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TOXICOLOGY AND CARCINOGENESIS STUDIES OF FURFURAL

(CAS NO. 98-01-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF FURFURAL

(CAS NO. 98-01-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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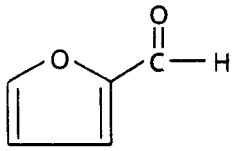

FURFURAL

CAS No. 98-01-1

$C_5H_4O_2$ Molecular weight 96.1

Synonyms: 2-Furancarboxaldehyde; 2-furaldehyde; pyromucic aldehyde
Common Name: Artificial oil of ants

ABSTRACT

Furfural is used as a precursor for the manufacture of furan, furfuryl alcohol, tetrahydrofuran, and their derivatives and as an industrial solvent. Furfural is also present in numerous processed food and beverage products. Toxicology and carcinogenesis studies were conducted by administering furfural (99% pure) in corn oil by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, mouse lymphoma cells, Chinese hamster ovary (CHO) cells, *Drosophila melanogaster*, and mouse bone marrow cells.

Sixteen-Day Studies: Rats received doses ranging from 15 to 240 mg/kg, and mice received doses from 25 to 400 mg/kg. Eight of 10 rats that received 240 mg/kg died within 3 days. Final mean body weights of chemically exposed animals were similar to those of vehicle controls; no compound-related histologic lesions were observed in any dosed groups.

Thirteen-Week Studies: Rats received doses ranging from 11 to 180 mg/kg, and mice received doses from 75 to 1,200 mg/kg. Most rats that received 180 mg/kg died; mean body weights of chemically exposed rats were similar to those of vehicle controls. Mean relative and absolute liver and kidney weights were increased in male rats that received 90 mg/kg, and cytoplasmic vacuolization of hepatocytes was increased in chemically exposed male rats.

Almost all mice that received doses of 600 or 1,200 mg/kg died within the first 3 weeks. Mean body weights of chemically exposed mice were similar to those of vehicle controls throughout the studies. Mean absolute liver weights and liver weight to body weight ratios were increased in females that received 300 mg/kg. Centrilobular coagulative necrosis and/or multifocal subchronic inflammation of the liver were present in chemically exposed mice but not in vehicle control mice.

Based on these results, doses selected for the 2-year studies were 0, 30, and 60 mg/kg for rats and 0, 50, 100, and 175 mg/kg for mice.

Body Weight and Survival in the Two-Year Studies: Mean body weights of chemically exposed and vehicle control animals were similar throughout the studies for rats and mice. Two-year survival of male rats, low dose female rats, and mice was unaffected by chemical exposure (male rats: vehicle control, 31/50; low dose, 28/50; high dose, 24/50; female rats: 28/50; 32/50; 18/50; male mice: vehicle control, 35/50; low dose, 28/50; mid dose, 24/50; high dose, 27/50; female mice: 33/50; 28/50; 29/50;

32/50). Survival of high dose female rats was reduced by deaths associated with gavage administration; the administration of furfural was considered to be a contributing factor in these gavage-related deaths.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Centrilobular necrosis of the liver occurred at increased incidences in chemically exposed male rats (vehicle control, 3/50; low dose, 9/50; high dose, 12/50). Two high dose male rats had bile duct dysplasia with fibrosis, and two had cholangiocarcinomas; neither lesion was seen in the other dose groups. The historical incidence of bile duct neoplasms in corn oil vehicle control male rats is 3/2,145 (0.1%).

Multifocal pigmentation and chronic inflammation of the subserosa of the liver occurred in chemically exposed mice (pigmentation--male: 0/50; 0/50; 8/49; 18/50; female: 0/50; 0/50; 0/50; 11/50; chronic inflammation--male: 0/50; 0/50; 8/49; 18/50; female: 0/50; 0/50; 1/50; 8/50). The incidences of hepatocellular adenomas and hepatocellular carcinomas in male mice and hepatocellular adenomas in female mice were significantly increased in the high dose group compared with those in the vehicle controls (male--adenomas: 9/50; 13/50; 11/49; 19/50; carcinomas: 7/50; 12/50; 6/49; 21/50; female--adenomas: 1/50; 3/50; 5/50; 8/50; adenomas or carcinomas, combined: 5/50; 3/50; 7/50; 12/50).

Three renal cortical adenomas or carcinomas occurred in chemically exposed male mice (0/50; 1/50; 1/49; 1/50), and a renal cortical adenoma was present in one low dose female mouse; the historical incidence of renal cortical neoplasms in National Toxicology Program 2-year corn oil gavage studies in male B6C3F$_1$ mice is 8/2,183.

Forestomach hyperplasia occurred in chemically exposed female mice, and squamous cell papillomas were increased in high dose female mice (hyperplasia: 0/50; 5/50; 5/50; 3/50; papillomas: 1/50; 0/50; 1/50; 6/50).

Genetic Toxicology: In gene mutation tests with four strains of Salmonella (TA98, TA100, TA1535, and TA1537), no mutagenic activity was observed in the presence or absence of exogenous metabolic activation (S9) in one laboratory and an equivocal response was observed in TA100 in the absence of S9 in a second laboratory. Exposure to furfural induced trifluorothymidine resistance in mouse L5178Y lymphoma cells in the absence of S9 (no evaluation was made in the presence of S9), sister chromatid exchanges (SCEs) and chromosomal aberrations in CHO cells in the presence or absence of S9, and an increase in sex-linked recessive lethal mutations but no reciprocal translocations in germ cells of *D. melanogaster*; furfural did not induce SCEs or chromosomal aberrations in the bone marrow of B6C3F$_1$ mice.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of furfural for male F344/N rats, based on the occurrence of uncommon cholangiocarcinomas in two animals and bile duct dysplasia with fibrosis in two other animals. There was *no evidence of carcinogenic activity* for female F344/N rats that received doses of 0, 30, or 60 mg/kg furfural. There was *clear evidence of carcinogenic activity* for male B6C3F$_1$ mice, based on increased incidences of hepatocellular adenomas and hepatocellular carcinomas. There was *some evidence of carcinogenic activity* in female B6C3F$_1$ mice, based on increased incidences of hepatocellular adenomas. Renal cortical adenomas or carcinomas in male mice and squamous cell papillomas of the forestomach in female mice may have been related to exposure to furfural.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 9-10.

SUMMARY OF THE TWO-YEAR GAVAGE STUDIES OF FURFURAL

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 30, or 60 mg/kg furfural in corn oil, 5 d/wk	0, 30, or 60 mg/kg furfural in corn oil, 5 d/wk	0, 50, 100, or 175 mg/kg furfural in corn oil, 5 d/wk	0, 50, 100, or 175 mg/kg furfural in corn oil, 5 d/wk
Body weights in the 2-year study			
Dosed and control groups similar	Dosed and control groups similar	Dosed and control groups similar	Dosed and control groups similar
Survival rates in the 2-year study			
31/50; 28/50; 24/50	28/50; 32/50; 18/50	35/50; 28/50; 24/50; 27/50	33/50; 28/50; 29/50; 32/50
Nonneoplastic effects			
Bile duct dysplasia with fibrosis (0/50; 0/50; 2/50)	None	None	None
Neoplastic effects			
Cholangiocarcinomas (0/50; 0/50; 2/50)	None	Hepatocellular adenomas (9/50; 13/50; 11/49; 19/50); hepatocellular carcinomas (7/50; 12/50; 6/49; 21/50)	Hepatocellular adenomas (1/50; 3/50; 5/50; 8/50)
Level of evidence of carcinogenic activity			
Some evidence	No evidence	Clear evidence	Some evidence
Other considerations			
		Renal cortical neoplasms (0/50; 1/50; 1/49; 1/50)	Forestomach squamous cell papillomas (1/50; 0/50; 1/50; 6/50)

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

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

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

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Furfural is based on 13-week studies that began in January 1981 and ended in April 1981 and on 2-year studies that began in March 1982 and ended in March 1984 at Southern Research Institute (Birmingham, AL).

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The members of the Peer Review Panel who evaluated the draft Technical Report on furfural on November 20, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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

On November 20, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of furfural received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

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

Dr. Ashby, a principal reviewer, agreed with the conclusions for male rats and male and female mice. Dr. Irwin commented that the difference in levels of evidence for mice was based on significant dose-related increases in both hepatocellular adenomas and carcinomas in males, as opposed to increases only in adenomas in female mice. Due to the reduced survival in the high dose group, Dr. Ashby thought that the conclusion in female rats could have been inadequate study of carcinogenic activity.

Dr. Hayden, the second principal reviewer, agreed with the conclusions for male rats and male and female mice. For female rats, which had poor survival, he wondered whether there were adequate numbers to make a valid assessment of carcinogenicity. Dr. Irwin said that overall survival in high dose female rats was considered to be adequate for evaluation, particularly as there was no indication of lesions in animals surviving to the end of the study. He said that two sets of survival curves would be provided in the Report, one with gavage-related deaths censored and the other uncensored. Dr. Hayden commented that, based on likely human occupational exposure, dermal or inhalation routes of administration would have been more appropriate.

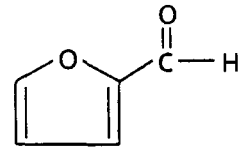
Dr. Gold, the third principal reviewer, agreed in principle with the conclusions. She said that the text should specify that the liver neoplasms in mice were significantly increased only at the high dose for each sex and that the maximum tolerated dose (MTD) was not reached. She thought that the correctness of the conclusion in male rats was dependent on whether the MTD had been reached and on the rarity of the nonneoplastic bile duct lesions. Dr. Irwin said that the bile duct lesions were histologically similar to the cholangiocarcinomas and would progress, and thus they supported a conclusion of some evidence of carcinogenic activity. He said that, based on liver toxicity and on mortality in the 13-week studies, higher doses likely would not have been tolerated. Dr. Gold stated that the most widespread exposure to furfural is dietary and that the chemical is a naturally occurring constituent in a large number of foods.

Dr. Ashby moved that the Technical Report on furfual be accepted with the conclusions as written. As part of the the motion, he said the the following clarifications should be included in the Report: (1) a justification for the dose levels used and a statement that MTDs were achieved; (2) for male rats, an explanation of how the nonneoplastic bile duct lesions were essential to the selection of the level of evidence; (3) for female rats, clear justification for why the study was not inadequate; (4) for male mice, an explanation for the level of evidence selected; and (5) for female mice, an explanation for why the forestomach papillomas did not affect the level of evidence selected. Dr. Hayden seconded the motion. In discussion, Dr. Gold asked that the numbers of neoplastic and nonneoplastic bile duct lesions in male rats be indicated in the conclusions and that the wording be changed to say that these lesions were not increased but rather that they "occurred." She also expressed concern about the number of hepatocellular carcinomas (4/50) in female vehicle control mice and why the incidences of carcinomas were not included in setting the level of evidence. Dr. R. Griesemer, NIEHS, said that only the

responses of dose-related increases in adenomas, and not the incidences of carcinomas, contributed to the level of evidence. Dr. J. Haseman, NIEHS, said that the incidences of carcinomas could be included in the Abstract. Dr. Ashby's motion was then accepted by nine affirmative votes, with two abstentions (Drs. Garman and Zeise).

I. INTRODUCTION

I. INTRODUCTION



FURFURAL

CAS No. 98-01-1

$C_5H_4O_2$ Molecular weight 96.1

Synonyms: 2-Furancarboxaldehyde; 2-furaldehyde; pyromucic aldehyde
Common Name: Artificial oil of ants

Furfural is a clear, colorless liquid with a boiling point of 162° C and a freezing point of −36.5° C at 760 mm mercury. Furfural is miscible with most common organic solvents but is only sparingly soluble in water (8.3% w/w at 20° C) (Quaker Oats Co., 1974). The time-weighted average/threshold limit value for furfural is 2 ppm or 8 mg/m^3 (ACGIH, 1988).

Furfural is an aromatic aldehyde; however, the aromatic properties of the furan ring differ somewhat from those of the benzene ring. The smaller stabilization energy of furan (23 ± 1 kcal/mol) compared with that of benzene (37 ± 1 kcal/mol) indicates that the furan ring has less aromatic character than the benzene ring; hence, furan compounds in general would be more reactive in ring addition reactions than the corresponding benzene analogs (Kirk-Othmer, 1978; March, 1978).

Furfural is produced from the digestion products of pentosan-containing nonfood agricultural residues, such as corncobs, cotton seed hulls, rice hulls, or oat hulls, as well as from wood wastes. The raw materials are heated in a digester with a strong inorganic acid, conditions under which the pentosans are hydrolyzed to pentoses; the pentoses undergo cyclodehydration to form furfural, which is recovered from the digester by steam distillation. Furfural is used for the production of furan, furfuryl alcohol, tetrahydrofuran, and their derivatives; as a solvent for selectively separating saturated from unsaturated compounds in petroleum lubricating oil, gas oil, and diesel fuel; in the extractive distillation of butadiene and other C_4 hydrocarbons used in the manufacture of synthetic rubber; as a resin solvent and wetting agent in the manufacture of abrasive wheels and automobile brake linings; and as a solvent in various other industrial processes (Quaker Oats Co., 1974; Kirk-Othmer, 1978).

Because of its formation during the thermal decomposition of carbohydrates, furfural is also found in numerous processed food and beverage products including cocoa, coffee, tea, beer, wine, milk products; fruits including grapes, cranberries, mangoes, oranges, pineapples; vegetables including asparagus, broccoli, cabbage, onions, peppers; potato products; bread; and many other food items (Maga, 1979).

The metabolism of furfural has been examined in humans (Flek and Sedivec, 1978; Sedivec and Flek, 1978), dogs, rabbits (Williams, 1959), and rats (Irwin et al., 1985; NTP, 1987a). In all species examined, urinary excretion is the major route of elimination and can be accounted for by the reactions illustrated in Figure 1. The major metabolite identified in each species is furoylglycine, suggesting that oxidation of furfural to furoic acid, followed by conjugation with glycine and excretion, is the major pathway of elimination. A secondary pathway involves condensation of furoic acid with acetate to form furanacrylic acid, which may become conjugated with glycine to form furanacryluric acid. Detailed evaluation of the absorption and disposition of [^{14}C]furfural administered in corn oil by gavage to F344/N rats indicates that it is absorbed well from the gastrointestinal tract; 85% of the administered radioactivity was excreted in the

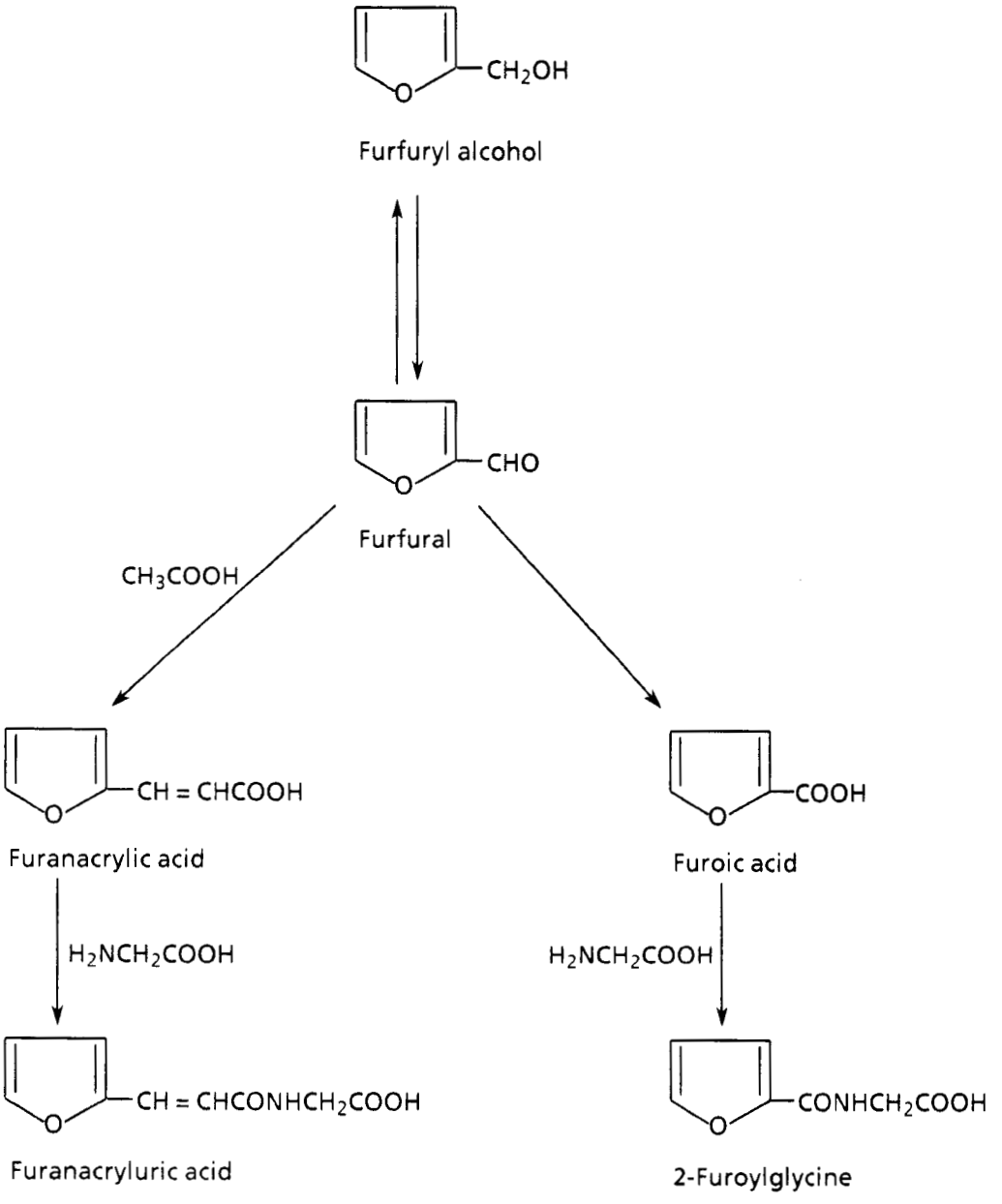


FIGURE 1. FORMATION OF URINARY METABOLITES OF FURFURAL

urine within 72 hours (the majority within the first 24 hours); approximately 80% was furoylglycine, 3%-4% was free furoic acid, and 1% was furanacrylic acid (NTP, 1987a). A similar metabolic profile was observed in volunteers exposed to furfural vapors for up to 8 hours (Flek and Sedivec, 1978; Sedivec and Flek, 1978). The mean pulmonary retention was determined to be 77.9% and was not dependent on exposure concentration. Analysis of urine samples collected every 2 hours over the 8-hour exposure period revealed that furoylglycine was the major metabolite and furanacrylic acid the minor urinary metabolite in humans, and together these metabolites accounted for over 90% of the absorbed material.

Dermal absorption was also found to be significant in humans. Volunteers exposed to vapor containing 30 mg/m^3 furfural while breathing pure air through a breathing tube absorbed 20%-30% of the dose retained by the lungs when exposure was conducted by inhalation at the same vapor concentrations. In another study, three volunteers immersed their left hand up to the wrist in a vessel of pure liquid furfural for 15 minutes; the amount absorbed percutaneously was evaluated from the quantity of urinary metabolites excreted over a 3-hour period after exposure. The 15-minute immersion in liquid furfural resulted in absorption of an amount of furfural equivalent to that absorbed during an 8-hour inhalation exposure to atmospheres containing 10-20 mg/m^3 of furfural vapor (Flek and Sedivec, 1978).

In addition to furoylglycine, furanacrylic acid, and furoic acid, furfuryl alcohol is indicated as a potential metabolite of furfural. Furfuryl alcohol has not been detected directly, but in studies comparing the metabolism of furfural and furfuryl alcohol, both compounds produced the same qualitative and quantitative profile of urinary metabolites in F344/N rats after oral administration, suggesting that they interconvert reversibly in vivo, most likely through alcohol dehydrogenase in the liver (Irwin et al., 1985; NTP, 1987a).

Compounds containing the furan ring are also metabolized by another pathway involving mixed-function-oxidase (cytochrome P450)-catalyzed formation of a reactive intermediate that may become cross-linked to cellular protein (Burka and Boyd, 1985). In studies with several furan-containing compounds (administered orally), organ toxicity invariably involved cell death and necrosis, which correlate with the extent of protein cross-linking and hence the amount of reactive intermediate formed. The liver, kidney, and lung are frequently observed target organs for furan compounds, although different compounds exhibit individual specificities. Furan, the parent compound, appears to be equally toxic to the liver and kidney (McMurty and Mitchell, 1977). However, alkyl-substituted furans exhibit a spectrum of toxicities; doses of 3-methylfuran which are toxic to the lung cause little toxicity to the kidney or liver, whereas 3-ethylfuran and 3-pentylfuran cause marked nephrotoxicity but only mild liver toxicity and no lung toxicity (Wiley et al., 1984; Gammal et al., 1984). 4-Ipomeanol and perilla ketone are primarily lung toxins when administered by noninhalation routes of exposure, but also produce mild liver and kidney toxicity (Boyd, 1980; Wolf et al., 1982; Durham et al., 1985).

There are three reports of carcinogenicity studies of furfural. In one study, groups of 35 male and 35 female Syrian golden hamsters were given intratracheal instillations of furfural, benzo[*a*]pyrene, or furfural plus benzo[*a*]pyrene once per week for 36 weeks and then maintained without further chemical exposure for an additional 58 weeks (Feron, 1972). Respiratory tract neoplasms were increased in animals receiving benzo[*a*]pyrene or benzo[*a*]pyrene plus furfural, but administration of both compounds together caused an earlier development of metaplasia of the tracheobronchial epithelium and a shorter latency period for development of tracheobronchial neoplasms. No neoplasms were related to chemical exposure in the group receiving furfural alone. This study was interpreted as indicating a potential cocarcinogenic effect of furfural.

In a second study, groups of Syrian golden hamsters were exposed to furfural vapor for 7 hours per day, 5 days per week for 52 weeks, while also receiving daily intratracheal instillations of

benzo[*a*]pyrene or subcutaneous injections of diethylnitrosamine (Feron and Kruysse, 1978). Although furfural exposure caused irritation of the nasal mucosa, growth retardation, and other toxic responses, there was no evidence that furfural was a carcinogen or cocarcinogen under these conditions.

In a third study, groups of 16 Wistar rats received diets containing furfural for 120 days, followed either by basal diet or by three cycles of diet containing *N*-2-fluorenylacetamide (2-FAA) for 3 weeks followed by untreated basal diet for 1 week (Shimizu, 1986). At the end of the 295-day study, the liver of rats that received both furfural and 2-FAA was found to contain more hyperplastic nodules than the liver of rats that received 2-FAA alone. No hyperplastic nodules were found in the liver of rats that received only furfural. No data on the stability of furfural in the diet formulations were provided. Analyses conducted in conjunction with the current 2-year studies indicated that furfural was not stable in formulations with NIH 07 Rat and Mouse Ration.

Furfural exhibits a somewhat inconsistent pattern of genotoxic activity, being generally negative in bacterial assays but positive in some eukaryotic systems. Volatility, interfering with effective exposure, may be a factor. Furfural was negative in bacterial assays for mutagenicity (McMahon et al., 1979; Marnett et al., 1985; Mortelmans et al., 1986) and DNA damage (Soska et al., 1981; Osawa and Namiki, 1982) with one exception: Zdzienicka et al. (1978) reported positive results for gene mutation induction in *Salmonella typhimurium* strain TA100 with and without S9 activation. Furfural was positive in the L5178Y/TK$^{+/-}$ mouse lymphoma assay (McGregor et al., 1988), and it induced sister chromatid exchanges (SCEs) (Gomez-Arroyo and Souza, 1985; Table H3) and chromosomal aberrations (Stich et al., 1981a; Table H4) in cultured mammalian cells. In Drosophila, results of a sex-linked recessive lethal test were positive, but no induction of reciprocal translocations was observed after exposure of adult male flies to furfural (Woodruff et al., 1985). Furfural administered by intraperitoneal injection was negative in tests for induction of SCEs and chromosomal aberrations in mouse bone marrow cells (Tables H7 and H8).

Furfural, furfuryl alcohol, and furan were nominated by the National Cancer Institute for toxicologic and carcinogenic evaluation because of their large production volume and the potential for significant human exposure based on their widespread and varied uses.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF FURFURAL

CHARACTERIZATION OF DOSE FORMULATIONS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
- Source and Specifications of Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF FURFURAL

Furfural was obtained in one lot (lot no. Q112979) from the Quaker Oats Co. (Chicago, IL). The chemical was received as a clear, yellow liquid. No purity information was provided by the manufacturer. Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix G). The study chemical was identified as furfural by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy.

Lot no. Q112979 was found to be 99% pure, as determined by elemental analysis, Karl Fischer water analysis, titrations to determine furfural and acid content, thin-layer chromatography, and gas chromatography.

Studies of the bulk chemical indicated that furfural was stable after storage for 2 weeks at temperatures of up to 60° C in the dark under a nitrogen headspace. Confirmation of the stability of the bulk chemical at the study laboratory during the the 13-week and 2-year studies was monitored by periodic analyses by gas chromatography and infrared spectrometry. No change in the bulk material was observed during the course of the studies.

CHARACTERIZATION OF DOSE FORMULATIONS

Formulations were prepared by mixing appropriate amounts of furfural and corn oil. No notable decrease in concentration was observed after storage in the dark at room temperature for 14 days. Some decomposition occurred near the air interface when the solution was stored under simulated dosing conditions (open to air and light for 3 hours). During the studies, the dose formulations were stored at 5° C under nitrogen in amber serum bottles for no longer than 2 weeks. Corn oil (Mazola) was purchased frequently and used as the vehicle. Peroxide levels were determined once per month and were within the specified limit of 10 meq/kg.

During the 2-year studies, the dose formulations were analyzed at approximately 8-week intervals by ultraviolet spectroscopy after methanol extraction. For the furfural studies, it is estimated that the formulations were prepared within ±10% of the target concentrations approximately 93% (69/74) of the time throughout the studies (Table G3). Results of periodic referee analyses performed by the analytical chemistry laboratory indicated generally good agreement with the results from the study laboratory (Table G4). For one set of samples, results from the analytical chemistry laboratory were 83% of the target concentrations, and those from the study laboratory were 103% of the target concentrations. It was concluded that chemical loss probably occurred during sample shipping or handling.

SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and were held for 14 days before the studies began. The rats were 6-7 weeks old when placed on study, and the mice were 7-8 weeks old.

Groups of five rats of each sex were administered 0, 15, 30, 60, 120, or 240 mg/kg furfural in corn oil by gavage, 5 days per week, for 12 doses over 16 days. Groups of five mice of each sex were administered 0, 25, 50, 100, 200, or 400 mg/kg on the same schedule.

Animals were housed five per cage. Water and feed were available ad libitum. The rats and mice were observed two times per day and were weighed on days 0 and 7 and at the end of the studies. Details of animal maintenance are presented in Table 1. A necropsy was performed on all animals.

THIRTEEN-WEEK STUDIES

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

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

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
Rats--0, 15, 30, 60, 120, or 240 mg/kg furfural in corn oil by gavage; mice--0, 25, 50, 100, 200, or 400 mg/kg; dose vol--5 (rats) or 10 (mice) ml/kg	Rats--0, 11, 22, 45, 90, or 180 mg/kg furfural in corn oil by gavage; mice--0, 75, 150, 300, 600, or 1,200 mg/kg; dose vol--5 (rats) or 10 (mice) ml/kg	Rats--0, 30, or 60 mg/kg furfural in corn oil by gavage; mice--0, 50, 100, or 175 mg/kg; dose vol--5 (rats) or 10 (mice) ml/kg
Date of First Dose		
11/4/80	1/22/81	Rats--3/16/82; mice--3/9/82
Date of Last Dose		
11/19/80	4/22/81	Rats--3/5/84; mice--2/27/84
Duration of Dosing		
5 d/wk for 16 d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially, 1 × wk for 13 wk, and 1 × mo thereafter
Necropsy and Histologic Examinations		
Necropsy and histologic exams performed on all animals	Necropsy performed on all animals; the following tissues examined histologically for all vehicle controls, rats receiving 90 or 180 mg/kg, and all mice dying before the end of the studies or receiving 300, 600, or 1,200 mg/kg: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), femur or sternebrae or vertebrae including marrow, gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, nasal passage and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland (rats), prostate/testes or ovaries/uterus, salivary glands, small intestine, spinal cord (if neurologic signs present), spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Liver and lungs examined for lower dose groups of rats. Organ weights obtained at necropsy	Necropsy and histologic exams performed on all animals; the following tissues examined: adrenal glands, brain, cecum, colon, duodenum, epididymis/seminal vesicles/prostate/testes or ovaries/uterus, esophagus, femur including marrow, gallbladder (mice), gross lesions and tissue masses, heart, ileum, jejunum, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, nasal passage and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland (rats), rectum, salivary glands, skin, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)	Rats--Charles River Breeding Laboratories (Portage, MI); mice--Frederick Cancer Research Center (Frederick, MD)

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

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Study Laboratory Southern Research Institute	Southern Research Institute	Southern Research Institute
Method of Animal Identification Ear punch	Ear punch	Ear mark and/or toe clip
Time Held Before Study 14 d	14 d	Rats--21 d; mice--20 d
Age When Placed on Study Rats--6-7 wk; mice--7-8 wk	Rats--6-7 wk; mice--8-9 wk	Rats--7-8 wk; mice--9 wk
Age When Killed Rats--8-11 wk; mice--10-11 wk	Rats--20 wk; mice--21 wk	Rats--111-113 wk; mice--113-114 wk
Necropsy Dates Rats and mice--1/20/80-1/24/80	Rats and mice--4/23/81-4/27/81	Rats--3/13/84-3/19/84; mice--3/6/84-3/12/84
Method of Animal Distribution Animals distributed to weight classes and then assigned to groups according to a table of random numbers	Same as 16-d studies	Same as 16-d studies
Diet NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 16-d studies	Same as 16-d studies
Bedding Beta Chips (Northeastern Products, Inc., Warrensburg, NY)	Same as 16-d studies	Same as 16-d studies
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 16-d studies	Same as 16-d studies
Cages Polycarbonate (Lab Products, Inc., Garfield, NJ)	Same as 16-d studies	Same as 16-d studies
Cage Filters Reemay® spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as 16-d studies	Same as 16-d studies
Animals per Cage 5	5	5
Other Chemicals on Study in the Same Room None	None	None
Animal Room Environment Temp--73.4°-75.2° F; hum--42%-63%; fluorescent light 12 h/d; 15 room air changes/h	Temp--72°-76° F; hum-- 34%-60%; fluorescent light 12 h/d except for a period before 5/4/81 when the automatic timer would not turn the lights off; 15 room air changes/h	Temp--66°-90° F; hum--28%-74%; fluorescent light 12 h/d; 15 room air changes/h

Four- to five-week-old male and female F344/N rats and 6- to 7-week-old male and female $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, observed for 14 days, distributed to weight classes, and assigned to cages by a table of random numbers; cages were assigned to groups by another table of random numbers. Rats were 6-7 weeks old when placed on study, and mice were 8-9 weeks old.

Groups of 10 rats of each sex were administered 0, 11, 22, 45, 90, or 180 mg/kg furfural in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 75, 150, 300, 600, or 1,200 mg/kg on the same schedule. The first set of formulations given to the 600 and 1,200 mg/kg groups of mice contained 209% and 246% of the target concentrations. Before the results of analyses were received, these formulations were administered to the animals and caused deaths at the highest dose. Therefore, the design of the mouse studies was altered by eliminating the original 1,200 mg/kg group, making the original 600 mg/kg dose group the new 1,200 mg/kg group, and placing a new 600 mg/kg group of mice on study.

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

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals. Complete histopathologic examinations were performed on all vehicle controls, all 90 and 180 mg/kg rats, all mice that died before the end of the studies, and all 300, 600, and 1,200 mg/kg mice. The lung and liver of the 11, 22, and 45 mg/kg rats were also examined microscopically. Tissues and groups examined are listed in Table 1.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 30, or 60 mg/kg furfural in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 0, 50, 100, or 175 mg/kg on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female $\times$ C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the study laboratory at 4-5 weeks (rats) and 6 weeks (mice) of age. The animals were quarantined at the study laboratory for 3 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rodents were placed on study at 7-8 weeks (rats) or 9 weeks (mice) of age. The health of the animals was monitored during the course of the studies according to the protocols of the National Toxicology Program (NTP) Sentinel Animal Program (Appendix E).

Animal Maintenance

Animals were housed five per cage. Feed (Appendix F) and water were available ad libitum. Cages were rotated vertically (top to bottom) within dose groups, and cage racks were rotated counterclockwise, alternating back and front against the wall every 2 weeks. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed two times per day. Individual body weights were recorded once per week for the first 13 weeks of the study and once per month thereafter. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals, including those found dead.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin,

embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined are listed in Table 1.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues (liver and pancreas for male rats; kidney, liver, pancreas, and thyroid gland for female rats; forestomach, kidney, liver, and lung for male mice; and forestomach, kidney, and liver for female mice), and all tissues from a randomly selected 10% of the animals were re-evaluated microscopically by a quality assessment pathologist. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the potential target organs and in the randomly selected 10% of animals.

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

Statistical Methods

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

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

Analysis of Tumor Incidence: The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, tumor 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 vehicle 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 tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of the time-specific tumor 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), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart et al., 1979), procedures based on the overall proportion of tumor-bearing animals.

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

Analysis of Continuous Variables: The statistical analysis of organ weight data was carried out by using the nonparametric multiple comparison procedures of Dunn (1964) or Shirley (1977) to assess the significance of pairwise comparisons between dosed and vehicle control groups. Jonckheere's test (Jonckheere, 1954) was used to evaluate the significance of dose-response trends and to determine whether Dunn's or Shirley's test was more appropriate for pairwise comparisons.

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

III. RESULTS

RATS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

III. RESULTS: RATS

SIXTEEN-DAY STUDIES

Eight of 10 rats that received 240 mg/kg died by day 3 (Table 2); the death of one other female was due to a gavage accident. Final mean body weights of rats that received 120 mg/kg or less were generally similar to those of vehicle controls. Labored breathing was seen in animals that received 240 mg/kg. Animals that received 120 mg/kg were slightly inactive. No compound-related lesions were observed at necropsy.

THIRTEEN-WEEK STUDIES

Nine of 10 males and all females that received 180 mg/kg and 1/10 male and 4/10 females that received 90 mg/kg died before the end of the studies (Table 3). Deaths of five dosed males and five dosed females were gavage related. The final mean body weights of dosed and vehicle control rats were similar. The absolute and relative liver and kidney weights of the 90 mg/kg group of male rats were significantly greater than those of the vehicle controls (Table I1). The incidences of cytoplasmic vacuolization of hepatocytes were increased in chemically exposed male rats (vehicle control, 4/10; 11 mg/kg, 10/10; 22 mg/kg, 10/10; 45 mg/kg, 10/10; 90 mg/kg, 9/10). The affected hepatocytes contained multiple small cytoplasmic vacuoles and were observed primarily in the centrilobular regions; the severity was minimal to mild in all dosed and vehicle control groups. This change is believed to result from the accumulation of glycogen and/or fat in the hepatocytes. There were no compound-related histologic lesions in the kidney of chemically exposed male rats.

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

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	131 ± 6	209 ± 9	+78 ± 4	
15	5/5	122 ± 3	195 ± 5	+73 ± 3	93
30	5/5	126 ± 5	200 ± 5	+74 ± 2	96
60	5/5	130 ± 6	206 ± 14	+76 ± 9	99
120	5/5	125 ± 5	206 ± 4	+81 ± 3	99
240	(d) 1/5	139 ± 3	182	+48	87
FEMALE					
0	5/5	100 ± 2	142 ± 2	+42 ± 1	
15	5/5	101 ± 2	141 ± 3	+40 ± 1	99
30	5/5	101 ± 2	140 ± 2	+39 ± 3	99
60	5/5	102 ± 3	142 ± 4	+40 ± 1	100
120	5/5	102 ± 2	141 ± 4	+39 ± 2	99
240	(e) 0/5	107 ± 2	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 2,2,2,3
(e) Day of death: 2,2,2,3; the fifth death, on day 15, was gavage related.
(f) No data are reported due to 100% mortality in this group.

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

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(d) 9/10	138 ± 3	368 ± 6	+231 ± 5	
11	10/10	133 ± 3	373 ± 6	+240 ± 5	101
22	10/10	139 ± 2	376 ± 7	+237 ± 6	102
45	10/10	136 ± 3	387 ± 4	+251 ± 4	105
90	(d) 9/10	137 ± 4	393 ± 7	+256 ± 6	107
180	(e) 1/10	139 ± 3	358	+224	97
FEMALE					
0	(d) 9/10	102 ± 1	198 ± 2	+95 ± 3	
11	10/10	102 ± 2	201 ± 3	+99 ± 3	102
22	10/10	101 ± 2	202 ± 2	+101 ± 3	102
45	10/10	102 ± 2	201 ± 3	+99 ± 2	102
90	(f) 6/10	104 ± 3	200 ± 3	+100 ± 4	101
180	(g) 0/10	101 ± 2	(h)	(h)	(h)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Death gavage related
(e) Week of death: 4,5,5,6,11,12; 3 deaths were gavage related.
(f) Week of death: 12; 3 deaths were gavage related.
(g) Week of death: 1,3,3,3,4,4,5,5,5; 1 death was gavage related.
(h) No data are reported due to 100% mortality in this group.

Dose Selection Rationale: Because of chemically related deaths at 90 and 180 mg/kg and increased liver weights in males at 90 mg/kg, these doses were considered too high for a 2-year study. At 45 mg/kg, cytoplasmic vacuolization of hepatocytes was the only chemically related effect, and this dose was considered too low for the high dose in a 2-year study. Therefore, 60 mg/kg, a dose intermediate between 45 and 90 mg/kg, was selected as the high dose and 30 mg/kg selected as the low dose for rats for the 2-year studies. Doses were administered in corn oil by gavage, 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control rats were similar throughout the studies (Table 4 and Figure 2). No compound-related clinical signs were observed.

TABLE 4. MEAN BODY WEIGHTS OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF FURFURAL

Week on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control Number Weighed	30 mg/kg Av. Wt. (grams)	30 mg/kg Wt. (percent of vehicle controls)	30 mg/kg Number Weighed	60 mg/kg Av. Wt. (grams)	60 mg/kg Wt. (percent of vehicle controls)	60 mg/kg Number Weighed
MALE								
1	196	50	195	99	50	196	100	50
2	242	50	240	99	50	243	100	50
3	266	50	263	99	50	265	100	50
4	282	50	280	99	50	282	100	50
5	301	50	296	98	50	301	100	50
6	314	50	311	99	50	315	100	50
7	316	50	321	102	50	317	100	50
8	334	50	332	99	50	336	101	50
9	345	50	343	99	50	348	101	50
10	356	50	353	99	50	359	101	50
11	366	50	363	99	50	368	101	50
12	376	50	373	99	50	377	100	50
13	385	50	382	99	50	385	100	49
17	411	50	408	99	48	411	100	48
21	431	50	429	100	48	431	100	48
26	452	50	451	100	48	452	100	48
30	464	50	464	100	48	467	101	48
34	473	50	474	100	48	474	100	48
38	485	50	490	101	48	486	100	48
42	492	49	498	101	47	498	101	47
45	497	48	503	101	47	502	101	46
49	502	48	514	102	46	511	102	46
53	508	47	517	102	46	514	101	46
57	509	46	515	101	46	517	102	45
61	513	45	524	102	46	520	101	45
65	515	42	524	102	46	520	101	44
69	512	41	524	102	46	516	101	43
73	515	40	524	102	45	519	101	41
77	514	38	523	102	43	516	100	41
81	517	36	525	102	41	514	99	39
85	505	35	517	102	40	515	102	36
89	502	33	504	100	40	506	101	32
93	496	33	501	101	39	501	101	32
97	494	32	492	100	36	492	100	28
101	481	31	492	102	31	478	99	26
Mean for weeks								
1-13	313.8		311.7	99		314.8	100	
17-49	467.4		470.1	101		470.2	101	
53-101	506.2		514.0	102		509.8	101	
FEMALE								
1	136	50	136	100	50	137	101	50
2	155	50	155	100	50	156	101	50
3	164	50	164	100	50	166	101	50
4	172	50	172	100	50	174	101	50
5	179	50	180	101	50	183	102	50
6	183	50	186	102	50	187	102	50
7	187	50	189	101	50	190	102	50
8	189	50	193	102	50	194	103	50
9	193	50	195	101	50	198	103	50
10	196	50	199	102	50	201	103	50
11	199	50	200	101	50	204	103	50
12	203	50	204	100	50	207	102	50
13	203	50	206	101	50	210	103	50
17	211	50	217	103	50	219	104	50
21	220	50	222	101	50	226	103	50
26	226	48	231	102	50	234	104	49
30	229	48	235	103	50	239	104	49
34	233	46	242	104	50	245	105	49
38	241	46	247	102	50	251	104	49
42	248	46	255	103	50	261	105	47
45	255	46	262	103	50	270	106	43
49	262	46	269	103	50	278	106	41
53	270	46	275	102	48	285	106	41
57	276	46	284	103	47	292	106	39
61	283	46	290	102	47	299	106	39
65	289	46	298	103	47	306	106	37
69	297	46	296	100	45	307	103	36
73	301	46	310	103	45	321	107	36
77	299	46	312	104	44	323	108	35
81	305	46	314	103	43	330	108	33
85	306	41	316	103	42	332	108	31
89	308	37	322	105	39	330	107	30
93	313	33	329	105	37	332	106	28
97	310	33	336	108	34	339	109	25
101	314	28	326	104	33	326	104	21
Mean for weeks								
1-13	181.5		183.0	101		185.2	102	
17-49	236.1		242.2	103		247.0	105	
53-101	297.8		308.3	104		317.1	106	

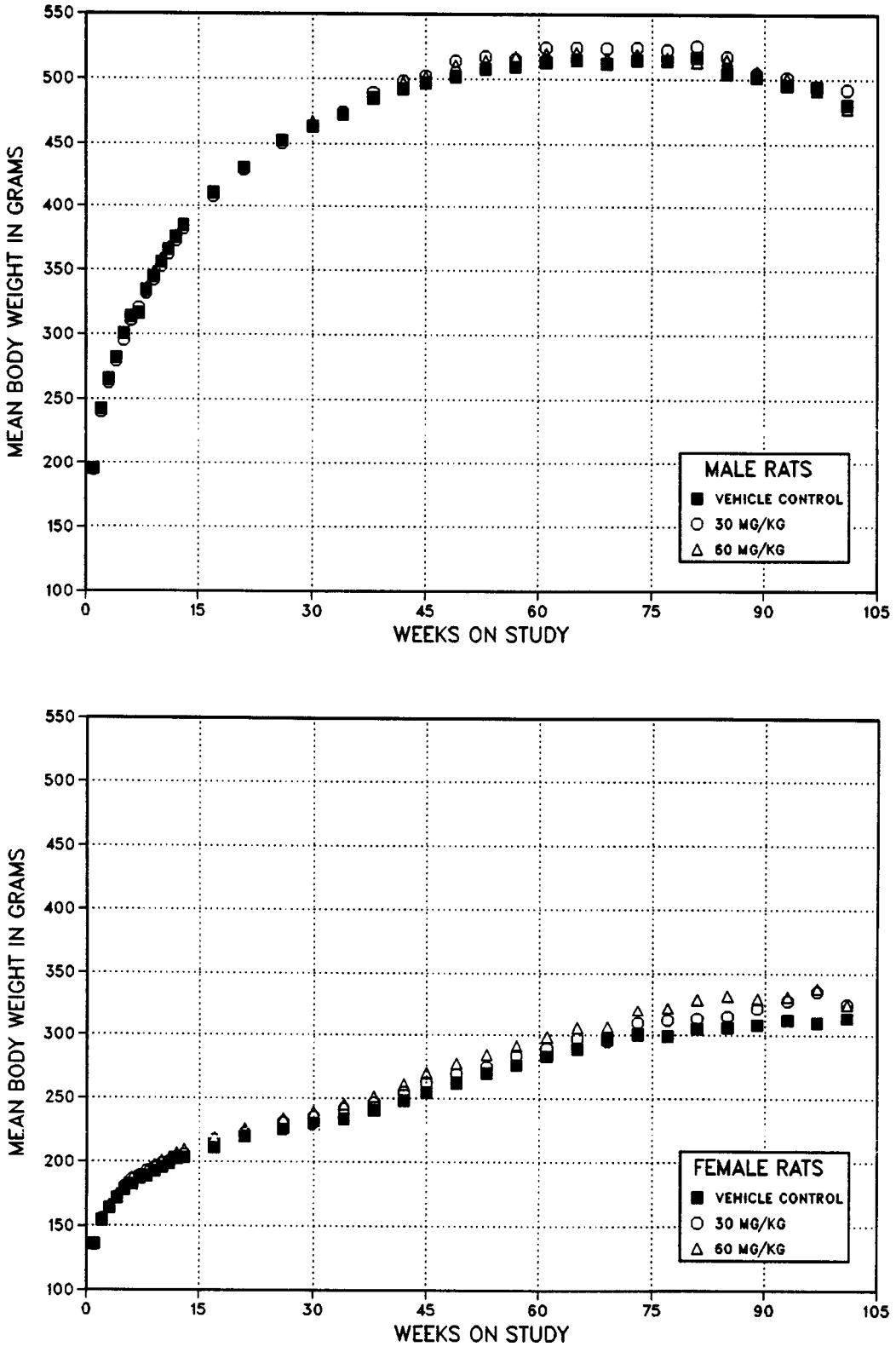


FIGURE 2. GROWTH CURVES FOR RATS ADMINISTERED FURFURAL IN CORN OIL BY GAVAGE FOR TWO YEARS

III. RESULTS: RATS

Survival

Estimates of the probabilities of survival for male and female rats administered furfural at the doses used in these studies and for vehicle controls are shown in Table 5 and in the Kaplan and Meier curves in Figure 3. Although the survival of the high dose group of female rats was not significantly lower than that of the vehicle controls by Kaplan-Meier analysis, the overall survival of the group was notably lower than that of the vehicle controls as a result of the large number (19) of accidental deaths in this group. The overall survival profile for female rats, without accidental deaths censored, is shown in Figure 4.

Pathology and Statistical Analyses of Results

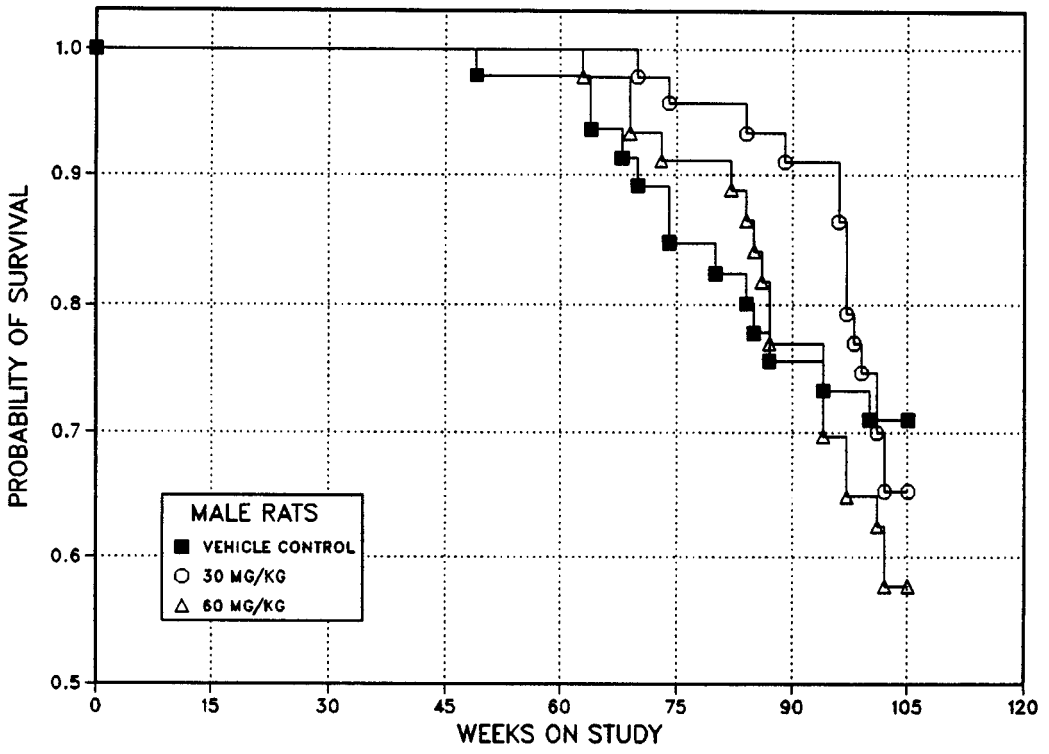
This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the liver, forestomach, and lung.

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

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

	Vehicle Control	30 mg/kg	60 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	2	4	7
Moribund kills	11	11	11
Killed accidentally	6	7	8
Animals surviving to study termination	31	28	24
Mean survival (days)	637	653	625
Survival P values (b)	0.343	0.965	0.451
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	9	5	4
Moribund kills	9	11	9
Killed accidentally	4	2	19
Animals surviving to study termination	28	32	18
Mean survival (days)	650	670	585
Survival P values (b)	0.849	0.741	0.943

(a) First day of termination period: 729
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.



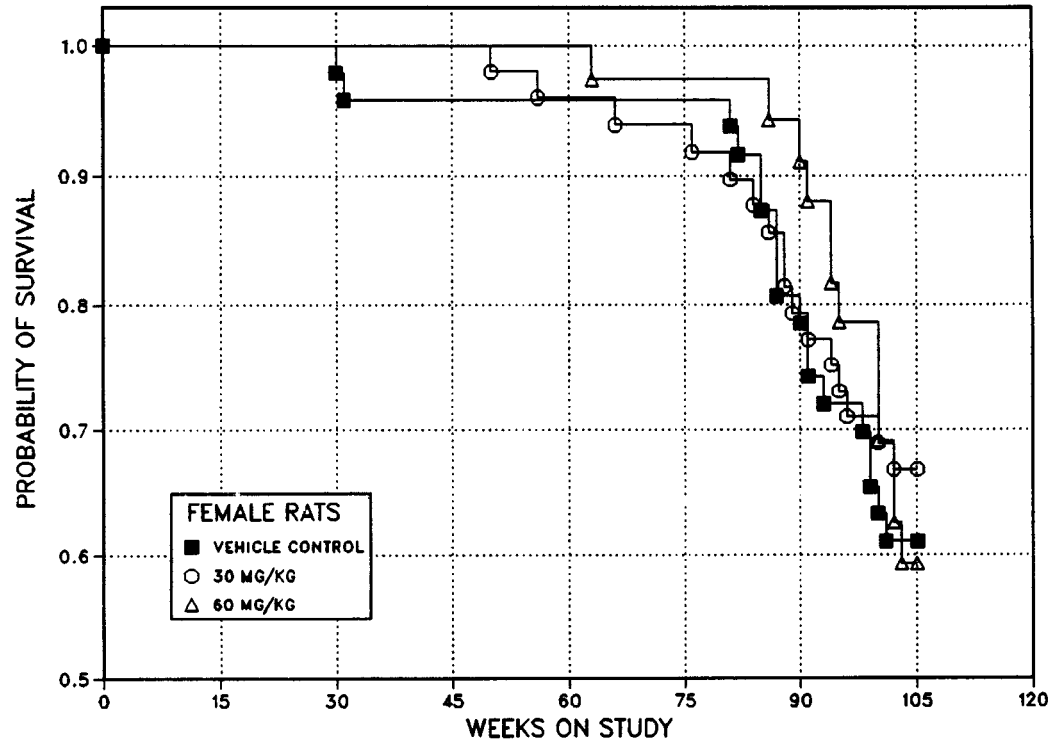


FIGURE 3. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED FURFURAL IN CORN OIL BY GAVAGE FOR TWO YEARS

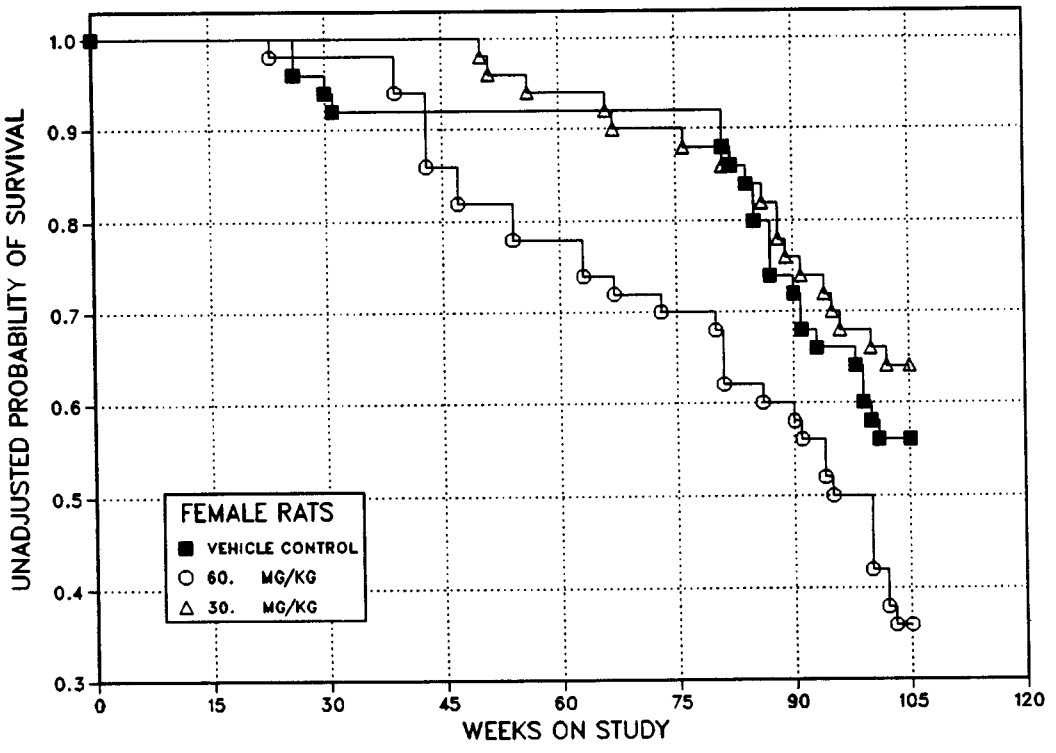


FIGURE 4. STANDARD SURVIVAL CURVES FOR FEMALE RATS ADMINISTERED FURFURAL IN CORN OIL BY GAVAGE FOR TWO YEARS

Liver: Centrilobular hepatocellular necrosis was observed at increased incidences in chemically exposed male rats (vehicle control, 3/50; low dose, 9/50; high dose, 12/50). The necrosis was generally minimal to mild in severity in all groups and affected only scattered lobules in the liver sections. Uncommon cholangiocarcinomas occurred in two high dose male rats (Figures 5 and 6), and biliary dysplasia with fibrosis, a lesion considered by the Pathology Working Group to be an early stage in the development of cholangiocarcinoma, occurred in two additional high dose males (Figure 7). The neoplasms displaced the hepatic parenchyma and had irregular, sometimes poorly defined borders with neoplastic epithelium extending the adjacent hepatic lobules. Cholangiocarcinomas consisted of cuboidal or columnar biliary epithelium arranged in irregular ductlike structures separated by varying amounts of fibrous connective tissue and a mixed inflammatory cell infiltrate. There was variable dilatation of the ducts, and the lumina sometimes contained inflammatory cells or mucus. The neoplastic biliary epithelium exhibted goblet cell differentiation and cellular pleomorphism and atypia. For comparison, a cholangioma found in a corn oil vehicle control F344/N male rat from a previous study conducted at the same laboratory at which the current study was conducted is shown in Figure 8.

The lesions diagnosed as biliary dysplasia and fibrosis were similar to the cholangiocarcinomas. However, with dysplasia the borders were better defined, there was more extensive dilatation of the biliary ducts affected by the lesions, and the amount of stromal connective tissue was greater. The epithelium of some of the ducts, particularly those surrounded by thick, dense collars of connective tissue, was atrophic or undergoing degeneration. This lesion has also been called "cholangiofibrosis" and "cholangiofibroma." The distinction between this lesion and cholangiocarcinoma is based on the relative degree of proliferation of ductular epithelium and the degree of epithelial anaplasia.

Forestomach: A squamous cell carcinoma occurred in one low dose male rat, and squamous cell papillomas occurred in two high dose male rats and in one low dose and one high dose female rat. Hyperplasia was observed at marginally increased incidences in low dose male rats, but incidences were not increased in high dose males or in females (male: vehicle control, 1/50; low dose, 5/50; high dose, 2/50; female: 2/50; 4/50; 3/50). Because of the low incidence of these lesions, they were not considered to be chemically related.

Lung: Congestion and foreign bodies were observed at increased incidences in dosed female rats (congestion: vehicle control, 6/50; low dose, 6/50; high dose, 23/50; foreign bodies: 5/50; 4/50; 19/50).

SIXTEEN-DAY STUDIES

One male that received 400 mg/kg furfural died before the end of the studies (Table 6). The deaths of one female that received 25 mg/kg and one female that received 200 mg/kg were considered to be gavage related. Final mean body weights of mice were not affected by furfural. No compound-related lesions were noted at necropsy.

THIRTEEN-WEEK STUDIES

All mice that received 1,200 mg/kg and 9/10 males and 9/10 females that received 600 mg/kg died before the end of the studies (Table 7). The deaths of one female that received 150 mg/kg and one female vehicle control were gavage related. The final body weight of the one mouse of each sex that received 600 mg/kg and lived to the end of the studies was 21% lower than that of the vehicle controls for the male and 5% lower for the female. The final mean body weights of male mice that received 150 or 300 mg/kg were 5% or 6% lower than that of vehicle controls. The liver weight to body weight ratios for females that received 75, 150, or 300 mg/kg and males that received 300 mg/kg were significantly greater than those of vehicle controls (Table I2). Centrilobular coagulative necrosis of hepatocytes was seen in the liver of 8/10 males and 2/10 females that received 1,200 mg/kg, 9/10 males that received 600 mg/kg, 1/10 males that received 300 mg/kg, and 1/10 males that received 150 mg/kg. Inflammation in the liver, characterized by a minimal-to-mild mononuclear inflammatory cell infiltrate, was also present in chemically exposed groups when necrosis occurred.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF FURFURAL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	24.6 ± 0.5	28.2 ± 0.8	+3.6 ± 0.4	
25	5/5	23.2 ± 0.2	26.8 ± 0.4	+3.6 ± 0.2	95
50	5/5	24.0 ± 0.4	26.8 ± 1.0	+2.8 ± 0.6	95
100	5/5	24.6 ± 0.6	27.4 ± 0.7	+2.8 ± 0.2	97
200	5/5	24.4 ± 0.5	27.6 ± 0.2	+3.2 ± 0.4	98
400	(d) 4/5	25.2 ± 0.4	28.3 ± 0.3	+3.3 ± 0.3	100
FEMALE					
0	5/5	18.6 ± 0.5	20.8 ± 0.4	+2.2 ± 0.4	
25	(e) 4/5	17.8 ± 0.2	20.3 ± 0.5	+2.5 ± 0.3	98
50	5/5	17.8 ± 0.4	20.4 ± 0.2	+2.6 ± 0.2	98
100	5/5	19.0 ± 0.6	21.2 ± 0.4	+2.2 ± 0.4	102
200	(e) 4/5	18.2 ± 0.5	18.3 ± 0.5	0.0 ± 0.4	88
400	5/5	18.6 ± 0.2	21.6 ± 0.2	+3.0 ± 0.0	104

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

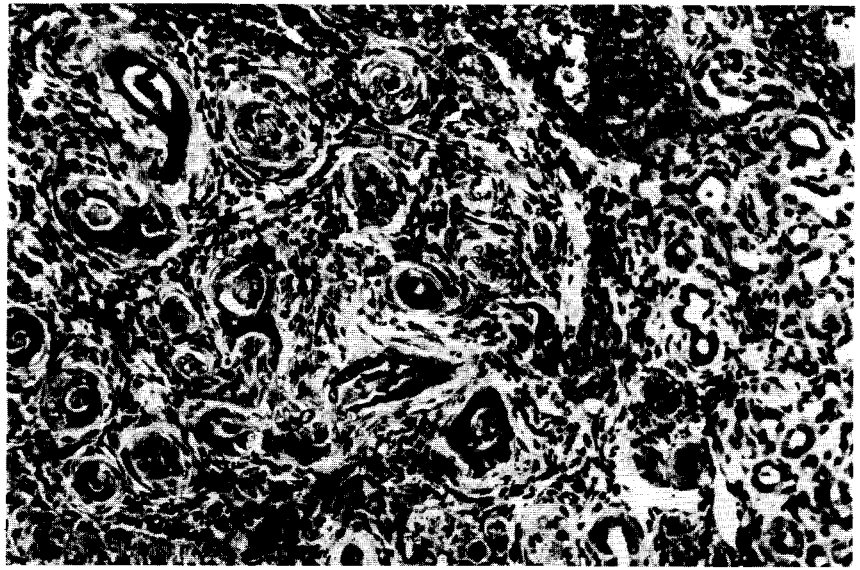


Figure 5. Cholangiocarcinoma from a male F344/N rat administered 60 mg/kg furfural by gavage for 2 years. The liver parenchyma has been replaced by a proliferation of glandular structures, representing neoplastic bile ducts, within a scant stroma that is infiltrated by mixed inflammatory cells. Many of the neoplastic ducts consist of large, highly pleomorphic epithelial cells.

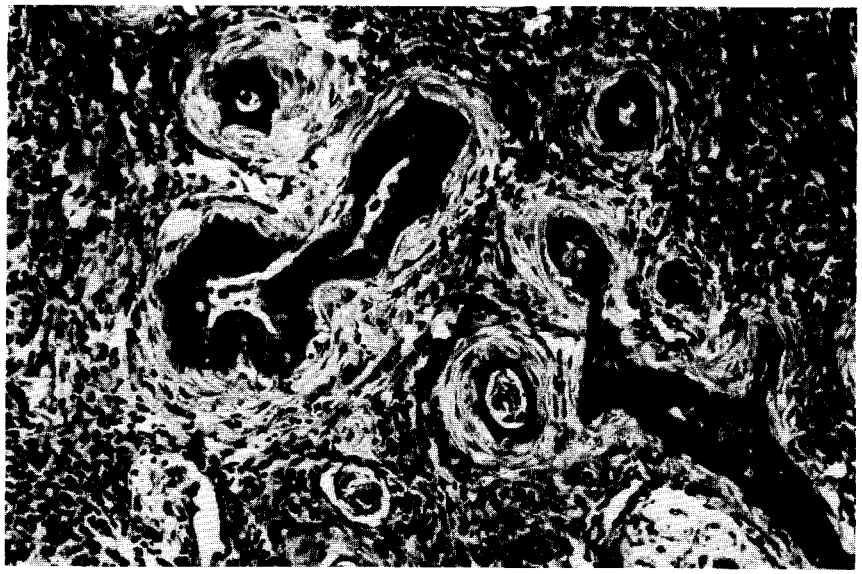


Figure 6. Cholangiocarcinoma from a male F344/N rat administered 60 mg/kg furfural by gavage for 2 years. Neoplastic bile ducts consist of highly pleomorphic epithelial cells, which are densely packed and form multiple layers in some areas. Some neoplastic epithelial cells contain clear cytoplasmic vacuoles and resemble goblet cells. The neoplastic ducts are surrounded by bands of loose fibrous tissue and a diffuse infiltrate of mixed inflammatory cells.

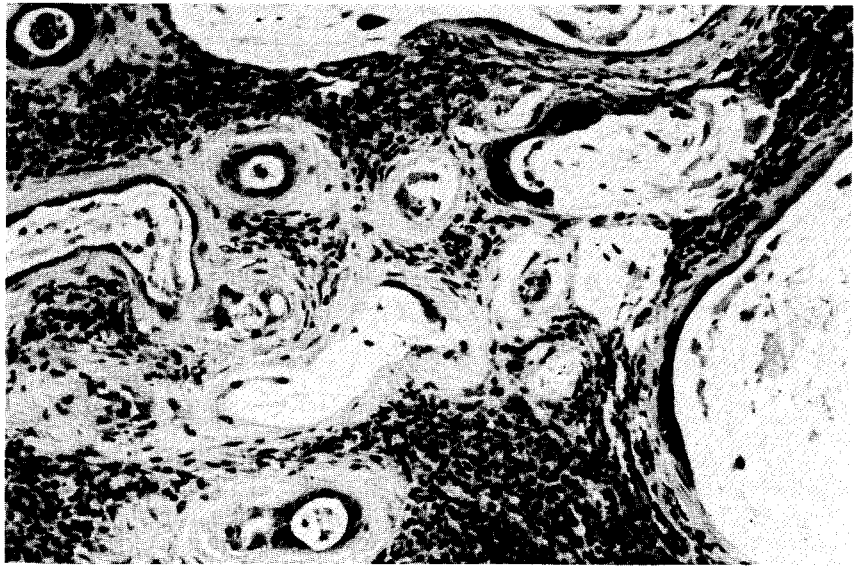


Figure 7. Bile duct dysplasia and fibrosis (cholangiofibrosis) from a male F344/N rat administered 60 mg/kg furfural by gavage for 2 years. The bile ducts are composed of a single layer of flattened-to-cuboidal epithelium and are surrounded by a moderate amount of dense fibrous tissue. Many of the ducts are dilated and filled with mucus and debris. The dense cellular infiltrate is mononuclear cell leukemia.

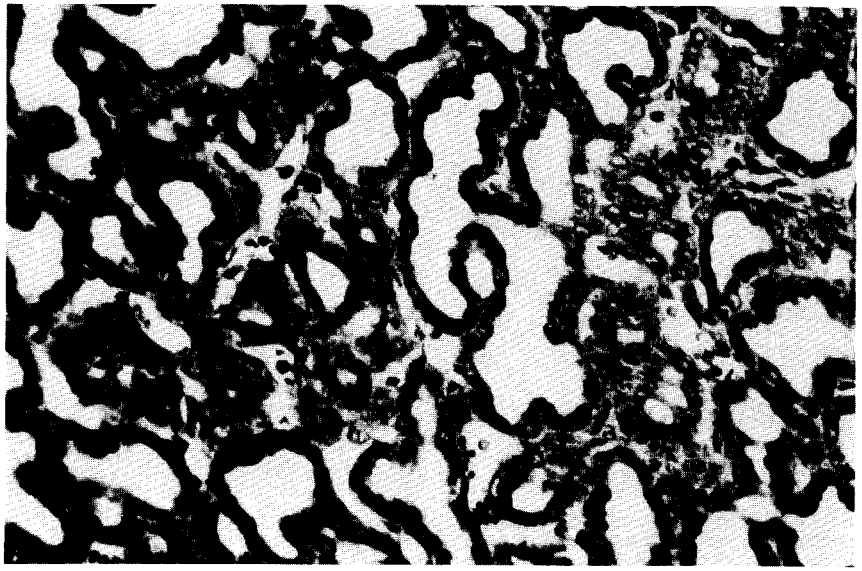


Figure 8. Cholangiocarcinoma found in a corn oil vehicle control F344/N male rat from a previous study conducted at the same laboratory at which the current study was conducted. Compare this with neoplasms in Figures 5 and 6. Note that the neoplastic bile ducts in this spontaneous neoplasm are composed of a single layer of relatively well-differentiated-appearing epithelium and that stroma is scant to inapparent.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF FURFURAL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	22.1 ± 0.1	36.7 ± 0.7	+14.6 ± 0.6	
75	10/10	21.4 ± 0.3	35.8 ± 0.4	+14.4 ± 0.5	97.5
150	10/10	21.2 ± 0.3	34.8 ± 0.6	+13.6 ± 0.5	94.8
300	10/10	21.3 ± 0.3	34.6 ± 0.7	+13.3 ± 0.5	94.3
600	(d) 1/10	22.3 ± 0.3	29.0	+7.0	79.0
1,200	(e) 0/10	21.5 ± 0.3	(f)	(f)	(f)
FEMALE					
0	(g) 9/10	17.5 ± 0.2	26.3 ± 0.5	+8.8 ± 0.4	
75	10/10	17.3 ± 0.4	27.1 ± 0.8	+9.8 ± 0.5	103.0
150	(g) 9/10	17.1 ± 0.2	26.9 ± 0.4	+9.8 ± 0.4	102.3
300	10/10	17.5 ± 0.2	27.5 ± 0.4	+10.0 ± 0.4	104.6
600	(h) 1/10	18.2 ± 0.2	25.0	+6.0	95.1
1,200	(i) 0/10	17.5 ± 0.3	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 1,1,1,1,1,1,1,1,9
(e) Week of death: 1,1,1,1,1,1,1,2,3,3
(f) No data are presented due to 100% mortality in this group.
(g) Death was gavage related.
(h) Week of death: all 1
(i) Week of death: 1,1,1,2,3,3,3,3,3,5

Dose Selection Rationale: Because of compound-related deaths in mice receiving 600 and 1,200 mg/kg and increased liver and kidney weights and liver lesions in mice receiving 300 mg/kg, these doses were considered too high for a 2-year study. Although minimal liver lesions were observed in one male receiving 150 mg/kg, 150 mg/kg was considered to be somewhat low for the high dose, since liver weights were not increased. Therefore, three doses were selected for the 2-year studies: 50, 100, and 175 mg/kg. Doses were administered in corn oil by gavage, 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of chemically exposed mice were similar to mean body weights of vehicle controls throughout most of the studies (Table 8 and Figure 9). No compound-related clinical signs were observed.

TABLE 8. MEAN BODY WEIGHTS OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF FURFURAL

Week on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control Number Weighed	50 mg/kg Av. Wt. (grams)	50 mg/kg Wt. (percent of veh. controls)	50 mg/kg Number Weighed	100 mg/kg Av. Wt. (grams)	100 mg/kg Wt. (percent of veh. controls)	100 mg/kg Number Weighed	175 mg/kg Av. Wt. (grams)	175 mg/kg Wt. (percent of veh. controls)	175 mg/kg Number Weighed
MALE											
1	22.8	50	22.7	99.6	50	23.0	100.9	50	23.0	100.9	50
2	24.5	49	24.4	99.6	50	24.3	99.2	50	24.7	100.8	50
3	25.7	49	26.3	102.3	49	26.6	103.5	50	26.7	103.9	50
4	27.8	49	27.7	99.6	49	27.6	99.3	50	28.0	100.7	50
5	28.1	49	28.9	102.8	49	29.4	104.6	50	29.7	105.7	50
6	30.2	49	29.4	97.4	49	30.0	99.3	50	31.1	103.0	50
7	31.1	49	30.6	98.4	49	30.6	98.4	50	31.3	100.6	50
8	31.5	49	30.7	97.5	49	31.3	99.4	50	32.3	102.5	50
9	32.3	49	33.0	102.2	49	33.5	103.7	50	32.0	99.1	45
10	33.3	49	33.4	100.3	48	34.2	102.7	50	33.7	101.2	45
11	34.0	49	33.9	99.7	48	34.9	102.6	50	34.6	101.8	45
12	34.3	49	34.7	101.2	48	36.0	105.0	50	35.8	104.4	45
13	32.6	49	36.0	110.4	48	36.6	112.3	50	33.5	102.8	45
18	36.3	49	37.6	103.6	48	38.6	106.3	50	38.2	105.2	45
22	38.9	48	39.4	101.3	48	40.4	103.9	49	39.1	100.5	45
27	40.2	48	40.6	101.0	48	41.2	102.5	49	41.6	103.5	45
31	43.2	48	43.4	100.5	47	43.8	101.4	49	43.4	100.5	45
35	43.0	48	44.0	102.3	47	43.0	100.0	49	44.2	102.8	44
38	43.8	48	45.2	103.2	47	45.0	102.7	49	44.4	101.4	44
41	44.9	48	46.0	102.4	47	46.5	103.6	49	46.2	102.9	44
45	44.9	48	46.6	103.8	47	48.1	107.1	49	48.0	106.9	44
49	45.6	48	48.9	107.2	47	49.5	108.6	49	48.4	106.1	44
53	45.6	48	48.0	105.3	47	47.3	103.7	49	47.6	104.4	44
57	46.5	47	48.9	105.2	47	47.6	102.4	49	47.8	102.8	44
61	47.0	47	49.7	105.7	47	49.0	104.3	46	49.1	104.5	44
65	46.0	47	49.6	107.8	46	49.2	107.0	46	48.7	105.9	44
69	46.1	44	48.8	105.9	46	49.7	107.8	45	48.6	105.4	40
73	45.8	44	49.7	108.5	44	50.0	109.2	44	47.4	103.5	40
77	48.0	43	49.7	103.5	43	49.1	102.3	44	47.7	99.4	40
81	47.6	43	48.5	101.9	43	47.9	100.6	44	46.2	97.1	39
85	47.9	42	46.2	96.5	40	46.7	97.5	42	48.1	100.4	36
89	45.2	41	45.9	101.5	38	45.9	101.5	40	44.3	98.0	36
93	47.2	40	44.6	94.5	38	45.6	96.6	34	45.7	96.8	35
97	46.4	38	43.5	93.7	34	46.4	100.0	30	44.7	96.3	33
101	46.8	37	45.8	97.9	29	46.8	100.0	27	45.6	97.4	30
Mean for weeks											
1-13	29.9		30.1	100.7		30.6	102.3		30.5	102.0	
18-49	42.3		43.5	102.8		44.0	104.0		43.7	103.3	
53-101	46.6		47.6	102.1		47.8	102.6		47.0	100.9	
FEMALE											
1	18.4	50	18.8	102.2	50	18.6	101.1	50	18.6	101.1	50
2	19.6	50	19.2	98.0	50	18.9	96.4	50	19.3	98.5	50
3	20.8	49	21.0	101.0	50	21.2	101.9	50	20.6	99.0	50
4	21.9	49	22.2	101.4	50	21.4	97.7	50	21.8	99.5	50
5	22.0	49	22.5	102.3	50	22.8	103.6	50	22.5	102.3	50
6	23.4	49	23.0	98.3	50	22.9	97.9	50	23.1	98.7	50
7	24.1	49	23.4	97.1	50	23.6	97.9	50	23.7	98.3	50
8	24.5	49	24.1	98.4	50	23.1	94.3	50	24.2	98.8	50
9	25.4	49	25.4	100.0	50	25.7	101.2	50	25.8	101.6	50
10	25.5	49	25.4	99.6	50	25.2	98.8	50	24.8	97.3	50
11	25.3	49	25.0	98.8	50	25.0	98.8	50	25.6	101.2	50
12	25.9	49	25.0	96.5	50	25.4	98.1	50	26.0	100.4	50
13	25.9	49	26.0	100.4	50	27.0	104.2	50	25.2	97.3	50
18	27.4	49	28.5	104.0	50	28.3	103.3	50	27.8	101.5	50
22	28.8	49	28.7	99.7	50	29.6	102.8	50	28.7	99.7	50
27	30.1	49	30.3	100.7	50	30.6	101.7	50	29.7	98.7	50
31	32.1	49	33.2	103.4	50	32.7	101.9	50	31.9	99.4	50
35	34.3	49	33.2	96.8	50	32.7	95.3	50	33.3	97.1	50
38	32.9	49	35.0	106.4	50	35.8	108.8	50	32.4	98.5	49
41	35.0	49	36.5	104.3	49	37.3	106.6	50	35.4	101.1	49
45	34.0	49	37.6	110.6	48	38.5	113.2	50	37.2	109.4	49
49	39.2	49	39.8	101.5	48	40.3	102.8	50	39.2	100.0	49
53	38.3	49	38.9	101.6	48	39.4	102.9	49	38.8	101.3	49
57	40.7	49	40.1	98.5	47	40.5	99.5	49	40.4	99.3	48
61	40.1	48	42.7	106.5	47	43.3	108.0	48	42.1	105.0	48
65	41.5	48	42.4	102.2	44	44.3	106.7	47	43.4	104.6	47
69	40.5	46	43.2	106.7	41	44.2	109.1	47	43.7	107.9	47
73	44.4	44	45.5	102.5	39	46.4	104.5	44	46.1	103.8	47
77	44.4	44	46.2	104.1	39	46.3	104.3	41	47.2	106.3	45
81	43.3	43	45.5	105.1	39	45.3	104.6	40	46.3	106.9	44
85	43.7	42	45.6	104.3	39	46.4	106.2	37	47.7	109.2	43
89	43.4	41	47.7	109.9	38	45.8	105.5	35	47.5	109.4	39
93	43.4	38	48.7	112.2	36	45.6	105.1	35	48.8	112.4	36
97	41.0	34	48.5	118.3	34	46.3	112.9	33	48.3	117.8	32
101	43.1	33	50.3	116.7	32	46.9	108.8	31	48.2	111.8	32
Mean for weeks											
1-13	23.3		23.2	99.6		23.1	99.1		23.2	99.6	
18-49	32.6		33.6	103.1		34.0	104.3		32.8	101.6	
53-101	42.1		45.0	106.9		44.7	106.2		45.3	107.6	

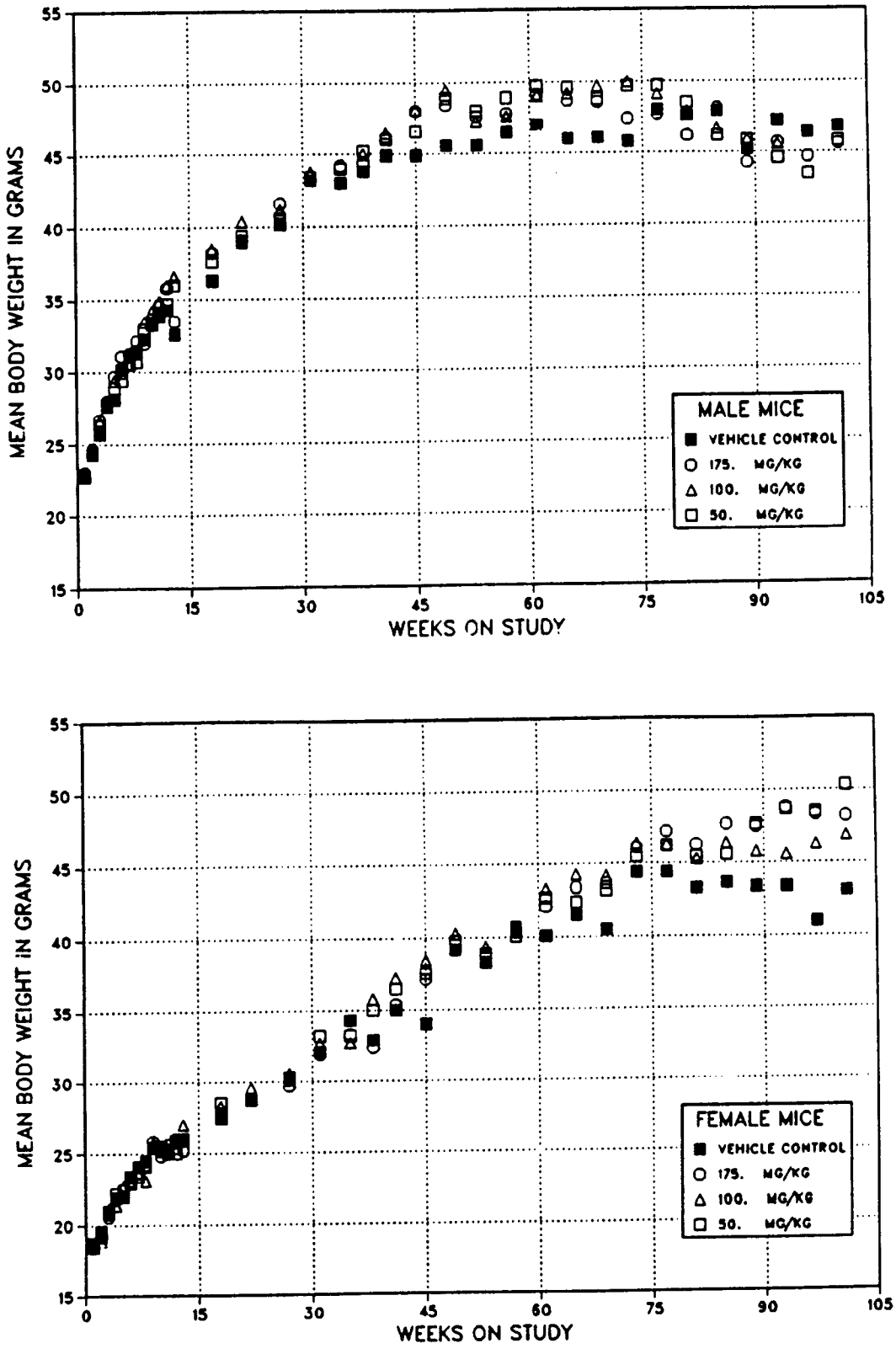


FIGURE 9. GROWTH CURVES FOR MICE ADMINISTERED FURFURAL IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered furfural at the doses used in these studies and for vehicle controls are shown in Table 9 and in the Kaplan and Meier curves in Figure 10. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

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

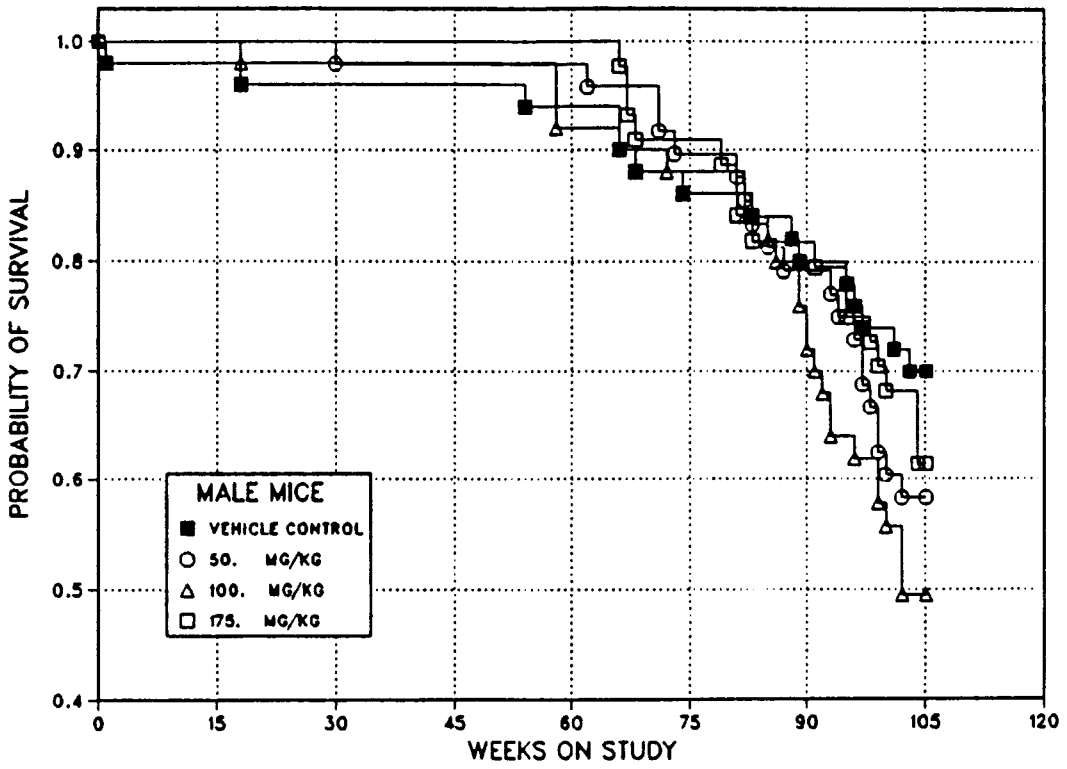
Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are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

Liver: Minimal multifocal chronic inflammation and pigmentation along or immediately below the serosal surface of the liver were seen in chemically exposed mice (pigmentation--male: vehicle control, 0/50; low dose, 0/50; mid dose, 8/49; high dose, 18/50; female: 0/50; 0/50; 0/50; 11/50; chronic inflammation--male: 0/50; 0/50; 8/49; 18/50; female: 0/50; 0/50; 1/50; 8/50). Chronic inflammation consisted of small aggregates of

TABLE 9. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF FURFURAL

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
MALE (a)				
Animals initially in study	50	50	50	50
Natural deaths	9	12	13	9
Moribund kills	6	8	12	8
Killed accidentally	0	2	0	6
Missing	0	0	1	0
Animals surviving to study termination	35	28	24	27
Mean survival (days)	663	646	655	610
Survival P values (b)	0.469	0.373	0.079	0.605
FEMALE (a)				
Animals initially in study	50	50	50	50
Natural deaths	8	9	12	11
Moribund kills	8	11	9	7
Killed accidentally	1	2	0	0
Animals surviving to study termination	33	28	29	32
Mean survival (days)	667	650	659	671
Survival P values (b)	0.839	0.486	0.401	0.842

(a) First day of termination period: 729
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.



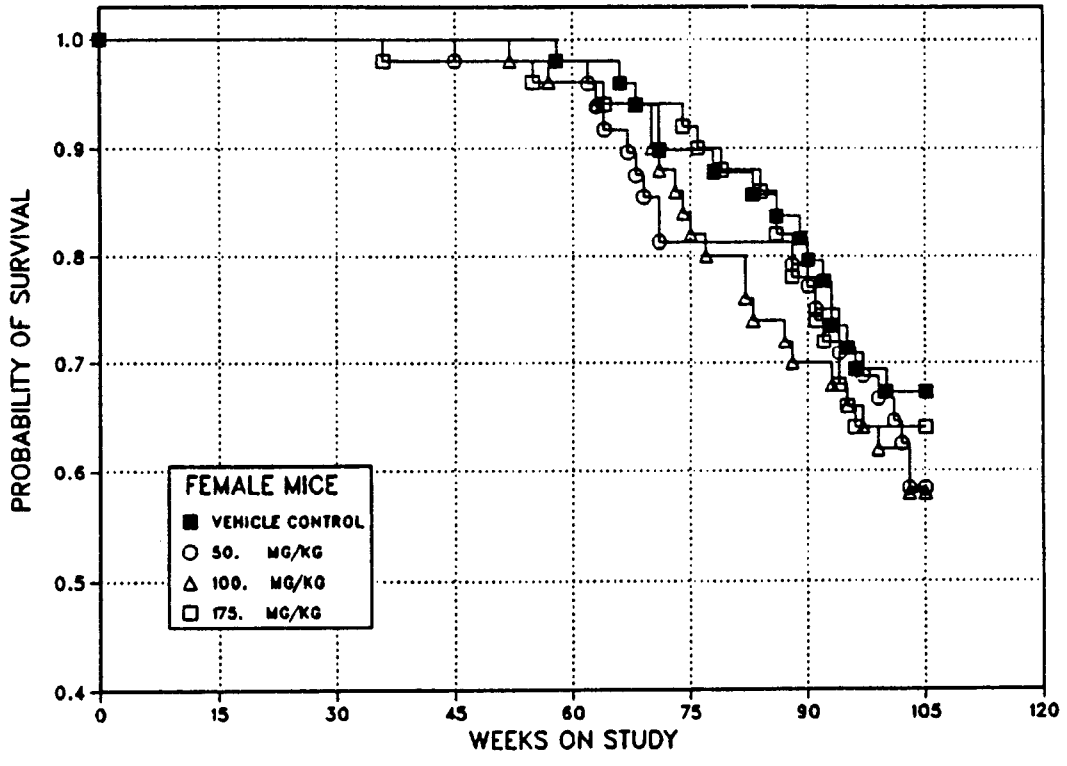


FIGURE 10. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED FURFURAL IN CORN OIL BY GAVAGE FOR TWO YEARS

chronic inflammatory cells, principally macrophages. The pigment was granular, light greenish-brown material that appeared to represent bile and was present within macrophages. Localization of the lesion near the serosa may be related to the direction of lymphatic flow.

Hepatocellular adenomas and hepatocellular carcinomas occurred with significant positive trends in dosed male mice and were significantly increased in high dose males. Hepatocellular adenomas occurred with a positive trend in dosed female mice and were significantly increased in high dose females (Table 10).

Hepatocellular adenomas were discrete expansile masses that compressed the surrounding parenchyma and were composed of closely packed cords of hepatocytes, which were no longer arranged in a normal lobular pattern. The

TABLE 10. HEPATOCELLULAR NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF FURFURAL (a)

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
MALE				
Adenoma				
Overall Rates	9/50 (18%)	13/50 (26%)	11/49 (22%)	19/50 (38%)
Terminal Rates	8/35 (23%)	9/28 (32%)	6/24 (25%)	13/27 (48%)
Day of First Observation	611	491	571	563
Logistic Regression Tests	P=0.008	P=0.201	P=0.292	P=0.008
Carcinoma				
Overall Rates	7/50 (14%)	12/50 (24%)	6/49 (12%)	21/50 (42%)
Terminal Rates	4/35 (11%)	5/28 (18%)	2/24 (8%)	9/27 (33%)
Day of First Observation	456	433	620	456
Logistic Regression Tests	P=0.002	P=0.157	P=0.516N	P=0.001
Adenoma or Carcinoma (b)				
Overall Rates	16/50 (32%)	22/50 (44%)	17/49 (35%)	32/50 (64%)
Terminal Rates	12/35 (34%)	13/28 (46%)	8/24 (33%)	17/27 (63%)
Day of First Observation	456	433	571	456
Logistic Regression Tests	P<0.001	P=0.136	P=0.431	P<0.001
FEMALE				
Adenoma				
Overall Rates	1/50 (2%)	3/50 (6%)	5/50 (10%)	8/50 (16%)
Terminal Rates	1/33 (3%)	3/28 (11%)	3/29 (10%)	6/32 (19%)
Day of First Observation	729	729	493	615
Logistic Regression Tests	P=0.007	P=0.247	P=0.100	P=0.017
Carcinoma				
Overall Rates	4/50 (8%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Terminal Rates	4/33 (12%)	0/28 (0%)	1/29 (3%)	3/32 (9%)
Day of First Observation	729		611	549
Logistic Regression Tests	P=0.402	P=0.085N	P=0.366N	P=0.640
Adenoma or Carcinoma (c)				
Overall Rates	5/50 (10%)	3/50 (6%)	7/50 (14%)	12/50 (24%)
Terminal Rates	5/33 (15%)	3/28 (11%)	4/29 (14%)	9/32 (28%)
Day of First Observation	729	729	493	549
Logistic Regression Tests	P=0.011	P=0.448N	P=0.352	P=0.051

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence at study laboratory (mean ± SD): 168/448 (38% ± 10%); historical incidence in NTP studies: 713/2,183 (33% ± 9%)
(c) Historical incidence at study laboratory (mean ± SD): 28/450 (6% ± 2%); historical incidence in NTP studies: 162/2,188 (7% ± 5%)

neoplastic hepatocytes appeared relatively well differentiated, although cytoplasmic staining was often more eosinophilic or, less commonly, more basophilic or vacuolated than normal hepatocytes. Carcinomas were also discrete expansile masses but differed from adenomas in that the neoplastic hepatocytes generally were moderately to highly pleomorphic or even anaplastic compared with adenomas and the growth patterns within carcinomas were often highly abnormal, with neoplastic cells forming broad trabeculae or glandlike structures that were many cell layers thick. A few carcinomas also metastasized, principally to the lung.

Forestomach: Hyperplasia was observed at increased incidences in dosed female mice (Table 11). Squamous cell papillomas in female mice occurred with a significant positive trend; the incidence in the high dose group was not significantly greater than that in vehicle controls.

Papillomas were focal exophytic masses consisting of a complex branching core of fibrous tissue connected to the forestomach wall by a fibrous stalk that was covered by a thickened layer of stratified squamous epithelium. Forestomach hyperplasia was characterized by focal thickening of the stratified squamous epithelium that was sometimes folded. Hyperplasia was a broad-based lesion that lacked the complex structure and fibrous tissue cores of the papillomas.

Kidney: Hyperplasia of the renal tubules occurred in one low dose male mouse. Cortical adenomas occurred in 1/49 mid dose and 1/50 high dose males, and a cortical carcinoma was seen in 1/50 low dose males. The incidences of cortical adenomas or carcinomas (combined) in male mice were 0/50 (vehicle control), 1/50 (low dose), 1/49 (mid dose), and 1/50 (high dose). The historical incidence of renal cortical or tubular cell neoplasms in male corn oil vehicle control $B6C3F_1$ mice is 8/2,183. A cortical adenoma occurred in one low dose female mouse.

Renal tubular hyperplasia, adenoma, and carcinoma are part of a morphologic continuum and were distinguished on the basis of size, degree of alteration of growth pattern, and cellular pleomorphism and atypia. The hyperplasia consisted of cross-sections of an enlarged, dilated tubule with a prominent epithelium several cell layers thick. The adenomas were discrete expansile masses that displaced the normal renal parenchyma. They consisted of small compact tubules or solid clusters of epithelial cells with enlarged nuclei. The carcinoma was larger than the adenomas, with a more heterogeneous growth pattern and greater cellular pleomorphism.

TABLE 11. FORESTOMACH LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL (a)

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
Hyperplasia				
Overall Rates	0/50 (0%)	5/50 (10%)	5/50 (10%)	3/50 (6%)
Squamous Papilloma (b)				
Overall Rates	1/50 (2%)	0/50 (0%)	1/50 (2%)	6/50 (12%)
Terminal Rates	1/33 (3%)	0/28 (0%)	0/29 (0%)	2/32 (6%)
Day of First Observation	729		523	596
Logistic Regression Tests	P=0.005	P=0.533N	P=0.763	P=0.058

(a) For a complete explanation of the entries in this table, see Table D3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of forestomach papillomas or carcinomas (combined) at study laboratory (mean ± SD): 8/446 (2% ± 3%); historical incidence in NTP studies: 37/2,144 (2% ± 3%)

Furfural (33-6,666 µg/plate) was tested in two laboratories for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 in a preincubation protocol with and without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Mortelmans et al., 1986; Table H1). Results of the Case Western Reserve University study were negative in all four strains, but in the study performed at SRI International, an equivocal response was noted in strain TA100 without S9. Furfural induced trifluorothymidine resistance in mouse L5178Y/TK lymphoma cells at doses of 200 and 400 µg/ml in the absence of S9; it was not tested with S9 (McGregor et al., 1988; Table H2). In cytogenetic tests with Chinese hamster ovary cells, furfural induced sister chromatid exchanges (SCEs) (Table H3) and chromosomal aberrations (Table H4) in both the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9. Chemical-induced cell cycle delay was observed in both tests; significant increases in SCEs were observed in trials where delayed harvest was used, as well as in trials harvested at the normal time (26 hours). In germ cells of male *Drosophila melanogaster*, furfural administered by abdominal injection (100 ppm) induced a significant increase in sex-linked recessive lethal mutations; no increase was observed when furfural was administered by feeding (1,000 ppm) (Woodruff et al., 1985; Table H5). Furfural administered by abdominal injection (100 ppm) did not induce reciprocal translocations in the germ cells of male Drosophila (Woodruff et al., 1985; Table H6). Furfural did not induce SCEs or chromosomal aberrations in bone marrow cells of male $B6C3F_1$ mice when administered by intraperitoneal injection at doses of 50, 100, or 200 mg/kg (Tables H7 and H8). The experimental procedures and results are presented in Appendix H.

IV. DISCUSSION AND CONCLUSIONS

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Furfural is a precursor for an industrially important class of aromatic compounds containing the furan ring, which includes furan, furfuryl alcohol, and tetrahydrofuran. Furfural is produced in large quantities and is used in numerous industrial processes that may involve occupational exposure. As a result of its formation from the thermal decomposition of carbohydrates, especially fructose, furfural is also present in numerous food and beverage products. Because of the absence of reliable data concerning the effects of long-term exposure to furfural, 2-year toxicology and carcinogenesis studies were conducted in F344/N rats and B6C3F$_1$ mice.

During the 16-day and 13-week studies, exposure to furfural at the highest dose reduced survival of both rats and mice. At doses below the highest in the 13-week studies, mean absolute kidney and liver weights, as well as their ratio to mean body weights, were increased for male rats; mean liver weights and liver to body weight ratios were increased for female mice. Histologic lesions associated with chemical exposure included cytoplasmic vacuolization of hepatocytes in male rats and hepatocellular necrosis and inflammation of the liver in male and female mice. These toxic responses were used as a basis for selecting doses for the 2-year studies.

In the 2-year studies, exposure to furfural had no effect on the mean body weights of male or female rats. Survival of male rats and low dose female rats was similar to that of vehicle controls. Survival of high dose female rats was slightly lower than survival of vehicle controls due to an unusually large number of accidental deaths. Many of these deaths appeared to be gavage related; consequently, early in the 2-year study, a concerted effort was begun, involving representatives from both the National Toxicology Program (NTP) and the study laboratory, to identify and correct the underlying cause(s) of the accidental deaths.

Nothing was found to indicate that gross error in the preparation or administration of the dose formulations was involved. The deaths were not clustered in time as might occur if technician error were involved but instead occurred throughout the studies, with the first gavage-related death occurring at week 39 and the last at week 100. Examination of necropsy forms for high dose female rats in the 2-year study revealed that deaths coded as dosing accidents nearly always involved gross observation of oil in the trachea. Conditions that would clearly indicate poor gavage technique, such as perforation of the esophagus or oil in the thoracic cavity, were seen in only three females. All rats were dosed at 5 ml/kg body weight, and since there were no significant body weight differences between groups of female rats, the high dose animals received dose volumes similar to those given all other groups. Therefore, differences in the volume of the dose formulation administered cannot account for these observations. The same technicians, using identical syringes and gavage needles, administered dose formulations to all rats; if poor gavage technique were a problem, a more even distribution of gavage-related deaths across other groups of rats would be expected. Moreover, there were only two gavage-related deaths in male mice and one gavage-related death in female mice, even though dosing technicians were rotated among rats and mice throughout the studies. Based on these considerations, gavage technique alone does not appear to account for the large number of accidental deaths in the high dose group of female rats. Although oil in the trachea or lung might have resulted from direct deposition of the chemical-vehicle formulation into the airway during gavage, reflex regurgitation after gavage would cause a similar finding. The potential influence of chemically related toxicity or of a pharmacologic effect is also a consideration; however, it was not possible to determine the exact cause of these deaths.

Since the gavage-related deaths occurred randomly throughout the study (weeks 39-100), the number of high dose female rats at risk was not precipitously reduced at an early time; survival was 85% that of vehicle controls at week 93 and 78% at week 97. This was considered adequate to detect carcinogenic activity. However, no compound-related neoplastic lesions or lesions generally considered to be preneoplastic were observed at any site in early death animals or 2-year survivors in either group of chemically exposed female rats. Moreover, exposure to furfural did not affect the incidence of spontaneous neoplasms in either dose group. In the absence

of any indication of carcinogenic activity and with adequate survival in both dose groups, this study was considered an adequate evaluation of carcinogenic potential and was interpreted as indicating no evidence of carcinogenic activity of furfural in female rats.

Cholangiocarcinomas were present in two high dose male rats, and a similar lesion (biliary dysplasia with fibrosis) was present in two additional high dose male rats. The Pathology Working Group that reviewed the lesions considered the latter to be an early stage in the development of cholangiocarcinoma. The terminology reported in the literature for this spectrum of lesions is confusing and reflects uncertainty about the biologic potential of the more benign-appearing lesions. Cholangiofibrosis, cholangiofibroma, cystic cholangioma, and cholangiocarcinoma are closely related lesions that are distinguished on the basis of the degree of proliferation and anaplasia of the biliary epithelium, evidence of invasive behavior, and the amount of fibrous connective tissue stroma. The lesion diagnosed as biliary dysplasia and fibrosis in these studies is similar to chemically induced lesions termed cholangiofibrosis or cholangiofibroma in other studies (Bannasch et al., 1985).

Although the biologic potential of biliary dysplasia with fibrosis (cholangiofibrosis) is uncertain, the malignant nature of cholangiocarcinoma is clear. In 2-year gavage studies conducted concurrently with the present studies in the same laboratory (NTP unpublished data), furan, a structurally related chemical, induced a high incidence of cholangiocarcinomas in rats of each sex. The malignancy of the neoplasms was confirmed by the presence of metastases to the lymph nodes, adrenal gland, and lung in several high dose male and female rats. In addition, fragments of cholangiocarcinomas taken at necropsy from several neoplasm-bearing animals and transplanted subcutaneously into the inguinal region of 6-week-old male and female F344 rats grew rapidly into large subcutaneous masses, several of which metastasized (Montgomery et al., 1986).

Cholangiocarcinomas are uncommon neoplasms in F344/N rats and have been observed in only 3/2,145 corn oil vehicle control male rats in previous NTP 2-year studies. Moreover, the spontaneous cholangiocarcinomas usually exhibited less fibrosis and atypia of the biliary epithelium than were observed in the neoplasms in the current studies. Since both cholangiocarcinoma and biliary dysplasia with fibrosis occurred in high dose male rats, their presence was judged to constitute some evidence of carcinogenic activity.

Exposure to furfural for 2 years had no effect on the survival or mean body weights of mice. In males, the incidences of hepatocellular adenomas and hepatocelluar carcinomas were significantly increased in the high dose group. The increase in carcinomas was particularly noteworthy, with the incidence in the high dose group being threefold greater than the incidence in the vehicle control group. The significant increases in the incidences of both benign and malignant neoplasms were considered to be chemically related and were interpreted as clear evidence of carcinogenic activity.

In female mice, incidences of hepatocellular adenomas increased with dose and were significantly greater in the high dose group; however, the incidences of carcinomas were not increased. Although this response was not as strong as that observed in males because of the lack of an increase in carcinomas, the dose response and significant increase in the high dose group were considered as some evidence of carcinogenic activity. This conclusion is supported by studies of other compounds containing a furan ring; in NTP 2-year studies of furan (NTP unpublished data) and benzofuran (NTP, 1989a), compounds structurally very similar to furfural, the liver was the major target organ in both short-term and 2-year studies; both compounds produced marked increases of hepatocellular neoplasms in each sex of mice .

As part of an effort to identify oncogenes expressed in chemically induced neoplasms, samples of tumor tissue from 3 hepatocellular adenomas and 13 hepatocellular carcinomas were collected at necropsy from furfural-exposed mice and were frozen in liquid nitrogen. DNA extracted from these samples was then evaluated for the presence of transforming genes in the NIH

3T3 transfection assay. Stable transfectants were obtained from 2/3 adenomas and 11/13 carcinomas, with approximately equal transformation efficiencies exhibited by DNA from both the adenomas and carcinomas. Hybridization to Southern blots of primary transfectant DNA revealed amplified H-*ras* sequences in the 2 adenomas and in 7 of the 11 carcinomas, and amplified K-*ras* was revealed in another carcinoma. Transfectant DNA from the remaining three carcinomas did not show any indication of amplified or rearranged sequences with any of the probes that were used, and therefore transforming genes from these neoplasms were not identified (Reynolds et al., 1987).

Analysis of activating mutations in H-*ras* revealed one adenoma and five carcinomas containing point mutations in codon 61. H-*ras* from the other adenoma and from one other carcinoma contained point mutations in codon 13, and H-*ras* from another carcinoma contained a point mutation in codon 117. Thus, transforming DNA from liver neoplasms in furfural-exposed mice contained H-*ras* with activating mutations in three separate codons, activated K-*ras*, and potentially up to three additional unidentified transforming genes.

A similar pattern of activation was found in samples of hepatocellular adenomas or carcinomas collected from chemically exposed mice at the end of the furan carcinogenicity study (Reynolds et al., 1987; NTP unpublished results). DNA from 9 of 19 adenomas and 4 of 10 carcinomas produced stable transfectants. Of the nine adenomas, seven were found to contain activated H-*ras* (four with mutations in codon 61, three with mutations in codon 117) and two contained activated K-*ras*. Three of the four carcinomas contained activated H-*ras* (one with a codon 61 mutation, one with a codon 117 mutation, one with a mutation in an unidentified codon), and one carcinoma contained activated *raf*.

Thus, liver neoplasms from mice exposed to furfural or furan exhibited a pattern of oncogene activation involving multiple *ras* alleles, mutations in multiple codons of the same *ras* allele, and activation of non-*ras* transforming genes. In contrast, a more restricted pattern of oncogene activation has been found in spontaneously occurring liver neoplasms in mice. Of 17 spontaneous liver neoplasms from $B6C3F_1$ mice evaluated in the NIH 3T3 transfection assay, 15 contained H-*ras* activated by point mutations in codon 61, 1 contained activated *raf*, and 1 contained an unidentified transforming gene (Reynolds et al., 1986, 1987).

Kidney neoplasms also were observed in chemically exposed male mice. Cortical adenomas were found in one mid dose male and one high dose male, and a cortical carcinoma was found in one low dose male; a cortical adenoma was found in one low dose female. These are uncommon neoplasms in $B6C3F_1$ mice, having been observed in only 8 of 2,183 male vehicle control $B6C3F_1$ mice in NTP corn oil gavage studies. Moreover, kidney neoplasms have occurred in chemically exposed mice in very few previous NTP or National Cancer Institute 2-year studies (nitrilotriacetic acid, NCI, 1977; tris(2,3-dibromopropyl)phosphate, NCI, 1978; bromodichloromethane, NTP, 1987b; *N*-phenyl-2-naphthylamine, NTP, 1988; and α-methyldopa sesquihydrate, NTP, 1989).

Renal tubular cell hyperplasia was observed in only a single mouse, a low dose male. Since tubular cell neoplasms are generally thought to be part of a morphologic continuum from hyperplasia to adenoma and carcinoma, a more substantial hyperplastic response might have been expected if induction due to chemical exposure were involved. Moreover, the incidences of these neoplasms were not dose related. Therefore, it is difficult to judge the strength of the association between chemical exposure and the presence of these neoplasms.

The incidences of hyperplasia and squamous papillomas of the forestomach were marginally increased in chemically exposed female mice. No papillomas occurred in the low dose group; one animal in the mid dose group and six animals in the high dose group had papillomas, compared with one in the vehicle controls. Incidences of hyperplasia were marginally increased in chemically exposed animals, but hyperplasia was not observed in vehicle controls. However, the biologic potential of the papillomas is uncertain, since none progressed to malignant neoplasms. Therefore, because of the low incidence of these neoplasms, their uncertain biologic

potential, and their possible relationship to gavage administration, the association with exposure to furfural was difficult to judge.

The doses used in the 2-year studies were considered adequate for evaluation of carcinogenic potential. Although mean body weights of chemically exposed animals were not reduced, body weight was not a sensitive indicator of furfural toxicity. During short-term studies, increased liver weights and incidences of hepatotoxic lesions in rats and mice and compound-related deaths in rats occurred at doses that did not affect body weight gain. In the 2-year studies, centrilobular necrosis was increased in chemically exposed male rats and minimal multifocal chronic inflammation and pigmentation were increased in chemically exposed mice of each sex. These results suggest that higher doses in the 2-year studies would have resulted in more severe and perhaps life-threatening hepatotoxicity. Therefore, the doses used in the 2-year studies provided an adequate challenge without producing severe toxic injury.

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

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of furfural for male F344/N rats, based on the occurrence of uncommon cholangiocarcinomas in two animals and bile duct dysplasia with fibrosis in two other animals. There was *no evidence of carcinogenic activity* for female F344/N rats that received doses of 0, 30, or 60 mg/kg furfural. There was *clear evidence of carcinogenic activity* for male $B6C3F_1$ mice, based on increased incidences of hepatocellular adenomas and hepatocellular carcinomas. There was *some evidence of carcinogenic activity* in female $B6C3F_1$ mice, based on increased incidences of hepatocellular adenomas. Renal cortical adenomas or carcinomas in male mice and squamous cell papillomas of the forestomach in female mice may have been related to exposure to furfural.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 9-10.

V. REFERENCES

V. REFERENCES

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APPENDIX A

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

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

	Vehicle Control	30 mg/kg	60 mg/kg
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Dosing accident	6	7	8
Moribund	11	11	11
Dead	2	4	7
Survivors			
Terminal sacrifice	31	28	24
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Intestine small, jejunum	(49)	(49)	(47)
Fibrosarcoma	1 (2%)		
Polyp adenomatous		1 (2%)	
Liver	(50)	(50)	(50)
Cholangiocarcinoma			2 (4%)
Chordoma, metastatic, uncertain primary site			1 (2%)
Hepatocellular adenoma	1 (2%)		
Mesentery	(5)	(8)	(9)
Sarcoma			2 (22%)
Pancreas	(50)	(50)	(47)
Acinus, adenoma	2 (4%)	3 (6%)	2 (4%)
Acinus, adenoma, multiple	1 (2%)		
Stomach, forestomach	(50)	(50)	(50)
Leiomyosarcoma		1 (2%)	
Papilloma squamous			2 (4%)
Squamous cell carcinoma		1 (2%)	
Stomach, glandular	(50)	(50)	(50)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Chordoma, metastatic, uncertain primary site			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(47)
Adrenal gland, medulla	(50)	(49)	(46)
Pheochromocytoma malignant	2 (4%)	2 (4%)	1 (2%)
Pheochromocytoma malignant, multiple		1 (2%)	
Pheochromocytoma benign	9 (18%)	12 (24%)	4 (9%)
Pheochromocytoma benign, multiple	2 (4%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(47)
Adenoma	4 (8%)	5 (10%)	2 (4%)
Carcinoma	1 (2%)	1 (2%)	2 (4%)
Pituitary gland	(50)	(49)	(50)
Pars distalis, adenoma	19 (38%)	18 (37%)	15 (30%)
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	3 (6%)	2 (4%)	2 (4%)
C-cell, adenoma, multiple	1 (2%)		
C-cell, carcinoma	1 (2%)		
Follicular cell, carcinoma	1 (2%)		
GENERAL BODY SYSTEM			
None			

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

	Vehicle Control	30 mg/kg	60 mg/kg
GENITAL SYSTEM			
Epididymis	(50)	(50)	(50)
Preputial gland	(49)	(50)	(47)
Adenoma	1 (2%)	4 (8%)	2 (4%)
Carcinoma	1 (2%)	1 (2%)	1 (2%)
Prostate	(50)	(50)	(50)
Seminal vesicle	(47)	(50)	(50)
Testes	(50)	(50)	(50)
Interstitial cell, adenoma	2 (4%)	9 (18%)	4 (8%)
Interstitial cell, adenoma, multiple	36 (72%)	35 (70%)	35 (70%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Lymph node	(50)	(50)	(48)
Lymph node, mandibular	(49)	(49)	(47)
Lymph node, mesenteric	(48)	(49)	(46)
Spleen	(50)	(50)	(49)
Sarcoma			1 (2%)
Thymus	(43)	(48)	(38)
INTEGUMENTARY SYSTEM			
Mammary gland	(45)	(49)	(47)
Adenocarcinoma		1 (2%)	
Fibroadenoma		1 (2%)	1 (2%)
Fibroadenoma, multiple	1 (2%)		
Skin	(50)	(50)	(49)
Basal cell carcinoma	2 (4%)		
Keratoacanthoma	2 (4%)	1 (2%)	4 (8%)
Papilloma squamous	1 (2%)	1 (2%)	
Squamous cell carcinoma	1 (2%)		
Sebaceous gland, adenoma	1 (2%)		
Subcutaneous tissue, fibroma	4 (8%)	5 (10%)	2 (4%)
Subcutaneous tissue, fibroma, multiple	1 (2%)		
Subcutaneous tissue, fibrosarcoma		2 (4%)	1 (2%)
Subcutaneous tissue, lipoma		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
Skeletal muscle	(1)		(2)
Chordoma, metastatic, uncertain primary site			1 (50%)
Fibrosarcoma	1 (100%)		
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Astrocytoma malignant		1 (2%)	
Granular cell tumor benign		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			1 (2%)
Basal cell carcinoma, metastatic, skin	1 (2%)		
Chordoma, metastatic, uncertain primary site			1 (2%)
Nose	(50)	(49)	(50)
Papilloma		1 (2%)	

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

	Vehicle Control	30 mg/kg	60 mg/kg
SPECIAL SENSES SYSTEM			
Ear	(1)	(1)	(1)
Pinna, schwannoma benign	1 (100%)		1 (100%)
Zymbal gland	(3)		
Adenoma	2 (67%)		
Carcinoma	1 (33%)		
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Urinary bladder	(50)	(50)	(49)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	13 (26%)	15 (30%)	15 (30%)
Mesothelioma malignant	3 (6%)	3 (6%)	2 (4%)
TUMOR SUMMARY			
Total animals with primary neoplasms **	47	46	44
Total primary neoplasms	122	131	106
Total animals with benign neoplasms	47	46	43
Total benign neoplasms	94	101	79
Total animals with malignant neoplasms	23	24	26
Total malignant neoplasms	28	30	27
Total animals with secondary neoplasms ***	2		1
Total secondary neoplasms	4		4
Total animals with malignant neoplasms			1

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

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

DAYS ON STUDY	267	292	340	371	398	444	448	451	470	484	517	517	554	564	583	595	603	654	697	729	729	729	729	729	729
CARCASS ID	01101	03101	07101	06101	07202	02101	02202	01202	01101	09101	06303	07303	05101	06401	01303	08101	10202	03202	06505	01404	01505	02303	02404	02505	03303
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																								X	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery							+				+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																								X	
Acinus, adenoma, multiple																									
Salivary glands	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, seminal vesicle																	X								
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Pheochromocytoma benign, multiple																	X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Carcinoma																			X						
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X		X					X	X									X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									X
C-cell, adenoma, multiple															X										
C-cell, carcinoma																									
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																					
Carcinoma																				X					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Interstitial cell, adenoma, multiple						X		X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	

+: Tissue examined microscopically
: Not examined
I: Insufficient tissue
M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

DAYS ON STUDY	729	729	729	729	729	729	729	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	TOTAL TISSUES TUMORS
CARCASS ID	03 4	03 5	04 1	04 2	04 3	04 4	04 5	05 2	05 3	05 4	05 5	06 2	07 4	07 5	08 2	08 3	08 4	08 5	09 2	09 3	09 4	09 5	10 3	10 4	10 5	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma															X											1
Mesentery						+		+								+										5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																								X		2
Acinus, adenoma, multiple																			X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, seminal vesicle																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant													X		X											2
Pheochromocytoma benign		X	X				X					X	X	X	X			X							X	9
Pheochromocytoma benign, multiple				X																						2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X		X						X			4
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X		X	X		X				X			X	X	X		X		X					19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell, adenoma																		X				X				3
C cell, adenoma, multiple																										1
C cell, carcinoma													X													1
Follicular cell, carcinoma					X																					1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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	36

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

DAYS ON STUDY	267	292	340	371	398	444	448	451	470	484	517	517	554	564	583	595	603	654	697	729	729	729	729	729	729
CARCASS ID	01 1	03 1	07 1	06 1	07 2	02 1	02 2	01 2	01 0	09 1	06 3	07 3	05 1	06 4	01 3	08 1	10 2	03 2	06 5	01 4	01 5	02 3	02 4	02 5	03 3
HEMATOPOIETIC SYSTEM																									
Blood																				+					+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M
Mediastinum, mesothelioma malignant, metastatic, seminal vesicle																	X								
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	+	M	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma, multiple																									X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma						X			X																
Keratoacanthoma																						X			
Papilloma squamous																									
Squamous cell carcinoma																					X				
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma															X				X						
Subcutaneous tissue, fibroma multiple																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																						+			
Fibrosarcoma																						X			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma, metastatic, skin						X																			
Pleura, mesothelioma malignant, metastatic, seminal vesicle																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
Pinna, schwannoma benign																									
Eye				+																	+			+	
Harderian gland			+																						
Zymbal gland										+								+							
Adenoma										X															
Carcinoma																		X							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X									X		X		X	X				
Mesothelioma malignant											X	X					X								

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

DAYS ON STUDY	729	729	729	729	729	729	729	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	
CARCASS ID	0034	0035	0041	0042	0043	0044	0045	0052	0053	0054	0055	0062	0074	0075	0082	0083	0084	0085	0092	0093	0094	0095	0103	0104	0105	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	43
Mediastinum, mesothelioma malignant, metastatic, seminal vesicle																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										2
Keratoacanthoma																								X		2
Papilloma squamous							X																			1
Squamous cell carcinoma																										1
Sebaceous gland, adenoma	X																									1
Subcutaneous tissue, fibroma					X														X							4
Subcutaneous tissue, fibroma, multiple	X																									1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Fibrosarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma, metastatic, skin																										1
Pleura, mesothelioma malignant, metastatic, seminal vesicle																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear										+																1
Pinna, schwannoma benign										X																1
Eye																	+									4
Harderian gland																										1
Zymbal gland													+													3
Adenoma													X													2
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X				X		X					X	X	X			X			X			13
Mesothelioma malignant																										3

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL: 30 mg/kg

DAYS ON STUDY	101	113	276	329	484	514	536	551	561	585	622	666	668	674	676	676	682	693	702	707	708	709	729	731	731
CARCASS ID	27 1	23 1	24 1	25 1	27 2	22 1	24 2	30 1	21 1	29 1	27 3	26 1	25 2	24 3	21 2	21 3	30 2	27 4	23 2	28 1	26 2	24 4	22 3	21 4	21 5
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																			X						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery												+	+						+				+		
Mesothelioma malignant, multiple																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma														X											
Squamous cell carcinoma						X																			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																	X	X							
Pheochromocytoma malignant, multiple																					X				
Pheochromocytoma benign					X	X																	X		X
Pheochromocytoma benign, multiple																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Carcinoma										X															
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X		X			X	X				X		X	X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									X
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland															+										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma					X			X		X	X				X		X								X
Interstitial cell, adenoma, multiple						X	X		X			X	X	X				X	X		X	X	X	X	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 30 mg/kg (Continued)

DAYS ON STUDY	731	731	731	731	731	731	731	731	731	731	732	732	732	735	735	735	735	735	735	735	735	735	735	735	TOTAL:
CARCASS ID	222	224	225	233	234	235	245	253	254	255	263	264	265	275	282	283	284	285	292	293	294	295	303	304	305	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery											+		+		+					●						8
Mesothelioma malignant, multiple													X													1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma				X																	X			X		3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										2
Pheochromocytoma malignant, multiple																										1
Pheochromocytoma benign		X					X					X	X	X					X		X				X	12
Pheochromocytoma benign, multiple																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X	X							X		X												5
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma					X		X		X			X			X		X			X	X		X		X	18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																					X					2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X	X				X												4
Carcinoma	X																									1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma											X										X					9
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	35

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 30 mg/kg (Continued)

DAYS ON STUDY	101	113	276	329	484	514	536	551	561	585	622	666	668	674	676	676	682	693	702	707	708	709	729	731
CARCASS ID	271	231	241	251	272	221	242	301	211	291	273	261	252	243	212	213	302	274	232	281	262	244	223	215
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
INTEGUMENTARY SYSTEM																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								
Fibroadenoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma											X													
Papilloma squamous																								
Subcutaneous tissue, fibroma						X									X									
Subcutaneous tissue, fibrosarcoma																						X		
Subcutaneous tissue, lipoma																				X				
MUSCULOSKELETAL SYSTEM																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma											X													
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant						X																		
Granular cell tumor benign																								
Spinal cord																								
RESPIRATORY SYSTEM																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																								
Ear																		+						
Eye														+	+									
Harderian gland																				+				
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X	X	X	X	X		X	X					
Mesothelioma malignant													X										X	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 30 mg/kg (Continued)

DAYS ON STUDY	731	731	731	731	731	731	731	731	731	731	732	732	732	732	735	735	735	735	735	735	735	735	735	735	735	TOTAL:
CARCASS ID	222	224	225	233	234	235	245	253	254	255	263	264	265	275	282	283	284	285	292	293	294	295	303	304	305	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Adenocarcinoma														X												1
Fibroadenoma							X																			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Papilloma squamous															X											1
Subcutaneous tissue, fibroma			X		X														X							5
Subcutaneous tissue, fibrosarcoma																						X				2
Subcutaneous tissue, lipoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Granular cell tumor benign						X																				1
Spinal cord																+										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma													X													1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										1
Eye																										2
Harderian gland																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X										X		X	X				X					X	X	15
Mesothelioma malignant													X													3

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL: 60 mg/kg

DAYS ON STUDY	084	099	287	309	371	438	479	481	508	547	564	568	582	589	597	599	604	606	655	655	657	675	676	702	708
CARCASS ID	131	141	121	132	171	191	111	122	133	181	142	182	161	192	123	183	151	112	143	152	134	144	184	153	162
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma											X														
Chordoma, metastatic, uncertain primary site													X												
Mesentery			+							+			+		+		+				+				
Sarcoma													X		X										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel																						+			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma, metastatic, uncertain primary site													X												
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign													X												
Pheochromocytoma benign, multiple																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Carcinoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X	X								X									X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 60 mg/kg (Continued)

DAYS ON STUDY	708	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	TOTAL: TISSUES TUMORS
CARCASS ID	172	113	114	115	124	125	135	145	154	155	163	164	165	173	174	175	185	193	194	195	201	202	203	204	205	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma									X																	2
Chordoma, metastatic, uncertain primary site																										1
Mesentery	+												+						+							9
Sarcoma																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	47
Acinus, adenoma																			X				X			2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous				X						X																2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel																	+									2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma, metastatic, uncertain primary site																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	47
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	47
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	46
Pheochromocytoma malignant												X														1
Pheochromocytoma benign							X		X								X									4
Pheochromocytoma benign, multiple														X												1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	47
Adenoma																			X							2
Carcinoma									X													X				2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X	X	X		X	X						X		X		X			X		X		15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X								X													2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	47
Adenoma						X				X																2
Carcinoma											X															1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma									X																	4
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	35

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 60 mg/kg (Continued)

DAYS ON STUDY	084	099	287	309	371	438	479	481	508	547	564	568	582	589	597	599	604	606	655	655	657	675	676	702	708
CARCASS ID	131	141	121	132	171	191	111	122	133	181	142	182	161	192	123	183	151	112	143	152	134	144	184	153	162
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																								X	
Thymus	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	M	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																				X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, fibroma																		X							
Subcutaneous tissue, fibrosarcoma																						X			
Subcutaneous tissue, lipoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle													+												
Chordoma, metastatic, uncertain primary site													X												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Chordoma, metastatic, uncertain primary site													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
Pinna, schwannoma benign																									
Eye																									
Harderian gland								+																	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X		X			X		X				X		X
Mesothelioma malignant																					X				

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 60 mg/kg
(Continued)

DAYS ON STUDY	708	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	TOTAL:
CARCASS ID	172	113	114	115	124	125	135	145	154	155	163	164	165	173	174	175	185	193	194	195	201	202	203	204	205	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	●	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	●	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	●	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	46
Spleen	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma																										1
Thymus	+	M	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	M	M	+	+	+	38
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	47
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Keratoacanthoma		X					X			X					X											4
Subcutaneous tissue, fibroma				X																						2
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, lipoma						X																				1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle			+																							2
Chordoma, metastatic, uncertain primary site																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																							1
Chordoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear	+																									1
Pinna, schwannoma benign	X																									1
Eye													+						+	M	+					3
Harderian gland																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X				X			X						X	X		X	X	X					15
Mesothelioma malignant	X																									2

TABLE A3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL

	Vehicle Control	30 mg/kg	60 mg/kg
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	11/50 (22%)	13/49 (27%)	5/46 (11%)
Adjusted Rates (b)	34.3%	40.4%	21.2%
Terminal Rates (c)	10/31 (32%)	10/28 (36%)	4/21 (19%)
Day of First Observation	603	484	582
Life Table Tests (d)	P=0.251N	P=0.333	P=0.251N
Logistic Regression Tests (d)	P=0.126N	P=0.489	P=0.147N
Cochran-Armitage Trend Test (d)	P=0.114N		
Fisher Exact Test (d)		P=0.385	P=0.117N
Adrenal Medulla: Malignant Pheochromocytoma			
Overall Rates (a)	2/50 (4%)	3/49 (6%)	1/46 (2%)
Adjusted Rates (b)	6.5%	9.0%	4.8%
Terminal Rates (c)	2/31 (6%)	0/28 (0%)	1/21 (5%)
Day of First Observation	729	682	729
Life Table Tests (d)	P=0.508N	P=0.487	P=0.635N
Logistic Regression Tests (d)	P=0.461N	P=0.535	P=0.635N
Cochran-Armitage Trend Test (d)	P=0.431N		
Fisher Exact Test (d)		P=0.490	P=0.532N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	11/50 (22%)	16/49 (33%)	6/46 (13%)
Adjusted Rates (b)	34.3%	45.8%	25.8%
Terminal Rates (c)	10/31 (32%)	10/28 (36%)	5/21 (24%)
Day of First Observation	603	484	582
Life Table Tests (d)	P=0.380N	P=0.145	P=0.373N
Logistic Regression Tests (d)	P=0.211N	P=0.241	P=0.236N
Cochran-Armitage Trend Test (d)	P=0.189N		
Fisher Exact Test (d)		P=0.168	P=0.190N
Preputial Gland: Adenoma			
Overall Rates (a)	1/49 (2%)	4/50 (8%)	2/47 (4%)
Adjusted Rates (b)	2.1%	13.7%	9.5%
Terminal Rates (c)	0/31 (0%)	3/28 (11%)	2/21 (10%)
Day of First Observation	371	708	729
Life Table Tests (d)	P=0.286	P=0.162	P=0.408
Logistic Regression Tests (d)	P=0.373	P=0.186	P=0.493
Cochran-Armitage Trend Test (d)	P=0.391		
Fisher Exact Test (d)		P=0.187	P=0.484
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	2/49 (4%)	5/50 (10%)	3/47 (6%)
Adjusted Rates (b)	5.3%	17.1%	14.3%
Terminal Rates (c)	1/31 (3%)	4/28 (14%)	3/21 (14%)
Day of First Observation	371	708	729
Life Table Tests (d)	P=0.263	P=0.188	P=0.358
Logistic Regression Tests (d)	P=0.367	P=0.233	P=0.468
Cochran-Armitage Trend Test (d)	P=0.401		
Fisher Exact Test (d)		P=0.226	P=0.480
Pancreatic Islets: Adenoma			
Overall Rates (a)	4/50 (8%)	5/50 (10%)	2/47 (4%)
Adjusted Rates (b)	12.9%	16.6%	7.0%
Terminal Rates (c)	4/31 (13%)	4/28 (14%)	1/21 (5%)
Day of First Observation	729	674	481
Life Table Tests (d)	P=0.443N	P=0.453	P=0.489N
Logistic Regression Tests (d)	P=0.339N	P=0.535	P=0.390N
Cochran-Armitage Trend Test (d)	P=0.310N		
Fisher Exact Test (d)		P=0.500	P=0.369N

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

	Vehicle Control	30 mg/kg	60 mg/kg
Pancreatic Islets: Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	6/50 (12%)	4/47 (9%)
Adjusted Rates (b)	15.6%	18.6%	16.3%
Terminal Rates (c)	4/31 (13%)	4/28 (14%)	3/21 (14%)
Day of First Observation	697	585	481
Life Table Tests (d)	P=0.511	P=0.468	P=0.583
Logistic Regression Tests (d)	P=0.511N	P=0.555	P=0.583N
Cochran-Armitage Trend Test (d)	P=0.474N		
Fisher Exact Test (d)		P=0.500	P=0.540N
Pancreas: Adenoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	2/47 (4%)
Adjusted Rates (b)	9.7%	10.7%	9.5%
Terminal Rates (c)	3/31 (10%)	3/28 (11%)	2/21 (10%)
Day of First Observation	729	729	729
Life Table Tests (d)	P=0.592N	P=0.617	P=0.676N
Logistic Regression Tests (d)	P=0.592N	P=0.617	P=0.676N
Cochran-Armitage Trend Test (d)	P=0.440N		
Fisher Exact Test (d)		P=0.661N	P=0.530N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	19/50 (38%)	18/49 (37%)	15/50 (30%)
Adjusted Rates (b)	53.2%	52.1%	51.5%
Terminal Rates (c)	15/31 (48%)	12/28 (43%)	11/24 (46%)
Day of First Observation	398	585	438
Life Table Tests (d)	P=0.494N	P=0.579N	P=0.525N
Logistic Regression Tests (d)	P=0.246N	P=0.417N	P=0.281N
Cochran-Armitage Trend Test (d)	P=0.231N		
Fisher Exact Test (d)		P=0.531N	P=0.263N
Skin: Keratoacanthoma			
Overall Rates (e)	2/50 (4%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	6.5%	2.6%	16.7%
Terminal Rates (c)	2/31 (6%)	0/28 (0%)	4/24 (17%)
Day of First Observation	729	666	729
Life Table Tests (d)	P=0.162	P=0.501N	P=0.223
Logistic Regression Tests (d)	P=0.195	P=0.474N	P=0.223
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.500N	P=0.339
Subcutaneous Tissue: Fibroma			
Overall Rates (e)	5/50 (10%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	14.9%	15.1%	7.1%
Terminal Rates (c)	3/31 (10%)	3/28 (11%)	1/24 (4%)
Day of First Observation	583	514	606
Life Table Tests (d)	P=0.251N	P=0.612	P=0.292N
Logistic Regression Tests (d)	P=0.183N	P=0.603N	P=0.227N
Cochran-Armitage Trend Test (d)	P=0.178N		
Fisher Exact Test (d)		P=0.630N	P=0.218N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (e)	5/50 (10%)	7/50 (14%)	3/50 (6%)
Adjusted Rates (b)	14.9%	21.3%	10.3%
Terminal Rates (c)	3/31 (10%)	4/28 (14%)	1/24 (4%)
Day of First Observation	583	514	606
Life Table Tests (d)	P=0.417N	P=0.359	P=0.447N
Logistic Regression Tests (d)	P=0.319N	P=0.416	P=0.370N
Cochran-Armitage Trend Test (d)	P=0.307N		
Fisher Exact Test (d)		P=0.380	P=0.357N

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

	Vehicle Control	30 mg/kg	60 mg/kg
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	38/50 (76%)	44/50 (88%)	39/50 (78%)
Adjusted Rates (b)	90.4%	100.0%	100.0%
Terminal Rates (c)	27/31 (87%)	28/28 (100%)	24/24 (100%)
Day of First Observation	444	484	481
Life Table Tests (d)	P=0.081	P=0.122	P=0.112
Logistic Regression Tests (d)	P=0.453	P=0.148	P=0.514
Cochran-Armitage Trend Test (d)	P=0.453		
Fisher Exact Test (d)		P=0.096	P=0.500
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	12.2%	7.1%	8.3%
Terminal Rates (c)	3/31 (10%)	2/28 (7%)	2/24 (8%)
Day of First Observation	583	729	729
Life Table Tests (d)	P=0.341N	P=0.366N	P=0.436N
Logistic Regression Tests (d)	P=0.271N	P=0.303N	P=0.359N
Cochran-Armitage Trend Test (d)	P=0.253N		
Fisher Exact Test (d)		P=0.339N	P=0.339N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	15.3%	7.1%	8.3%
Terminal Rates (c)	4/31 (13%)	2/28 (7%)	2/24 (8%)
Day of First Observation	583	729	729
Life Table Tests (d)	P=0.217N	P=0.244N	P=0.310N
Logistic Regression Tests (d)	P=0.160N	P=0.185N	P=0.238N
Cochran-Armitage Trend Test (d)	P=0.147N		
Fisher Exact Test (d)		P=0.218N	P=0.218N
Zymbal Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	8.4%	0.0%	0.0%
Terminal Rates (c)	1/31 (3%)	0/28 (0%)	0/24 (0%)
Day of First Observation	484		
Life Table Tests (d)	P=0.042N	P=0.113N	P=0.140N
Logistic Regression Tests (d)	P=0.037N	P=0.123N	P=0.119N
Cochran-Armitage Trend Test (d)	P=0.038N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (e)	13/50 (26%)	15/50 (30%)	15/50 (30%)
Adjusted Rates (b)	37.6%	41.5%	48.3%
Terminal Rates (c)	10/31 (32%)	8/28 (29%)	9/24 (38%)
Day of First Observation	448	666	568
Life Table Tests (d)	P=0.192	P=0.389	P=0.225
Logistic Regression Tests (d)	P=0.331	P=0.497	P=0.375
Cochran-Armitage Trend Test (d)	P=0.371		
Fisher Exact Test (d)		P=0.412	P=0.412
All Sites: Malignant Mesothelioma			
Overall Rates (e)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	7.8%	9.6%	7.1%
Terminal Rates (c)	0/31 (0%)	2/28 (7%)	0/24 (0%)
Day of First Observation	517	668	657
Life Table Tests (d)	P=0.458N	P=0.635N	P=0.517N
Logistic Regression Tests (d)	P=0.413N	P=0.658	P=0.491N
Cochran-Armitage Trend Test (d)	P=0.412N		
Fisher Exact Test (d)		P=0.661N	P=0.500N

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

	Vehicle Control	30 mg/kg	60 mg/kg
All Sites: Benign Tumors			
Overall Rates (e)	47/50 (94%)	46/50 (92%)	43/50 (86%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	31/31 (100%)	28/28 (100%)	24/24 (100%)
Day of First Observation	371	484	438
Life Table Tests (d)	P=0.303	P=0.536	P=0.361
Logistic Regression Tests (d)	P=0.035N	P=5.000	P=0.081N
Cochran-Armitage Trend Test (d)	P=0.114N		
Fisher Exact Test (d)		P=0.500N	P=0.159N
All Sites: Malignant Tumors			
Overall Rates (e)	23/50 (46%)	24/50 (48%)	26/50 (52%)
Adjusted Rates (b)	57.0%	58.1%	69.8%
Terminal Rates (c)	14/31 (45%)	11/28 (39%)	13/24 (54%)
Day of First Observation	444	514	564
Life Table Tests (d)	P=0.145	P=0.484	P=0.170
Logistic Regression Tests (d)	P=0.274	P=0.558	P=0.310
Cochran-Armitage Trend Test (d)	P=0.309		
Fisher Exact Test (d)		P=0.500	P=0.345
All Sites: All Tumors			
Overall Rates (e)	47/50 (94%)	46/50 (92%)	44/50 (88%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	31/31 (100%)	28/28 (100%)	24/24 (100%)
Day of First Observation	371	484	438
Life Table Tests (d)	P=0.248	P=0.536	P=0.303
Logistic Regression Tests (d)	P=0.076N	P=5.000	P=0.160N
Cochran-Armitage Trend Test (d)	P=0.187N		
Fisher Exact Test (d)		P=0.500N	P=0.243N

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

TABLE A4a. HISTORICAL INCIDENCE OF BILE DUCT NEOPLASMS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Adenomas or Carcinomas in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	0/50
Benzyl acetate	0/49
Allyl isovalerate	(b) 1/50
HC Red No. 3	0/50
C.I. Acid Orange 3	0/50
Chlorinated paraffins (C_{23}, 43% chlorine)	0/50
Chlorinated paraffins (C_{12}, 60% chlorine)	0/50
Allyl isothiocyanate	0/50
Geranyl acetate	(c) 1/50
TOTAL	2/449 (0.4%)
SD (d)	0.88%
Range (e)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(f) 3/2,145 (0.1%)
SD (d)	0.52%
Range (e)	
High	1/50
Low	0/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Bile duct adenoma
(c) Bile duct carcinoma
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes one bile duct adenoma and two bile duct carcinomas

TABLE A4b. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL NEOPLASMS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Papillomas or Carcinomas in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	(b) 1/50
Benzyl acetate	0/50
Allyl isovalerate	0/50
HC Red No. 3	0/50
C.I. Acid Orange 3	0/50
Chlorinated paraffins (C_{23}, 43% chlorine)	0/50
Chlorinated paraffins (C_{12}, 60% chlorine)	0/50
Allyl isothiocyanate	0/49
Geranyl acetate	0/50
TOTAL	(b) 1/449 (0.2%)
SD (c)	0.67%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 8/2,122 (0.4%)
SD (c)	0.79%
Range (d)	
High	1/49
Low	0/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Squamous cell papilloma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one papilloma, NOS, six squamous cell papillomas, and one squamous cell carcinoma

TABLE A4c. HISTORICAL INCIDENCE OF BODY CAVITY NEOPLASMS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Sarcomas in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	0/50
Benzyl acetate	0/50
Allyl isovalerate	0/50
HC Red No. 3	0/50
C.I. Acid Orange 3	0/50
Chlorinated paraffins (C_{23}, 43% chlorine)	0/50
Chlorinated paraffins (C_{12}, 60% chlorine)	0/50
Allyl isothiocyanate	0/50
Geranyl acetate	(b) 1/50
TOTAL	(b) 1/450 (0.2%)
SD (c)	0.67%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 2/2,149 (0.1%)
SD (c)	0.43%
Range (d)	
High	1/50
Low	0/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Fibrosarcoma of the mesentery
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one fibrosarcoma of the mesentery and one myxosarcoma of the peritoneum

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

	Vehicle Control	30 mg/kg	60 mg/kg
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Dosing accident	6	7	8
Moribund	11	11	11
Dead	2	4	7
Survivors			
Terminal sacrifice	31	28	24
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(50)	(50)	(48)
Parasite metazoan	3 (6%)	1 (2%)	2 (4%)
Intestine large, colon	(50)	(49)	(48)
Parasite metazoan	6 (12%)	5 (10%)	7 (15%)
Intestine large, rectum	(49)	(49)	(45)
Parasite metazoan	7 (14%)	6 (12%)	10 (22%)
Intestine small	(50)	(49)	(48)
Intussusception		1 (2%)	
Intestine small, duodenum	(48)	(48)	(47)
Erosion, multiple		1 (2%)	
Liver	(50)	(50)	(50)
Angiectasis, focal		1 (2%)	1 (2%)
Angiectasis, multifocal	1 (2%)		
Basophilic focus	37 (74%)	35 (70%)	26 (52%)
Clear cell focus	21 (42%)	19 (38%)	16 (32%)
Congestion			1 (2%)
Degeneration, cystic	5 (10%)	11 (22%)	2 (4%)
Degeneration, cystic, focal	1 (2%)		6 (12%)
Fatty change, diffuse		2 (4%)	2 (4%)
Granuloma, multiple	2 (4%)	7 (14%)	3 (6%)
Hematopoietic cell proliferation		1 (2%)	
Hepatodiaphragmatic nodule	4 (8%)	5 (10%)	1 (2%)
Hyperplasia, focal		1 (2%)	
Necrosis, multifocal		1 (2%)	
Bile duct, dysplasia, focal			2 (4%)
Bile duct, fibrosis, focal			2 (4%)
Bile duct, hyperplasia	45 (90%)	41 (82%)	42 (84%)
Bile duct, hyperplasia, focal			1 (2%)
Biliary tract, cyst multilocular			1 (2%)
Centrilobular, fatty change	10 (20%)	6 (12%)	3 (6%)
Centrilobular, necrosis	2 (4%)	8 (16%)	12 (24%)
Centrilobular, necrosis, focal		1 (2%)	
Centrilobular, necrosis, multifocal	1 (2%)		
Mesentery	(5)	(8)	(9)
Fat, necrosis, focal	3 (60%)	4 (50%)	6 (67%)
Pancreas	(50)	(50)	(47)
Inflammation, chronic, multifocal		1 (2%)	
Inflammation, subacute, multifocal		1 (2%)	
Acinus, atrophy, focal	6 (12%)	6 (12%)	4 (9%)
Acinus, atrophy, multifocal	13 (26%)	8 (16%)	12 (26%)
Acinus, hyperplasia, focal	10 (20%)	18 (36%)	16 (34%)
Acinus, hyperplasia, multifocal	1 (2%)	5 (10%)	
Artery, hypertrophy		2 (4%)	
Artery, inflammation, subacute		1 (2%)	
Artery, mineralization		1 (2%)	
Duct, ectasia			1 (2%)

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

	Vehicle Control	30 mg/kg	60 mg/kg
ALIMENTARY SYSTEM (Continued)			
Stomach, forestomach	(50)	(50)	(50)
Edema		2 (4%)	
Erosion	1 (2%)	1 (2%)	
Hyperplasia	1 (2%)	5 (10%)	2 (4%)
Inflammation, subacute	2 (4%)	5 (10%)	2 (4%)
Perforation		2 (4%)	
Ulcer		1 (2%)	1 (2%)
Ulcer, multiple	1 (2%)		
Stomach, glandular	(50)	(50)	(50)
Erosion	1 (2%)		1 (2%)
Inflammation, subacute		2 (4%)	
Mineralization	5 (10%)	11 (22%)	6 (12%)
CARDIOVASCULAR SYSTEM			
Blood vessel			(2)
Aorta, mineralization			2 (100%)
Heart	(50)	(50)	(50)
Cardiomyopathy	35 (70%)	32 (64%)	36 (72%)
Congestion			1 (2%)
Inflammation, chronic, focal		1 (2%)	1 (2%)
Mineralization, multifocal		1 (2%)	
Thrombus	1 (2%)	1 (2%)	2 (4%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(47)
Focal cellular change	6 (12%)	5 (10%)	3 (6%)
Focal cellular change, multiple		1 (2%)	
Hematopoietic cell proliferation	2 (4%)		1 (2%)
Hemorrhage, focal			1 (2%)
Hyperplasia, focal	1 (2%)		
Hypertrophy, focal	1 (2%)		1 (2%)
Capsule, accessory adrenal cortical nodule	2 (4%)	4 (8%)	
Adrenal gland, medulla	(50)	(49)	(46)
Hemorrhage		2 (4%)	
Hyperplasia, focal	6 (12%)	14 (29%)	8 (17%)
Pigmentation, hemosiderin		2 (4%)	
Islets, pancreatic	(50)	(50)	(47)
Hyperplasia		1 (2%)	1 (2%)
Hyperplasia, focal	5 (10%)		1 (2%)
Parathyroid gland	(49)	(48)	(47)
Hyperplasia	3 (6%)	4 (8%)	3 (6%)
Pituitary gland	(50)	(49)	(50)
Pars distalis, angiectasis	16 (32%)	20 (41%)	17 (34%)
Pars distalis, cyst	3 (6%)	4 (8%)	2 (4%)
Pars distalis, hemorrhage	1 (2%)		
Pars distalis, hyperplasia, focal	13 (26%)	9 (18%)	12 (24%)
Pars distalis, pigmentation, hematoidin		2 (4%)	
Pars distalis, pigmentation, hemosiderin	5 (10%)	14 (29%)	6 (12%)
Pars nervosa, cyst		1 (2%)	
Thyroid gland	(50)	(50)	(50)
Ultimobranchial cyst	1 (2%)		
C-cell, hyperplasia, focal	3 (6%)	7 (14%)	4 (8%)
C-cell, hyperplasia, multifocal	1 (2%)	2 (4%)	
Follicle, cyst	1 (2%)	5 (10%)	2 (4%)
GENERAL BODY SYSTEM			
None			

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

	Vehicle Control	30 mg/kg	60 mg/kg
GENITAL SYSTEM			
Coagulating gland		(1)	
Inflammation, subacute		1 (100%)	
Epididymis	(50)	(50)	(50)
Inflammation, subacute	1 (2%)		
Preputial gland	(49)	(50)	(47)
Foreign body	1 (2%)		
Inflammation, granulomatous	4 (8%)		3 (6%)
Inflammation, granulomatous, focal	1 (2%)		
Inflammation, subacute	6 (12%)	11 (22%)	5 (11%)
Inflammation, suppurative, acute	1 (2%)		
Duct, cyst	1 (2%)	5 (10%)	1 (2%)
Prostate	(50)	(50)	(50)
Inflammation, subacute	23 (46%)	19 (38%)	18 (36%)
Inflammation, suppurative, acute		1 (2%)	
Seminal vesicle	(47)	(50)	(50)
Dilatation	1 (2%)		1 (2%)
Inflammation, chronic		1 (2%)	
Inflammation, subacute			1 (2%)
Inflammation, suppurative, acute	1 (2%)		
Testes	(50)	(50)	(50)
Atrophy	6 (12%)	3 (6%)	11 (22%)
Developmental malformation	1 (2%)		
Mineralization		3 (6%)	1 (2%)
HEMATOPOIETIC SYSTEM			
Blood	(2)		
Anemia	2 (100%)		
Bone marrow	(50)	(50)	(50)
Hyperplasia	5 (10%)	4 (8%)	4 (8%)
Lymph node	(50)	(50)	(48)
Deep cervical, ectasia		1 (2%)	
Deep cervical, hyperplasia		1 (2%)	
Inguinal, ectasia	1 (2%)		
Inguinal, inflammation, suppurative, acute	1 (2%)		
Mediastinal, congestion	1 (2%)	1 (2%)	2 (4%)
Mediastinal, ectasia			2 (4%)
Mediastinal, pigmentation, hemosiderin			1 (2%)
Pancreatic, ectasia	1 (2%)		1 (2%)
Lymph node, mandibular	(49)	(49)	(47)
Ectasia	9 (18%)	6 (12%)	6 (13%)
Hyperplasia	1 (2%)		1 (2%)
Lymph node, mesenteric	(48)	(49)	(46)
Congestion	2 (4%)		
Spleen	(50)	(50)	(49)
Fibrosis, focal	1 (2%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	9 (18%)	5 (10%)	5 (10%)
Hemorrhage	1 (2%)		
Necrosis, focal		1 (2%)	
Necrosis, multifocal		1 (2%)	1 (2%)
Thrombus			1 (2%)
Thymus	(43)	(48)	(38)
Cyst		1 (2%)	
INTEGUMENTARY SYSTEM			
Mammary gland	(45)	(49)	(47)
Duct, cyst	21 (47%)	27 (55%)	24 (51%)
Skin	(50)	(50)	(49)
Inflammation, suppurative, acute, focal		1 (2%)	

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

	Vehicle Control	30 mg/kg	60 mg/kg
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Fibrous osteodystrophy		4 (8%)	2 (4%)
Skeletal muscle	(1)		(2)
Inflammation, granulomatous, multifocal			1 (50%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Compression	4 (8%)	2 (4%)	3 (6%)
Fungus			1 (2%)
Hemorrhage, multifocal	1 (2%)	1 (2%)	2 (4%)
Hydrocephalus	1 (2%)		
Inflammation, suppurative, acute			1 (2%)
Necrosis			1 (2%)
Thrombus, multiple			1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Congestion	7 (14%)	9 (18%)	9 (18%)
Foreign body	7 (14%)	8 (16%)	8 (16%)
Fungus			1 (2%)
Granuloma, multiple	6 (12%)	2 (4%)	
Hemorrhage, multifocal		1 (2%)	
Infiltration cellular, histiocytic, multifocal	1 (2%)	2 (4%)	1 (2%)
Inflammation, suppurative, acute, focal			2 (4%)
Necrosis, multifocal		1 (2%)	1 (2%)
Pigmentation, multifocal		1 (2%)	
Thrombus, multiple			1 (2%)
Alveolar epithelium, hyperplasia, focal	1 (2%)		3 (6%)
Alveolar epithelium, hyperplasia, multifocal		1 (2%)	
Fat, mediastinum, necrosis, multifocal		1 (2%)	
Mediastinum, foreign body		1 (2%)	1 (2%)
Pleura, fibrosis, focal		1 (2%)	
Nose	(50)	(49)	(50)
Foreign body	4 (8%)	10 (20%)	4 (8%)
Fungus	13 (26%)	10 (20%)	10 (20%)
Inflammation, suppurative, acute	13 (26%)	13 (27%)	10 (20%)
Mucosa, hyperkeratosis, focal	1 (2%)		
Mucosa, hyperplasia, focal	1 (2%)		
Nasolacrimal duct, cyst			1 (2%)
Nasolacrimal duct, foreign body	1 (2%)	2 (4%)	1 (2%)
Nasolacrimal duct, inflammation, subacute	4 (8%)	10 (20%)	5 (10%)
Nasolacrimal duct, inflammation, suppurative, acute	5 (10%)	1 (2%)	
Nasopharyngeal duct, cyst		1 (2%)	
Nasopharyngeal duct, foreign body			1 (2%)
Nasopharyngeal duct, inflammation, subacute		1 (2%)	1 (2%)
SPECIAL SENSES SYSTEM			
Eye	(4)	(2)	(3)
Cataract	2 (50%)	2 (100%)	3 (100%)
Retina, degeneration	3 (75%)	2 (100%)	3 (100%)

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

	Vehicle Control	30 mg/kg	60 mg/kg
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Developmental malformation		1 (2%)	
Hydronephrosis		1 (2%)	1 (2%)
Inflammation, suppurative, acute, multifocal		1 (2%)	
Nephropathy, chronic	42 (84%)	43 (86%)	43 (86%)
Capsule, fibrosis, focal		1 (2%)	
Cortex, cyst	3 (6%)	3 (6%)	
Papilla, necrosis		1 (2%)	
Pelvis, inflammation, suppurative, acute		1 (2%)	
Renal tubule, dilatation, multifocal		1 (2%)	
Renal tubule, mineralization, multifocal		1 (2%)	
Renal tubule, pigmentation, hemosiderin, multifocal		1 (2%)	1 (2%)
Urinary bladder	(50)	(50)	(49)
Hemorrhage			1 (2%)
Inflammation, suppurative, acute		1 (2%)	

APPENDIX B

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

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

	Vehicle Control	30 mg/kg	60 mg/kg
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Dead	9	5	4
Moribund	9	11	9
Dosing accident	4	2	19
Survivors			
Dead			1
Terminal sacrifice	28	32	17
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, colon	(49)	(50)	(49)
Sarcoma stromal, metastatic, uterus		1 (2%)	
Liver	(50)	(50)	(50)
Mesentery	(8)	(10)	(11)
Sarcoma	1 (13%)		
Pancreas	(50)	(50)	(48)
Acinus, adenoma			1 (2%)
Pharynx		(1)	
Papilloma squamous		1 (100%)	
Stomach, forestomach	(50)	(50)	(50)
Papilloma squamous		1 (2%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)
Tongue		(2)	
Papilloma squamous		1 (50%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(49)	(50)	(50)
Adenoma		1 (2%)	
Adrenal gland, medulla	(47)	(50)	(50)
Pheochromocytoma malignant	1 (2%)		1 (2%)
Pheochromocytoma complex		1 (2%)	1 (2%)
Pheochromocytoma benign	2 (4%)	1 (2%)	
Islets, pancreatic	(50)	(50)	(48)
Adenoma		1 (2%)	1 (2%)
Pituitary gland	(49)	(50)	(50)
Pars distalis, adenoma	23 (47%)	28 (56%)	12 (24%)
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	4 (8%)	2 (4%)	1 (2%)
C-cell, carcinoma		1 (2%)	
Follicular cell, adenoma			1 (2%)
Follicular cell, carcinoma	1 (2%)	1 (2%)	
GENERAL BODY SYSTEM			
None			

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

	Vehicle Control	30 mg/kg	60 mg/kg
GENITAL SYSTEM			
Clitoral gland	(50)	(49)	(47)
Adenoma	2 (4%)	4 (8%)	1 (2%)
Carcinoma	2 (4%)	1 (2%)	2 (4%)
Ovary	(50)	(50)	(50)
Granulosa cell tumor malignant	1 (2%)		
Uterus	(50)	(50)	(49)
Adenoma		1 (2%)	
Hemangioma			1 (2%)
Polyp		1 (2%)	
Polyp stromal	10 (20%)	8 (16%)	13 (27%)
Polyp stromal, multiple	2 (4%)		1 (2%)
Sarcoma stromal	2 (4%)		
Cervix, sarcoma stromal		2 (4%)	
Vagina		(1)	
Polyp		1 (100%)	
HEMATOPOIETIC SYSTEM			
Blood		(1)	(2)
Bone marrow	(50)	(47)	(50)
Lymph node	(50)	(50)	(49)
Lymph node, mandibular	(50)	(50)	(49)
Lymph node, mesenteric	(49)	(50)	(49)
Spleen	(50)	(50)	(50)
Thymus	(47)	(48)	(49)
INTEGUMENTARY SYSTEM			
Mammary gland	(49)	(50)	(50)
Adenocarcinoma	2 (4%)	3 (6%)	1 (2%)
Fibroadenoma	10 (20%)	10 (20%)	11 (22%)
Fibroadenoma, multiple	2 (4%)	4 (8%)	5 (10%)
Skin	(50)	(50)	(50)
Subcutaneous tissue, fibrosarcoma		1 (2%)	
Subcutaneous tissue, lipoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Cranium, fibrosarcoma, metastatic, skin		1 (2%)	
NERVOUS SYSTEM			
Brain	(50)	(50)	(49)
Glioma malignant	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)	
Alveolar/bronchiolar carcinoma		1 (2%)	
Mediastinum, schwannoma malignant		1 (2%)	
Nose	(50)	(50)	(50)
SPECIAL SENSES SYSTEM			
None			

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

	Vehicle Control	30 mg/kg	60 mg/kg
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Cortex, adenoma	1 (2%)		
Urinary bladder	(49)	(50)	(48)
Sarcoma stromal, metastatic, uterus		1 (2%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	18 (36%)	15 (30%)	8 (16%)
TUMOR SUMMARY			
Total animals with primary neoplasms **	43	44	33
Total primary neoplasms	85	93	63
Total animals with benign neoplasms	36	38	32
Total benign neoplasms	56	66	50
Total animals with malignant neoplasms	24	24	9
Total malignant neoplasms	29	27	13
Total animals with secondary neoplasms ***		2	
Total secondary neoplasms		3	

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

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

DAYS ON STUDY	177	178	210	217	567	667	571	585	589	592	605	606	606	626	631	637	645	686	690	692	697	703	729	729	729
CARCASS ID	391	351	352	331	311	341	401	361	342	371	321	362	363	332	392	381	393	333	382	334	364	372	312	313	314
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+					+						+	+					+					
Sarcoma																				X					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	
Adrenal gland, medulla	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	
Pheochromocytoma malignant																	X								
Pheochromocytoma benign																					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X		X	X	X			X	X				X	X	X	X		X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									X
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal								X								X	X				X				
Polyp stromal, multiple																									
Sarcoma stromal											X										X				
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma							X													X					
Fibroadenoma													X	X					X			X		X	
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant								X																	
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																		+							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortex, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X		X		X		X	X		X		X		X		X				X	

+: Tissue examined microscopically
: Not examined
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

DAYS ON STUDY	729	729	729	729	729	730	730	730	730	730	730	730	731	731	731	731	731	731	731	732	732	732	732	732	TOTAL:
CARCASS ID	315	322	323	324	325	335	343	344	345	353	354	355	365	373	374	375	383	384	385	394	395	402	403	404	405	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery											+		+								+					8
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma malignant																										1
Pheochromocytoma benign															X											2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X			X	X	X				X				X	X			X			X	X		23
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	50
C-cell, adenoma		X											X	X												4
Follicular cell, carcinoma										X																1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X												X		2
Carcinoma		X									X															2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant																			X							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X			X			X						X										X			10
Polyp stromal, multiple																				X	X					2
Sarcoma stromal																										2
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										2
Fibroadenoma					X	X								X			X			X						10
Fibroadenoma, multiple	X																							X		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye													+		+											3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortex, adenoma												X														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X													X	X	X		X					X	X		18

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL: 30 mg/kg

DAYS ON STUDY	3 4 6	3 5 4	3 8 8	4 5 9	4 6 5	5 3 1	5 6 2	5 8 2	5 9 9	6 1 0	6 1 1	6 1 8	6 3 3	6 5 4	6 6 1	6 6 8	7 0 0	7 0 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
CARCASS ID	5 2 1	5 4 1	5 4 2	5 2 2	5 9 1	5 5 1	5 7 1	5 6 1	5 2 3	5 9 2	5 8 1	5 4 3	5 2 4	5 6 2	5 4 4	5 3 1	5 3 2	5 9 3	5 1 1	5 1 2	5 1 3	5 1 4	5 1 5	5 2 5	5 3 3
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus			X																						
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery											●				+						+				+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									
Papilloma squamous																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue								+					+												
Papilloma squamous								X																	
CARDIOVASCULAR SYSTEM																									
Blood vessel																	●								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X	X		X	X				X	X		X	X	X		X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma									X															X	
C-cell, carcinoma																									
Follicular cell, carcinoma																					X				
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Polyp																									
Polyp stromal									X	X	X			X											
Cervix, sarcoma stromal			X																			X			
Vagina					+																				
Polyp					X																				

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 30 mg/kg (Continued)

DAYS ON STUDY	731	731	731	732	732	732	732	732	732	732	732	732	732	732	735	735	735	735	735	735	735	735	735	735	TOTAL:
CARCASS ID	534	535	545	552	553	554	555	563	564	565	572	573	574	575	582	583	584	585	594	595	601	602	603	604	605	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery							+							+			+		+	+				+		10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																				+						1
Papilloma squamous																				X						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous											X															1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										2
Papilloma squamous																										1
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex															X											1
Pheochromocytoma benign																	X									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X		X			X	X	X			X	X		X		X		X	X	X		X	X	28
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										2
C-cell, carcinoma							X																			1
Follicular cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X								X	X												4
Carcinoma																						X				1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Polyp									X																	1
Polyp stromal						X										X	X		X							8
Cervix, sarcoma stromal																										2
Vagina																										1
Polyp																										1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 30 mg/kg (Continued)

DAYS ON STUDY	346	354	388	459	465	531	562	582	599	610	611	618	633	654	661	668	700	709	731	731	731	731	731	731	731
CARCASS ID	521	541	542	522	591	551	571	561	523	592	581	543	524	562	544	531	532	593	511	512	513	514	515	525	533
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								X	
Fibroadenoma								X						X						X	X	X	X		
Fibroadenoma, multiple																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma												X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, fibrosarcoma, metastatic, skin												X													
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar carcinoma																									
Mediastinum, schwannoma malignant																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus			X																						
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X									X	X						X	X				

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 30 mg/kg (Continued)

DAYS ON STUDY	731	731	731	732	732	732	732	732	732	732	732	732	732	732	735	735	735	735	735	735	735	735	735	735	735	TOTAL:
CARCASS ID	534	535	545	552	553	554	555	563	564	565	572	573	574	575	582	583	584	585	594	595	601	602	603	604	605	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																+										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma					X																X					3
Fibroadenoma						X					X	X		X												10
Fibroadenoma, multiple			X										X												X	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, fibrosarcoma, metastatic, skin																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																	X									1
Mediastinum, schwannoma malignant															X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye		+												+	+					+						4
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X	X				X					X		X	X		X		X				X		15

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL: 60 mg/kg

DAYS ON STUDY	161	267	267	297	297	297	297	327	327	374	378	438	440	466	509	557	561	564	564	602	627	632	653	654	662
CARCASS ID	501	481	491	411	412	441	471	431	472	421	473	492	451	611	622	502	493	442	482	484	432	485	452	413	463
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery	+															+		+		+		+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																			X						
Pheochromocytoma complex																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	
Adenoma																	X								
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pars distalis, adenoma											X								X			X	X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
C-cell, adenoma																									
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																							X		
Polyp stromal									X						X			X					X		
Polyp stromal, multiple																									
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma																			X	X					X
Fibroadenoma, multiple																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, lipoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X	X	X				X

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 60 mg/kg (Continued)

DAYS ON STUDY	6 9 4	6 9 4	6 9 8	6 9 8	7 0 8	7 0 9	7 1 7	7 2 9	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	7 3 0	TOTAL:
CARCASS ID	4 9 4	4 9 5	4 4 3	5 0 3	4 3 3	4 6 4	4 2 2	4 2 3	4 3 4	4 7 4	4 7 5	4 1 4	4 1 5	4 2 4	4 2 5	4 3 5	4 4 4	4 4 5	4 5 3	4 5 4	4 5 5	4 6 5	4 8 3	5 0 4	5 0 5	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+						+	+		+							+		+					11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinus, adenoma												X														1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma complex																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma							X			X					X			X				X			X	12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																							X			1
Follicular cell, adenoma																		X								1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Adenoma	X																									1
Carcinoma						X															X					2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Polyp stromal	X			X	X				X								X		X	X			X		X	13
Polyp stromal, multiple							X																			1
HEMATOPOIETIC SYSTEM																										
Blood								+	+																	2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																					X					1
Fibroadenoma						X		X	X										X		X	X	X	X		11
Fibroadenoma, multiple		X	X				X				X															5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, lipoma																			X							1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye						+															+					2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X		X							X										X	8

TABLE B3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL

	Vehicle Control	30 mg/kg	60 mg/kg
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma			
Overall Rates (a)	3/47 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	9.8%	6.3%	3.2%
Terminal Rates (c)	1/27 (4%)	2/32 (6%)	0/18 (0%)
Day of First Observation	645	729	602
Life Table Tests (d)	P=0.314N	P=0.435N	P=0.417N
Logistic Regression Tests (d)	P=0.261N	P=0.466N	P=0.338N
Cochran-Armitage Trend Test (d)	P=0.203N		
Fisher Exact Test (d)		P=0.470N	P=0.285N
Clitoral Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	4/49 (8%)	1/47 (2%)
Adjusted Rates (b)	7.1%	12.5%	4.0%
Terminal Rates (c)	2/28 (7%)	4/32 (13%)	0/17 (0%)
Day of First Observation	729	729	694
Life Table Tests (d)	P=0.583N	P=0.399	P=0.635N
Logistic Regression Tests (d)	P=0.549N	P=0.399	P=0.616N
Cochran-Armitage Trend Test (d)	P=0.431N		
Fisher Exact Test (d)		P=0.329	P=0.523N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	5/49 (10%)	3/47 (6%)
Adjusted Rates (b)	14.3%	15.6%	14.2%
Terminal Rates (c)	4/28 (14%)	5/32 (16%)	1/17 (6%)
Day of First Observation	729	729	694
Life Table Tests (d)	P=0.487	P=0.585	P=0.582
Logistic Regression Tests (d)	P=0.535	P=0.585	P=0.629
Cochran-Armitage Trend Test (d)	P=0.462N		
Fisher Exact Test (d)		P=0.487	P=0.535N
Mammary Gland: Fibroadenoma			
Overall Rates (e)	12/50 (24%)	14/50 (28%)	16/50 (32%)
Adjusted Rates (b)	36.7%	39.5%	60.2%
Terminal Rates (c)	8/28 (29%)	11/32 (34%)	8/18 (44%)
Day of First Observation	606	582	602
Life Table Tests (d)	P=0.032	P=0.549	P=0.045
Logistic Regression Tests (d)	P=0.052	P=0.460	P=0.062
Cochran-Armitage Trend Test (d)	P=0.218		
Fisher Exact Test (d)		P=0.410	P=0.252
Mammary Gland: Adenocarcinoma			
Overall Rates (e)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	5.4%	9.4%	5.6%
Terminal Rates (c)	0/28 (0%)	3/32 (9%)	1/18 (6%)
Day of First Observation	571	729	729
Life Table Tests (d)	P=0.541N	P=0.542	P=0.615N
Logistic Regression Tests (d)	P=0.478N	P=0.514	P=0.545N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (e)	14/50 (28%)	17/50 (34%)	16/50 (32%)
Adjusted Rates (b)	40.1%	48.2%	60.2%
Terminal Rates (c)	8/28 (29%)	14/32 (44%)	8/18 (44%)
Day of First Observation	571	582	602
Life Table Tests (d)	P=0.072	P=0.482	P=0.101
Logistic Regression Tests (d)	P=0.118	P=0.378	P=0.149
Cochran-Armitage Trend Test (d)	P=0.374		
Fisher Exact Test (d)		P=0.333	P=0.414

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

	Vehicle Control	30 mg/kg	60 mg/kg
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	23/49 (47%)	28/50 (56%)	12/50 (24%)
Adjusted Rates (b)	61.1%	71.4%	46.8%
Terminal Rates (c)	13/27 (48%)	21/32 (66%)	6/18 (33%)
Day of First Observation	571	562	438
Life Table Tests (d)	P=0.215N	P=0.455	P=0.210N
Logistic Regression Tests (d)	P=0.060N	P=0.292	P=0.055N
Cochran-Armitage Trend Test (d)	P=0.013N		
Fisher Exact Test (d)		P=0.242	P=0.014N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	14.3%	5.4%	5.6%
Terminal Rates (c)	4/28 (14%)	1/32 (3%)	1/18 (6%)
Day of First Observation	729	599	729
Life Table Tests (d)	P=0.201N	P=0.284N	P=0.331N
Logistic Regression Tests (d)	P=0.170N	P=0.315N	P=0.331N
Cochran-Armitage Trend Test (d)	P=0.119N		
Fisher Exact Test (d)		P=0.339N	P=0.181N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	14.3%	8.5%	5.6%
Terminal Rates (c)	4/28 (14%)	2/32 (6%)	1/18 (6%)
Day of First Observation	729	599	729
Life Table Tests (d)	P=0.233N	P=0.434N	P=0.331N
Logistic Regression Tests (d)	P=0.196N	P=0.472N	P=0.331N
Cochran-Armitage Trend Test (d)	P=0.133N		
Fisher Exact Test (d)		P=0.500N	P=0.181N
Uterus: Stromal Polyp			
Overall Rates (e)	12/50 (24%)	9/50 (18%)	14/50 (28%)
Adjusted Rates (b)	36.4%	23.8%	51.0%
Terminal Rates (c)	8/28 (29%)	5/32 (16%)	6/18 (33%)
Day of First Observation	585	599	327
Life Table Tests (d)	P=0.114	P=0.230N	P=0.117
Logistic Regression Tests (d)	P=0.214	P=0.283N	P=0.219
Cochran-Armitage Trend Test (d)	P=0.360		
Fisher Exact Test (d)		P=0.312N	P=0.410
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (e)	18/50 (36%)	15/50 (30%)	8/50 (16%)
Adjusted Rates (b)	45.0%	42.0%	31.2%
Terminal Rates (c)	8/28 (29%)	12/32 (38%)	3/18 (17%)
Day of First Observation	210	459	602
Life Table Tests (d)	P=0.127N	P=0.245N	P=0.160N
Logistic Regression Tests (d)	P=0.032N	P=0.319N	P=0.035N
Cochran-Armitage Trend Test (d)	P=0.016N		
Fisher Exact Test (d)		P=0.335N	P=0.020N
All Sites: Benign Tumors			
Overall Rates (e)	36/50 (72%)	38/50 (76%)	32/50 (64%)
Adjusted Rates (b)	85.6%	90.3%	91.3%
Terminal Rates (c)	22/28 (79%)	28/32 (88%)	15/18 (83%)
Day of First Observation	571	465	327
Life Table Tests (d)	P=0.105	P=0.431N	P=0.131
Logistic Regression Tests (d)	P=0.301	P=0.493	P=0.364
Cochran-Armitage Trend Test (d)	P=0.220N		
Fisher Exact Test (d)		P=0.410	P=0.260N

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

	Vehicle Control	30 mg/kg	60 mg/kg
All Sites: Malignant Tumors			
Overall Rates (e)	24/50 (48%)	24/50 (48%)	9/50 (18%)
Adjusted Rates (b)	57.2%	64.1%	35.8%
Terminal Rates (c)	11/28 (39%)	19/32 (59%)	4/18 (22%)
Day of First Observation	210	388	602
Life Table Tests (d)	P=0.048N	P=0.407N	P=0.053N
Logistic Regression Tests (d)	P=0.004N	P=0.549N	P=0.004N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.579N	P=0.001N
All Sites: All Tumors			
Overall Rates (e)	43/50 (86%)	44/50 (88%)	33/50 (66%)
Adjusted Rates (b)	93.5%	95.6%	91.6%
Terminal Rates (c)	25/28 (89%)	30/32 (94%)	15/18 (83%)
Day of First Observation	210	388	327
Life Table Tests (d)	P=0.349	P=0.343N	P=0.372
Logistic Regression Tests (d)	P=0.104N	P=0.594N	P=0.159N
Cochran-Armitage Trend Test (d)	P=0.009N		
Fisher Exact Test (d)		P=0.500	P=0.017N

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

TABLE B4. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL NEOPLASMS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Papillomas or Carcinomas in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	1/50
Benzyl acetate	0/49
Allyl isovalerate	1/50
HC Red No. 3	0/50
C.I. Acid Orange 3	0/50
Chlorinated paraffins (C_{23}, 43% chlorine)	0/50
Chlorinated paraffins (C_{12}, 60% chlorine)	0/50
Allyl isothiocyanate	0/50
Geranyl acetate	1/50
TOTAL	(b) 3/449 (0.7%)
SD (c)	1.00%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 9/2,135 (0.4%)
SD (c)	0.94%
Range (d)	
High	(b) 2/49
Low	0/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Squamous cell papillomas
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one papilloma, NOS, seven squamous cell papillomas, and one squamous cell carcinoma

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

	Vehicle Control	30 mg/kg	60 mg/kg
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Dead	9	5	4
Moribund	9	11	9
Dosing accident	4	2	19
Survivors			
Dead			1
Terminal sacrifice	28	32	17
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(49)	(50)	(48)
Parasite metazoan		1 (2%)	1 (2%)
Intestine large, colon	(49)	(50)	(49)
Cyst		1 (2%)	
Parasite metazoan	4 (8%)	2 (4%)	2 (4%)
Intestine large, rectum	(50)	(50)	(47)
Parasite metazoan	3 (6%)	7 (14%)	3 (6%)
Liver	(50)	(50)	(50)
Angiectasis, focal		2 (4%)	2 (4%)
Basophilic focus	39 (78%)	45 (90%)	40 (80%)
Clear cell focus	8 (16%)	10 (20%)	14 (28%)
Degeneration, cystic		1 (2%)	
Eosinophilic focus		1 (2%)	
Fatty change	1 (2%)		
Fatty change, diffuse		2 (4%)	1 (2%)
Fatty change, focal		1 (2%)	
Granuloma, multiple	11 (22%)	22 (44%)	13 (26%)
Hematopoietic cell proliferation		1 (2%)	2 (4%)
Hepatodiaphragmatic nodule	3 (6%)	4 (8%)	5 (10%)
Hyperplasia, focal	2 (4%)	1 (2%)	2 (4%)
Mixed cell focus			2 (4%)
Necrosis, focal	2 (4%)		1 (2%)
Necrosis, multifocal		1 (2%)	1 (2%)
Vacuolization cytoplasmic, focal		1 (2%)	
Bile duct, hyperplasia	34 (68%)	28 (56%)	24 (48%)
Centrilobular, fatty change		2 (4%)	1 (2%)
Centrilobular, necrosis	10 (20%)	9 (18%)	4 (8%)
Hepatocyte, cytomegaly	1 (2%)		
Mesentery	(8)	(10)	(11)
Hemorrhage			1 (9%)
Fat, necrosis, focal	6 (75%)	10 (100%)	6 (55%)
Pancreas	(50)	(50)	(48)
Acinus, atrophy, focal	2 (4%)	5 (10%)	
Acinus, atrophy, multifocal	9 (18%)	6 (12%)	4 (8%)
Acinus, basophilic focus		1 (2%)	
Acinus, hyperplasia, focal		2 (4%)	1 (2%)
Acinus, hyperplasia, multifocal		1 (2%)	
Duct, ectasia	1 (2%)		
Salivary glands	(50)	(50)	(49)
Atrophy, multifocal	1 (2%)		
Inflammation, subacute		1 (2%)	1 (2%)

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

	Vehicle Control	30 mg/kg	60 mg/kg
ALIMENTARY SYSTEM (Continued)			
Stomach, forestomach	(50)	(50)	(50)
Erosion			1 (2%)
Hyperkeratosis		1 (2%)	
Hyperplasia	2 (4%)	4 (8%)	3 (6%)
Inflammation, subacute	2 (4%)	3 (6%)	2 (4%)
Mineralization			1 (2%)
Ulcer	2 (4%)	4 (8%)	
Stomach, glandular	(50)	(50)	(50)
Erosion		1 (2%)	1 (2%)
Erosion, multiple		1 (2%)	
Inflammation, subacute	1 (2%)	1 (2%)	1 (2%)
Mineralization	9 (18%)	9 (18%)	5 (10%)
Ulcer	1 (2%)	1 (2%)	1 (2%)
Tongue		(2)	
Foreign body		1 (50%)	
Granuloma		1 (50%)	
CARDIOVASCULAR SYSTEM			
Blood vessel		(1)	
Aorta, mineralization		1 (100%)	
Heart	(50)	(50)	(50)
Cardiomyopathy	16 (32%)	24 (48%)	18 (36%)
Inflammation, chronic, multifocal		1 (2%)	
Mineralization, multifocal		1 (2%)	
Valve, thrombus			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(49)	(50)	(50)
Focal cellular change	7 (14%)	9 (18%)	5 (10%)
Hematopoietic cell proliferation			3 (6%)
Hyperplasia	1 (2%)		
Hyperplasia, focal			2 (4%)
Hypertrophy, focal	1 (2%)		
Inflammation, granulomatous		1 (2%)	
Mineralization, multifocal		1 (2%)	
Necrosis, multifocal		1 (2%)	
Capsule, accessory adrenal cortical nodule	1 (2%)	5 (10%)	2 (4%)
Adrenal gland, medulla	(47)	(50)	(50)
Hyperplasia, focal	4 (9%)	5 (10%)	7 (14%)
Infiltration cellular, lymphocytic, multifocal	1 (2%)		
Islets, pancreatic	(50)	(50)	(48)
Hyperplasia	2 (4%)		
Hyperplasia, focal			1 (2%)
Parathyroid gland	(48)	(48)	(48)
Hyperplasia		1 (2%)	
Pituitary gland	(49)	(50)	(50)
Hyperplasia, focal			1 (2%)
Pars distalis, angiectasis	27 (55%)	30 (60%)	19 (38%)
Pars distalis, cyst	24 (49%)	16 (32%)	22 (44%)
Pars distalis, hyperplasia	1 (2%)	1 (2%)	1 (2%)
Pars distalis, hyperplasia, focal	12 (24%)	10 (20%)	17 (34%)
Pars distalis, pigmentation, hemosiderin	18 (37%)	22 (44%)	7 (14%)
Thyroid gland	(50)	(50)	(50)
Ultimobranchial cyst	1 (2%)	1 (2%)	1 (2%)
C-cell, hyperplasia, focal	11 (22%)	15 (30%)	11 (22%)
Follicle, cyst	1 (2%)	3 (6%)	1 (2%)
Follicular cell, hyperplasia	1 (2%)		

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

	Vehicle Control	30 mg/kg	60 mg/kg
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(50)	(49)	(47)
Inflammation, subacute	1 (2%)	3 (6%)	1 (2%)
Inflammation, suppurative, acute	2 (4%)	2 (4%)	
Duct, cyst	3 (6%)	5 (10%)	1 (2%)
Duct, cyst, multiple		1 (2%)	
Ovary	(50)	(50)	(50)
Cyst	7 (14%)	8 (16%)	7 (14%)
Inflammation, chronic			1 (2%)
Inflammation, granulomatous		1 (2%)	
Uterus	(50)	(50)	(49)
Cyst	1 (2%)	1 (2%)	1 (2%)
Fibrosis		1 (2%)	
Hemorrhage		1 (2%)	2 (4%)
Hydrometra	1 (2%)		1 (2%)
Hyperplasia, cystic	1 (2%)		
Neovascularization		1 (2%)	
Pigmentation, hemosiderin		1 (2%)	
Prolapse			1 (2%)
Cervix, abscess	1 (2%)		1 (2%)
Cervix, cyst	1 (2%)		1 (2%)
Cervix, hypertrophy		2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
Blood		(1)	(2)
Anemia			1 (50%)
Polychromasia			1 (50%)
Bone marrow	(50)	(47)	(50)
Hyperplasia	3 (6%)	6 (13%)	2 (4%)
Lymph node, mandibular	(50)	(50)	(49)
Ectasia	3 (6%)	3 (6%)	2 (4%)
Spleen	(50)	(50)	(50)
Atrophy		4 (8%)	
Fibrosis, focal	1 (2%)		
Hematopoietic cell proliferation	4 (8%)	6 (12%)	4 (8%)
Hemorrhage, focal	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(49)	(50)	(50)
Galactocele	1 (2%)		1 (2%)
Duct, cyst	44 (90%)	39 (78%)	29 (58%)
Duct, inflammation, suppurative, acute	1 (2%)		
Skin	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)		
Inflammation, subacute, focal	1 (2%)		
Subcutaneous tissue, abscess		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Fibrous osteodystrophy		1 (2%)	
Cranium, osteopetrosis	1 (2%)	2 (4%)	2 (4%)
Femur, osteopetrosis		3 (6%)	3 (6%)

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

	Vehicle Control	30 mg/kg	60 mg/kg
NERVOUS SYSTEM			
Brain	(50)	(50)	(49)
Compression	7 (14%)	8 (16%)	3 (6%)
Hemorrhage, multifocal	2 (4%)		1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Congestion	6 (12%)	6 (12%)	23 (46%)
Foreign body	5 (10%)	4 (8%)	19 (38%)
Granuloma, multiple	16 (32%)	15 (30%)	5 (10%)
Hemorrhage, multifocal		1 (2%)	
Infiltration cellular, histiocytic, multifocal	6 (12%)	6 (12%)	1 (2%)
Mineralization		1 (2%)	
Pigmentation, cholesterol, multifocal	4 (8%)	2 (4%)	
Alveolar epithelium, hyperplasia, focal		1 (2%)	
Nose	(50)	(50)	(50)
Fungus		1 (2%)	
Inflammation, suppurative, acute		2 (4%)	
Nasolacrimal duct, cyst		1 (2%)	
Nasolacrimal duct, foreign body	1 (2%)	1 (2%)	
Nasolacrimal duct, inflammation, subacute	8 (16%)	12 (24%)	6 (12%)
Nasolacrimal duct, inflammation, suppurative, acute	2 (4%)	2 (4%)	
SPECIAL SENSES SYSTEM			
Eye	(3)	(4)	(2)
Cataract	2 (67%)	4 (100%)	2 (100%)
Hemorrhage	1 (33%)		
Retina, degeneration	2 (67%)	4 (100%)	2 (100%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Hydronephrosis		1 (2%)	
Nephropathy, chronic	28 (56%)	39 (78%)	29 (58%)
Cortex, cyst		1 (2%)	1 (2%)
Medulla, inflammation, suppurative, acute	1 (2%)		
Papilla, necrosis	1 (2%)		
Renal tubule, dilatation, multifocal		1 (2%)	
Renal tubule, mineralization, focal		1 (2%)	
Renal tubule, mineralization, multifocal	1 (2%)	1 (2%)	
Urinary bladder	(49)	(50)	(48)
Inflammation, suppurative, acute	1 (2%)		

APPENDIX C

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

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Early deaths				
Dead	9	12	13	9
Moribund	6	8	12	8
Accidentally killed				6
Dosing accident		2		
Survivors				
Terminal sacrifice	35	28	24	27
Missing			1	
Animals examined microscopically	50	50	49	50
ALIMENTARY SYSTEM				
Gallbladder	(46)	(44)	(43)	(42)
Intestine large, cecum	(49)	(47)	(49)	(46)
Intestine large, rectum	(48)	(49)	(49)	(48)
Intestine small, ileum	(45)	(47)	(48)	(47)
Intestine small, jejunum	(47)	(46)	(47)	(45)
Polyp adenomatous			1 (2%)	
Liver	(50)	(50)	(49)	(50)
Carcinoma, metastatic, kidney				1 (2%)
Fibrosarcoma, extension, metastatic, mesentery			1 (2%)	
Hemangioma	1 (2%)			
Hemangiosarcoma	2 (4%)	4 (8%)	2 (4%)	
Hemangiosarcoma, two, multiple			1 (2%)	
Hemangiosarcoma, four, multiple		1 (2%)		
Hepatoblastoma	1 (2%)		1 (2%)	1 (2%)
Hepatocellular carcinoma	6 (12%)	12 (24%)	5 (10%)	15 (30%)
Hepatocellular carcinoma, multiple				1 (2%)
Hepatocellular carcinoma, two, multiple	1 (2%)		1 (2%)	4 (8%)
Hepatocellular carcinoma, three, multiple				1 (2%)
Hepatocellular adenoma	9 (18%)	12 (24%)	7 (14%)	14 (28%)
Hepatocellular adenoma, two				1 (2%)
Hepatocellular adenoma, two, multiple			4 (8%)	2 (4%)
Hepatocellular adenoma, three, multiple		1 (2%)		2 (4%)
Squamous cell carcinoma, metastatic, stomach	1 (2%)			
Mesentery	(4)	(3)	(5)	(5)
Carcinoma, metastatic, kidney				1 (20%)
Fibrosarcoma, extension, metastatic, skin			1 (20%)	
Fibrosarcoma, greater than five, multiple			1 (20%)	
Pancreas	(50)	(50)	(49)	(49)
Fibrosarcoma, extension, metastatic, mesentery			1 (2%)	
Salivary glands	(50)	(50)	(49)	(50)
Fibrosarcoma, extension, metastatic, skin	1 (2%)	1 (2%)	2 (4%)	
Stomach	(50)	(49)	(49)	(49)
Carcinoma, metastatic, seminal vesicle		1 (2%)		
Stomach, forestomach	(50)	(49)	(49)	(49)
Adenocarcinoma				1 (2%)
Fibrosarcoma, metastatic, mesentery			1 (2%)	
Papilloma squamous	1 (2%)			1 (2%)
Squamous cell carcinoma	1 (2%)			

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
CARDIOVASCULAR SYSTEM				
Heart	(50)	(50)	(49)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Carcinoma, metastatic, kidney				1 (2%)
Hemangiosarcoma	1 (2%)			
Sarcoma, metastatic, skeletal muscle				1 (2%)
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(50)	(50)	(49)	(50)
Capsule, fibrosarcoma, extension, metastatic, mesentery			1 (2%)	
Spindle cell, adenoma		1 (2%)		
Adrenal gland, medulla	(50)	(50)	(48)	(50)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma benign	2 (4%)	4 (8%)	2 (4%)	1 (2%)
Pheochromocytoma benign, multiple		1 (2%)		
Islets, pancreatic	(50)	(48)	(49)	(49)
Adenoma	1 (2%)			
Pituitary gland	(47)	(45)	(46)	(49)
Pars distalis, adenoma				2 (4%)
Thyroid gland	(49)	(50)	(48)	(50)
Follicular cell, adenoma	1 (2%)			2 (4%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Coagulating gland	(4)	(5)	(2)	(2)
Epididymis	(50)	(50)	(49)	(50)
Penis	(1)			
Fibrosarcoma	1 (100%)			
Preputial gland	(9)	(10)	(14)	(8)
Papilloma squamous			1 (7%)	
Prostate	(50)	(50)	(48)	(49)
Seminal vesicle	(50)	(50)	(48)	(50)
Carcinoma		1 (2%)		
Fibrosarcoma, extension, metastatic, mesentery			1 (2%)	
Testes	(50)	(50)	(49)	(50)
Interstitial cell, adenoma	1 (2%)		2 (4%)	
HEMATOPOIETIC SYSTEM				
Bone marrow	(50)	(49)	(49)	(50)
Hemangiosarcoma	1 (2%)	2 (4%)		1 (2%)
Lymph node	(50)	(50)	(49)	(50)
Axillary, histiocytic sarcoma			1 (2%)	
Iliac, histiocytic sarcoma			1 (2%)	
Inguinal, histiocytic sarcoma			1 (2%)	
Inguinal, squamous cell carcinoma, metastatic, skin				1 (2%)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Mediastinal, carcinoma, metastatic, kidney				1 (2%)
Mediastinal, carcinoma, metastatic, seminal vesicle		1 (2%)		
Mediastinal, fibrosarcoma, metastatic, mesentery			1 (2%)	

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
HEMATOPOIETIC SYSTEM				
Lymph node (Continued)	(50)	(50)	(49)	(50)
Pancreatic, histiocytic sarcoma			1 (2%)	
Pancreatic, squamous cell carcinoma, metastatic, stomach	1 (2%)			
Renal, histiocytic sarcoma			1 (2%)	
Lymph node, mandibular	(44)	(46)	(47)	(48)
Histiocytic sarcoma			1 (2%)	
Lymph node, mesenteric	(49)	(45)	(49)	(50)
Fibrosarcoma, metastatic, spleen	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Spleen	(50)	(50)	(48)	(49)
Fibrosarcoma	1 (2%)			
Hemangiosarcoma	2 (4%)	2 (4%)		
Thymus	(47)	(42)	(44)	(45)
Histiocytic sarcoma			1 (2%)	
Sarcoma, metastatic, skeletal muscle				1 (2%)
INTEGUMENTARY SYSTEM				
Skin	(50)	(50)	(49)	(50)
Basal cell adenoma			1 (2%)	
Keratoacanthoma		1 (2%)		
Papilloma squamous		2 (4%)		
Squamous cell carcinoma	1 (2%)			2 (4%)
Subcutaneous tissue, fibroma	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	2 (4%)	6 (12%)	10 (20%)	2 (4%)
Subcutaneous tissue, fibrosarcoma, multiple	1 (2%)			
Subcutaneous tissue, fibrous histiocytoma		1 (2%)		
Subcutaneous tissue, hemangioma		1 (2%)		
Subcutaneous tissue, hemangiosarcoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, sarcoma			1 (2%)	
MUSCULOSKELETAL SYSTEM				
Skeletal muscle	(1)	(3)	(2)	(1)
Alveolar/bronchiolar carcinoma, metastatic, two, multiple, lung		1 (33%)		
Fibrosarcoma, extension, metastatic, mesentery			1 (50%)	
Fibrosarcoma, extension, metastatic, skin			1 (50%)	
Hemangiosarcoma		1 (33%)		
Sarcoma				1 (100%)
Abdominal, carcinoma, metastatic, seminal vesicle		1 (33%)		
Diaphragm, carcinoma, metastatic, seminal vesicle		1 (33%)		
Intercostal, carcinoma, metastatic, seminal vesicle		1 (33%)		
NERVOUS SYSTEM				
Brain	(49)	(50)	(49)	(50)
Meningioma malignant		1 (2%)		
RESPIRATORY SYSTEM				
Lung	(50)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	9 (18%)	3 (6%)	2 (4%)	8 (16%)
Alveolar/bronchiolar carcinoma	3 (6%)	4 (8%)	2 (4%)	6 (12%)
Alveolar/bronchiolar carcinoma, greater than five, multiple		1 (2%)	1 (2%)	
Carcinoma, greater than five, metastatic, multiple, kidney				1 (2%)

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
RESPIRATORY SYSTEM				
Lung (Continued)	(50)	(50)	(49)	(50)
Carcinoma, greater than five, metastatic, multiple, seminal vesicle		1 (2%)		
Fibrosarcoma, metastatic			1 (2%)	
Fibrosarcoma, greater than five, metastatic, multiple, skin			1 (2%)	
Hemangiosarcoma		1 (2%)		
Hepatocellular carcinoma, metastatic, liver		2 (4%)		
Hepatocellular carcinoma, metastatic, two, multiple, liver				1 (2%)
Hepatocellular carcinoma, four, metastatic, multiple, liver		1 (2%)		
Hepatocellular carcinoma, greater than five, metastatic, multiple, liver		1 (2%)		1 (2%)
Sarcoma, metastatic, skeletal muscle				1 (2%)
Mediastinum, carcinoma, greater than five, metastatic, multiple, seminal vesicle		1 (2%)		
Mediastinum, fibrosarcoma, metastatic, mesentery			1 (2%)	
Nose	(49)	(50)	(49)	(50)
Polyp				1 (2%)
Trachea	(50)	(50)	(48)	(50)
Retinoblastoma, metastatic				1 (2%)
SPECIAL SENSES SYSTEM				
Harderian gland		(2)	(2)	(1)
Adenoma		2 (100%)	1 (50%)	1 (100%)
Carcinoma			1 (50%)	
URINARY SYSTEM				
Kidney	(50)	(50)	(49)	(50)
Carcinoma, metastatic, seminal vesicle		1 (2%)		
Cortex, adenoma			1 (2%)	1 (2%)
Cortex, carcinoma		1 (2%)		
Cortex, carcinoma, metastatic				1 (2%)
Urinary bladder	(49)	(50)	(49)	(49)
SYSTEMIC LESIONS				
Multiple organs	*(50)	*(50)	*(49)	*(50)
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic	2 (4%)		2 (4%)	1 (2%)
Lymphoma malignant mixed	3 (6%)	2 (4%)	5 (10%)	2 (4%)
TUMOR SUMMARY				
Total animals with primary neoplasms **	38	41	42	43
Total primary neoplasms	60	70	59	77
Total animals with benign neoplasms	24	24	20	30
Total benign neoplasms	28	29	24	37
Total animals with malignant neoplasms	22	31	27	33
Total malignant neoplasms	32	41	35	40
Total animals with secondary neoplasms ***	3	6	5	6
Total secondary neoplasms	4	16	15	13

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

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

DAYS ON STUDY	002	021	375	456	456	473	518	580	611	622	662	666	676	703	719	730	730	730	730	730	730	730	730	730	730
CARCASS ID	081	051	031	032	042	092	111	021	052	022	082	013	101	072	062	012	014	015	023	024	025	033	034	035	041
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	M	M	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma							X																		
Hemangiosarcoma														X											
Hepatoblastoma																						X			
Hepatocellular carcinoma				X				X								X						X			
Hepatocellular carcinoma, two, multiple										X															
Hepatocellular adenoma									X								X								
Squamous cell carcinoma, metastatic, stomach															X										
Mesentery											+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, extension, metastatic, skin									X																
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Squamous cell carcinoma															X										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth											+		+						+	+	+	+	+	+	
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																X									
Pheochromocytoma benign																	X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	M	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland																								+	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																		+							
Fibrosarcoma																		X							
Preputial gland						+	+	+					+										+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																					X				

+: Tissue examined microscopically
: Not examined
I: Insufficient tissue
M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

DAYS ON STUDY	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	0443	0444	0445	0553	0554	0555	0561	0563	0564	0565	0571	0573	0574	0575	0583	0584	0585	0591	0593	0594	0595	1002	1003	1004	1005	TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma													X													2
Hepatoblastoma																										1
Hepatocellular carcinoma					X																X					6
Hepatocellular carcinoma, two, multiple																										1
Hepatocellular adenoma				X			X					X		X	X			X							X	9
Squamous cell carcinoma, metastatic, *stomach*																										1
Mesentery													+	+					+							4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, extension, metastatic, skin																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous						X																				1
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+		+	+	+			+	+		+	+		+	+		+	+	+	+	+	+	+	27
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign												X														2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																				X						1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland																+								+	+	4
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Fibrosarcoma																										1
Preputial gland			+								+										+	+				9
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

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

DAYS ON STUDY	002	021	375	456	456	473	518	580	611	622	662	666	676	703	719	730	730	730	730	730	730	730	730	730	730
CARCASS ID	081	051	031	032	042	092	111	021	052	022	082	013	011	072	062	012	014	015	023	024	025	033	034	035	041
HEMATOPOIETIC SYSTEM																									
Blood												+													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic, squamous cell carcinoma, metastatic, stomach															X										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Hemangiosarcoma														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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma					X																				
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma												X													
Subcutaneous tissue, fibrosarcoma, multiple									X																
Subcutaneous tissue, hemangiosarcoma														X											
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+																			
NERVOUS SYSTEM																									
Brain	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord													+												
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X								X					
Alveolar/bronchiolar carcinoma															X										
Nose	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
None																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																								X	
Lymphoma malignant mixed											X												X		

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

DAYS ON STUDY	730	730	730	730	730	730	730	730	730	730	730	730	730	730	732	732	732	732	732	732	732	732	732	732	TOTAL:
CARCASS ID	043	044	045	053	054	055	061	063	064	065	071	073	074	075	083	084	085	091	093	094	095	102	103	104	105	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreatic, squamous cell carcinoma, metastatic, stomach																										1
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, spleen						X																				1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma						X																				1
Hemangiosarcoma													X													2
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	M	+	M	M	M	M	M	M	+	M	M	M	M	M	M	M	+	+	M	M	M	M	M	9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma							X	X		X																3
Subcutaneous tissue, fibrosarcoma										X																2
Subcutaneous tissue, fibrosarcoma, multiple																										1
Subcutaneous tissue, hemangiosarcoma													X													2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X		X				X					X	X	X								X		9
Alveolar/bronchiolar carcinoma			X											X												3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
None																										
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																						X				2
Lymphoma malignant mixed																					X					3

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL: 50 mg/kg

DAYS ON STUDY	0 1 1	0 1 6	2 0 5	4 3 3	4 9 1	4 9 2	5 0 6	5 6 3	5 7 3	5 7 9	5 9 5	6 0 9	6 4 7	6 5 2	6 6 8	6 7 3	6 7 5	6 8 2	6 8 8	6 9 3	6 9 7	7 1 1	7 3 2	7 3 2	7 3 2
CARCASS ID	3 9 1	3 6 1	3 3 1	3 6 2	3 9 2	3 1 1	3 8 1	3 5 1	3 7 2	3 8 2	3 2 1	3 1 2	3 4 1	3 7 3	3 2 2	3 1 3	3 6 3	3 7 4	3 3 2	3 8 3	3 3 3	3 6 4	3 1 4	3 1 5	3 2 3
ALIMENTARY SYSTEM																									
Esophagus	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	M	A	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	A	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine small, jejunum	+	+	A	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X																X				
Hemangiosarcoma, four, multiple																X						X			
Hepatocellular carcinoma				X		X	X		X						X			X	X						
Hepatocellular adenoma					X	X								X				X							X
Hepatocellular adenoma, three, multiple																									
Mesentery										+		+				+									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, extension, metastatic, skin																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Carcinoma, metastatic, seminal vesicle							X																		
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Tooth					+			+	+			+		+			+					+	+		+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung				X																					
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																		X	X			X			
Pheochromocytoma benign, multiple																									
Islets, pancreatic	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Parathyroid gland	M	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+
Pituitary gland	I	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland																									+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland			+					+			+				+	+			+						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X																		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 50 mg/kg (Continued)

DAYS ON STUDY	732	732	732	732	732	732	732	732	732	732	732	732	732	735	735	735	735	735	735	735	735	735	735	735	TOTAL:
CARCASS ID	324	325	334	335	342	343	344	345	352	353	354	355	365	371	375	384	385	393	394	395	401	402	403	404	405	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	●	+	●	+	+	+	+	●	+	●	+	+	+	+	+	+	+	+	●	●	●	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																								X		4
Hemangiosarcoma, four, multiple																										1
Hepatocellular carcinoma								X		X	X		X		X											12
Hepatocellular adenoma						X			X	X								X	X	X			X			12
Hepatocellular adenoma, three, multiple																						X				1
Mesentery																										3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, extension, metastatic, skin				X																						1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, seminal vesicle																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth		+	+	+			+		+							+	+		+		+	+	+		+	21
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spindle cell, adenoma																									X	1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign									X																	4
Pheochromocytoma benign, multiple										X																1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland		+		+												+								+		5
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland								+	+							+							+			10
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 50 mg/kg (Continued)

DAYS ON STUDY	0 1 1	0 6 0	2 0 5	4 3 3	4 9 1	4 9 2	5 0 6	5 6 3	5 7 3	5 7 9	5 9 5	6 0 9	6 4 7	6 5 2	6 6 8	6 7 3	6 7 5	6 8 2	6 8 8	6 9 3	6 9 7	7 1 1	7 3 2	7 3 2	7 3 2
CARCASS ID	3 9 1	3 6 1	3 3 1	3 6 2	3 9 2	3 1 1	3 8 1	3 5 1	3 7 2	3 8 2	3 2 1	3 1 2	3 4 1	3 7 3	3 2 2	3 1 3	3 6 3	3 7 4	3 3 2	3 8 3	3 3 3	3 6 4	3 1 4	3 1 5	3 2 3
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X	X			
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung				X																					
Mediastinal, carcinoma, metastatic, seminal vesicle							X																		
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X				
Thymus	+	+	+	+	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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Papilloma squamous																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma												X						X		X					
Subcutaneous tissue, fibrous histiocytoma																									
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, hemangiosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+			+			+															
Alveolar/bronchiolar carcinoma, metastatic, two, multiple, lung				X																					
Hemangiosarcoma										X															
Abdominal, carcinoma, metastatic, seminal vesicle							X																		
Diaphragm, carcinoma, metastatic, seminal vesicle							X																		
Intercostal, carcinoma, metastatic, seminal vesicle							X																		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma malignant											X														
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Alveolar/bronchiolar carcinoma																	X								
Alveolar/bronchiolar carcinoma, greater than five, multiple				X																					
Carcinoma, greater than five, metastatic, multiple, seminal vesicle							X																		
Hemangiosarcoma																						X			
Hepatocellular carcinoma, metastatic, liver				X														X							
Hepatocellular carcinoma, four, metastatic, multiple, liver																									
Hepatocellular carcinoma, greater than five, metastatic, multiple, liver																			X						
Mediastinum, carcinoma, greater than five, metastatic, multiple, seminal vesicle							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, seminal vesicle							X																		
Cortex, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X												X

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 50 mg/kg (Continued)

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 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	TOTAL:
CARCASS ID	3 2 4	3 2 5	3 3 4	3 3 5	3 4 2	3 4 3	3 4 4	3 4 5	3 5 2	3 5 3	3 5 4	3 5 5	3 6 5	3 7 1	3 7 5	3 8 4	3 8 5	3 9 3	3 9 4	3 9 5	4 0 1	4 0 2	4 0 3	4 0 4	4 0 5	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood				+	+																					2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, carcinoma, metastatic, seminal vesicle																										1
Lymph node, mandibular	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																								X		2
Thymus	+	+	+	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	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																X										1
Papilloma squamous																			X		X					2
Subcutaneous tissue, fibroma			X																							1
Subcutaneous tissue, fibrosarcoma				X	X									X												6
Subcutaneous tissue, fibrous histiocytoma				X																						1
Subcutaneous tissue, hemangioma																				X						1
Subcutaneous tissue, hemangiosarcoma																	X									1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										3
Alveolar/bronchiolar carcinoma, metastatic, two, multiple, lung																										1
Hemangiosarcoma																										1
Abdominal, carcinoma, metastatic, seminal vesicle																										1
Diaphragm, carcinoma, metastatic, seminal vesicle																										1
Intercostal, carcinoma, metastatic, seminal vesicle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma malignant																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X								X		3
Alveolar/bronchiolar carcinoma							X										X					X				4
Alveolar/bronchiolar carcinoma, greater than five, multiple																										1
Carcinoma, greater than five, metastatic, multiple, seminal vesicle																										1
Hemangiosarcoma																										1
Hepatocellular carcinoma, metastatic, liver																										2
Hepatocellular carcinoma, four, metastatic, multiple, liver															X											1
Hepatocellular carcinoma, greater than five, metastatic, multiple, liver																										1
Mediastinum, carcinoma, greater than five, metastatic, multiple, seminal vesicle																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland				+										+												2
Adenoma				X										X												2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, seminal vesicle																										1
Cortex, carcinoma																X										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										2

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL: 100 mg/kg

DAYS ON STUDY	1 2 3	4 0 1	4 0 3	4 0 5	4 5 9	5 0 4	5 7 1	5 7 3	5 9 0	5 9 9	6 1 7	6 2 0	6 2 9	6 3 0	6 3 5	6 3 8	6 4 8	6 5 0	6 6 1	6 6 6	6 8 8	6 8 8	6 9 8	7 1 0	7 1 3
CARCASS ID	2 1 1	3 0 1	3 0 2	2 9 1	2 3 2	2 7 2	2 7 3	2 1 3	2 2 1	2 8 1	2 6 2	2 4 1	3 0 3	2 3 3	2 4 2	2 1 2	2 9 3	2 5 1	2 5 2	2 1 4	2 8 2	2 9 2	2 2 2	2 3 4	2 9 4
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Gallbladder	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+		+	M	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	
Polyp adenomatous																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Fibrosarcoma, extension, metastatic, mesentery												X													
Hemangiosarcoma											X														
Hemangiosarcoma, two, multiple																									
Hepatoblastoma												X													
Hepatocellular carcinoma													X	X				X							
Hepatocellular carcinoma, two, multiple												X													
Hepatocellular adenoma																				X		X		X	
Hepatocellular adenoma, two, multiple							X																X		
Mesentery												+	+		+								+		
Fibrosarcoma, extension, metastatic, skin													X												
Fibrosarcoma, greater than five, multiple												X													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Fibrosarcoma, extension, metastatic, mesentery												X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Fibrosarcoma, extension, metastatic, skin					X				X																
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Fibrosarcoma, metastatic, mesentery												X													
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Tooth															+		+			+					
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Capsule, fibrosarcoma, extension, metastatic, mesentery												X													
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		M	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+		+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Preputial gland	+									+		+			+							+			+
Papilloma squamous																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Seminal vesicle	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Fibrosarcoma, extension, metastatic, mesentery												X													
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Interstitial cell, adenoma																									X

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 100 mg/kg
(Continued)

DAYS ON STUDY	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	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	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	TOTAL:
CARCASS ID	2 6 3	2 1 5	2 2 3	2 2 4	2 2 5	2 3 1	2 3 5	2 4 3	2 4 4	2 4 5	2 5 3	2 5 4	2 5 5	2 6 1	2 6 4	2 6 5	2 7 1	2 7 4	2 7 5	2 8 3	2 8 4	2 8 5	2 9 5	3 0 4	3 0 5	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	43
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Polyp adenomatous															X											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, extension, metastatic, mesentery																										1
Hemangiosarcoma										X																2
Hemangiosarcoma, two, multiple															X											1
Hepatoblastoma																										1
Hepatocellular carcinoma								X												X						5
Hepatocellular carcinoma, two, multiple																										1
Hepatocellular adenoma		X				X				X				X												7
Hepatocellular adenoma, two, multiple							X										X									4
Mesentery							+																			5
Fibrosarcoma, extension, metastatic, skin																										1
Fibrosarcoma, greater than five, multiple																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, extension, metastatic, mesentery																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, extension, metastatic, skin																										2
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, mesentery																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth	+	+	+		+			+	+	+		+			+	+			+					+		15
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, fibrosarcoma, extension, metastatic, mesentery																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign						X													X							2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland			+						+																	2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+		+			+		+	+												+		+	+		14
Papilloma squamous																					X					1
Prostate	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, extension, metastatic, mesentery																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell, adenoma																					X					2

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 100 mg/kg (Continued)

DAYS ON STUDY	123	401	403	405	459	504	571	573	590	599	617	620	629	630	635	638	648	650	661	666	688	688	699	710	713
CARCASS ID	211	301	302	291	232	272	273	213	221	281	262	241	303	233	242	212	293	251	252	214	282	292	222	234	294
HEMATOPOIETIC SYSTEM																									
Blood																	●			+	+				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Axillary, histiocytic sarcoma																X									
Iliac, histiocytic sarcoma																X									
Inguinal, histiocytic sarcoma																X									
Mediastinal, fibrosarcoma, metastatic, mesentery												X													
Pancreatic, histiocytic sarcoma																X									
Renal, histiocytic sarcoma																X									
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+		+	+	+	+	+	+
Histiocytic sarcoma																X									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Histiocytic sarcoma																X									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+		+	+	+	+	+	+
Thymus	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M		M	+	+	+	+	+
Histiocytic sarcoma																X									
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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Basal cell adenoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma					X	X		X	X				X	X			X			X	X				
Subcutaneous tissue, hemangiosarcoma			X																						
Subcutaneous tissue, sarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Skeletal muscle												+	+												
Fibrosarcoma, extension, metastatic, mesentery												X													
Fibrosarcoma, extension, metastatic, skin													X												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, greater than five, multiple										X															
Fibrosarcoma, metastatic												X													
Fibrosarcoma, greater than five, metastatic, multiple, skin																				X					
Mediastinum, fibrosarcoma, metastatic, mesentery												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
Eye					+																				
Harderian gland																						+			
Adenoma																						X			
Carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Cortex, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Histiocytic sarcoma																X									
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed															X			X							

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 100 mg/kg (Continued)

DAYS ON STUDY	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	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	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	TOTAL:
CARCASS ID	2 6 3	2 1 5	2 2 3	2 2 4	2 2 5	2 3 1	2 3 5	2 4 3	2 4 4	2 4 5	2 5 3	2 5 4	2 5 5	2 6 1	2 6 4	2 6 5	2 7 1	2 7 4	2 7 5	2 8 3	2 8 4	2 8 5	2 9 5	3 0 4	3 0 5	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																			+							4
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Axillary, histiocytic sarcoma																										1
Iliac, histiocytic sarcoma																										1
Inguinal, histiocytic sarcoma																										1
Mediastinal, fibrosarcoma, metastatic, mesentery																										1
Pancreatic, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Histiocytic sarcoma																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	M	M	M	M	M	M	M	M	M	+	M	M	+	M	M	+	+	M	M	M	+	M	M	9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell adenoma											X															1
Subcutaneous tissue, fibroma																							X		X	2
Subcutaneous tissue, fibrosarcoma																			X							10
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, sarcoma												X														1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										2
Fibrosarcoma, extension, metastatic, mesentery																										1
Fibrosarcoma, extension, metastatic, skin																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma			X																X							2
Alveolar/bronchiolar carcinoma								X									X									2
Alveolar/bronchiolar carcinoma, greater than five, multiple																										1
Fibrosarcoma, metastatic																										1
Fibrosarcoma, greater than five, metastatic, multiple, skin																										1
Mediastinum, fibrosarcoma, metastatic, mesentery																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSES SYSTEM																										
Ear																		+								1
Eye																										1
Harderian gland									+																	2
Adenoma																										1
Carcinoma									X																	1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortex, adenoma																									X	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic																				X						2
Lymphoma malignant mixed	X												X				X									5

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL: 175 mg/kg

DAYS ON STUDY	056	056	057	057	057	224	456	464	467	475	548	563	566	576	632	662	662	682	688	696	724	728	728	730	730
CARCASS ID	19 1	19 2	19 3	19 4	19 5	16 1	15 2	18 2	11 3	11 2	18 1	18 3	17 1	11 4	15 3	14 1	15 4	14 2	12 1	16 2	13 1	17 3	20 1	11 1	11 5
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	A	+	+	A	+	M	M	M	+	+	+	+	+	+	M	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine large, rectum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	A	+	A	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	A	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney											X														
Hepatoblastoma																									
Hepatocellular carcinoma							X		X	X		X							X			X	X		
Hepatocellular carcinoma, multiple																	X								
Hepatocellular carcinoma, two, multiple											X					X		X							
Hepatocellular carcinoma, three, multiple															X										
Hepatocellular adenoma												X	X	X										X	
Hepatocellular adenoma, two																									
Hepatocellular adenoma, two, multiple																			X			X			
Hepatocellular adenoma, three, multiple																				X					
Mesentery											+														
Carcinoma, metastatic, kidney											X														
Pancreas	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																+				+	+				
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney											X														
Sarcoma, metastatic, skeletal muscle																							X		
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pars distalis, adenoma								X																	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																							X		
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland																					+				
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland																+		+			+				
Prostate	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 175 mg/kg (Continued)

DAYS ON STUDY	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	TOTAL TISSUES TUMORS
CARCASS ID	122	123	124	125	132	133	134	135	143	144	145	151	155	163	164	165	172	174	175	184	185	202	203	204	205	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	42
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Hepatoblastoma																X										1
Hepatocellular carcinoma		X							X			X	X	X				X	X				X			15
Hepatocellular carcinoma, multiple																										1
Hepatocellular carcinoma, two, multiple																X										4
Hepatocellular carcinoma, three, multiple																										1
Hepatocellular adenoma	X	X			X			X	X		X					X	X		X				X			14
Hepatocellular adenoma, two							X																			1
Hepatocellular adenoma, two, multiple																										2
Hepatocellular adenoma, three, multiple			X																							2
Mesentery						+		+		+												+				5
Carcinoma, metastatic, kidney																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																				X						1
Papilloma squamous																									X	1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth	+		+		+			+	+	+	+		+	+	+		+				+	+	+	+	+	19
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Sarcoma, metastatic, skeletal muscle																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign													X													1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																					X					2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																								X		2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland															+											2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland				+						+		+		+	+											8
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 175 mg/kg (Continued)

DAYS ON STUDY	056	056	057	057	057	224	456	464	467	475	548	563	566	576	632	662	662	682	688	696	724	728	728	730	730
CARCASS ID	191	192	193	194	195	161	152	182	113	112	181	183	171	114	153	141	154	142	121	162	131	173	201	111	115
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, squamous cell carcinoma, metastatic, skin																									
Mediastinal, carcinoma, metastatic, kidney											X														
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	M	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skeletal muscle																							X		
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	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, hemangiosarcoma																				X					
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																							+		
Sarcoma																							X		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X					X						
Alveolar/bronchiolar carcinoma																X						X			
Carcinoma, greater than five, metastatic, multiple, kidney											X														
Hepatocellular carcinoma, metastatic, two, multiple, liver							X																		
Hepatocellular carcinoma, greater than five, metastatic, multiple, liver																			X						
Sarcoma, metastatic, skeletal muscle																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Retinoblastoma, metastatic																									
SPECIAL SENSES SYSTEM																									
Harderian gland																					+				
Adenoma																					X				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortex, adenoma																									
Cortex, carcinoma, metastatic											X														
Urinary bladder	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																					X				
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																	X								

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 175 mg/kg (Continued)

DAYS ON STUDY	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	TOTAL:
CARCASS ID	122	123	124	125	132	133	134	135	143	144	145	151	155	163	164	165	172	174	175	184	185	202	203	204	205	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood												+														1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Inguinal, squamous cell carcinoma, metastatic, skin													X													1
Mediastinal, carcinoma, metastatic, kidney																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Sarcoma, metastatic, skeletal muscle																										1
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	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma						X							X													2
Subcutaneous tissue, fibroma															X											1
Subcutaneous tissue, fibrosarcoma												X														2
Subcutaneous tissue, hemangiosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Sarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X						X	X		X				X							X	8
Alveolar/bronchiolar carcinoma							X			X	X				X											6
Carcinoma, greater than five, metastatic, multiple, kidney																										1
Hepatocellular carcinoma, metastatic, two, multiple, liver																										1
Hepatocellular carcinoma, greater than five, metastatic, multiple, liver																										1
Sarcoma, metastatic, skeletal muscle																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp																								X		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Retinoblastoma, metastatic				X																						1
SPECIAL SENSES SYSTEM																										
Harderian gland																										1
Adenoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortex, adenoma																							X			1
Cortex, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic								X																		1
Lymphoma malignant mixed																						X				2

TABLE C3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
Adrenal Medulla: Pheochromocytoma				
Overall Rates (a)	2/50 (4%)	5/50 (10%)	2/48 (4%)	1/50 (2%)
Adjusted Rates (b)	5.7%	15.8%	8.3%	3.7%
Terminal Rates (c)	2/35 (6%)	2/28 (7%)	2/24 (8%)	1/27 (4%)
Day of First Observation	729	682	729	729
Life Table Tests (d)	P=0.322N	P=0.151	P=0.553	P=0.591N
Logistic Regression Tests (d)	P=0.282N	P=0.181	P=0.553	P=0.591N
Cochran-Armitage Trend Test (d)	P=0.228N			
Fisher Exact Test (d)		P=0.218	P=0.676	P=0.500N
Liver: Hepatocellular Adenoma				
Overall Rates (a)	9/50 (18%)	13/50 (26%)	11/49 (22%)	19/50 (38%)
Adjusted Rates (b)	24.7%	38.8%	36.4%	56.7%
Terminal Rates (c)	8/35 (23%)	9/28 (32%)	6/24 (25%)	13/27 (48%)
Day of First Observation	611	491	571	563
Life Table Tests (d)	P=0.004	P=0.116	P=0.153	P=0.004
Logistic Regression Tests (d)	P=0.008	P=0.201	P=0.292	P=0.008
Cochran-Armitage Trend Test (d)	P=0.021			
Fisher Exact Test (d)		P=0.235	P=0.382	P=0.022
Liver: Hepatocellular Carcinoma				
Overall Rates (a)	(e) 7/50 (14%)	12/50 (24%)	(e) 6/49 (12%)	(e) 21/50 (42%)
Adjusted Rates (b)	17.4%	31.5%	18.2%	52.7%
Terminal Rates (c)	4/35 (11%)	5/28 (18%)	2/24 (8%)	9/27 (33%)
Day of First Observation	456	433	620	456
Life Table Tests (d)	P=0.001	P=0.107	P=0.562	P<0.001
Logistic Regression Tests (d)	P=0.002	P=0.157	P=0.516N	P=0.001
Cochran-Armitage Trend Test (d)	P=0.002			
Fisher Exact Test (d)		P=0.154	P=0.516N	P=0.002
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	16/50 (32%)	22/50 (44%)	17/49 (35%)	32/50 (64%)
Adjusted Rates (b)	40.2%	57.5%	49.5%	75.9%
Terminal Rates (c)	12/35 (34%)	13/28 (46%)	8/24 (33%)	17/27 (63%)
Day of First Observation	456	433	571	456
Life Table Tests (d)	P<0.001	P=0.064	P=0.183	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.136	P=0.431	P<0.001
Cochran-Armitage Trend Test (d)	P=0.002			
Fisher Exact Test (d)		P=0.151	P=0.472	P=0.001
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	9/50 (18%)	3/50 (6%)	2/49 (4%)	8/50 (16%)
Adjusted Rates (b)	24.8%	9.7%	8.3%	26.7%
Terminal Rates (c)	8/35 (23%)	2/28 (7%)	2/24 (8%)	6/27 (22%)
Day of First Observation	666	668	729	576
Life Table Tests (d)	P=0.423	P=0.118N	P=0.092N	P=0.496
Logistic Regression Tests (d)	P=0.505	P=0.085N	P=0.060N	P=0.601
Cochran-Armitage Trend Test (d)	P=0.502N			
Fisher Exact Test (d)		P=0.061N	P=0.028N	P=0.500N
Lung: Alveolar/Bronchiolar Carcinoma				
Overall Rates (a)	3/50 (6%)	5/50 (10%)	3/49 (6%)	6/50 (12%)
Adjusted Rates (b)	8.3%	15.2%	10.6%	20.1%
Terminal Rates (c)	2/35 (6%)	3/28 (11%)	2/24 (8%)	4/27 (15%)
Day of First Observation	719	433	599	662
Life Table Tests (d)	P=0.150	P=0.264	P=0.505	P=0.148
Logistic Regression Tests (d)	P=0.191	P=0.342	P=0.614	P=0.174
Cochran-Armitage Trend Test (d)	P=0.238			
Fisher Exact Test (d)		P=0.357	P=0.651	P=0.243

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	10/50 (20%)	8/50 (16%)	5/49 (10%)	13/50 (26%)
Adjusted Rates (b)	26.9%	24.1%	18.8%	41.1%
Terminal Rates (c)	8/35 (23%)	5/28 (18%)	4/24 (17%)	9/27 (33%)
Day of First Observation	666	433	599	576
Life Table Tests (d)	P=0.125	P=0.570N	P=0.343N	P=0.137
Logistic Regression Tests (d)	P=0.184	P=0.442N	P=0.210N	P=0.197
Cochran-Armitage Trend Test (d)	P=0.271			
Fisher Exact Test (d)		P=0.398N	P=0.140N	P=0.318
Subcutaneous Tissue: Fibroma				
Overall Rates (f)	3/50 (6%)	1/50 (2%)	2/49 (4%)	1/50 (2%)
Adjusted Rates (b)	8.6%	3.6%	8.3%	3.7%
Terminal Rates (c)	3/35 (9%)	1/28 (4%)	2/24 (8%)	1/27 (4%)
Day of First Observation	729	729	729	729
Life Table Tests (d)	P=0.361N	P=0.387N	P=0.670N	P=0.401N
Logistic Regression Tests (d)	P=0.361N	P=0.387N	P=0.670N	P=0.401N
Cochran-Armitage Trend Test (d)	P=0.266N			
Fisher Exact Test (d)		P=0.309N	P=0.510N	P=0.309N
Subcutaneous Tissue: Fibrosarcoma				
Overall Rates (f)	3/50 (6%)	6/50 (12%)	10/49 (20%)	2/50 (4%)
Adjusted Rates (b)	7.6%	18.4%	25.2%	5.9%
Terminal Rates (c)	1/35 (3%)	3/28 (11%)	1/24 (4%)	1/27 (4%)
Day of First Observation	611	609	459	464
Life Table Tests (d)	P=0.509	P=0.179	P=0.026	P=0.579N
Logistic Regression Tests (d)	P=0.477N	P=0.228	P=0.034	P=0.502N
Cochran-Armitage Trend Test (d)	P=0.478N			
Fisher Exact Test (d)		P=0.243	P=0.033	P=0.500N
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (f)	5/50 (10%)	7/50 (14%)	12/49 (24%)	3/50 (6%)
Adjusted Rates (b)	13.0%	21.6%	31.7%	9.6%
Terminal Rates (c)	3/35 (9%)	4/28 (14%)	3/24 (13%)	2/27 (7%)
Day of First Observation	611	609	459	464
Life Table Tests (d)	P=0.536	P=0.270	P=0.028	P=0.475N
Logistic Regression Tests (d)	P=0.428N	P=0.350	P=0.051	P=0.387N
Cochran-Armitage Trend Test (d)	P=0.403N			
Fisher Exact Test (d)		P=0.380	P=0.049	P=0.357N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma				
Overall Rates (f)	3/50 (6%)	6/50 (12%)	11/49 (22%)	2/50 (4%)
Adjusted Rates (b)	7.6%	18.4%	28.4%	5.9%
Terminal Rates (c)	1/35 (3%)	3/28 (11%)	2/24 (8%)	1/27 (4%)
Day of First Observation	611	609	459	464
Life Table Tests (d)	P=0.476	P=0.179	P=0.014	P=0.579N
Logistic Regression Tests (d)	P=0.509N	P=0.228	P=0.020	P=0.502N
Cochran-Armitage Trend Test (d)	P=0.505N			
Fisher Exact Test (d)		P=0.243	P=0.018	P=0.500N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma				
Overall Rates (f)	5/50 (10%)	7/50 (14%)	13/49 (27%)	3/50 (6%)
Adjusted Rates (b)	13.0%	21.6%	34.9%	9.6%
Terminal Rates (c)	3/35 (9%)	4/28 (14%)	4/24 (17%)	2/27 (7%)
Day of First Observation	611	609	459	464
Life Table Tests (d)	P=0.506	P=0.270	P=0.016	P=0.475N
Logistic Regression Tests (d)	P=0.458N	P=0.350	P=0.031	P=0.387N
Cochran-Armitage Trend Test (d)	P=0.428N			
Fisher Exact Test (d)		P=0.380	P=0.030	P=0.357N

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
Circulatory System: Hemangiosarcoma				
Overall Rates (f)	2/50 (4%)	7/50 (14%)	4/49 (8%)	1/50 (2%)
Adjusted Rates (b)	5.5%	19.6%	12.6%	3.2%
Terminal Rates (c)	1/35 (3%)	2/28 (7%)	2/24 (8%)	0/27 (0%)
Day of First Observation	703	491	403	696
Life Table Tests (d)	P=0.325N	P=0.056	P=0.234	P=0.574N
Logistic Regression Tests (d)	P=0.238N	P=0.078	P=0.329	P=0.541N
Cochran-Armitage Trend Test (d)	P=0.228N			
Fisher Exact Test (d)		P=0.080	P=0.329	P=0.500N
Circulatory System: Hemangioma or Hemangiosarcoma				
Overall Rates (f)	3/50 (6%)	8/50 (16%)	4/49 (8%)	1/50 (2%)
Adjusted Rates (b)	7.6%	22.7%	12.6%	3.2%
Terminal Rates (c)	1/35 (3%)	3/28 (11%)	2/24 (8%)	0/27 (0%)
Day of First Observation	518	491	403	696
Life Table Tests (d)	P=0.204N	P=0.070	P=0.386	P=0.376N
Logistic Regression Tests (d)	P=0.129N	P=0.098	P=0.491	P=0.318N
Cochran-Armitage Trend Test (d)	P=0.124N			
Fisher Exact Test (d)		P=0.100	P=0.489	P=0.309N
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (f)	5/50 (10%)	2/50 (4%)	7/49 (14%)	4/50 (8%)
Adjusted Rates (b)	13.6%	6.1%	22.6%	13.1%
Terminal Rates (c)	4/35 (11%)	1/28 (4%)	3/24 (13%)	2/27 (7%)
Day of First Observation	662	647	401	662
Life Table Tests (d)	P=0.365	P=0.298N	P=0.201	P=0.633N
Logistic Regression Tests (d)	P=0.442	P=0.241N	P=0.351	P=0.579N
Cochran-Armitage Trend Test (d)	P=0.495			
Fisher Exact Test (d)		P=0.218N	P=0.365	P=0.500N
All Sites: Benign Tumors				
Overall Rates (f)	24/50 (48%)	24/50 (48%)	20/49 (41%)	30/50 (60%)
Adjusted Rates (b)	62.8%	67.8%	66.0%	83.1%
Terminal Rates (c)	21/35 (60%)	17/28 (61%)	14/24 (58%)	21/27 (78%)
Day of First Observation	518	491	571	464
Life Table Tests (d)	P=0.016	P=0.237	P=0.312	P=0.013
Logistic Regression Tests (d)	P=0.041	P=0.483	P=0.490N	P=0.039
Cochran-Armitage Trend Test (d)	P=0.158			
Fisher Exact Test (d)		P=0.579N	P=0.303N	P=0.158
All Sites: Malignant Tumors				
Overall Rates (f)	22/50 (44%)	31/50 (62%)	27/49 (55%)	33/50 (66%)
Adjusted Rates (b)	49.7%	68.7%	62.1%	78.4%
Terminal Rates (c)	13/35 (37%)	14/28 (50%)	9/24 (38%)	18/27 (67%)
Day of First Observation	456	433	401	456
Life Table Tests (d)	P=0.014	P=0.030	P=0.061	P=0.007
Logistic Regression Tests (d)	P=0.020	P=0.047	P=0.184	P=0.007
Cochran-Armitage Trend Test (d)	P=0.036			
Fisher Exact Test (d)		P=0.054	P=0.183	P=0.022
All Sites: All Tumors				
Overall Rates (f)	38/50 (76%)	41/50 (82%)	42/49 (86%)	43/50 (86%)
Adjusted Rates (b)	84.4%	89.1%	89.4%	97.7%
Terminal Rates (c)	28/35 (80%)	23/28 (82%)	19/24 (79%)	26/27 (96%)
Day of First Observation	456	433	401	456
Life Table Tests (d)	P=0.018	P=0.075	P=0.015	P=0.014
Logistic Regression Tests (d)	P=0.013	P=0.232	P=0.147	P=0.013
Cochran-Armitage Trend Test (d)	P=0.109			
Fisher Exact Test (d)		P=0.312	P=0.166	P=0.154

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

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

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

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl acrylate	6/49	12/49	17/49
Benzyl acetate	0/50	10/50	10/50
Allyl isovalerate	7/50	18/50	23/50
HC Red No. 3	11/50	17/50	25/50
Chlorinated paraffins (C_{23}, 43% chlorine)	10/50	9/50	18/50
Allyl isothiocyanate	9/49	13/49	21/49
Geranyl acetate	3/50	11/50	13/50
C.I. Acid Orange 3	16/50	7/50	21/50
Chlorinated paraffins (C_{12}, 60% chlorine)	11/50	11/50	20/50
TOTAL	73/448 (16.3%)	108/448 (24.1%)	168/448 (37.5%)
SD (b)	9.51%	7.16%	9.57%
Range (c)			
High	16/50	18/50	25/50
Low	0/50	7/50	10/50
Overall Historical Incidence			
TOTAL	338/2,183 (15.5%)	418/2,183 (19.1%)	713/2,183 (32.7%)
SD (b)	7.01%	7.42%	8.55%
Range (c)			
High	16/50	19/50	25/50
Low	0/50	3/49	7/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C4b. HISTORICAL INCIDENCE OF RENAL CORTICAL NEOPLASMS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls
Historical Incidence at Southern Research Institute	0/448
Overall Historical Incidence	8/2,183

(a) Data as of March 1, 1989, for studies of at least 104 weeks

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Early deaths				
Dead	9	12	13	9
Moribund	6	8	12	8
Accidentally killed				6
Dosing accident		2		
Survivors				
Terminal sacrifice	35	28	24	27
Missing			1	
Animals examined microscopically	50	50	49	50
ALIMENTARY SYSTEM				
Esophagus	(50)	(49)	(49)	(50)
Foreign body		1 (2%)		
Inflammation, suppurative, acute		1 (2%)		
Intestine large, cecum	(49)	(47)	(49)	(46)
Inflammation, chronic		1 (2%)		
Intestine small, jejunum	(47)	(46)	(47)	(45)
Perforation			1 (2%)	
Liver	(50)	(50)	(49)	(50)
Angiectasis, focal			1 (2%)	
Basophilic focus	1 (2%)		1 (2%)	
Congestion				1 (2%)
Developmental malformation			1 (2%)	
Embolus tumor		1 (2%)		
Fibrosis, focal			1 (2%)	
Focal cellular change	3 (6%)	7 (14%)	4 (8%)	5 (10%)
Focal cellular change, multiple	1 (2%)		1 (2%)	
Granuloma, multiple	1 (2%)		2 (4%)	
Hematopoietic cell proliferation		2 (4%)	2 (4%)	1 (2%)
Hepatodiaphragmatic nodule			1 (2%)	
Inclusion body intranuclear				1 (2%)
Infiltration cellular, lymphocytic, multifocal	1 (2%)	2 (4%)	4 (8%)	1 (2%)
Mineralization, focal		1 (2%)		1 (2%)
Necrosis, focal	2 (4%)			2 (4%)
Necrosis, multifocal	1 (2%)	2 (4%)	7 (14%)	8 (16%)
Pigmentation, hematoidin		1 (2%)		
Vacuolization cytoplasmic, diffuse	1 (2%)			1 (2%)
Vacuolization cytoplasmic, focal		1 (2%)		
Vacuolization cytoplasmic, multifocal				1 (2%)
Biliary tract, cyst			1 (2%)	1 (2%)
Biliary tract, cyst multilocular				3 (6%)
Biliary tract, dilatation		1 (2%)		1 (2%)
Biliary tract, proliferation		1 (2%)		
Biliary tract, subserosa, hyperplasia, multifocal			3 (6%)	2 (4%)
Centrilobular, vacuolization cytoplasmic, diffuse			1 (2%)	
Kupffer cell, pigmentation, multifocal		2 (4%)		
Serosa, subserosa, inflammation, chronic, multifocal			8 (16%)	18 (36%)
Serosa, subserosa, pigmentation, multifocal			8 (16%)	18 (36%)
Sinusoid, infiltration cellular, polymorphonuclear		2 (4%)	1 (2%)	
Mesentery	(4)	(3)	(5)	(5)
Inflammation, granulomatous, multifocal	1 (25%)			
Fat, necrosis, focal	2 (50%)	2 (67%)	2 (40%)	4 (80%)

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
ALIMENTARY SYSTEM (Continued)				
Pancreas	(50)	(50)	(49)	(49)
Infiltration cellular, lymphocytic, multifocal			1 (2%)	
Necrosis, multifocal		1 (2%)		
Acinus, atrophy, focal	1 (2%)			1 (2%)
Acinus, atrophy, multifocal	1 (2%)	4 (8%)	1 (2%)	1 (2%)
Duct, cyst		1 (2%)		
Salivary glands	(50)	(50)	(49)	(50)
Infiltration cellular, lymphocytic, multifocal	28 (56%)	21 (42%)	21 (43%)	24 (48%)
Inflammation, suppurative, acute, focal		1 (2%)		
Stomach, forestomach	(50)	(49)	(49)	(49)
Erosion		1 (2%)	1 (2%)	
Foreign body			1 (2%)	
Hyperplasia	5 (10%)	2 (4%)	8 (16%)	6 (12%)
Inflammation, subacute	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Mineralization				1 (2%)
Ulcer	1 (2%)		1 (2%)	
Ulcer, multiple			1 (2%)	1 (2%)
Stomach, glandular	(50)	(49)	(49)	(49)
Erosion, multiple		1 (2%)		
Inflammation, subacute	3 (6%)	1 (2%)	1 (2%)	
Mineralization	5 (10%)	3 (6%)	2 (4%)	3 (6%)
Ulcer				1 (2%)
Tooth	(27)	(21)	(15)	(19)
Dysplasia	27 (100%)	20 (95%)	15 (100%)	19 (100%)
Inflammation, subacute	1 (4%)			
CARDIOVASCULAR SYSTEM				
Heart	(50)	(50)	(49)	(50)
Fibrosis, focal		1 (2%)		
Inflammation, subacute, focal		1 (2%)	4 (8%)	
Inflammation, subacute, multifocal		1 (2%)		
Mineralization, multifocal	1 (2%)			
Atrium, thrombus			1 (2%)	
Endothelium, hyperplasia		1 (2%)		
Pericardium, fibrosis			1 (2%)	
Pericardium, inflammation, subacute			1 (2%)	
Valve, bacterium		1 (2%)		
Valve, thrombus		1 (2%)		
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(50)	(50)	(49)	(50)
Cyst	1 (2%)			
Hyperplasia, focal	7 (14%)	4 (8%)	3 (6%)	5 (10%)
Hypertrophy, focal		2 (4%)	3 (6%)	2 (4%)
Capsule, accessory adrenal cortical nodule	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Spindle cell, hyperplasia, focal	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Adrenal gland, medulla	(50)	(50)	(48)	(50)
Hematopoietic cell proliferation			1 (2%)	
Hyperplasia, focal	5 (10%)	4 (8%)	7 (15%)	6 (12%)
Islets, pancreatic	(50)	(48)	(49)	(49)
Hyperplasia	14 (28%)	21 (44%)	15 (31%)	12 (24%)
Pigmentation, hemosiderin	1 (2%)			
Parathyroid gland	(43)	(43)	(47)	(44)
Cyst		1 (2%)		
Pituitary gland	(47)	(45)	(46)	(49)
Pars distalis, cyst		2 (4%)		3 (6%)
Pars distalis, hyperplasia, focal	1 (2%)	2 (4%)	2 (4%)	
Pars nervosa, fibrosis			1 (2%)	

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
ENDOCRINE SYSTEM (Continued)				
Thyroid gland	(49)	(50)	(48)	(50)
Ultimobranchial cyst			1 (2%)	2 (4%)
Follicle, cyst	6 (12%)	1 (2%)	2 (4%)	3 (6%)
Follicle, degeneration, cystic	17 (35%)	15 (30%)	14 (29%)	14 (28%)
Follicular cell, hyperplasia, cystic, focal			2 (4%)	1 (2%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Coagulating gland	(4)	(5)	(2)	(2)
Dilatation	4 (100%)	5 (100%)	2 (100%)	1 (50%)
Inflammation, chronic			1 (50%)	
Inflammation, subacute		1 (20%)		
Epididymis	(50)	(50)	(49)	(50)
Fibrosis, focal				1 (2%)
Infiltration cellular, lymphocytic, multifocal		1 (2%)	3 (6%)	
Pigmentation, cholesterol, focal				1 (2%)
Preputial gland	(9)	(10)	(14)	(8)
Hyperplasia		1 (10%)		
Inflammation, subacute	7 (78%)	8 (80%)	12 (86%)	6 (75%)
Duct, cyst	3 (33%)	8 (80%)	12 (86%)	5 (63%)
Duct, hyperplasia			1 (7%)	
Prostate	(50)	(50)	(48)	(49)
Infiltration cellular, lymphocytic, multifocal		2 (4%)	1 (2%)	
Inflammation, subacute	1 (2%)			1 (2%)
Seminal vesicle	(50)	(50)	(48)	(50)
Atrophy		1 (2%)		
Dilatation	7 (14%)	7 (14%)	6 (13%)	3 (6%)
Inflammation, subacute		1 (2%)	1 (2%)	1 (2%)
Necrosis, focal				1 (2%)
Testes	(50)	(50)	(49)	(50)
Capsule, mineralization			1 (2%)	
HEMATOPOIETIC SYSTEM				
Blood	(1)	(2)	(4)	(1)
Leukocytosis	1 (100%)	2 (100%)	3 (75%)	1 (100%)
Polychromasia		2 (100%)	2 (50%)	
Bone marrow	(50)	(49)	(49)	(50)
Hyperplasia	10 (20%)	7 (14%)	10 (20%)	8 (16%)
Necrosis		1 (2%)		
Lymph node	(50)	(50)	(49)	(50)
Hyperplasia, lymphoid			1 (2%)	
Axillary, hyperplasia, lymphoid		1 (2%)		
Iliac, hyperplasia, lymphoid			1 (2%)	
Inguinal, hyperplasia, lymphoid	2 (4%)	4 (8%)	2 (4%)	
Inguinal, inflammation, subacute		1 (2%)		
Inguinal, pigmentation, hemosiderin	1 (2%)			
Mediastinal, angiectasis				2 (4%)
Mediastinal, hyperplasia, lymphoid	1 (2%)		1 (2%)	
Renal, angiectasis		1 (2%)		
Lymph node, mandibular	(44)	(46)	(47)	(48)
Ectasia		1 (2%)		
Hyperplasia, lymphoid	3 (7%)	1 (2%)		3 (6%)
Necrosis				3 (6%)
Lymph node, mesenteric	(49)	(45)	(49)	(50)
Angiectasis	15 (31%)	18 (40%)	17 (35%)	12 (24%)
Hematopoietic cell proliferation		2 (4%)	3 (6%)	3 (6%)
Hyperplasia, lymphoid	10 (20%)	8 (18%)	7 (14%)	10 (20%)

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
HEMATOPOIETIC SYSTEM				
Lymph node, mesenteric (Continued)	(49)	(45)	(49)	(50)
Inflammation, chronic				1 (2%)
Necrosis				1 (2%)
Spleen	(50)	(50)	(48)	(49)
Atrophy		2 (4%)		3 (6%)
Developmental malformation			1 (2%)	
Hematopoietic cell proliferation	10 (20%)	19 (38%)	18 (38%)	12 (24%)
Hyperplasia, lymphoid	16 (32%)	14 (28%)	13 (27%)	16 (33%)
Necrosis				3 (6%)
Thymus	(47)	(42)	(44)	(45)
Atrophy		7 (17%)	1 (2%)	
Cyst	7 (15%)	2 (5%)	8 (18%)	2 (4%)
Necrosis				4 (9%)
INTEGUMENTARY SYSTEM				
Skin	(50)	(50)	(49)	(50)
Alopecia, focal			3 (6%)	1 (2%)
Fibrosis, multifocal			1 (2%)	
Ulcer, focal	1 (2%)		2 (4%)	
Epidermis, hyperplasia, focal	5 (10%)	5 (10%)	8 (16%)	1 (2%)
Epidermis, inflammation, suppurative, acute, focal	1 (2%)		2 (4%)	
Prepuce, developmental malformation		2 (4%)		
Sebaceous gland, hyperplasia, focal		1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, cyst		2 (4%)		
Subcutaneous tissue, edema, focal	1 (2%)		1 (2%)	
Subcutaneous tissue, fibrosis, focal	12 (24%)	5 (10%)	8 (16%)	10 (20%)
Subcutaneous tissue, hemorrhage, focal	1 (2%)			
Subcutaneous tissue, inflammation, granulomatous, multifocal	1 (2%)			
Subcutaneous tissue, inflammation, subacute, focal		3 (6%)		3 (6%)
Subcutaneous tissue, inflammation, suppurative, acute, focal	1 (2%)	1 (2%)		
Subcutaneous tissue, metaplasia, osseous, focal	1 (2%)	1 (2%)		1 (2%)
Subcutaneous tissue, mineralization, focal				1 (2%)
Subcutaneous tissue, necrosis, focal				1 (2%)
MUSCULOSKELETAL SYSTEM				
Bone	(50)	(49)	(49)	(50)
Arthrosis, chronic	6 (12%)	1 (2%)	2 (4%)	1 (2%)
Fracture			1 (2%)	
Skeletal muscle	(1)	(3)	(2)	(1)
Abdominal, inflammation, suppurative	1 (100%)			
NERVOUS SYSTEM				
Brain	(49)	(50)	(49)	(50)
Degeneration, focal			1 (2%)	
Edema, focal			1 (2%)	
Hemorrhage			1 (2%)	
Hydrocephalus			1 (2%)	
Meninges, infiltration cellular, lymphocytic, multifocal			1 (2%)	

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
RESPIRATORY SYSTEM				
Lung	(50)	(50)	(49)	(50)
Congestion	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Foreign body		1 (2%)		1 (2%)
Hemorrhage, focal	1 (2%)			
Hemorrhage, multifocal				1 (2%)
Infiltration cellular, histiocytic, multifocal	4 (8%)	4 (8%)	4 (8%)	6 (12%)
Alveolar epithelium, hyperplasia, focal			1 (2%)	
Alveolar epithelium, hyperplasia, multifocal		1 (2%)		
Mediastinum, foreign body		2 (4%)		
Mediastinum, inflammation, chronic		1 (2%)		
Mediastinum, inflammation, subacute, focal			1 (2%)	
Nose	(49)	(50)	(49)	(50)
Inflammation, suppurative, acute		1 (2%)		4 (8%)
Nasolacrimal duct, cyst			1 (2%)	
Nasolacrimal duct, exudate			1 (2%)	
Nasolacrimal duct, inflammation, subacute	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Nasolacrimal duct, inflammation, suppurative, acute	1 (2%)			
SPECIAL SENSES SYSTEM				
None				
URINARY SYSTEM				
Kidney	(50)	(50)	(49)	(50)
Bacterium, multifocal				1 (2%)
Fibrosis, focal	2 (4%)	4 (8%)	3 (6%)	2 (4%)
Infiltration cellular, lymphocytic, multifocal	25 (50%)	19 (38%)	25 (51%)	23 (46%)
Inflammation, suppurative, acute, multifocal		1 (2%)		1 (2%)
Metaplasia, osseous, focal	1 (2%)	1 (2%)		1 (2%)
Nephropathy, chronic	37 (74%)	39 (78%)	37 (76%)	36 (72%)
Renal tubule, dilatation, multifocal			1 (2%)	
Renal tubule, hyperplasia		1 (2%)		
Renal tubule, mineralization, multifocal	1 (2%)			1 (2%)
Renal tubule, necrosis, multifocal		1 (2%)	1 (2%)	
Urinary bladder	(49)	(50)	(49)	(49)
Inflammation, subacute		1 (2%)		

APPENDIX D

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

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	8	11	9	7
Dead	8	9	12	11
Dosing accident	1			
Accident		2		
Survivors				
Terminal sacrifice	33	28	29	32
Animals examined microscopically	50	50	50	50
ALIMENTARY SYSTEM				
Gallbladder	(46)	(46)	(48)	(43)
Intestine small, duodenum	(46)	(48)	(45)	(49)
Polyp adenomatous		1 (2%)	1 (2%)	
Intestine small, ileum	(49)	(47)	(48)	(49)
Intestine small, jejunum	(48)	(48)	(46)	(50)
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic			1 (2%)	
Hemangiosarcoma	1 (2%)			
Hepatocellular carcinoma	4 (8%)		2 (4%)	4 (8%)
Hepatocellular adenoma	1 (2%)	3 (6%)	5 (10%)	8 (16%)
Histiocytic sarcoma, metastatic		1 (2%)		
Mesentery	(6)	(10)	(7)	(11)
Hemangioma		1 (10%)		
Pancreas	(50)	(50)	(48)	(50)
Histiocytic sarcoma		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Papilloma squamous	1 (2%)		1 (2%)	6 (12%)
Stomach, glandular	(50)	(50)	(50)	(50)
CARDIOVASCULAR SYSTEM				
Heart	(50)	(50)	(50)	(50)
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Adrenal gland, medulla	(50)	(50)	(50)	(50)
Pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(50)	(50)	(48)	(50)
Adenoma		1 (2%)		1 (2%)
Carcinoma			1 (2%)	
Pituitary gland	(46)	(49)	(49)	(49)
Pars distalis, adenoma	7 (15%)	3 (6%)	4 (8%)	9 (18%)
Pars distalis, fibrosarcoma, extension, metastatic, skin			1 (2%)	
Thyroid gland	(50)	(50)	(49)	(50)
Follicular cell, adenoma			1 (2%)	2 (4%)
Follicular cell, adenoma, cystic	2 (4%)	1 (2%)	3 (6%)	
GENERAL BODY SYSTEM				
None				

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
GENITAL SYSTEM				
Ovary	(48)	(49)	(50)	(50)
Carcinoma	1 (2%)			
Cystadenoma, papillary	2 (4%)	1 (2%)		1 (2%)
Mixed tumor benign		1 (2%)		
Teratoma				1 (2%)
Yolk sac carcinoma		1 (2%)		
Uterus	(50)	(50)	(50)	(50)
Leiomyoma	1 (2%)			
Polyp stromal	1 (2%)		1 (2%)	
Sarcoma stromal		1 (2%)		
Cervix, histiocytic sarcoma		1 (2%)		
HEMATOPOIETIC SYSTEM				
Bone marrow	(50)	(49)	(49)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)		
Lymph node	(50)	(50)	(50)	(50)
Pancreatic, histiocytic sarcoma		1 (2%)		
Lymph node, mandibular	(47)	(47)	(49)	(48)
Carcinoma, metastatic, harderian gland		1 (2%)		
Lymph node, mesenteric	(48)	(46)	(49)	(48)
Spleen	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			1 (2%)
Hemangiosarcoma, multiple		1 (2%)		
Thymus	(49)	(47)	(44)	(46)
INTEGUMENTARY SYSTEM				
Mammary gland	(50)	(50)	(50)	(48)
Adenoacanthoma	1 (2%)			
Adenocarcinoma	1 (2%)		1 (2%)	1 (2%)
Adenocarcinoma, two, multiple		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Papilloma squamous	1 (2%)			
Squamous cell carcinoma				1 (2%)
Subcutaneous tissue, fibrosarcoma	2 (4%)		1 (2%)	2 (4%)
Subcutaneous tissue, hemangioma			1 (2%)	
Subcutaneous tissue, hemangiosarcoma	1 (2%)			1 (2%)
MUSCULOSKELETAL SYSTEM				
Bone	(50)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland		1 (2%)		
Cranium, fibrosarcoma, extension, metastatic, skin			1 (2%)	
Skeletal muscle	(1)	(3)	(1)	
Carcinoma, metastatic, harderian gland		1 (33%)		
Hemangiosarcoma		1 (33%)		
NERVOUS SYSTEM				
Brain	(50)	(50)	(50)	(50)
Meninges, fibrosarcoma, extension, metastatic, skin			1 (2%)	

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
RESPIRATORY SYSTEM				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	1 (2%)	1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)		
Alveolar/bronchiolar carcinoma, two, multiple	1 (2%)			
Carcinoma, four, metastatic, multiple, harderian gland		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Lumen, carcinoma, metastatic, harderian gland		1 (2%)		
Trachea	(50)	(50)	(49)	(50)
SPECIAL SENSES SYSTEM				
Harderian gland		(1)	(1)	(2)
Adenoma				2 (100%)
Carcinoma		1 (100%)		
Fibrosarcoma, extension, metastatic, skin			1 (100%)	
URINARY SYSTEM				
Kidney	(50)	(50)	(50)	(50)
Cortex, adenoma		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
SYSTEMIC LESIONS				
Multiple organs	*(50)	*(50)	*(50)	*(50)
Histiocytic sarcoma		2 (4%)		
Lymphoma malignant histiocytic	1 (2%)	1 (2%)		
Lymphoma malignant lymphocytic		2 (4%)	2 (4%)	
Lymphoma malignant mixed	8 (16%)	10 (20%)	7 (14%)	8 (16%)
Total animals with primary neoplasms **	33	26	24	31
Total primary neoplasms	45	37	32	51
Total animals with benign neoplasms	16	14	16	23
Total benign neoplasms	21	14	18	33
Total animals with malignant neoplasms	22	20	12	16
Total malignant neoplasms	24	23	14	18
Total animals with secondary neoplasms ***		2	2	
Total secondary neoplasms		6	5	

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

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

DAYS ON STUDY	0 1 1	4 0 5	4 5 6	4 7 3	4 9 1	4 9 2	5 4 3	5 7 6	5 9 8	6 2 0	6 3 0	6 4 4	6 4 8	6 4 8	6 6 2	6 7 1	7 0 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
CARCASS ID	4 6 1	4 8 1	4 3 1	4 6 2	4 5 1	4 5 2	4 9 1	4 9 2	4 3 2	4 7 1	5 0 1	4 3 3	4 8 2	5 0 2	4 7 2	4 8 3	4 1 1	4 1 2	4 1 3	4 1 4	4 1 5	4 2 1	4 2 2	4 2 3	4 2 4
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	M	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Hepatocellular carcinoma																						X			
Hepatocellular adenoma																				X					
Mesentery		+					+						+			+	+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pituitary gland	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma cystic																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Carcinoma									X																
Cystadenoma, papillary																							X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																	X								
Polyp stromal																									

+ Tissue examined microscopically
Not examined
I Insufficient tissue

M Missing
A Autolysis precludes examination
X Incidence of listed morphology

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

DAYS ON STUDY	731	731	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	TOTAL TISSUES TUMORS
CARCASS ID	425	434	435	441	442	443	444	445	453	454	455	463	464	465	473	474	475	484	485	493	494	495	503	504	505	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma							X	X												X						4
Hepatocellular adenoma																										1
Mesentery										+																6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Adenoma					X																					1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma			X	X		X	X				X				X						X					7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma, cystic				X			X																			2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																										1
Cystadenoma, papillary													X													2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Polyp stromal			X																							1

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

DAYS ON STUDY	0 1 1	4 0 5	4 5 6	4 7 3	4 9 1	4 9 2	5 4 3	5 7 6	5 9 8	6 2 0	6 3 0	6 4 4	6 4 8	6 4 8	6 6 2	6 7 1	7 0 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
CARCASS ID	4 6 1	4 8 1	4 3 1	4 6 2	4 5 1	4 5 2	4 9 1	4 9 2	4 3 2	4 7 1	5 0 1	4 3 3	4 8 2	5 0 2	4 7 2	4 8 3	4 1 1	4 1 2	4 1 3	4 1 4	4 1 5	4 2 1	4 2 2	4 2 3	4 2 4
HEMATOPOIETIC SYSTEM																									
Blood											+														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma																									
Adenocarcinoma																				X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, fibrosarcoma						X																			
Subcutaneous tissue, hemangiosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																+									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma																	X								
Alveolar/bronchiolar carcinoma, two, multiple										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																X									
Lymphoma malignant mixed								X					X	X							X				

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

DAYS ON STUDY	731	731	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	TOTAL:
CARCASS ID	425	434	435	441	442	443	444	445	453	454	455	463	464	465	473	474	475	484	485	493	494	495	503	504	505	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood										+																2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma														X												1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma														X												1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoacanthoma																		X								1
Adenocarcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																					X					1
Subcutaneous tissue, fibrosarcoma										X																2
Subcutaneous tissue, hemangiosarcoma														X												1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X								X			3
Alveolar/bronchiolar carcinoma																										1
Alveolar/bronchiolar carcinoma, two, multiple																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																					+					1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed	X			X								X							X						8

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL: 50 mg/kg

DAYS ON STUDY	2 6 1	3 0 9	3 7 4	4 3 4	4 3 5	4 4 5	4 6 4	4 7 3	4 7 7	4 9 1	4 9 2	6 1 6	6 3 0	6 3 4	6 5 4	6 5 7	6 7 9	6 9 3	7 0 4	7 1 0	7 1 5	7 1 9	7 3 2	7 3 2	7 3 2
CARCASS ID	7 4 1	8 0 1	8 0 2	7 2 1	7 6 1	7 2 2	8 0 3	7 9 1	7 9 2	7 5 1	7 3 1	7 2 3	7 1 1	7 9 3	7 1 2	7 7 1	7 7 2	7 1 3	7 9 4	7 3 2	8 8 1	7 2 4	7 1 4	7 1 5	7 2 5
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																						X			
Intestine small, ileum	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Histiocytic sarcoma, metastatic																						X			
Mesentery					+		+				+			+			+			+	+				
Hemangioma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																			X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma, cystic																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary																									
Mixed tumor benign																									
Yolk sac carcinoma																						X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal																									
Cervix, histiocytic sarcoma																						X			

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 50 mg/kg (Continued)

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 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	TOTAL:
CARCASS ID	7 3 3	7 3 4	7 3 5	7 4 2	7 4 3	7 4 4	7 4 5	7 5 2	7 5 3	7 5 4	7 5 5	7 6 2	7 6 3	7 6 4	7 6 5	7 7 3	7 7 4	7 7 5	7 8 2	7 8 3	7 8 4	7 8 5	7 9 5	8 0 4	8 0 5	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X					X		X												3
Histiocytic sarcoma, metastatic																										1
Mesentery				+		+							+													10
Hemangioma				X																						1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	–	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	●	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Pars distalis, adenoma																				X				X		3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma, cystic						X																				1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma, papillary			X																							1
Mixed tumor benign											X															1
Yolk sac carcinoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal	X																									1
Cervix, histiocytic sarcoma																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 50 mg/kg (Continued)

DAYS ON STUDY	261	309	374	434	435	445	464	473	477	491	492	616	630	634	654	657	679	693	704	710	715	719	732	732
CARCASS ID	741	801	802	721	761	722	803	791	792	751	731	723	711	793	712	771	772	713	794	732	781	724	714	725
HEMATOPOIETIC SYSTEM																								
Blood													+											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X											
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic, histiocytic sarcoma																								
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland																			X					
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple													X											
Thymus	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
INTEGUMENTARY SYSTEM																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, two, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland																			X					
Skeletal muscle													+						+					
Carcinoma, metastatic, harderian gland																			X					
Hemangiosarcoma													X											
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar carcinoma																							X	
Carcinoma, four, metastatic, multiple, harderian gland																			X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumen, carcinoma, metastatic, harderian gland																			X					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																								
Eye															+									
Harderian gland																			+					
Carcinoma																			X					
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortex, adenoma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X		
Lymphoma malignant histiocytic											X													
Lymphoma malignant lymphocytic																								
Lymphoma malignant mixed												X		X			X			X	X		X	

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 50 mg/kg (Continued)

DAYS ON STUDY	732	732	732	732	732	732	732	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	TOTAL:
CARCASS ID	733	734	735	742	743	744	745	752	753	754	755	762	763	764	765	773	774	775	782	783	784	785	795	804	805	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood							+																			2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49
Hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreatic, histiocytic sarcoma																				X						1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	47
Carcinoma, metastatic, harderian gland																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, two, multiple							X																			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Skeletal muscle						+																				3
Carcinoma, metastatic, harderian gland																										1
Hemangiosarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																					X					1
Alveolar/bronchiolar carcinoma																										1
Carcinoma, four, metastatic, multiple, harderian gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lumen, carcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																										1
Harderian gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortex, adenoma		X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																					X					2
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic											X		X													2
Lymphoma malignant mixed		X												X	X									X		10

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL: 100 mg/kg

DAYS ON STUDY	360	394	438	488	490	493	506	514	523	536	568	574	575	605	611	648	662	675	693	717	719	729	729	729	729
CARCASS ID	631	691	611	641	661	632	612	633	662	651	621	642	643	701	692	644	663	645	702	672	652	613	614	615	622
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	M	+	A	+	+	+	+	+	+	A	+	A	+	+	+	+
Polyp adenomatous																X									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic																									
Hepatocellular carcinoma															X										
Hepatocellular adenoma						X											X								
Mesentery		+															+	+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous									X																
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																							X		X
Pars distalis, fibrosarcoma, extension, metastatic, skin																X									
Thyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
Follicular cell, adenoma, cystic																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																						X			

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 100 mg/kg (Continued)

DAYS ON STUDY	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	732	732	732	732	732	
CARCASS ID	623	624	625	634	635	653	654	655	664	665	671	673	674	675	681	682	683	684	685	693	694	695	703	704	705	TOTAL: TISSUES / TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Polyp adenomatous																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																		X								1
Hepatocellular carcinoma																							X			2
Hepatocellular adenoma		X			X																	X				5
Mesentery		+		+													+		+							7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																		X								1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma															X										X	4
Pars distalis, fibrosarcoma, extension, metastatic, skin																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma		X																								1
Follicular cell, adenoma, cystic													X		X				X							3
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 100 mg/kg
(Continued)

DAYS ON STUDY	360	394	438	488	490	493	506	514	523	536	568	574	575	605	611	648	662	675	693	717	719	729	729	729	729
CARCASS ID	631	691	611	641	661	632	612	633	662	651	621	642	643	701	692	644	663	645	702	672	652	613	614	615	622
HEMATOPOIETIC SYSTEM																									
Blood																+									
Bone marrow	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	M	M	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																X									
Subcutaneous tissue, hemangioma												X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, fibrosarcoma, extension, metastatic, skin																X									
Skeletal muscle																	+								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, fibrosarcoma, extension, metastatic, skin																X									
Spinal cord	+					+																			
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear						+																			
Harderian gland																+									
Fibrosarcoma, extension, metastatic, skin																X									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									X
Lymphoma malignant mixed																							X		

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 100 mg/kg (Continued)

DAYS ON STUDY	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	732	732	732	732	732	TOTAL:
CARCASS ID	623	624	625	634	635	653	654	655	664	665	671	673	674	675	681	682	683	684	685	693	694	695	703	704	705	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangioma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, fibrosarcoma, extension, metastatic, skin																										1
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, fibrosarcoma, extension, metastatic, skin																										1
Spinal cord																										2
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																				X						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Ear				+																						2
Harderian gland																										1
Fibrosarcoma, extension, metastatic, skin																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																							X			2
Lymphoma malignant mixed			X				X			X			X	X										X		7

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL: 175 mg/kg

DAYS ON STUDY	246	384	442	514	526	549	586	596	601	615	615	633	634	643	654	654	662	670	731	731	731	731	731	731	731
CARCASS ID	561	511	551	571	521	591	522	562	581	523	582	583	524	592	584	585	541	542	512	513	514	515	525	531	532
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+
Hepatocellular carcinoma						X																			
Hepatocellular adenoma											X		X								X				
Mesentery				+			+		+		+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous								X			X		X	X											
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X						X	X	X		X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																				X					
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary																									X
Teratoma			X																						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Blood																+									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Thymus	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue, fibrosarcoma														X											
Subcutaneous tissue, hemangiosarcoma										X															
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland												+													
Adenoma												X													
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed					X			X			X										X				

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 175 mg/kg (Continued)

DAYS ON STUDY	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 1	7 3 1	7 3 1	7 3 1	TOTAL:
CARCASS ID	5 5 3 3	5 5 3 4	5 5 3 5	5 5 4 3	5 5 4 4	5 5 4 5	5 5 5 2	5 5 5 3	5 5 5 4	5 5 5 5	5 5 6 3	5 5 6 4	5 5 6 5	5 5 7 2	5 5 7 3	5 5 7 4	5 5 7 5	5 5 9 3	5 5 9 4	5 5 9 5	6 0 0 1	6 0 0 2	6 0 0 3	6 0 0 4	6 0 0 5	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	43
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X								X															4
Hepatocellular adenoma	X							X											X			X	X			8
Mesentery		+						+			+						+				+		+		+	11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous	X															X									6
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Parathyroid gland	M	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X														X						X			X		9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma												X														2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma, papillary																										1
Teratoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma						X																				1
Subcutaneous tissue, fibrosarcoma												X														2
Subcutaneous tissue, hemangiosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																		X		X					3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland																				+						2
Adenoma																				X						2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed			X				X												X	X						8

TABLE D3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF FURFURAL

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
Liver: Hepatocellular Adenoma				
Overall Rates (a)	1/50 (2%)	3/50 (6%)	5/50 (10%)	8/50 (16%)
Adjusted Rates (b)	3.0%	10.7%	14.9%	22.8%
Terminal Rates (c)	1/33 (3%)	3/28 (11%)	3/29 (10%)	6/32 (19%)
Day of First Observation	729	729	493	615
Life Table Tests (d)	P=0.008	P=0.247	P=0.087	P=0.017
Logistic Regression Tests (d)	P=0.007	P=0.247	P=0.100	P=0.017
Cochran-Armitage Trend Test (d)	P=0.007			
Fisher Exact Test (d)		P=0.309	P=0.102	P=0.015
Liver: Hepatocellular Carcinoma				
Overall Rates (a)	4/50 (8%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	12.1%	0.0%	6.1%	11.4%
Terminal Rates (c)	4/33 (12%)	0/28 (0%)	1/29 (3%)	3/32 (9%)
Day of First Observation	729		611	549
Life Table Tests (d)	P=0.403	P=0.085N	P=0.398N	P=0.632
Logistic Regression Tests (d)	P=0.402	P=0.085N	P=0.366N	P=0.640
Cochran-Armitage Trend Test (d)	P=0.400			
Fisher Exact Test (d)		P=0.059N	P=0.339N	P=0.643N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	5/50 (10%)	3/50 (6%)	7/50 (14%)	12/50 (24%)
Adjusted Rates (b)	15.2%	10.7%	20.5%	33.2%
Terminal Rates (c)	5/33 (15%)	3/28 (11%)	4/29 (14%)	9/32 (28%)
Day of First Observation	729	729	493	549
Life Table Tests (d)	P=0.012	P=0.448N	P=0.306	P=0.050
Logistic Regression Tests (d)	P=0.011	P=0.448N	P=0.352	P=0.051
Cochran-Armitage Trend Test (d)	P=0.011			
Fisher Exact Test (d)		P=0.357N	P=0.380	P=0.054
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	9.1%	3.6%	3.4%	9.4%
Terminal Rates (c)	3/33 (9%)	1/28 (4%)	1/29 (3%)	3/32 (9%)
Day of First Observation	729	729	729	729
Life Table Tests (d)	P=0.525	P=0.365N	P=0.352N	P=0.650
Logistic Regression Tests (d)	P=0.525	P=0.365N	P=0.352N	P=0.650
Cochran-Armitage Trend Test (d)	P=0.528			
Fisher Exact Test (d)		P=0.309N	P=0.309N	P=0.661N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	5/50 (10%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	13.9%	7.1%	3.4%	9.4%
Terminal Rates (c)	3/33 (9%)	2/28 (7%)	1/29 (3%)	3/32 (9%)
Day of First Observation	620	729	729	729
Life Table Tests (d)	P=0.274N	P=0.277N	P=0.138N	P=0.378N
Logistic Regression Tests (d)	P=0.270N	P=0.241N	P=0.116N	P=0.363N
Cochran-Armitage Trend Test (d)	P=0.264N			
Fisher Exact Test (d)		P=0.218N	P=0.102N	P=0.357N
Pituitary Gland/Pars Distalis: Adenoma				
Overall Rates (a)	7/46 (15%)	3/49 (6%)	4/49 (8%)	9/49 (18%)
Adjusted Rates (b)	22.6%	10.3%	13.8%	27.8%
Terminal Rates (c)	7/31 (23%)	2/27 (7%)	4/29 (14%)	8/31 (26%)
Day of First Observation	729	704	729	643
Life Table Tests (d)	P=0.240	P=0.211N	P=0.294N	P=0.386
Logistic Regression Tests (d)	P=0.224	P=0.173N	P=0.294N	P=0.385
Cochran-Armitage Trend Test (d)	P=0.256			
Fisher Exact Test (d)		P=0.134N	P=0.226N	P=0.447

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
Forestomach: Squamous Papilloma				
Overall Rates (e)	1/50 (2%)	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted Rates (b)	3.0%	0.0%	2.4%	15.4%
Terminal Rates (c)	1/33 (3%)	0/28 (0%)	0/29 (0%)	2/32 (6%)
Day of First Observation	729		523	596
Life Table Tests (d)	P=0.006	P=0.533N	P=0.741	P=0.061
Logistic Regression Tests (d)	P=0.005	P=0.533N	P=0.763	P=0.058
Cochran-Armitage Trend Test (d)	P=0.005			
Fisher Exact Test (d)		P=0.500N	P=0.753N	P=0.056
Thyroid Gland: Follicular Cell Adenoma				
Overall Rates (a)	2/50 (4%)	1/50 (2%)	4/49 (8%)	2/50 (4%)
Adjusted Rates (b)	6.1%	3.6%	13.8%	6.3%
Terminal Rates (c)	2/33 (6%)	1/28 (4%)	4/29 (14%)	2/32 (6%)
Day of First Observation	729	729	729	729
Life Table Tests (d)	P=0.431	P=0.558N	P=0.277	P=0.685
Logistic Regression Tests (d)	P=0.431	P=0.558N	P=0.277	P=0.685
Cochran-Armitage Trend Test (d)	P=0.430			
Fisher Exact Test (d)		P=0.500N	P=0.329	P=0.691N
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (e)	9/50 (18%)	13/50 (26%)	9/50 (18%)	8/50 (16%)
Adjusted Rates (b)	23.7%	37.1%	31.0%	21.3%
Terminal Rates (c)	5/33 (15%)	7/28 (25%)	9/29 (31%)	5/32 (16%)
Day of First Observation	576	492	729	526
Life Table Tests (d)	P=0.324N	P=0.167	P=0.491	P=0.521N
Logistic Regression Tests (d)	P=0.301N	P=0.202	P=0.546	P=0.498N
Cochran-Armitage Trend Test (d)	P=0.307N			
Fisher Exact Test (d)		P=0.235	P=0.602N	P=0.500N
All Sites: Benign Tumors				
Overall Rates (e)	16/50 (32%)	14/50 (28%)	16/50 (32%)	23/50 (46%)
Adjusted Rates (b)	47.1%	48.1%	45.6%	59.6%
Terminal Rates (c)	15/33 (45%)	13/28 (46%)	11/29 (38%)	17/32 (53%)
Day of First Observation	700	704	493	442
Life Table Tests (d)	P=0.057	P=0.563	P=0.427	P=0.088
Logistic Regression Tests (d)	P=0.054	P=0.521N	P=0.507	P=0.094
Cochran-Armitage Trend Test (d)	P=0.059			
Fisher Exact Test (d)		P=0.414N	P=0.585N	P=0.109
All Sites: Malignant Tumors				
Overall Rates (e)	22/50 (44%)	20/50 (40%)	12/50 (24%)	16/50 (32%)
Adjusted Rates (b)	52.1%	53.6%	38.1%	39.6%
Terminal Rates (c)	13/33 (39%)	11/28 (39%)	10/29 (34%)	9/32 (28%)
Day of First Observation	492	492	611	526
Life Table Tests (d)	P=0.096N	P=0.530	P=0.083N	P=0.206N
Logistic Regression Tests (d)	P=0.061N	P=0.491N	P=0.036N	P=0.148N
Cochran-Armitage Trend Test (d)	P=0.067N			
Fisher Exact Test (d)		P=0.420N	P=0.028N	P=0.151N
All Sites: All Tumors				
Overall Rates (e)	33/50 (66%)	26/50 (52%)	24/50 (48%)	31/50 (62%)
Adjusted Rates (b)	78.5%	70.0%	67.7%	73.2%
Terminal Rates (c)	24/33 (73%)	17/28 (61%)	18/29 (62%)	21/32 (66%)
Day of First Observation	492	492	493	442
Life Table Tests (d)	P=0.434N	P=0.358N	P=0.190N	P=0.488N
Logistic Regression Tests (d)	P=0.379N	P=0.173N	P=0.071N	P=0.405N
Cochran-Armitage Trend Test (d)	P=0.412N			
Fisher Exact Test (d)		P=0.111N	P=0.053N	P=0.418N

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

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

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

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl acrylate	1/50	2/50	3/50
Benzyl acetate	0/50	1/50	1/50
Allyl isovalerate	2/50	1/50	3/50
HC Red No. 3	4/50	0/50	4/50
Chlorinated paraffins (C_{23}, 43% chlorine)	3/50	1/50	4/50
Allyl isothiocyanate	2/50	0/50	2/50
Geranyl acetate	2/50	3/50	5/50
C.I. Acid Orange 3	3/50	0/50	3/50
Chlorinated paraffins (C_{12}, 60% chlorine)	0/50	3/50	3/50
TOTAL	17/450 (3.8%)	11/450 (2.4%)	28/450 (6.2%)
SD (b)	2.73%	2.40%	2.33%
Range (c)			
High	4/50	3/50	5/50
Low	0/50	0/50	1/50
Overall Historical Incidence			
TOTAL	104/2,188 (4.8%)	60/2,188 (2.7%)	162/2,188 (7.4%)
SD (b)	3.96%	2.41%	4.98%
Range (c)			
High	10/50	5/50	15/50
Low	0/50	0/50	0/49

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

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

Study	Incidence in Vehicle Controls	
	Papilloma	Papilloma or Carcinoma
Historical Incidence at Southern Research Institute		
Ethyl acrylate	1/50	1/50
Benzyl acetate	0/50	0/50
Allyl isovalerate	1/50	1/50
HC Red No. 3	0/50	0/50
Chlorinated paraffins (C_{23}, 43% chlorine)	0/49	0/49
Allyl isothiocyanate	0/47	0/47
Geranyl acetate	0/50	0/50
C.I. Acid Orange 3	4/50	4/50
Chlorinated paraffins (C_{12}, 60% chlorine)	2/50	2/50
TOTAL	8/446 (1.8%)	8/446 (1.8%)
SD (b)	2.73%	2.73%
Range (c)		
High	4/50	4/50
Low	0/50	0/50
Overall Historical Incidence		
TOTAL	(d) 34/2,144 (1.6%)	(d) 37/2,144 (1.7%)
SD (b)	2.74%	2.74%
Range (c)		
High	5/44	5/44
Low	0/50	0/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two papillomas, NOS

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	8	11	9	7
Dead	8	9	12	11
Dosing accident	1			
Accident		2		
Survivors				
Terminal sacrifice	33	28	29	32
Animals examined microscopically	50	50	50	50
ALIMENTARY SYSTEM				
Gallbladder	(46)	(46)	(48)	(43)
Infiltration cellular, lymphocytic, multifocal		1 (2%)		1 (2%)
Intestine small, jejunum	(48)	(48)	(46)	(50)
Inflammation, subacute, focal			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Abscess	1 (2%)		1 (2%)	
Angiectasis, focal		1 (2%)		
Focal cellular change	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Granuloma, multiple	1 (2%)	3 (6%)	1 (2%)	
Hematopoietic cell proliferation	5 (10%)	4 (8%)	1 (2%)	4 (8%)
Infiltration cellular, megakaryocyte		1 (2%)		
Infiltration cellular, lymphocytic			1 (2%)	
Necrosis, focal	2 (4%)			
Necrosis, multifocal		1 (2%)	3 (6%)	2 (4%)
Vacuolization cytoplasmic, diffuse		1 (2%)		1 (2%)
Kupffer cell, hyperplasia		1 (2%)		
Kupffer cell, pigmentation, multifocal		1 (2%)	1 (2%)	
Serosa, subserosa, inflammation, chronic, multifocal				6 (12%)
Serosa, subserosa, pigmentation, multifocal				10 (20%)
Sinusoid, infiltration cellular, polymorphonuclear	6 (12%)	3 (6%)	14 (28%)	2 (4%)
Subserosa, inflammation, chronic, multifocal			1 (2%)	2 (4%)
Subserosa, pigmentation, multifocal				1 (2%)
Mesentery	(6)	(10)	(7)	(11)
Abscess	1 (17%)			
Inflammation, subacute		1 (10%)		1 (9%)
Inflammation, suppurative, acute	2 (33%)		3 (43%)	2 (18%)
Fat, necrosis, focal	2 (33%)	1 (10%)	3 (43%)	7 (64%)
Fat, necrosis, multifocal		1 (10%)		
Pancreas	(50)	(50)	(48)	(50)
Infiltration cellular, lymphocytic, multifocal	6 (12%)	6 (12%)	5 (10%)	10 (20%)
Inflammation, suppurative, acute		2 (4%)	4 (8%)	
Acinus, atrophy, focal		1 (2%)		
Acinus, atrophy, multifocal	1 (2%)	5 (10%)	1 (2%)	
Acinus, necrosis, focal		1 (2%)		
Duct, cyst	2 (4%)	3 (6%)		
Duct, dilatation			1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Atrophy, focal		1 (2%)		
Hyperplasia, focal		1 (2%)		
Infiltration cellular, lymphocytic, multifocal	24 (48%)	22 (44%)	21 (42%)	23 (46%)
Pigmentation, hemosiderin, focal		1 (2%)		

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
ALIMENTARY SYSTEM (Continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Cyst epithelial inclusion		1 (2%)		
Hyperkeratosis, focal		1 (2%)		
Hyperplasia		5 (10%)	5 (10%)	3 (6%)
Inflammation, subacute		3 (6%)	4 (8%)	
Mineralization				1 (2%)
Ulcer		1 (2%)	1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion, multiple			1 (2%)	
Inflammation, subacute	1 (2%)	1 (2%)		2 (4%)
Mineralization		1 (2%)	2 (4%)	1 (2%)
CARDIOVASCULAR SYSTEM				
Heart	(50)	(50)	(50)	(50)
Angiectasis, focal		1 (2%)		
Inflammation, acute, focal			1 (2%)	
Inflammation, subacute, focal		2 (4%)	1 (2%)	
Mineralization, multifocal		1 (2%)		
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Degeneration, fatty, focal	1 (2%)			
Hematopoietic cell proliferation			2 (4%)	
Hyperplasia, focal	1 (2%)		2 (4%)	2 (4%)
Hypertrophy, focal			1 (2%)	
Capsule, accessory adrenal cortical nodule				1 (2%)
Spindle cell, hyperplasia, focal			2 (4%)	
Adrenal gland, medulla	(50)	(50)	(50)	(50)
Hyperplasia, focal		2 (4%)	2 (4%)	1 (2%)
Islets, pancreatic	(50)	(50)	(48)	(50)
Hyperplasia	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Parathyroid gland	(48)	(45)	(45)	(44)
Cyst	1 (2%)			
Pituitary gland	(46)	(49)	(49)	(49)
Pars distalis, angiectasis	5 (11%)	5 (10%)	6 (12%)	11 (22%)
Pars distalis, cyst		1 (2%)	1 (2%)	1 (2%)
Pars distalis, hyperplasia, focal	12 (26%)	14 (29%)	9 (18%)	6 (12%)
Pars distalis, pigmentation, hemosiderin	1 (2%)			
Thyroid gland	(50)	(50)	(49)	(50)
Ultimobranchial cyst		1 (2%)		
C-cell, hyperplasia, focal	2 (4%)		1 (2%)	
Follicle, cyst	2 (4%)	1 (2%)	3 (6%)	4 (8%)
Follicle, degeneration, cystic	14 (28%)	13 (26%)	11 (22%)	12 (24%)
Follicular cell, hyperplasia, cystic, focal	2 (4%)	2 (4%)		3 (6%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Ovary	(48)	(49)	(50)	(50)
Abscess	9 (19%)	6 (12%)	15 (30%)	3 (6%)
Angiectasis		1 (2%)		
Cyst	7 (15%)	11 (22%)	9 (18%)	12 (24%)
Cyst, two	1 (2%)	1 (2%)		
Hemorrhage				1 (2%)
Hyperplasia, tubular	1 (2%)		1 (2%)	
Infiltration cellular, lymphocytic, multifocal			1 (2%)	

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
GENITAL SYSTEM (Continued)				
Uterus	(50)	(50)	(50)	(50)
Angiectasis		3 (6%)		1 (2%)
Cyst			1 (2%)	
Hydrometra	6 (12%)	6 (12%)	3 (6%)	2 (4%)
Inflammation, suppurative, acute	2 (4%)	4 (8%)	8 (16%)	2 (4%)
Endometrium, hyperplasia, cystic	43 (86%)	42 (84%)	44 (88%)	48 (96%)
HEMATOPOIETIC SYSTEM				
Blood	(2)	(2)	(1)	(1)
Leukocytosis	1 (50%)	1 (50%)	1 (100%)	1 (100%)
Polychromasia		1 (50%)	1 (100%)	
Bone marrow	(50)	(49)	(49)	(50)
Hyperplasia	8 (16%)	13 (27%)	11 (22%)	8 (16%)
Infiltration cellular, megakaryocyte		1 (2%)		
Lymph node	(50)	(50)	(50)	(50)
Iliac, hyperplasia, lymphoid	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Mediastinal, hyperplasia, lymphoid	1 (2%)		1 (2%)	1 (2%)
Mediastinal, inflammation, suppurative, acute		1 (2%)	1 (2%)	
Renal, hyperplasia, lymphoid	2 (4%)	5 (10%)	5 (10%)	1 (2%)
Lymph node, mandibular	(47)	(47)	(49)	(48)
Hyperplasia, lymphoid		1 (2%)		7 (15%)
Infiltration cellular, megakaryocyte		1 (2%)		
Lymph node, mesenteric	(48)	(46)	(49)	(48)
Angiectasis		2 (4%)		
Hyperplasia, lymphoid	12 (25%)	9 (20%)	13 (27%)	13 (27%)
Infiltration cellular, megakaryocyte		1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Atrophy		1 (2%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	16 (32%)	17 (34%)	19 (38%)	11 (22%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)	
Infiltration cellular, megakaryocyte		1 (2%)		
Thymus	(49)	(47)	(44)	(46)
Cyst		4 (9%)	2 (5%)	1 (2%)
INTEGUMENTARY SYSTEM				
Mammary gland	(50)	(50)	(50)	(48)
Duct, cyst	4 (8%)	1 (2%)	2 (4%)	2 (4%)
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrosis, focal				1 (2%)
MUSCULOSKELETAL SYSTEM				
Bone	(50)	(50)	(50)	(50)
Femur, fracture		1 (2%)		
Skeletal muscle	(1)	(3)	(1)	
Inflammation, suppurative, acute			1 (100%)	
NERVOUS SYSTEM				
Brain	(50)	(50)	(50)	(50)
Compression				1 (2%)
Granuloma		1 (2%)		
Hemorrhage, focal		1 (2%)		1 (2%)
Meninges, inflammation, suppurative, acute	1 (2%)			

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

	Vehicle Control	50 mg/kg	100 mg/kg	175 mg/kg
RESPIRATORY SYSTEM				
Lung	(50)	(50)	(50)	(50)
Congestion		1 (2%)		
Hemorrhage, focal	1 (2%)			
Infiltration cellular, megakaryocyte		1 (2%)		
Infiltration cellular, polymorphonuclear			1 (2%)	
Infiltration cellular, histiocytic, multifocal	2 (4%)			
Inflammation, suppurative, acute, multifocal			1 (2%)	
Pigmentation, hemosiderin, multifocal				1 (2%)
Alveolar epithelium, hyperplasia, focal		1 (2%)		1 (2%)
Mediastinum, foreign body	1 (2%)			
Mediastinum, inflammation, subacute				1 (2%)
Mediastinum, inflammation, suppurative, acute	3 (6%)	2 (4%)	3 (6%)	
Nose	(50)	(50)	(50)	(50)
Foreign body			1 (2%)	
Inflammation, suppurative, acute		1 (2%)		
Nasolacrimal duct, foreign body	1 (2%)			
Nasolacrimal duct, inflammation, subacute	4 (8%)	5 (10%)	4 (8%)	2 (4%)
SPECIAL SENSES SYSTEM				
Eye		(1)		
Cataract		1 (100%)		
Hyperplasia, melanocyte		1 (100%)		
Harderian gland		(1)	(1)	(2)
Cyst			1 (100%)	
URINARY SYSTEM				
Kidney	(50)	(50)	(50)	(50)
Amyloid deposition				1 (2%)
Fibrosis, focal		3 (6%)		2 (4%)
Inflammation, suppurative, acute, multifocal	1 (2%)	1 (2%)	1 (2%)	
Metaplasia, osseous, focal	1 (2%)	2 (4%)		
Nephropathy, chronic	24 (48%)	33 (66%)	33 (66%)	35 (70%)
Renal tubule, degeneration, multifocal		1 (2%)		
Renal tubule, dilatation, multifocal			1 (2%)	1 (2%)
Renal tubule, mineralization, multifocal		1 (2%)		
Renal tubule, pigmentation, hemosiderin, multifocal				1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Infiltration cellular, lymphocytic, multifocal	7 (14%)	8 (16%)	9 (18%)	6 (12%)
Inflammation, subacute		1 (2%)		

APPENDIX E

SENTINEL ANIMAL PROGRAM

APPENDIX E. SENTINEL ANIMAL PROGRAM

Methods

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

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Data from animals surviving 24 months were collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests were performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai (12,18,24 mo)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (6 mo)	MHV (mouse hepatitis virus) *M. pul.* (*Mycoplasma pulmonis*) (18,24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (12,18,24 mo)	RCV (rat coronavirus) (6,12 mo) Sendai (6 mo)	*M. pul.* (18,24 mo) RCV/SDA (rat coronavirus/sialodacryoadenitis virus) (18,24 mo)

Results

No positive titers were observed.

APPENDIX F

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

Pellet Diet: January 1982 to January 1984

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

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

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

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

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

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

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

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

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.40 ± 0.98	21.8-26.3	25
Crude fat (percent by weight)	5.03 ± 0.58	3.3-5.7	25
Crude fiber (percent by weight)	3.43 ± 0.51	2.9-5.6	25
Ash (percent by weight)	6.53 ± 0.43	5.7-7.3	25
Amino Acids (percent 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	0.665-1.05	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	12,207 ± 480	3,600-24,000	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	16.7 ± 3.19	12.0-27.0	25
Riboflavin (ppm)	7.6 ± 0.85	6.18-8.2	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.8	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.7	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.30 ± 0.13	1.11-1.63	25
Phosphorus (percent)	0.98 ± 0.05	0.89-1.10	25
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.7-99.4	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

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

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.53 ± 0.15	0.17-0.77	25
Cadmium (ppm) (a)	<0.10		25
Lead (ppm)	0.79 ± 0.62	0.33-3.37	25
Mercury (ppm) (a)	<0.05		25
Selenium (ppm)	0.30 ± 0.07	0.13-0.40	25
Aflatoxins (ppb) (a)	<5.0		25
Nitrate nitrogen (ppm) (b)	8.75 ± 4.49	0.10-22.0	25
Nitrite nitrogen (ppm) (b)	2.08 ± 2.01	0.10-7.20	25
BHA (ppm) (c)	4.34 ± 4.68	2.0-17.0	25
BHT (ppm) (c)	2.47 ± 2.53	0.9-12.0	25
Aerobic plate count (CFU/g) (d)	40,477 ± 33,886	4,900-130,000	25
Coliform (MPN/g) (e)	46.27 ± 122.7	3.0-460	25
E. coli (MPN/g) (a)	<3.00		25
Total nitrosamines (ppb) (f)	5.17 ± 5.82	1.7-30.9	25
N-Nitrosodimethylamine (ppb) (f)	4.15 ± 5.81	0.8-30.0	25
N-Nitrosopyrrolidine (ppb) (f)	1.02 ± 0.25	0.81-1.7	25
Pesticides (ppm)			
α-BHC (a,g)	<0.01		25
β-BHC (a)	<0.02		25
γ-BHC (a)	<0.01		25
δ-BHC (a)	<0.01		25
Heptachlor (a)	<0.01		25
Aldrin (a)	<0.01		25
Heptachlor epoxide (a)	<0.01		25
DDE (a)	<0.01		25
DDD (a)	<0.01		25
DDT (a)	<0.01		25
HCB (a)	<0.01		25
Mirex (a)	<0.01		25
Methoxychlor (a)	<0.05		25
Dieldrin (a)	<0.01		25
Endrin (a)	<0.01		25
Telodrin (a)	<0.01		25
Chlordane (a)	<0.05		25
Toxaphene (a)	<0.10		25
Estimated PCBs (a)	<0.20		25
Ronnel (a)	<0.01		25
Ethion (a)	<0.02		25
Trithion (a)	<0.05		25
Diazinon (a)	<0.10		25
Methyl parathion (a)	<0.02		25
Ethyl parathion (a)	<0.02		25
Malathion (h)	0.10 ± 0.09	0.05-0.45	25
Endosulfan I (a)	<0.01		25
Endosulfan II (a)	<0.01		25
Endosulfan sulfate (a)	<0.03		25

(a) All values were less than the detection limit, given in the table as the mean.
(b) Source of contamination: alfalfa, grains, and fish meal
(c) Source 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 G

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION OF FURFURAL FOR THE TOXICOLOGY STUDIES

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APPENDIX G. CHEMICAL CHARACTERIZATION

Procurement and Characterization of Furfural

Furfural was obtained in one lot (lot no. Q112979) from the Quaker Oats Co. (Chicago, IL) as a clear, yellow liquid. The purity of the lot was 99%. Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the furfural studies are on file at the National Institute of Environmental Health Sciences.

The study chemical was identified as furfural by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra (Figures G1 and G2) were consistent with those expected for the structure and with literature spectra (Sadtler Standard Spectra; Varian NMR Spectra Catalog).

The purity of lot no. Q112979 was determined by elemental analysis, Karl Fischer water analysis, potentiometric back-titration of excess dimethylaminoethanol with 0.2 M perchloric acid after the study material was reacted with hydroxylammonium chloride in the presence of dimethylaminoethanol, titration with 0.1 N sodium hydroxide to the phenolphthalein endpoint to determine acid content, thin-layer chromatography, and gas chromatography. Thin-layer chromatography was performed on silica gel plates with two solvent systems: petroleum ether:diethyl ether (1:1) (system 1) and chloroform:methanol (93:7) (system 2). The samples were visualized under ultraviolet light (both 254 nm and 366 nm), with a *p*-phenylenediamine (2% in methanol) spray and a 50% aqueous sulfuric acid overspray. Gas chromatographic analysis was performed with flame ionization detection, a nitrogen carrier at a flow rate of 70 ml/minute, and a 20% SP2100/0.1% Carbowax 1500 column (system 1) or a 10% Carbowax 20M-TPA column (system 2).

The results of elemental analyses for carbon and hydrogen were in agreement with the theoretical values. This lot contained 0.022% water by Karl Fischer analysis. Back-titration with perchloric acid indicated a purity of 99.6%. Acid content was 0.0102 equivalents per liter by sodium hydroxide titration. Thin-layer chromatography by solvent system 1 indicated two minor and four trace impurities; solvent system 2 detected one minor impurity, two trace impurities, and one slight trace impurity. Gas chromatography with system 1 indicated three impurities after the major peak, one with an area of 0.8% relative to the major peak and the remaining two with a combined relative area of 0.2%; an additional four impurities were observed after the major peak, with individual areas less than 0.1% relative to the major peak area. Gas chromatography by system 2 indicated two impurities following the major peak, with areas of 0.1% and 0.9% relative to the major peak, and two additional impurities eluting after the major peak, with individual relative areas of less than 0.1%.

Stability studies were conducted with samples of bulk chemical stored at temperatures from 20° to 60° C under a nitrogen headspace in amber vials. Analyses performed by gas chromatography with the same column as described for system 2 and methylene chloride solutions containing 0.2% (v/v) furfural and 0.34% (v/v) hexadecane as an internal standard indicated that furfural is stable as the bulk chemical when stored for 2 weeks at temperatures up to 60° C. The samples progressively darkened with increasing temperature, indicating some decomposition at the higher temperatures which was not detected by the gas chromatographic system. Throughout the studies, the bulk chemical was stored at −20° C under nitrogen and repackaged as needed into smaller bottles. Confirmation of the stability of the bulk chemical at the study laboratory during the the 13-week and 2-year studies was obtained by gas chromatography with the same column as described before for system 1 and by infrared spectrometry. No changes in the bulk material were observed during the course of the studies by infrared spectrometry.

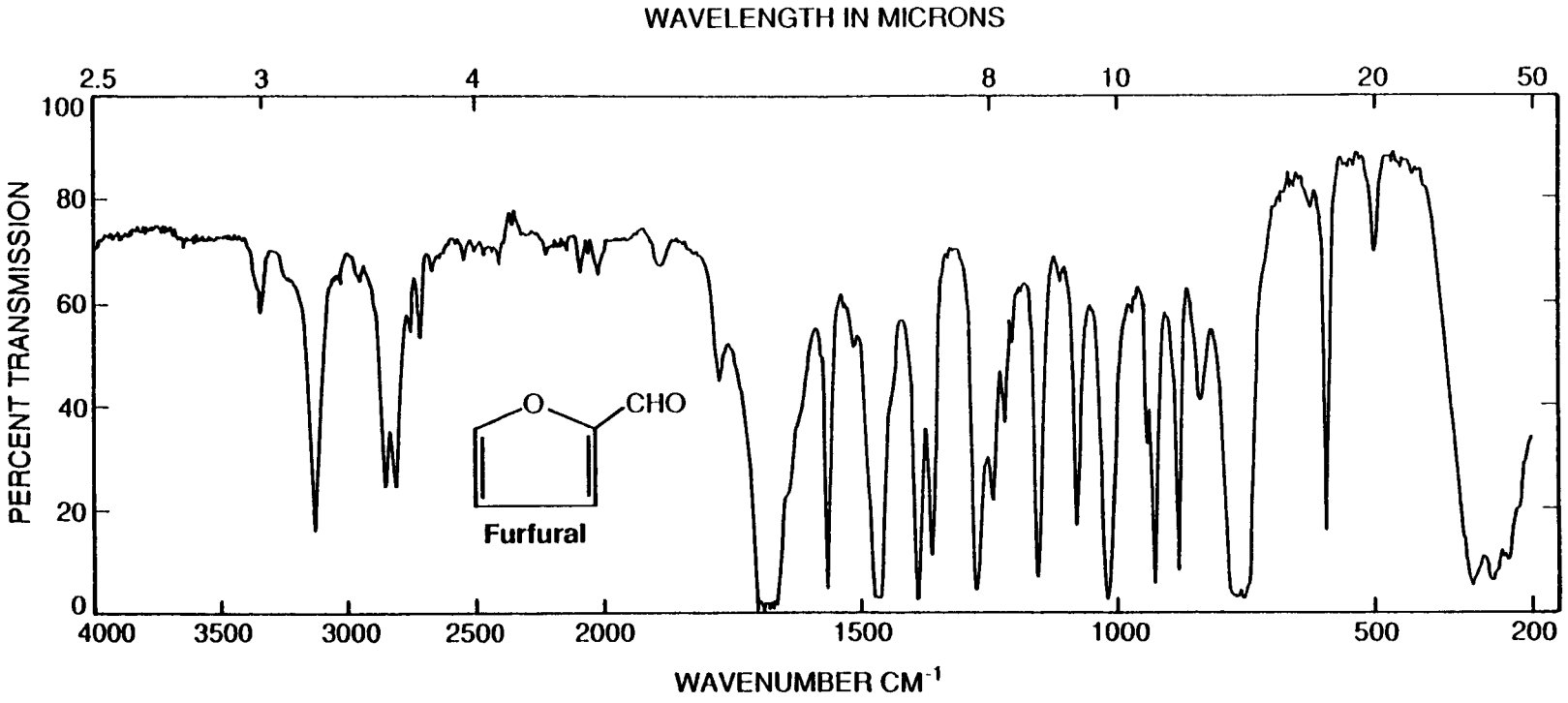

FIGURE G1. INFRARED ABSORPTION SPECTRUM OF FURFURAL (LOT NO. Q112979)

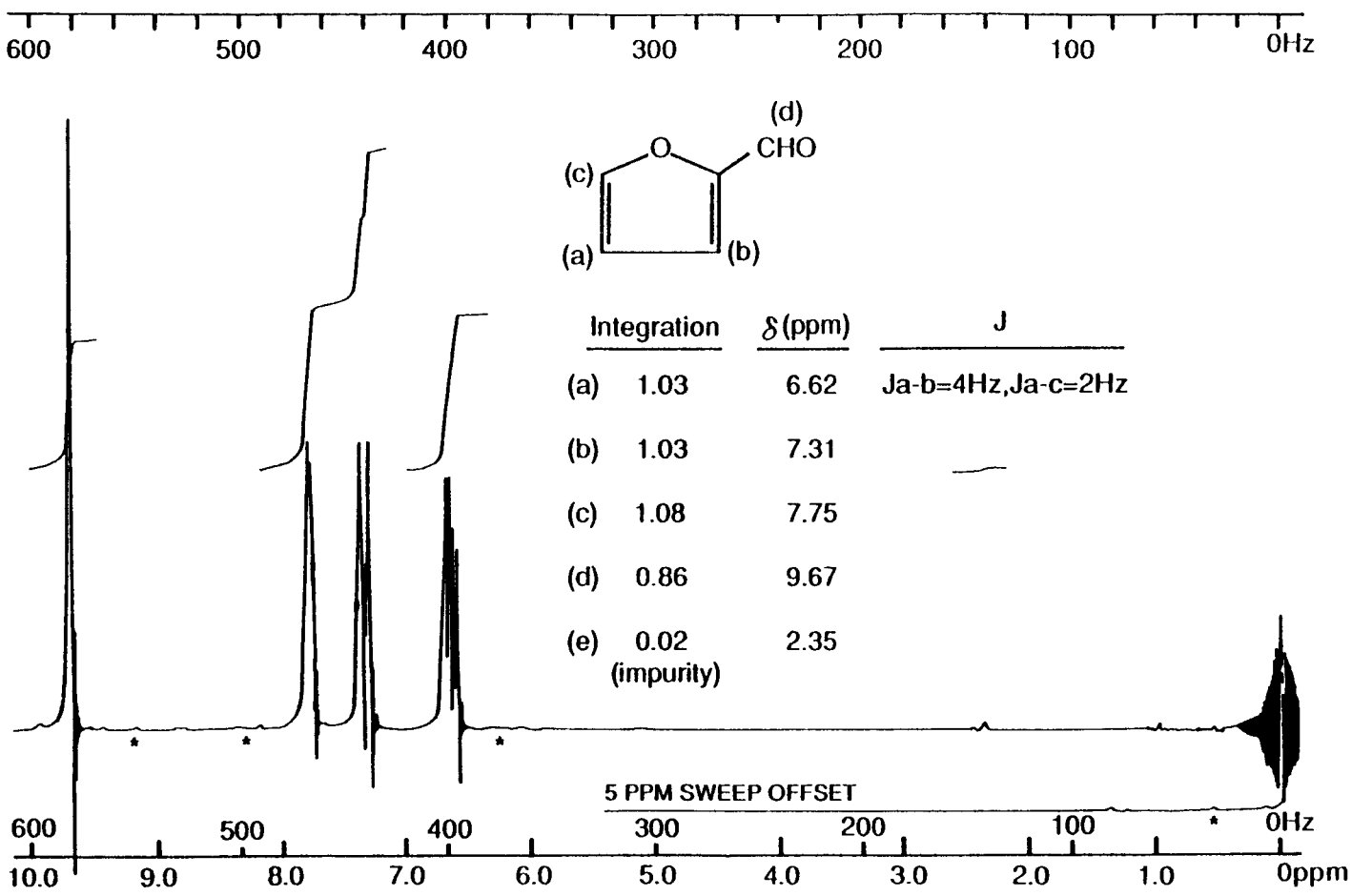

FIGURE G2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF FURFURAL (LOT NO. Q112979)

Preparation and Characterization of Dose Formulations

The appropriate amounts of furfural and corn oil were mixed by stirring in a beaker to give the desired concentrations (Table G1). The stability of furfural in corn oil (4 mg/ml) was determined by gas chromatographic analysis after extraction of a 5-ml sample with 20 ml methanol and the addition of 2 ml octanol in methanol (2 mg/ml) as an internal standard to an 8-ml aliquot of the methanol extract. Gas chromatography was performed with flame ionization detection, a nitrogen carrier, and a 10% Carbowax 20M + KOH column. The chemical in corn oil was found to undergo no notable decrease in concentration after storage in the dark at room temperature for 14 days. The results indicated that some decomposition occurred near the air interface when the solution was stored open to air and light for 3 hours. During the studies, the dose formulations were stored at 5° C under nitrogen and in amber serum bottles for no longer than 2 weeks.

Periodic analysis of furfural/corn oil dose formulations was conducted at the study laboratory and the analytical chemistry laboratory by extracting the mixtures with methanol and reading the absorbance of the methanol extract at 270 nm. Dose formulations were analyzed three times during the 13-week studies (Table G2).

During the 2-year studies, the dose formulations were analyzed at approximately 8-week intervals by ultraviolet spectroscopy after methanol extraction. One set of analyses was also performed by gas chromatography. Both sets of results were considered to be consistent. Based on the number of times that concentrations were within specifications, it was estimated that the mixtures were formulated within ±10% of the target concentrations approximately 93% (69/74) of the time throughout the studies (Table G3). Five times during the studies, aliquots of each dose formulation were taken from residual formulation after completion of dosing and were analyzed. Analysis of the first set of animal room samples indicated a decrease in furfural concentration due to evaporation during handling. With increased care in the handling of dose formulations in the animal rooms, no other decrease in furfural concentration was observed. Results of periodic referee analyses performed by the analytical chemistry laboratory indicated generally good agreement with the results from the study laboratory (Table G4). For one set of samples, results from the analytical chemistry laboratory were 83% of the target concentrations, and those from the study laboratory were 103% of the target concentrations. It was concluded that chemical loss probably occurred during sample shipping or handling.

TABLE G1. PREPARATION AND STORAGE OF DOSE FORMULATIONS IN THE GAVAGE STUDIES OF FURFURAL

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
Appropriate weight of chemical added to beaker. Corn oil added to volume. Mixture stirred with stir bar for 3 min	Appropriate volume of corn oil added to chemical in a beaker. Beaker flushed with nitrogen, covered with aluminum foil, and placed on magnetic stirrer for 3 min	Appropriate volume of chemical added to beaker containing appropriate weight of corn oil. Beaker flushed with nitrogen, covered with aluminum foil, and placed on magnetic stirrer for 1-2 min
Maximum Storage Time		
14 d	14 d	14 d
Storage Conditions		
5° C under nitrogen in amber serum bottles	5° C under nitrogen in amber serum bottles	5° C under nitrogen in amber serum bottles

TABLE G2. RESULTS OF ANALYSIS OF DOSE FORMULATIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF FURFURAL

Date Mixed	Concentration of Furfural in Corn Oil (a)		Determined as a Percent of Target
	Target	Determined (b)	
01/20/81	2.2	2.24	102.0
	4.4	4.16	94.5
	7.5	7.3	97.3
	9.0	8.41	93.4
	15.0	(c) 13.2	88.0
	18.0	17.5	97.2
	30.0	27.2	90.7
	36.0	33.5	93.6
	60.0	(c) 125.6	209.3
	120.0	(c) 295.6	246.3
01/23/81	60.0	(d) 63.2	105.3
01/27/81	2.2	2.12	96.4
	4.4	(c) 3.8	86.4
	7.5	7.92	105.6
	9.0	(c) 7.97	88.6
	15.0	(c) 12.2	81.3
	18.0	16.8	93.3
	30.0	27.5	91.7
	36.0	36.0	100.0
	60.0	58.0	96.7
	120.0	116.0	96.7
01/29/81	4.4	(c,d) 3.64	85.0
	9.0	(c,d) 7.97	88.5
	15.0	(d) 14.2	94.7
02/02/81	4.4	4.80	109.1
	9.0	9.65	107.2
03/03/81	2.4	(e) 2.16	90.0
	4.8	(c,e) 3.83	79.8
	8.2	(c,e) 7.10	86.6
	9.8	(c,e) 8.52	88.0
	16.0	(e) 15.3	95.6
	20.0	(e) 18.8	94.0
	33.0	(e) 31.9	96.7
	39.0	(e) 36.5	93.6
	65.0	(c,e) 57.0	87.7
03/06/81	4.8	(d) 4.4	91.6
	8.2	(d) 7.7	93.9
	9.8	(d) 9.3	94.8
	65.0	(d) 63.3	97.5

(a) Concentration of formulations prepared through 1/29/81 are expressed as milligrams per milliliter of corn oil; from 2/2/81 through 3/6/81, the concentration is expressed as milligrams per gram of corn oil.
(b) Results of duplicate analysis except as noted
(c) Out of specifications
(d) Remix
(e) Results of single analysis

TABLE G3. RESULTS OF ANALYSIS OF DOSE FORMULATIONS IN THE TWO-YEAR GAVAGE STUDIES OF FURFURAL

Date Mixed	Determined Concentration of Furfural in Corn Oil for Target Concentration (mg/g) (a)				
	5.4	6.5	10.9	13.1	19
03/02/82	5.45		10.6		18.4
03/09/82		6.44		12.6	
04/27/82	(b) 4.80	(b) 5.80	(b) 9.7	(b) 11.7	(b) 14.7
04/29/82	(c) 4.76	(c) 5.81	9.9	11.8	(c) 16.2
05/04/82	5.16	5.94	10.6	12.2	18.0
06/22/82	4.87	6.14	10.4	12.4	18.1
08/24/82	5.05	6.27	10.2	12.4	18.0
10/12/82	5.59	6.59	11.2	13.2	19.2
12/07/82	5.44	6.70	11.4	12.8	19.7
02/04/83	5.28	6.28	10.5	12.7	18.5
04/01/83	5.34	6.48	10.8	12.9	18.8
05/27/83	5.52	6.63	11.1	13.0	19.0
07/22/83	5.28	6.38	10.8	13.0	18.7
09/16/83	5.40	6.49	10.9	13.0	19.0
11/11/83	5.32	6.40	10.6	12.8	18.8
01/06/84	5.48	6.40	11.0	12.8	18.9
02/24/84		6.42		12.9	
Mean (mg/g)	5.28	6.36	10.6	12.6	18.4
Standard deviation	0.238	0.245	0.47	0.43	1.17
Coefficient of variation (percent)	4.5	3.9	4.4	3.4	6.4
Range (mg/g)	4.80-5.59	5.80-6.70	9.7-11.4	11.7-13.2	14.7-19.7
Number of samples	14	15	15	16	14

(a) Results of duplicate analysis
(b) Out of specifications; not used in studies.
(c) Remix; out of specifications; not included in the mean.

TABLE G4. RESULTS OF REFEREE ANALYSIS OF DOSE FORMULATIONS IN THE TWO-YEAR GAVAGE STUDIES OF FURFURAL

Date Mixed	Target Concentration (mg/g)	Determined Concentration (mg/g)	
		Study Laboratory (a)	Referee Laboratory (b)
03/02/82	5.4	5.45	5.5
10/12/82	6.5	6.59	6.44
12/07/82	19.0	19.7	15.9
05/27/83	13.1	13.0	13.0
11/11/83	5.4	5.32	5.17

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

APPENDIX H

GENETIC TOXICOLOGY

OF FURFURAL

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METHODS

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Haworth et al. (1983) and Mortelmans et al. (1986). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Chemicals were tested in a series (four strains used). Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 6.7 mg/plate. All negative assays were repeated, and all positive assays were repeated under the conditions that elicited the positive response.

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

Mouse Lymphoma Protocol: The experimental protocol is presented in detail by McGregor et al. (1988) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 800 µg/ml. Mouse L5178Y/TK lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM L-glutamine, 110 µg/ml sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (Tft)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added.

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

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr et al. (1985). This assay was performed without S9.

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/ml.

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

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

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

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

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

Drosophila Melanogaster Protocol: The assays for gene mutation and chromosomal translocation induction were performed as described by Woodruff et al. (1985). Study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). Initially, study chemicals were assayed in the

sex-linked recessive lethal (SLRL) test by feeding to adult Canton-S wild-type males that were no more than 24 hours old. If no response was obtained, the chemical was retested by injection into adult males. If either route of administration produced a positive result, the chemical was assayed for induction of reciprocal translocations (RTs) by using the same method of exposure. If, because of the physical nature of the chemical, feeding experiments were not possible, injection was selected as the method of study chemical administration, and a positive result was followed by an RT test.

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

Toxicity tests attempted to set concentrations of study chemical at a level that would produce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, exposure by feeding was done by allowing Canton-S males (10-20 flies per vial) to feed for 72 hours on a solution of the study chemical in 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were given a solution of the chemical dissolved in 0.7% saline or peanut oil and allowed 24 hours to recover. 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 as successively earlier postmeiotic stages. F_1 heterozygous females were allowed to mate with their siblings and then were 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 result 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. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. At least two experiments were performed for each study chemical, resulting in the testing of some 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 run.

Recessive lethal data were analyzed by the normal 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 than 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 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or (b) the P value was between 0.10 and 0.05 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%.

For the RT test, the exposure regimen was the same as that for the SLRL test except that small mass matings were used (10 males and 20 females). Exposed males were mated to X.Y;y;bw;st females for 3 days and discarded. The females were transferred to fresh medium every 3-4 days for a period of about 3 weeks to produce a total of six broods. The results of the SLRL test were used to narrow the germ-cell stage most likely to be affected by the chemical; for example, if earlier germ-cell stages seemed to exhibit increased sensitivity, mating of the males was continued and translocation tests were carried out from the offspring derived from these earlier germ cell stages. F_1 males were mated individually to X.Y;y;bw;st females and the progeny were examined for missing classes, which indicate the occurrence of a translocation in the parental male. Suspected RTs were retested. The

translocation data were analyzed according to the conditional binomial (Kastenbaum and Bowman, 1970).

In Vivo Mouse Bone Marrow Sister Chromatid Exchange Study Protocol: Doses of study chemical are determined by solubility of the chemical, animal lethality, and/or cell cycle delay induced by chemical exposure. Top dose should not exceed 5,000 mg/kg. A dose range-finding study was performed first, in the absence of adequate toxicity information from the literature. Based on animal mortality, the maximum dose of furfural was set at 200 mg/kg. Male $B6C3F_1$ mice (five animals per dose group) received intraperitoneal injections of furfural dissolved in phosphate-buffered saline (PBS) (injection volume = 0.4 ml). Solvent control mice received equivalent injections of PBS only. The positive control mice received injections of 0.5 mg/kg mitomycin C. One hour prior to intraperitoneal injection, the mice were implanted subcutaneously with a 50-mg BrdU tablet (McFee et al., 1983), and 2 hours before being killed, the mice received an intraperitoneal injection of 2 mg/kg colchicine (in saline). Twenty-three hours after administration of furfural, the animals were killed by cervical dislocation. One or both femurs were removed, and the marrow was flushed out with 5 ml 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 dose group. Responses were evaluated as SCE/cell, and the data were analyzed by trend test (Margolin et al., 1986).

In Vivo Mouse Bone Marrow Chromosomal Aberration Study Protocol: Doses of study chemical are determined by solubility of the chemical, animal lethality, and/or cell cycle delay induced by chemical exposure. Top dose should not exceed 5,000 mg/kg. A dose range-finding study was performed first in the absence of adequate toxicity information from the literature. Based on animal mortality, the maximum dose of furfural was set at 200 mg/kg. Male $B6C3F_1$ mice (10 animals per dose group) received intraperitoneal injections of furfural dissolved in PBS (injection volume = 0.4 ml). Solvent control mice received equivalent injections of PBS only. The positive control mice received injections of 1.0 mg/kg mitomycin C. One hour before injection with furfural, the mice were implanted subcutaneously with a 50-mg BrdU tablet (McFee et al., 1983). BrdU was used to allow selection of the appropriate cell population for scoring. (Chemically induced chromosomal aberrations are present in maximum number at the first metaphase after chemical administration; they decline in number during subsequent nuclear divisions due to cell death.) Two hours before being killed, the mice received an intraperitoneal injection of 2 mg/kg colchicine (in saline). Seventeen hours after furfural administration (18 hours after receiving BrdU), the animals were killed by cervical dislocation. 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 dose group. 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 trend test (Margolin et al., 1986).

RESULTS

Furfural (33-6,666 µg/plate) was tested in two laboratories for induction of gene mutations in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 in a preincubation protocol with and without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Mortelmans et al., 1986; Table H1). Results of the Case Western Reserve University study were negative in all four strains, but in the study performed at SRI International, an equivocal response was noted in strain TA100 without S9. Furfural induced Tft resistance in mouse L5178Y/TK lymphoma cells at doses of 200 and 400 µg/ml in the absence of S9; it was not tested with S9 (McGregor et al., 1988; Table H2). In cytogenetic tests with CHO cells, furfural induced SCEs (Table H3) and chromosomal aberrations (Table H4) in both the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9. Chemical-induced cell cycle delay was observed in both tests; significant increases in SCEs were observed in trials where delayed harvest was used, as well as in trials harvested at the normal time (26 hours). In germ cells of male Drosophila, furfural administered by abdominal injection (100 ppm) induced a significant increase in sex-linked recessive lethal mutations; no increase was observed when furfural was administered by feeding (1,000 ppm) (Woodruff et al., 1985; Table H5). Furfural administered by abdominal injection (100 ppm) did not induce reciprocal translocations in the germ cells of male Drosophila (Woodruff et al., 1985; Table H6). Furfural did not induce SCEs or chromosomal aberrations in bone marrow cells of male $B6C3F_1$ mice when administered by intraperitoneal injection at doses of 50, 100, or 200 mg/kg (Tables H7 and H8).

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

Strain	Dose (µg/plate)	Revertants/Plate (b)							
Studies conducted at Case Western Reserve University									
		−S9			+10% S9 (hamster)		+10% S9 (rat)		
TA100		Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 1	Trial 2	Trial 3
	0	117 ± 8.1	124 ± 5.1	89 ± 16.0	155 ± 3.5	123 ± 17.8	255 ±106.2	159 ± 15.1	146 ± 6.2
	33	108 ± 6.7	119 ± 3.5		153 ± 13.7		166 ± 3.5	162 ± 8.5	
	100	105 ± 12.7	125 ± 9.8		151 ± 15.3		173 ± 12.5	160 ± 16.8	
	333	106 ± 3.5	114 ± 3.6		152 ± 10.2		146 ± 7.5	166 ± 9.8	
	666			83 ± 1.5		159 ± 12.2			169 ± 5.8
	1,000	105 ± 3.0	137 ± 12.9	77 ± 6.4	185 ± 7.8	151 ± 12.7	147 ± 6.0	180 ± 12.3	174 ± 10.7
	1,666			64 ± 9.8		140 ± 23.2			163 ± 1.7
	3,333	87 ± 7.5	Toxic	Toxic	250 ± 13.7	Toxic	269 ± 19.8	Toxic	Toxic
	6,666			Toxic		Toxic			Toxic
Trial summary		Negative	Negative	Negative	Equivocal	Negative	Negative	Negative	Negative
Positive control (c)		334 ± 10.4	374 ± 15.6	467 ± 11.3	628 ± 39.1	868 ± 75.0	539 ± 86.0	367 ± 11.7	627 ± 35.8

		−S9		+10% S9 (hamster)		+10% S9 (rat)	
TA1535		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
	0	5 ± 1.2	6 ± 0.7	4 ± 0.9	7 ± 1.8	4 ± 1.5	7 ± 1.5
	33	5 ± 1.8	6 ± 0.9	8 ± 2.3	10 ± 2.7	7 ± 1.2	10 ± 1.2
	100	7 ± 1.3	7 ± 0.9	8 ± 1.5	10 ± 2.5	8 ± 1.9	10 ± 2.2
	333	5 ± 1.5	7 ± 0.7	7 ± 0.6	11 ± 0.9	9 ± 1.5	9 ± 3.4
	1,000	6 ± 0.9	6 ± 1.2	8 ± 1.2	10 ± 2.6	7 ± 1.5	8 ± 1.9
	3,333	5 ± 1.5	6 ± 0.3	9 ± 1.5	10 ± 3.7	7 ± 1.5	7 ± 2.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		447 ± 23.3	347 ± 32.6	48 ± 8.9	67 ± 11.5	21 ± 4.5	26 ± 2.6

		−S9		+S9 (hamster)		+S9 (rat)	
TA1537		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
	0	5 ± 0.0	3 ± 2.0	5 ± 0.7	8 ± 1.3	13 ± 2.8	6 ± 2.7
	33	5 ± 2.0	4 ± 0.6	8 ± 3.0	8 ± 2.0	7 ± 2.0	4 ± 0.0
	100	6 ± 0.7	4 ± 0.3	6 ± 1.2	7 ± 1.2	10 ± 2.1	6 ± 1.2
	333	3 ± 1.2	4 ± 1.0	4 ± 0.0	7 ± 0.3	8 ± 0.9	4 ± 0.6
	1,000	3 ± 0.3	6 ± 1.9	5 ± 0.9	6 ± 0.9	9 ± 1.3	9 ± 2.1
	3,333	2 ± 0.7	5 ± 2.0	8 ± 1.9	7 ± 2.3	8 ± 1.2	3 ± 0.6
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		332 ± 29.2	123 ± 7.0	29 ± 2.1	129 ± 12.7	29 ± 2.0	40 ± 12.3

		−S9		+S9 (hamster)		+S9 (rat)	
TA98		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
	0	17 ± 3.0	18 ± 2.3	25 ± 1.5	23 ± 1.5	28 ± 2.4	26 ± 3.6
	33	14 ± 0.9	17 ± 1.2	28 ± 0.3	22 ± 3.5	27 ± 2.0	20 ± 2.4
	100	10 ± 0.6	12 ± 2.2	23 ± 2.9	24 ± 1.5	32 ± 2.8	21 ± 4.5
	333	10 ± 1.3	17 ± 3.4	27 ± 1.8	30 ± 4.0	28 ± 2.7	20 ± 3.2
	1,000	11 ± 1.5	17 ± 5.5	25 ± 2.5	24 ± 2.3	28 ± 3.7	26 ± 1.5
	3,333	11 ± 2.5	27 ± 8.0	27 ± 3.0	29 ± 2.6	24 ± 3.0	35 ± 7.4
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		221 ± 19.1	446 ± 29.9	553 ± 21.7	901 ± 63.2	469 ± 29.0	384 ± 11.1

TABLE H1. MUTAGENICITY OF FURFURAL IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
Studies conducted at SRI International							
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	85 ± 6.6	91 ± 6.1	84 ± 6.2	89 ± 4.0	96 ± 10.0	92 ± 4.3
	33.3		92 ± 3.0				
	100	91 ± 1.5	100 ± 2.6	89 ± 3.8	111 ± 3.3	84 ± 2.0	108 ± 5.9
	333.3	94 ± 8.4	105 ± 0.3	77 ± 10.0	112 ± 6.0	92 ± 13.9	104 ± 8.4
	1,000	129 ± 7.2	174 ± 6.7	92 ± 6.7	126 ± 17.5	88 ± 6.4	159 ± 10.7
	3,333.3	(d) 69 ± 3.8	(d) 27 ± 17.2	116 ± 16.9	(d) 40 ± 5.7	90 ± 2.0	(d) 32 ± 7.3
	6,666.7	Toxic		(d) 25 ± 25.3	(d) 0 ± 0.0	(d) 67 ± 24.7	(d) 3 ± 1.5
Trial summary		Equivocal	Equivocal	Negative	Negative	Negative	Negative
Positive control (c)		413 ± 8.8	338 ± 11.6	1,383 ± 66.9	1,932 ± 40.0	528 ± 9.3	861 ± 48.2
TA1535	0	10 ± 1.3	8 ± 0.6	6 ± 2.5	6 ± 1.7	9 ± 1.5	6 ± 0.9
	33.3		14 ± 1.2				
	100	17 ± 1.2	11 ± 2.7	8 ± 2.3	12 ± 1.9	7 ± 1.2	6 ± 0.9
	333.3	12 ± 4.0	10 ± 2.2	3 ± 1.5	6 ± 2.1	9 ± 2.6	5 ± 0.3
	1,000	10 ± 2.5	7 ± 0.7	7 ± 1.5	9 ± 2.5	8 ± 0.7	6 ± 1.5
	3,333.3	(d) 5 ± 1.3	(d) 4 ± 0.3	5 ± 0.3	(d) 4 ± 2.3	8 ± 2.2	(d) 3 ± 1.0
	6,666.7	(d) 1 ± 1.0		2 ± 1.2	(d) 0 ± 0.0	4 ± 0.3	(d) 1 ± 0.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		350 ± 10.4	183 ± 10.7	470 ± 34.0	285 ± 23.9	313 ± 14.2	222 ± 8.2
TA1537	0	7 ± 1.5	7 ± 1.3	7 ± 3.1	3 ± 0.7	9 ± 2.1	3 ± 1.0
	33.3		9 ± 0.6		9 ± 1.2		12 ± 2.6
	100	7 ± 1.9	8 ± 2.1	11 ± 2.4	8 ± 1.9	7 ± 1.5	13 ± 1.2
	333.3	7 ± 1.2	5 ± 0.9	8 ± 2.3	12 ± 2.0	4 ± 0.9	12 ± 1.7
	1,000	3 ± 1.2	9 ± 2.3	5 ± 0.6	9 ± 1.9	6 ± 1.2	10 ± 3.7
	3,333.3	(d) 1 ± 0.7	(d) 6 ± 0.9	3 ± 0.6	(d) 4 ± 0.3	5 ± 0.9	(d) 0 ± 0.3
	6,666.7	(d) 0 ± 0.3		0 ± 0.3		3 ± 1.7	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		124 ± 40.2	197 ± 18.6	445 ± 13.0	159 ± 21.9	235 ± 5.8	132 ± 18.3
TA98	0	28 ± 1.7	23 ± 1.2	24 ± 1.7	27 ± 2.2	35 ± 5.9	29 ± 4.3
	33.3		24 ± 3.0				
	100	26 ± 5.4	15 ± 1.5	37 ± 3.9	29 ± 6.8	36 ± 8.0	34 ± 3.8
	333.3	31 ± 2.9	18 ± 2.5	30 ± 4.9	24 ± 1.8	37 ± 4.7	35 ± 2.7
	1,000	27 ± 1.2	20 ± 3.3	32 ± 3.8	28 ± 2.2	36 ± 2.8	31 ± 1.2
	3,333.3	(d) 6 ± 0.9	(d) 7 ± 1.2	19 ± 3.3	22 ± 1.5	(d) 14 ± 0.7	25 ± 0.6
	6,666.7	(d) 0 ± 0.0		(d) 0 ± 0.0	(d) 2 ± 1.7	(d) 1 ± 1.0	(d) 0 ± 0.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		797 ± 18.8	650 ± 22.0	1,177 ± 53.5	1,486 ± 13.8	326 ± 16.1	550 ± 17.9

(a) The detailed protocol and the data are presented in Mortelmans et al. (1986). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.
(d) Slight toxicity

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

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
Trial 1					
Distilled water (d)		66.7 ± 8.2	100.0 ± 11.2	127.3 ± 21.8	64.3 ± 11.1
Furfural	25	71.5 ± 0.5	122.0 ± 15.0	114.0 ± 12.0	53.0 ± 5.0
	50	71.5 ± 2.5	91.0 ± 1.0	127.5 ± 0.5	59.5 ± 2.5
	100	43.0 ± 9.0	60.0 ± 15.0	125.0 ± 4.0	100.5 ± 18.5
	200	51.5 ± 3.5	31.5 ± 3.5	205.0 ± 10.0	(e) 133.0 ± 16.0
	400	29.5 ± 5.5	9.5 ± 1.5	615.0 ± 12.0	(e) 721.0 ± 138.0
	800	Lethal			
Methyl methanesulfonate	15	20.5 ± 4.5	11.0 ± 3.0	376.0 ± 64.0	(e) 624.0 ± 33.0
Trial 2					
Distilled water (f)		80.0 ± 6.8	100.0 ± 5.4	224.0 ± 13.2	94.5 ± 3.9
Furfural	25	81.0 ± 5.0	104.5 ± 9.5	229.0 ± 10.0	95.0 ± 10.0
	50	86.5 ± 2.5	86.0 ± 2.0	250.0 ± 48.0	96.0 ± 16.0
	100	93.5 ± 12.5	55.0 ± 0.0	312.0 ± 40.0	111.5 ± 0.5
	200	65.0 ± 9.0	27.0 ± 1.0	430.5 ± 26.5	(e) 223.0 ± 16.0
	400	Lethal			
Methyl methanesulfonate	15	35.5 ± 10.5	19.5 ± 3.5	565.0 ± 161.0	(e) 529.0 ± 3.0

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

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

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

(d) Data presented are the average of three tests.

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

(f) Data presented are the average of four tests.

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

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/ Chromosome (percent) (b)
−S9 (c)--Summary: Positive								
Dimethyl sulfoxide		50	1,046	490	0.46	9.8	25.8	
Furfural	11.7	50	1,048	640	0.61	12.8	25.8	**30.36
	38.9	50	1,038	874	0.84	17.5	(d) 35.8	**79.74
	117	50	1,037	851	0.82	17.0	(d) 35.8	**75.18
Mitomycin C	0.001	50	1,048	762	0.72	15.2	25.8	55.21
	0.01	5	104	261	2.50	52.2	25.8	435.73
Trend test: P<0.001								
+S9 (e)--Summary: Positive								
Dimethyl sulfoxide		50	1,048	473	0.45	9.5	25.8	
Furfural	117	50	1,046	568	0.54	11.4	25.8	**20.32
	389	50	1,046	686	0.65	13.7	25.8	**45.31
	1,170	50	1,044	1,252	1.19	25.0	(d) 35.8	**165.71
Cyclophosphamide	0.3	50	1,053	777	0.73	15.5	25.8	63.49
	2	5	105	212	2.01	42.4	25.8	347.35
Trend test: P<0.001								

(a) Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as described in (c) and (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.
(b) Percentage change in the value of SCEs/chromosome for exposed culture compared with that for solvent control culture. An increase of 20% or more was considered to be a significant response.
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
(e) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
**P<0.01

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

−S9 (b) Dose (µg/ml)	Total Cells	Number of Abs	Abs/ Cell	Percent Cells with Abs	+S9 (c) Dose (µg/ml)	Total Cells	Number of Abs	Abs/ Cell	Percent Cells with Abs
Harvest time: 23.5 hours (d)					Harvest time: 22 hours (d)				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	3	0.03	3.0		100	5	0.05	5.0
Furfural					Furfural				
200	100	7	0.07	5.0	500	100	4	0.04	4.0
300	100	7	0.07	6.0	760	100	6	0.06	6.0
400	100	24	0.24	*15.0	1,000	100	118	1.18	*54.0
500	100	23	0.23	*22.0	1,230	0			
Summary: Positive					Summary: Weakly positive				
Mitomycin C					Cyclophosphamide				
0.05	50	26	0.52	28.0	10	50	12	0.24	22.0
Trend test: P<0.001					Trend test: P<0.001				

(a) Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as indicated in (b) and (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(d) Because of significant chemical-induced cell cycle delay, incubation time prior to addition of colcemid was lengthened to provide sufficient metaphases at harvest.
*P<0.05

TABLE H5. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN *DROSOPHILA MELANOGASTER* BY FURFURAL (a)

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested Mating 1	Mating 2	Mating 3	Overall Total (b)
Injection	100	0	0	2/1,919	4/1,977	2/1,817	8/5,713 (0.14%)
	0			0/1,950	0/2,018	0/1,897	0/5,865 (0.00%)
Feeding	1,000	2	0	1/1,915	2/2,257	3/2,120	6/6,292 (0.10%)
	0			2/2,033	2/2,259	1/2,082	5/6,374 (0.08%)

(a) Study performed at Brown University. A detailed protocol of the sex-linked recessive lethal assay is presented by Woodruff et al. (1985). Exposure by feeding was done by allowing 24-hour-old Canton-S males to feed for 3 days on a solution of the study chemical dissolved in 5% sucrose. In the injection experiments, 24-hour-old Canton-S males were treated with a solution of the chemical dissolved in 0.7% saline and allowed 24 hours to recover. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days; sample sperm from successive matings were treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; no clusters were found. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. Results of the injection experiment were significant at the 5% level (Margolin et al., 1983).
(b) Combined total of number of lethal mutations/number of X chromosomes tested for three mating trials

TABLE H6. INDUCTION OF RECIPROCAL TRANSLOCATIONS IN *DROSOPHILA MELANOGASTER* BY FURFURAL (a)

Route of Exposure	Dose (ppm)	Transfers Translocations/Total F_1 Tested 1	2	3	4	5	6	Total Number of Tests	Total Number of Translocations	Total Translocations (percent)
Injection	100	0/1,316	0/1,348	0/1,278	0/2,020	0/488	0/0	6,450	0	0.00
Historical control	0							116,163	2	0.00

(a) Study performed at Brown University. A detailed protocol of the reciprocal translocation assay is presented by Woodruff et al. (1985). Exposed males were mated to three X.Y;y;bw;st females for 3 days and discarded. The females were transferred to fresh medium every 3-4 days to produce a total of six cultures, and then they were discarded. In this manner, sample sperm from successive cultures were stored for increasing lengths of time. Individual F_1 males were backcrossed to X.Y;y;bw;st females, and the F_2 were screened for pseudolinkage. This procedure allows the recovery of translocations involving the Y, second, or third chromosomes in any combination. Presumptive translocations were retested. Results were not significant at the 5% level (Kastenbaum and Bowman, 1970).

TABLE H7. INDUCTION OF SISTER CHROMATID EXCHANGES IN MOUSE BONE MARROW CELLS BY FURFURAL (a)

Compound	Dose (mg/kg)	Mean SCEs/Cell (b)	Number of Animals
Phosphate-buffered saline		3.79 ± 0.278	4
Furfural	50	4.73 ± 0.503	4
	100	3.30 ± 0.427	4
	200	4.09 ± 0.318	4
Trend test (c) P = 0.456			
Mitomycin C	0.5	7.04 ± 0.505	4
P value (d)		P = 0.0006	

(a) Study performed at Brookhaven National Laboratory. Male B6C3F$_1$ mice were given an intraperitoneal injection of furfural dissolved in phosphate-buffered saline (PBS); positive control mice were injected with mitomycin C, and solvent control mice received PBS only. Twenty-three hours after chemical administration, the animals were killed by cervical dislocation. Bone marrow from one or both femurs was treated with 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 dose group.
(b) Mean ± standard error of the mean; SCE = sister chromatid exchange.
(c) One-tailed trend test, used to determine if a dose-related increase is present; P value significant at $\alpha = 0.05$ (Margolin et al., 1986).
(d) Pairwise comparison between the positive control group and solvent control group, conducted with Student's one-tailed *t*-test; P value significant at P = 0.0167.

TABLE H8. INDUCTION OF CHROMOSOMAL ABERRATIONS IN MOUSE BONE MARROW CELLS BY FURFURAL (a)

Compound	Dose (mg/kg)	Aberrations/Cell (b)	Damaged Cells (b) (percent)	Number of Animals
Phosphate-buffered saline		0.027	2.75	8
Furfural	50	0.007	0.75	8
	100	0.007	0.75	8
	200	0.012	1.25	8
Trend test (c)		P = 0.085	P = 0.085	
Mitomycin C	1	0.062	6.00	8
P value (d)		P = 0.038	P = 0.041	

(a) Study performed at Brookhaven National Laboratory. Male B6C3F$_1$ mice were given an intraperitoneal injection of furfural dissolved in phosphate-buffered saline (PBS); solvent control mice were injected with PBS, and positive control mice received mitomycin C. Seventeen hours after chemical administration, the animals were killed by cervical dislocation. 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. Gaps were scored but omitted from this analysis.
(b) Mean ± standard error of the mean
(c) One-tailed trend test used to determine if dose-related increase is present; P value significant at $\alpha = 0.05$ (Margolin et al., 1986)
(d) Pairwise comparison between the positive control group and the solvent control group, conducted using Student's one-tailed *t*-test; P value significant at P = 0.0167.

APPENDIX I

ORGAN WEIGHTS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF FURFURAL

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TABLE I1. ORGAN WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF FURFURAL (a)

	Vehicle Control	11 mg/kg	22 mg/kg	45 mg/kg	90 mg/kg
MALE					
Number weighed	9	10	10	10	9
Body weight (grams)	373 ± 6.2	382 ± 6.1	384 ± 7.1	*393 ± 3.9	**401 ± 6.9
Brain					
Absolute	2,011 ± 33	2,127 ± 126	1,988 ± 16	1,989 ± 15	1,960 ± 27
Relative	5.4 ± 0.07	5.6 ± 0.31	*5.2 ± 0.07	**5.1 ± 0.06	**4.9 ± 0.10
Heart					
Absolute	1,049 ± 30	1,066 ± 23	1,119 ± 32	1,106 ± 20	1,007 ± 120
Relative	2.8 ± 0.07	2.8 ± 0.04	2.9 ± 0.05	2.8 ± 0.04	2.5 ± 0.29
Kidney					
Absolute	1,276 ± 44	1,403 ± 39	1,357 ± 30	*1,336 ± 116	**1,509 ± 47
Relative	3.4 ± 0.09	3.7 ± 0.06	3.5 ± 0.05	3.4 ± 0.29	*3.8 ± 0.08
Liver					
Absolute	14,290 ± 520	15,660 ± 610	15,270 ± 370	14,760 ± 620	**16,820 ± 290
Relative	38.3 ± 1.19	40.9 ± 0.98	39.9 ± 0.96	37.5 ± 1.48	**42.0 ± 0.66
Lung					
Absolute	1,471 ± 63	1,592 ± 69	*1,631 ± 40	*1,601 ± 29	**1,710 ± 71
Relative	3.9 ± 0.13	4.2 ± 0.13	*4.2 ± 0.08	4.1 ± 0.08	4.3 ± 0.15
Thymus					
Absolute	553 ± 36	466 ± 40	480 ± 39	493 ± 41	498 ± 31
Relative	1.5 ± 0.10	1.2 ± 0.10	1.3 ± 0.10	1.3 ± 0.10	1.3 ± 0.08
FEMALE					
Number weighed	9	10	10	10	6
Body weight (grams)	202 ± 2.6	205 ± 2.9	207 ± 2.4	202 ± 3.9	209 ± 2.6
Brain					
Absolute	1,807 ± 10	1,834 ± 16	2,010 ± 131	1,805 ± 19	1,784 ± 23
Relative	9.0 ± 0.12	9.0 ± 0.15	9.7 ± 0.66	9.0 ± 0.18	8.6 ± 0.14
Heart					
Absolute	661 ± 10	675 ± 14	659 ± 5	630 ± 30	671 ± 15
Relative	3.3 ± 0.04	3.3 ± 0.05	3.2 ± 0.04	3.1 ± 0.14	3.2 ± 0.05
Kidney					
Absolute	693 ± 24	735 ± 16	**866 ± 95	711 ± 18	*820 ± 62
Relative	3.4 ± 0.11	3.6 ± 0.05	*4.2 ± 0.53	3.5 ± 0.04	3.9 ± 0.33
Liver					
Absolute	7,227 ± 234	7,184 ± 175	7,190 ± 93	6,934 ± 144	7,238 ± 306
Relative	35.9 ± 1.13	35.1 ± 0.54	34.8 ± 0.44	34.4 ± 0.74	34.7 ± 1.41
Lung					
Absolute	1,129 ± 89	1,031 ± 24	1,120 ± 20	(b) 1,051 ± 35	(c) 1,055 ± 26
Relative	5.6 ± 0.46	5.0 ± 0.06	5.4 ± 0.12	(b) 5.2 ± 0.15	(c) 5.0 ± 0.08
Thymus					
Absolute	317 ± 22	287 ± 16	294 ± 17	334 ± 64	315 ± 33
Relative	1.6 ± 0.11	1.4 ± 0.07	1.4 ± 0.08	1.7 ± 0.32	1.5 ± 0.15

(a) Mean ± standard error in milligrams (absolute) or milligrams per gram (relative); P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Lungs of nine animals were weighed.
(c) Lungs of four animals were weighed.
*P<0.05
**P<0.01

TABLE I2. ORGAN WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF FURFURAL (a)

	Vehicle Control	75 mg/kg	150 mg/kg	300 mg/kg
MALE				
Number weighed	10	10	10	10
Body weight (grams)	36.7 ± 0.68	35.8 ± 0.44	*34.9 ± 0.62	*34.5 ± 0.73
Brain				
Absolute	443 ± 6	433 ± 16	430 ± 6	436 ± 8
Relative	12.1 ± 0.22	12.1 ± 0.51	12.4 ± 0.34	12.6 ± 0.21
Heart				
Absolute	(b) 161 ± 5	178 ± 11	155 ± 4	149 ± 4
Relative	(b) 4.4 ± 0.12	5.0 ± 0.35	4.4 ± 0.07	4.3 ± 0.10
Kidney				
Absolute	282 ± 6	**323 ± 8	284 ± 6	293 ± 11
Relative	7.7 ± 0.11	**9.0 ± 0.26	**8.1 ± 0.11	**8.5 ± 0.26
Liver				
Absolute	1,602 ± 50	1,645 ± 35	1,509 ± 51	1,750 ± 92
Relative	43.6 ± 1.05	46.1 ± 1.26	43.2 ± 0.97	*50.9 ± 3.04
Lung				
Absolute	179 ± 4	187 ± 7	175 ± 4	183 ± 3
Relative	4.9 ± 0.12	5.2 ± 0.24	5.0 ± 0.12	*5.3 ± 0.12
Thymus				
Absolute	47.5 ± 2.50	47.5 ± 4.03	49.5 ± 3.29	49.5 ± 3.76
Relative	1.3 ± 0.07	1.3 ± 0.11	1.4 ± 0.09	1.4 ± 0.10
FEMALE				
Number weighed	9	10	9	10
Body weight (grams)	26.9 ± 0.51	26.9 ± 0.98	26.7 ± 0.53	27.6 ± 0.54
Brain				
Absolute	453 ± 16	447 ± 4	469 ± 9	476 ± 8
Relative	16.9 ± 0.60	16.8 ± 0.61	17.6 ± 0.36	17.3 ± 0.41
Heart				
Absolute	127 ± 5	121 ± 4	123 ± 3	133 ± 4
Relative	4.7 ± 0.19	4.5 ± 0.16	4.6 ± 0.06	4.8 ± 0.12
Kidney				
Absolute	184 ± 7	197 ± 5	185 ± 10	*209 ± 5
Relative	6.9 ± 0.30	7.4 ± 0.12	7.0 ± 0.40	7.6 ± 0.19
Liver				
Absolute	1,104 ± 25	1,227 ± 52	1,185 ± 42	**1,444 ± 37
Relative	41.1 ± 0.64	**45.6 ± 0.76	**44.5 ± 1.33	**52.3 ± 0.74
Lung				
Absolute	172 ± 4	169 ± 14	176 ± 4	184 ± 7
Relative	6.4 ± 0.22	6.4 ± 0.59	6.6 ± 0.17	6.7 ± 0.27
Thymus				
Absolute	42.2 ± 4.94	57.0 ± 14.01	56.1 ± 3.20	48.5 ± 3.17
Relative	1.6 ± 0.19	2.0 ± 0.38	2.1 ± 0.10	1.8 ± 0.12

(a) Mean ± standard error in milligrams (absolute) or milligrams per gram (relative); P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Hearts of nine animals were weighed.
*P<0.05
**P<0.01

APPENDIX J

AUDIT SUMMARY

APPENDIX J. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft NTP Technical Report for the 2-year studies of furfural in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives. The audit included review of:

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

Procedures and events for the exposure phase of the studies were documented adequately by records at the Archives. Review of the archival records indicated that protocol-specified procedures for animal care were followed adequately. Records that documented the generation, analysis, distribution, and delivery of doses to animals were complete and accurate. Review of body weight records for rats showed that 24/24 recalculated mean values were correct.

Data entries on necropsy forms were made appropriately for rats and mice. The thoroughness for observation of external potential masses for rats and mice was fair inlife (>88% of the external masses noted at necropsy had an inlife correlate) and good at necropsy (>95% of the external masses noted inlife correlated with a necropsy observation). The date of death recorded at necropsy for each unscheduled-death animal (139 rats and 164 mice) had a matching entry among the inlife records. The reason for animal removal recorded among the inlife records was in agreement with the disposition code recorded at necropsy for all rats and mice. The condition code for each animal was consistent with the dispostion code and gross observations assigned at necropsy.

Individual animal identifiers (ear mark and toe clip) were present and correct in the residual tissue bag for 61/62 rats and 87/89 mice examined. Review of the entire data trail for the three animals with less than complete and correct identifiers indicated that the integrity of their individual animal identity had been maintained throughout the studies. A total of 4 untrimmed potential lesions were found in the wet tissues of 62 rats examined, and 3 were found in those of 89 mice. The gastrointestinal

tract was not saved completely for 58/62 rats examined, and the liver, stomach, and small intestine were not saved for 21/89 mice. Each gross observation made at necropsy had a corresponding microscopic diagnosis for all but six in rats and five in rats; after microscopic review of the slides involved in these noncorrelations, only one was considered to be a discrepancy. Blocks and slides were present, and corresponding tissue sections matched each other properly. All post-Pathology Working Group changes in diagnoses had been incorporated into the final pathology tables. The P values and incidences of neoplasms given in the Technical Report were the same as those in the final pathology tables at the Archives.

This summary describes general audit findings and the extent to which the data and factual information presented in the Technical Report are supported by records at the NTP Archives. Full details are presented in audit reports that are on file at the NIEHS.