18%)	13 (26%)	21 (42%)
Mineralization, focal		1 (2%)	
Mucosa, edema		1 (2%)	
Mucosa, erosion	2 (4%)	5 (10%)	6 (12%)
Mucosa, hyperplasia, papillary	7 (14%)	14 (28%)	22 (44%)
Mucosa, inflammation, focal			1 (2%)
Mucosa, mineralization			2 (4%)
Mucosa, ulcer	3 (6%)	3 (6%)	3 (6%)
Mucosa, ulcer, two, multiple			1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Alimentary System (continued)			
Stomach, glandular	(49)	(50)	(50)
Inflammation, focal	1 (2%)	6 (12%)	4 (8%)
Mineralization		3 (6%)	
Epithelium, degeneration, hyaline	1 (2%)	2 (4%)	
Epithelium, metaplasia, squamous		1 (2%)	
Mucosa, cyst	1 (2%)	1 (2%)	1 (2%)
Mucosa, cyst, multiple		1 (2%)	
Mucosa, dysplasia			1 (2%)
Mucosa, erosion		1 (2%)	1 (2%)
Mucosa, hyperplasia, papillary			1 (2%)
Mucosa, mineralization	1 (2%)		1 (2%)
Tongue		(1)	(1)
Hemorrhage			1 (100%)
Tooth	(43)	(36)	(32)
Incisor, dysplasia	43 (100%)	35 (97%)	32 (100%)
Incisor, inflammation, suppurative	4 (9%)	3 (8%)	5 (16%)
Molar, inflammation, suppurative			1 (3%)
Cardiovascular System			
Blood vessel	(2)	(2)	(4)
Abdominal, inflammation, chronic			1 (25%)
Abdominal, thrombus	1 (50%)		
Abdominal, adventitia, thrombus			1 (25%)
Aorta, mineralization		1 (50%)	
Aorta, media, mineralization			2 (50%)
Mesenteric artery, inflammation, chronic		1 (50%)	2 (50%)
Mesenteric artery, media, mineralization			1 (25%)
Renal artery, mineralization		1 (50%)	
Thoracic, artery, mineralization	1 (50%)		
Heart	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Mineralization		1 (2%)	
Coronary artery, mineralization			1 (2%)
Myocardium, mineralization			1 (2%)
Endocrine System			
Adrenal gland	(50)	(50)	(50)
Hyperplasia, focal			1 (2%)
Adrenal gland, cortex	(50)	(50)	(50)
Depletion	1 (2%)		
Focal cellular change		1 (2%)	
Hyperplasia		1 (2%)	
Hyperplasia, focal	2 (4%)		1 (2%)
Vacuolization cytoplasmic, focal	1 (2%)		
Subcapsular, hyperplasia		2 (4%)	
Subcapsular, hyperplasia, focal	7 (14%)	2 (4%)	1 (2%)
Adrenal gland, medulla	(49)	(50)	(50)
Hyperplasia	2 (4%)	3 (6%)	3 (6%)
Hyperplasia, focal		3 (6%)	9 (18%)
Extra adrenal tissue, ectopic tissue			1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Endocrine System (continued)			
Parathyroid gland	(49)	(48)	(50)
Cyst	1 (2%)		
Cyst, multiple		1 (2%)	
Hyperplasia		1 (2%)	
Pituitary gland	(50)	(44)	(48)
Cyst			1 (2%)
Pars distalis, angiectasis		1 (2%)	
Pars distalis, cyst	6 (12%)	1 (2%)	3 (6%)
Pars distalis, focal cellular change			1 (2%)
Pars distalis, hyperplasia, focal	2 (4%)	1 (2%)	1 (2%)
Pars nervosa, angiectasis		1 (2%)	
Thyroid gland	(50)	(50)	(50)
Degeneration		1 (2%)	
Degeneration, cystic	6 (12%)	7 (14%)	4 (8%)
Follicle, cyst			1 (2%)
Follicular cell, hyperplasia	4 (8%)	4 (8%)	3 (6%)
General Body System			
None			
Genital System			
Coagulating gland	(1)	(1)	
Dilatation	1 (100%)	1 (100%)	
Hyperplasia, adenomatous		1 (100%)	
Epididymis	(50)	(50)	(50)
Granuloma		1 (2%)	
Granuloma, sperm		1 (2%)	
Hyperplasia, lymphoid	2 (4%)		2 (4%)
Inflammation, chronic			1 (2%)
Preputial gland	(6)	(6)	(5)
Degeneration, cystic	1 (17%)	4 (67%)	4 (80%)
Fibrosis		1 (17%)	
Inflammation, suppurative	5 (83%)	3 (50%)	3 (60%)
Prostate	(49)	(50)	(50)
Degeneration, cystic	1 (2%)	1 (2%)	
Dilatation	1 (2%)	1 (2%)	2 (4%)
Edema		2 (4%)	2 (4%)
Granuloma	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
Inflammation, chronic	2 (4%)		
Artery, media, hyperplasia	1 (2%)		
Seminal vesicle	(50)	(50)	(50)
Dilatation	2 (4%)		
Inflammation, chronic	1 (2%)		
Testes	(50)	(50)	(50)
Granuloma, sperm	1 (2%)		
Mineralization	1 (2%)	4 (8%)	1 (2%)
Germinal epithelium, degeneration	3 (6%)	2 (4%)	2 (4%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Furan
(continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
Metaplasia, osseous, focal			1 (2%)
Lymph node	(50)	(50)	(49)
Iliac, hyperplasia	1 (2%)		
Inguinal, angiectasis	2 (4%)		1 (2%)
Inguinal, congestion	1 (2%)		
Inguinal, hyperplasia	4 (8%)		1 (2%)
Pancreatic, hyperplasia, lymphoid		1 (2%)	
Pancreatic, inflammation, chronic, focal	1 (2%)		
Renal, hyperplasia	1 (2%)		
Lymph node, bronchial	(14)	(27)	(26)
Hyperplasia, lymphoid		2 (7%)	
Lymph node, mandibular	(49)	(48)	(43)
Hyperplasia	2 (4%)	1 (2%)	
Hyperplasia, lymphoid		4 (8%)	
Pigmentation		1 (2%)	
Lymph node, mediastinal	(38)	(45)	(41)
Depletion lymphoid			1 (2%)
Hyperplasia		1 (2%)	2 (5%)
Hyperplasia, lymphoid	1 (3%)	5 (11%)	
Lymph node, mesenteric	(50)	(50)	(48)
Angiectasis	21 (42%)	7 (14%)	6 (13%)
Hematopoietic cell proliferation	1 (2%)		
Hyperplasia			1 (2%)
Hyperplasia, lymphoid		2 (4%)	1 (2%)
Inflammation, suppurative			1 (2%)
Spleen	(50)	(50)	(49)
Depletion	2 (4%)		
Depletion, lymphoid		1 (2%)	
Hematopoietic cell proliferation	5 (10%)	11 (22%)	15 (31%)
Hyperplasia, lymphoid	2 (4%)	7 (14%)	
Artery, degeneration, hyaline			1 (2%)
Red pulp, depletion		2 (4%)	
Thymus	(42)	(44)	(42)
Cyst	1 (2%)		
Depletion lymphoid	3 (7%)	4 (9%)	1 (2%)
Hyperplasia, lymphoid		3 (7%)	
Epithelial cell, hyperplasia		1 (2%)	
Integumentary System			
Skin	(50)	(50)	(50)
Erosion	1 (2%)		
Exudate	1 (2%)		1 (2%)
Inflammation, chronic	10 (20%)	6 (12%)	7 (14%)
Ulcer	4 (8%)	2 (4%)	4 (8%)
Hair follicle, atrophy			1 (2%)
Prepuce, fibrosis		1 (2%)	1 (2%)
Prepuce, inflammation, chronic	1 (2%)		1 (2%)
Prepuce, ulcer	1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Furan
(continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Integumentary System (continued)			
Skin (continued)			
Subcutaneous tissue, congestion		1 (2%)	
Subcutaneous tissue, edema	1 (2%)	2 (4%)	
Subcutaneous tissue, inflammation, chronic		1 (2%)	
Subcutaneous tissue, inflammation, suppurative	1 (2%)	1 (2%)	
Subcutaneous tissue, thrombus	1 (2%)		
Subcutaneous tissue, fat, necrosis	1 (2%)		
Subcutaneous tissue, head, hyperplasia, mast cell		1 (2%)	
Musculoskeletal System			
Bone	(50)	(50)	(50)
Cranium, hyperostosis	1 (2%)		
Distal, joint, femur, arthrosis		5 (10%)	
Nervous System			
None			
Respiratory System			
Lung	(50)	(50)	(50)
Congestion	1 (2%)	4 (8%)	4 (8%)
Granuloma			2 (4%)
Hyperplasia, lymphoid	23 (46%)	20 (40%)	23 (46%)
Hyperplasia, macrophage	15 (30%)	12 (24%)	17 (34%)
Infiltration cellular, polymorphonuclear			1 (2%)
Inflammation, chronic, focal			1 (2%)
Inflammation, focal			1 (2%)
Inflammation, granulomatous, focal			1 (2%)
Inflammation, suppurative	1 (2%)		
Pigmentation			1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)	3 (6%)	2 (4%)
Bronchiole, hyperplasia			1 (2%)
Bronchus, epithelium, hyperplasia, papillary	1 (2%)		
Mediastinum, foreign body		2 (4%)	
Mediastinum, hemorrhage			1 (2%)
Mediastinum, inflammation, suppurative		2 (4%)	
Pleura, inflammation, suppurative		1 (2%)	
Nose	(50)	(50)	(50)
Lumen, exudate	16 (32%)	9 (18%)	1 (2%)
Lumen, foreign body	16 (32%)	13 (26%)	6 (12%)
Lumen, hemorrhage	2 (4%)		
Lumen, inflammation, suppurative	2 (4%)	2 (4%)	3 (6%)
Mucosa, inflammation, suppurative	1 (2%)		1 (2%)
Nasolacrimal duct, inflammation, suppurative	1 (2%)	2 (4%)	
Special Senses System			
None			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Furan
(continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Urinary System			
Kidney	(50)	(50)	(50)
Atrophy		1 (2%)	1 (2%)
Congestion		3 (6%)	1 (2%)
Cyst		1 (2%)	
Fibrosis	2 (4%)	2 (4%)	1 (2%)
Fibrosis, focal	1 (2%)		
Hydronephrosis	1 (2%)	3 (6%)	4 (8%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Infarct		2 (4%)	
Inflammation, chronic		1 (2%)	
Inflammation, suppurative		1 (2%)	
Metaplasia, osseous	1 (2%)	1 (2%)	
Mineralization	36 (72%)	34 (68%)	41 (82%)
Nephropathy	41 (82%)	36 (72%)	38 (76%)
Thrombus		1 (2%)	
Capsule, fibrosis			1 (2%)
Papilla, necrosis	1 (2%)		
Pelvis, dilatation	1 (2%)		
Renal tubule, cyst	3 (6%)		
Renal tubule, dilatation	3 (6%)	2 (4%)	
Renal tubule, necrosis	1 (2%)		
Renal tubule, pigmentation	1 (2%)		
Renal tubule, vacuolization cytoplasmic	6 (12%)	2 (4%)	
Ureter	(1)	(2)	(2)
Mineralization		1 (50%)	
Necrosis		1 (50%)	
Serosa, hyperplasia, lymphoid		1 (50%)	2 (100%)
Urinary bladder	(50)	(49)	(50)
Hemorrhage	1 (2%)		1 (2%)
Hyperplasia, lymphoid	1 (2%)		2 (4%)

[a] Number of animals examined microscopically at site and number of animals with lesion.

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF FURAN

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TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Furan

	Vehicle Control	8 mg/kg	15 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Natural deaths	1	1	
Accidental deaths	4	8	11
Moribund kills	16	16	37
Survivors			
Terminal sacrifice	28	25	2
Died last week of study	1		
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(50)	(50)	(50)
Papilloma squamous	1 (2%)		
Gallbladder	(49)	(49)	(43)
Intestine small, duodenum	(49)	(47)	(45)
Polyp adenomatous	1 (2%)		
Intestine small, ileum	(48)	(47)	(44)
Liver	(50)	(50)	(50)
Carcinoma		1 (2%)	
Hemangiosarcoma			1 (2%)
Hepatocellular carcinoma	2 (4%)	6 (12%)	22 (44%)
Hepatocellular carcinoma, two, multiple			4 (8%)
Hepatocellular carcinoma, three, multiple			1 (2%)
Hepatocellular adenoma	5 (10%)	17 (34%)	8 (16%)
Hepatocellular adenoma, two, multiple		8 (16%)	4 (8%)
Hepatocellular adenoma, three, multiple		4 (8%)	10 (20%)
Hepatocellular adenoma, four, multiple		2 (4%)	4 (8%)
Hepatocellular adenoma, five, multiple			8 (16%)
Hepatocellular adenoma, greater than five, multiple			14 (28%)
Sarcoma, metastatic		1 (2%)	
Sarcoma stromal, metastatic, uterus	1 (2%)		
Mesentery	(24)	(27)	(4)
Carcinoma, metastatic, liver		1 (4%)	
Hemangiosarcoma		1 (4%)	
Hepatocellular carcinoma, metastatic, liver			1 (25%)
Sarcoma, metastatic	1 (4%)	1 (4%)	
Sarcoma stromal, metastatic, uterus	1 (4%)		
Pancreas	(50)	(49)	(50)
Carcinoma, metastatic, liver		1 (2%)	
Sarcoma, metastatic	1 (2%)	1 (2%)	
Sarcoma stromal, metastatic, uterus	1 (2%)		
Salivary glands	(50)	(50)	(50)
Adventitia, hemangioma	1 (2%)		
Stomach, forestomach	(50)	(49)	(49)
Mucosa, papilloma squamous	2 (4%)	6 (12%)	3 (6%)
Stomach, glandular	(50)	(49)	(50)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Cardiovascular System			
Heart	(50)	(50)	(50)
Endocrine System			
Adrenal gland, cortex	(50)	(50)	(50)
Extra adrenal tissue, carcinoma, metastatic, liver		1 (2%)	
Subcapsular, adenoma			1 (2%)
Adrenal gland, medulla	(50)	(50)	(50)
Pheochromocytoma benign	2 (4%)	1 (2%)	3 (6%)
Pheochromocytoma benign, multiple			3 (6%)
Islets, pancreatic	(50)	(50)	(50)
Carcinoma		1 (2%)	
Pituitary gland	(49)	(47)	(46)
Adenoma		1 (2%)	
Pars distalis, adenoma	25 (51%)	18 (38%)	9 (20%)
Pars distalis, carcinoma	1 (2%)		
Pars intermedia, adenoma			1 (2%)
Thyroid gland	(50)	(50)	(50)
Follicular cell, adenoma	2 (4%)	3 (6%)	1 (2%)
Follicular cell, adenoma, two, multiple			1 (2%)
General Body System			
Tissue NOS	(1)	(1)	
Abdominal, sarcoma	1 (100%)		
Genital System			
Ovary	(49)	(49)	(50)
Cystadenoma, papillary			1 (2%)
Granulosa cell neoplasm benign	1 (2%)		
Granulosa-theca neoplasm benign	1 (2%)		
Periovarian tissue, carcinoma, metastatic, liver		1 (2%)	
Oviduct	(4)	(4)	(1)
Carcinoma, metastatic, liver		1 (25%)	
Uterus	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
Sarcoma stromal	2 (4%)		
Endometrium, polyp stromal	1 (2%)		4 (8%)
Endometrium, polyp stromal, multiple	1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Hematopoietic System			
Blood	(1)	(1)	
Bone marrow	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
Lymph node	(50)	(50)	(50)
Lymph node, bronchial	(21)	(29)	(21)
Lymph node, mandibular	(47)	(46)	(48)
Lymph node, mediastinal	(41)	(45)	(43)
Lymph node, mesenteric	(49)	(49)	(49)
Spleen	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		2 (4%)
Thymus	(46)	(46)	(45)
Epithelial cell, thymoma benign		1 (2%)	
Integumentary System			
Mammary gland	(49)	(50)	(48)
Adenocarcinoma	2 (4%)	1 (2%)	3 (6%)
Carcinoma	1 (2%)		
Skin	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		
Head, sebaceous gland, adenoma		1 (2%)	
Sebaceous gland, adenoma		1 (2%)	
Subcutaneous tissue, hemangiosarcoma			1 (2%)
Subcutaneous tissue, sarcoma		1 (2%)	
Subcutaneous tissue, sarcoma, metastatic		1 (2%)	
Tail, papilloma squamous			1 (2%)
Tail, subcutaneous tissue, sarcoma		1 (2%)	
Musculoskeletal System			
Skeletal muscle	(3)	(2)	
Abdominal, sarcoma		1 (50%)	
Diaphragm, sarcoma, metastatic		1 (50%)	
Nervous System			
Brain	(50)	(50)	(50)
Meningioma benign			1 (2%)
Peripheral nerve	(1)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Respiratory System			
Lung	(50)	(50)	(50)
Adenocarcinoma, greater than five, metastatic, multiple, mammary gland			1 (2%)
Alveolar/bronchiolar adenoma	3 (6%)	4 (8%)	3 (6%)
Alveolar/bronchiolar carcinoma	2 (4%)	2 (4%)	1 (2%)
Hemangiosarcoma		1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)		1 (2%)
Hepatocellular carcinoma, three, metastatic, multiple, liver	1 (2%)		
Hepatocellular carcinoma, four, metastatic, multiple, liver			1 (2%)
Sarcoma, metastatic		1 (2%)	
Parenchyma, mediastinum, carcinoma, metastatic, liver		1 (2%)	
Nose	(50)	(50)	(50)
Trachea	(50)	(50)	(50)
Special Senses System			
Harderian gland	(4)	(6)	(4)
Adenoma	2 (50%)	4 (67%)	2 (50%)
Urinary System			
Kidney	(50)	(50)	(49)
Urinary bladder	(50)	(50)	(50)
Systemic Lesions			
Multiple organs[a]	(50)	(50)	(50)
Lymphoma malignant lymphocytic	3 (6%)	3 (6%)	
Lymphoma malignant mixed	17 (34%)	11 (22%)	7 (14%)
Neoplasm Summary			
Total animals with primary neoplasms[b]	43	43	50
Total primary neoplasms	83	101	124
Total animals with benign neoplasms	34	38	48
Total benign neoplasms	48	71	82
Total animals with malignant neoplasms	30	24	32
Total malignant neoplasms	35	30	42
Total animals with metastatic neoplasms	4	2	3
Total metastatic neoplasms	7	12	4

[a] Number of animals with any tissue examined microscopically
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: Vehicle Control

Number of Days on Study	4 1 4	4 3 0	4 8 5	4 9 4	5 3 4	5 5 7	5 5 7	6 2 3	6 4 2	6 4 6	6 8 0	6 8 0	6 9 0	6 9 5	6 9 8	7 0 9	7 1 3	7 1 8	7 2 4	7 2 4	7 2 5	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	4 0 1	3 9 1	3 2 1	3 1 1	3 5 1	3 2 2	3 6 1	3 6 2	4 0 2	3 4 1	3 3 1	3 6 3	3 9 2	3 9 3	3 1 2	3 5 2	3 7 1	3 2 3	3 1 3	3 7 2	3 9 4	3 1 4	3 1 5	3 2 4	3 2 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous														X											
Gallbladder	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																X									
Intestine small, ileum	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma										X															
Hepatocellular adenoma																						X			
Sarcoma stromal, metastatic, uterus				X																					
Mesentery				+	+	+	+	+			+	+	+	+		+		+	+		+		+		+
Sarcoma, metastatic																X									
Sarcoma stromal, metastatic, uterus				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic																X									
Sarcoma stromal, metastatic, uterus				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adventitia, hemangioma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucosa, papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel				+	+																				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	3 4 2	3 3 2	3 3 3	3 3 4	3 3 5	3 4 3	3 4 4	3 4 5	3 5 3	3 5 4	3 5 5	3 6 4	3 6 5	3 7 3	3 7 4	3 7 5	3 8 1	3 8 2	3 8 3	3 8 4	3 8 5	3 9 5	4 0 3	4 0 4	4 0 5	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																									1
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous																									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X																								2
Hepatocellular adenoma						X									X			X		X					5
Sarcoma stromal, metastatic, uterus																									1
Mesentery	+			+					+		+	+						+		+			+	+	24
Sarcoma, metastatic																									1
Sarcoma stromal, metastatic, uterus																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic																									1
Sarcoma stromal, metastatic, uterus																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adventitia, hemangioma																			X						1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucosa, papilloma squamous												X						X							2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth														+										+	2
Cardiovascular System																									
Blood vessel																									2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	4 1 4	4 3 0	4 8 5	4 9 4	5 3 4	5 5 7	5 5 7	6 2 3	6 4 2	6 4 6	6 8 0	6 8 0	6 9 0	6 9 0	6 9 5	6 9 8	7 0 9	7 1 3	7 1 8	7 2 4	7 2 4	7 2 5	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	4 0 1	3 9 1	3 2 1	3 1 1	3 5 1	3 2 2	3 6 1	3 6 2	4 0 2	3 4 1	3 3 1	3 6 3	3 9 2	3 9 3	3 1 2	3 5 2	3 7 2	3 2 1	3 1 3	3 7 3	3 9 2	3 4 4	3 1 4	3 1 5	3 2 4	3 2 5
Endocrine System (continued)																										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign												X														
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X			X	X	X				X				X	X				X	X
Pars distalis, carcinoma																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																										
General Body System																										
Tissue NOS																+										
Abdominal, sarcoma																X										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																										
Granulosa-theca tumor benign																					X					
Oviduct					+		+													+						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																								
Sarcoma stromal				X																						
Endometrium, polyp stromal																		X								
Endometrium, polyp stromal, multiple																										
Hematopoietic System																										
Blood				+																						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	M	M	M	M	M	+	M	M	M	M	+	M	M	M	+	M	M	+	M	+	M	+	M	+	
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma																							X			
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	3 4 2	3 3 2	3 3 3	3 3 4	3 3 5	3 4 3	3 4 4	3 4 5	3 5 3	3 5 4	3 5 5	3 6 4	3 6 5	3 7 3	3 7 4	3 7 5	3 8 1	3 8 2	3 8 3	3 8 4	3 8 5	3 9 5	4 0 3	4 0 4	4 0 5	**Total Tissues/ Tumors**
Endocrine System (continued)																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign													X												2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X	X	X		X	X	X		X	X					X			X	X	X	X		X	X	25
Pars distalis, carcinoma					X																				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																				X		X			2
General Body System																									
Tissue NOS																									1
Abdominal, sarcoma																									1
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Granulosa cell tumor benign													X												1
Granulosa-theca tumor benign																									1
Oviduct																		+							4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									1
Sarcoma stromal								X																	2
Endometrium, polyp stromal																									1
Endometrium, polyp stromal, multiple																	X								1
Hematopoietic System																									
Blood																									1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	+	M	M	M	M	M	+	+	+	M	+	+	+	+	M	+	+	M	M	M	+	M	+	21
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	47
Lymph node, mediastinal	+	M	M	+	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									1
Thymus	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	46

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	4 1 4	4 3 0	4 8 5	4 9 4	5 3 4	5 5 7	5 5 7	6 2 3	6 4 2	6 4 6	6 8 0	6 8 0	6 9 0	6 9 5	6 9 8	7 0 9	7 1 3	7 1 8	7 2 4	7 2 4	7 2 5	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	4 0 1	3 9 1	3 2 1	3 1 1	3 5 1	3 2 2	3 6 1	3 6 2	4 0 2	3 4 1	3 3 1	3 6 3	3 9 2	3 9 3	3 1 2	3 5 2	3 7 1	3 2 3	3 1 3	3 7 2	3 9 4	3 1 4	3 1 5	3 2 4	3 2 5
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenocarcinoma																						X			
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+		+																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																			+						
Spinal cord					+																				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X			X									
Alveolar/bronchiolar carcinoma													X												
Hepatocellular carcinoma, metastatic, liver										X															
Hepatocellular carcinoma, three, metastatic, multiple, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear					+																				
Harderian gland						+													+			+			
Adenoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic						X										X									
Lymphoma malignant mixed	X										X							X	X					X	X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: Vehicle Control (continued)

Number of Days on Study	7 3 3 7	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	7 3 3 8	
Carcass ID Number	3 4 2	3 3 2	3 3 3	3 3 4	3 3 5	3 4 3	3 4 4	3 4 5	3 5 3	3 5 4	3 5 5	3 6 4	3 6 5	3 7 3	3 7 4	3 7 5	3 8 1	3 8 2	3 8 3	3 8 4	3 8 5	3 9 5	4 0 3	4 0 4	4 0 5	**Total Tissues/ Tumors**
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma			X																						2
Carcinoma					X																				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle											+														3
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																									1
Spinal cord																									1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X										3
Alveolar/bronchiolar carcinoma							X																		2
Hepatocellular carcinoma, metastatic, liver																									1
Hepatocellular carcinoma, three, metastatic, multiple, liver	X																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Ear																									1
Harderian gland												+													4
Adenoma												X													2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic											X														3
Lymphoma malignant mixed	X			X		X		X	X	X		X				X			X			X	X		17

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: 8 mg/kg

Number of Days on Study	3 3 0	4 4 0	4 7 0	4 9 0	5 9 0	6 2 0	6 3 0	6 4 0	6 4 0	6 4 0	6 7 0	6 8 0	6 8 0	6 9 0	7 0 0	7 0 0	7 0 0	7 1 0	7 1 0	7 1 0	7 2 0	7 2 0	7 2 0	7 2 0	7 3 0
Carcass ID Number	5 7 1	5 7 2	5 8 1	5 9 1	5 5 1	5 7 3	5 5 2	5 3 1	5 3 2	5 5 3	5 8 2	5 6 1	5 6 2	5 7 4	5 6 3	6 0 1	5 4 1	5 3 3	6 0 2	5 4 2	5 1 1	5 9 2	5 2 1	5 9 3	5 3 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, duodenum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, ileum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X																					
Hepatocellular carcinoma																	X			X	X				
Hepatocellular adenoma		X			X				X	X				X	X				X			X		X	
Hepatocellular adenoma, two, multiple											X					X					X				
Hepatocellular adenoma, three, multiple						X																			
Hepatocellular adenoma, four, multiple																							X		
Sarcoma, metastatic														X											
Mesentery	+	+	+	+	+	+			+			+	+	+		+	+	+	+	+			+	+	+
Carcinoma, metastatic, liver				X																					
Hemangiosarcoma																									
Sarcoma, metastatic														X											
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, liver				X																					
Sarcoma, metastatic														X											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucosa, papilloma squamous							X													X			X		
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue						+									+										
Tooth																									
Cardiovascular System																									
Blood vessel													+												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 1 2	5 1 3	5 1 4	5 1 5	5 2 2	5 2 3	5 2 4	5 2 5	5 3 5	5 4 3	5 4 4	5 4 5	5 5 4	5 5 5	5 6 4	6 6 5	5 7 5	5 8 3	5 8 4	5 8 5	5 9 4	5 9 5	6 0 3	6 0 4	6 0 5	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																									1
Hepatocellular carcinoma							X						X		X										6
Hepatocellular adenoma	X				X			X			X		X	X	X									X	17
Hepatocellular adenoma, two, multiple		X	X									X					X		X						8
Hepatocellular adenoma, three, multiple				X					X													X			4
Hepatocellular adenoma, four, multiple						X																			2
Sarcoma, metastatic																									1
Mesentery		+	+					+	+	+					+		+	+				+			27
Carcinoma, metastatic, liver																									1
Hemangiosarcoma																	X								1
Sarcoma, metastatic																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, liver																									1
Sarcoma, metastatic																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mucosa, papilloma squamous			X									X					X								6
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																									2
Tooth												+													1
Cardiovascular System																									
Blood vessel																								+	2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	3 3 0	4 4 6	4 7 9	4 9 9	5 9 2	6 2 7	6 3 8	6 4 2	6 4 2	6 4 6	6 7 3	6 8 6	6 8 8	6 9 5	7 0 1	7 0 2	7 0 3	7 1 5	7 1 6	7 1 7	7 2 1	7 2 4	7 2 5	7 2 8	7 3 3
Carcass ID Number	5 7 1	5 7 2	5 8 1	5 9 1	5 5 1	5 7 3	5 5 2	5 3 1	5 3 2	5 5 3	5 8 2	5 6 1	5 6 2	5 7 4	5 6 3	6 0 1	5 4 1	5 3 3	6 0 2	5 4 2	5 1 1	5 9 2	5 2 1	5 9 3	5 3 4
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Extra adrenal tissue, carcinoma, metastatic, liver				X																					
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									X
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																									
Pars distalis, adenoma										X			X			X			X		X		X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS		+																							
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Periovarian tissue, carcinoma, metastatic, liver				X																					
Oviduct		+		+		+																			
Carcinoma, metastatic, liver				X																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood		+																							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	M	+	M	M	M	+	M	+	+	M	+	+	M	+	+	M	+	+	+	+	M	+	M	+
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	I	M	+	+
Epithelial cell, thymoma benign											X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 1 2	5 1 3	5 1 4	5 1 5	5 2 2	5 2 3	5 2 4	5 2 5	5 3 5	5 4 3	5 4 4	5 4 5	5 5 4	5 5 5	5 6 4	5 6 5	5 7 5	5 8 3	5 8 4	5 8 5	5 9 4	5 9 5	6 0 3	6 0 4	6 0 5	**Total Tissues/ Tumors**
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Extra adrenal tissue, carcinoma, metastatic, liver																									1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign														X											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																									1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Adenoma																			X						1
Pars distalis, adenoma	X	X	X	X	X						X						X	X				X	X		18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma						X						X						X							3
General Body System																									
Tissue NOS																									1
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Periovarian tissue, carcinoma, metastatic, liver																									1
Oviduct														+											4
Carcinoma, metastatic, liver																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																									
Blood																									1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	M	+	+	M	M	M	M	+	+	+	+	+	+	+	+	M	M	+	+	M	M	+	+	M	+ 29
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+ 46
Lymph node, mediastinal	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+ 45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ 49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ 50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ 46
Epithelial cell, thymoma benign																									1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	330	346	479	499	592	627	638	642	644	646	663	678	686	688	695	701	700	703	711	715	716	717	721	724	722	725	729	733
Carcass ID Number	57 1	57 2	58 1	59 1	55 1	57 3	55 2	53 1	53 2	55 3	58 2	56 1	66 2	67 4	56 3	60 1	64 1	53 3	60 2	64 2	51 1	59 2	52 1	59 3	53 4
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Head, sebaceous gland, adenoma																												
Sebaceous gland, adenoma																								X				
Subcutaneous tissue, sarcoma							X																					
Subcutaneous tissue, sarcoma, metastatic														X														
Tail, subcutaneous tissue, sarcoma																				X								
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+									+														
Abdominal, sarcoma														X														
Diaphragm, sarcoma, metastatic														X														
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X																X	
Alveolar/bronchiolar carcinoma						X									X													
Hemangiosarcoma																												
Sarcoma, metastatic														X														
Parenchyma, mediastinum, carcinoma, metastatic, liver				X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																												
Ear																												
Eye																												
Harderian gland		+									+																	
Adenoma											X																	
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																		X		X						
Lymphoma malignant mixed										X						X		X										X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: 8 mg/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 1 2	5 1 3	5 1 4	5 1 5	5 2 2	5 2 3	5 2 4	5 2 5	5 3 5	5 4 3	5 4 4	5 4 5	5 5 4	5 5 5	5 6 4	5 6 5	5 7 5	5 8 3	5 8 4	5 8 5	5 9 4	5 9 5	6 0 3	6 0 4	6 0 5	**Total Tissues/ Tumors**
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Head, sebaceous gland, adenoma		X																								1
Sebaceous gland, adenoma																										1
Subcutaneous tissue, sarcoma																										1
Subcutaneous tissue, sarcoma, metastatic																										1
Tail, subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Abdominal, sarcoma																										1
Diaphragm, sarcoma, metastatic																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X												X										4
Alveolar/bronchiolar carcinoma																										2
Hemangiosarcoma													X													1
Sarcoma, metastatic																										1
Parenchyma, mediastinum, carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear		+																								1
Eye								+																		1
Harderian gland	+							+					+					+								6
Adenoma								X					X					X								4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed	X	X			X				X	X				X	X											11

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: 15 mg/kg

Number of Days on Study	3 6 0	4 5 6	4 7 5	5 1 3	5 1 4	5 1 7	5 4 0	5 4 1	5 4 2	5 4 9	5 6 2	5 7 0	5 7 7	5 8 6	5 8 6	6 0 1	6 2 1	6 2 1	6 2 5	6 3 2	6 4 2	6 5 2	6 5 2	6 5 9	6 5 9
Carcass ID Number	4 4 6 1	4 4 7 1	4 4 5 1	4 4 9 1	4 4 4 1	4 4 2 1	4 4 8 1	4 4 2 2	4 4 5 2	4 4 7 2	4 4 2 3	4 4 7 3	4 4 3 1	4 4 7 4	4 4 8 2	4 4 1 1	4 4 8 3	4 4 9 2	4 4 9 3	4 4 6 2	5 0 1 2	4 4 2 3	4 4 4 3	4 4 3 2	4 4 8 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	A	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine large, cecum	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A
Intestine small	A	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine small, duodenum	A	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine small, ileum	A	A	+	+	+	A	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	A
Intestine small, jejunum	A	A	+	+	+	A	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma			X			X		X						X		X			X	X	X			X	X
Hepatocellular carcinoma, two, multiple																									
Hepatocellular carcinoma, three, multiple																									
Hepatocellular adenoma	X	X									X							X		X				X	X
Hepatocellular adenoma, two, multiple				X					X																
Hepatocellular adenoma, three, multiple								X		X		X	X			X						X	X		
Hepatocellular adenoma, four, multiple														X			X								
Hepatocellular adenoma, five, multiple							X								X										
Hepatocellular adenoma, greater than five, multiple					X														X				X		
Mesentery						+						+				+									
Hepatocellular carcinoma, metastatic, liver																X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Mucosa, papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																			+						
Tooth								+								+									
Cardiovascular System																									
Blood vessel																								+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: 15 mg/kg (continued)

Number of Days on Study	6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	
	6 7 8 9 0 0 0 1 1 1 1 1 1 1 1 1 2 2 2 2 3 3 3 3	
	8 6 5 5 1 1 9 2 5 6 6 7 7 7 7 9 9 3 4 4 5 1 3 6 6	
Carcass ID Number	4 4 4 4 4 4 5 5 4 4 5 4 4 4 5 4 4 4 4 4 4 4 4 4 4	**Total Tissues/ Tumors**
	6 1 4 5 4 9 0 0 1 3 0 3 3 5 0 5 7 1 8 9 1 2 2 6 6	
	3 2 4 3 5 4 2 3 3 3 4 4 5 4 5 5 5 4 5 5 5 4 5 4 5	
Alimentary System		
Esophagus	+ +	50
Gallbladder	+ + + + + + + + + + M M + + M + + + + + + + + +	43
Intestine large	+ +	49
Intestine large, cecum	+ +	46
Intestine large, colon	+ +	48
Intestine large, rectum	+ +	48
Intestine small	+ +	45
Intestine small, duodenum	+ +	45
Intestine small, ileum	+ +	44
Intestine small, jejunum	+ +	44
Liver	+ +	50
Hemangiosarcoma	X	1
Hepatocellular carcinoma	X X X X X X X X X	22
Hepatocellular carcinoma, two, multiple	X X X X	4
Hepatocellular carcinoma, three, multiple	X	1
Hepatocellular adenoma	X	8
Hepatocellular adenoma, two, multiple	X X	4
Hepatocellular adenoma, three, multiple	X X X	10
Hepatocellular adenoma, four, multiple	X X	4
Hepatocellular adenoma, five, multiple	X X X X X	8
Hepatocellular adenoma, greater than five, multiple	X X X X X X X X X X	14
Mesentery	+	4
Hepatocellular carcinoma, metastatic, liver		1
Pancreas	+ +	50
Salivary glands	+ +	50
Stomach	+ +	50
Stomach, forestomach	+ +	49
Mucosa, papilloma squamous	X X X	3
Stomach, glandular	+ +	50
Tongue		1
Tooth	+	3
Cardiovascular System		
Blood vessel	+ +	3
Heart	+ +	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: 15 mg/kg (continued)

Number of Days on Study	3 6 0	4 5 6	4 7 5	5 1 3	5 1 4	5 1 7	5 4 0	5 4 1	5 4 2	5 4 9	5 5 2	5 6 0	5 7 7	5 7 7	5 8 6	5 8 6	6 0 1	6 2 1	6 2 1	6 2 5	6 3 2	6 4 2	6 5 2	6 5 2	6 5 9	6 5 9
Carcass ID Number	4 4 6 1	4 4 7 1	4 4 5 1	4 4 9 1	4 4 4 1	4 4 2 1	4 4 8 1	4 4 2 2	4 4 5 2	4 4 7 2	4 4 2 3	4 4 7 3	4 4 3 1	4 4 7 4	4 4 8 2	4 4 1 1	4 4 8 3	4 4 9 2	4 4 9 3	4 4 6 2	4 5 0 1	4 4 4 2	4 4 4 3	4 4 3 2	4 4 8 4
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																					X					
Pheochromocytoma benign, multiple																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	I	M	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X					X		X					X			X
Pars intermedia, adenoma																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																	X									
Follicular cell, adenoma, two, multiple																										X
General Body System																										
None																										
Genital System																										
Clitoral gland										+																
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary																										
Oviduct	+																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal										X								X	X							
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	M	M	+	M	M	M	M	+	M	M	+	M	M	M	+	+	+	M	M	M	+	+	M	M	
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mediastinal	+	M	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma																										
Thymus	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: 15 mg/kg (continued)

Number of Days on Study	6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 6 7 8 9 0 0 0 1 1 1 1 1 1 1 1 1 2 2 2 2 3 3 3 3 8 6 5 5 1 1 9 2 5 6 6 7 7 7 7 9 9 3 4 4 5 1 3 6 6	
Carcass ID Number	4 4 4 4 4 4 5 5 4 4 5 4 4 4 5 4 4 4 4 4 4 4 4 4 6 1 4 5 4 9 0 0 1 3 0 3 3 5 0 5 7 1 8 9 1 2 2 6 6 3 2 4 3 5 4 2 3 3 3 4 4 5 4 5 5 5 4 5 5 5 4 5 4 5	**Total Tissues/ Tumors**
Endocrine System		
Adrenal gland	+ +	50
Adrenal gland, cortex	+ +	50
Subcapsular, adenoma	X	1
Adrenal gland, medulla	+ +	50
Pheochromocytoma benign	X X	3
Pheochromocytoma benign, multiple	X X X	3
Islets, pancreatic	+ +	50
Parathyroid gland	+ +	50
Pituitary gland	+ +	46
Pars distalis, adenoma	X X X X X	9
Pars intermedia, adenoma	X	1
Thyroid gland	+ +	50
Follicular cell, adenoma		1
Follicular cell, adenoma, two, multiple		1
General Body System		
None		
Genital System		
Clitoral gland		1
Ovary	+ +	50
Cystadenoma, papillary	X	1
Oviduct		1
Uterus	+ +	50
Endometrium, polyp stromal	X	4
Hematopoietic System		
Bone marrow	+ +	50
Lymph node	+ +	50
Lymph node, bronchial	+ + + M + M M M + + + M + + M M + M M M + M + M +	21
Lymph node, mandibular	+ + + + + + + + + + + + + + + M + + + + + + + +	48
Lymph node, mediastinal	M + + + M + M + + + + + + + + + + + + + + + + +	43
Lymph node, mesenteric	+ +	49
Spleen	+ +	50
Hemangiosarcoma	X X	2
Thymus	+ + + M +	45

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: 15 mg/kg (continued)

Number of Days on Study	3 6 0	4 5 6	4 7 5	5 1 3	5 1 4	5 1 7	5 4 0	5 4 1	5 4 2	5 4 9	5 6 2	5 7 0	5 7 7	5 8 6	5 8 6	6 0 1	6 2 1	6 2 1	6 2 5	6 3 2	6 4 2	6 5 2	6 5 2	6 5 9	6 5 9
Carcass ID Number	4 6 1	4 7 1	4 5 1	4 9 1	4 4 1	4 2 1	4 8 1	4 2 2	4 5 2	4 7 2	4 2 3	4 7 3	4 3 1	4 7 4	4 8 2	4 1 1	4 8 3	4 9 2	4 9 3	4 6 2	5 0 1	4 4 2	4 4 3	4 3 2	4 8 4
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	A
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Tail, papilloma squamous																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma benign		X																							
Spinal cord									+																
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, greater than five, metastatic, multiple, mammary gland																									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma															X										
Hepatocellular carcinoma, metastatic, liver																									
Hepatocellular carcinoma, four, metastatic, multiple, liver																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																							+		
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																							X	X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Furan: 15 mg/kg (continued)

Number of Days on Study	6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	
	6 7 8 9 0 0 0 1 1 1 1 1 1 1 1 1 2 2 2 2 3 3 3 3	
	8 6 5 5 1 1 9 2 5 6 6 7 7 7 9 9 3 4 4 5 1 3 6 6	
Carcass ID Number	4 4 4 4 4 4 5 5 4 4 5 4 4 4 5 4 4 4 4 4 4 4 4 4 4	**Total Tissues/ Tumors**
	6 1 4 5 4 9 0 0 1 3 0 3 3 5 0 5 7 1 8 9 1 2 2 6 6	
	3 2 4 3 5 4 2 3 3 3 4 4 5 4 5 5 5 4 5 5 5 4 5 4 5	
Integumentary System		
Mammary gland	+ +	48
Adenocarcinoma	X X	3
Skin	+ +	50
Subcutaneous tissue, hemangiosarcoma	X	1
Tail, papilloma squamous	X	1
Musculoskeletal System		
Bone	+ +	50
Nervous System		
Brain	+ +	50
Meningioma benign		1
Spinal cord		1
Respiratory System		
Lung	+ +	50
Adenocarcinoma, greater than five, metastatic, multiple, mammary gland	X	1
Alveolar/bronchiolar adenoma	X X X	3
Alveolar/bronchiolar carcinoma		1
Hepatocellular carcinoma, metastatic, liver	X	1
Hepatocellular carcinoma, four, metastatic, multiple, liver		1
Nose	+ +	50
Trachea	+ +	50
Special Senses System		
Harderian gland	+ + +	4
Adenoma	X X	2
Urinary System		
Kidney	+ +	49
Urinary bladder	+ +	50
Systemic Lesions		
Multiple organs	+ +	50
Lymphoma malignant mixed	X X X X X	7

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Furan

	Vehicle Control	8 mg/kg	15 mg/kg
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	2/50 (4%)	1/50 (2%)	6/50 (12%)
Adjusted rates[b]	5.9%	4.0%	47.1%
Terminal rates[c]	1/29 (3%)	1/25 (4%)	0/2 (0%)
First incidence (days)	680	736 (T)	642
Life table tests[d]	P=0.003	P=0.537N	P=0.003
Logistic regression tests[d]	P=0.028	P=0.499N	P=0.040
Cochran-Armitage test[d]	P=0.081		
Fisher exact test[d]		P=0.500N	P=0.134
Harderian Gland: Adenoma			
Overall rates	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adjusted rates	6.9%	14.2%	13.9%
Terminal rates	2/29 (7%)	3/25 (12%)	0/2 (0%)
First incidence (days)	736 (T)	673	685
Life table tests	P=0.083	P=0.281	P=0.150
Logistic regression tests	P=0.357	P=0.332	P=0.482
Cochran-Armitage test	P=0.578		
Fisher exact test		P=0.339	P=0.691N
Liver: Hepatocellular Adenoma			
Overall rates	5/50 (10%)	31/50 (62%)	48/50 (96%)
Adjusted rates	17.2%	78.5%	100.0%
Terminal rates	5/29 (17%)	17/25 (68%)	2/2 (100%)
First incidence (days)	736 (T)	446	360
Life table tests	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Liver: Hepatocellular Carcinoma			
Overall rates	2/50 (4%)	7/50 (14%)	27/50 (54%)
Adjusted rates	5.8%	21.8%	94.7%
Terminal rates	1/29 (3%)	3/25 (12%)	1/2 (50%)
First incidence (days)	646	499	475
Life table tests	P<0.001	P=0.070	P<0.001
Logistic regression tests	P<0.001	P=0.081	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.080	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	7/50 (14%)	34/50 (68%)	50/50 (100%)
Adjusted rates	22.6%	82.3%	100.0%
Terminal rates	6/29 (21%)	18/25 (72%)	2/2 (100%)
First incidence (days)	646	446	360
Life table tests	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted rates	8.7%	13.6%	37.0%
Terminal rates	1/29 (3%)	2/25 (8%)	0/2 (0%)
First incidence (days)	690	673	668
Life table tests	P=0.104	P=0.454	P=0.159
Logistic regression tests	P=0.391	P=0.502	P=0.474
Cochran-Armitage test	P=0.578		
Fisher exact test		P=0.500	P=0.661N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	4/50 (8%)	6/50 (12%)	4/50 (8%)
Adjusted rates	11.9%	17.9%	38.7%
Terminal rates	2/29 (7%)	2/25 (8%)	0/2 (0%)
First incidence (days)	690	627	586
Life table tests	P=0.089	P=0.336	P=0.099
Logistic regression tests	P=0.445	P=0.372	P=0.507
Cochran-Armitage test	P=0.561		
Fisher exact test		P=0.370	P=0.643N
Mammary Gland: Adenocarcinoma			
Overall rates	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rates	6.9%	2.9%	28.3%
Terminal rates	2/29 (7%)	0/25 (0%)	0/2 (0%)
First incidence (days)	736 (T)	702	685
Life table tests	P=0.091	P=0.534N	P=0.034
Logistic regression tests	P=0.254	P=0.502N	P=0.238
Cochran-Armitage test	P=0.419		
Fisher exact test		P=0.500N	P=0.500
Mammary Gland: Adenocarcinoma or Carcinoma			
Overall rates	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rates	10.3%	2.9%	28.3%
Terminal rates	3/29 (10%)	0/25 (0%)	0/2 (0%)
First incidence (days)	736 (T)	702	685
Life table tests	P=0.168	P=0.346N	P=0.046
Logistic regression tests	P=0.415	P=0.310N	P=0.342
Cochran-Armitage test	P=0.583N		
Fisher exact test		P=0.309N	P=0.661N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	25/49 (51%)	18/47 (38%)	9/46 (20%)
Adjusted rates	68.7%	55.0%	35.9%
Terminal rates	18/29 (62%)	10/24 (42%)	0/2 (0%)
First incidence (days)	557	646	549
Life table tests	P=0.327	P=0.283N	P=0.215
Logistic regression tests	P=0.008N	P=0.147N	P=0.008N
Cochran-Armitage test	P=0.001N		
Fisher exact test		P=0.147N	P=0.001N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Pituitary Gland (Pars Distalis or Unspecified Site): Adenoma			
Overall rates	25/49 (51%)	19/47 (40%)	9/46 (20%)
Adjusted rates	68.7%	58.2%	35.9%
Terminal rates	18/29 (62%)	11/24 (46%)	0/2 (0%)
First incidence (days)	557	646	549
Life table tests	P=0.284	P=0.357N	P=0.215
Logistic regression tests	P=0.009N	P=0.204N	P=0.008N
Cochran-Armitage test	P=0.001N		
Fisher exact test		P=0.201N	P=0.001N
Pituitary Gland (Pars Distalis or Unspecified Site): Adenoma or Carcinoma			
Overall rates	26/49 (53%)	19/47 (40%)	9/46 (20%)
Adjusted rates	71.5%	58.2%	35.9%
Terminal rates	19/29 (66%)	11/24 (46%)	0/2 (0%)
First incidence (days)	557	646	549
Life table tests	P=0.328	P=0.295N	P=0.225
Logistic regression tests	P=0.005N	P=0.149N	P=0.005N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.150N	P<0.001N
Stomach (Forestomach): Squamous Papilloma			
Overall rates	2/50 (4%)	6/50 (12%)	3/50 (6%)
Adjusted rates	6.9%	19.7%	26.9%
Terminal rates	2/29 (7%)	3/25 (12%)	0/2 (0%)
First incidence (days)	736 (T)	638	709
Life table tests	P=0.018	P=0.108	P=0.025
Logistic regression tests	P=0.172	P=0.133	P=0.178
Cochran-Armitage test	P=0.406		
Fisher exact test		P=0.134	P=0.500
Thyroid Gland (Follicular Cell): Adenoma			
Overall rates	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rates	6.9%	12.0%	6.5%
Terminal rates	2/29 (7%)	3/25 (12%)	0/2 (0%)
First incidence (days)	736 (T)	736 (T)	601
Life table tests	P=0.112	P=0.431	P=0.252
Logistic regression tests	P=0.481	P=0.431	P=0.659
Cochran-Armitage test	P=0.592		
Fisher exact test		P=0.500	P=0.691N
Uterus: Stromal Polyp			
Overall rates	2/50 (4%)	0/50 (0%)	4/50 (8%)
Adjusted rates	6.4%	0.0%	14.0%
Terminal rates	1/29 (3%)	0/25 (0%)	0/2 (0%)
First incidence (days)	718	–[e]	549
Life table tests	P=0.085	P=0.267N	P=0.082
Logistic regression tests	P=0.270	P=0.240N	P=0.345
Cochran-Armitage test	P=0.249		
Fisher exact test		P=0.247N	P=0.339

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Uterus: Stromal Polyp or Stromal Sarcoma			
Overall rates	4/50 (8%)	0/50 (0%)	4/50 (8%)
Adjusted rates	11.6%	0.0%	14.0%
Terminal rates	2/29 (7%)	0/25 (0%)	0/2 (0%)
First incidence (days)	494	–	549
Life table tests	P=0.327	P=0.079N	P=0.217
Logistic regression tests	P=0.503N	P=0.063N	P=0.597N
Cochran-Armitage test	P=0.563N		
Fisher exact test		P=0.059N	P=0.643N
All Organs: Hemangiosarcoma			
Overall rates	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rates	5.4%	8.0%	21.7%
Terminal rates	1/29 (3%)	2/25 (8%)	0/2 (0%)
First incidence (days)	430	736 (T)	716
Life table tests	P=0.076	P=0.654	P=0.132
Logistic regression tests	P=0.386	P=0.694	P=0.506
Cochran-Armitage test	P=0.417		
Fisher exact test		P=0.691N	P=0.500
All Organs: Hemangioma or Hemangiosarcoma			
Overall rates	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted rates	8.8%	8.0%	21.7%
Terminal rates	2/29 (7%)	2/25 (8%)	0/2 (0%)
First incidence (days)	430	736 (T)	716
Life table tests	P=0.139	P=0.554N	P=0.154
Logistic regression tests	P=0.552	P=0.501N	P=0.639
Cochran-Armitage test	P=0.586N		
Fisher exact test		P=0.500N	P=0.661N
All Organs: Malignant Lymphoma (Lymphocytic or Mixed)			
Overall rates	20/50 (40%)	14/50 (28%)	7/50 (14%)
Adjusted rates	55.9%	41.8%	50.1%
Terminal rates	14/29 (48%)	7/25 (28%)	0/2 (0%)
First incidence (days)	414	446	652
Life table tests	P=0.438	P=0.266N	P=0.217
Logistic regression tests	P=0.011N	P=0.141N	P=0.023N
Cochran-Armitage test	P=0.003N		
Fisher exact test		P=0.146N	P=0.003N
All Organs: Benign Neoplasms			
Overall rates	34/50 (68%)	38/50 (76%)	48/50 (96%)
Adjusted rates	86.9%	88.1%	100.0%
Terminal rates	24/29 (83%)	20/25 (80%)	2/2 (100%)
First incidence (days)	557	446	360
Life table tests	P<0.001	P=0.136	P<0.001
Logistic regression tests	P<0.001	P=0.264	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.252	P<0.001

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
All Organs: Malignant Neoplasms			
Overall rates	30/50 (60%)	24/50 (48%)	32/50 (64%)
Adjusted rates	73.9%	59.7%	95.9%
Terminal rates	19/29 (66%)	10/25 (40%)	1/2 (50%)
First incidence (days)	414	446	475
Life table tests	P<0.001	P=0.336N	P<0.001
Logistic regression tests	P=0.289	P=0.158N	P=0.224
Cochran-Armitage test	P=0.408		
Fisher exact test		P=0.158N	P=0.418
All Organs: Benign or Malignant Neoplasms			
Overall rates	43/50 (86%)	43/50 (86%)	50/50 (100%)
Adjusted rates	97.7%	93.4%	100.0%
Terminal rates	28/29 (97%)	22/25 (88%)	2/2 (100%)
First incidence (days)	414	446	360
Life table tests	P<0.001	P=0.315	P<0.001
Logistic regression tests	P=0.006	P=0.606N	P=0.005
Cochran-Armitage test	P=0.015		
Fisher exact test		P=0.613N	P=0.006

(T)Terminal sacrifice

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

[e] Not applicable; no neoplasms in animal group

TABLE D4a
Historical Incidence of Benign Pheochromocytomas of the Adrenal Medulla in Untreated Female B6C3F$_1$ Mice Receiving Corn Oil Vehicle by Gavage[a]

Study	Incidence of Benign Pheochromocytoma in Controls
Historical Incidence at Southern Research Institute	
Benzaldehyde	1/50
Dichlorvos	4/50
Furan	2/50
Furfural	1/50
γ-Butyrolactone	0/50
Total	8/250 (3.2%)
Standard deviation	3.0%
Range	0%–8%
Overall Historical Incidence	
Total	9/584 (1.5%)
Standard deviation	2.4%
Range	0%–8%

[a] Data as of 17 September 1990

TABLE D4b
Historical Incidence of Liver Neoplasms in Untreated Female B6C3F$_1$ Mice Receiving Corn Oil Vehicle by Gavage[a]

Study	Incidence in Controls		
	Hepatocellular Adenoma or Neoplastic Nodule	Hepatocellular Carcinoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Neoplastic Nodule
Historical Incidence at Southern Research Institute			
Benzaldehyde	1/50	1/50	2/50
Dichlorvos	2/50	4/50	6/50
Furan	5/50	2/50	7/50
Furfural	1/50	4/50	5/50
γ-Butyrolactone	5/50	4/50	8/50
Total	14/250 (5.6%)	15/250 (6.0%)	28/250 (11.2%)
Standard deviation	4.1%	2.8%	4.6%
Range	2%–10%	2%–8%	4%–16%
Overall Historical Incidence			
Total	38/597 (6.4%)	24/597 (4.0%)	60/597 (10.1%)
Standard deviation	3.7%	2.7%	4.3%
Range	2%–14%	0%–8%	2%–16%

[a] Data as of 17 September 1990

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Furan[a]

	Vehicle Control	8 mg/kg	15 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Natural deaths	1	1	
Accidntal deaths	4	8	11
Moribund kills	16	16	37
Survivors			
Terminal sacrifice	28	25	2
Died last week of study	1		
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(50)	(50)	(50)
Perforation			1 (2%)
Gallbladder	(49)	(49)	(43)
Infarct			1 (2%)
Intestine large, cecum	(49)	(49)	(46)
Edema		1 (2%)	
Intestine large, rectum	(49)	(49)	(48)
Inflammation, chronic			1 (2%)
Intestine small, duodenum	(49)	(47)	(45)
Congestion			1 (2%)
Inflammation, chronic		1 (2%)	
Mucosa, hyperplasia, adenomatous			1 (2%)
Mucosa, ulcer		1 (2%)	1 (2%)
Intestine small, ileum	(48)	(47)	(44)
Lymphoid tissue, mineralization	1 (2%)		
Intestine small, jejunum	(49)	(47)	(44)
Mucosa, amyloid deposition		1 (2%)	
Liver	(50)	(50)	(50)
Angiectasis		2 (4%)	3 (6%)
Basophilic focus		1 (2%)	
Clear cell focus			1 (2%)
Congestion	2 (4%)	1 (2%)	
Cyst		1 (2%)	1 (2%)
Eosinophilic focus		1 (2%)	1 (2%)
Granuloma			1 (2%)
Hematopoietic cell proliferation	11 (22%)	9 (18%)	2 (4%)
Hemorrhage		1 (2%)	1 (2%)
Hyperplasia, lymphoid	27 (54%)	33 (66%)	42 (84%)
Hyperplasia, multifocal		48 (96%)	48 (96%)
Infarct		7 (14%)	11 (22%)
Infiltration cellular, mixed cell	8 (16%)	23 (46%)	32 (64%)
Inflammation, multifocal	27 (54%)	13 (26%)	
Mineralization		1 (2%)	2 (4%)
Mixed cell focus	1 (2%)	5 (10%)	3 (6%)
Necrosis, multifocal	3 (6%)	1 (2%)	3 (6%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Alimentary System (continued)			
Liver (continued)			
Thrombus			3 (6%)
Vacuolization cytoplasmic	6 (12%)	29 (58%)	36 (72%)
Bile duct, dilatation		1 (2%)	11 (22%)
Biliary tract, fibrosis		47 (94%)	50 (100%)
Biliary tract, granuloma			1 (2%)
Biliary tract, hyperplasia		47 (94%)	50 (100%)
Biliary tract, inflammation, chronic	2 (4%)	48 (96%)	50 (100%)
Hepatocyte, cytomegaly		48 (96%)	50 (100%)
Hepatocyte, degeneration		47 (94%)	48 (96%)
Hepatocyte, necrosis		44 (88%)	47 (94%)
Kupffer cell, pigmentation	5 (10%)	48 (96%)	50 (100%)
Parenchyma, atrophy, focal		1 (2%)	
Parenchyma, atrophy, multifocal		47 (94%)	50 (100%)
Mesentery	(24)	(27)	(4)
Edema	1 (4%)		
Inflammation, chronic		1 (4%)	1 (25%)
Inflammation, suppurative	8 (33%)	7 (26%)	3 (75%)
Fat, necrosis	4 (17%)	7 (26%)	1 (25%)
Pancreas	(50)	(49)	(50)
Atrophy, focal	1 (2%)		2 (4%)
Fibrosis, focal			1 (2%)
Hyperplasia, lymphoid		5 (10%)	
Infarct	1 (2%)		
Inflammation, chronic		1 (2%)	1 (2%)
Inflammation, suppurative	1 (2%)		
Acinar cell, hyperplasia		1 (2%)	
Acinus, hypoplasia			1 (2%)
Artery, inflammation, chronic			2 (4%)
Duct, cyst			2 (4%)
Duct, dilatation			1 (2%)
Salivary glands	(50)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)	4 (8%)	
Stomach, forestomach	(50)	(49)	(49)
Edema		1 (2%)	
Erosion			1 (2%)
Hyperplasia, papillary		1 (2%)	
Hyperplasia, squamous			2 (4%)
Inflammation, focal	10 (20%)	7 (14%)	9 (18%)
Ulcer			1 (2%)
Mucosa, cyst			1 (2%)
Mucosa, erosion	1 (2%)	2 (4%)	1 (2%)
Mucosa, hyperplasia, papillary	10 (20%)	10 (20%)	8 (16%)
Mucosa, ulcer	2 (4%)		1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Alimentary System (continued)			
Stomach, glandular	(50)	(49)	(50)
Edema		1 (2%)	
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
Inflammation, focal	1 (2%)		
Mineralization	2 (4%)	3 (6%)	
Epithelium, degeneration, hyaline	2 (4%)	5 (10%)	2 (4%)
Epithelium, metaplasia, squamous	2 (4%)	1 (2%)	
Epithelium, vacuolization cytoplasmic, multifocal		1 (2%)	
Mucosa, cyst	11 (22%)	12 (24%)	10 (20%)
Mucosa, dysplasia, focal			1 (2%)
Mucosa, erosion	1 (2%)	2 (4%)	2 (4%)
Mucosa, hemorrhage			2 (4%)
Mucosa, hyperplasia	3 (6%)	5 (10%)	3 (6%)
Mucosa, mineralization		1 (2%)	2 (4%)
Mucosa, necrosis, focal			1 (2%)
Mucosa, necrosis, multifocal			1 (2%)
Mucosa, pigmentation			1 (2%)
Serosa, inflammation, chronic		1 (2%)	
Tongue		(2)	(1)
Angiectasis		1 (50%)	
Hemorrhage			1 (100%)
Necrosis			1 (100%)
Tooth	(2)	(1)	(3)
Incisor, dysplasia	2 (100%)	1 (100%)	3 (100%)
Cardiovascular System			
Blood vessel	(2)	(2)	(3)
Abdominal, inflammation, chronic			1 (33%)
Mesenteric artery, inflammation, chronic	1 (50%)	1 (50%)	2 (67%)
Pulmonary artery, inflammation, chronic		1 (50%)	
Pulmonary artery, mineralization	1 (50%)		
Heart	(50)	(50)	(50)
Artery, inflammation, chronic			1 (2%)
Atrium, inflammation, chronic		1 (2%)	
Atrium, thrombus	1 (2%)		2 (4%)
Endocrine System			
Adrenal gland, cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule		2 (4%)	1 (2%)
Cyst	1 (2%)		
Cytologic alterations, focal		1 (2%)	
Developmental malformation		1 (2%)	
Hyperplasia, focal			1 (2%)
Vacuolization cytoplasmic, focal		1 (2%)	
Extra adrenal tissue, accessory adrenal cortical nodule		2 (4%)	
Subcapsular, hyperplasia, focal	4 (8%)	1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Endocrine System (continued)			
Adrenal gland, medulla	(50)	(50)	(50)
Ectopic tissue		1 (2%)	
Hyperplasia			1 (2%)
Hyperplasia, focal	2 (4%)	1 (2%)	8 (16%)
Parathyroid gland	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
Pituitary gland	(49)	(47)	(46)
Pars distalis, angiectasis	3 (6%)	2 (4%)	4 (9%)
Pars distalis, cyst	1 (2%)	1 (2%)	2 (4%)
Pars distalis, focal cellular change		1 (2%)	
Pars distalis, hyperplasia	1 (2%)		1 (2%)
Pars distalis, hyperplasia, focal	8 (16%)	8 (17%)	5 (11%)
Pars intermedia, vacuolization cytoplasmic		1 (2%)	
Pars nervosa, hyperplasia, focal		1 (2%)	
Rathke's cleft, hemorrhage		1 (2%)	
Thyroid gland	(50)	(50)	(50)
Degeneration, cystic	4 (8%)	4 (8%)	7 (14%)
Follicle, cyst		1 (2%)	
Follicular cell, hyperplasia	14 (28%)	11 (22%)	8 (16%)
General Body System			
None			
Genital System			
Clitoral gland			(1)
Inflammation, suppurative			1 (100%)
Ovary	(49)	(49)	(50)
Angiectasis	2 (4%)	2 (4%)	
Cyst			1 (2%)
Ectopic tissue			1 (2%)
Fibrosis			1 (2%)
Inflammation, chronic		1 (2%)	
Inflammation, suppurative	7 (14%)	10 (20%)	3 (6%)
Mineralization			1 (2%)
Pigmentation			1 (2%)
Artery, inflammation, chronic			1 (2%)
Corpus luteum, degeneration		1 (2%)	1 (2%)
Corpus luteum, granuloma		1 (2%)	1 (2%)
Follicle, cyst	19 (39%)	15 (31%)	21 (42%)
Oviduct	(4)	(4)	(1)
Ectopic tissue			1 (100%)
Inflammation, suppurative	3 (75%)	2 (50%)	
Uterus	(50)	(50)	(50)
Angiectasis		1 (2%)	3 (6%)
Hydrometra	8 (16%)	7 (14%)	7 (14%)
Hyperplasia, lymphoid		1 (2%)	
Inflammation, suppurative	8 (16%)	9 (18%)	5 (10%)
Thrombus	1 (2%)		
Endometrium, hyperplasia, cystic	48 (96%)	47 (94%)	42 (84%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Angiectasis		1 (2%)	
Hyperplasia		1 (2%)	
Hyperplasia, neutrophil	2 (4%)	1 (2%)	
Myelofibrosis		1 (2%)	
Lymph node	(50)	(50)	(50)
Iliac, hyperplasia	2 (4%)	1 (2%)	
Iliac, hyperplasia, lymphoid	1 (2%)		
Inguinal, hyperplasia		2 (4%)	
Inguinal, hyperplasia, lymphoid	3 (6%)	2 (4%)	
Lumbar, hyperplasia, lymphoid		1 (2%)	
Pancreatic, hyperplasia, lymphoid		1 (2%)	
Pancreatic, inflammation, suppurative		1 (2%)	
Popliteal, hyperplasia, lymphoid		1 (2%)	
Renal, hyperplasia	5 (10%)	2 (4%)	1 (2%)
Renal, hyperplasia, lymphoid	1 (2%)		
Lymph node, bronchial	(21)	(29)	(21)
Hyperplasia	1 (5%)	4 (14%)	1 (5%)
Hyperplasia, lymphoid	4 (19%)	4 (14%)	
Lymph node, mandibular	(47)	(46)	(48)
Angiectasis		1 (2%)	
Cyst	1 (2%)		
Hyperplasia	1 (2%)	1 (2%)	3 (6%)
Hyperplasia, lymphoid	1 (2%)	4 (9%)	
Lymph node, mediastinal	(41)	(45)	(43)
Angiectasis			2 (5%)
Hyperplasia	7 (17%)	6 (13%)	2 (5%)
Hyperplasia, lymphoid	1 (2%)	6 (13%)	2 (5%)
Inflammation, suppurative	2 (5%)	2 (4%)	1 (2%)
Artery, inflammation, chronic			1 (2%)
Lymph node, mesenteric	(49)	(49)	(49)
Angiectasis		3 (6%)	1 (2%)
Hematopoietic cell proliferation			1 (2%)
Hyperplasia		2 (4%)	
Hyperplasia, lymphoid	7 (14%)	5 (10%)	5 (10%)
Inflammation, suppurative	1 (2%)		
Spleen	(50)	(50)	(50)
Hematopoietic cell proliferation	17 (34%)	17 (34%)	34 (68%)
Hyperplasia, lymphoid	8 (16%)	14 (28%)	7 (14%)
Thymus	(46)	(46)	(45)
Angiectasis		1 (2%)	
Depletion, lymphoid	4 (9%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid		2 (4%)	
Infiltration cellular, mixed cell		1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Integumentary System			
Mammary gland	(49)	(50)	(48)
Dilatation	19 (39%)	17 (34%)	18 (38%)
Hyperplasia, cystic	1 (2%)		
Inflammation	1 (2%)		
Skin	(50)	(50)	(50)
Inflammation, chronic	5 (10%)	5 (10%)	2 (4%)
Ulcer	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, hemorrhage			2 (4%)
Subcutaneous tissue, hyperplasia, lymphoid			1 (2%)
Subcutaneous tissue, infiltration cellular, mixed cell		1 (2%)	
Subcutaneous tissue, inflammation, chronic		1 (2%)	
Subcutaneous tissue, inflammation, suppurative		2 (4%)	1 (2%)
Subcutaneous tissue, fat, necrosis		1 (2%)	
Musculoskeletal System			
Bone	(50)	(50)	(50)
Distal, joint, femur, arthrosis		1 (2%)	
Femur, fracture			1 (2%)
Trabecula, cranium, hyperostosis		1 (2%)	
Skeletal muscle	(3)	(2)	
Necrosis, multifocal	1 (33%)		
Hindlimb, inflammation, suppurative		1 (50%)	
Nervous System			
Brain	(50)	(50)	(50)
Compression	1 (2%)	1 (2%)	
Hemorrhage, focal	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
Respiratory System			
Lung	(50)	(50)	(50)
Congestion			4 (8%)
Hemorrhage	2 (4%)		
Hyperplasia, lymphoid	22 (44%)	27 (54%)	28 (56%)
Hyperplasia, macrophage	1 (2%)	2 (4%)	2 (4%)
Infiltration cellular, mixed cell	2 (4%)	7 (14%)	2 (4%)
Inflammation, suppurative	1 (2%)	2 (4%)	
Alveolar epithelium, hyperplasia	1 (2%)		
Fat, mediastinum, necrosis		1 (2%)	
Mediastinum, foreign body			1 (2%)
Mediastinum, hemorrhage			1 (2%)
Mediastinum, hyperplasia, lymphoid	1 (2%)	1 (2%)	2 (4%)
Mediastinum, inflammation, suppurative	3 (6%)	5 (10%)	1 (2%)
Pleura, fibrosis			1 (2%)
Pleura, inflammation, suppurative			1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Furan (continued)

	Vehicle Control	8 mg/kg	15 mg/kg
Respiratory System (continued)			
Nose	(50)	(50)	(50)
Lumen, exudate	23 (46%)	18 (36%)	20 (40%)
Lumen, foreign body	27 (54%)	26 (52%)	26 (52%)
Lumen, hemorrhage			1 (2%)
Lumen, inflammation, suppurative			1 (2%)
Mucosa, cyst	1 (2%)		
Nasolacrimal duct, inflammation, suppurative			2 (4%)
Trachea	(50)	(50)	(50)
Artery, peritracheal tissue, inflammation, chronic	2 (4%)		
Special Senses System			
Harderian gland	(4)	(6)	(4)
Acinus, dilatation		1 (17%)	1 (25%)
Urinary System			
Kidney	(50)	(50)	(49)
Atrophy	1 (2%)		
Cyst		1 (2%)	
Fibrosis	2 (4%)	4 (8%)	
Hydronephrosis			1 (2%)
Infiltration cellular, polymorphonuclear			1 (2%)
Infiltration cellular, mixed cell	1 (2%)	3 (6%)	
Metaplasia, osseous	1 (2%)	2 (4%)	
Mineralization	2 (4%)	2 (4%)	4 (8%)
Nephropathy	16 (32%)	21 (42%)	22 (45%)
Artery, inflammation, chronic			2 (4%)
Capsule, fibrosis, focal	1 (2%)		
Interstitial tissue, pigmentation			2 (4%)
Renal tubule, bacterium		1 (2%)	
Renal tubule, casts			1 (2%)
Renal tubule, degeneration, hyaline	1 (2%)	1 (2%)	
Renal tubule, dilatation	2 (4%)	1 (2%)	4 (8%)
Renal tubule, necrosis			4 (8%)
Renal tubule, pigmentation	1 (2%)	1 (2%)	
Renal tubule, vacuolization cytoplasmic		1 (2%)	
Renal tubule, epithelium, depletion	1 (2%)		
Urinary bladder	(50)	(50)	(50)
Hyperplasia, lymphoid	3 (6%)	6 (12%)	2 (4%)

[a] Number of animals examined microscopically at site and number of animals with lesion.

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983) and Mortelmans *et al.* (1986). Furan was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, 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 prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin, and subsequent plating on minimal glucose agar plates. Incubation continued for an additional 48 hours.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of furan. High dose was limited by toxicity, and was not to exceed 10,000 μg per plate. All assays were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which was not dose-related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following 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). Furan was supplied as a coded aliquot by Radian Corporation (Austin, TX). The highest dose of furan was determined by toxicity. Mouse L5178Y lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM *l*-glutamine, 110 μg per 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 THMG (thymidine, hypoxanthine, methotrexate, glycine) for one day, to THG for one day, and to normal medium for 3 to 5 days. For cloning, horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6 x 10^6 cells in a 10 mL volume of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with furan continued for 4 hours, at 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 allow expression of the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3 x 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 in 5% CO_2 for 10 to 12 days. All data were evaluated statistically for both trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for a chemical to be considered "positive," i.e., capable of inducing TFT-resistance; a single significant response led to a "questionable" 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 is initially performed without

exogenous metabolic activation; because a clearly positive response was obtained, the experiment was not repeated with induced S9.

CHINESE HAMSTER OVARY CELL CYTOGENETICS ASSAYS

Testing was performed as reported by Galloway *et al.* (1985, 1987) and is presented briefly below. Furan was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCE) and chromosomal aberrations (Abs), 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-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of furan; the high dose was limited by toxicity, and did not exceed 5 μg/mL.

In the SCE test without S9, CHO cells were incubated for 26 hours with furan in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing furan was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 to 3 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 furan, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no furan and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 to 3 hours. Harvesting and staining procedures were the same as for cells treated without S9.

In the Abs test without S9, cells were incubated in McCoy's 5A medium with furan for 8 to 10 hours; Colcemid was added and incubation continued for 2 to 3 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with furan and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 11 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.

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 scored for frequency of SCE per cell from each dose level; 200 first-division metaphase cells were scored at each dose level, except the high-dose, for the Abs 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. Abs data are presented as percentage of cells with aberrations. As with SCE data, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P \leq 0.05$) difference for one dose point was considered weak evidence for a positive response (+w); significant differences for two or more doses indicated the trial was positive (+) (Galloway *et al.*, 1987).

DROSOPHILA PROTOCOL

The assay for induction of mutations was performed as described in Zimmering *et al.* (1985). Furan was supplied as a coded aliquot from Radian Corporation (Austin, TX). Initially, furan was assayed in the sex-linked recessive lethal (SLRL) test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. If no response was obtained, the chemical was retested by injection into adult males. Because no positive response was obtained by either route of administration, furan was not assayed for induction of reciprocal translocations.

To administer a chemical by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament and the tip was broken off to allow delivery of the test solution. Injection was performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2 to 0.3 μL) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector which automatically delivered a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of double stick tape; furan was injected into the thorax under the wing with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of furan at a level which would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, oral exposure was achieved by allowing Canton-S males (10 to 20 flies per vial) to feed for 72 hours on a solution of furan in 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were treated with a saline solution of furan dissolved in 10% ethanol and were allowed to recover for 24 hours. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days; sample sperm from successive matings were treated at successively earlier post-meiotic stages. F_1 heterozygous females were allowed to mate with their siblings and were then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male results from a single spontaneous premeiotic mutation event, and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as occurring in vials containing no wild-type males after 17 days; these were retested. The feeding and injection experiments combined resulted in the testing of approximately 5,000 treated and 5,000 control chromosomes. The only exceptions occurred when the results of the first experiment were clearly positive (induced frequency of recessive lethal mutations equal to or greater than 1%); then the second trial was not performed.

Recessive lethal data were analyzed by the normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered to be positive if the P value was less than 0.01 and the mutation frequency in the tested group was greater that 0.10%, or if the P value was less than 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if (a) the P value was between 0.01 and 0.05 but the frequency in the treatment group was between 0.10% and 0.15%, or (b) the P value was between 0.05 and 0.10 but the frequency in the treatment group was greater than 0.10%. A result was considered to be negative if the P value was greater than 0.10 or if the frequency in the treatment group was less than 0.10%.

IN VIVO BONE MARROW SISTER CHROMATID EXCHANGE TEST PROTOCOL

A dose range-finding study was performed first in the absence of adequate toxicity information from the literature. The highest dose of furan was limited to 350 mg/kg. Furan was tested for the induction of SCEs in mouse bone marrow cells using two protocols. Male $B6C3F_1$ mice (five animals per dose group) were injected intraperitoneally with furan dissolved in corn oil (injection volume = 0.4 mL). Solvent control mice received equivalent injections of corn oil only. The positive control mice received injections of 100 mg/kg dimethylbenzanthracene. The first experiment had a standard harvest time of 23 hours, and the second had a delayed harvest of 42 hours. The mice were implanted subcutaneously with a 50 mg

BrdU tablet (McFee *et al.*, 1983) 24 hours before harvest (one hour prior to furan treatment in the case of the standard protocol). The use of BrdU allowed selection of the appropriate cell population for scoring. (Chromosomal Abs induced by chemical administration are present in maximum number at the first metaphase following treatment; they decline in number during subsequent nuclear divisions due to cell death.) Two hours prior to sacrifice, the mice received an intraperitoneal (IP) injection of 2 mg/kg colchicine in saline. The animals were killed by cervical dislocation 23 or 42 hours after treatment with furan. One or both femurs were removed and the marrow was flushed out with 5 mL phosphate-buffered saline (PBS) (pH 7.0). The cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained by the fluorescence-plus-Giemsa method and scored. Twenty-five second-division metaphase cells were scored from each of four animals per treatment. Responses were evaluated as SCEs per cell and the data were analyzed by the trend test (Margolin *et al.*, 1986).

In Vivo Bone Marrow Chromosomal Aberration Test Protocol

An initial dose range-finding study was performed to determine the appropriate dosing regimen, due to an absence of adequate information in the literature. The highest dose was limited to 350 mg/kg. Furan was tested for induction of chromosomal Abs in mouse bone marrow cells using two different protocols. The first experiment used a standard harvest time of 17 hours and the second used a delayed harvest of 36 hours. Male B6C3F$_1$ mice (10 animals per dose group) were injected intraperitoneally with furan dissolved in corn oil (injection volume = 0.4 mL). Solvent control mice received equivalent injections of corn oil only. The positive control mice received injections of 100 mg/kg dimethylbenzanthracene. The mice were subcutaneously implanted with a 50 mg BrdU tablet (McFee *et al.*, 1983) 18 hours before the scheduled harvest (for the standard protocol, this required BrdU implantation to precede injection with furan by 1 hour). Two hours prior to sacrifice, the mice received an IP injection of 2 mg/kg colchicine in saline. The animals were killed by cervical dislocation 17 or 36 hours after furan injection (18 hours after BrdU dosing). One or both femurs were removed and the marrow was flushed out with 5 mL PBS (pH 7.0). Cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained and scored. Fifty first-division metaphase cells were scored from each of eight animals per treatment. Responses were evaluated as the percentage of aberrant metaphase cells, excluding gaps. The number of aberrations per cell, excluding gaps, was also analyzed to provide information on the extent of individual cell damage. The data were analyzed by the trend test (Margolin *et al.*, 1986).

Results

Furan was tested for mutagenicity in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 using a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; no mutagenic activity was observed in any of the strain/activation combinations (Table E1; Mortelmans *et al.*, 1986). The maximum concentration of furan tested was 10,000 μg/plate; a precipitate was observed in several of the trials at the 1,000 μg/plate concentration. Furan induced TFT resistance in mouse L5178Y lymphoma cells at concentrations of 1,139 μg/mL to 3,800 μg/mL in the absence of S9 activation; it was not tested with S9 (Table E2; McGregor *et al.*, 1988). In cytogenetic tests with CHO cells, furan induced both SCEs (Table E3) and chromosomal Abs (Table E4) in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9. Concentrations of 1.6 to 160 μg/mL furan produced significant responses in the SCE test without S9; with S9, a significant induction of SCE was observed only at the highest dose tested, 500 μg/mL. Positive responses in the chromosomal Abs test were seen at furan concentrations of 100 to 500 μg/mL without S9 and at concentrations of 500 and 1,000 μg/mL with S9. Furan was tested for induction of SLRL mutations in germ cells of male *Drosophila melanogaster*; no significant increase in mutations was observed following administration of furan in feed (10,000 ppm) or by abdominal injection (25,000 ppm) (Table E5). No increase in SCEs was observed in bone marrow cells of male B6C3F$_1$ mice administered furan by IP

injection (Table E6). Two sampling times were used to maximize the detection of effects: mice treated with 87.5 to 350 mg/kg furan were sampled 23 hours after injection and mice treated with 25 to 100 mg/kg furan were sampled 42 hours after injection. Lower doses were used with the longer exposure time due to the toxicity of furan. Significantly increased frequencies of chromosome Abs were observed in bone marrow cells of male $B6C3F_1$ mice treated with furan (Table E7). An extended harvest protocol was necessary to detect this increase and increases in aberrations were observed only at the highest dose tested (250 mg/kg) in both trials. The magnitude of the response was similar to the positive control response.

TABLE E1
Mutagenicity of Furan in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	91 ± 0.9	106 ± 5.0	104 ± 2.1	109 ± 4.6	82 ± 5.1	130 ± 10.7
	33		113 ± 6.9		113 ± 10.7		118 ± 6.1
	100	102 ± 4.6	103 ± 7.2	103 ± 5.2	114 ± 6.4	93 ± 7.1	112 ± 6.9
	333	93 ± 6.2	97 ± 3.7	93 ± 8.7	109 ± 7.4	102 ± 6.4	128 ± 13.2
	1,000	83 ± 3.5	113 ± 5.8[c]	88 ± 2.2	103 ± 6.8[c]	98 ± 9.5	109 ± 9.5[c]
	3,333	79 ± 6.4[c]	84 ± 2.0[c]	89 ± 11.7	89 ± 10.2[c]	105 ± 1.7	101 ± 6.9[c]
	10,000	73 ± 12.3[d]		63 ± 1.0		105 ± 4.4	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[e]		352 ± 16.0	237 ± 6.4	1,482 ± 54.3	2,327 ± 23.1	338 ± 9.4	731 ± 45.2
TA1535	0	11 ± 2.0	16 ± 1.0	5 ± 0.3	5 ± 0.3	7 ± 1.5	8 ± 2.3
	33		12 ± 2.2		9 ± 1.0		9 ± 0.9
	100	15 ± 0.3	13 ± 2.3	10 ± 4.8	11 ± 3.7	10 ± 2.9	10 ± 2.2
	333	12 ± 2.6	11 ± 2.7	7 ± 0.6	6 ± 0.0	11 ± 1.8	10 ± 2.0
	1,000	13 ± 2.2	9 ± 1.2[c]	8 ± 0.7	8 ± 2.5[c]	8 ± 0.9	9 ± 1.8[c]
	3,333	6 ± 0.3[c]	7 ± 2.0[c]	7 ± 0.0	9 ± 0.3[c]	10 ± 2.4	6 ± 0.7[c]
	10,000	3 ± 1.5[d]		6 ± 1.2		7 ± 0.3	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		285 ± 7.8	143 ± 14.5	404 ± 18.0	446 ± 13.8	211 ± 12.4	238 ± 31.8
TA1537	0	7 ± 0.7	4 ± 1.2	7 ± 1.0	7 ± 2.6	18 ± 0.3	8 ± 1.2
	33		4 ± 0.7		6 ± 1.0		7 ± 0.3
	100	5 ± 1.8	4 ± 0.0	7 ± 0.9	6 ± 1.2	19 ± 3.0	6 ± 1.5
	333	5 ± 1.8	7 ± 0.9	5 ± 1.5	5 ± 1.2	17 ± 0.9	8 ± 0.3
	1,000	5 ± 0.3	7 ± 0.7[c]	5 ± 0.6	5 ± 0.6[c]	18 ± 1.7	10 ± 2.0[c]
	3,333	5 ± 0.3[c]	6 ± 1.7[c]	4 ± 1.2	6 ± 1.2[c]	16 ± 1.5	7 ± 0.9[c]
	10,000	4 ± 0.9[d]		4 ± 0.6		7 ± 2.8	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		312 ± 24.1	228 ± 17.0	466 ± 35.1	499 ± 30.5	83 ± 6.9	190 ± 9.6
TA98	0	24 ± 4.2	30 ± 1.7	33 ± 4.1	39 ± 3.5	36 ± 3.1	35 ± 3.9
	33		29 ± 1.8		36 ± 2.7		45 ± 1.5
	100	29 ± 0.3	26 ± 3.8	28 ± 4.8	30 ± 1.5	33 ± 3.2	44 ± 4.5
	333	25 ± 4.2	28 ± 1.7	31 ± 4.2	33 ± 2.8	36 ± 1.8	40 ± 2.5
	1,000	19 ± 3.2	20 ± 2.3[c]	25 ± 0.3	23 ± 2.2[c]	34 ± 1.2	39 ± 3.8[c]
	3,333	10 ± 1.5[c]	12 ± 2.7[c]	20 ± 3.4	26 ± 4.2[c]	33 ± 0.3	31 ± 2.4[c]
	10,000	1 ± 1.3[d]		13 ± 2.8		38 ± 0.7	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		529 ± 11.8	445 ± 29.2	1,222 ± 59.4	1,725 ± 58.0	153 ± 12.2	578 ± 18.6

[a] Study performed at SRI, International. The detailed protocol and these data are presented in Mortelmans *et al.* (1986).
[b] Revertants are presented as mean ± standard error from three plates.
[c] Precipitate on plate
[d] Slight toxicity
[e] 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE E2
Induction of TFT Resistance in Mouse L5178Y Lymphoma Cells by Furan[a]

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction[c]
-S9						
Trial 1						
Dimethylsulfoxide						
		73	100	97	44	
		72	100	80	37	
		75	105	94	42	
		78	94	87	37	40
Methylmethanesulfonate						
		34	26	180	177	
	15	37	23	162	146	162*
Furan						
	125	72	98	78	36	
		73	88	74	34	35
	250	68	86	86	42	
		77	103	98	43	42
	500	75	83	63	28	
		70	88	78	37	32
	1,000	80	80	88	37	
		67	76	72	36	36
	2,000	62	62	118	63	
		66	68	90	45	54
Trial 2						
Dimethylsulfoxide						
		55	71	45	27	
		90	108	33	12	
		92	107	97	35	
		72	115	60	28	26
Ethylmethanesulfonate						
		80	97	318	133	
	250	69	81	213	103	118*
Methylmethanesulfonate						
		43	31	85	65	
	15	43	30	60	47	56*
Furan						
	1,400	80	98	72	30	
		83	103	61	24	27
	2,000	101	73	121	40	
		88	76	57	22	31
	2,600	77	52	227	99	
		78	51	125	54	76*
	3,200	71	42	536	252	
		54	38	408	250	251*
	3,800	51	6	1,819	1,181	
		35	4	1,235	1,165	1,173*

TABLE E2
Induction of TFT Resistance in Mouse L5178Y Lymphoma Cells by Furan (continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
-S9						
Trial 3						
Dimethylsulfoxide						
		64	99	63	33	
		69	99	67	33	
		62	107	69	37	
		67	95	66	33	34
Ethylmethanesulfonate						
		62	82	338	183	
	250	66	96	322	163	173*
Methylmethanesulfonate						
		38	34	99	86	
	15	38	29	79	70	78*
Furan						
	1,139	56	67	137	82	
		76	86	115	51	66*
	1,627	81	79	177	73	
		71	85	104	49	61*
	2,116	72	71	334	154	
		67	60	264	131	143*
	2,604	57	28	2,021	1,182	
		75	41	1,494	668	925*
	3,090	71	15	2,433	1,142	
		45	13	2,560	1,882	1,512*

* Significant positive response ($P \leq 0.05$)
[a] Study performed at Inveresk Research International. These data and the experimental protocol are presented in detail by McGregor *et al.* (1988).
[b] Mutant fraction (frequency) is the ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/10^6 cells treated)
[c] Mean from three replicate plates of approximately 10^6 cells each

TABLE E3
Induction of SCEs in CHO Cells by Furan[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)[b]
-S9								
Trial 1								
Summary: Positive								
Dimethylsulfoxide		50	1,050	396	0.37	7.9	26.0	
Mitomycin-C	0.0005	50	1,051	516	0.49	10.3	26.0	30.18
	0.0050	10	210	311	1.48	31.1	26.0	292.68
Furan	1.6	50	1,050	483	0.46	9.7	26.0	21.97*
	5.0	50	1,050	509	0.48	10.2	26.0	28.54*
	16.0	50	1,049	518	0.49	10.4	26.0	30.93*
	50.0	50	1,050	587	0.55	11.7	26.0	48.23*
	160.0	6	125	70	0.56	11.7	26.0	48.49*
								P<0.001[c]
Trial 2								
Summary: Weak positive								
Dimethylsulfoxide		50	1,050	463	0.44	9.3	26.0	
Mitomycin-C	0.0007	50	1,046	589	0.56	11.8	26.0	27.70
	0.0050	10	210	296	1.40	29.6	26.0	219.66
Furan	5.0	50	1,049	406	0.38	8.1	26.0	-12.23
	16.0	50	1,050	471	0.44	9.4	26.0	1.73
	50.0	50	1,051	519	0.49	10.4	26.0	11.99
	160.0	50	1,049	591	0.56	11.8	26.0	27.77*
								P<0.001
+S9								
Trial 1								
Summary: Weak positive								
Dimethylsulfoxide		50	1,050	441	0.42	8.8	26.0	
Cyclophosphamide	0.1	50	1,049	550	0.52	11.0	26.0	24.83
	0.6	10	210	207	0.98	20.7	26.0	134.69
Furan	16.0	50	1,049	486	0.46	9.7	26.0	10.31
	50.0	50	1,049	491	0.46	9.8	26.0	11.44
	160.0	50	1,049	493	0.46	9.9	26.0	11.90
	500.0	50	1,048	602	0.57	12.0	26.0	36.77*
								P<0.001

* Positive (≥20% increase over solvent control)
[a] Study performed at Environmental Health Research and Testing, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine.
[b] Percent increase in SCEs/chromosome of culture exposed to furan relative to those of culture exposed to solvent
[c] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

TABLE E4
Induction of Chromosomal Abs in CHO Cells by Furan[a]

Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
-S9				
Trial 1 – Harvest time: 12.0 hours				
Summary: Positive				
Dimethylsulfoxide				
	200	1	0.01	0.5
Mitomycin-C				
0.0625	200	37	0.19	18.0
0.2500	50	28	0.56	38.0
Furan				
100	200	7	0.04	3.5*
160	200	15	0.08	7.5*
300	200	42	0.21	17.0*
				P<0.001[b]
Trial 2 – Harvest time: 12.0 hours				
Summary: Positive				
Dimethylsulfoxide				
	200	3	0.02	1.5
Mitomycin-C				
0.0625	200	39	0.20	16.0
0.2500	50	20	0.40	36.0
Furan				
160	200	19	0.10	8.0*
300	200	38	0.19	12.0*
500	200	35	0.18	11.5*
				P<0.001
+S9				
Trial 1 – Harvest time: 13.0 hours				
Summary: Positive				
Dimethylsulfoxide				
	200	2	0.01	1.0
Cyclophosphamide				
2.5000	200	44	0.22	21.0
7.5000	50	30	0.60	44.0
Furan				
160	200	2	0.01	1.0
300	200	5	0.03	2.5
500	200	15	0.08	7.5*
1,000	93	32	0.34	24.7*
				P<0.001

* Positive ($P \leq 0.05$)

[a] Study performed at Environmental Health Research and Testing, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal Abs is found in Galloway *et al.* (1985, 1987).

[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

TABLE E5
Induction of SLRL Mutations in *Drosophila melanogaster* by Furan[a]

Route of Exposure	Dose (ppm)	Incidence of Deaths (%)	Incidence of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested			
				Mating 1	Mating2	Mating 3	Total[b]
Feeding	10,000	21	3	2/1,853	0/1,895	3/1,741	5/5,489 (0.09%)
	0			1/1,893	1/1,933	0/1,674	2/5,500 (0.04%)
Injection	25,000	28	22	1/2,498	3/1,635	2/1,484	6/5,617 (0.11%)
	0			3/2,493	0/1,939	4/1,087	7/5,519 (0.13%)

[a] Study performed at the University of Wisconsin-Madison. A detailed protocol of the SLRL assay is presented in Zimmering *et al.* (1985).
[b] Combined total number of lethal mutations/number of X chromosomes tested for three mating trials

TABLE E6
Induction of SCEs in Mouse Bone Marrow Cells by Furan[a]

	Dose (mg/kg)	SCEs/Cell[b]
Trial 1		
Standard protocol, 23-hour harvest		
Corn oil		4.44 ± 0.40
Dimethylbenzanthracene[c]	100.0	11.70 ± 0.50
Furan	87.5	4.82 ± 0.27
	175.0	3.95 ± 0.75
	350.0	4.22 ± 0.49
		P=0.2723[d]
Trial 2		
Extended Protocol, 42-hour harvest		
Corn oil		6.12 ± 1.05
Dimethylbenzanthracene	100.0	18.28 ± 1.09
Furan	25.0	5.41 ± 0.67
	50.0	5.85 ± 0.66
	100.0	5.57 ± 0.48
		P=0.3945

[a] Study performed at Oak Ridge Associated Universities.
[b] Mean ± standard error of the means among animals
[c] Positive control
[d] Cochran-Armitage trend test, used to determine if treatment-related increase is present; P≤0.05 is considered significant (Margolin *et al.*, 1986).

TABLE E7
Induction of Chromosomal Abs in Mouse Bone Marrow Cells by Furan[a]

	Dose (mg/kg)	Percent Cells with Abs[b]
Trial 1		
Standard protocol, 17-hour harvest		
Corn oil		2.0 ± 0.01
Dimethylbenzanthracene[c]	100.0	17.0 ± 0.07
		P<0.001[d]
Furan	87.5	1.0 ± 0.01
	175.0	1.0 ± 0.00
	350.0	2.3 ± 0.01
		P=0.305[e]
Trial 2		
Extended protocol, 36-hour harvest		
Corn oil		1.43 ± 0.01
Dimethylbenzanthracene	100.0	27.5 ± 0.10
		P=0.000
Furan	62.5	3.5 ± 0.01*
	125.0	3.25 ± 0.01
	250.0	16.75 ± 0.06***
		P<0.001
Trial 3		
Extended protocol, 36-hour harvest		
Corn oil		1.75 ±0.01
Dimethylbenzanthracene	100.0	18.00 ± 0.06
		P=0.000
Furan	62.5	3.50 ± 0.01
	125.0	3.00 ± 0.01
	250.0	19.50 ± 0.06***
		P<0.001

* Positive (P≤0.05)
*** Positive (P≤0.001)
a Study performed at Oak Ridge Associated Universities
b Mean ± standard error of the means among animals
c Positive control
d Paired P value; pairwise comparison to solvent control. P≤0.05 is considered significant.
e Significance tested by the one-tailed trend test; significant at P≤0.05 (Margolin *et al.*, 1986).

APPENDIX F
ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS IN THE 13-WEEK AND 15-MONTH STUDIES

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TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Studies of Furan[a]

	Vehicle Control	4 mg/kg	8 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
Male						
n	10	10	10	10	10	1[b]
Necropsy body wt	377 ± 4	383 ± 7	376 ± 6	354 ± 8*	309 ± 6**	127
Brain						
Absolute	1.95 ± 0.03	1.99 ± 0.02	1.93 ± 0.01	1.94 ± 0.02	1.87 ± 0.02*	1.71
Relative	5.18 ± 0.11	5.20 ± 0.08	5.14 ± 0.08	5.49 ± 0.11*	6.08 ± 0.11**	13.43
Heart						
Absolute	1.05 ± 0.02	1.08 ± 0.02	1.09 ± 0.02	1.00 ± 0.03	0.84 ± 0.02**	0.76
Relative	2.78 ± 0.03	2.82 ± 0.04	2.88 ± 0.04	2.83 ± 0.06	2.71 ± 0.08	5.98
R. Kidney						
Absolute	1.36 ± 0.03	1.38 ± 0.03	1.40 ± 0.04	1.37 ± 0.03	1.45 ± 0.04	1.25
Relative	3.59 ± 0.06	3.61 ± 0.06	3.70 ± 0.07	3.85 ± 0.02*	4.71 ± 0.11**	9.84
Liver						
Absolute	15.12 ± 0.48	15.21 ± 0.53	15.19 ± 0.53	15.94 ± 0.78	18.18 ± 0.66**	6.16
Relative	39.8 ± 1.1	39.7 ± 1.0	40.4 ± 1.2	44.8 ± 1.3*	58.9 ± 1.6**	48.5
Lung						
Absolute	1.59 ± 0.08	1.56 ± 0.03	1.55 ± 0.06	1.61 ± 0.09	1.31 ± 0.03**	0.89
Relative	4.21 ± 0.22	4.08 ± 0.12	4.12 ± 0.13	4.52 ± 0.15	4.25 ± 0.11	6.97
Thymus						
Absolute	0.54 ± 0.04	0.49 ± 0.04	0.47 ± 0.04	0.43 ± 0.05	0.30 ± 0.02**	0.11
Relative	1.44 ± 0.11	1.28 ± 0.12	1.26 ± 0.10	1.22 ± 0.14	0.96 ± 0.07**	0.83
Female						
n	10	10	10	10	10	6
Necropsy body wt	207 ± 3	209 ± 4	215 ± 3	206 ± 3	202 ± 5	159 ± 5**
Brain						
Absolute	1.81 ± 0.03	1.84 ± 0.02	1.83 ± 0.01	1.77 ± 0.03	1.82 ± 0.02	1.71 ± 0.03*
Relative	8.75 ± 0.14	8.81 ± 0.10	8.54 ± 0.13	8.62 ± 0.18	9.03 ± 0.19	10.83 ± 0.43**
Heart						
Absolute	0.64 ± 0.03	0.67 ± 0.01	0.69 ± 0.01	0.67 ± 0.01	0.61 ± 0.01	0.65 ± 0.02
Relative	3.11 ± 0.16	3.19 ± 0.05	3.22 ± 0.06	3.27 ± 0.06	3.03 ± 0.04	4.09 ± 0.17**
R. Kidney						
Absolute	0.75 ± 0.03	0.76 ± 0.01	0.78 ± 0.01	0.85 ± 0.05*	0.87 ± 0.02*	1.00 ± 0.07**
Relative	3.66 ± 0.17	3.64 ± 0.04	3.65 ± 0.08	4.14 ± 0.24*	4.33 ± 0.13**	6.29 ± 0.33**
Liver[c]						
Absolute	7.01 ± 0.21	6.91 ± 0.11	7.88 ± 0.19*	8.42 ± 0.28**	10.60 ± 0.33**	8.95 ± 0.38**
Relative	34.0 ± 1.3	33.1 ± 0.6	36.7 ± 0.9	40.8 ± 1.0**	52.6 ± 1.8**	56.5 ± 1.7**
Lung						
Absolute	1.07 ± 0.04	1.07 ± 0.03	1.08 ± 0.03	1.06 ± 0.03	1.03 ± 0.04	0.95 ± 0.03*
Relative	5.19 ± 0.21	5.12 ± 0.16	5.01 ± 0.11	5.14 ± 0.12	5.11 ± 0.17	6.00 ± 0.15*
Thymus						
Absolute	0.37 ± 0.02	0.33 ± 0.02	0.37 ± 0.04	0.33 ± 0.02	0.30 ± 0.02	0.23 ± 0.05**
Relative	1.78 ± 0.10	1.60 ± 0.10	1.71 ± 0.16	1.62 ± 0.09	1.50 ± 0.11	1.45 ± 0.28

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] No standard deviation calculated due to high mortality.
[c] n=9

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Rats at the 15-Month Interim Evaluation in the Stop-Exposure Gavage Study of Furan[a]

	Vehicle Control	30 mg/kg
n	9	10
Necropsy body wt	475 ± 16	428 ± 6*
R. Kidney		
Absolute	1.49 ± 0.07	1.86 ± 0.05**
Relative	3.13 ± 0.08	4.35 ± 0.13**
Liver		
Absolute	16.01 ± 1.11	44.92 ± 5.79**
Relative	33.5 ± 1.3	105.5 ± 13.9**
Lungs		
Absolute	1.74 ± 0.10	1.73 ± 0.06
Relative	3.65 ± 0.13	4.04 ± 0.13*
Spleen		
Absolute	0.72 ± 0.04	1.96 ± 0.22**
Relative	1.51 ± 0.04	4.61 ± 0.52**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Studies of Furan[a]

	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Male				
n	9	9	9	6
Necropsy body wt	475 ± 16	509 ± 14	506 ± 15	447 ± 19
R. Kidney				
Absolute	1.49 ± 0.07	1.54 ± 0.05	1.57 ± 0.06	1.47 ± 0.05
Relative	3.13 ± 0.08	3.03 ± 0.08	3.11 ± 0.09	3.29 ± 0.07
Liver				
Absolute	16.01 ± 1.11	16.29 ± 0.59	18.10 ± 0.77	25.14 ± 0.84*
Relative	33.5 ± 1.3	32.0 ± 0.5	35.7 ± 0.7	56.4 ± 0.8*
Lung				
Absolute	1.74 ± 0.10	1.83 ± 0.05	1.71 ± 0.06	1.83 ± 0.12
Relative	3.65 ± 0.13	3.62 ± 0.10	3.39 ± 0.08	4.12 ± 0.29
Female				
n	9	10	9	7
Necropsy body wt	276 ± 4	281 ± 9	300 ± 6	275 ± 10
R. Kidney				
Absolute	0.86 ± 0.02	0.86 ± 0.02	0.89 ± 0.02	1.00 ± 0.05**
Relative	3.11 ± 0.11	3.06 ± 0.06	2.98 ± 0.06	3.62 ± 0.10**
Liver				
Absolute	8.81 ± 0.24	9.56 ± 0.45	11.13 ± 0.21**	15.35 ± 1.15**
Relative	31.9 ± 0.8	34.0 ± 1.1	37.2 ± 0.7*	55.8 ± 3.3**
Lung				
Absolute	1.27 ± 0.07	1.26 ± 0.06	1.21 ± 0.05	1.30 ± 0.04
Relative	4.60 ± 0.26	4.49 ± 0.21	4.04 ± 0.15	4.76 ± 0.25

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

TABLE F4
Organ Weights and Organ Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Studies of Furan[a]

Male	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg	15 mg/kg	30 mg/kg
n	10	10	9	10	10	10
Necropsy body wt	36.0 ± 1.4	38.9 ± 0.7	37.8 ± 0.7	39.5 ± 0.9*	36.8 ± 1.0	35.9 ± 0.8
Brain						
Absolute	0.466 ± 0.004	0.471 ± 0.006	0.453 ± 0.008	0.453 ± 0.006	0.466 ± 0.005	0.470 ± 0.002
Relative	13.1 ± 0.5	12.1 ± 0.2	12.0 ± 0.2	11.5 ± 0.3**	12.8 ± 0.4	13.1 ± 0.3
Heart						
Absolute	0.165 ± 0.009	0.181 ± 0.005	0.175 ± 0.005	0.176 ± 0.005	0.159 ± 0.006	0.144 ± 0.003*
Relative	4.57 ± 0.18	4.64 ± 0.07	4.64 ± 0.15	4.45 ± 0.09	4.32 ± 0.07	4.02 ± 0.06**
R. Kidney						
Absolute	0.305 ± 0.017	0.360 ± 0.019	0.352 ± 0.007	0.320 ± 0.009	0.330 ± 0.009	0.289 ± 0.010
Relative	8.44 ± 0.32	9.25 ± 0.46	9.32 ± 0.17	8.10 ± 0.22	9.00 ± 0.24	8.04 ± 0.18
Liver						
Absolute	1.60 ± 0.11	1.87 ± 0.07	1.85 ± 0.06	1.73 ± 0.07	1.95 ± 0.10**	2.04 ± 0.06**
Relative	44.1 ± 1.9	48.0 ± 1.6	49.2 ± 2.0	43.8 ± 1.4	53.1 ± 2.8**	56.9 ± 0.9**
Lung						
Absolute	0.217 ± 0.011	0.209 ± 0.006	0.183 ± 0.007*	0.195 ± 0.010*	0.184 ± 0.004**	0.183 ± 0.004**
Relative	6.09 ± 0.37	5.37 ± 0.17*	4.87 ± 0.19**	4.92 ± 0.20**	5.02 ± 0.11**	5.09 ± 0.10**
Thymus[b]						
Absolute	53.00 ± 4.36	53.00 ± 5.88	41.88 ± 4.11[c]	67.00 ± 8.10	43.50 ± 2.36	55.00 ± 3.07
Relative	1.48 ± 0.11	1.35 ± 0.14	1.11 ± 0.11[c]	1.70 ± 0.20	1.18 ± 0.06	1.54 ± 0.09

Female	Vehicle Control	4 mg/kg	8 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
n	10	10	10	10	9	10
Necropsy body wt	27.0 ± 0.5	28.0 ± 0.7	27.7 ± 0.9	27.1 ± 0.6	27.1 ± 0.5	26.0 ± 0.3
Brain						
Absolute	0.480 ± 0.013	0.480 ± 0.005	0.456 ± 0.008	0.471 ± 0.006	0.459 ± 0.005	0.462 ± 0.008
Relative	17.8 ± 0.4	17.2 ± 0.4	16.6 ± 0.5	17.5 ± 0.5	17.0 ± 0.2	17.8 ± 0.3
Heart						
Absolute	0.125 ± 0.004	0.132 ± 0.005	0.127 ± 0.004	0.127 ± 0.003	0.110 ± 0.005	0.118 ± 0.001
Relative	4.61 ± 0.14	4.73 ± 0.17	4.59 ± 0.10	4.70 ± 0.12	4.05 ± 0.13	4.54 ± 0.05
R. Kidney						
Absolute	0.210 ± 0.014	0.201 ± 0.007	0.190 ± 0.012	0.196 ± 0.003	0.198 ± 0.006	0.213 ± 0.006
Relative	7.81 ± 0.59	7.18 ± 0.18	6.82 ± 0.36	7.27 ± 0.22	7.29 ± 0.13	8.19 ± 0.19
Liver						
Absolute	1.21 ± 0.03	1.27 ± 0.04	1.31 ± 0.04	1.24 ± 0.03	1.59 ± 0.07**	1.61 ± 0.06**
Relative	44.6 ± 0.9	45.4 ± 0.8	47.3 ± 1.0	45.8 ± 0.7	58.6 ± 1.9**	61.7 ± 1.8**
Lung						
Absolute	0.193 ± 0.015	0.181 ± 0.006	0.166 ± 0.007	0.174 ± 0.006	0.157 ± 0.007*	0.187 ± 0.004
Relative	7.16 ± 0.55	6.44 ± 0.11	6.02 ± 0.28*	6.43 ± 0.21	5.78 ± 0.22**	7.20 ± 0.16
Thymus[b]						
Absolute	51.50 ± 3.80	62.00 ± 6.92	56.00 ± 4.07	50.50 ± 2.63	53.33 ± 4.25	64.50 ± 3.61
Relative	1.90 ± 0.13	2.22 ± 0.26	2.02 ± 0.14	1.86 ± 0.08	1.97 ± 0.17	2.48 ± 0.14

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ and body weights are given in grams unless otherwise noted; organ-weight-to-body-weight ratios are given as mg organ weight per g body weight (mean ± standard error)
[b] Weights are given in milligrams.
[c] n=8

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE G1 Hematology and Clinical Chemistry Results for Rats at the 9-Month Interim Evaluation in the 2-Year Gavage Studies of Furan 268

TABLE G1
Hematology and Clinical Chemistry Results for Rats at the 9-Month Interim Evaluation in the 2-Year Gavage Studies of Furan[a]

Analysis	Vehicle Control	2 mg/kg	4 mg/kg	8 mg/kg
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)	37.5 ± 0.4	36.4 ± 0.5*	37.7 ± 0.8	35.1 ± 0.2**
Hemoglobin (g/dL)	17.0 ± 0.2	16.3 ± 0.3*	16.6 ± 0.7	15.4 ± 0.1**
Erythrocytes (10^6/μL)	9.42 ± 0.08	9.16 ± 0.12*	9.48 ± 0.18	8.79 ± 0.05**
Leukocytes (10^3/μL)	5.63 ± 0.24	4.35 ± 0.40**	4.02 ± 0.16**	4.95 ± 0.34
Segmented neutrophils (10^3/μL)	1.53 ± 0.21	1.08 ± 0.09	1.33 ± 0.17	1.35 ± 0.12
Lymphocytes (10^3/μL)	4.05 ± 0.16	3.23 ± 0.40*	2.65 ± 0.14**	3.56 ± 0.26
Clinical chemistry				
BUN (mg/dL)	16.4 ± 0.5	15.1 ± 0.4	14.5 ± 0.6*	16.0 ± 0.4
Creatinine (mg/dL)	0.57 ± 0.02	0.53 ± 0.02	0.60 ± 0.05	0.52 ± 0.02
Total bilirubin (mg/dL)	0.25 ± 0.02	0.19 ± 0.04*	0.27 ± 0.02	0.21 ± 0.01
ALT (IU/L)	61 ± 4	25 ± 7**[b]	37 ± 3**	37 ± 3**
AST (IU/L)	77 ± 6	28 ± 7**[b]	60 ± 5[b]	53 ± 4*
LDH (IU/L)	123 ± 11	124 ± 32[b]	123 ± 16	80 ± 12**
SDH (IU/L)	11 ± 1	14 ± 2[b]	15 ± 1*[c]	17 ± 2**
Female				
n	10	9	10	9
Hematology				
Hematocrit (%)	36.2 ± 0.5	35.0 ± 0.4	38.2 ± 0.6	34.9 ± 0.5
Hemoglobin (g/dL)	16.5 ± 0.2	15.9 ± 0.2	17.0 ± 0.3	15.6 ± 0.2
Erythrocytes (10^6/μL)	8.37 ± 0.09	8.22 ± 0.08	8.93 ± 0.15	8.28 ± 0.12
Leukocytes (10^3/μL)	3.03 ± 0.21	2.87 ± 0.14	3.34 ± 0.37	3.81 ± 0.31*
Segmented neutrophils (10^3/μL)	0.73 ± 0.09	0.68 ± 0.10	0.74 ± 0.12	0.95 ± 0.12
Lymphocytes (10^3/μL)	2.27 ± 0.17	2.16 ± 0.14	2.59 ± 0.28	2.84 ± 0.26
Clinical chemistry				
BUN (mg/dL)	17.8 ± 0.8	15.6 ± 1.0[d]	19.2 ± 1.1	19.3 ± 0.4
Creatinine (mg/dL)	0.55 ± 0.02	0.24 ± 0.03**[e]	0.39 ± 0.05**	0.40 ± 0.03**
Total bilirubin (mg/dL)	0.23 ± 0.02	0.17 ± 0.01[e]	0.21 ± 0.04	0.24 ± 0.01
ALT (IU/L)	46 ± 3	33 ± 2**[d]	24 ± 1**	29 ± 2**
AST (IU/L)	72 ± 6	52 ± 4**[d]	56 ± 2	61 ± 4
LDH (IU/L)	104 ± 10	67 ± 28[d]	182 ± 28	155 ± 22
SDH (IU/L)	10 ± 1	11 ± 2[d]	15 ± 1**	16 ± 1**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] BUN=blood urea nitrogen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; LDH=lactate dehydrogenase; SDH=sorbitol dehydrogenase
[b] n=9
[c] n=8
[d] n=10
[e] n=3

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Furan was obtained from Quaker Oats Company in one lot (OF20-M) without stabilization with butylated hydroxytoluene (BHT). This lot was used throughout the 16-day, 13-week, and 2-year studies. Purity, identity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (MRI; Kansas City, MO), and confirmed by the study laboratory. Reports of analyses performed in support of the studies are on file at NIEHS.

The study chemical, a clear volatile liquid, was identified as furan by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The spectra were consistent with those expected for the structure of furan and with the literature (*Sadtler Standard Spectra*) (Figures H1 and H2).

The purity of the lot was determined to be greater than 99% by Karl Fischer water analysis, elemental analyses, and gas chromatography (GC). Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for furan. GC was performed with two columns with a flame ionization detector (FID) and a nitrogen carrier gas at 70 mL/minute:

1) 80/100 Carbopack C/0.1% SP-1000, column temperature program of 40° C for 4 minutes and then 40° C to 170° C at 10° C/minute, and
2) 20% SP-2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, column temperature program of 40° C for 4 minutes, then 40° to 170° C at 10° C/minute.

Two impurities, with areas of less than 0.02% of the major peak area, were detected by the first system. The second system detected no impurities up to 29 minutes after the major peak.

A GC analysis was conducted to determine if any BHT was present. An FID was used as well as a nitrogen carrier gas at a flow rate of 70 mL/min. The column was 5% SP-1000 on 100/120 mesh Supelcoport, and the column temperature was 150° C. The special analysis did not detect any BHT present at a concentration of 2 ppm or above.

Heat stability studies performed with GC (column: 80/100 Carbopack C/0.1% SP-1000; column temperature 60° C isothermal, carrier gas N_2 at 70 mL/minute) found that the bulk chemical was stable for 2 weeks at temperatures up to 25° C when stored under a nitrogen head space, protected from light. The bulk chemical was stored in amber-glass bottles at −20° C under nitrogen at the study laboratory throughout the study period. The stability of the bulk chemical was monitored periodically at the study laboratory during all phases of the studies by infrared spectroscopy and by GC, using method 1 above, or with an 80/100 mesh column Porapak QS with a column temperature program of 50° C for 5 minutes, 50° to 170° C at 10° C/minute, then 170° C for 15 minutes. No change in the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by allowing furan to come to room temperature, then mixing appropriate amounts of furan and corn oil to obtain the required concentrations (Table H1). The dose formulations were mixed twice during the 16-day study and weekly during the 13-week and 2-year studies. Because tests by the analytical laboratory indicated that furan may oxidize in air, dose formulations were stored under nitrogen in amber-glass bottles at 5° C for no longer than 2 weeks, and were shaken by hand before administration.

Studies were conducted by the analytical chemistry laboratory to determine the stability of the furan/corn oil formulations. Eight mL aliquots of the formulations were quantitatively transferred and diluted to 200 mL with hexane, then analyzed by GC (80/100 mesh Poropak QS column; column temperature program of 130° C for 5 minutes, then 130° to 200° C at 15° C/minute, and held at 200° C for 5 minutes; carrier gas N_2 at 30 mL/minute). Stability was confirmed for solutions stored in the dark under a nitrogen atmosphere at room temperature for up to 2 weeks. However, refrigeration was recommended.

The study laboratory conducted periodic analyses of the furan dose formulations with GC, using the same system as the analytical chemistry laboratory. Dose formulations were analyzed twice during the 13-week studies and at 8-week intervals during the 2-year studies. During the 13-week studies, 90% (9/10) of the dose formulations for rats and 92% (11/12) of the dose formulations for mice were within 10% of target concentrations (Table H2). The rat dose formulation that did not meet acceptable limits was remixed, the remix was used despite being slightly outside acceptable limits (−11% of target). During the 2-year studies, 76% (32/42) of the dose formulations for rats and 92% (24/26) of the dose formulations for mice were within 10% of the target concentrations (Tables H3a,b). Three of the 11 dose formulations for rats which were outside acceptable limits were used for dosing due to lack of time for remixing. Animal room samples from each dose level were analyzed every 5 to 6 months during the chronic studies; as expected because of the volatility of furan, a number of the animal room samples were out of specification. Of the dose formulations for rats, 80% (12/15) were within 10% of the target concentrations, while 62.5% (5/8) of the dose formulations for mice achieved the same target concentration. Those animal room samples which were out of specification ranged from −11% to −15% of target. Peroxide analyses of the corn oil vehicle by the study laboratory indicated peroxide levels below the limit of 10 mEq/kg (≥10 mEq/kg is considered rancid).

Results of periodic referee analyses performed by the analytical chemistry laboratory were not always in agreement with the results from the study laboratory (Table H4); a special study by the analytical chemistry laboratory indicated that the differences in values were analytical in nature. The special study analyses were performed with the same GC system used for the regular dose analyses, but with a column temperature program of 130° C for 5 minutes, with an increase of 130° to 201° C at intervals of 15° C/min, and held at 201° C for 10 minutes.

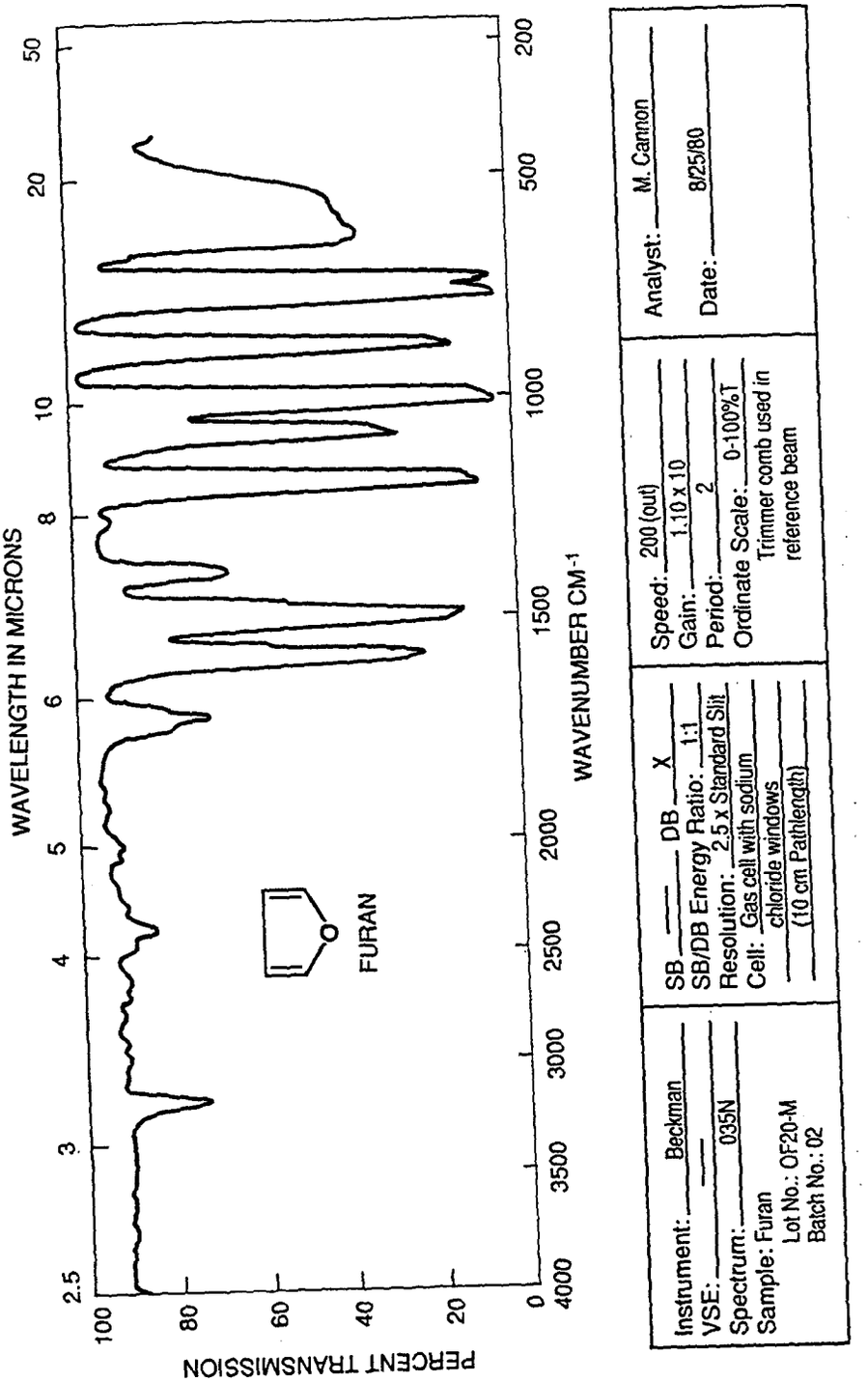

FIGURE H1
Infrared Absorption Spectrum of Furan

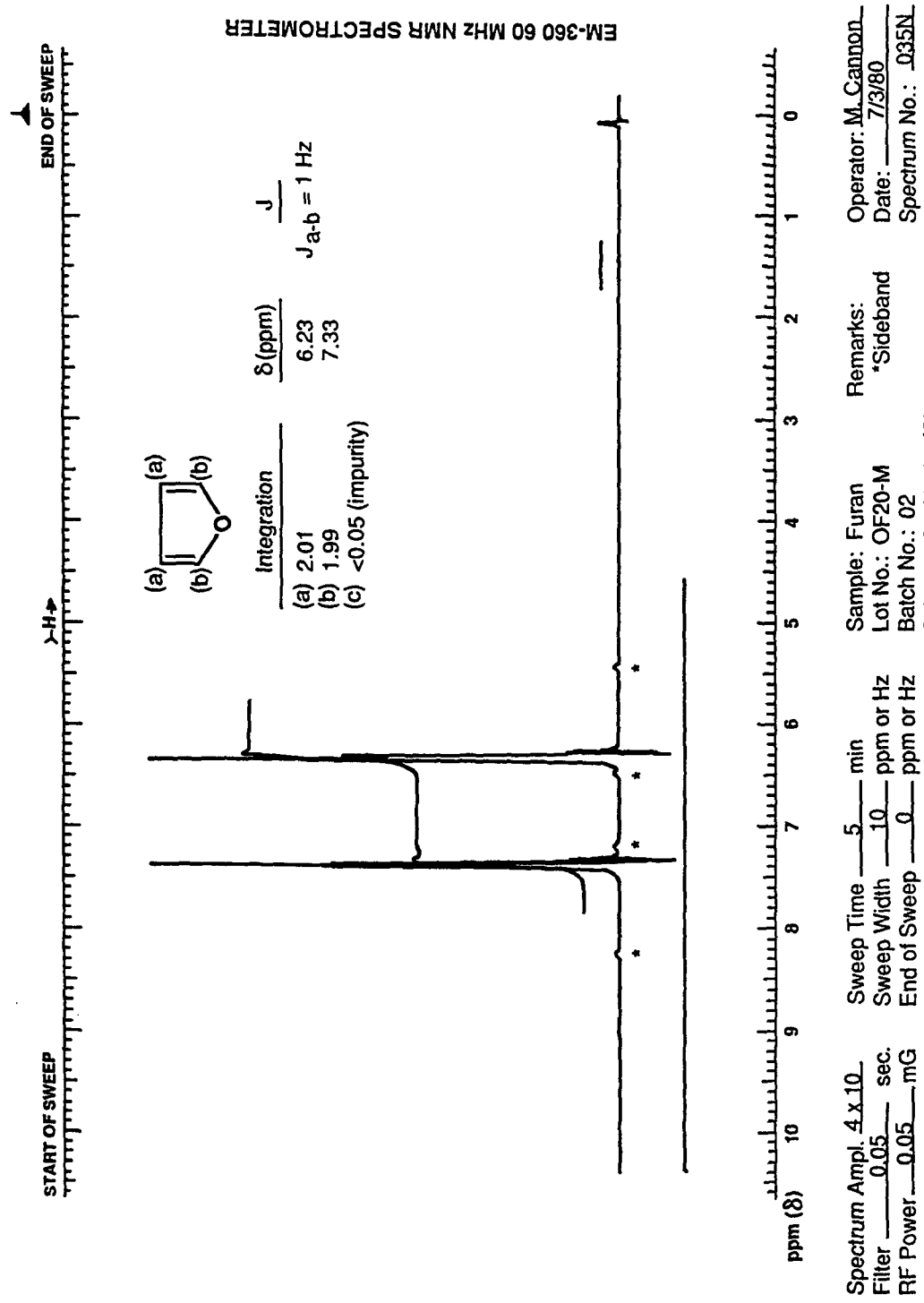

FIGURE H2
Nuclear Magnetic Resonance Spectrum of Furan

TABLE H1
Preparation and Storage of Dose Formulations in the Gavage Studies of Furan

16-Day Studies	13-Week Studies	2-Year Studies
Preparation		
Furan was allowed to come to room temperature, then stirred in corn oil in appropriate concentrations (weight/weight).	Furan was allowed to come to room temperature, then stirred in corn oil in appropriate concentrations (weight/weight). Stored mixtures were shaken by hand for 15 seconds before administration.	Same as 13-week studies
Chemical Lot Number		
OF20-M	OF20-M	OF20-M
Maximum Storage Time		
14 days from date of preparation	Same as 16-day studies	Same as 16-day studies
Storage Conditions		
In the dark under a nitrogen atmosphere at 5° C	Same as 16-day studies	Same as 16-day studies
Study Laboratory		
Southern Research Institute, Birmingham, AL	Same as 16-day studies	Same as 16-day studies
Referee Laboratory		
Midwest Research Institute, Kansas City, MO	Same as 16-day studies	Same as 16-day studies

TABLE H2
Results of Analysis of Dose Formulations in the 13-Week Gavage Studies of Furan

Date Prepared	Date Analyzed	Target Concentration (wt/wt%)	Determined Concentration[a] (wt/wt%)	% Difference from Target
Rats[b]				
20 February 1981	25 February 1981	0.09	0.082	–9
		0.17	0.154	–9
		0.33	0.313	–5
		0.65	0.635	–2
		1.31	1.22	–7
10 April 1981	10 April 1981	0.09	0.081	–10
		0.17	0.147	–14[c]
		0.33	0.315	–5
		0.65	0.592	–9
		1.31	1.19	–9
13 April 1981	13 April 1981[d]	0.17	0.152	–11[c]
14 April 1981	15 April 1981[d]	0.17	0.144	–15[e]
Mice[f]				
20 February 1981	25 February 1981	0.02	0.016	–20[c]
		0.04	0.036	–10
		0.09	0.084	–7
		0.16	0.144	–10
		0.33	0.326	–1
		0.65	0.604	–7
27 February 1981	27 February 1981[d]	0.02	0.019	–5
10 April 1981	10 April 1981	0.02	0.018	–10
		0.04	0.036	–10
		0.09	0.088	–2
		0.16	0.147	–8
		0.33	0.318	–4
		0.65	0.605	–7

[a] Results of duplicate analyses
[b] Wt/wt% values: 0.09%=4 mg/kg; 0.17%=15 mg/kg; 0.33%=8 mg/kg; 0.65%=30 mg/kg; 1.31%=60 mg/kg
[c] Not within tolerance. Sample remixed.
[d] Results of remix
[e] Second remix; not used for dosing. 13 April 1981 remix used for dosing.
[f] Wt/wt% values: 0.02%=2 mg/kg; 0.04%=4 mg/kg; 0.09%=8 mg/kg; 0.16%=15 mg/kg; 0.33%=30 mg/kg; 0.65%=60 mg/kg

TABLE H3a
Results of Analysis of Dose Formulations for Rats in the 2-Year Gavage Studies of Furan

Date Prepared	Date Analyzed	Target Concentration[a] (wt/wt%)	Determined Concentration[b] (wt/wt%)	% Difference from Target
16 June 1982	17 June 1982	0.0435	0.0381	–12[c]
		0.0871	0.0738	–15[c]
		0.174	0.144	–17[c]
21 June 1982	24 June 1982[d]	0.0435	0.0396	–9
		0.0871	0.0774	–11
		0.174	0.159	–9
14 July 1982	20 July 1982	0.0435	0.0369	–15[e]
		0.0871	0.0762	–13[e]
		0.174	0.157	–10
	23 July 1982[f]	0.0435	0.0384	–12
		0.0871	0.0783	–10
		0.174	0.159	–9
8 September 1982	9 September 1982	0.0435	0.0413	–5
		0.0871	0.0855	–2
		0.174	0.164	–6
3 November 1982	4 November 1982[g]	0.0435	0.0396	–9
		0.0871	0.0822	–6
		0.174	0.162	–7
29 December 1982	29 December 1982	0.0435	0.0402	–8
		0.0871	0.0819	–6
		0.174	0.166	–5
	6 January 1983[f]	0.0435	0.0369	–15
		0.0871	0.0778	–11
		0.174	0.160	–8
25 February 1983	25 February 1983	0.0435	0.0356	–18[c]
		0.0871	0.0770	–12[c]
		0.174	0.160	–8
28 February 1983	28 February 1983[d]	0.0435	0.0416	–4
		0.0871	0.0848	–3
22 April 1983	22 April 1983	0.0435	0.0405	–7
		0.0871	0.0784	–10
		0.174	0.154	–11[c]
26 April 1983	26 April 1983[d]	0.174	0.166	–5
17 June 1983	17 June 1983	0.0435	0.0412	–5
		0.0871	0.0813	–7
		0.174	0.164	–6
	29 June 1983[f]	0.0435	0.0392	–10
		0.0871	0.0789	–9
		0.174	0.160	–8

TABLE H3a
Results of Analysis of Dose Formulations for Rats in the 2-Year Gavage Studies of Furan (continued)

Date Prepared	Date Analyzed	Target Concentration (wt/wt%)	Determined Concentration (wt/wt%)	% Difference from Target
12 August 1983	12 August 1983	0.0435	0.0422	-3
		0.0871	0.0810	-7
		0.174	0.159	-9
7 October 1983	7 October 1983	0.0435	0.0396	-9
		0.0871	0.0788	-10
		0.174	0.169	-3
2 December 1983	2 December 1983	0.0435	0.0366	-16[c]
		0.0871	0.0766	-12[c]
		0.174	0.158	-9
	13 December 1983[f]	0.174	0.164	-6
5 December 1983	5 December 1983[d]	0.0435	0.0422	-3
		0.0871	0.0844	-3
	13 December 1983[f]	0.0435	0.0420	-3
		0.0871	0.0840	-4
10 February 1984	10 February 1984	0.0435	0.0426	-2
		0.0871	0.0855	-2
		0.174	0.169	-3
6 April 1984	6 April 1984	0.0435	0.0424	-3
		0.0871	0.0854	-2
		0.174	0.172	-1
18 May 1984	18 May 1984	0.0435	0.0477	+10
		0.0871	0.0906	+4
		0.174	0.175	+1
	1 June 1984[f]	0.0435	0.0416	-4
		0.0871	0.0852	-2
		0.174	0.168	-3

[a] Weight/weight % values: 0.0435%=2 mg/kg; 0.0871%=4 mg/kg; 0.174%=8 mg/kg
[b] Results of duplicate analyses
[c] Sample remixed
[d] Analysis results of remix
[e] Used for dosing due to lack of time for remixing
[f] Animal room samples
[g] Analyses of doses completed on 8 November 1982

TABLE H3b
Results of Analysis of Dose Formulations for Mice in the 2-Year Gavage Studies of Furan

Date Prepared	Date Analyzed	Target Concentration[a] (wt/wt%)	Determined Concentration[b] (wt/wt%)	% Difference from Target
19 May 1982	21 May 1982	0.087	0.0786	–10
		0.163	0.146	–10
14 July 1982	20 July 1982	0.087	0.0828	–5
		0.163	0.153	–6
	23 July 1982[c]	0.087	0.0800	–8
		0.163	0.150	–8
8 September 1982	9 September 1982	0.087	0.0790	–9
		0.163	0.147	–10
3 November 1982	4 November 1982	0.087	0.0820	–6
		0.163	0.153	–6
29 December 1982	29 December 1982	0.087	0.0794	–9
		0.163	0.152	–7
	6 January 1983[c]	0.087	0.0752	–14
		0.163	0.146	–10
25 February 1983	25 February 1983	0.087	0.0756	–13[d]
		0.163	0.150	–8
28 February 1983	28 February 1983[e]	0.087	0.0826	–5
22 April 1983	22 April 1983	0.087	0.0801	–8
		0.163	0.150	–8
17 June 1983	17 June 1983	0.087	0.0810	–7
		0.163	0.152	–7
	29 June 1983[c]	0.087	0.0770	–11
		0.163	0.144	–12
12 August 1983	12 August 1983	0.087	0.0820	–6
		0.163	0.150	–8
7 October 1983	7 October 1983	0.087	0.0798	–8
		0.163	0.157	–4
2 December 1983	2 December 1983	0.087	0.0753	–13[d]
		0.163	0.149	–9
5 December 1983	5 December 1983[e]	0.087	0.0826	–5
2 December 1983[f]	13 December 1983[c]	0.087	0.0840	–3
		0.163	0.157	–4
10 February 1984	10 February 1984	0.087	0.0848	–3
		0.163	0.156	–4

TABLE H3b
Results of Analysis of Dose Formulations for Mice in the 2-Year Gavage Studies of Furan (continued)

Date Prepared	Date Analyzed	Target Concentration (wt/wt%)	Determined Concentration (wt/wt%)	% Difference from Target
6 April 1984	6 April 1984	0.087	0.0835	–4
		0.163	0.156	–4

[a] Wt/wt% values: 0.087%=8 mg/kg; 0.163%=15 mg/kg
[b] Results of duplicate analyses
[c] Animal room samples
[d] Sample remixed
[e] Analysis results of remix
[f] Mixing completed on 5 December 1983

TABLE H4
Results of Referee Analysis of Dose Formulations in the 2-Year Gavage Studies of Furan

Date Mixed	Target Concentration[a] (wt/wt%)	Determined Concentration (wt/wt%)	
		Study Laboratory[b]	Referee Laboratory[c]
Rats			
16 June 1982	0.0871	0.0738	0.0848 ± 0.0009
21 June 1982	0.0871	0.0774	0.0897 ± 0.0006
8 September 1982	0.0435	0.0413	0.0459 ± 0.0018
12 August 1983	0.0435	0.0422	0.0580 ± 0.0003
7 October 1983	0.0435	0.0396	0.0446 ± 0.0025
18 May 1984	0.174	0.175	0.157 ± 0.004
Mice			
19 May 1982	0.087	0.0786	0.094 ± 0.002
25 February 1983	0.163	0.150	0.152 ± 0.002

[a] Wt/wt% values: 0.0435%=2 mg/kg, 0.0871%=4 mg/kg, 0.174%=8 mg/kg (rats); 0.087%=8 mg/kg, 0.163%=15 mg/kg (mice)
[b] Results of duplicate analysis
[c] Results of triplicate analysis. Mean ± standard deviation

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

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TABLE I1
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 I2
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 I3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.21 ± 1.06	21.3–26.3	26
Crude fat (% by weight)	5.10 ± 0.54	3.3–5.7	26
Crude fiber (% by weight)	3.46 ± 0.51	2.9–5.6	26
Ash (% by weight)	6.58 ± 0.41	5.7–7.3	26
Amino Acids (% of total diet)			
Arginine	1.320 ± 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	0.665–1.050	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 (% of total diet)			
Linoleic	2.290 ± 0.313	1.830–2.520	5
Linolenic	0.258 ± 0.040	0.210–0.308	5
Vitamins			
Vitamin A (IU/kg)	12,638 ± 4,501	4,100–24,000	26
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)	17.12 ± 3.51	12.0–27.0	26
Riboflavin (ppm)	7.60 ± 0.85	6.10–8.20	5
Niacin (ppm)	97.80 ± 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	5.60–8.80	5
Folic acid (ppm)	2.62 ± 0.89	1.80–3.70	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 ± 417	2,400–3,430	5
Minerals			
Calcium (%)	1.28 ± 0.11	1.11–1.54	26
Phosphorus (%)	0.97 ± 0.05	0.89–1.10	26
Potassium (%)	0.900 ± 0.098	0.772–0.971	3
Chloride (%)	0.513 ± 0.114	0.380–0.635	5
Sodium (%)	0.323 ± 0.043	0.258–0.371	5
Magnesium (%)	0.167 ± 0.012	0.151–0.181	5
Sulfur (%)	0.304 ± 0.064	0.268–0.420	5
Iron (ppm)	410.3 ± 94.0	262.0–523.0	5
Manganese (ppm)	90.29 ± 7.15	81.70–99.40	5
Zinc (ppm)	52.78 ± 4.94	46.10–58.20	5
Copper (ppm)	10.72 ± 2.76	8.090–15.39	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)	0.68 ± 0.14	0.490–0.780	4

TABLE I4
Contaminant Levels in NIH-07 Rat and Mouse Ration

Contaminants	Mean ± Standard Deviation[a]	Range	Number of Samples
Arsenic (ppm)	0.51 ± 0.14	0.17–0.77	26
Cadmium (ppm)	<0.10		26
Lead (ppm)	0.75 ± 0.63	0.33–3.37	26
Mercury (ppm)	<0.05		26
Selenium (ppm)	0.32 ± 0.07	0.13–0.42	26
Aflatoxins (ppb)	<5.0		26
Nitrate nitrogen (ppm)[b]	9.02 ± 4.66	0.10–22.0	26
Nitrite nitrogen (ppm)[b]	1.86 ± 2.01	0.10–7.20	26
BHA (ppm)[c]	4.04 ± 4.67	2.00–17.0	26
BHT (ppm)[c]	2.62 ± 2.52	1.00–12.0	26
Aerobic plate count (CFU/g)[d]	48,615 ± 32,607	4,900–130,000	26
Coliform (MPN/g)[e]	47.65 ± 122.37	3.00–460	26
E. coli (MPN/g)	3.00		26
Total nitrosoamines (ppb)[f]	5.30 ± 5.78	1.80–30.00	26
N-Nitrosodimethylamine (ppb)[f]	4.26 ± 5.77	0.80–30.00	26
N-Nitrosopyrrolidine (ppb)[f]	1.03 ± 0.25	0.81–1.00	26
Pesticides (ppm)			
α-BHC[g]	<0.01		26
β-BHC	<0.02		26
γ-BHC	<0.01		26
δ-BHC	<0.01		26
Heptachlor	<0.01		26
Aldrin	<0.01		26
Heptachlor epoxide	<0.01		26
DDE	<0.01		26
DDD	<0.01		26
DDT	<0.01		26
HCB	<0.01		26
Mirex	<0.01		26
Methoxychlor	<0.05		26
Dieldrin	<0.01		26
Endrin	<0.01		26
Telodrin	<0.01		26
Chlordane	<0.05		26
Toxaphene	<0.1		26
Estimated PCBs	<0.2		26
Ronnel	<0.01		26
Ethion	<0.02		26
Trithion	<0.05		26
Diazinon	<0.1		26
Methyl parathion	<0.02		26
Ethyl parathion	<0.02		26
Malathion[h]	0.10 ± 0.09	0.05–0.45	26
Endosulfan I	<0.01		26
Endosulfan II	<0.01		26
Endosulfan sulfate	<0.03		26

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Sources of contamination: alfalfa, grains, and fish meal
[c] Sources of contamination: soy oil and fish meal
[d] CFU = colony-forming unit
[e] MPN = most probable number
[f] All values were corrected for percent recovery.
[g] BHC = hexachlorocyclohexane or benzene hexachloride
[h] Fourteen lots contained more than 0.05 ppm.

APPENDIX J
SENTINEL ANIMAL PROGRAM

METHODS 286
Table J1 Murine Virus Antibody Determinations for Rats in the 2-Year Gavage Studies of Furan 287

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 serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are 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.

Rats

Fifteen 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. Samples for viral screening at 24 months were collected from five diet control animals of each sex. Blood collected from each animal was allowed to clot, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	6, 12, 18, and 24 months
PVM (pneumonia virus of mice)	
Sendai	
KRV (Kilham rat virus)	
H-1 (Toolan's H-1 virus)	
ELISA	12, 18, and 24 months
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	
Mycoplasma pulmonis	
Complement Fixation	6 months
RCV	

Test results are presented in Table J1.

Mice

Fifteen B6C3F$_1$ mice 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. Samples for viral screening at 24 months were collected from five diet control animals of each sex. Blood collected from each animal was allowed to clot, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM	6, 12, 18, and 24 months
Reovirus 3	6, 12, 18, and 24 months
GDVII (mouse encephalomyelitis virus)	6, 12, and 18 months
Polyoma virus	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
MVM (minute virus of mice)	6, 12, 18, and 24 months
Ectromelia virus (mouse pox)	6, 12, 18, and 24 months
Complement Fixation	6, 12, 18, and 24 months
Mouse adenoma virus	
LCM (lymphocytic choriomeningitis virus)	
ELISA	
MHV (mouse hepatitis virus)	6, 12, 18, and 24 months
Mycoplasma pulmonis	12, 18, and 24 months
GDVII	24 months

TABLE J1
Murine Virus Antibody Determinations in the 2-Year Gavage Studies of Furan

Interval (months)	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
Rats		
6	10/10	PVM
	8/10	Sendai
12	10/10	PVM
	4/10	Sendai
	8/10	*M. pulmonis*[a]
18	10/10	PVM
	4/10	Sendai
24	10/10	PVM
	4/10	Sendai
Mice		
6	0/10	
12	0/10	
18	0/10	
24	0/10	

[a] Further evaluation of this assay indicated that it was not specific for *Mycoplasma pulmonis*, and these results were considered to be false positive.

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-Ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-Methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichlorethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosponium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Pariffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF DECEMBER 1992 (CONT.)

TR No.	CHEMICAL
336	Penicillin VK
337	Nitrofurazone
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
399	Titanocene Dichloride
401	2,4-Diaminophenol Dihydrochloride
403	Resorcinol
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
409	Quercetin
410	Naphthalene
411	C.I. Pigment Red 23
412	4,4-Diamino-2,2-Stilbenedisulfonic Acid
415	Polysorbate 80
419	HC Hellow 4

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