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No. 341

TOXICOLOGY AND CARCINOGENESIS STUDIES OF NITROFURANTOIN

(CAS NO. 67-20-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED 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 NITROFURANTOIN

(CAS NO. 67-20-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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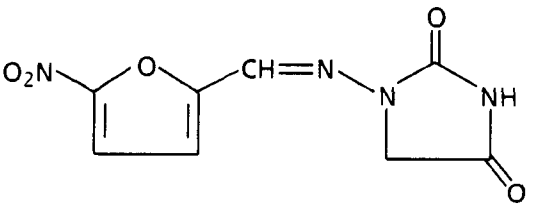

NITROFURANTOIN

CAS No. 67-20-9

$C_8H_6N_4O_5$ Molecular weight 238.2

Synonyms: 1-(((5-nitro-2-furanyl)methylene)amino-2,4-imidazolidinedione); 1-(5-nitro-2-furfurylideneamino)-hydantoin; *N*-(5-nitro-2-furfurylidene)-1-aminohydantoin; 1-((5-nitrofurfurylidene)amino)hydantoin

Trade names: Benkfuran; Berkfurin; Chemiofuran; Cyantin; Dantafur; Furadantin; Furadantine; Furadantoin; Furadonin; Furadonine; Furantoin; Furatoin; Furobactina; Ituran; Macrodantin; Nifurantin; NSC 2107; N-Toin; Orafuran; Parafuran; Urizept; USAF EA-2; Welfurin; Zoofurin

ABSTRACT

Nitrofurantoin was studied and evaluated because of its widespread use as a drug for treating urinary tract infections in humans, its structural relationship to known carcinogenic 5-nitrofuran compounds, and the lack of adequate studies to assess its carcinogenicity. Toxicology and carcinogenesis studies of nitrofurantoin were conducted by administering nitrofurantoin (greater than 99% pure) in feed to groups of F344/N rats and B6C3F$_1$ mice of each sex for 14 days, 13 weeks, or 2 years.

Fourteen-Day and Thirteen-Week Studies: None of the rats (at dietary concentrations up to 20,000 ppm) died before the end of the 14-day studies. Rats that received 5,000, 10,000, or 20,000 ppm lost weight. Four of five male and 4/5 female mice that received 10,000 ppm and 1/5 females that received 5,000 ppm nitrofurantoin died before the end of the studies. Mice that received 5,000 ppm and male mice that received 10,000 ppm lost weight.

In the 13-week studies, final mean body weights of rats that received 2,500, 5,000, or 10,000 ppm were 10%, 34%, or 47% lower than that of the controls for males and 15%, 31%, or 41% lower for females. Feed consumption by dosed and control rats was generally similar. Degeneration of the germinal epithelium of the seminiferous tubules of the testis was observed in male rats that received 2,500 to 10,000 ppm nitrofurantoin. Necrosis of the ovarian follicles was observed in 8/10 female rats that received 10,000 ppm, in 3/10 females that received 5,000 ppm, and in 1/10 that received 2,500 ppm.

For mice, final mean body weights of the 5,000-ppm groups were 13% lower than that of the controls for males and 15% lower for females. Two of 10 male mice that received 5,000 ppm and 1/10 males that received 300 ppm died before the end of the 13-week studies. Estimated feed consumption was similar for dosed and control groups. Degeneration of the germinal epithelium of the testis was observed in males that received 1,300 to 5,000 ppm; necrosis of the ovarian follicles was observed in females that received 5,000 ppm but not in the lower dose groups. Necrosis of the renal tubular epithelium was observed in 2/9 males that received 5,000 ppm.

Based on these results, 2-year studies of nitrofurantoin were conducted by feeding diets containing 0, 1,300, or 2,500 ppm nitrofurantoin to groups of 50 male F344/N rats and to groups of 50 male and

female B6C3F$_1$ mice for 103 weeks. Groups of 50 female F344/N rats were fed diets containing 0, 600, or 1,300 ppm nitrofurantoin on the same schedule.

Body Weight and Survival in the Two-Year Studies: Mean body weights and average daily feed consumption of dosed male and female rats were similar to those of the controls throughout the studies. The average amount of nitrofurantoin consumed per day was estimated to be 60 and 110 mg/kg for low and high dose male rats and 30 and 60 mg/kg for low and high dose female rats. No significant differences in the number of rats surviving to the end of the studies were observed between any groups of rats of either sex (male: control, 24/50; low dose, 27/50; high dose, 26/50; female: 25/50; 26/50; 31/50).

Mean body weights of high dose male and female mice were up to 12% lower than those of the controls throughout most of the studies. The average daily feed consumption by dosed mice ranged from 93% to 100% that by controls. The average amount of nitrofurantoin consumed per day was estimated to be 280-300 mg/kg and 570-580 mg/kg for low and high dose mice. The survival of the control group of female mice was lower than that of the dosed groups (control, 19/50; low dose, 37/50; high dose, 37/50). The decrease in survival was most likely related to the increase in microbial infection in the reproductive tract observed in the controls. Groups of male mice had similar survival (28/50; 29/50; 34/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Organs showing toxicity from nitrofurantoin exposure identified in the short-term studies were the testis in male rats and mice, the ovary in female rats and mice, and the kidney in male mice. Lesions observed in the 2-year studies were in the testis in male rats and mice, ovary in female mice, and kidney in male rats.

Chronic nephropathy was observed in nearly all rats, but the severity of the lesions was judged to be greater in dosed male rats. Hyperplasia of the transitional cell epithelium (control, 0/50; low dose, 5/50; high dose, 2/50) and hydronephrosis of the renal pelvis (0/50; 5/50; 2/50) were also observed in dosed male rats. In the standard single sections of the left and right kidney from each rat, tubular cell adenomas were observed in one low dose and two high dose males; a tubular cell carcinoma was observed in another high dose male. Because the number of renal tubular cell neoplasms identified by standard procedures in the dosed male rats was low, additional step-sections of the kidney were evaluated. The incidences of tubular cell adenomas derived from the step-sections and original sections (combined) were significantly increased in dosed male rats (adenomas: 3/50; 11/50; 19/50); tubular cell carcinomas occurred in two high dose males only.

Lesions considered to be associated with the nephropathy and nitrofurantoin exposure were observed in male rats and included hyperplasia of the parathyroid glands (3/49; 18/47; 23/49), fibrous osteodystrophy of the bone (0/50; 5/50; 5/50), and mineralization of the glandular stomach (1/49; 8/50; 14/50).

Atypical cells of the epididymis (0/50; 0/50; 12/50) and degeneration of the testis (0/50; 0/50; 36/50) were observed in high dose male rats. Fibrinoid necrosis of arterioles (1/50; 8/50; 15/50) and perivascular infiltration of mononuclear cells (3/50; 9/50; 19/50) were also observed in the testis of male rats. Interstitial cell adenomas of the testis occurred with a negative trend (47/50; 45/50; 21/50), and no adenomas or carcinomas of the preputial gland were seen in high dose male rats (12/48; 11/50; 0/47). The incidence of clitoral gland neoplasms was increased in low dose female rats (5/44; 10/38; 4/42).

Osteosarcomas were observed in the bone of one low dose and two high dose male rats. The historical incidence of osteosarcomas in untreated male F344/N rats is 8/1,937 (0.4%). The incidences of subcutaneous tissue neoplasms in dosed male rats were greater than that in the controls (1/50; 7/50; 5/50).

No neoplastic lesions in dosed female rats or male mice were considered to be compound related at the doses of nitrofurantoin administered.

For female mice, ovarian atrophy was observed in 48/50 low dose and 49/50 high dose mice but not in controls. Tubular cell adenomas of the ovary (0/50; 0/50; 5/50), benign mixed tumors (tubular and stromal) (0/50; 0/50; 4/50), and granulosa cell tumors (0/50; 3/50; 2/50) were observed in dosed female mice. One granulosa cell tumor in the high dose group was malignant. Ovarian abscesses (18/50) and suppurative inflammation of the uterus (11/50) were observed in control female mice but not in dosed female mice and are believed to be related to indigenous microbial infections and most likely were the cause of early deaths in this group. Adenocarcinomas of the uterus were seen in one low dose and in one high dose mouse.

Testicular aspermatogenesis (1/49; 1/49; 16/50), degeneration of the germinal epithelium (0/49; 3/49; 23/50), and atypical cells (0/50; 0/49; 26/50) and depletion (1/50; 1/49; 15/50) of the epididymis were observed at increased incidences in high dose male mice.

Spindle cell hyperplasia of the adrenal cortex was observed in dosed female mice (3/50; 41/50; 45/50). A spindle cell adenoma (adrenal capsule adenoma) was seen in one low dose female mouse, and a spindle cell carcinoma (adrenal capsule carcinoma) was seen in one low dose male mouse.

Mineralization of the renal medulla (male: 0/50; 0/50; 17/50; female: 0/50; 0/50; 7/50) and dilatation of the renal tubules (male: 0/50; 0/50; 14/50) were observed in high dose mice.

Hepatocellular neoplasms (adenomas or carcinomas, combined) were observed at an increased incidence in high dose female mice (2/50; 2/50; 8/50). An Ito cell tumor of the liver was observed in one low dose and one high dose female mouse. Malignant lymphomas occurred in female mice (12/50; 19/50; 24/50).

Genetic Toxicology: Nitrofurantoin was mutagenic in *Salmonella typhimurium* strains TA98 and TA100, with and without metabolic activation, but was not mutagenic for strains TA1535 or TA1537. Nitrofurantoin induced forward mutations at the $TK^{+/-}$ locus of L5178Y mouse lymphoma cells in the absence of metabolic activation (it was not tested with activation). Nitrofurantoin induced increased numbers of sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells with and without metabolic activation. Results of the sex-linked recessive lethal assay in Drosophila were negative after administration of nitrofurantoin by feeding or by injection.

Conclusions: Under the conditions of these 2-year feed studies, there was *some evidence of carcinogenic activity** of nitrofurantoin for male F344/N rats as shown by increased incidences of uncommon kidney tubular cell neoplasms. Uncommon osteosarcomas of the bone and neoplasms of the subcutaneous tissue were observed in dosed male rats. Incidences of interstitial cell adenomas of the testis and neoplasms of the preputial gland were decreased in the 2,500-ppm group of male rats. There was *no evidence of carcinogenic activity* of nitrofurantoin for female F344/N rats fed diets containing 600 ppm or 1,300 ppm for 2 years. Female rats may have been able to tolerate higher doses. There was *no evidence of carcinogenic activity* of nitrofurantoin for male $B6C3F_1$ mice fed diets containing 1,300 ppm or 2,500 ppm for 2 years. There was *clear evidence of carcinogenic activity* of nitrofurantoin for female $B6C3F_1$ mice as shown by increased incidences of tubular adenomas, benign mixed tumors, and granulosa cell tumors of the ovary.

Nonneoplastic lesions considered related to nitrofurantoin exposure were chronic nephropathy and associated lesions (hyperplasia of the parathyroid gland, fibrous osteodystrophy of the bone, and mineralization of the glandular stomach) in male rats and testicular degeneration in male rats and mice. Ovarian atrophy and hyperplasia of the adrenal cortex spindle cells were observed in dosed female mice.

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*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 11-13.

SUMMARY OF THE TWO-YEAR FEED AND GENETIC TOXICOLOGY STUDIES OF NITROFURANTOIN

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Dietary concentrations			
1,300 or 2,500 ppm nitrofurantoin	600 or 1,300 ppm nitrofurantoin	1,300 or 2,500 ppm nitrofurantoin	1,300 or 2,500 ppm nitrofurantoin
Survival rates in the 2-year study			
24/50; 27/50; 26/50	25/50; 26/50; 31/50	28/50; 29/50; 34/50	19/50; 37/50; 37/50
Nonneoplastic effects			
Chronic nephropathy; testicular degeneration	None	Testicular degeneration	Ovarian atrophy; hyperplasia of adrenal cortex spindle cells
Neoplastic effects			
Renal tubular cell neoplasms	None	None	Tubular adenomas, benign mixed tumors, and granulosa cell tumors of the ovary
Level of evidence of carcinogenic activity			
Some evidence	No evidence	No evidence	Clear evidence
Genetic toxicology			
Mutagenic in *S. typhimurium* strains TA98 and TA100 with and without metabolic activation; induced forward mutations in mouse L5178Y lymphoma cells without activation; induced increased numbers of sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells with and without S9; did not induce sex-linked recessive lethal mutations in Drosophila.			

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 Nitrofurantoin is based on the 13-week studies that began in May 1980 and ended in August 1980 and on the 2-year studies that began in February 1981 and ended in March 1983 at Southern Research Institute (Birmingham, AL).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on nitrofurantoin on July 14, 1987, and on April 18, 1988, 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 NITROFURANTOIN

On July 14, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of nitrofurantoin received peer 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 (NIEHS), Research Triangle Park, NC.

Dr. J.E. French, NIEHS, introduced the studies 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, no evidence of carcinogenic activity for male mice, clear evidence of carcinogenic activity for female mice).

Dr. Popp, a principal reviewer, agreed with the conclusions for female rats and male and female mice; he said that the Panel should discuss the concomitant ovarian toxicity in female mice. Dr. Popp opined that the results for male rats, a slight increase in renal tubular neoplasms (control, 0/50; low dose, 1/50; high dose, 3/50) coupled with a corresponding lack of an increase in renal tubular hyperplasia, more closely supported equivocal evidence of carcinogenic activity. Dr. French acknowledged that the lack of hyperplasia must be considered but felt that the presence of a carcinoma was evidence supporting progression and, although the numbers of renal tubular cell tumors were relatively low, there was a twentyfold difference between the high dose and mean historical control incidences. Dr. Hughes pointed out that there was one study in the historical control data base with two tubular neoplasms. Dr. J. Haseman, NIEHS, reported that for the most recent 73 corn oil gavage and feed studies, 57 had a zero incidence of tubular neoplasms in controls, 15 had an incidence of one, and 1 had an incidence of two.

As a second principal reviewer, Dr. Ashby agreed with the conclusions for male and female rats and male mice, while suggesting that the conclusion for female mice be changed to some evidence of carcinogenic activity. He stated that two of the three types of ovarian tumors were observed only in the high dose groups. He questioned whether those tumors could be combined for assessment. Also confounding the interpretation was the presence of ovarian atrophy in almost all of the exposed animals. Dr. French remarked that both ovarian tubular adenomas and benign mixed tumors were uncommon and histogenetically it was considered appropriate to combine them.

As a third principal reviewer, Dr. Chinchilli agreed with the conclusions for male and female rats and male mice, noting that osteosarcomas of the bone and subcutaneous tumors observed in male rats are uncommon. For female mice, he questioned why statistical analyses for the ovary were based on a sample of 50 when tissues from only 39 control mice were available for microscopic evaluation. Dr. S. Eustis, NIEHS, explained that ovaries from all 50 control female mice were examined; however, ovarian abcesses had destroyed much of the tissues from 11 animals. In his opinion, the examination was sufficient to determine whether a tumor was present. Dr. Haseman commented that whether the denominator was 39 or 50, the differences in tumor incidences were highly significant and quite striking. Dr. Chinchilli inquired if a statistical comparison test using historical control data could be used in analysis of uncommon tumors. Dr. Haseman agreed that rare or uncommon tumors might be the one instance in which a formal analysis incorporating historical data should be considered, although lack of agreement as to which test is most appropriate was still a problem.

Dr. William H. Butler, of the British Industrial Biological Research Association and representing Norwich Eaton Pharmaceuticals, Inc., presented a review of his observations from an examination of the slides containing ovary sections from the female mice. He contended that the occurrence of ovarian abcesses in a number of controls obviated a proper analysis. He also suggested that the tubular

cell adenomas might have resulted from hormonal stimulation due to ovarian atrophy and that the existence of other negative studies supported equivocal evidence of carcinogenic activity. Dr. Butler opined further that there was no evidence of carcinogenic activity in male rats because the incidence of renal tubular cell neoplasms was low and within the expected historical range, because there was no evidence of similar lesions in female rats, because there was no increase in hyperplasia, and because there was a high incidence of chronic nephropathy. Dr. E. McConnell, NIEHS, emphasized that both increases and decreases in hyperplasia are considered in the evaluations. In the case of the renal tumors in male rats, the lack of hyperplasia was noteworthy but did not necessarily offset the increase in an uncommon tumor.

Dr. Popp moved that the conclusion for male rats be changed to equivocal evidence of carcinogenic activity and that the conclusion for female rats, no evidence of carcinogenic activity, be accepted as written. Dr. Ashby seconded the motion, which was defeated by four votes (Dr. Ashby, Dr. Chinchilli, Dr. Hooper, and Dr. Mirer) to three (Dr. Gallo, Dr. Popp, and Dr. Sivak), with two abstentions (Dr. Capen and Dr. Hughes). Dr. Hooper moved that the conclusions be accepted as written for male rats, some evidence of carcinogenic activity, and for female rats, no evidence of carcinogenic activity. Dr. Ashby seconded the motion, which was approved by four votes (Dr. Ashby, Dr. Chinchilli, Dr. Hooper, and Dr. Mirer) to three (Dr. Gallo, Dr. Popp, and Dr. Sivak), with two abstentions (Dr. Capen and Dr. Hughes). Dr. Popp moved that the conclusions for male mice, no evidence of carcinogenic activity, and for female mice, clear evidence of carcinogenic activity, be accepted as written. Dr. Chinchilli seconded the motion, which was approved by five votes to two (Dr. Ashby and Dr. Gallo), with two abstentions (Dr. Capen and Dr. Hughes).

Update and Reevaluation of Further Pathology on Kidneys from Male Rats (April 18, 1988)

At the Peer Review meeting on April 18, 1988, Dr. French summarized the discussion from the Peer Review meeting on July 14, 1987, when an important portion of the discussion focused on the tubular cell neoplasms in the kidney of dosed male rats and the level of evidence for carcinogenic activity recommended by the staff. The level of evidence selected for male rats (some evidence of carcinogenic activity) was based on: dose-related, albeit marginally increased, incidences of uncommon neoplasms of the tubular cells in the kidney (0/50; 1/50; 3/50) (see Table 11), the possibility of progression to malignancy as evidenced by a tubular cell carcinoma in the kidney in a high dose male rat, and comparison with historical controls.

Dr. French went on to explain that because of the microscopic size of the majority of these tumors and questions concerning the dose-response relationship, additional histologic sections of the kidneys were prepared for evaluation. The purpose was to obviate the possibility of bias due to chance and to determine if the number of tumors found in each group would increase proportionally in relation to dose. The data derived only from the additional step-sections are shown in Table 12. All of the additional kidney tumors were observed microscopically, and there was an increase in the number of multiple adenomas observed in the high dose male rats. The composite results of both data sets are shown in Table 13. The incidences of tubular cell neoplasms in the kidney of male rats were as follows: control, 3/50; low dose, 11/50; high dose, 20/50. The low dose incidence was statistically different from that in the controls at the 0.05 level, and the high dose incidence was statistically different at the 0.001 level.

Dr. French said that the data indicate that male rats receiving 0, 1,300, or 2,500 ppm nitrofurantoin in feed at for 2 years developed compound-related tubular cell neoplasms and that these data support the conclusion previously written in the Technical Report and approved by the Panel. Summary

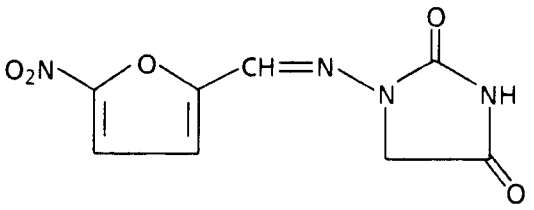
tables and representative photomicrographs of selected tumors were included in the Results section of the Report, and the Discussion section was modified to reflect the additional findings.

Discussion among the Panel members and the staff centered around several issues: the size and relative numbers of lesions in the recut sections vs. the original histologic sections (it was noted that all of the adenomas were quite small and that there were no concomitant increases in hyperplasia and carcinomas in the recut sections); which sets of numbers could be compared with, or added to, the historical control data base (it was agreed that only the original incidences could be compared or added); whether the Panel should move to affirm or change the level of evidence in male rats; and the generic issue of when and why the NTP should return to a study and do additional sections (there was agreement that this would not be done routinely).

Dr. Hooper moved that the conclusion for male rats be changed to clear evidence of carcinogenic activity. Dr. Perera seconded the motion, which was defeated by five votes (Dr. Ashby, Dr. Capen, Dr. Gallo, Dr. Popp, and Dr. Sivak) to four (Dr. Chinchilli, Dr. Hooper, Dr. Lijinsky, and Dr. Perera), with one abstention (Dr. Hughes). Dr. Popp moved that the Panel concur with the staff's original recommendation, some evidence of carcinogenic activity. The motion was seconded and approved by five votes (Dr. Ashby, Dr. Capen, Dr. Gallo, Dr. Popp, and Dr. Sivak) to four (Dr. Chinchilli, Dr. Hooper, Dr. Lijinsky, and Dr. Perera), with one abstention (Dr. Hughes).

I. INTRODUCTION

I. INTRODUCTION



NITROFURANTOIN

CAS No. 67-20-9

$C_8H_6N_4O_5$ Molecular weight 238.2

Synonyms: 1-(((5-nitro-2-furanyl)methylene)amino-2,4-imidazolidinedione); 1-(5-nitro-2-furfurylideneamino)-hydantoin; *N*-(5-nitro-2-furfurylidene)-1-aminohydantoin; 1-((5-nitrofurfurylidene)amino)hydantoin

Trade names: Benkfuran; Berkfurin; Chemiofuran; Cyantin; Dantafur; Furadantin; Furadantine; Furadantoin; Furadonin; Furadonine; Furantoin; Furatoin; Furobactina; Ituran; Macrodantin; Nifurantin; NSC 2107; N-Toin; Orafuran; Parafuran; Urizept; USAF EA-2; Welfurin; Zoofurin

Use, Production, and Exposure

Nitrofurantoin is used extensively in the treatment of urinary tract infections in humans (D'Arcy, 1985). A derivative of 5-nitrofuran, nitrofurantoin is structurally related to furan and to nitrofurazone, the first 5-nitrofuran described by Dodd and Stillman (1944) to be an effective broad-spectrum antibiotic, as well as to many other nitrofurans (Bryan, 1978). The 5-nitrofuran derivatives have been used extensively in topically and parenterally administered antiseptics in humans and animals and as antitumor agents, food preservatives, and feed additives for food production animals.

The starting material for synthesis of 5-nitrofurans with antimicrobial properties is 2-furaldehyde (Ichikawa, 1978). 2-Furaldehyde is converted by air oxidation and metal catalysts to furoic acid and is thermally decarboxylated to furan. Preferential electrophilic substitution of the furan ring occurs at the 2-position. However, nitration of the furan nucleus in the 2 and 5 positions is favored under conditions of fuming nitric acid and acetic anhydride (containing the active species $CH_3CO_2^-NO_2^+$). The 2,5-dinitrofuran is converted to 5-nitrofuran by weak bases, which eliminate acetic acid.

Clinical use of nitrofurantoin began after World War II; between 1953 and 1984, an estimated 121,430,000 courses of therapy were given, according to data from one manufacturer (D'Arcy, 1985). Nitrofurantoin treatment for infections may occur over periods of up to 30 months (Simonian et al., 1977). Recent production figures are not available, but in 1974, commercial production was reported to the International Trade Commission (USITC, 1976) (implying that production was greater than 1,000 lb/year) and was listed with the U.S. Environmental Protection Agency TSCA in 1980 (NIOSH, 1983). In 1986, 9,300 kg of nitrofurantoin in various preparations was purchased by drugstores and hospitals (U.S. Pharmaceutical Market Data Base, 1986). Exposure to nitrofurantoin in the United States has been estimated at 8,900 kg/year (NCI/SRI, 1978).

Absorption, Metabolism, and Excretion

After oral or parenteral administration, nitrofurantoin is rapidly absorbed and is excreted primarily unchanged in the urine and bile of humans (Conklin and Hailey, 1969; Conklin, 1972a,b), rats (Paul, H.E., et al., 1960; Buzard et al., 1961; Veronese et al., 1974; Wierzba et al., 1982), mice (Maiti and Banerjee, 1978), and dogs

(Conklin and Wagner, 1971). Sites of optimal absorption of nitrofurantoin in the gastrointestinal tract may vary between humans (duodenum) (Conklin and Hailey, 1969) and rodents (mice, ileum) (Maiti and Banerjee, 1978).

After a single oral administration of 50 or 150 mg nitrofurantoin to healthy male volunteers (19-43 years old, 63-96 kg), the terminal elimination half-life was 1.2 or 1.7 hours, respectively (Liedtke et al., 1980). Intravenous administration of 50 mg nitrofurantoin (male, 25-35 years old, 62-80 kg) resulted in a half-life value of 58 ± 15 minutes, and 47% ± 13% and 1.2% ± 0.3% were excreted unchanged as parent compound and aminofurantoin, respectively, in the urine (Hoener and Patterson, 1981). These half-life values are significantly longer than those in earlier reports that suggested approximately 50% of the administered dose was excreted in humans within 20-30 minutes (Reckendorf et al., 1962; Paul and Paul, 1964; Schirmeister et al., 1965; Sachs et al., 1968; Conklin, 1972a; Bron et al., 1979). Liedtke et al. (1980) suggested that this discrepancy in half-life is due to improved analytical methods (high-performance liquid chromatography vs. spectrophotometry). A decrease in urine pH increased the half-life, which suggests that changes in pH may influence dissolution, bioavailability, and/or the rate of excretion in humans (Bron et al., 1979). Absorption of nitrofurantoin is increased with the presence of food in the gastrointestinal tract (Bates et al., 1974; Rosenberg and Bates, 1976; Hoener and Patterson, 1981). Absorption of nitrofurantoin in humans (male, 21-32 years old) was also influenced by the presence and size of the macrocrystals in the formulation (Bates et al., 1974; Meyer et al., 1974). During conditions of renal impairment, nitrofurantoin excretion is greatly diminished (Kunin, 1972).

Under aerobic conditions, the reduction of nitrofurantoin by the addition of an electron to the 5-nitrofuran ring via a nitroreductase, NADPH, and a flavoprotein has been reported to occur in vitro in hepatic and/or lung microsomes from rats (male, CD, 160-180 g, Mason and Holtzman, 1975a; male, HLA-SD, 150 g, Boyd et al., 1979a; male, Sprague Dawley, 135-140 g, Sasame and Boyd, 1979), chickens (Leghorn, 8 days old, Peterson et al., 1982a), guinea pigs (age and sex not specified, 400-600 g, Leskovac and Popovic, 1980), or Erhlich ascites tumor cells (Biaglow et al., 1977). This results in a transient nitroaromatic anion radical that may react with molecular oxygen, producing superoxide anion free radical, and possibly hydrogen peroxide and the regeneration of nitrofurantoin. Oxidative metabolism of the nitrofurantoin side chain has also been reported to occur (Pugh et al., 1972). Jonen and Kaufman (1980) reported that in rats (male, Sprague Dawley, 250-300 g, age not specified), 3-methylcholanthrene and β-nitroflavone, but not phenobarbital, pretreatment increased the clearance of napthofurantoin from the isolated perfused liver and increased the formation of a polar metabolite, similar to a hydroxylated furan derivative (1-[[(5-*aci*-nitro-4,5-dihydro-4-oxo-2-furanyl)-methylene]amino]-2,4-imidazolidinedione) (Olivard et al., 1976).

Reductive metabolism of nitrofurantoin under anaerobic conditions has been described in both rodents and bacteria. Without oxygen, nitrofurantoin is believed to be permanently reduced to nitroso and/or hydroxylamine forms (Mason and Holtzman, 1975b; Biaglow et al., 1977; Leskovac and Popovic, 1980). Aufrere et al. (1978) studied the reductive metabolism of nitrofurantoin under anaerobic conditions with young male Sprague Dawley rats (60 g) and reported that the metabolism of nitrofurantoin was greatest in homogenates of cecum and colon contents of germ-free acclimatized and control rats but not germ-free rats and in liver, small intestine walls, and kidney (in decreasing order of activity) in all groups. Nitrofurantoin was reduced under these conditions to two metabolites, 1-[[(3-cyano-1-oxopropyl)-methylene]-amino]-2,4-imidazolidinedione (major) and 1-[[(5-amino-2-furanyl)methylene]-amino]-2,4-imidazolidinedione (aminofurantoin) (minor). Two other pathways were reported by Olivard et al. (1962) to occur in the gastrointestinal tract: reduction of nitrofurantoin to the 5-aminofuran and acetylation to form the 5-acetamidofuran or 5-diacetylaminofuran, and acid hydrolysis of the azomethine bridge to produce 5-nitro-2-furanocarboxaldehyde, which may be excreted as 5-nitro-2-furoic acid or as a hydrazine derivative, which may be acetylated and excreted.

Nitrofurantoin is excreted rapidly in adult rats (male and female, Wistar, at least 33 days old), but not in young rats (male and female, Wistar, 5-15 days old) due to greater renal tubular reabsorption rates in young rats (Braunlich et al., 1978). Wierzba et al. (1982) reported that nitrofurantoin excretion is age dependent in both humans and rats. Patients under 2 years of age (sex unspecified) with a urinary tract infection and normal renal function excreted 25% ± 5.7% of their first dose (oral) after 12 hours at an initial excretion rate of 0.68 ± 0.23 mg/hour. Patients older than 2 years of age (sex and age range not given, same clinical conditions) excreted 44% ± 16% at an initial rate of 4.55 ± 2.64 mg/hour. In comparison, Wierzba et al. reported that intravenous administration of nitrofurantoin (20 mg/kg) to 2-week-old or 2- to 3-month-old rats (Wistar, sex unspecified) resulted in half-life values of 0.95 and 0.41 hours, respectively.

After a single oral dose of nitrofurantoin (gavage, 25 mg/kg) to female albino rats (strain, age, and sex unspecified), 52% and 2.6% nitrofurantoin (percentage total dose) were recovered in the urine and feces, respectively (Paul, M.F., et al., 1960). When administered intravenously to rats (strain, age and sex unspecified) to specific organ sites of the digestive tract (25 or 100 mg/kg), nitrofurantoin was absorbed rapidly via the small intestine, metabolized by liver, intestine, and kidney, and excreted (half-life of 25 minutes) in the urine (50% recovered as nitrofurantoin) (Buzard et al., 1961). Veronese et al. (1974) reported that after intravenous administration of nitrofurantoin to rats (male, Sprague Dawley, 150-200 g), 16%-30% of the total dose was recovered in the urine. The proportion of nitrofurantoin or metabolite recovered was inversely related to dose; relative urinary excretion of nitrofurantoin decreased with increasing dose. Statham et al. (1985) compared the pharmacokinetics between control and vitamin E-deficient male Sprague Dawley rats (age unspecified, 200 g) administered nitrofurantoin subcutaneously (15 mg/kg) and found that nitrofurantoin was rapidly absorbed and cleared from blood, lung, liver, and kidney in a biphasic manner. Metabolism of nitrofurantoin occurred in control animals, but there were increased levels of unchanged nitrofurantoin in vitamin E-deficient rats. Urinary excretion was 68% of the total dose administered in control rats and 35% in vitamin E-deficient rats.

Intravenous administration of nitrofurantoin (1.5-24 mg/kg) to adult male beagles (10-16 kg) stimulated bile secretion, and nitrofurantoin was excreted in bile (at 6 mg/kg, 22.6% ± 4.7% total dose) and urine (24.1% ± 4.7%) (Conklin and Wagner, 1971). In these studies, carbon tetrachloride administration was found to impair bile flow and nitrofurantoin excretion. Nitrofurantoin (after intravenous administration) is excreted in bile, reabsorbed, and enterohepatically recirculated (Conklin et al., 1973).

Oral administration of nitrofurantoin also may result in the excretion of nitrofurantoin in the milk of lactating humans (Varsano et al., 1973), rats, and dogs (Paul, M.F., et al., 1960). Administration of nitrofurantoin (oral, 100 or 200 mg) to lactating women with normal glucose-6-phosphate dehydrogenase levels who had stopped nursing resulted in excretion of nitrofurantoin in their milk. The milk to serum ratio was approximately 0.29 in those with detectable levels. Sixteen hours after being dosed, rats (age, sex, and strain unspecified, 100 mg/kg) excreted 5 mg/liter, and dogs (age, sex, and strain unspecified, 20 mg/kg) excreted 2.33 mg/liter.

Acute Toxicity

Acute toxicity varies somewhat between rats (LD_{50} = 112 mg/kg by intraperitoneal injection; 604 mg/kg by gavage; vehicle, 5%-15% acacia in water; male, Sprague Dawley, 180 g; Preti, 1970) and mice (LD_{50} = 150 mg/kg by intraperitoneal injection; 360 mg/kg by gavage; vehicle, age, and sex unspecified; NIOSH, 1983). The oral TD_{Lo} for humans is 80 mg/kg. Dietary deficiencies in both selenium (Burk and Lane, 1983) and vitamin E (Boyd et al., 1979b) increased the acute toxicity of nitrofurantoin to rats (male, Holtzman and Sprague Dawley, respectively).

Cellular and Subcellular Toxicity

In vitro studies indicate that under aerobic conditions, reduction of nitrofurantoin stimulates consumption of oxygen and production of superoxide anion free radical and hydrogen peroxide

in avian liver and mammalian liver, lung, small intestine, kidney, and gastrointestinal contents, which may result in cytotoxicity and localized injury in vivo to cellular membranes (Mason and Holtzman, 1975a; Biaglow et al., 1977; Aufrere et al., 1978; Boyd et al., 1979a; Sasame and Boyd, 1979; Leskovac and Popovic, 1980; Peterson et al., 1982a) and to microbial organisms (Hassan and Fridovich, 1979). Using rat (age, sex, and strain unspecified) lung explants treated in culture with 10^{-3} M nitrofurantoin, Martin (1983) found significant lung cell injury, which was increased with increased oxygen tension and decreased in the presence of superoxide dismutase, catalase, α-tocopherol, and other antioxidants. Rose et al. (1982) reported that 100 mg/kg nitrofurantoin administered intraperitoneally to rats (Wistar, age and sex not reported) for 7 consecutive days caused changes in β-glucuronidase and β-galactosidase activity in nerve homogenates, which indicated significantly increased enzyme activity and nerve degeneration.

Under anaerobic conditions, lung and liver microsomal and soluble fractions (male, HLA-SD, 150 g) mediated the covalent binding of [^{14}C]nitrofurantoin-derived radioactivity to acid-precipitated macromolecules (Boyd et al., 1979a). Covalent binding of [^{14}C]nitrofurantoin activity was greatest in the kidney, liver, ileum, lung, and heart of rats. Reduced glutathione was reported to decrease covalent binding of [^{14}C]nitrofurantoin-derived radioactivity. Olive and McCalla (1977) reported that nitrofurantoin, nitrofurazone, and other 5-nitrofurans are toxic to L cells in culture under aerobic conditions but that toxicity and DNA damage increase as oxygen content in the culture decreases. Russo et al. (1982) reported liver DNA damage in rats (male, Sprague Dawley, 100-200 g) 72-96 hours after administration of a single oral dose of 56 or 112 mg/kg of nitrofurantoin (gavage, 0.9% saline with 1% carboxymethylcellulose). Nitrofurazone, a related 5-nitrofuran, has been shown to bind to nucleic acids and proteins in vivo and in vitro (Tatsumi et al., 1977).

Under aerobic and anaerobic conditions in vitro, nitrofurantoin depletes human erythrocyte glutathione, according to Dershwitz and Novak (1982). Minimal binding of nitrofurantoin or metabolites occurs to erythrocyte macromolecules. Nitrofurantoin was reported to increase the rate of superoxide anion radical formation under aerobic conditions from oxyhemoglobin. Under reduced oxygen tension, nitrofurantoin is reduced and requires both an NADPH-dependent flavoprotein and hemoglobin for superoxide anion radical formation to induce erythrocyte toxicity.

Peterson et al. (1982b) reported that a potential mechanism of detoxication of nitrofurantoin (or its reaction products) is by a selenium-dependent glutathione peroxidase. In selenium-deficient chicks, the LD_{50} value is 53 mg/kg, whereas in normal chicks, the LD_{50} value is 148 mg/kg; toxicity can be counteracted by adding selenium, but not vitamin E, back into the diet. Nitrofurantoin in the diet initially decreased glutathione peroxidase activity but not liver glutathione, catalase, or superoxide dismutase content, except at highly toxic doses over time. In selenium-deficient rats (male, Holtzman) but not in controls, nitrofurantoin (100 mg/kg in feed, 2-5 months after they were weaned) caused renal tubular necrosis and an associated increase in serum glutamic-pyruvic transferase activity (Burk and Lane, 1983).

Epidemiology and Systemic Toxicity

Adverse reactions to the administration of nitrofurantoin in the treatment of infections in humans have been reported (Delaney et al., 1977; Penn and Griffin, 1982; D'Arcy, 1985). Adverse effects reported included allergic (dermatologic), gastrointestinal, hematologic, hepatic, pulmonary, and neurologic reactions with varying degrees of incidence, time of treatment to onset, and severity of symptoms. The overall incidence of adverse reactions (all types) to nitrofurantoin administration reported worldwide between 1953 and 1984 was 0.0028% (D'Arcy, 1985). Allergic reactions, acute lung reactions, peripheral neuropathologic effects, and gastrointestinal (including liver) reactions (in descending order of occurrence) were the most frequently reported (Penn and Griffin, 1982; D'Arcy, 1985).

Nitrofurantoin-induced acute pulmonary reactions are characterized by development of fever, cough, and shortness of breath within hours to days after initiation of therapy in humans, according to Whitcomb and Domby (1978). Eosinophilia and diffuse alveolar or interstitial

infiltrates may be present. Chronic interstitial lung disease may also result after nitrofurantoin therapy of 6 months or longer, according to these authors. Development of progressive dyspnea and diffuse interstitial infiltration was stated to be characteristic. Both acute and chronic forms are usually reversible after discontinuation of nitrofurantoin therapy or with discontinuation of nitrofurantoin and corticosteroid treatment. Rats (male, Sprague Dawley, 350 g) administered 300-500 mg/kg nitrofurantoin by subcutaneous injection developed lung injury (severe respiratory distress, pulmonary edema, and hemorrhage) (Boyd et al., 1979b). Rats raised on a vitamin E-deficient diet or fed enriched vitamin E diets and exposed in an oxygen-rich environment were stated to have increased susceptibility to nitrofurantoin toxicity. Selenium-deficient or control rats (male, Holtzman, 2-5 months old) administered 100 mg nitrofurantoin/kg did not have lung injury (Burk and Lane, 1983).

Anttinen et al. (1982) reported a focal nodular hyperplasia of the liver which developed in a young girl after 7 months of nitrofurantoin treatment for infection. No epidemiologic studies were found on the use of nitrofurantoin, other than for adverse reactions.

Behar et al. (1965) reported that rats (male and female, Sabra, age unspecified) administered nitrofurantoin orally (0, 20, 50, or 100 mg/kg, two times per day) developed structural and functional changes in the sciatic nerve. Nitrofurantoin plasma levels were dependent on the dose and the duration of administration. The degree of axonal degeneration was time related but not dose related. Decreases in the conduction velocity of sciatic nerve transmission were time and dose related, but clinical neurologic changes were not observed. Toole et al. (1968) prospectively examined volunteers (male and female, age 22-58 with normal renal and hematologic function) who received 100 mg nitrofurantoin, four times per day for 14 consecutive days. This treatment was associated with impaired nerve conduction velocity (normal renal function); 8/14 subjects had no side effects. Five subjects complained of epigastric discomfort, nausea, or anorexia, and two had clinical vasomotor changes (ataxia) that were reversed after treatment was stopped. In an evaluation of four case reports, Yiannikas et al. (1981) stated that neuropathologic effects in all the patients were directly associated with nitrofurantoin treatment and were characterized by acute, severe axonal degeneration; they concluded that a direct neurotoxic effect was responsible. Hepatic injury (hepatocellular and cholestatic) (Goldstein et al., 1974), granulomatous formation (Strohscheer and Wegener, 1977), and chronic active hepatitis and necrosis (Sharp et al., 1980) have been associated with nitrofurantoin therapy.

Glucose-6-phosphate dehydrogenase deficiency and nitrofurantoin administration have been associated with the development of megaloblastic anemia (Pritchard et al., 1965; Toole et al., 1968). Glucose-6-phosphate dehydrogenase is required for the NADPH-dependent reduction of glutathione, which is required for erythrocyte protection from peroxides. Initiation of nitrofurantoin administration may result immediately in dizziness, weakness, headache, anorexia, and intermittent vomiting. Loss of erythrocytes, oxygen deficiency, and possibly renal problems are associated with lysis of erythrocytes and methemoglobinemia.

Reproductive and Developmental Toxicity

Paul and Harrington (1967) found that nitrofurantoin did not inhibit maternal or neonatal liver or kidney glucuronyl transferase in rabbits (male and female, strain unspecified; neonatal, 1-2 days old; adult, age unspecified) or rats (male and female, strain unspecified; neonatal, 2 hours to 3 days old; adult, 11 months old). There were no differences in nitrofurantoin metabolism between adult or neonatal rabbit liver or kidney and rat liver, but neonatal rat kidney metabolized nitrofurantoin significantly more slowly than did adult rat kidney.

Oral administration of nitrofurazone, a 5-nitrofuran analog of nitrofurantoin, has been reported to inhibit spermatogenesis at the spermatocyte or spermatid stage in rats (sex, strain, and age unspecified), which under long-term administration results in testicular atrophy. Generally, this effect was reversible upon discontinuation of drug administration. A similar effect was also reported in mice, along with interstitial cell hyperplasia and seminal vesicle hypertrophy

(Prior and Ferguson, 1950; Nissim, 1957; Montemurro, 1969).

In a continuous breeding study conducted by the National Toxicology Program (NTP) on nitrofurazone, timed-pregnant CD®-1 mice were fed dietary concentrations of nitrofurazone ranging from 38 to 500 ppm. Exposure was from gestational age of 6-15 days, and observations were continued through day 17. No teratogenic effects were seen in fetuses evaluated on day 17. Selective embryotoxicity, expressed as an increased incidence of late fetal death and intrauterine growth retardation, was observed at exposure concentrations that were only marginally toxic to the exposed dams (Price et al., 1985).

Long-Term Toxicity and Carcinogenicity

Female Holtzman rats (age not reported) given 3,000 ppm nitrofurantoin in feed for either 36 or 44.5 weeks (survival and body weights were not reported) did not develop any compound-related tumors (Morris et al., 1969). Similarly, tumors were not induced in young female Sprague Dawley rats (40-72 g) fed nitrofurantoin at 1,870 ppm from week 0 to 16, at 1,000 ppm from week 16 to 75, and control diets from week 75 to 80 (Cohen et al., 1973). Body weights of dosed animals were stated to be reduced, but not significantly, relative to those of the controls. The data indicate that 19/36 nitrofurantoin-dosed rats developed mammary gland tumors (fibroadenomas or adenocarcinomas, combined), whereas 12/30 control animals developed these tumors. Six of 36 dosed and 6/30 control rats were diagnosed with mammary gland adenocarcinomas. No details were given on survival of the dosed animals.

Ito et al. (1983) reported that nitrofurantoin administered in feed to BDF_1 mice (C57BL/6N × DBA/2N)F_1 (50 males and females per dose group, from 9 weeks to 2 years of age) at 0, 750, or 3,000 ppm caused no differences in survival but that the high dose group body weight was significantly lower than that of controls ($P < 0.05$) in each sex. They concluded that there were no differences in tumor incidence between dosed and control animals. However, they stated that negative differences did occur in male mice for liver adenomas (control, 6; low dose, 1; high dose, 0); the number of animals examined in each group was not given. In female mice, uterine tumors (reticulum cell sarcoma type A) occurred at incidences of 7, 5, and 12. Metastases from the uterine tumors were reported to have been found in the peritoneal cavity, lymph nodes, liver, and lungs at incidences of 2, 3, and 5. The earliest uterine tumor was found in the high dose group at week 44.

Sutton et al. (1987a,b) reported in abstracts on studies in which nitrofurantoin was fed to Sprague Dawley rats (50 males and 50 females per dose; 0, 15, 27, or 49 mg/kg per day) and Swiss mice (Crl:CD®-1[ICR]BR; 50 males and 50 females per dose; 0, 50, 100, or 200 mg/kg per day). No evidence of compound-related tumor incidences was reported for either rats or mice. The increased number of deaths in high dose male mice indicates that the maximum tolerated dose may have been exceeded in their studies.

Genetic Toxicology

Results from a variety of bacterial and fungal assays have shown that nitrofurantoin is a mutagen in vitro. Growth inhibition due to DNA damage was noted in *Bacillus subtilis* (McCarroll et al., 1981; Suter and Jaeger, 1982) and in *Escherichia coli* (Yahagi et al., 1974; McCalla and Voutsinos, 1974) following exposure to nitrofurantoin. The mutagenic activity of nitrofurantoin has been demonstrated in numerous bacterial gene reversion tests with *E. coli* (Yahagi et al., 1974; McCalla and Voutsinos, 1974; Simmon and Eckford, 1978; Lu et al., 1979; Olive, 1979a,b) and *Salmonella typhimurium*, particularly strains TA98 and TA100, which initiate error-prone DNA repair processes (Wang and Lee, 1976; Goodman et al., 1977; Simmon and Eckford, 1978; De Flora, 1979; Ebringer and Bencova, 1980; Zeiger et al., 1981). By comparing the results of nitrofurantoin exposure of Salmonella strain TA100 with those of the nitro reductase-deficient strain TA100-FR1, Rosenkranz and Speck (1976) demonstrated that reduction of the nitro group is required to produce a mutagenic response in the absence of metabolic activation. However, they observed significant gene reversion in both strains of Salmonella treated with nitrofurantoin in the

presence of rat liver S9, indicating that mammalian liver enzymes are also capable of metabolizing nitrofurantoin to a mutagenic intermediate. In numerous independent NTP-sponsored tests on chemical mutagenicity in Salmonella with a preincubation protocol, nitrofurantoin was consistently mutagenic to strains TA98 and TA100 both with and without metabolic activation by Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9. No significant increase in mutant colonies was observed in strains TA1535 or TA1537, which, unlike TA100 and TA98, do not exhibit enhanced error-prone repair of damaged DNA (Haworth et al., 1983). A representative sample of these tests as conducted by one laboratory is presented in Table E1.

Exposure to nitrofurantoin induced formation of white (lacking chlorophyll) colonies of *Euglena gracilis* strain z (McCalla, 1962, 1965; Ebringer et al., 1978); this bleached condition is heritable, but whether it is the result of direct interaction of the nitrofurantoin with chloroplast DNA is unknown. Mitotic recombination in *Saccharomyces cerevisiae* (Siebert et al., 1979; Callen, 1981) and mitotic nondisjunction in *Aspergillus nidulans* (Bignami et al., 1974) were observed after treatment with nitrofurantoin.

Mutagenicity results from assay systems that use cultured mammalian cells are variable. Without S9, single-strand breaks in the DNA of cultured mouse L cells were detected after incubation with 430 µM nitrofurantoin for 1 hour (Olive and McCalla, 1977), and resistance to 6-thioguanine was induced in Chinese hamster V79 spheroids after treatment with 100-300 µg/ml nitrofurantoin (Olive, 1981). Induction of forward mutations at the TK locus of mouse L5178Y lymphoma cells was observed after treatment with 5-500 µg/ml nitrofurantoin in the absence of S9; it was not tested with S9 (Table E2). Incubation of Chinese hamster ovary cells with 40 µM nitrofurantoin for 1 hour produced a 74% increase in sister chromatid exchanges over the baseline frequency (Shirai and Wang, 1980). Chromosomal aberrations were observed in 19% of cultured Chinese hamster fibroblast cells incubated with 0.062 mg/ml nitrofurantoin (Ishidate et al., 1978). In NTP studies, nitrofurantoin induced increased numbers of sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells with and without metabolic activation (Tables E3 and E4). Results of other investigations with in vitro assays that use mammalian systems showed no effect of nitrofurantoin treatment on sister chromatid exchange frequencies (Sasaki et al., 1980), chromosomal aberrations (Tonomura and Sasaki, 1973), and unscheduled DNA synthesis (Tonomura and Sasaki, 1973). No meiotic chromosomal abnormalities were observed in mice (Fonatsch, 1977), induction of micronuclei was not observed in rats (Setnikar et al., 1976; Goodman et al., 1977), sperm morphologic abnormalities were absent in dosed male mice (Topham, 1980), and dominant lethal mutations were not detected in two strains of exposed male mice (Epstein et al., 1972; Setnikar et al., 1976).

In tests by Kramers (1982), nitrofurantoin fed to adult male Drosophila, strain Oregon R, at a concentration of 5 mM produced a marginally significant increase in the frequency of sex-linked recessive lethal mutations, but considerable inconsistency occurred between tests, leaving the question of nitrofurantoin's mutagenic activity in this assay unresolved. In an NTP Drosophila sex-linked recessive lethal assay, no increase in mutations was observed in adult male Canton-S flies after administration of nitrofurantoin orally (2,000 ppm in sucrose for 3 days) or by injection (10,000 ppm in saline) (Zimmering et al., 1985; Table E5).

Study Rationale

Nitrofurantoin was nominated and selected for study by the National Cancer Institute as a result of a review of International Agency for Research on Cancer chemicals, because it had the largest production volume and was the most widely used 5-nitrofuran drug, and because it is structurally similar to other 5-nitrofuran derivatives reported to be carcinogenic in rodent studies. Administration of nitrofurantoin in feed was chosen to obtain exposure by the oral route, which is the primary route for administration of the drug in humans.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF NITROFURANTOIN

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF NITROFURANTOIN

Nitrofurantoin was obtained in one lot (lot no. 03540) from Norwich Eaton Pharmaceuticals (Norwich, NY). Purity and identity determinations were conducted by Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on analyses performed in support of the nitrofurantoin studies are on file at the National Institute of Environmental Health Sciences.

Lot no. 03540 was obtained as a yellow, microcrystalline powder with a melting point of 251°-255° C. The identity of nitrofurantoin was confirmed by infrared (Figure 1), ultraviolet/visible, and nuclear magnetic resonance (Figure 2) spectroscopy. The infrared and nuclear magnetic resonance spectra were consistent with literature spectra (Analytical Profiles of Drug Substances, 1976).

The purity of nitrofurantoin was determined by elemental analysis, water analysis, titration of the imide group, thin-layer chromatography, and high-performance liquid chromatography. Cumulative data indicated that lot no. 03540 was greater than 99% pure. Results of elemental analyses for carbon, hydrogen, and nitrogen agreed with the theoretical values. Water content by Karl Fischer titration was less than 0.02%. Titration of the imide group with tetrabutylammonium hydroxide indicated a purity of 99.6%. Thin-layer chromatography on silica gel plates with either a cyclohexane:acetone:methanol:acetic acid (45:45:5:5) or a toluene:2-butanone:acetic acid (40:60:1) solvent system detected a single spot with visualization by ultraviolet and visible light and a sodium hydroxide-saturated methanol spray. No impurities with a peak area greater than 0.1% of the major peak area were detected by high-performance liquid chromatography on a μBondapak C_{18} column with a water:acetonitrile (88:12) mobile phase at a flow rate of 1 ml/minute and ultraviolet detection at 365 nm. Analysis of lot no. 03540 by the same high-performance liquid chromatographic system (with a slightly different solvent ratio) did not detect nitrofurazone, 5-nitro-2-furaldehyde, or 3-[[(5-nitro-2-furanyl)-methylene]amino]-2,4-imidizolidinedione at concentrations equal to or greater than the minimal detectable concentrations (0.03%, 2.4%, and 0.2% w/v).

Stability studies performed by high-performance liquid chromatography with a μBondapak C_{18} column, a water:acetonitrile (70:30) mobile phase at a flow rate of 1.5 ml/minute, and ultraviolet detection at 254 nm indicated that nitrofurantoin was stable for 2 weeks at temperatures up to 60° C. Further confirmation of the stability of the bulk chemical (stored at 5° C) during the toxicity studies was obtained by titration with tetrabutylammonium hydroxide and high-performance liquid chromatography with a Hewlett-Packard RP-8 column or a Perkin-Elmer ODS Sil-X column, ultraviolet detection at 365 nm, and a water:acetonitrile mobile phase at a flow rate of 1 ml/minute. The acetonitrile concentration was increased from 30% to 50% over 20 minutes or from 5% to 45% over 15 minutes. No degradation of the bulk chemical was seen over the course of the studies. Identity of the chemical at the study laboratory was confirmed by infrared spectroscopy.

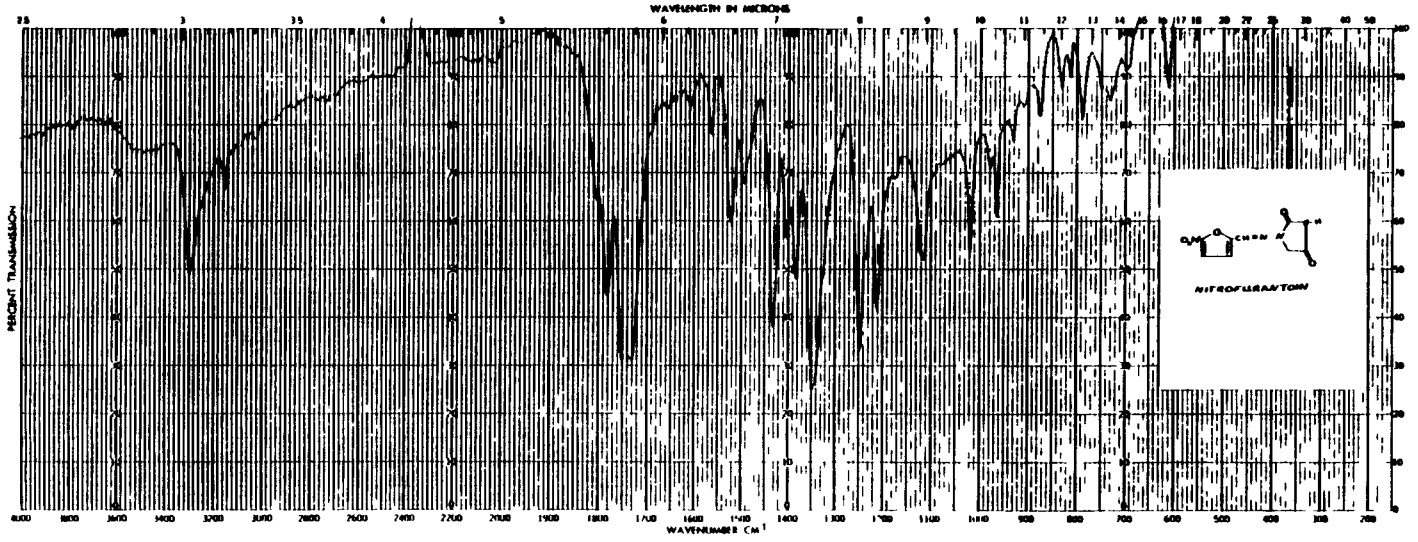


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF NITROFURANTOIN (LOT NO. 03540)

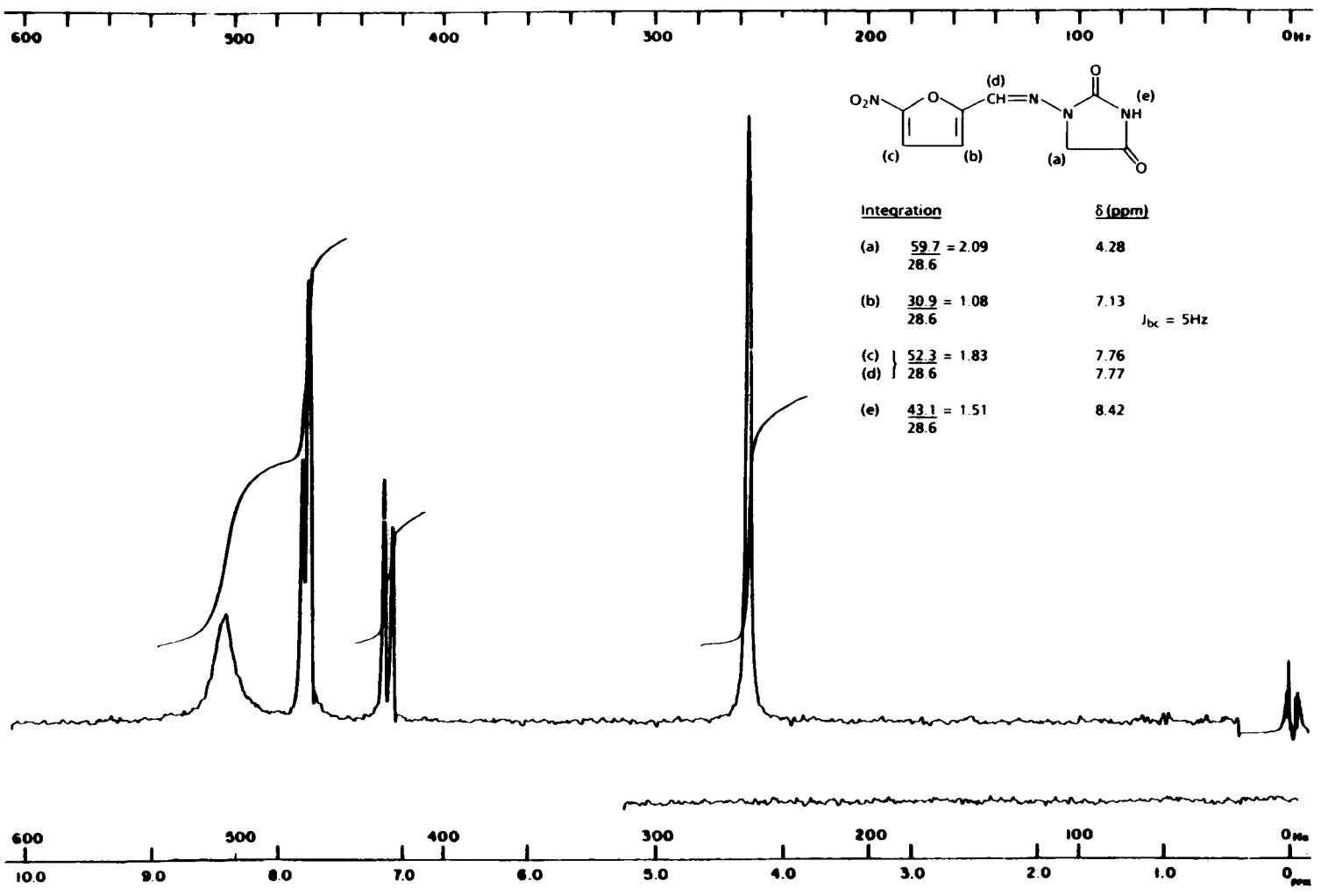


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF NITROFURANTOIN (LOT NO. 03540)

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

Formulated diets were prepared by adding a dry premix (approximately equal amounts of feed and nitrofurantoin) to the appropriate amount of feed (Table 1). The mixture was blended for 15 minutes. The homogeneity of diet mixtures formulated at the analytical chemistry and study laboratories was evaluated by extracting feed samples (taken from three positions in the blender) with acetonitrile and determining the absorption at 365 nm (analytical chemistry laboratory) or from 360 to 380 nm (study laboratory). Further studies indicated that nitrofurantoin was stable in feed at 2,000 ppm when stored for 2 weeks in the dark at temperatures up to 45° C. In these studies, samples were extracted with acetonitrile:acetic acid (99:1) and analyzed by high-performance liquid chromatography with a μBondapak C_{18} column, a water/acetonitrile (80:20) mobile phase, and ultraviolet detection at 254 nm. In the 13-week and 2-year studies, formulated diets were stored at 5° C for no longer than 14 days.

Periodic analyses of feed mixtures by the same analytical methods used for the homogeneity studies were conducted by the study and analytical chemistry laboratories to determine if the formulated diets contained the correct concentrations of nitrofurantoin. Formulated diets were analyzed once during the 13-week studies. The results ranged from 93% to 103% of the target concentrations (Table 2). During the 2-year studies, feed mixtures were analyzed every 1-2 months, and concentrations varied from 80% to 113% of the target concentrations (Table 3). Because 78/83 formulated diets analyzed were within 10% of the target concentrations, it is estimated that the formulated diets were prepared

TABLE 1. PREPARATION AND STORAGE OF FORMULATED DIETS IN THE FEED STUDIES OF NITROFURANTOIN

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation Premix prepared by mixing weighed amounts of nitrofurantoin and feed in a specimen cup for 1 min; remaining feed mixed with premix in a 16-qt blender for 15 min	Same as 14-d studies	Same as 14-d studies
Maximum Storage Time 14 d	14 d	14 d
Storage Conditions Room temperature in the dark	5° C in the dark	5° C in the dark before use and then at room temperature

TABLE 2. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE THIRTEEN-WEEK FEED STUDIES OF NITROFURANTOIN (a)

Target Concentration (ppm)	Determined Concentration (b) (ppm)	Determined as a Percent of Target
300	(c) 287	95.7
600	560	93.3
1,300	1,340	103.1
2,500	2,520	100.8
5,000	4,990	99.8
10,000	(c) 9,723	97.2

(a) Mix date: 4/29/80
(b) Results of duplicate analysis
(c) Average of values obtained from three locations in the blender

TABLE 3. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF NITROFURANTOIN

Date Mixed	Concentration of Nitrofurantoin in Feed for Target Concentration (ppm) (a)		
	600	1,300	2,500
02/11/81		1,300	2,480
02/18/81	602	1,310	2,450
		1,316	2,500
		1,320	
03/18/81	600	1,320	2,580
04/15/81		1,300	2,620
		1,410	
05/13/81	(b) 680	1,430	2,350
05/18/81	(c) 490		
05/19/81	(d) 596		
06/10/81		1,340	2,540
		1,350	
07/08/81	608	1,340	2,480
08/05/81		1,370	2,450
		1,230	
09/02/81	630	1,280	2,320
09/30/81		(e) 1,190	2,560
		1,330	
10/28/81	593	1,200	(b) 2,000
10/30/81			(d) 2,310
11/18/81		1,230	2,300
		1,240	
12/16/81	605	1,250	2,510
02/10/82	541	1,180	2,450
		(b) 1,140	2,370
		1,220	
02/12/82		(d) 1,290	
04/07/82	578	1,240	2,380
		1,210	2,350
		1,240	
06/02/82	570	1,220	2,460
		1,280	2,440
		1,310	
07/28/82	602	1,300	2,410
		1,300	2,410
		1,310	
09/22/82	609	1,290	2,490
		1,260	2,350
		1,250	
11/17/82	587	1,240	2,490
		1,280	2,510
		1,300	
01/12/83	618	1,410	2,740
		1,330	(b) 2,810
		(b) 1,470	
01/18/83		(d) 1,380	(d) 2,650
Mean (ppm)	602	1,289	2,457
Standard deviation	31.4	69.6	146.5
Coefficient of variation (percent)	5.2	5.4	6.0
Range (ppm)	541-680	1,140-1,470	2,000-2,810
Number of samples	14	41	28

(a) Results of duplicate analysis
(b) Out of specifications; not used in study.
(c) Remix out of specifications; not used in study or included in the mean.
(d) Remix; not included in the mean.
(e) Result of triplicate analysis

within specifications 94% of the time. Referee analyses were performed periodically by the analytical chemistry laboratory. Good agreement was generally found between the laboratories (Table 4).

TABLE 4. RESULTS OF REFEREE ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF NITROFURANTOIN

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory (a)	Referee Laboratory (b)
02/11/81	1,300	1,300	1,270
10/28/81	600	593	640
06/02/82	2,500	2,460	2,650
11/17/82	1,300	1,240	1,290

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

FOURTEEN-DAY STUDIES

Four- to five-week-old F344/N rats and 4- to 6-week-old B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories. Rats were observed for 21 days and mice for 14 days before being placed on study. Groups of five rats of each sex were fed diets containing 0, 1,300, 2,500, 5,000, 10,000, or 20,000 ppm nitrofurantoin for 14 consecutive days. Groups of five mice of each sex were fed diets containing 0, 600, 1,300, 2,500, 5,000, or 10,000 ppm. Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 5.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to nitrofurantoin and to determine the concentrations to be used in the 2-year studies.

Five- to six-week-old F344/N rats and B6C3F$_1$ mice of each sex were obtained from Charles River Breeding Laboratories 18 days before being placed on study. Groups of 10 rats of each sex were fed diets containing 0, 600, 1,300, 2,500, 5,000, or 10,000 ppm nitrofurantoin for 13 weeks. Groups of 10 mice of each sex were fed diets containing 0, 300, 600, 1,300, 2,500, or 5,000 ppm. Animals were housed five per cage. Feed and water were available ad libitum.

Animals were observed two times per day; moribund animals were killed. Feed consumption was measured once per week by cage. Individual animal weights were recorded once per week. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Liver weights were determined at necropsy. Groups and tissues examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 female rats were fed diets containing 0, 600, or 1,300 ppm nitrofurantoin for 103 weeks. Groups of 50 male rats and 50 mice of each sex were fed diets containing 0, 1,300, or 2,500 ppm for 103 weeks. On January 8, 1982, eight cages of control male rats were inadvertently fed diets containing 600 ppm nitrofurantoin.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Harlan Industries. 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. Rats were shipped to the study laboratory at 4-5 weeks of age and mice at 6-7 weeks of age. The animals were quarantined at the study laboratory for 16 days. Thereafter, a complete necropsy was performed on five animals of each sex and

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF NITROFURANTOIN

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
Rats--0, 1,300, 2,500, 5,000, 10,000, or 20,000 ppm nitrofurantoin in feed; mice--0, 600, 1,300, 2,500, 5,000, or 10,000 ppm	Rats--0, 600, 1,300, 2,500, 5,000, or 10,000 ppm nitrofurantoin in feed; mice--0, 300, 600, 1,300, 2,500, or 5,000 ppm	Rats--male: 0, 1,300, or 2,500 ppm nitrofurantoin in feed; female: 0, 600, or 1,300 ppm; mice--0, 1,300, or 2,500 ppm
Date of First Dose		
Rats--2/19/80; mice--3/12/80	5/5/80	Rats--2/26/81; mice--2/19/81
Date of Last Dose		
Rats--3/3/80; mice--3/27/80	8/3/80	Rats--2/16/83; mice--2/9/83
Duration of Dosing		
14 consecutive d	13 wk	103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed 1 × wk	Observed 2 × d; weighed initially, 1 × wk for 12 wk (rats) or 13 wk (mice), and then 1 × mo; palpated at weighing starting at wk 44 or earlier if masses were noted
Necropsy and Histologic Examinations		
Necropsy performed on all animals; histologic exams not performed	Necropsy performed on all animals; the following tissues examined histologically for control and high dose groups: adrenal glands, brain, cecum, colon, esophagus, heart, kidneys, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, pancreas, parathyroid glands, pituitary gland, prostate/testes/seminal vesicles or ovaries/uterus, regional lymph nodes, salivary glands, skin, small intestine, spleen, sternum including marrow, stomach, thigh muscle, thymus, thyroid gland, trachea, and urinary bladder. Liver weights recorded at necropsy	Necropsy and histologic exams performed on all animals; the following tissues examined histologically: adrenal glands, brain, cecum, colon, duodenum, esophagus, gallbladder (mice), gross lesions, heart, ileum, jejunum, kidneys, larynx, liver, lungs and mainstem bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland, prostate/testes/seminal vesicles/epididymis or ovaries/uterus, rectum, regional lymph nodes, salivary glands, skin, spleen, sternebrae or femur or vertebrae including marrow, stomach, thymus, thyroid gland, tissue masses, 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		
Rats--Charles River Breeding Laboratories (Portage, MI); mice--Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)	Harlan Industries (Indianapolis, IN)
Study Laboratory		
Southern Research Institute	Southern Research Institute	Southern Research Institute
Method of Animal Identification		
Ear marked with poultry punch	Ear marked with poultry punch	Ear marked with poultry punch

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF NITROFURANTOIN (Continued)

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Time Held Before Study Rats--21 d; mice--14 d	18 d	16 d
Age When Placed on Study Rats--7-8 wk; mice--6-8 wk	Rats--8 wk; mice--8-9 wk	Rats--6-7 wk; mice--8-9 wk
Age When Killed Rats--9-10 wk; mice--8-10 wk	Rats--22-23 wk; mice--22-24 wk	Rats--110-112 wk; mice--112-114 wk
Necropsy Dates Rats--3/5/80-3/7/80; mice--3/27/80-3/28/80	Rats--8/6/80-8/15/80; mice--8/4/80-8/14/80	Rats--2/25/83-3/2/83; mice--2/18/83-2/23/83
Method of Animal Distribution Animals distributed to weight classes and assigned to cages according to one table of random numbers; cages assigned to groups according to another table of random numbers	Same as 14-d studies	Same as 14-d studies
Feed NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 14-d studies	Same as 14-d studies
Bedding Beta Chip® hardwood chips (Northeastern Products Corp., Warrensburg, NY)	Same as 14-d studies	Same as 14-d studies
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 14-d studies	Same as 14-d studies
Cages Polycarbonate (Lab Products, Inc., Garfield, NJ)	Same as 14-d studies	Same as 14-d studies
Cage Filters Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as 14-d studies	Same as 14-d studies
Animals per Cage 5	5	5
Other Chemicals on Study in the Same Room None	None	None
Animal Room Environment Temp--22°-23° C; hum--41%-52% (rats), 41%-49% (mice); fluorescent light 12 h/d; 15 room air changes/h	Temp--22°-24° C; hum--44%-70%; fluorescent light 12 h/d; 15 room air changes/h	Temp--17.2°-31.1° C; hum--50% ± 10%; fluorescent light 12 h/d; 15 room air changes/h

species to assess their health status. Rats were placed on study at 6-7 weeks of age and mice at 8-9 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

Animal Maintenance

All animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 5.

Clinical Examinations and Pathology

All animals were observed two times per day. Body weights were recorded once per week for the first 12 (rats) or 13 (mice) weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals, including those found dead. Some tissues were excessively autolyzed or cannibalized, and thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

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 microscopically are listed in Table 5.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which included the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses 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).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Additional histologic sections of the right and left kidney of male rats in each dose group and the controls were prepared and reviewed by a special PWG. Three or four longitudinal sections were prepared from the remaining half of each of the right and left kidney at approximately 1-mm intervals by standard procedures. All lesions observed during this special PWG review were evaluated in a "blind" fashion.

Statistical Methods

Data Recording: Data on body weight and feed consumption for this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). Other data elements were recorded in the Toxicology Data Management System. The data elements include animals, experimental design, survival, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

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: Three statistical methods are used to analyze tumor incidence data: life table tests, logistic regression, and Fisher exact/Cochran-Armitage trend analyses. Tests of significance include pairwise comparisons of high dose and low dose groups with controls and tests for overall dose-response trends. For studies in which administration of the study compound has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described below also were used to evaluate selected nonneoplastic lesions.

Life Table Analyses--This method of analysis assumes that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method (1959) to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Logistic Regression Analyses--This method of analysis assumes that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they did not alter the risk of death and were discovered merely as the result of death from an unrelated cause. According to this approach, tumor prevalence was modeled as a logistic function of dose and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). If the tumor type is nonlethal, prevalence analyses and incidence analyses are equivalent.

Fisher Exact/Cochran-Armitage Trend Analyses--In addition to survival-adjusted methods, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendixes containing the analyses of tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

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

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

FOURTEEN-DAY STUDIES

None of the rats died before the end of the studies (Table 6). Rats that received 5,000, 10,000, or 20,000 ppm lost weight, and those that received 2,500 ppm gained notably less than did the controls. Feed consumption by rats that received 5,000, 10,000, or 20,000 ppm was notably less than that by controls during week 1. Compound-related clinical signs included inactivity, rough hair coats, sunken eyes, bright yellow urine, and/or yellow fur. Blue discoloration of the joints was observed in rats that received 20,000 ppm.

TABLE 6. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE FOURTEEN-DAY FEED STUDIES OF NITROFURANTOIN

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 1	Week 2
MALE							
0	5/5	190 ± 8	249 ± 5	+59 ± 5		18	17
1,300	5/5	208 ± 7	258 ± 8	+50 ± 4	104	19	20
2,500	5/5	187 ± 8	225 ± 7	+38 ± 4	90	15	16
5,000	5/5	182 ± 3	176 ± 4	−6 ± 2	71	8	9
10,000	5/5	187 ± 6	147 ± 4	−40 ± 2	59	13	17
20,000	5/5	186 ± 6	117 ± 5	−69 ± 3	47	11	14
FEMALE							
0	5/5	127 ± 5	154 ± 4	+27 ± 1		11	12
1,300	5/5	135 ± 4	157 ± 4	+22 ± 1	102	11	11
2,500	5/5	127 ± 4	143 ± 3	+16 ± 1	93	9	11
5,000	5/5	124 ± 1	122 ± 6	−2 ± 5	79	5	11
10,000	5/5	137 ± 3	103 ± 2	−34 ± 3	67	8	15
20,000	5/5	130 ± 4	84 ± 3	−46 ± 3	55	5	12

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean
(d) Grams of feed consumed per animal per day; average of daily determinations; not corrected for scatter.

THIRTEEN-WEEK STUDIES

One of 10 female rats that received 10,000 ppm died before the end of the studies (Table 7). The final mean body weights of rats that received 2,500, 5,000, or 10,000 ppm were 10%, 34%, or 47% lower than that of the controls for males and 15%, 31%, or 41% lower for females. Feed consumption by dosed and control groups was generally similar. The urine of dosed rats was bright yellow. Minimal-to-mild degeneration of the germinal epithelium of the seminiferous tubules of the testis with aspermatogenesis was observed in 29/30 males that received 2,500 ppm or more. Minimal-to-mild necrosis of the ovarian follicles was observed in 8/10 females that received 10,000 ppm, and minimal necrosis was observed in 3/10 females that received 5,000 ppm and 1/10 females that received 2,500 ppm. The liver weight to body weight ratios for rats that received 5,000 or 10,000 ppm were significantly greater than those of controls (Table 8).

Dose Selection Rationale: Because of lower body weight gain at higher concentrations, dietary concentrations selected for rats for the 2-year studies were 1,300 and 2,500 ppm nitrofurantoin for males and 600 and 1,300 ppm for females.

TABLE 7. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF NITROFURANTOIN

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 4	Week 12
MALE							
0	10/10	130 ± 2	344 ± 8	+214 ± 8		17	16
600	10/10	129 ± 2	366 ± 6	+237 ± 6	106	17	16
1,300	10/10	127 ± 2	334 ± 7	+207 ± 8	97	17	16
2,500	10/10	129 ± 1	311 ± 6	+182 ± 6	90	15	16
5,000	10/10	130 ± 2	228 ± 6	+98 ± 5	66	15	13
10,000	10/10	128 ± 1	182 ± 3	+54 ± 3	53	18	20
FEMALE							
0	10/10	109 ± 2	198 ± 3	+89 ± 2		14	12
600	10/10	109 ± 2	189 ± 2	+80 ± 2	95	13	11
1,300	10/10	111 ± 1	191 ± 1	+80 ± 1	96	12	12
2,500	10/10	107 ± 1	168 ± 3	+61 ± 3	85	10	9
5,000	10/10	110 ± 1	136 ± 2	+26 ± 2	69	12	11
10,000	(e) 9/10	110 ± 1	116 ± 4	+6 ± 4	59	16	22

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams of feed consumed per animal per day; not corrected for scatter.
(e) Week of death: 12

TABLE 8. ABSOLUTE AND RELATIVE LIVER WEIGHTS OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF NITROFURANTOIN (a)

Concentration (ppm)	Number of Animals	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/Necropsy Body Weight (mg/g)
MALE				
0	10	348 ± 7.8	13,191 ± 447	38.0 ± 1.26
600	10	367 ± 6.5	12,893 ± 660	35.1 ± 1.64
1,300	10	337 ± 7.3	12,261 ± 295	36.4 ± 0.80
2,500	10	(b) 313 ± 6.1	12,350 ± 337	39.4 ± 0.98
5,000	10	(b) 246 ± 5.6	(b) 10,772 ± 345	(c) 43.8 ± 0.59
10,000	10	(b) 182 ± 3.6	(b) 8,972 ± 250	(b) 49.4 ± 1.91
FEMALE				
0	10	198 ± 3.5	6,698 ± 229	33.8 ± 0.90
600	10	192 ± 2.2	6,945 ± 131	36.1 ± 0.53
1,300	10	197 ± 1.7	(b) 7,950 ± 162	40.4 ± 0.71
2,500	10	(b) 172 ± 3.0	6,227 ± 177	36.3 ± 1.13
5,000	10	(b) 146 ± 1.6	6,837 ± 226	(b) 46.8 ± 1.53
10,000	9	(b) 118 ± 4.4	(b) 5,270 ± 549	(b) 44.7 ± 4.35

(a) Mean ± standard error; P values vs. the controls by Dunnett's test (Dunnett, 1955).
(b) $P<0.01$
(c) $P<0.05$

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of high dose male rats were 6%-9% lower than those of the controls from week 1 to week 11 and thereafter were within 5% of the control weights (Table 9 and Figure 3). Mean body weights of dosed female rats were within 6% of those of the controls throughout the studies. The average daily feed consumption per rat by low dose and high dose rats was 99% and 95% that by controls for males (Table G1) and 101% and 98% for females (Table G2). The average amount of nitrofurantoin consumed per day was estimated to be 60 and 110 mg/kg for low and high dose male rats and 30 and 60 mg/kg for low and high dose female rats. Dosed rats had bright yellow urine.

TABLE 9. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF NITROFURANTOIN

Weeks on Study	Control Av. Wt. (grams)	Control No. of Survivors	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of controls)	Low Dose No. of Survivors	High Dose Av. Wt. (grams)	High Dose Wt. (percent of controls)	High Dose No. of Survivors
MALE				**1,300 ppm**			**2,500 ppm**	
0	117	50	119	102	50	116	99	50
1	159	50	159	100	50	149	94	50
2	190	50	192	101	50	177	93	50
3	218	50	217	100	50	198	91	50
4	236	50	238	101	50	214	91	50
5	254	50	256	101	50	231	91	50
6	264	50	268	102	50	240	91	50
7	280	50	286	102	50	257	92	50
8	293	50	296	101	50	268	91	50
9	306	50	311	102	50	283	92	50
10	312	50	316	101	50	291	93	50
11	321	50	327	102	50	300	93	50
12	329	50	334	102	50	312	95	50
17	363	50	365	101	50	340	94	50
21	381	50	381	100	50	361	95	50
25	393	50	391	99	50	374	95	50
29	404	50	406	100	50	385	95	50
34	416	50	416	100	50	402	97	50
38	422	50	426	101	50	414	98	50
44	430	50	427	99	50	420	98	50
48	443	50	448	101	49	438	99	50
52	449	50	452	101	49	446	99	50
55	445	50	450	101	49	439	99	49
59	452	49	452	100	49	448	99	47
64	455	49	451	99	49	456	100	47
69	454	48	445	98	49	453	100	47
74	442	47	439	99	47	444	100	46
78	446	46	440	99	47	442	99	45
82	441	44	434	98	45	437	99	44
86	440	41	428	97	45	435	99	44
90	440	37	432	98	42	430	98	43
94	436	33	426	98	41	425	97	37
98	435	30	422	97	38	413	95	35
104	412	27	401	97	29	391	95	28
FEMALE				**600 ppm**			**1,300 ppm**	
0	98	50	98	100	50	96	98	50
1	121	50	121	100	50	117	97	50
2	135	50	138	102	50	136	101	50
3	148	50	151	102	50	148	100	50
4	157	50	160	102	50	156	99	50
5	166	50	170	102	50	163	98	50
6	170	50	174	102	50	167	98	50
7	177	50	181	102	50	174	98	50
8	180	50	184	102	50	176	98	50
9	185	50	191	103	50	184	99	50
10	189	50	194	103	50	187	99	50
11	193	50	198	103	50	191	99	50
12	195	50	201	103	50	194	99	50
17	210	50	216	103	50	206	98	50
21	214	50	223	104	50	212	99	50
25	225	50	231	103	50	217	96	50
29	228	50	239	105	50	223	98	50
34	237	50	248	105	50	233	98	50
38	245	50	256	104	50	237	97	50
44	256	50	271	106	50	246	96	50
48	267	50	279	104	50	256	96	50
52	283	50	294	104	50	270	95	50
55	288	50	300	104	50	277	96	50
59	303	50	310	102	49	291	96	48
64	316	49	325	103	47	302	96	48
69	328	48	339	103	46	314	96	46
74	332	47	343	103	44	318	96	44
78	340	47	347	102	44	324	95	44
82	343	46	355	103	41	331	97	43
86	345	46	359	104	41	339	98	42
90	352	44	367	104	39	344	98	41
94	353	42	368	104	37	346	98	40
98	361	37	375	104	34	352	98	36
104	352	28	359	102	28	351	100	31

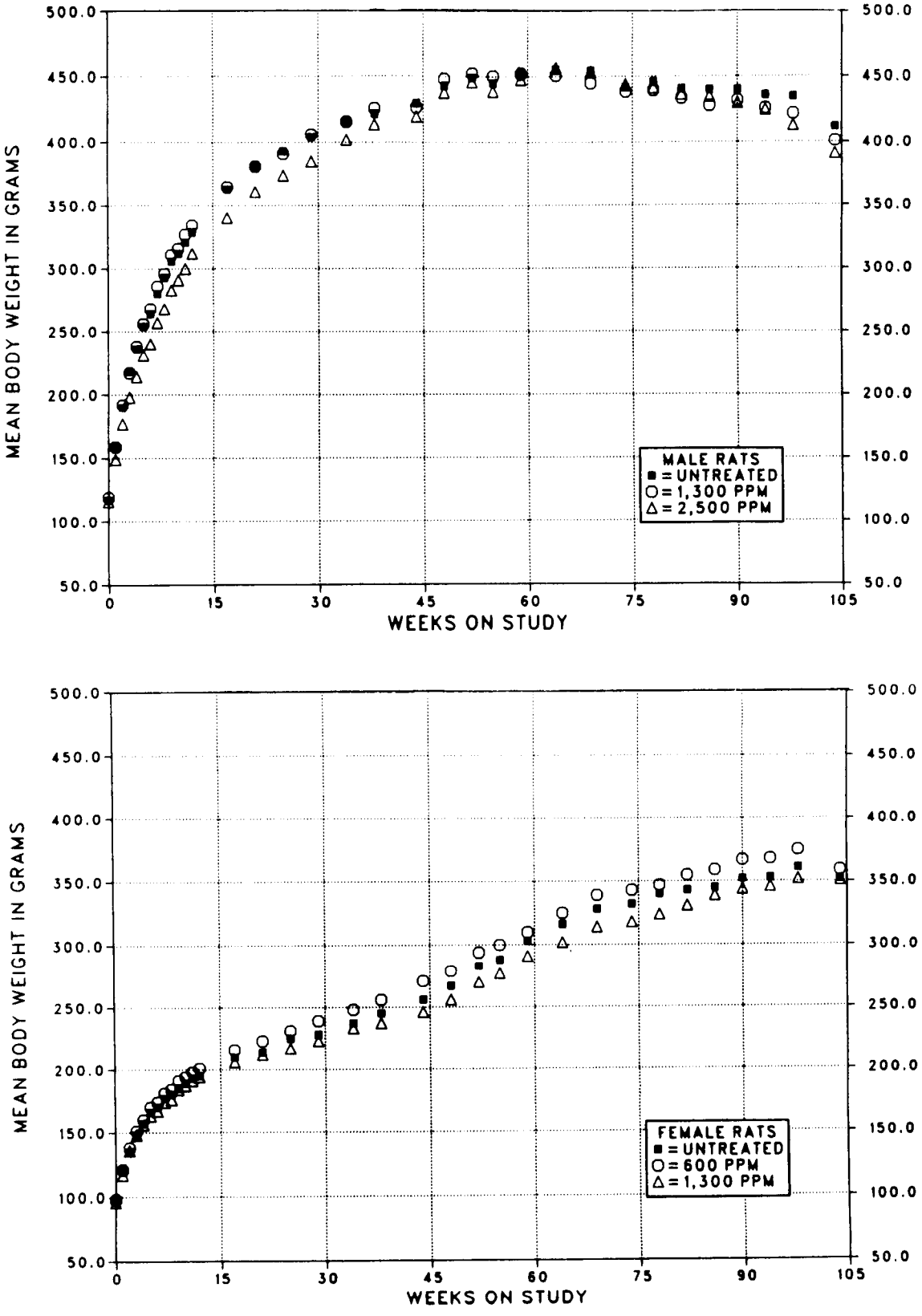


FIGURE 3. GROWTH CURVES FOR RATS FED DIETS CONTAINING NITROFURANTOIN FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing nitrofurantoin at the concentrations used in these studies and for controls are shown in Table 10 and in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of rats of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the kidney, parathyroid glands, glandular stomach, bone, subcutaneous tissue, testis, epididymis, preputial gland, clitoral gland, mammary gland, and eye.

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 10. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF NITROFURANTOIN

	Control	600 ppm	1,300 ppm	2,500 ppm
MALE (a)				
Animals initially in study	50		50	50
Nonaccidental deaths before termination (b)	26		23	24
Killed at termination	23		27	26
Died during termination period	1		0	0
Survival P values (c)	0.668		0.512	0.732
FEMALE (a)				
Animals initially in study	50	50	50	
Nonaccidental deaths before termination (b)	25	24	19	
Killed at termination	25	26	31	
Survival P values (c)	0.446	0.951	0.489	

(a) First day of termination period: 730
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

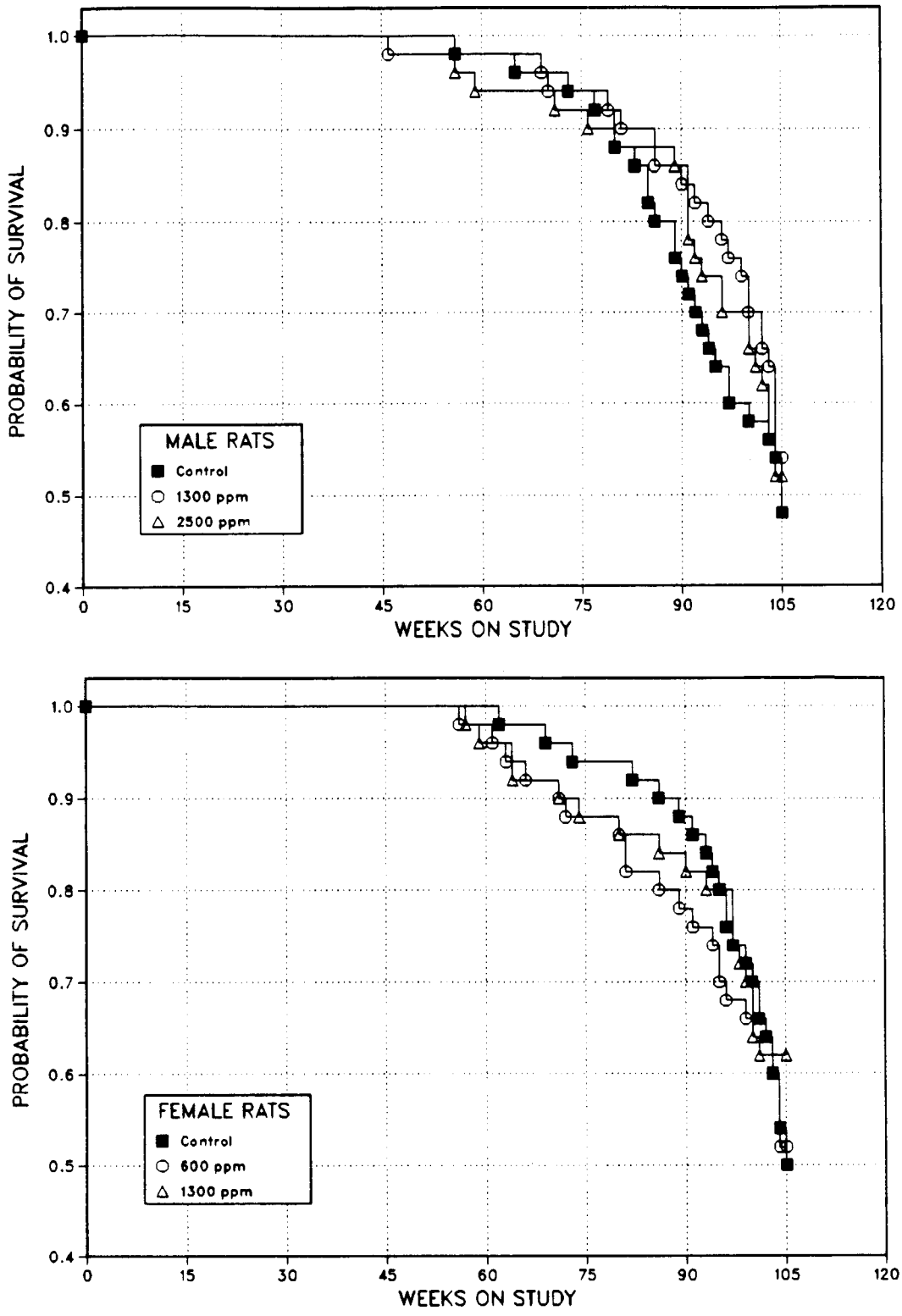


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING NITROFURANTOIN FOR TWO YEARS

Kidney: Chronic nephropathy occurred in nearly all rats. This spontaneous disease was characterized by varying degrees of tubular degeneration with atrophy of the epithelium and dilatation of the tubules, regeneration of tubular epithelium, thickening of the tubular basement membranes, interstitial fibrosis, chronic inflammation, and glomerulosclerosis. The severity of this disease in each rat was judged on a scale of 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. The mean severity of the nephropathy was somewhat increased in dosed male rats relative to controls but was decreased in dosed female rats (male: control, 50/50 [severity, 3.1]; low dose, 48/50 [3.3]; high dose, 48/50 [3.5]; female: 44/50 [2.4]; 40/50 [2.2]; 48/50 [2.0]). Hyperplasia of the transitional epithelium lining the renal pelvis and hydronephrosis were also observed in some dosed male rats (transitional epithelium hyperplasia: 0/50; 5/50; 2/50; hydronephrosis: 0/50; 5/50; 2/50).

A single section of the left and right kidney of each rat was examined microscopically as a standard procedure during the histopathologic evaluation. With this procedure, renal tubular cell adenomas were seen in 1/50 low dose and 2/50 high dose male rats, and a tubular cell carcinoma was observed in 1/50 high dose male rats; none was seen in controls (Table 11). Tubular cell hyperplasia was seen in all groups of males, including controls.

Because the number of renal tubular cell neoplasms identified by standard procedures in the dosed male rats was low, the marginally increased incidence was not statistically significant relative to concurrent controls. Since tubular cell neoplasms are often late appearing and are seen only during microscopic examination in 2-year-old rats (i.e., they are often not seen grossly at necropsy), step-sections of kidney were made to provide additional data. The remaining half of the right and left kidney from each male rat was embedded, and three or four additional step-sections from each half kidney were made at approximately 1-mm intervals. These were examined microscopically, and additional tubular cell neoplasms were observed in all groups (Tables 12 and 13). The tubular cell adenomas occurred with a significant positive trend, and the incidences in the low and high dose groups were significantly greater than that in the controls.

TABLE 11. RENAL TUBULAR CELL LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN: ORIGINAL EVALUATION (a)

	Control	1,300 ppm (b)	2,500 ppm (b)
Hyperplasia			
Overall Rates	2/50 (4%)	2/50 (4%)	1/50 (2%)
Adenoma			
Overall Rates	0/50 (0%)	1/50 (2%)	2/50 (4%)
Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adenoma or Carcinoma (c)			
Overall Rates	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates	0.0%	3.7%	10.9%
Terminal Rates	0/24 (0%)	1/27 (4%)	2/26 (8%)
Day of First Observation		730	719
Life Table Tests	P=0.068	P=0.523	P=0.134
Logistic Regression Tests	P=0.066	P=0.523	P=0.134

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table A3 (footnotes).
(b) The estimated dose in milligrams per kilograms per day is given in Section III (Body Weights, Feed Consumption, and *Clinical Signs)* and in *Appendix G.*
(c) Historical incidence at study laboratory (mean ± SD): 2/439 (0.5% ± 0.9%); historical incidence in NTP studies: 8/1,929 (0.4% ± 0.9%)

TABLE 12. RENAL TUBULAR CELL LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN: ADDITIONAL STEP-SECTIONS (a)

Lesion	Control	1,300 ppm	2,500 ppm
Hyperplasia	9/50 (18%)	9/50 (18%)	7/50 (14%)
Hyperplasia, cystic	1/50 (2%)	5/50 (10%)	3/50 (6%)
Adenoma	3/50 (6%)	10/50 (20%)	17/50 (34%)
Carcinoma	0/50 (0%)	0/50 (0%)	1/50 (2%)

(a) Hyperplasia and adenomas observed in one control and three low dose males; hyperplasia, adenoma, and carcinoma observed in one high dose male.

TABLE 13. RENAL TUBULAR CELL LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN: COMPOSITE RESULTS

Lesion	Control	1,300 ppm	2,500 ppm
Hyperplasia	10/50 (20%)	11/50 (22%)	8/50 (16%)
Hyperplasia, cystic	1/50 (2%)	5/50 (10%)	3/50 (6%)
Adenoma	3/50 (6%)	11/50 (22%)	19/50 (38%)
Carcinoma	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adenoma and carcinoma (combined)			
Overall Rates	3/50 (6%)	11/50 (22%)	20/50 (40%)
Terminal Rates	2/21 (10%)	5/23 (22%)	1/1 (100%)
Day of First Observation	723	489	619
Logistic Regression Tests	P<0.001	P=0.026	P<0.001

Tubular cell hyperplasia, adenoma, and carcinoma occurred in the cortex of the kidney and appeared to encompass a morphologic continuum. Tubular cell hyperplasia generally was characterized by one or two cross-sections of a normal-to-slightly enlarged tubule with stratified epithelium that partially or completely occluded the tubular lumen. The cells were often enlarged and contained nuclei with prominent nucleoli. Adenomas were circumscribed masses of epithelial cells usually larger than the cross-sectional diameter of three tubules. The epithelium formed a solid sheet of cells within the mass or was arranged in packets separated by basement membrane. The cells were generally uniform in appearance and similar to those in hyperplasia. The tubular cell carcinomas were larger than the adenomas and exhibited some cellular atypia or pleomorphism. The carcinomas did not metastasize to other organs.

Characteristic differences between tubular cell hyperplasia and adenomas in control and dosed male rats are shown in Figures 5 through 8. The malignant character of the tubular cell carcinoma in the high dose male rat is shown in Figures 9 and 10.

Parathyroid Glands, Glandular Stomach, and Bone: Hyperplasia of the parathyroid glands occurred at increased incidences in dosed male rats (male: control, 3/49; low dose, 18/47; high dose, 23/49; female: 0/49; 0/50; 1/47). This lesion frequently accompanies severe renal disease, and the increased incidence reflects the increased severity of the nephropathy in dosed male rats. Mineralization of the glandular stomach (male: 1/49; 8/50; 14/50; female: 0/50; 2/48; 3/50) and fibrous osteodystrophy of the bone also occurred with increased incidences in dosed male rats (male: 0/50; 5/50; 5/50; female: none observed) and were probably the result of the calcium-phosphate imbalance that accompanies severe renal disease.

Osteosarcomas were observed in 1/50 low dose and 2/50 high dose male rats. The overall historical incidence of osteosarcomas in untreated control male F344/N rats is 8/1,937 (0.4%). The highest incidence observed in an untreated control group is 2/50.

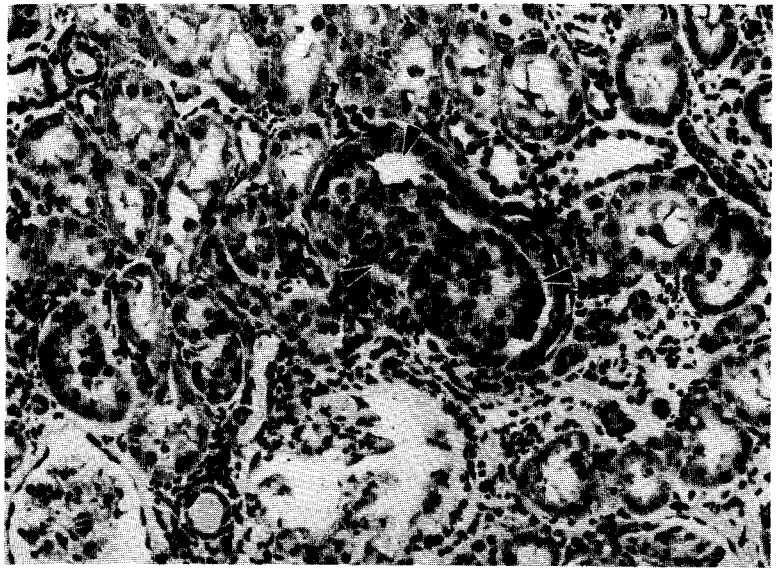


Figure 5. Tubular cell hyperplasia (arrows) in kidney of a control male rat. Note the slightly enlarged tubule with epithelial cells partially filling the lumen.

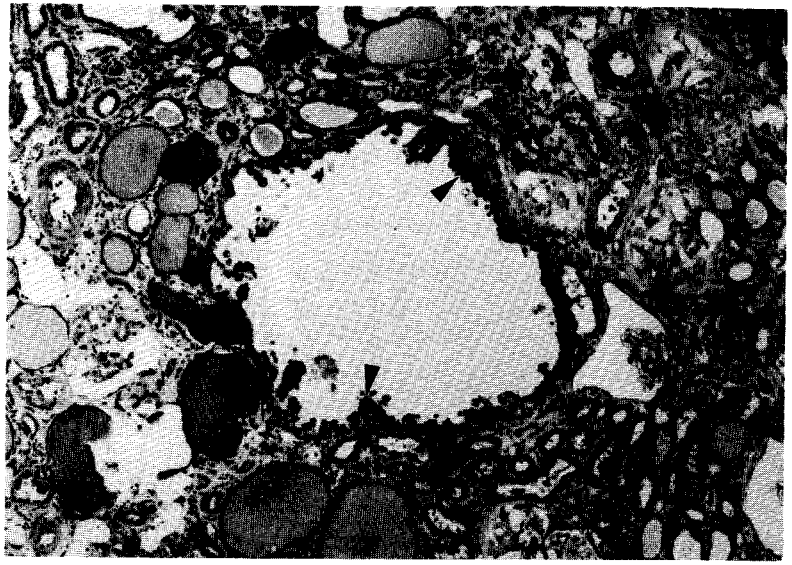


Figure 6. Cystic hyperplasia of renal tubule in a low dose male rat. Note the hyperplastic epithelium (arrow) lining the moderately dilated tubule.

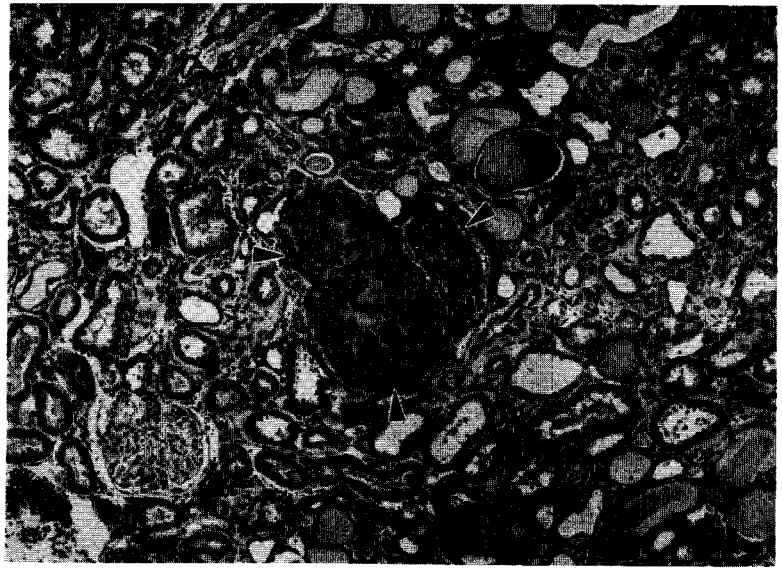


Figure 7. Tubular cell adenoma (arrows) in kidney of a control male rat.

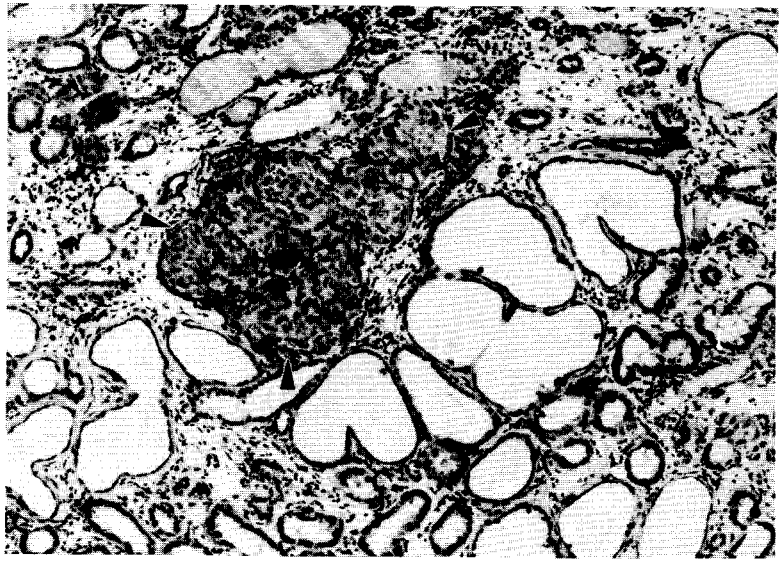


Figure 8. Tubular cell adenoma (arrows) in kidney of a high dose male rat.

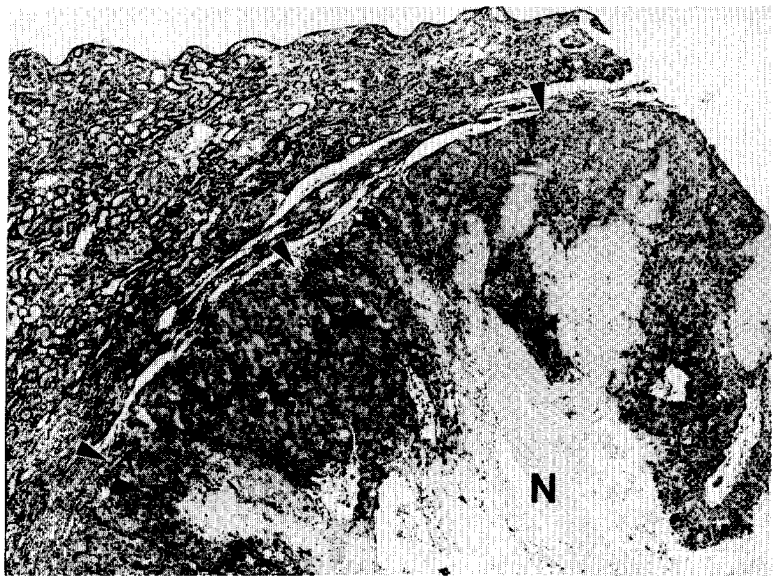


Figure 9. Tubular cell carcinoma (arrows) in kidney of a high dose male rat. Note the necrosis in the center of the large mass.

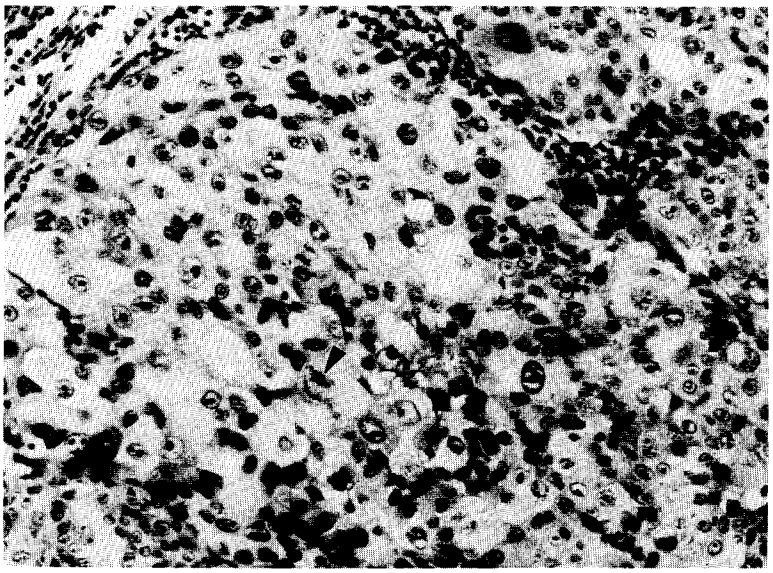


Figure 10. Higher magnification of the tubular cell carcinoma shown in Figure 9. Note the pleomorphic cells with large vesicular nuclei and prominent nucleoli and cell in mitosis (arrow).

Subcutaneous Tissue: The incidences of fibromas and fibromas or fibrosarcomas (combined) in low dose male rats were significantly greater than those in controls (Table 14).

Testis and Epididymis: Aspermatogenesis and atrophy are frequently observed in the testis of 2-year-old F344/N rats and are usually associated with the occurrence of interstitial cell tumors. Although these lesions were present in control and dosed male rats, the incidence and severity were higher in dosed rats. Degeneration of the spermatogenic (germinal) epithelium, fibrinoid necrosis of arterioles, and perivascular infiltration of mononuclear inflammatory cells also occurred at increased incidences in dosed rats (Table 15). The degeneration of the spermatogenic epithelium was characterized by a decrease in the number of cells, nuclear pyknosis (necrosis), cytoplasmic vacuolization, formation of spermatid giant cells, and accumulation of cellular debris in the tubular lumens. The fibrinoid necrosis involved small arteries and arterioles and consisted of the deposition of hyaline material within the intima and media. This was usually accompanied by perivascular accumulations of lymphocytes, plasma cells, and macrophages. Atypical cells occurred in the epididymis of dosed rats.

Interstitial cell adenomas of the testis occurred with a significant negative trend, and the incidence in the high dose group was significantly lower than that in the controls (Table 16).

TABLE 14. SUBCUTANEOUS TISSUE TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Control	1,300 ppm	2,500 ppm
Fibroma			
Overall Rates	0/50 (0%)	5/50 (10%)	4/50 (8%)
Adjusted Rates	0.0%	16.2%	15.4%
Terminal Rates	0/24 (0%)	3/27 (11%)	4/26 (15%)
Day of First Observation		644	730
Life Table Tests	P=0.077	P=0.047	P=0.071
Logistic Regression Tests	P=0.076	P=0.042	P=0.071
Fibrosarcoma			
Overall Rates	1/50 (2%)	2/50 (4%)	1/50 (2%)
Fibroma or Fibrosarcoma (a)			
Overall Rates	1/50 (2%)	7/50 (14%)	5/50 (10%)
Adjusted Rates	2.7%	21.9%	17.5%
Terminal Rates	0/24 (0%)	4/27 (15%)	4/26 (15%)
Day of First Observation	633	644	636
Life Table Tests	P=0.127	P=0.054	P=0.128
Logistic Regression Tests	P=0.109	P=0.039	P=0.109

(a) Historical incidence of fibromas, fibrosarcomas, sarcomas, neurofibromas, or neurofibrosarcomas (combined) at study laboratory (mean ± SD): 28/439 (6% ± 4%); historical incidence in NTP studies: 144/1,937 (7% ± 4%)

TABLE 15. NUMBER OF RATS WITH SELECTED LESIONS OF THE EPIDIDYMIS, PREPUTIAL GLAND, TESTIS, OR CLITORAL GLAND IN THE TWO-YEAR FEED STUDIES OF NITROFURANTOIN

Site/Lesion	Control	600 ppm	1,300 ppm	2,500 ppm
MALE				
Number examined microscopically (a)	50		50	50
Epididymis				
Atypical cells	0		0	12
Preputial gland				
Adenoma	(b) 6		5	(c) 0
Carcinoma	(b) 6		6	(c) 0
Testis				
Degeneration	0		0	36
Fibrinoid necrosis of arterioles	1		8	15
Perivascular infiltration of mononuclear cells	3		9	19
Interstitial cell adenoma	47		45	21
FEMALE				
Number examined microscopically	44	38	42	
Clitoral gland				
Adenoma	1	7	4	
Carcinoma	4	3	0	

(a) Unless otherwise specified
(b) Forty-eight animals were examined.
(c) Forty-seven animals were examined.

TABLE 16. TESTICULAR INTERSTITIAL CELL ADENOMAS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN (a)

	Control	1,300 ppm	2,500 ppm
Overall Rates	47/50 (94%)	45/50 (90%)	21/50 (42%)
Adjusted Rates	100.0%	100.0%	61.8%
Terminal Rates	24/24 (100%)	27/27 (100%)	14/26 (54%)
Day of First Observation	455	548	559
Life Table Tests	P<0.001N	P=0.162N	P<0.001N
Logistic Regression Tests	P<0.001N	P=0.221N	P<0.001N

(a) Historical incidence of interstitial cell tumors at study laboratory (mean ± SD): 384/439 (87% ± 8%); historical incidence in NTP studies: 1,681/1,909 (88% ± 7%)

Preputial and Clitoral Glands: Adenomas, carcinomas, and adenomas or carcinomas (combined) of the preputial gland in male rats occurred with significant negative trends; none was seen in the high dose group (Table 17). The incidence of adenomas or carcinomas (combined) of the clitoral gland in low dose female rats, although not significantly greater than that in the controls (control, 5/44; low dose, 10/38; high dose, 4/42) (see Table 15), was greater than the highest incidence in untreated historical control female F344/N rats (6/49).

TABLE 17. PREPUTIAL GLAND TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Control	1,300 ppm	2,500 ppm
Adenoma			
Overall Rates	6/48 (13%)	5/50 (10%)	0/47 (0%)
Adjusted Rates	21.9%	15.2%	0.0%
Terminal Rates	4/22 (18%)	3/27 (11%)	0/26 (0%)
Day of First Observation	533	630	
Life Table Tests	P=0.011N	P=0.388N	P=0.013N
Logistic Regression Tests	P=0.018N	P=0.461N	P=0.018N
Carcinoma			
Overall Rates	6/48 (13%)	6/50 (12%)	0/47 (0%)
Adjusted Rates	18.3%	17.3%	0.0%
Terminal Rates	2/22 (9%)	2/27 (7%)	0/26 (0%)
Day of First Observation	455	320	
Life Table Tests	P=0.019N	P=0.522N	P=0.015N
Logistic Regression Tests	P=0.038N	P=0.603	P=0.028N
Adenoma or Carcinoma (a)			
Overall Rates	12/48 (25%)	11/50 (22%)	0/47 (0%)
Adjusted Rates	37.6%	30.6%	0.0%
Terminal Rates	6/22 (27%)	5/27 (19%)	0/26 (0%)
Day of First Observation	455	320	
Life Table Tests	P<0.001N	P=0.352N	P<0.001N
Logistic Regression Tests	P=0.001N	P=0.494N	P<0.001N

(a) Historical incidence at study laboratory (mean ± SD): 23/439 (5% ± 4%); historical incidence in NTP studies: 123/1,937 (6% ± 5%)

Mammary Gland: Adenocarcinomas in female rats occurred with a significant negative trend; none occurred in the high dose group (Table 18).

Eye: Cataracts and retinal degeneration were observed at increased incidences in high dose male and low dose female rats (cataracts--male: control, 1/4; low dose, 0/6; high dose, 14/22; female: 0/1; 16/19; 2/6; retinal degeneration--male: 2/4; 0/6; 17/22; female: 0/1; 17/19; 3/6).

TABLE 18. MAMMARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Control	600 ppm	1,300 ppm
Hyperplasia, Cystic or Lobular			
Overall Rates	10/49 (20%)	24/50 (48%)	14/50 (28%)
Adenocarcinoma (a)			
Overall Rates	6/50 (12%)	5/50 (10%)	0/50 (0%)
Adjusted Rates	19.4%	17.2%	0.0%
Terminal Rates	3/25 (12%)	3/26 (12%)	0/31 (0%)
Day of First Observation	661	687	
Life Table Tests	P=0.013N	P=0.497N	P=0.015N
Logistic Regression Tests	P=0.018N	P=0.553N	P=0.019N

(a) Historical incidence of adenomas or adenocarcinomas (combined) at study laboratory (mean ± SD): 17/439 (4% ± 3%); historical incidence in NTP studies: 64/1,984 (3% ± 3%)

FOURTEEN-DAY STUDIES

Four of five male and 4/5 female mice that received 10,000 ppm and 1/5 females that received 5,000 ppm nitrofurantoin died before the end of the studies (Table 19). Mice that received 5,000 and male mice that received 10,000 ppm lost weight. Final mean body weights of other dosed groups were similar to those of the controls. Estimated feed consumption by the groups that received 10,000 ppm was notably higher than that by the controls during the second week of the studies. Mice that received 10,000 ppm were inactive, had sunken eyes, and walked on tiptoe.

TABLE 19. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF NITROFURANTOIN

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 1	Week 2
MALE							
0	5/5	24.8 ± 0.6	27.2 ± 1.2	+2.4 ± 0.6		6	6
600	5/5	24.2 ± 0.4	28.6 ± 0.4	+4.4 ± 0.2	105.1	6	6
1,300	5/5	24.0 ± 0.8	27.0 ± 0.8	+3.0 ± 0.0	99.3	7	6
2,500	5/5	25.0 ± 0.0	27.4 ± 0.2	+2.4 ± 0.2	100.7	7	6
5,000	5/5	24.6 ± 0.5	20.2 ± 0.7	−4.4 ± 1.2	74.3	6	6
10,000	(e) 1/5	24.6 ± 0.2	19.0	−6.0	69.9	7	13
FEMALE							
0	5/5	18.6 ± 0.4	21.0 ± 0.5	+2.4 ± 0.2		6	7
600	5/5	19.0 ± 0.5	22.0 ± 0.3	+3.0 ± 0.3	104.8	7	7
1,300	5/5	18.8 ± 0.4	21.4 ± 0.4	+2.6 ± 0.2	101.9	8	6
2,500	5/5	18.6 ± 0.5	21.0 ± 0.5	+2.4 ± 0.4	100.0	7	6
5,000	(f) 4/5	19.0 ± 0.3	17.5 ± 1.0	−1.5 ± 1.2	83.3	7	6
10,000	(g) 1/5	18.8 ± 0.5	20.0	+2.0	95.2	6	12

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams of feed consumed per animal per day; average of daily determinations; not corrected for scatter.
(e) Day of death: 6,6,6,15
(f) Day of death: 12
(g) Day of death: 6,7,8,9

THIRTEEN-WEEK STUDIES

Two of 10 male mice that received 5,000 ppm and 1/10 males that received 300 ppm died before the end of the studies (Table 20). The final mean body weight of mice that received 5,000 ppm was 13% lower than that of the controls for males and 15% lower for females. Estimated feed consumption by dosed groups was similar to that by controls. The urine of mice that received 5,000 ppm was bright yellow. Inactivity, hypothermia, and sunken eyes were observed in mice that received 5,000 ppm but not in those that received 2,500 ppm. Minimal-to-mild degeneration of the germinal epithelium of the testis (accompanied by aspermatogenesis) was observed in all males that received 1,300, 2,500, or 5,000 ppm; necrosis of the ovarian follicle was observed in 8/10 females that received 5,000 ppm but not in those that received lower doses. Minimal-to-mild necrosis of the kidney epithelium was observed in 2/9 males that received 5,000 ppm. The liver weight to body weight ratios were not affected by administration of nitrofurantoin (Table 21).

Dose Selection Rationale: Because of lower mean body weight gain in males and females at higher concentrations and kidney necrosis and deaths in males at 5,000 ppm, dietary concentrations selected for mice in the 2-year studies were 1,300 and 2,500 ppm nitrofurantoin.

TABLE 20. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF NITROFURANTOIN

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 4	Week 12
MALE							
0	10/10	25.2 ± 0.4	35.0 ± 0.5	+9.8 ± 0.6		7	8
300	(e) 9/10	25.4 ± 0.5	35.3 ± 0.8	+10.1 ± 0.8	100.9	7	9
600	10/10	25.5 ± 0.3	36.2 ± 0.8	+10.7 ± 1.0	103.4	8	7
1,300	10/10	25.1 ± 0.4	35.3 ± 0.7	+10.2 ± 0.5	100.9	6	8
2,500	10/10	25.6 ± 0.3	34.3 ± 0.7	+8.7 ± 0.6	98.0	7	8
5,000	(f) 8/10	24.8 ± 0.6	30.3 ± 0.9	+5.8 ± 0.8	86.6	9	10
FEMALE							
0	10/10	19.3 ± 0.3	27.4 ± 0.5	+8.1 ± 0.5		5	6
300	10/10	19.1 ± 0.3	27.9 ± 0.9	+8.8 ± 0.8	101.8	7	8
600	10/10	19.1 ± 0.2	28.2 ± 0.3	+9.1 ± 0.4	102.9	7	9
1,300	10/10	19.3 ± 0.2	28.2 ± 0.5	+8.9 ± 0.5	102.9	7	8
2,500	10/10	18.7 ± 0.2	26.6 ± 0.6	+7.9 ± 0.6	97.1	7	8
5,000	10/10	19.0 ± 0.4	23.3 ± 0.3	+4.3 ± 0.4	85.0	7	6

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams of feed consumed per animal per day; not corrected for scatter.
(e) Week of death: 11
(f) Week of death: 2,2

TABLE 21. ABSOLUTE AND RELATIVE LIVER WEIGHTS OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF NITROFURANTOIN (a)

Concentration (ppm)	Number of Animals	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/Necropsy Body Weight (mg/g)
MALE				
0	10	35.8 ± 0.22	1,801 ± 48	50.3 ± 1.06
300	9	35.7 ± 0.91	(b) 1,599 ± 70	(b) 44.9 ± 1.82
600	10	36.6 ± 0.93	(c) 1,529 ± 26	(c) 42.0 ± 1.20
1,300	10	35.4 ± 0.79	1,668 ± 67	47.2 ± 1.69
2,500	10	35.4 ± 0.82	1,635 ± 51	46.3 ± 1.33
5,000	8	(c) 30.5 ± 0.93	(c) 1,490 ± 56	48.8 ± 0.92
FEMALE				
0	10	27.8 ± 0.71	1,263 ± 32	45.5 ± 0.83
300	10	30.3 ± 1.17	1,220 ± 50	(c) 40.3 ± 0.81
600	10	29.0 ± 0.88	1,253 ± 50	43.3 ± 1.32
1,300	10	27.7 ± 0.58	1,244 ± 26	45.0 ± 0.94
2,500	10	26.8 ± 0.59	1,266 ± 49	47.2 ± 1.24
5,000	10	(c) 23.5 ± 0.22	(b) 1,101 ± 19	46.9 ± 0.90

(a) Mean ± standard error; P values vs. the controls by Dunnett's test (Dunnett, 1955).
(b) $P<0.05$
(c) $P<0.01$

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of high dose male mice were 5%-17% lower than those of the controls after week 1 (Table 22 and Figure 11). Mean body weights of high dose female mice were 4%-14% lower than those of the controls from week 11 to the end of the study. The average daily feed consumption by low dose and high dose male mice was 100% and 95% that by controls (Table G3) and by low dose and high dose female mice, 93% and 96% that by controls (Table G4). The average amount of nitrofurantoin consumed per day was estimated to be 300 mg/kg and 570 mg/kg for low and high dose male mice and 280 mg/kg and 580 mg/kg for low and high dose female mice. Dosed mice had bright yellow urine.

TABLE 22. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF NITROFURANTOIN

Weeks on Study	Control		1,300 ppm			2,500 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	24.2	50	24.5	101	50	23.5	97	50
1	25.8	50	25.9	100	50	22.0	85	50
2	26.0	50	26.1	100	50	23.7	91	50
3	26.7	50	24.9	93	50	22.2	83	50
4	27.6	50	27.6	100	50	25.3	92	50
5	29.2	50	28.8	99	50	26.9	92	50
6	29.9	50	29.1	97	50	27.4	92	50
7	30.0	50	29.7	99	50	27.8	93	50
8	30.9	49	29.7	96	49	28.5	92	50
9	31.4	47	30.8	98	49	29.3	93	50
10	31.6	47	30.8	97	49	29.6	94	49
11	31.9	47	31.3	98	49	29.7	93	49
12	31.8	46	31.5	99	49	30.1	95	49
13	33.4	46	31.7	95	49	31.0	93	49
18	34.9	45	33.9	97	49	32.0	92	49
22	36.0	45	35.0	97	49	33.1	92	49
26	37.2	45	35.3	95	48	34.1	92	49
30	37.4	44	36.4	97	47	34.0	91	49
35	38.0	44	36.8	97	46	34.9	92	49
40	38.1	44	36.2	95	46	35.4	93	49
45	39.1	44	37.9	97	46	36.0	92	49
49	40.0	44	37.6	94	45	36.6	92	49
53	41.4	44	39.0	94	45	37.6	91	48
57	41.5	44	39.6	95	44	37.8	91	48
61	41.3	43	39.1	95	44	37.7	91	48
65	41.4	42	40.2	97	44	37.9	92	48
69	41.1	39	39.6	96	44	37.5	91	48
74	40.7	39	38.0	93	43	36.4	89	48
78	40.4	38	38.2	95	42	36.3	90	47
82	41.0	38	38.6	94	41	37.0	90	46
86	39.6	38	37.2	94	39	36.3	92	44
90	40.0	37	38.6	97	36	36.3	91	43
94	40.1	35	38.5	96	35	36.0	90	42
98	39.9	34	38.9	97	33	36.3	91	38
104	39.6	28	39.1	99	29	36.5	92	35
FEMALE								
0	18.1	50	18.1	100	50	17.3	96	50
1	18.4	50	18.0	98	50	17.7	96	50
2	18.7	50	19.4	104	50	18.9	101	50
3	20.1	50	19.9	99	50	19.6	98	50
4	21.0	50	21.4	102	50	21.1	100	50
5	22.1	50	22.8	103	50	21.9	99	50
6	22.7	50	22.7	100	50	22.1	97	50
7	23.1	50	23.1	100	50	22.6	98	50
8	23.5	50	23.9	102	50	23.2	99	50
9	23.8	50	23.9	100	50	23.2	97	50
10	24.1	50	24.0	100	50	23.6	98	50
11	24.7	50	24.1	98	50	23.6	96	50
12	25.1	50	24.4	97	50	23.6	94	50
13	25.4	50	25.0	98	50	24.3	96	50
18	26.6	50	26.2	98	50	25.3	95	50
22	28.4	49	27.3	96	50	26.1	92	50
26	29.2	49	28.2	97	50	27.0	92	50
30	29.6	49	28.8	97	50	26.8	91	50
35	30.8	49	29.6	96	50	27.7	90	50
40	32.1	49	29.8	93	50	28.4	88	50
45	32.7	49	31.0	95	50	28.6	87	50
49	34.3	49	32.4	94	50	29.6	86	50
53	35.4	49	33.8	95	50	31.0	88	50
57	35.2	49	34.6	98	50	31.3	89	50
61	36.1	49	35.1	97	50	32.1	89	50
65	37.0	47	36.5	99	50	34.2	92	50
69	37.1	45	37.1	100	49	34.7	94	50
74	36.4	44	36.7	101	49	34.4	95	50
78	36.8	41	36.9	100	49	34.9	95	50
82	38.1	40	38.7	102	48	36.6	96	49
86	37.7	36	38.7	103	47	35.7	95	49
90	39.0	34	40.2	103	45	36.4	93	47
94	39.8	30	40.5	102	45	36.6	92	44
98	40.5	29	41.0	101	44	37.0	91	42
104	41.7	21	40.5	97	37	37.0	89	40

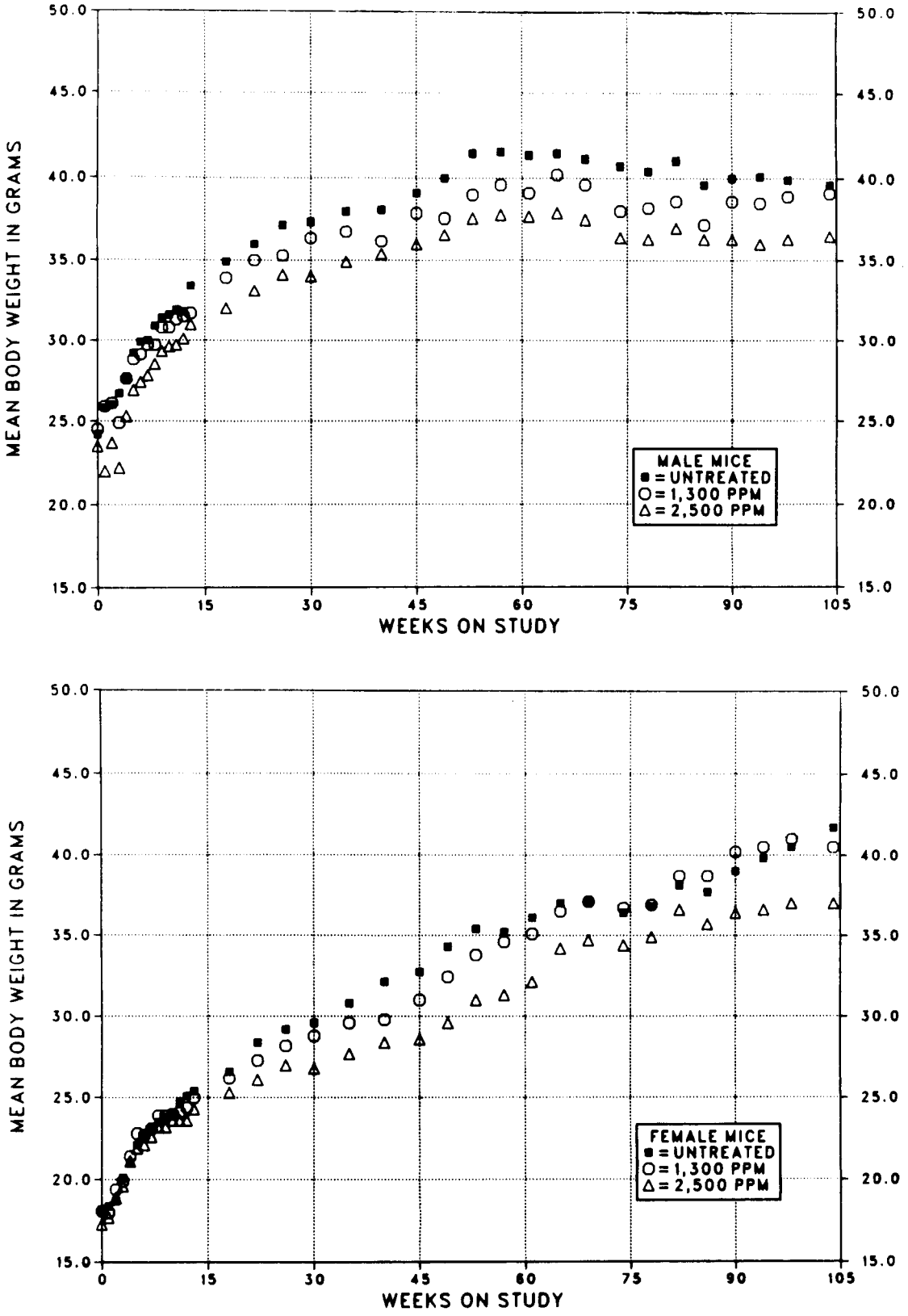


FIGURE 11. GROWTH CURVES FOR MICE FED DIETS CONTAINING NITROFURANTOIN FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing nitrofurantoin at the concentrations used in these studies and for controls are shown in Table 23 and in the Kaplan and Meier curves in Figure 12. The survival of the control group of female mice was significantly lower than that of both the low and high dose groups. No significant differences in survival were observed between any groups of male mice.

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 ovary, hematopoietic system, uterus, liver, testis, epididymis, kidney, and adrenal glands.

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.

TABLE 23. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF NITROFURANTOIN

	Control	1,300 ppm	2,500 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	22	21	16
Killed at termination	28	29	33
Died during termination period	0	0	1
Survival P values (c)	0.173	0.897	0.197
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	31	13	13
Killed at termination	19	36	37
Died during termination period	0	1	0
Survival P values (c)	<0.001	<0.001	<0.001

(a) First day of termination period: 730
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

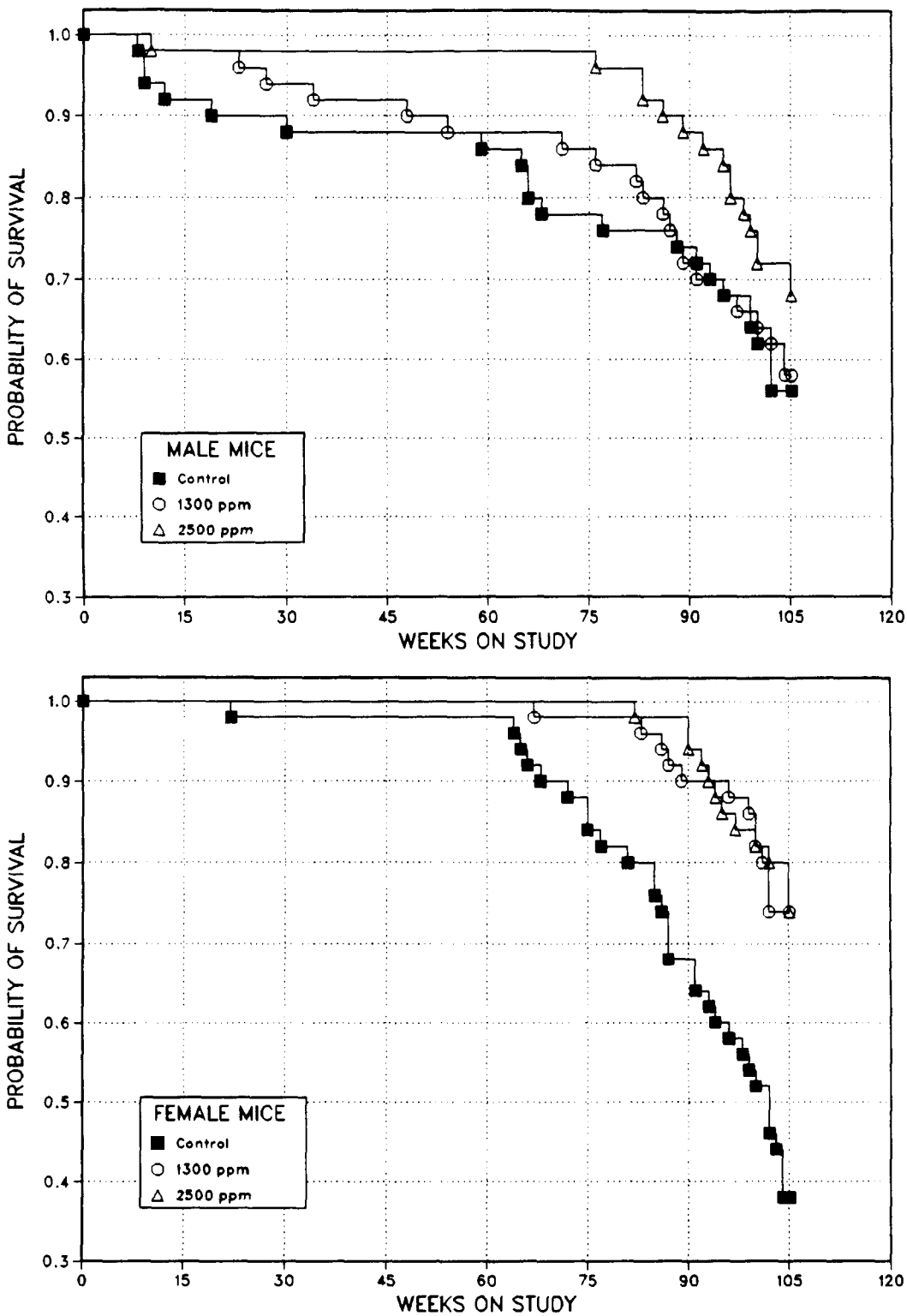


FIGURE 12. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING NITROFURANTOIN FOR TWO YEARS

Ovary: Ovarian abscesses were observed in 18/50 control female mice but in none of the dosed mice (Table 24). Atrophy, characterized by the absence of graafian follicles and corpora lutea, occurred in 48/50 low dose and 49/50 high dose female mice but not in controls. Uncommon ovarian tumors including tubular adenomas, benign mixed tumors, and granulosa cell tumors occurred only in dosed female mice (Table 25). Tubulostromal tumors form a continuous morphologic spectrum and typically consist of complex branching tubules originating from the surface mesothelium and varying numbers of intertubular cells derived from the ovarian stroma. Those tumors with a minimum of stromal cells were classified as tubular adenomas, whereas those with a prominent stromal cell component were classified as benign mixed tumors (Figures 13 and 14). The granulosa cell tumors were characterized by the predominant component of typical granulosa cells arranged in a variety of patterns. The tumor diagnosed as a neoplasm, NOS, is an extremely uncommon tumor in $B6C3F_1$ mice. The pattern of growth and cellular morphology were characteristic of the Sertoli cell tumor that occurs in the testis. Although of unusual morphologic pattern, this tumor is of sex cord origin similar to that of the granulosa cell tumors.

TABLE 24. NUMBER OF FEMALE MICE WITH OVARIAN LESIONS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

Lesion	Control	1,300 ppm	2,500 ppm
Number examined microscopically	50	50	50
Abscess	18	0	0
Atrophy	0	48	49
Tubular adenoma	0	0	5
Cystadenoma	0	0	1
Papillary cystadenoma	2	1	0
Granulosa cell tumor, benign	0	3	1
Granulosa cell tumor, malignant	0	0	1
Mixed tumor, benign	0	0	4
Neoplasm, NOS	0	0	1

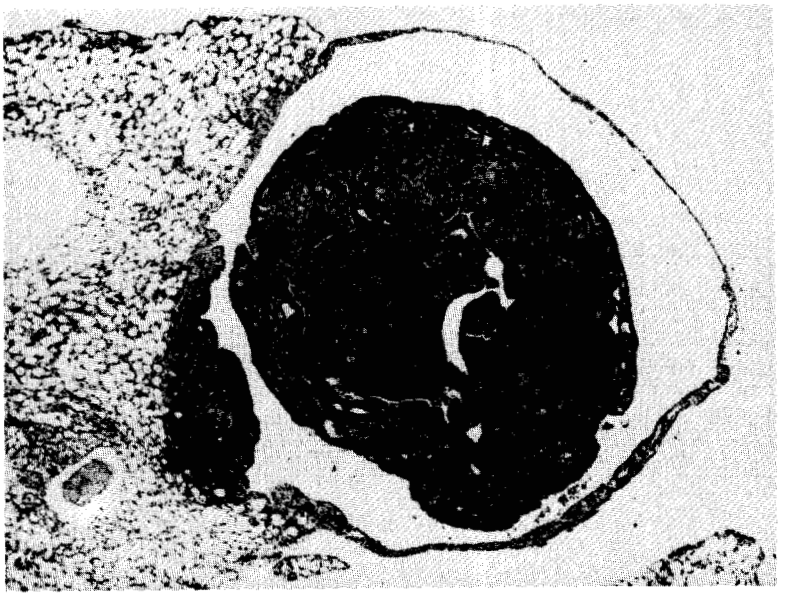


Figure 13. Benign mixed tumor obliterating all normal tissue in ovary of a high dose female mouse.

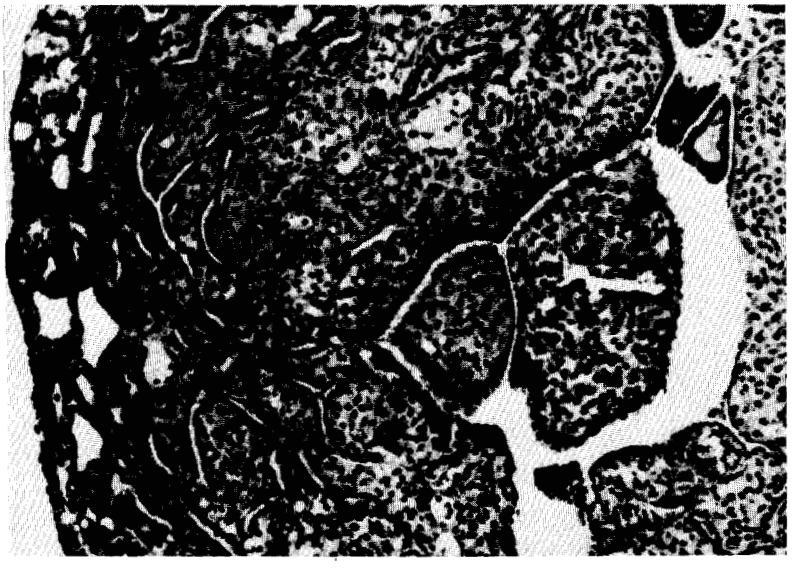


Figure 14. Higher magnification of ovarian mixed tumor shown in Figure 13. The tumor consists of gonadal stromal cells and tubules lined by cuboidal epithelium. The tubules appear to be a downgrowth of the modified mesothelium covering the surface of the ovary.

TABLE 25. OVARIAN TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN (a)

	Control	1,300 ppm (b)	2,500 ppm (b)
Tubular Adenoma (c)			
Overall Rates	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates	0.0%	0.0%	13.0%
Terminal Rates	0/19 (0%)	0/37 (0%)	4/37 (11%)
Day of First Observation			729
Life Table Tests	P=0.019	(d)	P=0.127
Logistic Regression Tests	P=0.018	(d)	P=0.112
Mixed Tumor, Benign (e)			
Overall Rates	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates	0.0%	0.0%	10.0%
Terminal Rates	0/19 (0%)	0/37 (0%)	3/37 (8%)
Day of First Observation			630
Life Table Tests	P=0.035	(d)	P=0.162
Logistic Regression Tests	P=0.018	(d)	P=0.084
Tubular Adenoma or Mixed Tumor, Benign			
Overall Rates	0/50 (0%)	0/50 (0%)	9/50 (18%)
Adjusted Rates	0.0%	0.0%	22.6%
Terminal Rates	0/19 (0%)	0/37 (0%)	7/37 (19%)
Day of First Observation			630
Life Table Tests	P=0.001	(d)	P=0.028
Logistic Regression Tests	P<0.001	(d)	P=0.010
Granulosa Cell Tumor, Benign			
Overall Rates	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates	0.0%	8.1%	2.7%
Terminal Rates	0/19 (0%)	3/37 (8%)	1/37 (3%)
Day of First Observation		730	730
Life Table Tests	P=0.564	P=0.260	P=0.633
Logistic Regression Tests	P=0.564	P=0.260	P=0.633
Granulosa Cell Tumor, Benign or Malignant (f)			
Overall Rates	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted Rates	0.0%	8.1%	5.1%
Terminal Rates	0/19 (0%)	3/37 (8%)	1/37 (3%)
Day of First Observation		730	729
Life Table Tests	P=0.375	P=0.260	P=0.404
Logistic Regression Tests	P=0.362	P=0.260	P=0.374

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table D3 (footnotes).
(b) The equivalent dose in milligrams per kilograms per day is given in Section III (Body Weights, Feed Consumption, and Clinical Signs) and in Appendix G.
(c) Historical incidence in NTP studies (mean): 4/1,858 (0.2%)
(d) No P value is reported because no tumors were observed in the 1,300-ppm and control groups.
(e) Historical incidence in NTP studies (mean): 1/1,858 (<0.1%)
(f) Historical incidence of granulosa cell tumors or luteomas (combined) in NTP studies (mean): 8/1,858 (0.4%)

Hematopoietic System: Lymphomas in female mice occurred with a significant positive trend by the logistic regression test; the incidence in the high dose group was not significantly greater than that in the controls (Table 26).

Uterus: Suppurative inflammation was observed in 11/50 control mice but in none of the dosed animals. Adenocarcinomas were seen in 1/50 low dose and in 1/50 high dose mice. The highest observed incidence of uterine adenomas or adenocarcinomas (combined) in untreated historical control female B6C3F$_1$ mice is 1/47; the overall historical incidence is 6/2,010 (0.3%).

Liver: An Ito cell tumor was observed in 1/50 low dose and 1/50 high dose female mice. These tumors consisted of well-differentiated fat cells and varying amounts of collagen-containing mesenchymal tissue. Previously, these tumors have been classified as lipomas or liposarcomas because of their component of fat cells. A lipoma has been diagnosed in 1/2,033 (<0.1%) untreated historical control female B6C3F$_1$ mice. Hepatocellular adenomas and hepatocellular adenomas or carcinomas (combined) in female mice occurred with significant positive trends by the logistic regression test; the incidences in the dosed groups were not significantly different from those in the controls (Table 27).

TABLE 26. MALIGNANT LYMPHOMAS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN (a)

	Control	1,300 ppm	2,500 ppm
Overall Rates	12/50 (24%)	19/50 (38%)	24/50 (48%)
Adjusted Rates	50.2%	43.4%	52.7%
Terminal Rates	8/19 (42%)	13/37 (35%)	16/37 (43%)
Day of First Observation	631	596	568
Life Table Tests	P=0.352	P=0.447N	P=0.449
Logistic Regression Tests	P=0.038	P=0.295	P=0.076

(a) Historical incidence of lymphomas or leukemia (combined) at study laboratory (mean ± SD): 104/448 (23% ± 7%); historical incidence in NTP studies: 616/2,041 (30% ± 12%)

TABLE 27. HEPATOCELLULAR TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Control	1,300 ppm	2,500 ppm
Adenoma			
Overall Rates	1/50 (2%)	1/50 (2%)	7/50 (14%)
Adjusted Rates	2.7%	2.7%	18.1%
Terminal Rates	0/19 (0%)	1/37 (3%)	6/37 (16%)
Day of First Observation	603	730	660
Life Table Tests	P=0.042	P=0.658N	P=0.147
Logistic Regression Tests	P=0.016	P=0.758	P=0.054
Carcinoma			
Overall Rates	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adenoma or Carcinoma (a)			
Overall Rates	2/50 (4%)	2/50 (4%)	8/50 (16%)
Adjusted Rates	6.6%	4.9%	20.0%
Terminal Rates	0/19 (0%)	1/37 (3%)	6/37 (16%)
Day of First Observation	603	670	660
Life Table Tests	P=0.093	P=0.531N	P=0.217
Logistic Regression Tests	P=0.029	P=0.704N	P=0.079

(a) Historical incidence at study laboratory (mean ± SD): 36/447 (8% ± 5%); historical incidence in NTP studies: 177/2,033 (9% ± 5%)

Testis: Aspermatogenesis and degeneration of the germinal epithelium were observed at increased incidences in high dose male mice (aspermatogenesis: control, 1/49; low dose, 1/49; high dose, 16/50; degeneration of the germinal epithelium: 0/49; 3/49; 23/50).

Epididymis: Atypical cells and depletion were observed in high dose male mice (atypical cells: control, 0/50; low dose, 0/49; high dose, 26/50; depletion: 1/50; 1/49; 15/50).

Kidney: Mineralization of the medulla was observed in high dose mice (male: control, 0/50; low dose, 0/50; high dose, 17/50; female: 0/50; 0/50; 7/50). Dilatation of the tubules was observed in high dose male mice (male: 0/50; 0/50; 14/50; female: 0/50; 1/50; 1/50).

Adrenal Glands: Cortical spindle cell hyperplasia was observed at increased incidences in dosed female mice (male: control, 5/50; low dose, 3/49; high dose, 4/50; female: 3/50; 41/50; 45/50). A spindle cell (adrenal capsule) adenoma was seen in 1/50 low dose female mice, and a spindle cell (adrenal capsule) carcinoma was seen in 1/49 low dose male mice. The historical incidences of these tumors are unknown because neither has been entered into the data base as a category separate from adenoma, NOS. Pheochromocytomas or malignant pheochromocytomas (combined) in male mice occurred with a significant negative trend; the incidences in the dosed groups were significantly lower than that in the controls (Table 28).

TABLE 28. ADRENAL MEDULLARY LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Control	1,300 ppm	2,500 ppm
Hyperplasia			
Overall Rates	4/49 (8%)	6/48 (13%)	5/49 (10%)
Pheochromocytoma			
Overall Rates	4/49 (8%)	0/48 (0%)	1/49 (2%)
Adjusted Rates	13.3%	0.0%	3.0%
Terminal Rates	3/28 (11%)	0/28 (0%)	1/33 (3%)
Day of First Observation	688		730
Life Table Tests	P=0.062N	P=0.065N	P=0.138N
Logistic Regression Tests	P=0.059N	P=0.061N	P=0.132N
Malignant Pheochromocytoma			
Overall Rates	2/49 (4%)	0/48 (0%)	0/49 (0%)
Pheochromocytoma or Malignant Pheochromocytoma (a)			
Overall Rates	6/49 (12%)	0/48 (0%)	1/49 (2%)
Adjusted Rates	19.7%	0.0%	3.0%
Terminal Rates	4/28 (14%)	0/28 (0%)	1/33 (3%)
Day of First Observation	688		730
Life Table Tests	P=0.010N	P=0.018N	P=0.038N
Logistic Regression Tests	P=0.009N	P=0.016N	P=0.034N

(a) Historical incidence at study laboratory (mean ± SD): 4/437 (1% ± 1%); historical incidence in NTP studies: 25/1,962 (1% ± 2%)

IV. DISCUSSION AND CONCLUSIONS

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Nitrofurantoin was studied and evaluated because of its widespread use as a drug for treating urinary tract infections in humans, its structural relationship to known carcinogenic 5-nitrofuran compounds (IARC, 1974; Cohen, 1978), and the lack of adequate studies to assess its carcinogenicity. Toxicology and carcinogenesis studies of nitrofurantoin were conducted by administering USP-grade nitrofurantoin (greater than 99% pure) in feed to groups of F344/N rats and B6C3F$_1$ mice of each sex for 14 days, 13 weeks, or 2 years. In the 2-year studies, nitrofurantoin was administered in feed at 0, 1,300, or 2,500 ppm to male rats and male and female mice and at 0, 600, or 1,300 ppm to female rats.

In the 13-week studies, only one rat (a high dose female) died. Mean body weights relative to those of controls were similar for dosed male and dosed female rats, but because of the lower relative mean body weight of females in the 2,500-ppm group, the dietary concentrations selected for the 2-year studies were lower for females than for other groups. For mice, two deaths occurred in the high dose male group, but final mean body weights relative to those of controls were similar for males and females. Organs affected in the 13-week studies were the testis or ovary in rats and mice and the kidney in male mice.

In the 2-year studies, there were no significant differences in survival between dosed and control groups of rats of either sex or male mice (see Tables 10 and 23). Regarding female mice, the survival of the control group was lower than that of both the low and high dose groups. Ovarian abscesses and suppurative inflammation of the uterus were observed only in control female mice. These infections are believed to be indigenous and were absent in dosed mice, most likely due to the therapeutic activity of nitrofurantoin. Treatment at the doses used in these studies would be expected to achieve the minimally effective dose level (~30 μg/ml urine) against a broad spectrum of bacteria (Paul, M.F., et al., 1960; Buzard et al., 1961; Veronese et al., 1974; Liedtke et al., 1980; Hoener and Patterson, 1981).

Generally, body weights and estimated feed consumption values indicate that no or minimal overt toxicity or feed palatability problems were encountered in these studies except for female mice. Absorption, metabolism, and excretion of nitrofurantoin are rapid (Paul, M.F., et al., 1960; Buzard et al., 1961; Conklin and Hailey, 1969; Conklin, 1972a,b; Veronese et al., 1974; Maiti and Banerjee, 1978; Wierzba et al., 1982) and change with age in both humans and rats (Braunlich et al., 1978; Wierzba et al., 1982). After an initial decrease relative to controls, body weight differences between dosed and control rats leveled off. This adaptive response may be due to an age difference in susceptibility to nitrofurantoin, toxicity, or possible metabolic adaptation (enzyme induction) to chemical exposure. High dose male mice demonstrated similar differences in body weight relative to those of controls throughout the study. The exception may be the high dose female mice, whose body weights were decreased relative to those of the controls. Interpretation is made more difficult because of the decreased survival of control female mice. Survival of dosed female mice was not affected, and body weight differences may have been due to palatability of nitrofurantoin or to induced neoplasia.

The oral (gavage) toxicity of nitrofurantoin varies somewhat between rats (LD_{50} = 604 mg/kg) and mice (LD_{50} = 360 mg/kg) (Preti, 1970; NIOSH, 1983). The toxicity of nitrofurantoin administered in feed over longer daily time periods is different. The absorption and urinary excretion of macrocrystalline nitrofurantoin (administered in a capsule) were greater in nonfasting than in fasting volunteers (Bates et al., 1974); a much smaller difference was observed for the microcrystalline form (given as a tablet). In the current NTP studies, the doses of nitrofurantoin consumed by rats (up to 110 mg/kg per day) would not be expected to be overtly toxic. In mice, the doses (300 or 570 mg/kg, males; 280 or 580 mg/ kg, females) might have been lethal if given as a single bolus but apparently were well tolerated given over a period of 24 hours. The recommended dosage of nitrofurantoin for humans is 50-100 mg, four times a day for 2 weeks (Penn and Griffin, 1982). However, treatment may continue for longer periods (6-30 months) and at higher doses (Simonian et al., 1977; Penn and Griffin, 1982); for an individual weighing 70 kg,this is equivalent to approximately 3-6 mg/kg per day up to 10 mg/kg per day.

Metabolically, under aerobic conditions, the reduction of nitrofurantoin stimulates the consumption of oxygen and the production of superoxide anion free radical and hydrogen peroxide in avian liver and in mammalian liver, lung, small intestine, kidney, and gastrointestinal contents which may result in toxicity and localized injury (Mason and Holtzman, 1975a; Biaglow et al., 1977; Aufrere et al., 1978; Boyd et al., 1979a; Sasame and Boyd, 1979; Leskovac and Popovic, 1980; Peterson et al., 1982a). Under anaerobic conditions, nitrofurantoin is permanently reduced to nitroso and/or hydroxylamine forms (Mason and Holtzman, 1975a; Biaglow et al., 1977; Leskovac and Popovic, 1980), which may result in binding to cellular macromolecules (DNA and protein) (Boyd et al., 1979b). The covalent binding to macromolecules is apparently greatest in the kidney, liver, ileum, lung, and heart of rats (Aufrere et al., 1978). Toxicity and DNA damage may increase as oxygen tension decreases (Russo et al., 1982).

The kidney is a primary organ of metabolism and excretion and is the site of chemical-related toxicity. The severity of chronic nephropathy was greatest in high dose male rats. This spontaneous disease occurs in nearly all laboratory rats, and the onset is generally earlier and the effects are more severe in males than in females (Chennekatu et al., 1986). Proteinuria begins when the male rat is several months old and increases progressively as the animal ages, which indicates progressive impairment of some renal functions. The reason for the apparent selective toxicity of nitrofurantoin to the kidney of male rats may be related to the fact that the kidneys receive up to 20% of the cardiac output of blood, have a large endothelial and epithelial surface area that is exposed to the blood or glomerular filtrate containing the chemical, perform diverse metabolic functions, have a high concentrating function for excreted and absorbed metabolites, and have an age-related deterioration in kidney function. The nonneoplastic lesions observed in this study (parathyroid gland hyperplasia, fibrous osteodystrophy of the bone, and mineralization of the glandular stomach) are characteristic of renal secondary parathyroidism and are believed to be secondary to the chronic nephropathy (Burns, 1979).

The kidney was identified as a target organ in mice in the 13-week studies in which mineralization of the renal medulla in dosed male and female mice and dilatation of the renal tubules in dosed male mice were observed. The original evaluation of the kidney by standard procedures (i.e., microscopic examination of single longitudinal sections of the left and right kidney) identified small numbers of tubular cell neoplasms in dosed male rats but not in controls (control, 0/50; low dose, 1/50; high dose, 3/50). The incidences in dosed rats were not statistically greater than that in concurrent controls, but tubular cell neoplasms occur rarely in untreated historical controls (8/1,929, 0.4%) (Table A4a). Thus, an informal comparison of the incidences in dosed male rats with historical controls suggested that the neoplasms may be chemical related.

Kurokawa et al. (1983) compared results of examination of single vs. multiple sections of kidney and found that incidences were greater with multiple sections. Therefore, the NTP prepared step-sections of the remaining right and left halves of the kidney to provide additional data and to clarify the potential relationship of the tubular cell neoplasms to the administration of nitrofurantoin. The results of this subsequent evaluation unequivocally demonstrated a dose-related and significantly increased incidence of renal tubular cell adenomas in male rats given nitrofurantoin (low dose, $P<0.05$; high dose, $P<0.001$). The data are considered to represent some, rather than clear, evidence of carcinogenic activity for the following reasons: standard histologic procedures (single sections of kidney) showed only small numbers of tubular cell neoplasms in dosed male rats; the tubular cell neoplasms in dosed rats were predominantly adenomas; the adenomas were small, microscopic tumors; some were difficult to distinguish from hyperplasia; and the biologic potential of many of the small adenomas is uncertain.

The liver has been identified as a major site of metabolism, a minor site of excretion, and a potential target organ. Hepatocellular neoplasms (adenomas or carcinomas, combined) in female mice occurred with a positive trend (see Table 27). An Ito cell tumor of the liver was

observed in one low dose and in one high dose female mouse (Table D1). Although these Ito cell neoplasms are relatively uncommon, they were considered to be unrelated to nitrofurantoin administration.

Osteosarcomas observed in the bone (Table A1) of dosed male rats are also of marginal incidence but are rare in control animals (8/1,937, 0.4%). The incidences of subcutaneous fibromas or fibrosarcomas (combined) were greater in dosed male rats than in controls (see Table 14).

Effects on the testis in male rats and mice in the 13-week studies included aspermatogenesis and degeneration. Nitrofurazone, an analog of nitrofurantoin, inhibits spermatogenesis in rats, which results in testicular atrophy after long-term administration (Prior and Ferguson, 1950; Nissim, 1957; Montemurro, 1969). A similar effect was reported in mice, together with interstitial cell hyperplasia and seminal vesicle hypertrophy. In the current 2-year studies, administration of nitrofurantoin was associated with the induction of atypical cells of the epididymis, testicular degeneration, and a decrease in the incidence of interstitial cell adenomas of the testis in rats (see Table 15) and an increase in the incidence of atypical cells and depletion of the epididymis in high dose male mice (Table C5). In high dose male mice, testicular aspermatogenesis and degeneration of the germinal epithelium were observed. No reports have been published on whether this effect has been observed or studied in humans. Other compound-related changes in the reproductive tissues of dosed male animals relative to those of controls were decreases in adenomas or carcinomas (combined) of the preputial gland in high dose male rats (see Table 17).

No neoplastic lesions in dosed female rats or dosed male mice were considered to be compound related at the doses of nitrofurantoin administered in these 2-year studies. The absence of any observed toxicity-related effects suggests that female rats might have been able to tolerate higher doses. Only the incidence of clitoral gland neoplasms in low dose female rats (Tables B1 and B4a) gave any indication of a potential compound-related effect; this effect was not supported by a similar observation in the higher dose group.

Ovarian atrophy was associated with increased incidences of tubular adenomas of the ovary, benign mixed tumors, and granulosa cell tumors in dosed mice (see Table 25). Ovarian follicular necrosis was associated with nitrofurantoin administration in the 13-week studies. Biskind and Biskind (1944) reported the influence of gonadotropic hormones on the biologic behavior of ovarian tumors. Ovarian atrophy is recognized as an event that is common to and associated with the development of ovarian tumors. In a model developed for studying ovarian tumorigenesis, Murphy (1972) reported that B6C3F$_1$-*W*^{x}/*W*^{v} mice, (C57BL/6J × C3H/HeJ)F$_1$-*W*^{x}/*W*^{v} hybrids, develop spontaneous complex tubular adenomas (mesothelial adenomas) (95%-100% incidence). Homozygous recessive *W* allele mutants are sterile, develop macrocytic anemia, and lack hair pigmentation. Ovaries of these hybrid mice contain less than 1% of the normal complement of oocytes. Tumor development is associated with loss of oocytes and follicular cells and increased levels of pituitary gonadotropic hormones (luteinizing hormone and follicle stimulating hormone, two to four times normal values) (Murphy, 1972; Murphy and Beamer, 1973). Prolonged stimulation of the ovary by gonadotropins apparently induces tubular adenomas of the ovary. More recently, Tennent and Beamer (1986) and Beamer and Tennent (1986) reported that gonadotropins are necessary for normal follicular atresia and stromal leuteinization following oocyte death (x-irradiation) but were not sufficient to induce adenomas in hypogonal (*hpg*/*hpg*) mice, which retain follicular structure in the absence of oocytes and are deficient in gonadotropin-releasing hormone.

Ovarian atrophy and loss of follicular cells result in increased gonadotropin stimulation. Prolonged stimulation may promote hyperplasia of ovarian cells, resulting in benign tumors; however, under certain conditions (e.g., oocyte death due to irradiation or possibly to chemical toxicity), prolonged stimulation alone is insufficient to induce complex tubular adenomas. Increased gonadotropin stimulation may promote tumor mass by hypertrophy and/or hyperplasia. The initiating events are not clear; however, genetics and age may influence the progression of events. Although the majority of ovarian tumors observed in the current studies were not

considered to be malignant (tubular cell adenomas or mixed tumors), granulosa cell tumors may progress to malignancy in mice (Beamer et al., 1985). Progression from complex tubular adenomas or granulosa cell tumors to malignant neoplasms may occur in $B6C3F_1$ mice as in other strains (Murphy and Russell, 1963; Alison et al., 1987). Nitrofurantoin toxicity observed in the gonads of female mice in these studies is difficult to interpret; it may initiate genetic events leading to tumor development, or it may upset hormonal balance between the pituitary gland and the gonads and indirectly cause or enhance tumor development as described in studies with 7,12-dimethylbenz[*a*]anthracene (DMBA) (Taguchi et al., 1988). In another study of a 5-nitrofuran (nitrofurazone), there were dose-related increased incidences of ovarian tumors of these same types (NTP, 1988).

Ovarian abscesses and suppurative inflammation of the uterus were observed in control but not in dosed female mice (Table D5) and are believed to be related to indigenous microbial infections. Adenocarcinomas of the uterus were seen in two dosed mice (Table D1); uterine adenomas and adenocarcinomas are observed rarely in historical controls (6/2,010, 0.3%).

Spindle cell ("Type A" cell) hyperplasia of the adrenal gland was observed in dosed female mice. A spindle cell adenoma was seen in one low dose female mouse, and a spindle cell carcinoma was seen in one low dose male mouse. Since gonadectomy of mice is known to result in hyperplasia and neoplasia of the "Type A" cells in the adrenal cortex (Turusov, 1979), the spindle cell hyperplasia in female mice given nitrofurantoin is likely related to the ovarian atrophy and disruption of normal hormone levels.

Nitrofurantoin was mutagenic for Salmonella strains TA98 and TA100, with and without metabolic activation, but not for strains TA1535 or TA1537 (Table E1). Nitrofurantoin induced forward mutations at the TK locus of mouse L5178Y lymphoma cells in the absence of metabolic activation (Table E2), induced increased numbers of sister chromatid exchanges (SCEs) (Table E3) and chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells with and without metabolic activation (Table E4), and was negative for sex-linked recessive lethal mutations in Drosophila (Table E5). The mutagenicity of nitrofurantoin has been attributed to a reduced nitro group on the furan ring as a result of the metabolic action of either a bacterial nitroreductase or a eukaryotic cell enzyme system. In bacteria, anaerobic conditions favoring rapid action of the nitroreductase enzyme system have been shown to enhance the mutagenicity of nitrofurantoin (Rosenkranz and Speck, 1976). Availability of at least one alternate nitroreductive pathway has been demonstrated in Salmonella, in that the nitroreductase deficient strain TA100-FR1 is mutated by nitrofurantoin in the absence of oxygen but not in its presence. Kramers (1982) has also shown that Drosophila are able to carry out a presumably similar metabolism. Several compounds with nitro groups which are known to be Salmonella mutagens have also been shown to induce mutations in germ-free (lacking gut flora) Drosophila. Hence, the flies were able to appropriately metabolize nitro compounds to active intermediates. Further, extracts from germ-free flies enabled a nitroreductase-deficient *Escherichia coli* strain to reduce the related 5-nitrofuran, nitrofurazone, to a mutagenic form.

Olive (1980) demonstrated that the reduction potential (electron affinity) of nitroheterocyclic compounds including nitrofurantoin is directly correlated with the mutagenic activity of these chemicals in hamster V79 spheroids. Further, Shirai and Wang (1980) investigated the relationship between the strength of the mutagenic response of eight different nitrofurans, including nitrofurantoin, in Salmonella and their ability to induce SCEs in cultured CHO cells. The magnitude of the responses in both test systems correlated well; i.e., weak Salmonella mutagens were weak inducers of SCEs, and vice versa. Thus, nitrofurantoin is mutagenic in cultured mammalian cells as well as in bacteria, both of which apparently have the capacity to transform these chemicals into mutagenic intermediates.

The reductive metabolism of nitrofurantoin in mammalian cell systems is mediated by NADPH-cytochrome c reductase and xanthine oxidase. The presumed active intermediate is the hydroxylamino compound that has been isolated by some investigators but is extremely oxygen-labile and difficult to detect. Another

potential metabolic reaction could involve hydrolysis of the carbon-nitrogen bond, resulting in production of a furfuraldehyde and an imidazole. Aldehydes, hydrazines, semicarbazides, imidazoles, and related compounds have clastogenic potential. However, nitrofurantoin has not demonstrated mutagenic activity in any of the in vivo somatic and germ cell test systems in which it has been studied.

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

Under the conditions of these 2-year feed studies, there was *some evidence of carcinogenic activity** of nitrofurantoin for male F344/N rats as shown by increased incidences of uncommon kidney tubular cell neoplasms. Uncommon osteosarcomas of the bone and neoplasms of the subcutaneous tissue were observed in dosed male rats. Incidences of interstitial cell adenomas of the testis and neoplasms of the preputial gland were decreased in the 2,500-ppm group of male rats. There was *no evidence of carcinogenic activity* of nitrofurantoin for female F344/N rats fed diets containing 600 ppm or 1,300 ppm for 2 years. Female rats may have been able to tolerate higher doses. There was *no evidence of carcinogenic activity* of nitrofurantoin for male B6C3F$_1$ mice fed diets containing 1,300 ppm or 2,500 ppm for 2 years. There was *clear evidence of carcinogenic activity* of nitrofurantoin for female B6C3F$_1$ mice as shown by increased incidences of tubular adenomas, benign mixed tumors, and granulosa cell tumors of the ovary.

Nonneoplastic lesions considered related to nitrofurantoin exposure were chronic nephropathy and associated lesions (hyperplasia of the parathyroid gland, fibrous osteodystrophy of the bone, and mineralization of the glandular stomach) in male rats and testicular degeneration in male rats and mice. Ovarian atrophy and hyperplasia of the adrenal cortex spindle cells were observed in dosed female mice.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 11-13.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, colon	(50)	(50)	(48)
Polyp adenomatous		1 (2%)	
Muscularis, leiomyosarcoma			1 (2%)
Intestine small, ileum	(50)	(49)	(47)
Leukemia mononuclear	1 (2%)		
Intestine small, jejunum	(50)	(50)	(48)
Cystadenocarcinoma	1 (2%)		
Leukemia mononuclear	1 (2%)		
Liver	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)	
Hepatocellular carcinoma		1 (2%)	
Leukemia mononuclear	23 (46%)	14 (28%)	15 (30%)
Mesothelioma malignant	1 (2%)		
Neoplastic nodule	1 (2%)	2 (4%)	
Neoplastic nodule, multiple		1 (2%)	
Mesentery	*(50)	*(50)	*(50)
Mesothelioma malignant	3 (6%)	1 (2%)	
Mesothelioma malignant, multiple		1 (2%)	
Pancreas	(50)	(50)	(49)
Leukemia mononuclear	3 (6%)	1 (2%)	1 (2%)
Mesothelioma malignant	1 (2%)	2 (4%)	
Acinus, adenoma	2 (4%)		
Stomach	(49)	(50)	(50)
Serosa, mesothelioma malignant	1 (2%)	2 (4%)	
Stomach, forestomach	(49)	(50)	(49)
Papilloma squamous			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)	2 (4%)	1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma			1 (2%)
Leukemia mononuclear	9 (18%)	4 (8%)	
Adrenal gland, medulla	(50)	(50)	(50)
Leukemia mononuclear	5 (10%)	5 (10%)	1 (2%)
Pheochromocytoma malignant	3 (6%)	1 (2%)	2 (4%)
Pheochromocytoma benign	18 (36%)	16 (32%)	21 (42%)
Pheochromocytoma benign, multiple	5 (10%)	4 (8%)	2 (4%)
Islets, pancreatic	(50)	(50)	(49)
Adenoma	2 (4%)	2 (4%)	1 (2%)
Carcinoma			2 (4%)
Pituitary gland	(50)	(50)	(50)
Leukemia mononuclear	4 (8%)		2 (4%)
Pars distalis, adenoma	10 (20%)	12 (24%)	13 (26%)
Pars distalis, carcinoma	1 (2%)	2 (4%)	3 (6%)
Thyroid gland	(50)	(50)	(50)
Leukemia mononuclear		1 (2%)	
C-cell, adenoma	2 (4%)	7 (14%)	6 (12%)
C-cell, adenoma, multiple	1 (2%)		
C-cell, carcinoma		3 (6%)	1 (2%)
Follicular cell, adenoma		2 (4%)	
Follicular cell, carcinoma		1 (2%)	

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

	Untreated Control	Low Dose	High Dose
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(50)	(50)	(50)
Mesothelioma malignant	2 (4%)	5 (10%)	
Preputial gland	(48)	(50)	(47)
Adenoma	6 (13%)	4 (8%)	
Adenoma, multiple		1 (2%)	
Carcinoma	6 (13%)	6 (12%)	
Leukemia mononuclear		1 (2%)	
Prostate	(50)	(50)	(49)
Leukemia mononuclear	3 (6%)		
Seminal vesicle	(50)	(50)	(50)
Leukemia mononuclear		1 (2%)	
Mesothelioma malignant		2 (4%)	
Testes	(50)	(50)	(50)
Mesothelioma malignant	1 (2%)		
Interstitial cell, adenoma	13 (26%)	4 (8%)	15 (30%)
Interstitial cell, adenoma, multiple	34 (68%)	41 (82%)	6 (12%)
Tunic, mesothelioma benign		1 (2%)	2 (4%)
Tunic, mesothelioma malignant	2 (4%)	5 (10%)	1 (2%)
Tunic, sarcoma			1 (2%)
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia mononuclear	16 (32%)	11 (22%)	10 (20%)
Bone marrow	(50)	(50)	(50)
Leukemia mononuclear	16 (32%)	7 (14%)	4 (8%)
Lymph node	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)	
Bronchial, carcinoma, metastatic, Zymbal gland			1 (2%)
Bronchial, leukemia mononuclear	1 (2%)		
Deep cervical, leukemia mononuclear			1 (2%)
Iliac, leukemia mononuclear	1 (2%)		1 (2%)
Inguinal, leukemia mononuclear	4 (8%)	2 (4%)	1 (2%)
Mediastinal, leukemia mononuclear	9 (18%)	4 (8%)	1 (2%)
Pancreatic, leukemia mononuclear	3 (6%)	2 (4%)	2 (4%)
Renal, leukemia mononuclear	1 (2%)	1 (2%)	1 (2%)
Lymph node, mandibular	(46)	(50)	(47)
Leukemia mononuclear	8 (17%)	7 (14%)	3 (6%)
Lymph node, mesenteric	(49)	(48)	(49)
Leukemia mononuclear	8 (16%)	4 (8%)	3 (6%)
Spleen	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
Leukemia mononuclear	23 (46%)	13 (26%)	13 (26%)
Mesothelioma malignant	1 (2%)	2 (4%)	
Sarcoma	1 (2%)		
Thymus	(40)	(36)	(34)
Leukemia mononuclear	3 (8%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(46)	(49)	(46)
Adenoma	1 (2%)		
Fibroadenoma	2 (4%)	4 (8%)	2 (4%)

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

	Untreated Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM (Continued)			
Skin	(50)	(50)	(50)
Basal cell carcinoma	3 (6%)		3 (6%)
Carcinoma		1 (2%)	
Keratoacanthoma	4 (8%)	5 (10%)	4 (8%)
Keratoacanthoma, multiple		1 (2%)	
Papilloma squamous	1 (2%)	1 (2%)	2 (4%)
Sebaceous gland, carcinoma	1 (2%)		
Subcutaneous tissue, basosquamous tumor benign			1 (2%)
Subcutaneous tissue, fibroma		5 (10%)	4 (8%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibrosarcoma, multiple		1 (2%)	
Subcutaneous tissue, hemangioma			1 (2%)
Subcutaneous tissue, hemangiosarcoma	2 (4%)		
Subcutaneous tissue, leukemia mononuclear	1 (2%)		
Subcutaneous tissue, neoplasm, NOS			1 (2%)
Subcutaneous tissue, schwannoma, NOS		1 (2%)	
Subcutaneous tissue, sebaceous gland, adenoma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin	1 (2%)		
Femur, osteosarcoma		1 (2%)	1 (2%)
Vertebra, osteosarcoma			1 (2%)
Skeletal muscle	*(50)	*(50)	*(50)
Abdominal, mesothelioma malignant	1 (2%)	1 (2%)	
Diaphragm, mesothelioma malignant	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Astrocytoma malignant	1 (2%)		
Leukemia mononuclear		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Carcinoma, metastatic, skin		1 (2%)	
Carcinoma, metastatic, Zymbal gland			1 (2%)
Fibrosarcoma, metastatic, skin		1 (2%)	
Leukemia mononuclear	21 (42%)	10 (20%)	10 (20%)
Osteosarcoma, metastatic, bone			1 (2%)
Bronchus, squamous cell carcinoma		1 (2%)	
Pleura, mediastinum, alveolar/bronchiolar carcinoma, metastatic, uncertain primary site	1 (2%)		
Nose	(50)	(49)	(48)
Submucosa, leukemia mononuclear	1 (2%)		
SPECIAL SENSES SYSTEM			
Ear	*(50)	*(50)	*(50)
Pinna, schwannoma malignant	1 (2%)		
Harderian gland	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma	2 (4%)		1 (2%)

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

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Carcinoma, metastatic, Zymbal gland			1 (2%)
Fibrosarcoma, metastatic, skin		1 (2%)	
Leukemia mononuclear	4 (8%)	3 (6%)	1 (2%)
Mesothelioma malignant		1 (2%)	
Osteosarcoma, metastatic, bone			1 (2%)
Pelvis, transitional epithelium, carcinoma			1 (2%)
Renal tubule, adenoma		1 (2%)	2 (4%)
Renal tubule, carcinoma			1 (2%)
Urinary bladder	(50)	(50)	(50)
Leukemia mononuclear		1 (2%)	1 (2%)
Mesothelioma malignant	1 (2%)	1 (2%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	23 (46%)	14 (28%)	15 (30%)
Mesothelioma malignant	3 (6%)	5 (10%)	1 (2%)
Hemangiosarcoma	2 (4%)	1 (2%)	
Mesothelioma benign		1 (2%)	2 (4%)
Hemangioma			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Moribund	24	22	21
Terminal sacrifice	23	27	26
Dead	3	1	3
TUMOR SUMMARY			
Total animals with primary neoplasms**	49	50	48
Total primary neoplasms	151	156	120
Total animals with benign neoplasms	49	47	40
Total benign neoplasms	102	116	84
Total animals with malignant neoplasms	37	31	30
Total malignant neoplasms	49	39	35
Total animals with secondary neoplasms***	2	2	2
Total secondary neoplasms	2	5	5
Total animals with malignant neoplasms--uncertain primary site	1		
Total animals with neoplasms--uncertain benign or malignant		1	1
Total uncertain neoplasms		1	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 FEED STUDY OF NITROFURANTOIN: UNTREATED CONTROL

WEEKS ON STUDY	056	065	073	077	080	080	083	085	085	086	089	089	090	091	092	093	094	095	097	097	100	103	104	105	105
CARCASS ID	101	051	031	032	021	091	092	033	052	061	081	093	075	111	012	034	062	094	071	072	022	013	082	023	102
ALIMENTARY SYSTEM																									
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																				
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenocarcinoma						X																			
Leukemia mononuclear					X																				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X	X	X	X			X	X	X	X	X	X	X	X		X		X
Mesothelioma malignant			X																						
Neoplastic nodule																									
Mesentery			+			+														+	+				
Mesothelioma malignant			X																		X				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X					X	X										
Mesothelioma malignant			X																						
Acinus, adenoma																			X						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant			X																						
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X										
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X	X	X		X	X			X		X
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X	X	X		X	X					
Pheochromocytoma malignant																								X	
Pheochromocytoma benign								X				X							X		X	X		X	
Pheochromocytoma benign, multiple																				X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X	X				X					
Pars distalis, adenoma			X				X		X				X			Y					X	X			
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma																									
C cell, adenoma, multiple																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland													+												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant			X																		X				
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X							X														
Carcinoma		X							Y				X									X			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X				X							X									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																									
Interstitial cell, adenoma			X	X	X	X	X	X	X					X	X							X			
Interstitial cell, adenoma, multiple		X								X	X	X				X	X	X		X	X		X	X	X
Tunic, mesothelioma malignant			X																		X				

+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A Autolysis precludes examination
X Incidence of listed morphology

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	103	041	063	095	014	015	024	025	035	042	043	044	045	053	054	055	064	065	073	074	083	084	085	104	105	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenocarcinoma																										1
Leukemia mononuclear																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X		X		X						X				X	X							X	23
Mesothelioma malignant																										1
Neoplastic nodule						X																				1
Mesentery						+																	+			6
Mesothelioma malignant						X																				3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Mesothelioma malignant																										1
Acinus, adenoma															X											2
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Serosa, mesothelioma malignant																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X																						X	9
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										5
Pheochromocytoma malignant			X																		X					3
Pheochromocytoma benign	X	X	X		X		X	X				X	X	X					X	X					X	18
Pheochromocytoma benign, multiple				X					X		X						X									5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X														X						2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X								4
Pars distalis, adenoma					X			X								X										10
Pars distalis, carcinoma																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X					X																2
C-cell, adenoma, multiple																					X					1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma							X		X							X								X		6
Carcinoma				X															X							6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant						X																				1
Interstitial cell, adenoma						X	X									X										13
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	34
Tunic, mesothelioma malignant																										2

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

WEEKS ON STUDY	056	065	073	077	080	080	083	085	085	086	089	089	090	091	092	093	094	095	097	097	100	103	104	105	105
CARCASS ID	101	051	031	032	021	091	092	033	052	061	081	093	075	111	012	034	062	094	071	072	022	013	082	023	102
HEMATOPOIETIC SYSTEM																									
Blood					+				+		+					M	+	+	+	+	+	+	+		+
Leukemia mononuclear					X				X		X							X	X	X	X		X		X
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X						X	X	X	X	X	X	X		X		X
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, leukemia mononuclear									X																
Iliac, leukemia mononuclear					X																				
Inguinal, leukemia mononuclear					X				X							X									
Mediastinal, leukemia mononuclear					X				X							X				X	X				X
Pancreatic, leukemia mononuclear					X																				X
Renal, leukemia mononuclear																									
Lymph node, mandibular	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X				X							X		X		X					
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X				X						X	X							X		X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X	X	X	X			X	X	X	X	X	X	X	X		X		X
Mesothelioma malignant			X																						
Sarcoma				X																					
Thymus	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+
Leukemia mononuclear																									X
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma											X														
Keratoacanthoma		X										X												X	
Papilloma squamous																				X					
Sebaceous gland, carcinoma																								X	
Subcutaneous tissue, fibrosarcoma														X											
Subcutaneous tissue, hemangiosarcoma												X					X								
Subcutaneous tissue, leukemia mononuclear																X									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin														X											
Skeletal muscle			+																						
Abdominal, mesothelioma malignant			X																						
Diaphragm, mesothelioma malignant			X																						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																					X				
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X	X	X	X			X	X	X		X	X	X	X		X		X
Pleura, mediastinum, alveolar/bronchiolar carcinoma, metastatic, uncertain primary site				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Submucosa, leukemia mononuclear																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear								+	+			+			+			+							+
Pinna, schwannoma malignant												X													
Eye														+											
Harderian gland																+									
Leukemia mononuclear																X									
Lacrimal gland					+																				
Zymbal gland					+													+							
Carcinoma					X													X							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X				X						X	X									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant			X																						

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	103	041	063	095	014	015	024	025	035	042	043	044	045	053	054	055	064	065	073	074	083	084	085	104	105		TISSUES TUMORS
HEMATOPOIETIC SYSTEM																											
Blood		+	+		+		+						+				+	+								18
Leukemia mononuclear		X	X		X		X						X				X	X								16
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X														X	X							X	16
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, leukemia mononuclear																										1
Iliac, leukemia mononuclear																										1
Inguinal, leukemia mononuclear		X																								4
Mediastinal, leukemia mononuclear		X	X				X																			9
Pancreatic, leukemia mononuclear		X																								3
Renal, leukemia mononuclear		X																								1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leukemia mononuclear			X				X											X								8
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Leukemia mononuclear													X												X	8
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X		X		X						X				X	X							X	23
Mesothelioma malignant																										1
Sarcoma																										1
Thymus	+	M	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	40
Leukemia mononuclear			X															X								3
INTEGUMENTARY SYSTEM																											
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	46
Adenoma													X													1
Fibroadenoma											X				X											2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																						X		X		3
Keratoacanthoma														X												4
Papilloma squamous																										1
Sebaceous gland, carcinoma																										1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																										2
Subcutaneous tissue, leukemia mononuclear																										1
MUSCULOSKELETAL SYSTEM																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Skeletal muscle																										1
Abdominal, mesothelioma malignant																										1
Diaphragm, mesothelioma malignant																										1
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
RESPIRATORY SYSTEM																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X		X		X						X					X							X	21
Pleura, mediastinum, alveolar/bronchiolar carcinoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Submucosa, leukemia mononuclear																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																											
Ear		+	+	+					+			+	+		+	+							+	+		16
Pinna, schwannoma malignant																										1
Eye		+													+	+										4
Harderian gland																										1
Leukemia mononuclear																										1
Lacrimal gland																										1
Zymbal gland																										2
Carcinoma																										2
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1

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

WEEKS ON STUDY	046	069	070	079	081	086	086	090	092	094	096	097	099	100	100	102	102	103	104	104	104	104	104	105	105
CARCASS ID	261	271	251	291	262	211	241	281	301	302	303	263	282	221	272	252	273	222	283	284	265	212	292	213	231
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																	X								
Intestine large, rectum	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Hepatocellular carcinoma																									
Leukemia mononuclear					X		X			X						X	X				X		X		
Neoplastic nodule														X											
Neoplastic nodule, multiple																									
Mesentery						+		+			+	+							+						
Mesothelioma malignant								X																	
Mesothelioma malignant, multiple												X													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																				
Mesothelioma malignant								X				X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant								X				X													
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel																		+							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X												X								
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X												X								
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X					X							X								
Pheochromocytoma malignant																			X						
Pheochromocytoma benign				X							X					X									
Pheochromocytoma benign, multiple																	X							X	X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X		X					X			X				X			X				X
Pars distalis, carcinoma									X																
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X															
C cell, adenoma					X												X								X
C cell, carcinoma										X	X														X
Follicular cell, adenoma																									
Follicular cell, carcinoma										X															
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland			+																						
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant								X				X					X			X					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X	X																
Adenoma, multiple																									
Carcinoma	X											X							X			X			
Leukemia mononuclear					X																				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Mesothelioma malignant								X				X													
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma									X														X		
Interstitial cell, adenoma, multiple				X	X		X	X		X	X	X	X	X	X	X	X	X	X		X	X		X	X
Tunic, mesothelioma benign																								X	
Tunic, mesothelioma malignant								X				X					X			X					

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	293	304	214	215	223	224	225	232	233	234	235	242	243	244	245	253	254	255	264	274	275	285	294	295	305	TOTAL: TISSUES / TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin						X																				1
Hepatocellular carcinoma																			X							1
Leukemia mononuclear			X											X	X			X			X	X			X	14
Neoplastic nodule									X																	2
Neoplastic nodule, multiple																					X					1
Mesentery			+										+					+						+		9
Mesothelioma malignant																										1
Mesothelioma malignant, multiple																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Mesothelioma malignant																										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Serosa, mesothelioma malignant																										2
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																					X				X	4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																					X				X	5
Pheochromocytoma malignant																										1
Pheochromocytoma benign	X					X	X	X			X		X	X	X		X	X			X	X	X			16
Pheochromocytoma benign, multiple		X																								4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								2
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma						X	X	X											X							12
Pars distalis, carcinoma													X													2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
C-cell, adenoma	X							X				X										X				7
C cell, carcinoma																										3
Follicular cell, adenoma								X									X									2
Follicular cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																				X						5
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X											X								4
Adenoma, multiple																							X			1
Carcinoma			X																	X						6
Leukemia mononuclear																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Mesothelioma malignant																										2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																		X			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	41
Tunic, mesothelioma benign																										1
Tunic, mesothelioma malignant																				X						5

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

WEEKS ON STUDY	046	069	070	079	081	086	086	090	092	094	096	097	099	100	100	102	102	103	104	104	104	104	104	105	105
CARCASS ID	261	271	251	291	262	211	241	281	301	302	303	263	282	221	272	252	273	222	283	284	265	212	292	213	231
HEMATOPOIETIC SYSTEM																									
Blood							M			+		+				+	+				+		+		
Leukemia mononuclear										X						X	X				X		X		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X			X						X	X				X				
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Inguinal, leukemia mononuclear					X											X									
Mediastinal, leukemia mononuclear										X						X	X								
Pancreatic, leukemia mononuclear										X						X									
Renal, leukemia mononuclear										X															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X			X						X	X								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X					X						X	X								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																							
Leukemia mononuclear					X		X			X						X	X				X				
Mesothelioma malignant								X				X													
Thymus	+	+	+	+	M	+	+	+	M	+	M	+	+	M	M	M	+	+	M	M	M	M	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma									X									X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X																					
Keratoacanthoma									X					X											X
Keratoacanthoma, multiple																									
Papilloma squamous																									
Subcutaneous tissue, fibroma									X														X		
Subcutaneous tissue, fibrosarcoma															X										
Subcutaneous tissue, fibrosarcoma, multiple																									
Subcutaneous tissue, schwannoma, NOS															X										
Subcutaneous tissue, sebaceous gland, adenoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma																								X	
Skeletal muscle								+																	
Abdominal, mesothelioma malignant								X																	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X									
Spinal cord				+													+								
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, skin				X																					
Fibrosarcoma, metastatic, skin																									
Leukemia mononuclear					X		X			X						X	X				X				
Bronchus, squamous cell carcinoma																									
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear									+								+						+	+	+
Eye									+				+					+					+		
Harderian gland		+	+																						
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Leukemia mononuclear					X					X											X				
Mesothelioma malignant								X																	
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																				
Mesothelioma malignant												X													

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	293	304	214	215	223	224	225	232	233	234	235	242	243	244	245	253	254	255	264	274	275	285	294	295	305	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood														+	+			+			+	+		+	+	13
Leukemia mononuclear														X	X			X			X	X			X	11
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X																							7
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin						X																				1
Inguinal, leukemia mononuclear																										2
Mediastinal, leukemia mononuclear																						X				4
Pancreatic, leukemia mononuclear																										2
Renal, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear															X							X				7
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Leukemia mononuclear			X											X	X			X			X	X			X	13
Mesothelioma malignant																										2
Thymus	M	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	36
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma																				X				X		4
Skin	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Keratoacanthoma						X	X																			5
Keratoacanthoma, multiple																	X									1
Papilloma squamous													X													1
Subcutaneous tissue, fibroma	X		X												X											5
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, fibrosarcoma, multiple						X																				1
Subcutaneous tissue, *schwannoma, NOS*																										1
Subcutaneous tissue, sebaceous gland, adenoma					X																					1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femur, osteosarcoma																										1
Skeletal muscle																										1
Abdominal, mesothelioma malignant																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Spinal cord																										2
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, skin																										1
Fibrosarcoma, metastatic, skin						X																				1
Leukemia mononuclear			X												X			X							X	10
Bronchus, squamous cell carcinoma																					X					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear		+	+					+							+				+	+		+	+			13
Eye																				+					+	6
Harderian gland												+									+	+				5
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin						X																				1
Leukemia mononuclear																										3
Mesothelioma malignant																										1
Renal tubule, adenoma				X																						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Mesothelioma malignant																										1

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

WEEKS ON STUDY	056	056	059	071	076	080	089	091	091	091	091	092	093	096	096	100	100	101	102	103	103	103	104	104	105
CARCASS ID	171	111	181	141	182	112	131	172	121	201	202	151	142	183	203	152	153	113	191	184	114	132	115	161	122
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Muscularis, leiomyosarcoma																	X								
Intestine large, rectum	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X			X	X		X	X	X		X		X	X	X			
Mesentery								+							+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Leukemia mononuclear																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																				X					
Pheochromocytoma malignant																									
Pheochromocytoma benign						X					X	X		X	X			X		X	X	X			X
Pheochromocytoma benign, multiple																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenoma																						X			
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X	X			
Pars distalis, adenoma													X					X	X				X		
Pars distalis, carcinoma		X													X										X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma												X						X							X
C cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma									X			X		X			X					X			
Interstitial cell, adenoma, multiple						X					X														
Tunic, mesothelioma benign										X		X													
Tunic, mesothelioma malignant																									
Tunic, sarcoma							X																		
HEMATOPOIETIC SYSTEM																									
Blood			M					+			+			+	+					+		+			
Leukemia mononuclear								X			X			X	X					X		X			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X																	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, carcinoma, metastatic, Zymbal gland					X																				
Deep cervical, leukemia mononuclear			X																						
Iliac, leukemia mononuclear			X																						
Inguinal, leukemia mononuclear			X																						
Mediastinal, leukemia mononuclear			X																						
Pancreatic, leukemia mononuclear			X																						
Renal, leukemia mononuclear																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Leukemia mononuclear			X									X		X											
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X														X			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X			X	X		X	X	X					X	X			
Thymus	+	+	+	+	+	+	M	+	M	M	+	+	+	M	+	+	M	+	M	M	+	M	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	123	124	125	133	134	135	143	144	145	154	155	162	163	164	165	173	174	175	185	192	193	194	195	204	205	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Muscularis, leiomyosarcoma																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X										X	X				X							15
Mesentery					+				+										+			+				6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																				X						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Pheochromocytoma malignant													X					X								2
Pheochromocytoma benign	X	X				X		X					X	X			X	X	X		X	X				21
Pheochromocytoma benign, multiple									X							X										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Carcinoma		X																	X							2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Pars distalis, adenoma	X		X	X		X	X						X	X	X									X		13
Pars distalis, carcinoma																										3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell, adenoma				X			X												X							6
C cell, carcinoma										X																1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma		X	X	X	X		X		X		X				X			X							X	15
Interstitial cell, adenoma, multiple																				X	X	X	X			6
Tunic, mesothelioma benign																										2
Tunic, mesothelioma malignant	X																									1
Tunic, sarcoma																										1
HEMATOPOIETIC SYSTEM																										
Blood				+										+	+				+							10
Leukemia mononuclear				X										X	X				X							10
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear														X	X											4
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, carcinoma, metastatic, Zymbal gland																										1
Deep cervical, leukemia mononuclear																										1
Iliac, leukemia mononuclear																										1
Inguinal, leukemia mononuclear																										1
Mediastinal, leukemia mononuclear																										1
Pancreatic, leukemia mononuclear														X												2
Renal, leukemia mononuclear															X											1
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X										X	X				X							13
Thymus	+	M	+	M	M	+	M	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	M	+	34

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

WEEKS ON STUDY	056	056	059	071	076	080	089	091	091	091	092	093	096	096	100	100	101	102	103	103	103	104	104	105
CARCASS ID	171	111	181	141	182	112	131	172	121	201	202	151	142	183	203	152	153	113	191	184	114	132	115	161	122
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma										X												X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma						X																			
Keratoacanthoma																					X				
Papilloma squamous																							X		
Subcutaneous tissue, basosquamous tumor benign																				X					
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma											X														
Subcutaneous tissue, hemangioma													X												
Subcutaneous tissue, neoplasm, NOS																			X						
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma				X																					
Vertebra, osteosarcoma	X																								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X																						
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal gland					X																				
Leukemia mononuclear			X					X				X		X		X				X	X	X			
Osteosarcoma, metastatic, bone				X																					
Nose	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear					+								+	+				+			+		+	+	
Eye													+		+		+				+	+			+
Harderian gland												+				+						+			
Zymbal gland					+																				
Carcinoma					X																				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal gland					X																				
Leukemia mononuclear			X																						
Osteosarcoma, metastatic, bone				X																					
Pelvis, transitional epithelium, carcinoma																									
Renal tubule, adenoma																									
Renal tubule, carcinoma																						X			
Ureter								+																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	123	124	125	133	134	135	143	144	145	154	155	162	163	164	165	173	174	175	185	192	193	194	195	204	205	
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibroadenoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma															X								X			3
Keratoacanthoma					X				X															X		4
Papilloma squamous																X										2
Subcutaneous tissue, basosquamous tumor benign																										1
Subcutaneous tissue, fibroma														X					X	X					X	4
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, neoplasm, NOS																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femur, osteosarcoma																										1
Vertebra, osteosarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal gland																										1
Leukemia mononuclear				X											X											10
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear	+	+	+	+	+		+	+		+	+	+	+	+		+	+	+				+	+	+	+	26
Eye		+	+	+	+	+	+	+		+	+	+	+			+	+						+	+	+	22
Harderian gland				+																						4
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal gland																										1
Leukemia mononuclear																										1
Osteosarcoma, metastatic, bone																										1
Pelvis, transitional epithelium, carcinoma																	X									1
Renal tubule, adenoma						X																X				2
Renal tubule, carcinoma																										1
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Control	1,300 ppm	2,500 ppm
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	23/50 (46%)	20/50 (40%)	23/50 (46%)
Adjusted Rates (b)	71.1%	63.3%	64.5%
Terminal Rates (c)	15/24 (63%)	16/27 (59%)	14/26 (54%)
Day of First Observation	591	548	559
Life Table Tests (d)	P=0.403N	P=0.177N	P=0.443N
Logistic Regression Tests (d)	P=0.433N	P=0.163N	P=0.477N
Cochran-Armitage Trend Test (d)	P=0.535N		
Fisher Exact Test (d)		P=0.343N	P=0.579N
Adrenal Gland: Malignant Pheochromocytoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	11.7%	3.1%	7.7%
Terminal Rates (c)	2/24 (8%)	0/27 (0%)	2/26 (8%)
Day of First Observation	729	722	730
Life Table Tests (d)	P=0.376N	P=0.276N	P=0.474N
Logistic Regression Tests (d)	P=0.365N	P=0.247N	P=0.486N
Cochran-Armitage Trend Test (d)	P=0.395N		
Fisher Exact Test (d)		P=0.309N	P=0.500N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	24/50 (48%)	21/50 (42%)	23/50 (46%)
Adjusted Rates (b)	74.3%	64.5%	64.5%
Terminal Rates (c)	16/24 (67%)	16/27 (59%)	14/26 (54%)
Day of First Observation	591	548	559
Life Table Tests (d)	P=0.330N	P=0.174N	P=0.368N
Logistic Regression Tests (d)	P=0.345N	P=0.152N	P=0.386N
Cochran-Armitage Trend Test (d)	P=0.456N		
Fisher Exact Test (d)		P=0.344N	P=0.500N
Preputial Gland: Adenoma			
Overall Rates (a)	6/48 (13%)	5/50 (10%)	0/47 (0%)
Adjusted Rates (b)	21.9%	15.2%	0.0%
Terminal Rates (c)	4/22 (18%)	3/27 (11%)	0/26 (0%)
Day of First Observation	533	630	
Life Table Tests (d)	P=0.011N	P=0.388N	P=0.013N
Logistic Regression Tests (d)	P=0.018N	P=0.461N	P=0.018N
Cochran-Armitage Trend Test (d)	P=0.019N		
Fisher Exact Test (d)		P=0.471N	P=0.014N
Preputial Gland: Carcinoma			
Overall Rates (a)	6/48 (13%)	6/50 (12%)	0/47 (0%)
Adjusted Rates (b)	18.3%	17.3%	0.0%
Terminal Rates (c)	2/22 (9%)	2/27 (7%)	0/26 (0%)
Day of First Observation	455	320	
Life Table Tests (d)	P=0.019N	P=0.522N	P=0.015N
Logistic Regression Tests (d)	P=0.038N	P=0.603	P=0.028N
Cochran-Armitage Trend Test (d)	P=0.024N		
Fisher Exact Test (d)		P=0.591N	P=0.014N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	12/48 (25%)	11/50 (22%)	0/47 (0%)
Adjusted Rates (b)	37.6%	30.6%	0.0%
Terminal Rates (c)	6/22 (27%)	5/27 (19%)	0/26 (0%)
Day of First Observation	455	320	
Life Table Tests (d)	P<0.001N	P=0.352N	P<0.001N
Logistic Regression Tests (d)	P=0.001N	P=0.494N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.455N	P<0.001N

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

	Control	1,300 ppm	2,500 ppm
Pancreatic Islets: Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	3/49 (6%)
Adjusted Rates (b)	8.3%	6.5%	10.9%
Terminal Rates (c)	2/24 (8%)	1/27 (4%)	2/26 (8%)
Day of First Observation	730	712	719
Life Table Tests (d)	P=0.443	P=0.648N	P=0.532
Logistic Regression Tests (d)	P=0.441	P=0.636N	P=0.530
Cochran-Armitage Trend Test (d)	P=0.404		
Fisher Exact Test (d)		P=0.691	P=0.490
Kidney: Tubular Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	3.7%	10.9%
Terminal Rates (c)	0/24 (0%)	1/27 (4%)	2/26 (8%)
Day of First Observation		730	719
Life Table Tests (d)	P=0.068	P=0.523	P=0.134
Logistic Regression Tests (d)	P=0.066	P=0.523	P=0.134
Cochran-Armitage Trend Test (d)	P=0.063		
Fisher Exact Test (d)		P=0.500	P=0.121
Liver: Neoplastic Nodule			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	4.2%	9.9%	0.0%
Terminal Rates (c)	1/24 (4%)	2/27 (7%)	0/26 (0%)
Day of First Observation	730	699	
Life Table Tests (d)	P=0.366N	P=0.360	P=0.484N
Logistic Regression Tests (d)	P=0.369N	P=0.360	P=0.484N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	4.2%	13.5%	0.0%
Terminal Rates (c)	1/24 (4%)	3/27 (11%)	0/26 (0%)
Day of First Observation	730	699	
Life Table Tests (d)	P=0.379N	P=0.225	P=0.484N
Logistic Regression Tests (d)	P=0.380N	P=0.228	P=0.484N
Cochran-Armitage Trend Test (d)	P=0.415N		
Fisher Exact Test (d)		P=0.181	P=0.500N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	8.3%	12.4%	5.8%
Terminal Rates (c)	2/24 (8%)	2/27 (7%)	0/26 (0%)
Day of First Observation	730	644	635
Life Table Tests (d)	P=0.568N	P=0.402	P=0.663N
Logistic Regression Tests (d)	P=0.584N	P=0.390	P=0.681N
Cochran-Armitage Trend Test (d)	P=0.582		
Fisher Exact Test (d)		P=0.339	P=0.691N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	12.5%	12.4%	5.8%
Terminal Rates (c)	3/24 (13%)	2/27 (7%)	0/26 (0%)
Day of First Observation	730	644	635
Life Table Tests (d)	P=0.391N	P=0.572	P=0.463N
Logistic Regression Tests (d)	P=0.403N	P=0.569	P=0.511N
Cochran-Armitage Trend Test (d)	P=0.427N		
Fisher Exact Test (d)		P=0.500	P=0.500N

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

	Control	1,300 ppm	2,500 ppm
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	10/50 (20%)	12/50 (24%)	13/50 (26%)
Adjusted Rates (b)	27.8%	32.1%	42.3%
Terminal Rates (c)	3/24 (13%)	5/27 (19%)	9/26 (35%)
Day of First Observation	506	489	646
Life Table Tests (d)	P=0.355	P=0.520	P=0.401
Logistic Regression Tests (d)	P=0.282	P=0.371	P=0.333
Cochran-Armitage Trend Test (d)	P=0.278		
Fisher Exact Test (d)		P=0.405	P=0.318
Pituitary Gland/Pars Distalis: Carcinoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	4.2%	6.0%	8.4%
Terminal Rates (c)	1/24 (4%)	1/27 (4%)	1/26 (4%)
Day of First Observation	730	644	387
Life Table Tests (d)	P=0.248	P=0.548	P=0.333
Logistic Regression Tests (d)	P=0.223	P=0.522	P=0.303
Cochran-Armitage Trend Test (d)	P=0.225		
Fisher Exact Test (d)		P=0.500	P=0.309
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	11/50 (22%)	14/50 (28%)	16/50 (32%)
Adjusted Rates (b)	31.2%	36.7%	48.3%
Terminal Rates (c)	4/24 (17%)	6/27 (22%)	10/26 (38%)
Day of First Observation	506	489	387
Life Table Tests (d)	P=0.232	P=0.453	P=0.268
Logistic Regression Tests (d)	P=0.157	P=0.297	P=0.188
Cochran-Armitage Trend Test (d)	P=0.157		
Fisher Exact Test (d)		P=0.322	P=0.184
Skin: Basal Cell Carcinoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	10.6%	0.0%	9.7%
Terminal Rates (c)	2/24 (8%)	0/27 (0%)	2/26 (8%)
Day of First Observation	621		559
Life Table Tests (d)	P=0.563N	P=0.105N	P=0.631N
Logistic Regression Tests (d)	P=0.588N	P=0.113N	P=0.660N
Cochran-Armitage Trend Test (d)	P=0.589N		
Fisher Exact Test (d)		P=0.121N	P=0.661
Skin: Sebaceous Gland Adenoma, Sebaceous Gland Carcinoma, or Basal Cell Carcinoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	13.9%	3.7%	9.7%
Terminal Rates (c)	2/24 (8%)	1/27 (4%)	2/26 (8%)
Day of First Observation	621	730	559
Life Table Tests (d)	P=0.379N	P=0.158N	P=0.473N
Logistic Regression Tests (d)	P=0.407N	P=0.185N	P=0.492N
Cochran-Armitage Trend Test (d)	P=0.404N		
Fisher Exact Test (d)		P=0.181N	P=0.500N
Skin: Keratoacanthoma			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	11.9%	19.1%	14.5%
Terminal Rates (c)	1/24 (4%)	4/27 (15%)	3/26 (12%)
Day of First Observation	455	644	716
Life Table Tests (d)	P=0.535N	P=0.441	P=0.614N
Logistic Regression Tests (d)	P=0.569N	P=0.367	P=0.642N
Cochran-Armitage Trend Test (d)	P=0.564		
Fisher Exact Test (d)		P=0.370	P=0.643N

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

	Control	1,300 ppm	2,500 ppm
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	0/50 (0%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	0.0%	16.2%	15.4%
Terminal Rates (c)	0/24 (0%)	3/27 (11%)	4/26 (15%)
Day of First Observation		644	730
Life Table Tests (d)	P=0.077	P=0.047	P=0.071
Logistic Regression Tests (d)	P=0.076	P=0.042	P=0.071
Cochran-Armitage Trend Test (d)	P=0.067		
Fisher Exact Test (d)		P=0.028	P=0.059
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	7/50 (14%)	5/50 (10%)
Adjusted Rates (b)	2.7%	21.9%	17.5%
Terminal Rates (c)	0/24 (0%)	4/27 (15%)	4/26 (15%)
Day of First Observation	633	644	636
Life Table Tests (d)	P=0.127	P=0.054	P=0.128
Logistic Regression Tests (d)	P=0.109	P=0.039	P=0.109
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test (d)		P=0.030	P=0.102
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	47/50 (94%)	45/50 (90%)	21/50 (42%)
Adjusted Rates (b)	100.0%	100.0%	61.8%
Terminal Rates (c)	24/24 (100%)	27/27 (100%)	14/26 (54%)
Day of First Observation	455	548	559
Life Table Tests (d)	P<0.001N	P=0.162N	P<0.001N
Logistic Regression Tests (d)	P<0.001N	P=0.221N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.357N	P<0.001N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/50 (6%)	7/50 (14%)	6/50 (12%)
Adjusted Rates (b)	12.5%	22.6%	20.1%
Terminal Rates (c)	3/24 (13%)	5/27 (19%)	4/26 (15%)
Day of First Observation	730	561	639
Life Table Tests (d)	P=0.241	P=0.207	P=0.285
Logistic Regression Tests (d)	P=0.227	P=0.200	P=0.278
Cochran-Armitage Trend Test (d)	P=0.205		
Fisher Exact Test (d)		P=0.159	P=0.243
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	8.4%	3.8%
Terminal Rates (c)	0/24 (0%)	1/27 (4%)	1/26 (4%)
Day of First Observation		656	730
Life Table Tests (d)	P=0.394	P=0.159	P=0.516
Logistic Regression Tests (d)	P=0.373	P=0.121	P=0.516
Cochran-Armitage Trend Test (d)	P=0.367		
Fisher Exact Test (d)		P=0.121	P=0.500
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	9/50 (18%)	7/50 (14%)
Adjusted Rates (b)	12.5%	26.4%	23.7%
Terminal Rates (c)	3/24 (13%)	5/27 (19%)	5/26 (19%)
Day of First Observation	730	561	639
Life Table Tests (d)	P=0.176	P=0.100	P=0.193
Logistic Regression Tests (d)	P=0.155	P=0.076	P=0.189
Cochran-Armitage Trend Test (d)	P=0.140		
Fisher Exact Test (d)		P=0.061	P=0.159

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

	Control	1,300 ppm	2,500 ppm
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	9.7%	0.0%
Terminal Rates (c)	0/24 (0%)	2/27 (7%)	0/26 (0%)
Day of First Observation		656	
Life Table Tests (d)	P=0.644N	P=0.150	(e)
Logistic Regression Tests (d)	P=0.635	P=0.133	(e)
Cochran-Armitage Trend Test (d)	P=0.623		
Fisher Exact Test (d)		P=0.121	(e)
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	23/50 (46%)	14/50 (28%)	15/50 (30%)
Adjusted Rates (b)	57.0%	39.2%	38.1%
Terminal Rates (c)	8/24 (33%)	7/27 (26%)	4/26 (15%)
Day of First Observation	554	561	413
Life Table Tests (d)	P=0.053N	P=0.037N	P=0.076N
Logistic Regression Tests (d)	P=0.054N	P=0.044N	P=0.075N
Cochran-Armitage Trend Test (d)	P=0.055N		
Fisher Exact Test (d)		P=0.048N	P=0.074N
All Sites: Malignant Mesothelioma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	9.3%	13.9%	3.8%
Terminal Rates (c)	1/24 (4%)	1/27 (4%)	1/26 (4%)
Day of First Observation	506	630	730
Life Table Tests (d)	P=0.247N	P=0.437	P=0.284N
Logistic Regression Tests (d)	P=0.277N	P=0.349	P=0.307N
Cochran-Armitage Trend Test (d)	P=0.278N		
Fisher Exact Test (d)		P=0.357	P=0.309N
All Sites: All Mesothelioma			
Overall Rates (a)	3/50 (6%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	9.3%	17.2%	8.6%
Terminal Rates (c)	1/24 (4%)	2/27 (7%)	1/26 (4%)
Day of First Observation	506	630	635
Life Table Tests (d)	P=0.538N	P=0.320	P=0.622N
Logistic Regression Tests (d)	P=0.564	P=0.242	P=0.659
Cochran-Armitage Trend Test (d)	P=0.564		
Fisher Exact Test (d)		P=0.243	P=0.661

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 2,500-ppm and control groups.

TABLE A4a. HISTORICAL INCIDENCE OF KIDNEY TUBULAR CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Adenomas or Adenocarcinomas in Controls
Historical Incidence at Southern Research Institute	
HC Blue No. 2	0/50
C.I. Disperse Blue 1	0/49
Eugenol	0/40
Stannous chloride	0/50
D-Mannitol	0/50
Ziram	0/50
Propyl gallate	(b) 1/50
Zearalenone	0/50
HC Blue No. 1	(c) 1/50
TOTAL	2/439 (0.5%)
SD (d)	0.88%
Range (e)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(f) 8/1,929 (0.4%)
SD (d)	0.94%
Range (e)	
High	2/50
Low	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Tubular cell adenoma
(c) Adenoma, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes one adenoma, NOS, six tubular cell adenomas, and one tubular cell adenocarcinoma

TABLE A4b. HISTORICAL INCIDENCE OF SKELETAL SYSTEM TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Osteosarcomas in Controls
Historical Incidence at Southern Research Institute	
HC Blue No. 2	2/50
C.I. Disperse Blue 1	0/49
Eugenol	0/40
Stannous chloride	0/50
D-Mannitol	1/50
Ziram	0/50
Propyl gallate	0/50
Zearalenone	0/50
HC Blue No. 1	0/50
TOTAL	3/439 (0.7%)
SD (b)	1.41%
Range (c)	
High	2/50
Low	0/50
Overall Historical Incidence	
TOTAL	8/1,937 (0.4%)
SD (b)	0.94%
Range (c)	
High	2/50
Low	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks; no osteomas have been observed.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4c. HISTORICAL INCIDENCE OF SUBCUTANEOUS TISSUE TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Fibroma	Fibrosarcoma	Fibroma or Fibrosarcoma
Historical Incidence at Southern Research Institute			
HC Blue No. 2	5/50	(b) 2/50	(b) 7/50
C.I. Disperse Blue 1	4/49	1/49	5/49
Eugenol	3/40	0/40	3/40
Stannous chloride	1/50	1/50	2/50
D-Mannitol	2/50	0/50	2/50
Ziram	2/50	0/50	2/50
Propyl gallate	1/50	0/50	1/50
Zearalenone	3/50	1/50	4/50
HC Blue No. 1	2/50	0/50	2/50
TOTAL	23/439 (5.2%)	5/439 (1.1%)	28/439 (6.4%)
SD (c)	2.79%	1.46%	3.85%
Range (d)			
High	5/50	2/50	7/50
Low	1/50	0/50	1/50
Overall Historical Incidence			
TOTAL	(e) 107/1,937 (5.5%)	(f) 38/1,937 (2.0%)	(e,f) 144/1,937 (7.4%)
SD (c)	3.22%	2.69%	4.31%
Range (d)			
High	6/50	7/50	12/50
Low	0/50	0/50	0/49

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Includes one sarcoma, NOS, and one neurofibrosarcoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes five neurofibromas
(f) Includes eight sarcomas, NOS, and six neurofibrosarcomas

TABLE A4d. HISTORICAL INCIDENCE OF TESTICULAR TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Adenomas in Controls (b)
Historical Incidence at Southern Research Institute	
HC Blue No. 2	45/50
C.I. Disperse Blue 1	44/49
Eugenol	38/40
Stannous chloride	34/50
D-Mannitol	45/50
Ziram	41/50
Propyl gallate	47/50
Zearalenone	45/50
HC Blue No. 1	45/50
TOTAL	384/439 (87.5%)
SD (c)	8.21%
Range (d)	
High	38/40
Low	34/50
Overall Historical Incidence	
TOTAL	(e) 1,681/1,909 (88.1%)
SD (c)	7.32%
Range (d)	
High	49/50
Low	34/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Diagnosed as interstitial cell tumors
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one malignant interstitial cell tumor

TABLE A4e. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
HC Blue No. 2	0/50	1/50	1/50
C.I. Disperse Blue 1	0/49	4/49	4/49
Eugenol	0/40	2/40	2/40
Stannous chloride	0/50	0/50	0/50
D-Mannitol	0/50	(b) 1/50	(b) 1/50
Ziram	3/50	4/50	7/50
Propyl gallate	0/50	1/50	1/50
Zearalenone	1/50	(c) 2/50	(c) 3/50
HC Blue No. 1	2/50	2/50	4/50
TOTAL	6/439 (1.4%)	17/439 (3.9%)	23/439 (5.2%)
SD (d)	2.24%	2.79%	4.37%
Range (e)			
High	3/50	4/49	7/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	(f) 57/1,937 (2.9%)	(g) 66/1,937 (3.4%)	(f,g) 123/1,937 (6.4%)
SD (d)	4.02%	2.93%	4.77%
Range (e)			
High	8/50	5/50	9/50
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Adenocarcinoma, NOS
(c) Includes one squamous cell carcinoma
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes one papillary adenoma and one cystadenoma, NOS
(g) Includes two squamous cell carcinomas, eight adenocarcinomas, NOS, and one sebaceous adenocarcinoma

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

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(50)	(50)	(48)
Parasite metazoan	1 (2%)		2 (4%)
Submucosa, edema	1 (2%)	1 (2%)	3 (6%)
Intestine large, colon	(50)	(50)	(48)
Parasite metazoan	6 (12%)	5 (10%)	2 (4%)
Intestine large, rectum	(50)	(48)	(47)
Parasite metazoan		1 (2%)	
Liver	(50)	(50)	(50)
Angiectasis	2 (4%)	2 (4%)	1 (2%)
Basophilic focus	1 (2%)		1 (2%)
Congestion		2 (4%)	
Cytologic alterations, focal	5 (10%)	5 (10%)	4 (8%)
Cytologic alterations, multifocal	1 (2%)	2 (4%)	2 (4%)
Degeneration, cystic, focal	4 (8%)	2 (4%)	2 (4%)
Developmental malformation		1 (2%)	1 (2%)
Hematopoietic cell proliferation		1 (2%)	
Hyperplasia, nodular	1 (2%)		1 (2%)
Infiltration cellular, lymphocytic, multifocal			1 (2%)
Inflammation, granulomatous, multifocal		3 (6%)	4 (8%)
Mixed cell focus			1 (2%)
Necrosis, coagulative, multifocal	3 (6%)		3 (6%)
Vacuolization cytoplasmic, diffuse	1 (2%)		1 (2%)
Vacuolization cytoplasmic, focal	3 (6%)	1 (2%)	1 (2%)
Vacuolization cytoplasmic, multifocal	2 (4%)		
Bile duct, hyperplasia	10 (20%)	15 (30%)	21 (42%)
Bile duct, hyperplasia, multifocal	1 (2%)		
Centrilobular, degeneration	1 (2%)		
Portal, fibrosis	1 (2%)	1 (2%)	
Serosa, fibrosis, focal			1 (2%)
Mesentery	(6)	(9)	(6)
Fibrosis, focal			1 (17%)
Inflammation, granulomatous	1 (17%)		
Pigmentation, hematoidin, hemosiderin			1 (17%)
Artery, inflammation, chronic		1 (11%)	1 (17%)
Artery, mineralization			1 (17%)
Artery, thrombus			1 (17%)
Fat, edema	1 (17%)		
Fat, necrosis, focal	1 (17%)	5 (56%)	3 (50%)
Vein, mineralization		1 (11%)	
Pancreas	(50)	(50)	(49)
Hyperplasia, focal			1 (2%)
Pigmentation, hematoidin, hemosiderin			1 (2%)
Acinus, atrophy	9 (18%)	10 (20%)	15 (31%)
Adventitia, edema	1 (2%)		1 (2%)
Artery, inflammation, chronic		2 (4%)	1 (2%)
Salivary glands	(48)	(50)	(50)
Hyperplasia			1 (2%)
Stomach, forestomach	(49)	(50)	(49)
Edema	2 (4%)		2 (4%)
Inflammation, chronic		3 (6%)	1 (2%)
Inflammation, suppurative			1 (2%)
Mineralization		3 (6%)	3 (6%)
Necrosis	1 (2%)		
Ulcer, focal	1 (2%)		2 (4%)
Stomach, glandular	(49)	(50)	(50)
Edema			1 (2%)
Mineralization	1 (2%)	8 (16%)	14 (28%)

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

	Untreated Control	Low Dose	High Dose
CARDIOVASCULAR SYSTEM			
Blood vessel		(1)	
Aorta, mineralization		1 (100%)	
Heart	(50)	(50)	(50)
Fibrosis, multifocal	44 (88%)	45 (90%)	39 (78%)
Inflammation, suppurative			1 (2%)
Mineralization, multifocal		1 (2%)	
Atrium, thrombus	3 (6%)	3 (6%)	2 (4%)
Valve, bacterium			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(50)	(50)
Fibrosis			1 (2%)
Adrenal gland, cortex	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	
Cyst	1 (2%)		
Hyperplasia, focal	3 (6%)	2 (4%)	
Hypertrophy, focal		2 (4%)	
Necrosis, multifocal	1 (2%)		
Vacuolization cytoplasmic, diffuse		1 (2%)	
Vacuolization cytoplasmic, focal	11 (22%)	6 (12%)	15 (30%)
Vacuolization cytoplasmic, multifocal		1 (2%)	2 (4%)
Adrenal gland, medulla	(50)	(50)	(50)
Angiectasis			1 (2%)
Hemorrhage		1 (2%)	
Hyperplasia, focal	10 (20%)	8 (16%)	7 (14%)
Hyperplasia, multifocal	1 (2%)	2 (4%)	
Mineralization	1 (2%)	1 (2%)	
Parathyroid gland	(49)	(47)	(49)
Hyperplasia	3 (6%)	18 (38%)	23 (47%)
Pituitary gland	(50)	(50)	(50)
Pars distalis, angiectasis	9 (18%)	7 (14%)	14 (28%)
Pars distalis, cyst	1 (2%)	2 (4%)	3 (6%)
Pars distalis, cyst, multiple		1 (2%)	2 (4%)
Pars distalis, hemorrhage			1 (2%)
Pars distalis, hyperplasia, focal	7 (14%)	6 (12%)	5 (10%)
Pars distalis, hyperplasia, multifocal			1 (2%)
Pars distalis, necrosis			1 (2%)
Pars nervosa, infiltration cellular		1 (2%)	
Thyroid gland	(50)	(50)	(50)
Ultimobranchial cyst		1 (2%)	2 (4%)
C-cell, hyperplasia, focal	6 (12%)	2 (4%)	5 (10%)
C-cell, hyperplasia, multifocal	1 (2%)	1 (2%)	
Follicle, cyst	1 (2%)	1 (2%)	
Follicle, cyst, multiple	1 (2%)		
Follicle, hyperplasia, cystic	2 (4%)	1 (2%)	
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Coagulating gland	(1)	(1)	
Hyperplasia		1 (100%)	
Inflammation, chronic	1 (100%)		
Inflammation, suppurative		1 (100%)	

TABE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN (Continued)

	Untreated Control	Low Dose	High Dose
GENITAL SYSTEM (Continued)			
Epididymis	(50)	(50)	(50)
Atypical cells			12 (24%)
Degeneration			1 (2%)
Depletion	40 (80%)	43 (86%)	46 (92%)
Fibrosis		1 (2%)	
Inflammation, granulomatous		1 (2%)	
Preputial gland	(48)	(50)	(47)
Atrophy	1 (2%)		
Fibrosis	7 (15%)	3 (6%)	5 (11%)
Hyperplasia	1 (2%)	1 (2%)	
Inflammation, suppurative	11 (23%)	6 (12%)	
Duct, cyst	9 (19%)	13 (26%)	3 (6%)
Prostate	(50)	(50)	(49)
Cyst		2 (4%)	2 (4%)
Cyst, multiple			3 (6%)
Fibrosis		4 (8%)	
Inflammation		1 (2%)	
Inflammation, chronic	3 (6%)	2 (4%)	
Inflammation, chronic, focal	1 (2%)		
Inflammation, suppurative	24 (48%)	19 (38%)	39 (80%)
Mineralization, focal	1 (2%)		
Mineralization, multifocal			1 (2%)
Epithelium, hyperplasia		1 (2%)	1 (2%)
Seminal vesicle	(50)	(50)	(50)
Atrophy	1 (2%)	8 (16%)	8 (16%)
Dilatation			1 (2%)
Fibrosis		1 (2%)	
Mineralization		1 (2%)	
Epithelium, hyperplasia			4 (8%)
Testes	(50)	(50)	(50)
Aspermatogenesis	38 (76%)	40 (80%)	44 (88%)
Atrophy	41 (82%)	44 (88%)	48 (96%)
Degeneration			36 (72%)
Hemorrhage	1 (2%)		
Mineralization	1 (2%)		
Arteriole, necrosis, fibrinoid	1 (2%)	8 (16%)	15 (30%)
Interstitial cell, hyperplasia	4 (8%)	3 (6%)	2 (4%)
Perivascular, infiltration cellular, mononuclear cell	3 (6%)	9 (18%)	19 (38%)
HEMATOPOIETIC SYSTEM			
Blood	(18)	(13)	(10)
Anemia		1 (8%)	
Hypochromasia	1 (6%)		
Polychromasia	1 (6%)	1 (8%)	1 (10%)
Bone marrow	(50)	(50)	(50)
Atrophy			1 (2%)
Hyperplasia, reticulum cell	2 (4%)		
Myelofibrosis	1 (2%)		2 (4%)
Myeloid cell, hyperplasia	1 (2%)	2 (4%)	
Lymph node	(50)	(50)	(50)
Inguinal, hyperplasia, lymphoid	1 (2%)	2 (4%)	1 (2%)
Mediastinal, angiectasis			2 (4%)
Mediastinal, congestion	1 (2%)	1 (2%)	
Mediastinal, hyperplasia, lymphoid		1 (2%)	2 (4%)
Mediastinal, pigmentation, hemosiderin	1 (2%)		
Pancreatic, hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)
Pancreatic, inflammation, granulomatous			1 (2%)
Pancreatic, mineralization			1 (2%)
Renal, angiectasis			4 (8%)
Renal, hyperplasia, lymphoid		1 (2%)	3 (6%)

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

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Lymph node, mandibular	(46)	(50)	(47)
Angiectasis		1 (2%)	1 (2%)
Cyst	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	4 (9%)	2 (4%)	10 (21%)
Infiltration cellular, plasma cell			1 (2%)
Lymph node, mesenteric	(49)	(48)	(49)
Angiectasis	3 (6%)		3 (6%)
Ectasia		2 (4%)	
Hyperplasia, lymphoid		3 (6%)	4 (8%)
Inflammation, chronic	1 (2%)		
Mineralization			1 (2%)
Spleen	(50)	(50)	(50)
Congestion		4 (8%)	4 (8%)
Fibrosis	1 (2%)		
Fibrosis, diffuse			1 (2%)
Fibrosis, focal	1 (2%)	2 (4%)	6 (12%)
Hematopoietic cell proliferation	3 (6%)	1 (2%)	2 (4%)
Hyperplasia, lymphoid			2 (4%)
Necrosis	1 (2%)		
Pigmentation, hemosiderin			1 (2%)
Thymus	(40)	(36)	(34)
Artery, inflammation			1 (3%)
INTEGUMENTARY SYSTEM			
Mammary gland	(46)	(49)	(46)
Duct, cyst	6 (13%)	11 (22%)	7 (15%)
Skin	(50)	(50)	(50)
Alopecia	2 (4%)		
Cyst epithelial inclusion	2 (4%)	3 (6%)	
Fibrosis, focal		3 (6%)	1 (2%)
Hyperkeratosis, focal	2 (4%)		2 (4%)
Hyperplasia, focal		1 (2%)	2 (4%)
Inflammation, chronic			2 (4%)
Ulcer, focal		1 (2%)	1 (2%)
Prepuce, ulcer	1 (2%)		
Subcutaneous tissue, mineralization, focal		1 (2%)	
Subcutaneous tissue, necrosis, focal			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Fibrous osteodystrophy		5 (10%)	5 (10%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Compression	1 (2%)	2 (4%)	2 (4%)
Cerebellum, degeneration		1 (2%)	
Cerebellum, hemorrhage, acute, multifocal			1 (2%)
Cerebellum, hemorrhage, focal	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Atelectasis	1 (2%)		2 (4%)
Congestion	2 (4%)	2 (4%)	3 (6%)
Hemorrhage, multifocal	1 (2%)	1 (2%)	
Infiltration cellular, lymphocytic, focal			1 (2%)
Infiltration cellular, histiocytic	3 (6%)	8 (16%)	2 (4%)
Inflammation, suppurative		1 (2%)	

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

	Untreated Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung (Continued)	(50)	(50)	(50)
Alveolar epithelium, hyperplasia, focal		1 (2%)	3 (6%)
Alveolar epithelium, hyperplasia, multifocal		1 (2%)	
Alveolus, edema		1 (2%)	1 (2%)
Alveolus, mineralization, multifocal		1 (2%)	
Arteriole, hypertrophy	1 (2%)		
Bronchiole, foreign body		1 (2%)	
Interstitium, edema		1 (2%)	
Interstitium, infiltration cellular, mononuclear cell			1 (2%)
Interstitium, infiltration cellular, histiocytic, diffuse	1 (2%)		
Mediastinum, pigmentation, hemosiderin		1 (2%)	
Nose	(50)	(49)	(48)
Lumen, foreign body		1 (2%)	
Lumen, fungus	2 (4%)		
Lumen, inflammation, suppurative	3 (6%)	1 (2%)	1 (2%)
Nasolacrimal duct, inflammation, suppurative	1 (2%)	4 (8%)	2 (4%)
SPECIAL SENSES SYSTEM			
Eye	(4)	(6)	(22)
Cataract	1 (25%)		14 (64%)
Anterior chamber, hemorrhage			1 (5%)
Anterior chamber, inflammation, suppurative		1 (17%)	1 (5%)
Cornea, infiltration cellular, lymphocytic		1 (17%)	
Cornea, inflammation, granulomatous, focal			1 (5%)
Cornea, mineralization		1 (17%)	
Lens, mineralization			2 (9%)
Retina, degeneration	2 (50%)		17 (77%)
Harderian gland	(1)	(5)	(4)
Atrophy			1 (25%)
Ectasia		2 (40%)	
Fibrosis	1 (100%)	3 (60%)	4 (100%)
Lacrimal gland	(1)		
Atrophy	1 (100%)		
Inflammation, chronic	1 (100%)		
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Embolus bacterial, multifocal			1 (2%)
Infiltration cellular, lymphocytic, multifocal			1 (2%)
Inflammation, chronic		1 (2%)	
Inflammation, suppurative		1 (2%)	1 (2%)
Mineralization		2 (4%)	3 (6%)
Nephropathy, chronic	50 (100%)	48 (96%)	48 (96%)
Cortex, cyst	2 (4%)	2 (4%)	2 (4%)
Cortex, cyst, multiple		3 (6%)	1 (2%)
Cortex, necrosis	1 (2%)		
Medulla, congestion			1 (2%)
Pelvis, hydronephrosis		5 (10%)	2 (4%)
Pelvis, transitional epithelium, hyperplasia		5 (10%)	2 (4%)
Renal tubule, hyperplasia, focal	2 (4%)	2 (4%)	1 (2%)
Renal tubule, pigmentation, hemosiderin	1 (2%)	1 (2%)	
Ureter			(1)
Dilatation			1 (100%)
Urinary bladder	(50)	(50)	(50)
Mucosa, hyperplasia		1 (2%)	2 (4%)
Mucosa, inflammation, chronic		1 (2%)	

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Liver	(50)	(50)	(50)
Leukemia mononuclear	12 (24%)	13 (26%)	9 (18%)
Neoplastic nodule		1 (2%)	
Osteosarcoma, metastatic, bone			1 (2%)
Sarcoma stromal, metastatic, uterus	1 (2%)		
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		1 (2%)
Sarcoma stromal, metastatic, uterus	1 (2%)		
Pancreas	(50)	(48)	(49)
Leukemia mononuclear		1 (2%)	2 (4%)
Sarcoma stromal, metastatic, uterus	1 (2%)		
Acinus, adenoma		1 (2%)	
Salivary glands	(49)	(49)	(50)
Adenocarcinoma			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Leukemia mononuclear	2 (4%)	2 (4%)	2 (4%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(49)	(50)
Adenoma		2 (4%)	1 (2%)
Leukemia mononuclear	4 (8%)	7 (14%)	4 (8%)
Adrenal gland, medulla	(48)	(48)	(50)
Leukemia mononuclear	4 (8%)	4 (8%)	4 (8%)
Pheochromocytoma malignant			1 (2%)
Pheochromocytoma benign	2 (4%)	1 (2%)	4 (8%)
Islets, pancreatic	(50)	(48)	(49)
Carcinoma	1 (2%)		
Parathyroid gland	(49)	(50)	(47)
Adenoma		1 (2%)	
Pituitary gland	(50)	(48)	(48)
Leukemia mononuclear	3 (6%)	3 (6%)	1 (2%)
Pars distalis, adenoma	23 (46%)	16 (33%)	21 (44%)
Pars distalis, carcinoma	3 (6%)	9 (19%)	2 (4%)
Thyroid gland	(50)	(50)	(50)
Leukemia mononuclear		1 (2%)	
C-cell, adenoma	3 (6%)	2 (4%)	2 (4%)
C-cell, adenoma, multiple		1 (2%)	2 (4%)
C-cell, carcinoma	4 (8%)	2 (4%)	2 (4%)
GENERAL BODY SYSTEM			
Tissue, NOS	*(50)	*(50)	*(50)
Osteosarcoma, metastatic, bone			1 (2%)

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

	Untreated Control	Low Dose	High Dose
GENITAL SYSTEM			
Clitoral gland	(44)	(38)	(42)
Adenoma	1 (2%)	7 (18%)	4 (10%)
Carcinoma	4 (9%)	3 (8%)	
Ovary	(50)	(50)	(50)
Leukemia mononuclear		4 (8%)	1 (2%)
Uterus	(50)	(50)	(50)
Leiomyosarcoma			1 (2%)
Leukemia mononuclear	1 (2%)		1 (2%)
Polyp stromal	9 (18%)	16 (32%)	10 (20%)
Polyp stromal, multiple	1 (2%)		
Sarcoma stromal	2 (4%)		
Cervix, sarcoma stromal			1 (2%)
Cervix, squamous cell carcinoma		1 (2%)	
Endometrium, adenoma			2 (4%)
Endometrium, sarcoma stromal		1 (2%)	
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia mononuclear	7 (14%)	1 (2%)	6 (12%)
Bone marrow	(49)	(48)	(50)
Leukemia mononuclear	7 (14%)	4 (8%)	6 (12%)
Sarcoma	1 (2%)		
Lymph node	(50)	(50)	(50)
Inguinal, leukemia mononuclear			1 (2%)
Mediastinal, leukemia mononuclear	2 (4%)		2 (4%)
Pancreatic, leukemia mononuclear	1 (2%)	1 (2%)	1 (2%)
Lymph node, mandibular	(48)	(47)	(50)
Leukemia mononuclear	2 (4%)	3 (6%)	5 (10%)
Lymph node, mesenteric	(50)	(48)	(49)
Leukemia mononuclear	3 (6%)	3 (6%)	3 (6%)
Spleen	(50)	(49)	(50)
Leukemia mononuclear	12 (24%)	13 (27%)	9 (18%)
Sarcoma stromal, metastatic, uterus	1 (2%)		
Thymus	(43)	(34)	(40)
Leukemia mononuclear	1 (2%)		1 (3%)
INTEGUMENTARY SYSTEM			
Mammary gland	(49)	(50)	(50)
Adenocarcinoma	6 (12%)	4 (8%)	
Adenocarcinoma, multiple		1 (2%)	
Fibroadenoma	23 (47%)	16 (32%)	16 (32%)
Fibroadenoma, multiple	5 (10%)	10 (20%)	15 (30%)
Fibrosarcoma	1 (2%)		
Skin	(50)	(49)	(50)
Basal cell carcinoma			1 (2%)
Keratoacanthoma			1 (2%)
Papilloma squamous			1 (2%)
Foot, papilloma squamous		1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)	2 (4%)	
Subcutaneous tissue, fibrosarcoma		1 (2%)	
Subcutaneous tissue, hemangiosarcoma	1 (2%)		
Subcutaneous tissue, leukemia mononuclear	1 (2%)		
Subcutaneous tissue, sarcoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Diaphragm, sarcoma stromal, metastatic, uterus	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Astrocytoma malignant		1 (2%)	
Carcinoma, metastatic, pituitary gland		1 (2%)	1 (2%)
Leukemia mononuclear		3 (6%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)		
Carcinoma, metastatic, thyroid gland			1 (2%)
Leukemia mononuclear	12 (24%)	12 (24%)	8 (16%)
Sarcoma stromal, metastatic, uterus	1 (2%)		
SPECIAL SENSES SYSTEM			
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma	1 (2%)	1 (2%)	
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Leukemia mononuclear	3 (6%)	4 (8%)	2 (4%)
Sarcoma stromal, metastatic, uterus	1 (2%)		
Renal tubule, adenoma			1 (2%)
Urinary bladder	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)		1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	13 (26%)	13 (26%)	9 (18%)
Hemangiosarcoma	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Moribund	22	12	17
Terminal sacrifice	25	26	31
Dead	3	12	2
TUMOR SUMMARY			
Total animals with primary neoplasms **	49	48	46
Total primary neoplasms	109	116	100
Total animals with benign neoplasms	43	41	42
Total benign neoplasms	70	79	82
Total animals with malignant neoplasms	31	28	17
Total malignant neoplasms	39	37	18
Total animals with secondary neoplasms ***	1	1	3
Total secondary neoplasms	7	1	4

* Number of animals receiving complete necropsy examinations; 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 FEED STUDY OF NITROFURANTOIN: UNTREATED CONTROL

WEEKS ON STUDY	062	069	073	082	086	089	091	093	094	095	096	096	097	099	100	101	101	102	103	103	104	104	104	105	105
CARCASS ID	391	331	341	321	371	322	361	311	372	401	402	332	351	323	324	342	333	403	373	404	325	392	374	312	393
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X			X	X									X	X	X		X		X	
Sarcoma stromal, metastatic, uterus						X																			
Mesentery						+													+	+		+		+	
Leukemia mononuclear																						X			
Sarcoma stromal, metastatic, uterus						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus						X																			
Salivary glands	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X				X		
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X						X									X							
Adrenal gland, medulla	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X	X									X							
Pheochromocytoma benign																									X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X		X		X		
Pars distalis, adenoma				X		X	X	X	X	X	X	X	X					X	X				X		
Pars distalis, carcinoma															X					X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									X
C-cell, carcinoma		X																							
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	M	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Carcinoma							X																		X
Ovary	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Polyp stromal							X									X						X			X
Polyp stromal, multiple																									
Sarcoma stromal						X																			
HEMATOPOIETIC SYSTEM																									
Blood		+							+		+							+		+		+		+	+
Leukemia mononuclear		X							X									X		X				X	X
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X			X											X		X				
Sarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear					X																X				
Pancreatic, leukemia mononuclear																			X						
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																X				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																			X		X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X			X	X									X	X	X		X		X	
Sarcoma stromal, metastatic, uterus						X																			
Thymus	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	M	+	+	+	+	M	+	+	+	+
Leukemia mononuclear					X																				

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

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

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	381	313	314	315	334	335	343	344	345	352	353	354	355	362	363	364	365	375	382	383	384	385	394	395	405	TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X																	X							12
Sarcoma stromal, metastatic, uterus																										1
Mesentery	+				+																			+		8
Leukemia mononuclear																										1
Sarcoma stromal, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X																								4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										4
Pheochromocytoma benign											X															2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma										X																1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Pars distalis, adenoma	X		X		X			X	X		X	X				X		X			X	X				23
Pars distalis, carcinoma																							X			3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma												X						X								3
C-cell, carcinoma							X			X														X		4
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Adenoma																										1
Carcinoma																				X				X		4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Polyp stromal									X							X	X		X		X					9
Polyp stromal, multiple														X												1
Sarcoma stromal																	X									2
HEMATOPOIETIC SYSTEM																										
Blood																			+							9
Leukemia mononuclear																			X							7
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	49
Leukemia mononuclear																			X							7
Sarcoma																	X									1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear																										2
Pancreatic, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X																	X							12
Sarcoma stromal, metastatic, uterus																										1
Thymus	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Leukemia mononuclear																										1

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

WEEKS ON STUDY	062	069	073	082	086	089	091	093	094	095	096	096	097	099	100	101	101	102	103	103	104	104	104	105	105
CARCASS ID	391	331	341	321	371	322	361	311	372	401	402	332	351	323	324	342	333	403	373	404	325	392	374	312	393
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma										X								X		X					
Fibroadenoma	X		X					X	X	X				X			X	X	X		X	X		X	
Fibroadenoma, multiple															X	X									
Fibrosarcoma																X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, hemangiosarcoma																						X			
Subcutaneous tissue, leukemia mononuclear					X																				
Subcutaneous tissue, sarcoma																		X							
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+																			
Diaphragm, sarcoma stromal, metastatic, uterus						X																			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																								+	
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma																									
Leukemia mononuclear		X	X		X			X	X								X	X	X		X		X		
Sarcoma stromal, metastatic, uterus						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear					+								+	+			+			+	+				+
Eye					+																				
Harderian gland																									
Zymbal gland														+											
Carcinoma														X											
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X															X							
Sarcoma stromal, metastatic, uterus						X																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	381	313	314	315	334	335	343	344	345	352	353	354	355	362	363	364	365	375	382	383	384	385	394	395	405	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma	X								X										X							6
Fibroadenoma		X		X					X		X		X		X		X	X		X	X			X		23
Fibroadenoma, multiple	X						X									X										5
Fibrosarcoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma			X																							1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, leukemia mononuclear																										1
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Diaphragm, sarcoma stromal, metastatic, uterus																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																									2
Alveolar/bronchiolar carcinoma																									X	1
Leukemia mononuclear		X																	X							12
Sarcoma stromal, metastatic, uterus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear		+												+			•						+			11
Eye																										1
Harderian gland	+																									1
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Sarcoma stromal, metastatic, uterus																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1

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

WEEKS ON STUDY	056	061	063	066	071	072	080	081	081	086	089	091	094	095	095	096	099	102	103	103	104	104	104	104	105
CARCASS ID	581	521	511	601	591	561	571	512	522	551	562	563	592	541	572	531	582	593	583	602	552	532	533	594	523
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Intestine large, colon	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Intestine small	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Intestine small, duodenum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Intestine small, ileum	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Intestine small, jejunum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X		X		X		X	X						X				X					
Neoplastic nodule																								X	
Mesentery										+															
Pancreas	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Leukemia mononuclear																									
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue						+																			
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X						X																		
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Adenoma																								X	
Leukemia mononuclear	X				X		X			X						X				X					
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Leukemia mononuclear							X			X						X									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Pituitary gland	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X				X					
Pars distalis, adenoma									X		X						X					X	X		X
Pars distalis, carcinoma								X						X	X			X						X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
C-cell, adenoma																				X		X			
C-cell, adenoma, multiple																								X	
C-cell, carcinoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS				+															+						
GENITAL SYSTEM																									
Clitoral gland	M	M	M	M	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	A	+	+	+	+
Adenoma											X				X										X
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X					X															
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal										X	X						X		X	X	X	X			
Cervix, squamous cell carcinoma																									
Endometrium, sarcoma stromal		X																							
HEMATOPOIETIC SYSTEM																									
Blood																				+					
Leukemia mononuclear																				X					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Leukemia mononuclear										X										X					
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic, leukemia mononuclear																				X					
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Leukemia mononuclear							X									X				X					
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Leukemia mononuclear							X									X				X					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Leukemia mononuclear	X		X		X		X		X	X						X				X					
Thymus	+	M	M	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	M	+	M	M	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	534	553	564	573	574	513	514	515	524	525	535	542	543	544	545	554	555	565	575	584	585	595	603	604	605	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X							X			X	X					X									13
Neoplastic nodule																										1
Mesentery						+			+	+													+			9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																	X									1
Acinus, adenoma								X																		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Tongue																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																								X		2
Leukemia mononuclear											X															7
Adrenal gland, medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear											X															4
Pheochromocytoma benign		X																								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																X										3
Pars distalis, adenoma		X		X		X	X				X				X	X	X	X				X	X			16
Pars distalis, carcinoma			X		X																				X	9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																	X									1
C-cell, adenoma																										2
C-cell, adenoma, multiple																										1
C-cell, carcinoma				X								X														2
GENERAL BODY SYSTEM																										
Tissue, NOS						+																				3
GENITAL SYSTEM																										
Clitoral gland	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	38
Adenoma								X											X	X					X	7
Carcinoma	X	X																			X					3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X															4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X				X	X	X					X		X		X	X		X					16
Cervix, squamous cell carcinoma				X																						1
Endometrium, sarcoma stromal																										1
HEMATOPOIETIC SYSTEM																										
Blood								+																		2
Leukemia mononuclear																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear								X			X															4
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreatic, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X							X			X	X					X									13
Thymus	+	+	+	+	+	+	+	M	M	M	+	+	M	+	M	+	M	+	+	+	+	+	M	+	+	34

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

WEEKS ON STUDY	056	061	063	066	071	072	080	081	081	086	089	091	094	095	095	096	099	102	103	103	104	104	104	104	105
CARCASS ID	581	521	511	601	591	561	571	512	522	551	562	563	592	541	572	531	582	593	583	602	552	532	533	594	523
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								X	
Adenocarcinoma, multiple																	X								
Fibroadenoma				X				X			X	X		X	X	X	X		X						X
Fibroadenoma, multiple																		X					X		
Skin	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Foot, papilloma squamous																									
Subcutaneous tissue, fibroma													X												
Subcutaneous tissue, fibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																				X					
Carcinoma, metastatic, pituitary gland																									
Leukemia mononuclear	X						X			X															
Spinal cord																		+							
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Leukemia mononuclear	X		X		X		X		X	X						X				X					
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																								+	
Eye	+										+			+		+						+	+		+
Harderian gland												+	+				+	+					+		
Zymbal gland											+														
Carcinoma											X														
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X				X		X									X									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	534	553	564	573	574	513	514	515	524	525	535	542	543	544	545	554	555	565	575	584	585	595	603	604	605	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma					X			X									X									4
Adenocarcinoma, multiple																										1
Fibroadenoma						X	X												X		X		X		X	16
Fibroadenoma, multiple		X	X		X					X	X					X				X				X		10
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Foot, papilloma squamous														X												1
Subcutaneous tissue, fibroma						X																				2
Subcutaneous tissue, fibrosarcoma				X																						1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Carcinoma, metastatic, pituitary gland			X																							1
Leukemia mononuclear																										3
Spinal cord																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																					X					2
Leukemia mononuclear	X							X			X						X									12
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear			+	+	+	+	+	+		+	+		+	+	+	+	+	+			+		+		+	18
Eye		+				+	+	+	+	+	+	+	+	+	+	+	+										19
Harderian gland										+					+				+					+		9
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	057	059	064	064	071	074	080	086	090	093	097	097	097	098	099	100	100	100	101	105	105	105	105	105	105
CARCASS ID	411	471	472	491	431	451	421	432	501	422	502	452	492	441	461	503	423	462	442	433	434	443	412	413	414
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X			X		X	X		X		X								
Osteosarcoma, metastatic, bone																			X						
Mesentery		+					+						●							+			+		
Leukemia mononuclear													X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X						X												
Pharynx					●																				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma		X																							
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X						X												
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Leukemia mononuclear							X					X			X			X							
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X					X			X			X							
Pheochromocytoma malignant					X																				
Pheochromocytoma benign					X																				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Leukemia mononuclear													X												
Pars distalis, adenoma				X			X	X				X	X	X		X	X		X	X		X			
Pars distalis, carcinoma											X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, adenoma, multiple																									
C-cell, carcinoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS																			●						
Osteosarcoma, metastatic, bone																			X						
GENITAL SYSTEM																									
Clitoral gland	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+
Adenoma																		X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Leukemia mononuclear													X												
Polyp stromal																	X	X				X			X
Cervix, sarcoma stromal															X										
Endometrium, adenoma																									
HEMATOPOIETIC SYSTEM																									
Blood				+		+	+			+			+		+		+								
Leukemia mononuclear						X	X			X			X				X								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X						X	X		X		X								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, leukemia mononuclear													X												
Mediastinal, leukemia mononuclear							X								X										
Pancreatic, leukemia mononuclear															X										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X			X		X		X								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X						X												
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X			X		X	X		X		X								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	M
Leukemia mononuclear													X												

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	415	424	425	435	444	445	453	545	555	563	644	655	733	744	755	811	822	833	844	855	933	944	955	504	505	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X								X															9
Osteosarcoma, metastatic, bone																										1
Mesentery	+		+	+											+										+	10
Leukemia mononuclear																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Pharynx																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Leukemia mononuclear																										4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Pheochromocytoma malignant																										1
Pheochromocytoma benign														X				X						X		4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										1
Pars distalis, adenoma	X			X	X		X		X					X			X					X	X	X		21
Pars distalis, carcinoma																									X	2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma													X							X						2
C-cell, adenoma, multiple	X	X																								2
C-cell, carcinoma				X															X							2
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
Osteosarcoma, metastatic, bone																										1
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenoma							X						X								X					4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma														X												1
Leukemia mononuclear																										1
Polyp stromal	X		X											X		X				X			X			10
Cervix, sarcoma stromal																										1
Endometrium, adenoma												X				X										2
HEMATOPOIETIC SYSTEM																										
Blood			+																							8
Leukemia mononuclear			X																							6
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X																							6
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Inguinal, leukemia mononuclear																										1
Mediastinal, leukemia mononuclear																										2
Pancreatic, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										5
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear			X																							3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X								X															9
Thymus	M	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	40
Leukemia mononuclear																										1

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

WEEKS ON STUDY	057	059	064	064	071	074	080	086	090	093	097	097	097	098	099	100	100	100	101	105	105	105	105	105	105
CARCASS ID	411	471	472	491	431	451	421	432	501	422	502	452	492	441	461	503	423	462	442	433	434	443	412	413	414
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma				X					X		X			X		X	X		X				X	X	X
Fibroadenoma, multiple												X								X	X	X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																X									
Keratoacanthoma											X														
Papilloma squamous																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland											X														
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Carcinoma, metastatic, thyroid gland																									
Leukemia mononuclear						X	X			X		X	X		X		X								
Nose	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear							+				+														
Eye								+			+												+		
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X		X										
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X												

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	415	424	425	435	444	445	453	454	455	463	464	465	473	474	475	481	482	483	484	485	493	494	495	504	505	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma	X				X								X			X	X		X							16
Fibroadenoma, multiple		X		X		X	X	X	X					X				X		X		X			X	15
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Keratoacanthoma																										1
Papilloma squamous																X										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X													2
Carcinoma, metastatic, thyroid gland																			X							1
Leukemia mononuclear			X																							8
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear	+												+	+												5
Eye							+	+															+			6
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Renal tubule, adenoma												X														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Control	600 ppm	1,300 ppm
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	2/48 (4%)	1/48 (2%)	(b) 4/50 (8%)
Adjusted Rates (c)	7.6%	4.0%	11.6%
Terminal Rates (d)	1/25 (4%)	1/25 (4%)	3/31 (10%)
Day of First Observation	729	730	491
Life Table Tests (e)	P=0.297	P=0.504N	P=0.413
Logistic Regression Tests (e)	P=0.235	P=0.520N	P=0.353
Cochran-Armitage Trend Test (e)	P=0.244		
Fisher Exact Test (e)		P=0.500N	P=0.359
Clitoral Gland: Adenoma			
Overall Rates (a)	1/44 (2%)	7/38 (18%)	4/42 (10%)
Adjusted Rates (c)	2.4%	26.8%	13.3%
Terminal Rates (d)	0/23 (0%)	5/22 (23%)	3/28 (11%)
Day of First Observation	658	621	700
Life Table Tests (e)	P=0.270	P=0.027	P=0.212
Logistic Regression Tests (e)	P=0.189	P=0.018	P=0.163
Cochran-Armitage Trend Test (e)	P=0.191		
Fisher Exact Test (e)		P=0.017	P=0.166
Clitoral Gland: Carcinoma			
Overall Rates (a)	4/44 (9%)	3/38 (8%)	0/42 (0%)
Adjusted Rates (c)	14.1%	13.6%	0.0%
Terminal Rates (d)	2/23 (9%)	3/22 (14%)	0/28 (0%)
Day of First Observation	633	730	
Life Table Tests (e)	P=0.036N	P=0.532N	P=0.052N
Logistic Regression Tests (e)	P=0.057N	P=0.607N	P=0.069N
Cochran-Armitage Trend Test (e)	P=0.055N		
Fisher Exact Test (e)		P=0.583N	P=0.064N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	5/44 (11%)	10/38 (26%)	4/42 (10%)
Adjusted Rates (c)	16.1%	39.7%	13.3%
Terminal Rates (d)	2/23 (9%)	8/22 (36%)	3/28 (11%)
Day of First Observation	633	621	700
Life Table Tests (e)	P=0.315N	P=0.107	P=0.436N
Logistic Regression Tests (e)	P=0.449N	P=0.063	P=0.532N
Cochran-Armitage Trend Test (e)	P=0.443N		
Fisher Exact Test (e)		P=0.072	P=0.530N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (c)	11.1%	6.4%	5.8%
Terminal Rates (d)	2/25 (8%)	1/26 (4%)	1/31 (3%)
Day of First Observation	727	665	686
Life Table Tests (e)	P=0.365N	P=0.499N	P=0.439N
Logistic Regression Tests (e)	P=0.432N	P=0.534N	P=0.512N
Cochran-Armitage Trend Test (e)	P=0.418N		
Fisher Exact Test (e)		P=0.500N	P=0.500N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	28/50 (56%)	26/50 (52%)	31/50 (62%)
Adjusted Rates (c)	70.4%	69.0%	79.2%
Terminal Rates (d)	14/25 (56%)	15/26 (58%)	23/31 (74%)
Day of First Observation	428	456	448
Life Table Tests (e)	P=0.503N	P=0.449N	P=0.517N
Logistic Regression Tests (e)	P=0.230	P=0.507N	P=0.262
Cochran-Armitage Trend Test (e)	P=0.297		
Fisher Exact Test (e)		P=0.421N	P=0.342

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

	Control	600 ppm	1,300 ppm
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (c)	19.4%	17.2%	0.0%
Terminal Rates (d)	3/25 (12%)	3/26 (12%)	0/31 (0%)
Day of First Observation	661	687	
Life Table Tests (e)	P=0.013N	P=0.497N	P=0.015N
Logistic Regression Tests (e)	P=0.018N	P=0.553N	P=0.019N
Cochran-Armitage Trend Test (e)	P=0.016N		
Fisher Exact Test (e)		P=0.500N	P=0.013N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	23/50 (46%)	16/48 (33%)	21/48 (44%)
Adjusted Rates (c)	59.1%	50.4%	51.7%
Terminal Rates (d)	11/25 (44%)	11/26 (42%)	12/31 (39%)
Day of First Observation	568	567	448
Life Table Tests (e)	P=0.264N	P=0.148N	P=0.293N
Logistic Regression Tests (e)	P=0.492N	P=0.163N	P=0.501N
Cochran-Armitage Trend Test (e)	P=0.471N		
Fisher Exact Test (e)		P=0.141N	P=0.492N
Pituitary Gland/Pars Distalis: Carcinoma			
Overall Rates (a)	3/50 (6%)	9/48 (19%)	2/48 (4%)
Adjusted Rates (c)	9.7%	26.9%	5.6%
Terminal Rates (d)	1/25 (4%)	4/26 (15%)	1/31 (3%)
Day of First Observation	700	564	675
Life Table Tests (e)	P=0.342N	P=0.069	P=0.462N
Logistic Regression Tests (e)	P=0.426N	P=0.048	P=0.527N
Cochran-Armitage Trend Test (e)	P=0.417N		
Fisher Exact Test (e)		P=0.052	P=0.520N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	26/50 (52%)	25/48 (52%)	23/48 (48%)
Adjusted Rates (c)	64.3%	68.6%	55.4%
Terminal Rates (d)	12/25 (48%)	15/26 (58%)	13/31 (42%)
Day of First Observation	568	564	448
Life Table Tests (e)	P=0.192N	P=0.524N	P=0.236N
Logistic Regression Tests (e)	P=0.407N	P=0.524	P=0.435N
Cochran-Armitage Trend Test (e)	P=0.381N		
Fisher Exact Test (e)		P=0.577	P=0.420N
Skin: Fibroma or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (c)	4.0%	10.1%	0.0%
Terminal Rates (d)	1/25 (4%)	2/26 (8%)	0/31 (0%)
Day of First Observation	730	653	
Life Table Tests (e)	P=0.313N	P=0.307	P=0.457N
Logistic Regression Tests (e)	P=0.368N	P=0.280	P=0.457N
Cochran-Armitage Trend Test (e)	P=0.357N		
Fisher Exact Test (e)		P=0.301	P=0.500N
Skin: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (c)	6.9%	10.1%	0.0%
Terminal Rates (d)	1/25 (4%)	2/26 (8%)	0/31 (0%)
Day of First Observation	709	653	
Life Table Tests (e)	P=0.169N	P=0.502	P=0.223N
Logistic Regression Tests (e)	P=0.202N	P=0.469	P=0.243N
Cochran-Armitage Trend Test (e)	P=0.192N		
Fisher Exact Test (e)		P=0.500	P=0.247N

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

	Control	600 ppm	1,300 ppm
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (c)	11.4%	10.2%	12.9%
Terminal Rates (d)	2/25 (8%)	0/26 (0%)	4/31 (13%)
Day of First Observation	729	726	730
Life Table Tests (e)	P=0.514	P=0.656N	P=0.611
Logistic Regression Tests (e)	P=0.434	P=0.656	P=0.547
Cochran-Armitage Trend Test (e)	P=0.423		
Fisher Exact Test (e)		P=0.661N	P=0.500
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (c)	13.8%	7.7%	6.5%
Terminal Rates (d)	3/25 (12%)	2/26 (8%)	2/31 (6%)
Day of First Observation	481	730	730
Life Table Tests (e)	P=0.199N	P=0.326N	P=0.262N
Logistic Regression Tests (e)	P=0.276N	P=0.344N	P=0.338N
Cochran-Armitage Trend Test (e)	P=0.265N		
Fisher Exact Test (e)		P=0.339N	P=0.339N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (c)	24.5%	17.1%	19.4%
Terminal Rates (d)	5/25 (20%)	2/26 (8%)	6/31 (19%)
Day of First Observation	481	726	730
Life Table Tests (e)	P=0.329N	P=0.372N	P=0.356N
Logistic Regression Tests (e)	P=0.476N	P=0.425N	P=0.527N
Cochran-Armitage Trend Test (e)	P=0.453N		
Fisher Exact Test (e)		P=0.380N	P=0.500N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	10/50 (20%)	16/50 (32%)	10/50 (20%)
Adjusted Rates (c)	32.8%	47.2%	30.2%
Terminal Rates (d)	6/25 (24%)	9/26 (35%)	8/31 (26%)
Day of First Observation	633	601	700
Life Table Tests (e)	P=0.377N	P=0.142	P=0.456N
Logistic Regression Tests (e)	P=0.543	P=0.081	P=0.574
Cochran-Armitage Trend Test (e)	P=0.522N		
Fisher Exact Test (e)		P=0.127	P=0.598N
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	13/50 (26%)	13/50 (26%)	9/50 (18%)
Adjusted Rates (c)	32.6%	33.7%	21.9%
Terminal Rates (d)	2/25 (8%)	5/26 (19%)	2/31 (6%)
Day of First Observation	481	390	513
Life Table Tests (e)	P=0.201N	P=0.545	P=0.243N
Logistic Regression Tests (e)	P=0.147N	P=0.447N	P=0.191N
Cochran-Armitage Trend Test (e)	P=0.200N		
Fisher Exact Test (e)		P=0.590N	P=0.235N

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

TABLE B4a. HISTORICAL INCIDENCE OF CLITORAL GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
HC Blue No. 2	0/50	0/50	0/50
C.I. Disperse Blue 1	1/49	2/49	3/49
Eugenol	0/40	1/40	1/40
Stannous chloride	0/50	0/50	0/50
D-Mannitol	1/50	0/50	1/50
Ziram	2/50	3/50	5/50
Propyl gallate	2/50	0/50	2/50
Zearalenone	0/50	1/50	1/50
HC Blue No. 1	1/50	3/50	4/50
TOTAL	7/439 (1.6%)	10/439 (2.3%)	17/439 (3.9%)
SD (b)	1.67%	2.55%	3.51%
Range (c)			
High	2/50	3/50	5/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	(d) 39/1,984 (2.0%)	(e) 57/1,984 (2.9%)	(d,e) 96/1,984 (4.8%)
SD (b)	2.31%	2.95%	3.40%
Range (c)			
High	5/49	6/49	6/49
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one cystadenoma, NOS
(e) Includes five squamous cell carcinomas and five adenocarcinomas, NOS

TABLE B4b. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Adenocarcinoma	Adenoma or Adenocarcinoma
Historical Incidence at Southern Research Institute			
HC Blue No. 2	1/50	1/50	2/50
C.I. Disperse Blue 1	0/49	0/49	0/49
Eugenol	0/40	0/40	0/40
Stannous chloride	1/50	3/50	4/50
D-Mannitol	0/50	3/50	3/50
Ziram	0/50	3/50	3/50
Propyl gallate	0/50	1/50	1/50
Zearalenone	0/50	1/50	1/50
HC Blue No. 1	0/50	3/50	3/50
TOTAL	2/439 (0.5%)	15/439 (3.4%)	17/439 (3.9%)
SD (b)	0.88%	2.65%	2.91%
Range (c)			
High	1/50	3/50	4/50
Low	0/50	0/49	0/49
Overall Historical Incidence			
TOTAL	13/1,984 (0.7%)	(d) 51/1,984 (2.6%)	(d) 64/1,984 (3.2%)
SD (b)	1.32%	2.32%	2.81%
Range (c)			
High	3/49	4/49	7/49
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one squamous cell carcinoma, six papillary adenocarcinomas, and two papillary cystadenocarcinomas, NOS

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

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(50)	(48)	(48)
Parasite metazoan		1 (2%)	1 (2%)
Submucosa, edema, diffuse	1 (2%)		
Submucosa, hemorrhage, multifocal	1 (2%)		
Submucosa, inflammation, diffuse	1 (2%)		
Intestine large, colon	(50)	(46)	(48)
Parasite metazoan	6 (12%)	3 (7%)	2 (4%)
Mucosa, mineralization		1 (2%)	
Intestine large, rectum	(50)	(47)	(47)
Parasite metazoan			1 (2%)
Liver	(50)	(50)	(50)
Angiectasis, focal	1 (2%)		
Basophilic focus, multiple	10 (20%)	8 (16%)	10 (20%)
Clear cell focus	1 (2%)		1 (2%)
Cytologic alterations, focal	1 (2%)		1 (2%)
Developmental malformation	2 (4%)	4 (8%)	1 (2%)
Focal cellular change			1 (2%)
Hematopoietic cell proliferation			1 (2%)
Hyperplasia, focal	1 (2%)		
Infiltration cellular, lymphocytic, multifocal	2 (4%)	1 (2%)	
Inflammation, granulomatous, focal	2 (4%)		2 (4%)
Inflammation, granulomatous, multifocal	2 (4%)	5 (10%)	7 (14%)
Necrosis, coagulative, diffuse		1 (2%)	
Necrosis, coagulative, focal	2 (4%)		2 (4%)
Vacuolization cytoplasmic, diffuse		5 (10%)	2 (4%)
Vacuolization cytoplasmic, focal	3 (6%)	1 (2%)	1 (2%)
Vacuolization cytoplasmic, multifocal	2 (4%)	2 (4%)	1 (2%)
Bile duct, hyperplasia	1 (2%)	7 (14%)	4 (8%)
Centrilobular, congestion		1 (2%)	
Kupffer cell, pigmentation, bile		1 (2%)	
Mesentery	(8)	(9)	(10)
Hemorrhage, focal			1 (10%)
Infiltration cellular, lymphocytic		1 (11%)	
Inflammation, granulomatous, focal		1 (11%)	
Fat, fibrosis, focal			1 (10%)
Fat, necrosis, focal	6 (75%)	7 (78%)	8 (80%)
Pancreas	(50)	(48)	(49)
Acinus, atrophy			1 (2%)
Acinus, atrophy, focal	5 (10%)	5 (10%)	8 (16%)
Acinus, atrophy, multifocal	1 (2%)		
Acinus, hyperplasia, focal		2 (4%)	1 (2%)
Duct, cyst	1 (2%)		
Pharynx			(1)
Hyperplasia			1 (100%)
Inflammation, suppurative			1 (100%)
Stomach	(50)	(48)	(50)
Inflammation, chronic	1 (2%)	1 (2%)	
Stomach, forestomach	(50)	(48)	(50)
Cyst		1 (2%)	
Edema	3 (6%)	3 (6%)	2 (4%)
Hyperkeratosis		2 (4%)	1 (2%)
Hyperplasia		2 (4%)	
Inflammation, chronic		1 (2%)	1 (2%)
Mineralization		1 (2%)	
Ulcer, focal	3 (6%)	3 (6%)	1 (2%)
Epithelium, hyperplasia			1 (2%)

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

	Untreated Control	Low Dose	High Dose
ALIMENTARY SYSTEM (Continued)			
Stomach, glandular	(50)	(48)	(50)
Dysplasia, focal			1 (2%)
Erosion	1 (2%)		2 (4%)
Mineralization		2 (4%)	3 (6%)
Necrosis, focal			1 (2%)
Ulcer		1 (2%)	
Tongue		(1)	
Inflammation		1 (100%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Fibrosis, multifocal	33 (66%)	34 (68%)	25 (50%)
Inflammation, multifocal	1 (2%)	1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(49)	(50)
Angiectasis	6 (12%)	5 (10%)	1 (2%)
Congestion	1 (2%)		
Cyst	1 (2%)		
Degeneration, fatty, focal	2 (4%)	5 (10%)	7 (14%)
Hemorrhage, diffuse		1 (2%)	
Hemorrhage, focal		1 (2%)	
Hyperplasia, focal	3 (6%)	3 (6%)	6 (12%)
Hypertrophy, focal			1 (2%)
Necrosis		2 (4%)	
Vacuolization cytoplasmic, diffuse	1 (2%)		
Vacuolization cytoplasmic, focal	4 (8%)		2 (4%)
Extra adrenal tissue, accessory adrenal cortical nodule	1 (2%)		
Adrenal gland, medulla	(48)	(48)	(50)
Angiectasis	1 (2%)	1 (2%)	1 (2%)
Cyst, multiple	1 (2%)		
Hyperplasia, focal		2 (4%)	1 (2%)
Infiltration cellular, lymphocytic, multifocal		1 (2%)	
Parathyroid gland	(49)	(50)	(47)
Hyperplasia			1 (2%)
Pituitary gland	(50)	(48)	(48)
Pars distalis, angiectasis	26 (52%)	24 (50%)	26 (54%)
Pars distalis, cyst	8 (16%)	8 (17%)	4 (8%)
Pars distalis, cyst, multiple	5 (10%)	1 (2%)	3 (6%)
Pars distalis, hemorrhage	1 (2%)	1 (2%)	
Pars distalis, hyperplasia, focal	2 (4%)	7 (15%)	5 (10%)
Pars distalis, necrosis	1 (2%)		
Pars distalis, pigmentation	1 (2%)		
Thyroid gland	(50)	(50)	(50)
Ultimobranchial cyst	1 (2%)	3 (6%)	
C-cell, hyperplasia, focal	5 (10%)	9 (18%)	4 (8%)
C-cell, hyperplasia, multifocal	3 (6%)	5 (10%)	2 (4%)
Follicle, cyst	1 (2%)		
Follicle, hyperplasia, cystic			1 (2%)
GENERAL BODY SYSTEM			
Tissue, NOS		(3)	(1)
Hemorrhage		1 (33%)	

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

	Untreated Control	Low Dose	High Dose
GENITAL SYSTEM			
Clitoral gland	(44)	(38)	(42)
Inflammation, suppurative	2 (5%)	5 (13%)	1 (2%)
Duct, cyst	12 (27%)	13 (34%)	7 (17%)
Ovary	(50)	(50)	(50)
Cyst	2 (4%)	1 (2%)	
Uterus	(50)	(50)	(50)
Hemorrhage, chronic, focal	1 (2%)		
Hydrometria		2 (4%)	2 (4%)
Cervix, abscess		4 (8%)	2 (4%)
Cervix, cyst	2 (4%)	5 (10%)	1 (2%)
Cervix, cyst, multiple		1 (2%)	
Cervix, inflammation, suppurative	1 (2%)	4 (8%)	3 (6%)
Endometrium, cyst	1 (2%)		
Endometrium, hyperplasia, cystic	5 (10%)	10 (20%)	10 (20%)
Endometrium, inflammation, suppurative		2 (4%)	1 (2%)
Endometrium, necrosis, focal		1 (2%)	
Lumen, inflammation, suppurative		1 (2%)	
Muscularis, cyst			1 (2%)
HEMATOPOIETIC SYSTEM			
Blood	(9)	(2)	(8)
Anemia	1 (11%)		
Anisocytosis			1 (13%)
Bone marrow	(49)	(48)	(50)
Hyperplasia, reticulum cell	1 (2%)		2 (4%)
Myelofibrosis		2 (4%)	1 (2%)
Myeloid cell, hyperplasia		2 (4%)	4 (8%)
Lymph node	(50)	(50)	(50)
Axillary, hyperplasia, lymphoid		1 (2%)	1 (2%)
Axillary, infiltration cellular, plasma cell			1 (2%)
Axillary, infiltration cellular, histiocytic			1 (2%)
Iliac, hyperplasia, lymphoid		1 (2%)	
Inguinal, hyperplasia, lymphoid	1 (2%)		
Mediastinal, congestion	1 (2%)	1 (2%)	
Mediastinal, erythrophagocytosis			1 (2%)
Mediastinal, hyperplasia, lymphoid	1 (2%)		
Renal, sinus, ectasia		1 (2%)	
Lymph node, mandibular	(48)	(47)	(50)
Erythrophagocytosis			1 (2%)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	1 (2%)
Infiltration cellular, plasma cell			2 (4%)
Inflammation, suppurative	1 (2%)		
Lymph node, mesenteric	(50)	(48)	(49)
Angiectasis	1 (2%)	1 (2%)	
Erythrophagocytosis			1 (2%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
Infiltration cellular, histiocytic		1 (2%)	1 (2%)
Spleen	(50)	(49)	(50)
Atrophy		1 (2%)	
Congestion	1 (2%)	4 (8%)	2 (4%)
Fibrosis		1 (2%)	
Hematopoietic cell proliferation	4 (8%)	6 (12%)	8 (16%)
Hemorrhage			1 (2%)
Hyperplasia, lymphoid, focal		2 (4%)	
Necrosis, coagulative			1 (2%)
Pigmentation, hemosiderin	1 (2%)	1 (2%)	1 (2%)
Thymus	(43)	(34)	(40)
Congestion		1 (3%)	
Hyperplasia, lymphoid		1 (3%)	

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

	Untreated Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Mammary gland	(49)	(50)	(50)
Hyperplasia, cystic	5 (10%)	19 (38%)	11 (22%)
Hyperplasia, lobular	5 (10%)	5 (10%)	3 (6%)
Duct, cyst	38 (78%)	33 (66%)	39 (78%)
Skin	(50)	(49)	(50)
Cyst epithelial inclusion	1 (2%)	1 (2%)	
Hyperkeratosis, focal		2 (4%)	1 (2%)
Hyperplasia, focal		1 (2%)	
Subcutaneous tissue, cyst		1 (2%)	
Subcutaneous tissue, inflammation, suppurative		2 (4%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Osteopetrosis	1 (2%)		
Cranium, hyperostosis	4 (8%)	4 (8%)	5 (10%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Compression	6 (12%)	2 (4%)	1 (2%)
Degeneration, multifocal	1 (2%)	1 (2%)	3 (6%)
Hemorrhage, focal		1 (2%)	
Hemorrhage, multifocal		1 (2%)	1 (2%)
Hydrocephalus		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Angiectasis			2 (4%)
Congestion	1 (2%)	4 (8%)	4 (8%)
Edema		1 (2%)	
Infiltration cellular, lymphocytic, multifocal		2 (4%)	
Infiltration cellular, histiocytic, focal	2 (4%)	3 (6%)	5 (10%)
Inflammation, chronic	4 (8%)	2 (4%)	1 (2%)
Alveolar epithelium, hyperplasia, focal		1 (2%)	2 (4%)
Alveolar epithelium, hyperplasia, multifocal			1 (2%)
Bronchiole, inflammation, chronic active			1 (2%)
Bronchiole, inflammation, suppurative			1 (2%)
Interstitium, edema		2 (4%)	
Nose	(50)	(49)	(47)
Lumen, foreign body	1 (2%)	1 (2%)	1 (2%)
Lumen, fungus	2 (4%)		1 (2%)
Lumen, inflammation, suppurative	4 (8%)	1 (2%)	3 (6%)
Nasolacrimal duct, inflammation, suppurative		5 (10%)	4 (9%)
Trachea	(50)	(50)	(50)
Infiltration cellular, lymphocytic	1 (2%)		
SPECIAL SENSES SYSTEM			
Ear	(11)	(18)	(5)
Middle ear, inflammation, suppurative	1 (9%)		
Eye	(1)	(19)	(6)
Cataract		16 (84%)	2 (33%)
Inflammation, suppurative	1 (100%)	1 (5%)	
Synechia			1 (17%)
Cornea, edema			2 (33%)
Lens, mineralization		2 (11%)	
Retina, degeneration		17 (89%)	3 (50%)
Harderian gland	(1)	(9)	
Fibrosis	1 (100%)	8 (89%)	
Infiltration cellular, lymphocytic, multifocal		1 (11%)	

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

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Mineralization, multifocal	1 (2%)	1 (2%)	
Nephropathy, chronic	44 (88%)	40 (80%)	48 (96%)
Pigmentation, hemosiderin		1 (2%)	
Cortex, fibrosis, focal		1 (2%)	
Pelvis, hydronephrosis		1 (2%)	
Pelvis, infiltration cellular, lymphocytic	1 (2%)		
Renal tubule, degeneration	1 (2%)	2 (4%)	
Renal tubule, hyperplasia, focal		1 (2%)	1 (2%)
Renal tubule, pigmentation, hemosiderin	1 (2%)	2 (4%)	2 (4%)
Urinary bladder	(50)	(50)	(50)
Mucosa, hyperplasia, diffuse			1 (2%)

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(49)	(49)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Intestine small, ileum	(47)	(43)	(47)
Lymphoma malignant mixed			1 (2%)
Intestine small, jejunum	(49)	(45)	(49)
Lymphoma malignant lymphocytic		1 (2%)	
Liver	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
Hemangiosarcoma, multiple	1 (2%)		
Hepatocellular carcinoma	8 (16%)	6 (12%)	7 (14%)
Hepatocellular carcinoma, multiple	1 (2%)	1 (2%)	
Hepatocellular adenoma	1 (2%)	4 (8%)	3 (6%)
Hepatocellular adenoma, multiple	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant histiocytic		2 (4%)	1 (2%)
Lymphoma malignant lymphocytic	3 (6%)		
Lymphoma malignant mixed			1 (2%)
Mesentery	*(50)	*(50)	*(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Lymphoma malignant histiocytic		1 (2%)	1 (2%)
Pancreas	(50)	(49)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Stomach, forestomach	(49)	(48)	(49)
Fibrosarcoma	1 (2%)		
Squamous cell carcinoma	1 (2%)		
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(49)	(50)
Adenoma		1 (2%)	
Spindle cell, carcinoma		1 (2%)	
Adrenal gland, medulla	(49)	(48)	(49)
Pheochromocytoma malignant	2 (4%)		
Pheochromocytoma benign	4 (8%)		1 (2%)
Islets, pancreatic	(50)	(49)	(50)
Adenoma		1 (2%)	
Thyroid gland	(48)	(47)	(48)
Follicular cell, adenoma	2 (4%)		
GENERAL BODY SYSTEM			
None			

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

	Untreated Control	Low Dose	High Dose
GENITAL SYSTEM			
Epididymis	(50)	(49)	(50)
Lymphoma malignant lymphocytic			1 (2%)
Preputial gland	*(50)	*(50)	*(50)
Hemangiosarcoma	1 (2%)		
Testes	(49)	(49)	(50)
Interstitial cell, adenoma, multiple	1 (2%)		
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia	1 (2%)		
Bone marrow	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
Lymph node	(50)	(49)	(49)
Lymphoma malignant lymphocytic	1 (2%)		
Bronchial, lymphoma malignant lymphocytic	1 (2%)		
Bronchial, mediastinal, fibrosarcoma, metastatic, stomach	1 (2%)		
Pancreatic, lymphoma malignant mixed			1 (2%)
Renal, lymphoma malignant lymphocytic		1 (2%)	
Lymph node, mandibular	(45)	(41)	(46)
Lymphoma malignant lymphocytic	1 (2%)		
Bronchial, mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Lymph node, mesenteric	(47)	(46)	(44)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	3 (6%)	1 (2%)	
Lymphoma malignant mixed			2 (5%)
Spleen	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)		
Lymphoma malignant histiocytic		2 (4%)	1 (2%)
Lymphoma malignant lymphocytic	4 (8%)	1 (2%)	1 (2%)
Lymphoma malignant mixed			2 (4%)
Thymus	(44)	(43)	(41)
Lymphoma malignant lymphocytic	2 (5%)		
Mediastinum, fibrosarcoma, metastatic, skin			1 (2%)
INTEGUMENTARY SYSTEM			
Skin	(50)	(50)	(50)
Melanoma benign		1 (2%)	
Squamous cell carcinoma		1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	3 (6%)
Subcutaneous tissue, fibroma, multiple		1 (2%)	
Subcutaneous tissue, fibrosarcoma	7 (14%)	5 (10%)	11 (22%)
Subcutaneous tissue, fibrosarcoma, multiple	2 (4%)		1 (2%)
Subcutaneous tissue, schwannoma malignant	2 (4%)		
Subcutaneous tissue, schwannoma malignant, multiple	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Fibrosarcoma, metastatic, stomach	1 (2%)		
Diaphragm, intercostal, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	2 (4%)	4 (8%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)
Fibrosarcoma, metastatic, stomach	1 (2%)		
Hepatocellular carcinoma, metastatic, liver	1 (2%)	2 (4%)	1 (2%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	3 (6%)		
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenoma	2 (4%)	3 (6%)	2 (4%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Fibrosarcoma, metastatic, stomach	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed			1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic	5 (10%)	1 (2%)	1 (2%)
Hemangiosarcoma	3 (6%)	1 (2%)	
Leukemia	1 (2%)		
Lymphoma malignant histiocytic		2 (4%)	1 (2%)
Lymphoma malignant mixed			4 (8%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Dead	7	12	2
Terminal sacrifice	28	29	33
Moribund	15	9	15
TUMOR SUMMARY			
Total animals with primary neoplasms **	31	27	33
Total primary neoplasms	52	35	42
Total animals with benign neoplasms	12	11	14
Total benign neoplasms	17	15	14
Total animals with malignant neoplasms	28	20	24
Total malignant neoplasms	35	20	28
Total animals with secondary neoplasms ***	1	2	3
Total secondary neoplasms	5	2	6

* Number of animals receiving complete necropsy examinations; 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 FEED STUDY OF NITROFURANTOIN: UNTREATED CONTROL

WEEKS ON STUDY	008	009	009	012	019	030	059	065	066	066	068	077	088	091	093	095	099	099	100	102	102	102	105	105	105
CARCASS ID	011	101	102	061	041	051	042	031	032	071	082	103	104	033	105	043	021	022	062	091	044	092	023	012	013
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																			X						
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple																									
Hepatocellular carcinoma													X	X				X							X
Hepatocellular carcinoma, multiple															X										
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Lymphoma malignant lymphocytic																			X		X				
Mesentery					+										+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma														X											
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																+					+			+	
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																					X				
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																						X			
Pheochromocytoma benign																		X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	M	+	+	M	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Thyroid gland	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma											X														
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland		M																							
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																								+	
Preputial gland	+								+	+							+		+				+		
Hemangiosarcoma																									
Prostate	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+			+							+								+		+				
Testes	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma, multiple																									

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

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

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	014	015	024	025	034	035	045	052	053	054	055	063	064	065	072	073	074	075	081	083	084	085	093	094	095	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Gallbladder	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple																									X	1
Hepatocellular carcinoma									X		X					X	X									8
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma									X																	1
Hepatocellular adenoma, multiple																	X									1
Lymphoma malignant lymphocytic																							X			3
Mesentery																+										3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																										1
Squamous cell carcinoma				X																						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth		+		+	+	+						+		+								+				10
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant										X																2
Pheochromocytoma benign								X	X							X										4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma		X																								2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis		+																								2
Preputial gland						+		+			+															9
Hemangiosarcoma								X																		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle																+										6
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell, adenoma, multiple				X																						1

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

WEEKS ON STUDY	008	009	009	012	019	030	059	065	066	066	068	077	088	091	093	095	099	099	100	102	102	102	105	105	105
CARCASS ID	011	101	102	061	041	051	042	031	032	071	082	103	104	033	105	043	021	022	062	091	044	092	023	012	013
HEMATOPOIETIC SYSTEM																									
Blood																									
Leukemia																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Bronchial, lymphoma malignant lymphocytic																			X						
Bronchial, mediastinal, fibrosarcoma, metastatic, stomach														X											
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymphoma malignant lymphocytic																			X						
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+
Lymphoma malignant lymphocytic																					X				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Lymphoma malignant lymphocytic																			X						
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Lymphoma malignant lymphocytic																			X		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	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																		X							
Subcutaneous tissue, fibrosarcoma							X			X						X				X			X		
Subcutaneous tissue, fibrosarcoma, multiple																						X			
Subcutaneous tissue, schwannoma malignant																	X								
Subcutaneous tissue, schwannoma malignant, multiple												X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle														+											
Fibrosarcoma, metastatic, stomach														X											
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																			X						
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X					X	X						
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic, stomach														X											
Hepatocellular carcinoma, metastatic, liver														X											
Lymphoma malignant lymphocytic																			X		X				
Nose	M	M	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, stomach														X											
Lymphoma malignant lymphocytic																									
Ureter															+										
Urethra	+															+									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	014	015	024	025	034	035	045	052	053	054	055	063	064	065	072	073	074	075	081	083	084	085	093	094	095	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood		+																					+			2
Leukemia																							X			1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																							X			1
Bronchial, lymphoma malignant lymphocytic																										1
Bronchial, mediastinal, fibrosarcoma, metastatic, stomach																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Lymphoma malignant lymphocytic																										1
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic									X						X											3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymphoma malignant lymphocytic									X						X								X			4
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	M	+	44
Lymphoma malignant lymphocytic																										2
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	+	6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma		X								X																7
Subcutaneous tissue, fibrosarcoma, multiple																X										2
Subcutaneous tissue, schwannoma malignant																								X		2
Subcutaneous tissue, schwannoma malignant, multiple																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Fibrosarcoma, metastatic, stomach																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X					X					5
Alveolar/bronchiolar carcinoma														X												1
Fibrosarcoma, metastatic, stomach																										1
Hepatocellular carcinoma, metastatic, liver																										1
Lymphoma malignant lymphocytic																							X			3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Harderian gland			+					+																		2
Adenoma			X					X																		2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, stomach																										1
Lymphoma malignant lymphocytic									X																	1
Ureter																										1
Urethra																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	0 0 8	0 2 3	0 2 7	0 3 4	0 4 8	0 5 4	0 7 1	0 7 6	0 8 2	0 8 3	0 8 6	0 8 7	0 8 8	0 8 9	0 9 1	0 9 5	0 9 7	1 0 0	1 0 2	1 0 4	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	2 7 1	2 2 1	2 6 1	2 2 2	2 5 1	2 6 2	2 4 1	2 3 1	2 5 2	2 3 2	2 4 2	2 8 1	3 0 1	2 9 1	2 3 3	2 6 3	3 0 2	2 3 4	2 6 4	2 9 2	3 0 3	2 3 5	2 1 1	2 1 2	2 1 3
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	A	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	M	+	+	+	+	A	A	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	M	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	M	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine small, ileum	A	M	+	+	+	A	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	M	+	+	+	A	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Hepatocellular carcinoma							X								X										
Hepatocellular carcinoma, multiple													X												
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Lymphoma malignant histiocytic												X									X				
Mesentery																					+				
Lymphoma malignant histiocytic																					X				
Pancreas	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Spindle cell, carcinoma																									
Adrenal gland, medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis		+			+	+																	+	+	
Preputial gland																			+						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle									+												+				
Testes	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	214	215	223	224	225	243	244	245	253	254	255	265	272	273	274	275	282	283	284	285	293	294	295	304	305	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	44
Intestine small, ileum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant lymphocytic																		X								1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma				X			X	X															X			6
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X				X													X		X						4
Hepatocellular adenoma, multiple																X										1
Lymphoma malignant histiocytic																										2
Mesentery																										1
Lymphoma malignant histiocytic																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth	+	+					+		+	+			+		+				+	+				+	+	12
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X																							1
Spindle cell, carcinoma													X													1
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																				X						1
Parathyroid gland	M	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis										+							+				+					8
Preputial gland	+																									2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+																+									4
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

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

WEEKS ON STUDY	008	023	027	034	048	054	071	076	082	083	086	087	088	089	091	095	097	100	102	104	104	105	105	105	105
CARCASS ID	271	221	261	222	251	262	241	231	252	232	242	281	301	291	233	263	302	234	264	292	303	235	211	212	213
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal, lymphoma malignant lymphocytic																									
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M
Lymph node, mesenteric	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Spleen	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic												X									X				
Lymphoma malignant lymphocytic																									
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	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Melanoma benign																									
Squamous cell carcinoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, fibrosarcoma					X						X					X	X	X							
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X							
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver													X		X										
Nose	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																				+					
Adenoma																				X					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	214	215	223	224	225	243	244	245	253	254	255	265	272	273	274	275	282	283	284	285	293	294	295	304	305	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal, lymphoma malig lymphocytic																		X								1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	M	+	+	+	+	+	41
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant lymphocytic																		X								1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																		X								1
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	43
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Melanoma benign						X																				1
Squamous cell carcinoma																						X				1
Subcutaneous tissue, fibroma																		X								1
Subcutaneous tissue, fibroma, multiple								X																		1
Subcutaneous tissue, fibrosarcoma																										5
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X												2
Alveolar/bronchiolar carcinoma	X								X																	2
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Trachea	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Harderian gland			+			+																				3
Adenoma			X			X																				3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

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

WEEKS ON STUDY	010	076	083	083	086	089	092	095	096	096	098	099	100	100	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	151	141	201	191	202	111	142	171	121	112	152	161	172	153	131	181	113	114	115	122	123	124	132	133	134
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																					X				
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma					X				X		X		X						X						
Hepatocellular adenoma															X										
Hepatocellular adenoma, multiple																									
Lymphoma malignant histiocytic		X																							
Lymphoma malignant mixed										X															
Mesentery		+			+																				
Alveolar/bronchiolar carcinoma, metastatic, lung					X																				
Lymphoma malignant histiocytic		X																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung					X																				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																			+			+			
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																							X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Penis																									
Preputial gland																					+				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle																			+						
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	135	143	144	145	154	155	162	163	164	165	173	174	175	182	183	184	185	192	193	194	195	203	204	205	225	TOTAL: TISSUES / TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	M	+	M	+	+	M	+	M	+	+	M	+	+	+	+	M	M	+	+	M	+	37
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant mixed																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma		X													X											7
Hepatocellular adenoma					X					X																3
Hepatocellular adenoma, multiple													X													1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																										1
Mesentery																										2
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymphoma malignant histiocytic																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth											+						+									4
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	M	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	43
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	50
Lymphoma malignant lymphocytic																				X						1
Penis																								+		1
Preputial gland												+	+		+											4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	010	076	083	083	086	089	092	095	096	096	098	099	100	100	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	151	141	201	191	202	111	142	171	211	112	152	161	172	153	131	181	113	114	115	122	123	124	132	133	134
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pancreatic, lymphoma malignant mixed																					X				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Bronchial, mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung					X																				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymphoma malignant histiocytic		X																							
Lymphoma malignant mixed															X						X				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic		X																							
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed									X																
Thymus	M	+	+	M	M	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinum, fibrosarcoma, metastatic, skin																									
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	+	M	+	M	+	M	+	M	M	+	M	M	M	M	+	+	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma														X											
Subcutaneous tissue, fibrosarcoma			X	X		X	X			X		X		X					X						
Subcutaneous tissue, fibrosarcoma, multiple									X																
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																				
Diaphragm, intercostal, alveolar/bronchiolar carcinoma, metastatic, lung					X																				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X	X	X				X	
Alveolar/bronchiolar carcinoma					X																		X		
Alveolar/bronchiolar carcinoma, multiple																X									
Hepatocellular carcinoma, metastatic, liver																									
Lymphoma malignant histiocytic		X																							
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
Harderian gland													+												
Adenoma													X												
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed										X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	135	143	144	145	154	155	162	163	164	165	173	174	175	182	183	184	185	192	193	194	195	203	204	205	125	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreatic, lymphoma malignant mixed																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	46
Bronchial, mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	M	+	+	+	M	44
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																			X							1
Lymphoma malignant mixed																								X		2
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	41
Mediastinum, fibrosarcoma, metastatic, skin																									X	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	8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma						X	X																			3
Subcutaneous tissue, fibrosarcoma																X		X							X	11
Subcutaneous tissue, fibrosarcoma, multiple																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Diaphragm, intercostal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										4
Alveolar/bronchiolar carcinoma																										2
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver		X																								1
Lymphoma malignant histiocytic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Ear							+																			1
Harderian gland	+																									2
Adenoma	X																									2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Control	1,300 ppm	2,500 ppm
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	4/49 (8%)	0/48 (0%)	1/49 (2%)
Adjusted Rates (b)	13.3%	0.0%	3.0%
Terminal Rates (c)	3/28 (11%)	0/28 (0%)	1/33 (3%)
Day of First Observation	688		730
Life Table Tests (d)	P=0.062N	P=0.065N	P=0.138N
Logistic Regression Tests (d)	P=0.059N	P=0.061N	P=0.132N
Cochran-Armitage Trend Test (d)	P=0.079N		
Fisher Exact Test (d)		P=0.061N	P=0.181N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	6/49 (12%)	0/48 (0%)	1/49 (2%)
Adjusted Rates (b)	19.7%	0.0%	3.0%
Terminal Rates (c)	4/28 (14%)	0/28 (0%)	1/33 (3%)
Day of First Observation	688		730
Life Table Tests (d)	P=0.010N	P=0.018N	P=0.038N
Logistic Regression Tests (d)	P=0.009N	P=0.016N	P=0.034N
Cochran-Armitage Trend Test (d)	P=0.015N		
Fisher Exact Test (d)		P=0.014N	P=0.056N
Harderian Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	7.1%	9.9%	5.5%
Terminal Rates (c)	2/28 (7%)	2/29 (7%)	1/34 (3%)
Day of First Observation	730	723	694
Life Table Tests (d)	P=0.515N	P=0.522	P=0.624N
Logistic Regression Tests (d)	P=0.518N	P=0.521	P=0.626N
Cochran-Armitage Trend Test (d)	P=0.592		
Fisher Exact Test (d)		P=0.500	P=0.691
Liver: Hepatocellular Adenoma			
Overall Rates (a)	2/50 (4%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	7.1%	17.2%	11.4%
Terminal Rates (c)	2/28 (7%)	5/29 (17%)	3/34 (9%)
Day of First Observation	730	730	729
Life Table Tests (d)	P=0.380	P=0.226	P=0.434
Logistic Regression Tests (d)	P=0.400	P=0.225	P=0.448
Cochran-Armitage Trend Test (d)	P=0.278		
Fisher Exact Test (d)		P=0.218	P=0.339
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	9/50 (18%)	7/50 (14%)	7/50 (14%)
Adjusted Rates (b)	26.6%	20.2%	17.3%
Terminal Rates (c)	5/28 (18%)	4/29 (14%)	3/34 (9%)
Day of First Observation	611	496	602
Life Table Tests (d)	P=0.220N	P=0.380N	P=0.263N
Logistic Regression Tests (d)	P=0.260N	P=0.362N	P=0.297N
Cochran-Armitage Trend Test (d)	P=0.338N		
Fisher Exact Test (d)		P=0.393N	P=0.393N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	12/50 (24%)	11/50 (22%)
Adjusted Rates (b)	29.8%	36.2%	27.4%
Terminal Rates (c)	6/28 (21%)	9/29 (31%)	6/34 (18%)
Day of First Observation	611	496	602
Life Table Tests (d)	P=0.449N	P=0.433	P=0.503N
Logistic Regression Tests (d)	P=0.499N	P=0.445	P=0.551N
Cochran-Armitage Trend Test (d)	P=0.450		
Fisher Exact Test (d)		P=0.405	P=0.500

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

	Control	1,300 ppm	2,500 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	15.0%	6.4%	11.8%
Terminal Rates (c)	2/28 (7%)	1/29 (3%)	4/34 (12%)
Day of First Observation	611	699	730
Life Table Tests (d)	P=0.328N	P=0.214N	P=0.394N
Logistic Regression Tests (d)	P=0.325N	P=0.200N	P=0.397N
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test (d)		P=0.218N	P=0.500N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	3.6%	6.9%	7.7%
Terminal Rates (c)	1/28 (4%)	2/29 (7%)	1/34 (3%)
Day of First Observation	730	730	602
Life Table Tests (d)	P=0.296	P=0.512	P=0.384
Logistic Regression Tests (d)	P=0.280	P=0.513	P=0.352
Cochran-Armitage Trend Test (d)	P=0.225		
Fisher Exact Test (d)		P=0.500	P=0.309
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	4/50 (8%)	7/50 (14%)
Adjusted Rates (b)	18.3%	13.1%	18.9%
Terminal Rates (c)	3/28 (11%)	3/29 (10%)	5/34 (15%)
Day of First Observation	611	699	602
Life Table Tests (d)	P=0.549N	P=0.356N	P=0.592N
Logistic Regression Tests (d)	P=0.560N	P=0.343N	P=0.618N
Cochran-Armitage Trend Test (d)	P=0.448		
Fisher Exact Test (d)		P=0.370N	P=0.500
Skin: Fibroma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	2.9%	6.9%	8.4%
Terminal Rates (c)	0/28 (0%)	2/29 (7%)	2/34 (6%)
Day of First Observation	688	730	695
Life Table Tests (d)	P=0.285	P=0.505	P=0.366
Logistic Regression Tests (d)	P=0.287	P=0.513	P=0.367
Cochran-Armitage Trend Test (d)	P=0.225		
Fisher Exact Test (d)		P=0.500	P=0.309
Skin: Fibrosarcoma			
Overall Rates (a)	9/50 (18%)	5/50 (10%)	12/50 (24%)
Adjusted Rates (b)	25.8%	12.8%	27.0%
Terminal Rates (c)	4/28 (14%)	0/29 (0%)	4/34 (12%)
Day of First Observation	408	335	575
Life Table Tests (d)	P=0.429	P=0.192N	P=0.495
Logistic Regression Tests (d)	P=0.269	P=0.190N	P=0.336
Cochran-Armitage Trend Test (d)	P=0.269		
Fisher Exact Test (d)		P=0.194N	P=0.312
Skin: Fibroma or Fibrosarcoma			
Overall Rates (a)	10/50 (20%)	7/50 (14%)	14/50 (28%)
Adjusted Rates (b)	28.0%	18.8%	31.9%
Terminal Rates (c)	4/28 (14%)	2/29 (7%)	6/34 (18%)
Day of First Observation	408	335	575
Life Table Tests (d)	P=0.372	P=0.289N	P=0.433
Logistic Regression Tests (d)	P=0.229	P=0.285N	P=0.282
Cochran-Armitage Trend Test (d)	P=0.204		
Fisher Exact Test (d)		P=0.298N	P=0.241

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

	Control	1,300 ppm	2,500 ppm
Skin: Malignant Schwannoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	8.8%	0.0%	0.0%
Terminal Rates (c)	1/28 (4%)	0/29 (0%)	0/34 (0%)
Day of First Observation	533		
Life Table Tests (d)	P=0.029N	P=0.119N	P=0.096N
Logistic Regression Tests (d)	P=0.033N	P=0.117N	P=0.114N
Cochran-Armitage Trend Test (d)	P=0.036N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	9.6%	2.3%	0.0%
Terminal Rates (c)	2/28 (7%)	0/29 (0%)	0/34 (0%)
Day of First Observation	611	530	
Life Table Tests (d)	P=0.047N	P=0.293N	P=0.092N
Logistic Regression Tests (d)	P=0.057N	P=0.298N	P=0.099N
Cochran-Armitage Trend Test (d)	P=0.061N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	16.4%	9.0%	15.3%
Terminal Rates (c)	3/28 (11%)	1/29 (3%)	3/34 (9%)
Day of First Observation	697	605	527
Life Table Tests (d)	P=0.567	P=0.336N	P=0.614N
Logistic Regression Tests (d)	P=0.535	P=0.333N	P=0.601
Cochran-Armitage Trend Test (d)	P=0.444		
Fisher Exact Test (d)		P=0.357N	P=0.500

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

TABLE C4. HISTORICAL INCIDENCE OF ADRENAL MEDULLARY PHEOCHROMOCYTOMAS IN MALE $B6C3F_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
HC Blue No. 2	0/50
C.I. Disperse Blue 1	1/49
D-Mannitol	0/49
Ziram	0/49
Eugenol	0/43
Propyl gallate	1/49
Zearalenone	0/50
HC Blue No. 1	2/49
Stannous chloride	0/49
TOTAL	4/437 (0.9%)
SD (b)	1.48%
Range (c)	
High	2/49
Low	0/50
Overall Historical Incidence	
TOTAL	(d) 25/1,962 (1.3%)
SD (b)	1.78%
Range (c)	
High	3/49
Low	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one malignant pheochromocytoma

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

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(44)	(45)	(37)
Hyperplasia			1 (3%)
Intestine large, rectum	(48)	(47)	(50)
Cyst	2 (4%)		1 (2%)
Hyperplasia, focal			1 (2%)
Inflammation, chronic, focal		1 (2%)	
Inflammation, subacute	2 (4%)		1 (2%)
Perforation		1 (2%)	
Prolapse	3 (6%)	1 (2%)	2 (4%)
Intestine small, jejunum	(49)	(45)	(49)
Cyst	1 (2%)		
Liver	(50)	(50)	(50)
Basophilic focus			1 (2%)
Cyst			1 (2%)
Fibrosis, focal		1 (2%)	
Granuloma, multiple	1 (2%)		
Hematopoietic cell proliferation	1 (2%)		
Mixed cell focus		2 (4%)	
Necrosis, multifocal	1 (2%)	1 (2%)	1 (2%)
Thrombus		1 (2%)	
Mesentery	(3)	(1)	(2)
Inflammation, subacute, focal	1 (33%)		
Inflammation, suppurative, acute, multifocal	2 (67%)		
Thrombus	1 (33%)		
Stomach, forestomach	(49)	(48)	(49)
Cyst	1 (2%)		1 (2%)
Hyperkeratosis		1 (2%)	
Hyperplasia	2 (4%)	1 (2%)	
Inflammation, chronic, focal	1 (2%)		
Inflammation, suppurative, acute, focal		1 (2%)	
Mineralization	1 (2%)		
Stomach, glandular	(50)	(48)	(49)
Mineralization			1 (2%)
Tooth	(10)	(12)	(4)
Dysplasia	10 (100%)	12 (100%)	4 (100%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Inflammation, acute, multifocal	1 (2%)		
Inflammation, subacute, multifocal	2 (4%)		
Thrombus	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(49)	(50)
Hyperplasia, focal	1 (2%)		2 (4%)
Spindle cell, hyperplasia	5 (10%)	3 (6%)	3 (6%)
Spindle cell, hyperplasia, focal			1 (2%)
Adrenal gland, medulla	(49)	(48)	(49)
Hyperplasia	3 (6%)	6 (13%)	5 (10%)
Hyperplasia, focal	1 (2%)		
Pituitary gland	(46)	(48)	(43)
Pars distalis, cyst			1 (2%)

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

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Thyroid gland	(48)	(47)	(48)
Hyperplasia, cystic	1 (2%)		
Follicle, cyst		1 (2%)	3 (6%)
Follicle, degeneration	1 (2%)	1 (2%)	1 (2%)
Follicle, hyperplasia, cystic		2 (4%)	2 (4%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(50)	(49)	(50)
Atypical cells			26 (52%)
Depletion	1 (2%)	1 (2%)	15 (30%)
Granuloma sperm		3 (6%)	
Penis	(2)	(8)	(1)
Developmental malformation	2 (100%)	8 (100%)	1 (100%)
Preputial gland	(9)	(2)	(4)
Inflammation, subacute	5 (56%)		
Inflammation, suppurative, acute	1 (11%)		
Duct, cyst	6 (67%)	2 (100%)	4 (100%)
Prostate	(49)	(50)	(50)
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation, suppurative, acute	4 (8%)	4 (8%)	
Seminal vesicle	(6)	(4)	(1)
Dilatation	3 (50%)	4 (100%)	1 (100%)
Inflammation, chronic	1 (17%)	1 (25%)	
Inflammation, suppurative, acute	2 (33%)		
Testes	(49)	(49)	(50)
Aspermatogenesis	1 (2%)	1 (2%)	16 (32%)
Atrophy		1 (2%)	
Mineralization	1 (2%)		1 (2%)
Germinal epithelium, degeneration		3 (6%)	23 (46%)
Seminiferous tubule, dilatation, focal			1 (2%)
HEMATOPOIETIC SYSTEM			
Blood	(2)		
Anemia	1 (50%)		
Lymph node	(50)	(49)	(49)
Axillary, hyperplasia			1 (2%)
Deep cervical, hyperplasia	1 (2%)		
Iliac, hyperplasia	1 (2%)		1 (2%)
Inguinal, hyperplasia	1 (2%)		
Lymph node, mesenteric	(47)	(46)	(44)
Angiectasis	6 (13%)		
Ectasia		1 (2%)	
Hyperplasia	1 (2%)		
Thrombus	1 (2%)		
Spleen	(50)	(49)	(50)
Angiectasis	1 (2%)	1 (2%)	
Atrophy		3 (6%)	1 (2%)
Hematopoietic cell proliferation	10 (20%)	11 (22%)	4 (8%)
Necrosis, focal	1 (2%)		
Thymus	(44)	(43)	(41)
Cyst	1 (2%)		1 (2%)

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

	Untreated Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Skin	(50)	(50)	(50)
Alopecia	4 (8%)	5 (10%)	3 (6%)
Alopecia, multifocal	3 (6%)		
Fibrosis	7 (14%)	5 (10%)	12 (24%)
Fungus		1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)		2 (4%)
Inflammation, chronic		1 (2%)	
Inflammation, granulomatous, focal		2 (4%)	1 (2%)
Inflammation, subacute, focal	7 (14%)	12 (24%)	9 (18%)
Inflammation, suppurative, acute	2 (4%)	2 (4%)	1 (2%)
Mineralization, focal	1 (2%)	1 (2%)	2 (4%)
Ulcer		4 (8%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Cranium, hyperostosis	1 (2%)		
NERVOUS SYSTEM			
None			
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Congestion	3 (6%)		
Fibrosis, multifocal		1 (2%)	
Infiltration cellular, histiocytic, multifocal		1 (2%)	
Inflammation, subacute, multifocal	32 (64%)	34 (68%)	30 (60%)
Alveolar epithelium, hyperplasia	1 (2%)		2 (4%)
Nose	(42)	(44)	(48)
Hemorrhage			1 (2%)
SPECIAL SENSES SYSTEM			
None			
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Calculus gross observation	1 (2%)		
Hydronephrosis	1 (2%)		
Inflammation, suppurative, acute, multifocal	1 (2%)		
Metaplasia, osseous, focal	1 (2%)		
Nephropathy	3 (6%)		
Cortex, infarct			1 (2%)
Cortex, infarct, focal	1 (2%)	2 (4%)	1 (2%)
Medulla, mineralization			17 (34%)
Papilla, necrosis	1 (2%)		
Renal tubule, degeneration, multifocal		1 (2%)	1 (2%)
Renal tubule, dilatation			14 (28%)
Renal tubule, hyperplasia		1 (2%)	
Renal tubule, hyperplasia, focal		1 (2%)	
Renal tubule, necrosis, multifocal			1 (2%)
Renal tubule, nephropathy	1 (2%)	1 (2%)	
Ureter	(1)		
Inflammation, suppurative, acute	1 (100%)		

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

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
Urethra	(2)		
Inflammation, suppurative, subacute	1 (50%)		
Bulbourethral gland, dilatation	1 (50%)		
Urinary bladder	(50)	(49)	(50)
Calculus gross observation	1 (2%)		
Calculus micro observation only	1 (2%)		
Inflammation, chronic		1 (2%)	
Inflammation, suppurative, acute	2 (4%)		
Transitional epithelium, hyperplasia	2 (4%)		

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(41)	(39)	(42)
Lymphoma malignant histiocytic			1 (2%)
Intestine large, cecum	(43)	(49)	(50)
Lymphoma malignant histiocytic			1 (2%)
Intestine small, ileum	(44)	(47)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Intestine small, jejunum	(45)	(48)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Liver	(50)	(50)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma	1 (2%)		
Hepatocellular carcinoma	1 (2%)	1 (2%)	2 (4%)
Hepatocellular adenoma	1 (2%)	1 (2%)	7 (14%)
Ito cell tumor, NOS		1 (2%)	1 (2%)
Lymphoma malignant histiocytic	1 (2%)	4 (8%)	6 (12%)
Lymphoma malignant lymphocytic	5 (10%)	3 (6%)	4 (8%)
Lymphoma malignant mixed		3 (6%)	
Mesentery	*(50)	*(50)	*(50)
Fibrosarcoma			1 (2%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	3 (6%)		3 (6%)
Sarcoma		1 (2%)	1 (2%)
Pancreas	(47)	(50)	(50)
Fibrosarcoma, metastatic, mesentery			1 (2%)
Lymphoma malignant histiocytic			2 (4%)
Lymphoma malignant lymphocytic		1 (2%)	1 (2%)
Sarcoma		1 (2%)	
Salivary glands	(49)	(50)	(50)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		
Stomach	(49)	(49)	(50)
Squamous cell carcinoma	1 (2%)		
Stomach, forestomach	(49)	(49)	(50)
Lymphoma malignant lymphocytic			1 (2%)
Papilloma squamous	1 (2%)		1 (2%)
Sarcoma		1 (2%)	
Glandular, fibrosarcoma, metastatic, mesentery			1 (2%)
Stomach, glandular	(49)	(49)	(49)
Sarcoma		1 (2%)	
Tongue	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic	1 (2%)		
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		
Sarcoma		1 (2%)	

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

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(50)	(50)
Fibrosarcoma, metastatic, mesentery			1 (2%)
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma			1 (2%)
Osteosarcoma, metastatic, bone		1 (2%)	
Spindle cell, adenoma		1 (2%)	
Adrenal gland, medulla	(48)	(49)	(49)
Hepatocellular carcinoma, metastatic, liver	1 (2%)		
Pheochromocytoma malignant	1 (2%)		
Pheochromocytoma benign	1 (2%)		
Islets, pancreatic	(47)	(50)	(49)
Carcinoma			1 (2%)
Pituitary gland	(48)	(44)	(49)
Pars distalis, adenoma	3 (6%)	1 (2%)	2 (4%)
Thyroid gland	(48)	(49)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Follicular cell, adenoma	3 (6%)	1 (2%)	
Follicular cell, carcinoma	1 (2%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(50)	(50)	(50)
Adenoma, tubular			5 (10%)
Cystadenoma			1 (2%)
Cystadenoma, papillary	2 (4%)	1 (2%)	
Granulosa cell tumor malignant			1 (2%)
Granulosa cell tumor benign		3 (6%)	1 (2%)
Hemangioma		1 (2%)	1 (2%)
Lymphoma malignant histiocytic		1 (2%)	3 (6%)
Lymphoma malignant lymphocytic			5 (10%)
Mixed tumor benign			4 (8%)
Neoplasm, NOS			1 (2%)
Uterus	(50)	(50)	(50)
Adenocarcinoma		1 (2%)	1 (2%)
Lymphoma malignant histiocytic		2 (4%)	2 (4%)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed		1 (2%)	
Polyp stromal	2 (4%)	2 (4%)	1 (2%)
Sarcoma stromal			2 (4%)
Cervix, lymphoma malignant mixed		1 (2%)	
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Lymphoma malignant lymphocytic	3 (6%)		
Lymph node	(50)	(50)	(49)
Axillary, lymphoma malignant histiocytic			1 (2%)
Bronchial, lymphoma malignant histiocytic		1 (2%)	1 (2%)
Bronchial, lymphoma malignant lymphocytic	1 (2%)		3 (6%)
Bronchial, lymphoma malignant mixed		1 (2%)	
Deep cervical, lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Iliac, lymphoma malignant lymphocytic			1 (2%)

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

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(50)	(50)	(49)
Iliac, lymphoma malignant mixed			1 (2%)
Inguinal, lymphoma malignant histiocytic		2 (4%)	
Inguinal, lymphoma malignant lymphocytic			1 (2%)
Inguinal, lymphoma malignant mixed			1 (2%)
Lumbar, lymphoma malignant lymphocytic			1 (2%)
Mediastinal, lymphoma malignant histiocytic		1 (2%)	1 (2%)
Mediastinal, lymphoma malignant lymphocytic			4 (8%)
Mediastinal, lymphoma malignant mixed		1 (2%)	1 (2%)
Pancreatic, lymphoma malignant lymphocytic	2 (4%)		2 (4%)
Pancreatic, lymphoma malignant mixed			1 (2%)
Renal, lymphoma malignant histiocytic	1 (2%)		
Renal, lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Renal, lymphoma malignant mixed			1 (2%)
Lymph node, mandibular	(50)	(50)	(45)
Lymphoma malignant histiocytic	1 (2%)	2 (4%)	3 (7%)
Lymphoma malignant lymphocytic	7 (14%)	6 (12%)	12 (27%)
Lymphoma malignant mixed		2 (4%)	1 (2%)
Lymph node, mesenteric	(45)	(45)	(48)
Fibrosarcoma, metastatic, mesentery			1 (2%)
Lymphoma malignant histiocytic		2 (4%)	4 (8%)
Lymphoma malignant lymphocytic	5 (11%)	2 (4%)	10 (21%)
Lymphoma malignant mixed		1 (2%)	1 (2%)
Spleen	(49)	(50)	(50)
Fibrosarcoma, metastatic, mesentery			1 (2%)
Hemangiosarcoma	1 (2%)		
Lymphoma malignant histiocytic	1 (2%)	3 (6%)	4 (8%)
Lymphoma malignant lymphocytic	9 (18%)	10 (20%)	16 (32%)
Lymphoma malignant mixed		3 (6%)	1 (2%)
Thymus	(47)	(48)	(48)
Lymphoma malignant histiocytic	1 (2%)		2 (4%)
Lymphoma malignant lymphocytic	8 (17%)	2 (4%)	2 (4%)
Lymphoma malignant mixed		2 (4%)	
Mediastinum, lymphoma malignant lymphocytic			1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(48)	(48)
Adenoacanthoma			1 (2%)
Adenocarcinoma	5 (10%)	3 (6%)	
Adenocarcinoma, multiple			1 (2%)
Skin	(50)	(50)	(50)
Basal cell carcinoma			1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		
Squamous cell carcinoma		1 (2%)	
Sebaceous gland, adenoma			1 (2%)
Subcutaneous tissue, fibrosarcoma		1 (2%)	1 (2%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)		
Subcutaneous tissue, schwannoma benign		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
Skeletal muscle	*(50)	*(50)	*(50)
Fibrosarcoma, metastatic, mesentery			1 (2%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		
Sarcoma		1 (2%)	

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

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(49)	(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Meningioma benign		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Adenocarcinoma, metastatic, mammary gland		1 (2%)	
Alveolar/bronchiolar adenoma	2 (4%)	2 (4%)	
Alveolar/bronchiolar carcinoma	1 (2%)		
Basal cell carcinoma, metastatic, skin			1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)		1 (2%)
Lymphoma malignant histiocytic	1 (2%)	2 (4%)	5 (10%)
Lymphoma malignant lymphocytic	3 (6%)	4 (8%)	6 (12%)
Lymphoma malignant mixed		1 (2%)	
Osteosarcoma, metastatic, bone		1 (2%)	
Sarcoma		1 (2%)	
Mediastinum, lymphoma malignant lymphocytic	3 (6%)		
Mediastinum, sarcoma		1 (2%)	
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenocarcinoma	1 (2%)	1 (2%)	
Adenoma	1 (2%)	2 (4%)	1 (2%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Lymphoma malignant histiocytic		2 (4%)	5 (10%)
Lymphoma malignant lymphocytic	3 (6%)	5 (10%)	5 (10%)
Lymphoma malignant mixed		1 (2%)	1 (2%)
Sarcoma		1 (2%)	
Renal tubule, carcinoma			1 (2%)
Urinary bladder	(50)	(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)	3 (6%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Hemangioma	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	11 (22%)	10 (20%)	17 (34%)
Lymphoma malignant histiocytic	1 (2%)	5 (10%)	6 (12%)
Hemangiosarcoma	2 (4%)		
Lymphoma malignant mixed		4 (8%)	1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Dead	19	5	2
Moribund	12	9	11
Terminal sacrifice	19	36	37

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

	Untreated Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary neoplasms **	30	35	41
Total primary neoplasms	42	55	67
Total animals with benign neoplasms	15	15	22
Total benign neoplasms	17	17	27
Total animals with malignant neoplasms	21	27	31
Total malignant neoplasms	25	37	38
Total animals with secondary neoplasms ***	1	2	3
Total secondary neoplasms	2	3	8
Total animals with neoplasms-- uncertain benign or malignant		1	2
Total uncertain neoplasms		1	2

* 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 FEED STUDY OF NITROFURANTOIN: UNTREATED CONTROL

WEEKS ON STUDY	022	064	065	066	068	072	075	075	077	081	085	085	086	087	087	087	091	091	093	094	096	098	099	100	102
CARCASS ID	331	401	381	382	402	371	372	403	391	361	392	393	373	332	351	374	321	341	352	533	311	375	394	312	322
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	M	+	+	+	+	M	+	+	M	+
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	A	+	M	+	+	A	M
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	A	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	M	+	+	+	+
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	A	+	M	+	+	A	+
Lymphoma malignant lymphocytic																									
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+	+	A	+
Lymphoma malignant lymphocytic																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																									
Hepatocellular carcinoma																									
Hepatocellular adenoma														X											
Lymphoma malignant histiocytic																			X						
Lymphoma malignant lymphocytic																	X								
Mesentery		+	+	+	+	+	+	+			+	+	+			+	+			+	+			+	+
Lymphoma malignant lymphocytic																	X								
Pancreas	A	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Lymphoma malignant lymphocytic																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymphoma malignant lymphocytic																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Hepatocellular carcinoma, metastatic, liver																									
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Islets, pancreatic	A	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Follicular cell, adenoma																		X							
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary																					X				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Polyp stromal																									

+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A Autolysis precludes examination
X Incidence of listed morphology

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

WEEKS ON STUDY	102	102	103	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	342	395	313	354	383	384	314	315	323	324	325	333	334	335	343	344	345	355	362	363	364	365	385	404	405	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	41
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymphoma malignant lymphocytic																		X								1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant lymphocytic																				X						1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma							X																			1
Hemangiosarcoma					X																					1
Hepatocellular carcinoma		X																								1
Hepatocellular adenoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic						X											X	X			X					5
Mesentery	+			+		+										+					+					21
Lymphoma malignant lymphocytic						X															X					3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic						X																				1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Squamous cell carcinoma																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Papilloma squamous																X										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Tongue						+																				1
Lymphoma malignant lymphocytic						X																				1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																						X				1
Lymphoma malignant lymphocytic						X																				1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic, liver		X																								1
Pheochromocytoma malignant		X																								1
Pheochromocytoma benign						X																				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	43
Pituitary gland	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma											X				X							X				3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic						X																				1
Follicular cell, adenoma				X				X																		3
Follicular cell, carcinoma												X														1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland																				+						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma, papillary										X																2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic						X																				1
Polyp stromal				X																				X		2

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

WEEKS ON STUDY	022	064	065	066	068	072	075	075	077	081	085	085	086	087	087	087	091	091	093	094	096	098	099	100	102
CARCASS ID	331	401	381	382	402	371	372	403	391	361	392	393	373	332	351	374	321	341	352	353	311	375	394	312	322
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																	X								X
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, lymphoma malignant lymphocytic																	X								
Deep cervical, lymphoma malignant lymphocytic																									
Pancreatic, lymphoma malignant lymphocytic																									
Renal, lymphoma malignant histiocytic																			X						
Renal, lymphoma malignant lymphocytic																	X								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																			X						
Lymphoma malignant lymphocytic																	X								X
Lymph node, mesenteric	M	+	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	+	A	+	+	+	+	+	+
Lymphoma malignant lymphocytic																	X								X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymphoma malignant histiocytic																			X						
Lymphoma malignant lymphocytic																	X								X
Thymus	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymphoma malignant histiocytic																			X						
Lymphoma malignant lymphocytic																	X								X
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																		X					X		X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Subcutaneous tissue, hemangiosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																						+			
Lymphoma malignant lymphocytic																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar carcinoma										X															
Hepatocellular carcinoma, metastatic, liver																									
Lymphoma malignant histiocytic																			X						
Lymphoma malignant lymphocytic																	X								X
Mediastinum, lymphoma malignant lymphocytic																	X								X
Nose	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																						+			
Adenocarcinoma																									
Adenoma																						X			
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									

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

WEEKS ON STUDY	102	102	103	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	342	395	313	354	383	384	314	315	323	324	325	333	334	335	343	344	345	355	362	363	364	365	385	404	405	TOTAL TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic						X																				3
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, lymphoma malignant lymphocytic																										1
Deep cervical, lymphoma malignant lymphocytic																					X					1
Pancreatic, lymphoma malignant lymphocytic						X															X					2
Renal, lymphoma malignant histiocytic																										1
Renal, lymphoma malig lymphocytic																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic						X						X			X		X	X								7
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant lymphocytic						X						X						X								5
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Hemangiosarcoma					X																					1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic						X						X		X	X		X	X		X						9
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic						X						X			X		X	X						X		8
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma								X									X									5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic						X																				1
Subcutaneous tissue, hemangiosarcoma					X																					1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle						+																				2
Lymphoma malignant lymphocytic						X																				1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic						X																				1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X													2
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver		X																								1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic						X																				3
Mediastinum, lymphoma malignant lymphocytic						X																				3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Harderian gland																+										2
Adenocarcinoma																X										1
Adenoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic						X										X			X							3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic						X																				1

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

WEEKS ON STUDY	067	083	086	087	089	096	099	100	100	101	102	102	102	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	601	591	581	602	561	571	541	603	582	562	531	532	551	572	573	511	512	513	514	515	521	522	523	524	525
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma						X																			
Hepatocellular adenoma																									
Ito cell tumor, NOS							X																		
Lymphoma malignant histiocytic			X	X			X				X														
Lymphoma malignant lymphocytic									X							X									
Lymphoma malignant mixed					X																				
Mesentery						+																			
Sarcoma						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic									X																
Sarcoma						X																			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma						X																			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma						X																			
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma						X																			
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone													X												
Spindle cell, adenoma																									
Adrenal gland, medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M
Pituitary gland	M	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																					X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary															X		X								
Granulosa cell tumor benign																									
Hemangioma																									
Lymphoma malignant histiocytic			X																						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Lymphoma malignant histiocytic			X																						
Lymphoma malignant mixed					X																				
Polyp stromal																									
Cervix, lymphoma malignant mixed					X																				

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	53 3	53 4	53 5	54 2	54 3	54 4	54 5	55 2	55 3	55 4	55 5	56 3	56 4	56 5	57 4	57 5	58 3	58 4	58 5	59 2	59 3	59 4	59 5	60 4	60 5	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	M	+	+	+	+	+	+	M	+	+	M	M	+	+	M	+	+	+	M	M	+	M	39
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma																									X	1
Ito cell tumor, NOS																										1
Lymphoma malignant histiocytic																										4
Lymphoma malignant lymphocytic								X																		3
Lymphoma malignant mixed																				X			X			3
Mesentery																									+	2
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Sarcoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Sarcoma																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Spindle cell, adenoma															X											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	44
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																								X		1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma, papillary														X												1
Granulosa cell tumor benign									X																	3
Hemangioma																	X									1
Lymphoma malignant histiocytic																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma															X											1
Lymphoma malignant histiocytic																								X		2
Lymphoma malignant mixed																										1
Polyp stromal		X								X																2
Cervix, lymphoma malignant mixed																										1

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

WEEKS ON STUDY	0 6 7	0 8 3	0 8 6	0 8 7	0 8 9	0 9 6	0 9 9	1 0 0	1 0 0	1 0 1	1 0 2	1 0 2	1 0 2	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	6 0 1	5 9 1	5 8 1	6 0 2	5 6 1	5 7 1	5 4 1	6 0 3	5 8 2	5 6 2	5 3 1	5 3 2	5 5 1	5 7 2	5 7 3	5 1 1	5 1 2	5 1 3	5 1 4	5 1 5	5 2 1	5 2 2	5 2 3	5 2 4	5 2 5
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, lymphoma malignant histiocytic							X																		
Bronchial, lymphoma malignant mixed																									
Deep cervical, lymphoma malignant lymphocytic									X																
Inguinal, lymphoma malignant histiocytic							X				X														
Mediastinal, lymphoma malignant histiocytic							X																		
Mediastinal, lymphoma malignant mixed																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic							X				X														
Lymphoma malignant lymphocytic									X					X		X	X								
Lymphoma malignant mixed					X																				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X			X																		
Lymphoma malignant lymphocytic									X							X									
Lymphoma malignant mixed					X																				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X			X				X														
Lymphoma malignant lymphocytic									X					X		X	X					X			
Lymphoma malignant mixed					X															X					
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed					X																				
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenocarcinoma			X									X													
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, schwannoma benign															X										
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma													X												
Skeletal muscle						+																			
Sarcoma						X																			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma benign		X																							
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland												X													
Alveolar/bronchiolar adenoma															X										
Lymphoma malignant histiocytic							X				X														
Lymphoma malignant lymphocytic									X													X			
Lymphoma malignant mixed						X																			
Osteosarcoma, metastatic, bone													X												
Sarcoma						X																			
Mediastinum, sarcoma						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland					+																+				
Adenocarcinoma																					X				
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic			X				X																		
Lymphoma malignant lymphocytic									X							X	X								
Lymphoma malignant mixed					X																				
Sarcoma						X																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																X						X			

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	533	534	535	542	543	544	545	552	553	554	555	563	564	565	574	575	583	584	585	592	593	594	595	604	605	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, lymphoma malignant histiocytic																										1
Bronchial, lymphoma malignant mixed																				X						1
Deep cervical, lymphoma malignant lymphocytic																										1
Inguinal, lymphoma malignant histiocytic																										2
Mediastinal, lymphoma malignant histiocytic																										1
Mediastinal, lymphoma malig. mixed																				X						1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic			X											X												6
Lymphoma malignant mixed																				X						2
Lymph node, mesenteric	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	45
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic		X	X	X				X						X												10
Lymphoma malignant mixed																				X						3
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic														X												2
Lymphoma malignant mixed																				X						2
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Adenocarcinoma											X															3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma													X													1
Subcutaneous tissue, fibrosarcoma																										1
Subcut tissue, schwannoma benign																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										1
Sarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma benign																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, mammary gland																										1
Alveolar/bronchiolar adenoma																				X						2
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic				X				X																		4
Lymphoma malignant mixed																										1
Osteosarcoma, metastatic, bone																										1
Sarcoma																										1
Mediastinum, sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland												+									+				+	5
Adenocarcinoma																										1
Adenoma												X									X					2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic			X					X																		5
Lymphoma malignant mixed																										1
Sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic								X																		3

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

WEEKS ON STUDY	082	090	090	092	093	094	095	097	100	102	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	4411	4911	4331	4661	4992	4111	4211	4711	4511	5011	4525	4772	5022	4122	4133	4114	4155	4222	4232	4244	4255	4332	4334	4344	4335
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	M	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M
Lymphoma malignant histiocytic	X																								
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																	X								
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X																	
Hepatocellular adenoma							X								X										
Ito cell tumor, NOS																									
Lymphoma malignant histiocytic	X	X	X	X								X					X								
Lymphoma malignant lymphocytic								X			X													X	
Mesentery	+						+		+		+					+				+					
Fibrosarcoma									X																
Lymphoma malignant histiocytic	X																								
Lymphoma malignant lymphocytic											X									X					
Sarcoma							X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, mesentery									X																
Lymphoma malignant histiocytic	X			X																					
Lymphoma malignant lymphocytic								X																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X																					
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic											X														
Papilloma squamous																									
Glandular, fibrosarcoma, metastatic, mesentery									X																
Stomach, glandular	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, mesentery									X																
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Islets, pancreatic	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																							X		
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X							X												
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, tubular											X					X			X						
Cystadenoma										X															
Granulosa cell tumor malignant													X												
Granulosa cell tumor benign																									
Hemangioma																									
Lymphoma malignant histiocytic	X		X									X													
Lymphoma malignant lymphocytic								X		X	X														
Mixed tumor benign			X																						X
Neoplasm, NOS				X																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																					X				
Lymphoma malignant histiocytic	X	X																							
Polyp stromal															X										
Sarcoma stromal													X	X											

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	44 2	44 3	44 4	44 5	45 3	45 4	46 2	46 3	46 4	46 5	47 3	47 4	47 5	48 1	48 2	48 3	48 4	48 5	49 3	49 4	49 5	50 3	50 4	50 5	45 5	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Lymphoma malignant histiocytic																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma															X											2
Hepatocellular adenoma					X	X							X		X							X				7
Ito cell tumor, NOS							X																			1
Lymphoma malignant histiocytic																										6
Lymphoma malignant lymphocytic																					X					4
Mesentery															+	+										8
Fibrosarcoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic															X											3
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, mesentery																										1
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Papilloma squamous					X																					1
Glandular, fibrosarcoma, metastatic, mesentery																										1
Stomach glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, mesentery																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, tubular							X													X						5
Cystadenoma																										1
Granulosa cell tumor malignant																										1
Granulosa cell tumor benign										X																1
Hemangioma			X																							1
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic															X							X				5
Mixed tumor benign				X									X													4
Neoplasm, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Lymphoma malignant histiocytic																										2
Polyp stromal																										1
Sarcoma stromal																										2

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

WEEKS ON STUDY	0 8 2	0 9 0	0 9 0	0 9 2	0 9 3	0 9 4	0 9 5	0 9 7	1 0 0	1 0 2	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	4 4 1	4 9 1	4 3 1	4 6 1	4 9 2	4 1 1	4 2 1	4 7 1	4 5 1	5 0 1	4 5 2	4 7 2	5 0 2	4 1 2	4 1 3	4 1 4	4 1 5	4 2 2	4 2 3	4 2 4	4 2 5	4 3 2	4 3 3	4 3 4	4 3 5
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, lymphoma malignant histiocytic																	X							
Bronchial, lymphoma malignant histiocytic																	X							
Bronchial, lymphoma malignant lymphocytic								X			X													
Iliac, lymphoma malignant lymphocytic											X													
Iliac, lymphoma malignant mixed																								
Inguinal, lymphoma malignant lymphocytic										X														
Inguinal, lymphoma malignant mixed																								
Lumbar, lymphoma malignant lymphocytic																							X	
Mediastinal, lymphoma malignant histiocytic																	X							
Mediastinal, lymphoma malignant lymphocytic								X			X												X	
Mediastinal, lymphoma malignant mixed																								
Pancreatic, lymphoma malignant lymphocytic										X	X													
Pancreatic, lymphoma malignant mixed																								
Renal, lymphoma malignant lymphocytic																								
Renal, lymphoma malignant mixed																								
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Lymphoma malignant histiocytic			X	X													X							
Lymphoma malignant lymphocytic								X		X	X												X	X	
Lymphoma malignant mixed																								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, mesentery									X															
Lymphoma malignant histiocytic	X		X	X													X							
Lymphoma malignant lymphocytic								X		X	X									X			X	X	
Lymphoma malignant mixed																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, mesentery									X															
Lymphoma malignant histiocytic			X	X								X					X							
Lymphoma malignant lymphocytic								X		X	X									X			X	X	
Lymphoma malignant mixed																								
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic			X	X																				
Lymphoma malignant lymphocytic								X		X														
Mediastinum, lymphoma malignant lymphocytic											X													
INTEGUMENTARY SYSTEM																								
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoacanthoma													X											
Adenocarcinoma, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																								
Sebaceous gland, adenoma																							X	
Subcutaneous tissue, fibrosarcoma																								
MUSCULOSKELETAL SYSTEM																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+			+													
Fibrosarcoma, metastatic, mesentery									X																
Lymphoma malignant histiocytic												X													
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic								X																	
Meningioma benign															X										
RESPIRATORY SYSTEM																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma, metastatic, skin																									
Hepatocellular carcinoma, metastatic, liver																									
Lymphoma malignant histiocytic	X	X	X	X								X													
Lymphoma malignant lymphocytic								X		X	X													X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic	X	X	X	X								X													
Lymphoma malignant lymphocytic								X			X													X	
Lymphoma malignant mixed																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	44 2	44 3	44 4	44 5	45 3	45 4	46 2	46 3	46 4	46 5	47 3	47 4	47 5	48 1	48 2	48 3	48 4	48 5	49 3	49 4	49 5	50 3	50 4	50 5	45 5	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Axillary, lymphoma malignant histiocytic																										1
Bronchial, lymphoma malignant histiocytic																										1
Bronchial, lymphoma malignant lymphocytic																X										3
Iliac, lymphoma malignant lymphocytic																										1
Iliac, lymphoma malignant mixed		X																								1
Inguinal, lymphoma malignant lymphocytic																										1
Inguinal, lymphoma malignant mixed		X																								1
Lumbar, lymphoma malig lymphocytic																										1
Mediastinal, lymphoma malignant histiocytic																										1
Mediastinal, lymphoma malignant lymphocytic						X																				4
Mediastinal, lymphoma malig mixed		X																								1
Pancreatic, lymphoma malignant lymphocytic																										2
Pancreatic, lymphoma malignant mixed		X																								1
Renal, lymphoma malig lymphocytic					X																					1
Renal, lymphoma malignant mixed		X																								1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	45
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic			X			X	X		X	X		X										X				12
Lymphoma malignant mixed		X																								1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	48
Fibrosarcoma, metastatic, mesentery																										1
Lymphoma malignant histiocytic																										4
Lymphoma malignant lymphocytic			X		X										X							X				10
Lymphoma malignant mixed		X																								1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, mesentery																										1
Lymphoma malignant histiocytic																										4
Lymphoma malignant lymphocytic			X		X	X	X		X			X			X	X					X	X				16
Lymphoma malignant mixed		X																								1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																										2
Mediastinum, lymphoma malignant lymphocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoacanthoma																										1
Adenocarcinoma, multiple															X											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma												X														1
Sebaceous gland, adenoma																										1
Subcutaneous tissue, fibrosarcoma																							X			1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Fibrosarcoma, metastatic, mesentery																										1
Lymphoma malignant histiocytic																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Meningioma benign																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma, metastatic, skin												X														1
Hepatocellular carcinoma, metastatic, liver															X											1
Lymphoma malignant histiocytic																										5
Lymphoma malignant lymphocytic					X																X					6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland	+																									1
Adenoma	X																									1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										5
Lymphoma malignant lymphocytic																X					X					5
Lymphoma malignant mixed		X																								1
Renal tubule, carcinoma																									X	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

	Control	1,300 ppm	2,500 ppm
Harderian Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	8.5%	8.1%	2.7%
Terminal Rates (c)	1/19 (5%)	3/37 (8%)	1/37 (3%)
Day of First Observation	686	730	730
Life Table Tests (d)	P=0.198N	P=0.596N	P=0.308N
Logistic Regression Tests (d)	P=0.259N	P=0.673	P=0.384N
Cochran-Armitage Trend Test (d)	P=0.411N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	7/50 (14%)
Adjusted Rates (b)	2.7%	2.7%	18.1%
Terminal Rates (c)	0/19 (0%)	1/37 (3%)	6/37 (16%)
Day of First Observation	603	730	660
Life Table Tests (d)	P=0.042	P=0.658N	P=0.147
Logistic Regression Tests (d)	P=0.016	P=0.758	P=0.054
Cochran-Armitage Trend Test (d)	P=0.012		
Fisher Exact Test (d)		P=0.753N	P=0.030
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	8/50 (16%)
Adjusted Rates (b)	6.6%	4.9%	20.0%
Terminal Rates (c)	0/19 (0%)	1/37 (3%)	6/37 (16%)
Day of First Observation	603	670	660
Life Table Tests (d)	P=0.093	P=0.531N	P=0.217
Logistic Regression Tests (d)	P=0.029	P=0.704N	P=0.079
Cochran-Armitage Trend Test (d)	P=0.023		
Fisher Exact Test (d)		P=0.691N	P=0.046
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	10.1%	5.4%	0.0%
Terminal Rates (c)	1/19 (5%)	2/37 (5%)	0/37 (0%)
Day of First Observation	561	730	
Life Table Tests (d)	P=0.030N	P=0.292N	P=0.065N
Logistic Regression Tests (d)	P=0.099N	P=0.526N	P=0.161N
Cochran-Armitage Trend Test (d)	P=0.085N		
Fisher Exact Test (d)		P=0.500N	P=0.121N
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	19.6%	7.2%	2.7%
Terminal Rates (c)	2/19 (11%)	1/37 (3%)	1/37 (3%)
Day of First Observation	635	596	730
Life Table Tests (d)	P=0.016N	P=0.144N	P=0.026N
Logistic Regression Tests (d)	P=0.053N	P=0.301N	P=0.056N
Cochran-Armitage Trend Test (d)	P=0.071N		
Fisher Exact Test (d)		P=0.357N	P=0.102N
Ovary: Tubular Adenoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	0.0%	0.0%	13.0%
Terminal Rates (c)	0/19 (0%)	0/37 (0%)	4/37 (11%)
Day of First Observation			729
Life Table Tests (d)	P=0.019	(e)	P=0.127
Logistic Regression Tests (d)	P=0.018	(e)	P=0.112
Cochran-Armitage Trend Test (d)	P=0.007		
Fisher Exact Test (d)		(e)	P=0.028

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

	Control	1,300 ppm	2,500 ppm
Ovary: Granulosa Cell Tumor, Benign			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	8.1%	2.7%
Terminal Rates (c)	0/19 (0%)	3/37 (8%)	1/37 (3%)
Day of First Observation		730	730
Life Table Tests (d)	P=0.564	P=0.260	P=0.633
Logistic Regression Tests (d)	P=0.564	P=0.260	P=0.633
Cochran-Armitage Trend Test (d)	P=0.367		
Fisher Exact Test (d)		P=0.121	P=0.500
Ovary: Granulosa Cell Tumor, Benign or Malignant			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	0.0%	8.1%	5.1%
Terminal Rates (c)	0/19 (0%)	3/37 (8%)	1/37 (3%)
Day of First Observation		730	729
Life Table Tests (d)	P=0.375	P=0.260	P=0.404
Logistic Regression Tests (d)	P=0.362	P=0.260	P=0.374
Cochran-Armitage Trend Test (d)	P=0.197		
Fisher Exact Test (d)		P=0.121	P=0.247
Ovary: Mixed Tumor, Benign			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	10.0%
Terminal Rates (c)	0/19 (0%)	0/37 (0%)	3/37 (8%)
Day of First Observation			630
Life Table Tests (d)	P=0.035	(e)	P=0.162
Logistic Regression Tests (d)	P=0.018	(e)	P=0.084
Cochran-Armitage Trend Test (d)	P=0.017		
Fisher Exact Test (d)		(e)	P=0.059
Ovary: Tubular Adenoma or Mixed Tumor, Benign			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	9/50 (18%)
Adjusted Rates (b)	0.0%	0.0%	22.6%
Terminal Rates (c)	0/19 (0%)	0/37 (0%)	7/37 (19%)
Day of First Observation			630
Life Table Tests (d)	P=0.001	(e)	P=0.028
Logistic Regression Tests (d)	P<0.001	(e)	P=0.010
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		(e)	P=0.001
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	3/48 (6%)	1/44 (2%)	2/49 (4%)
Adjusted Rates (b)	16.7%	2.9%	4.7%
Terminal Rates (c)	3/18 (17%)	1/35 (3%)	0/36 (0%)
Day of First Observation	730	730	656
Life Table Tests (d)	P=0.178N	P=0.107N	P=0.229N
Logistic Regression Tests (d)	P=0.256N	P=0.107N	P=0.330N
Cochran-Armitage Trend Test (d)	P=0.390N		
Fisher Exact Test (d)		P=0.342N	P=0.490N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	3/48 (6%)	1/49 (2%)	0/50 (0%)
Adjusted Rates (b)	12.3%	2.8%	0.0%
Terminal Rates (c)	1/19 (5%)	1/36 (3%)	0/37 (0%)
Day of First Observation	635	730	
Life Table Tests (d)	P=0.018N	P=0.146N	P=0.047N
Logistic Regression Tests (d)	P=0.039N	P=0.233N	P=0.087N
Cochran-Armitage Trend Test (d)	P=0.057N		
Fisher Exact Test (d)		P=0.301N	P=0.114N

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

	Control	1,300 ppm	2,500 ppm
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	4/48 (8%)	1/49 (2%)	0/50 (0%)
Adjusted Rates (b)	17.2%	2.8%	0.0%
Terminal Rates (c)	2/19 (11%)	1/36 (3%)	0/37 (0%)
Day of First Observation	635	730	
Life Table Tests (d)	P=0.005N	P=0.058N	P=0.016N
Logistic Regression Tests (d)	P=0.012N	P=0.109N	P=0.033N
Cochran-Armitage Trend Test (d)	P=0.023N		
Fisher Exact Test (d)		P=0.175N	P=0.054N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	14.8%	2.7%	2.7%
Terminal Rates (c)	2/19 (11%)	1/37 (3%)	1/37 (3%)
Day of First Observation	728	730	730
Life Table Tests (d)	P=0.067N	P=0.116N	P=0.112N
Logistic Regression Tests (d)	P=0.072N	P=0.134N	P=0.120N
Cochran-Armitage Trend Test (d)	P=0.201N		
Fisher Exact Test (d)		P=0.309N	P=0.309N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	12/50 (24%)	19/50 (38%)	24/50 (48%)
Adjusted Rates (b)	50.2%	43.4%	52.7%
Terminal Rates (c)	8/19 (42%)	13/37 (35%)	16/37 (43%)
Day of First Observation	631	596	568
Life Table Tests (d)	P=0.352	P=0.447N	P=0.449
Logistic Regression Tests (d)	P=0.038	P=0.295	P=0.076
Cochran-Armitage Trend Test (d)	P=0.008		
Fisher Exact Test (d)		P=0.097	P=0.011

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 1,300-ppm and control groups.

TABLE D4a. HISTORICAL INCIDENCE OF OVARIAN TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	No. Examined	No. of Tumors	Diagnosis
Historical Incidence at Southern Research Institute			
HC Blue No. 2	49	2	Granulosa cell tumor
		1	Adenocarcinoma, NOS
C.I. Disperse Blue 1	49	2	Granulosa cell tumor
All others	321	0	
Overall Historical Incidence			
	1,858	1	Adenoma, NOS
		2	Papillary adenoma
		3	Cystadenoma, NOS
		8	Papillary cystadenoma, NOS
		1	Luteoma
		4	Tubular adenoma
		1	Mixed tumor, benign
		6	Granulosa cell tumor
		1	Carcinoma, NOS
		1	Adenocarcinoma, NOS
		1	Cystadenocarcinoma, NOS
		1	Papillary cystadenocarcinoma, NOS
		1	Mucinous adenocarcinoma
		1	Granulosa cell carcinoma
TOTAL		8 (0.4%)	Stromal (granulosa cell or luteoma)
		15 (0.8%)	Epithelial (adenoma or carcinoma)
		4 (0.2%)	Glandular (adenocarcinoma)
		1 (0.1%)	Mixed tumor
		4 (0.2%)	Tubular

(a) Data as of August 7, 1986, for studies of at least 104 weeks

TABLE D4b. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls	
	Lymphoma	Lymphoma or Leukemia
Historical Incidence at Southern Research Institute		
HC Blue No. 2	12/50	12/50
C.I. Disperse Blue 1	17/50	17/50
D-Mannitol	14/48	14/48
Ziram	6/50	11/50
Eugenol	12/50	13/50
Propyl gallate	8/50	9/50
Zearalenone	15/50	15/50
HC Blue No. 1	6/50	7/50
Stannous chloride	5/50	6/50
TOTAL	95/448 (21.2%)	104/448 (23.2%)
SD (b)	8.96%	7.46%
Range (c)		
High	17/50	17/50
Low	5/50	6/50
Overall Historical Incidence		
TOTAL	590/2,041 (28.9%)	616/2,041 (30.2%)
SD (b)	12.56%	12.24%
Range (c)		
High	37/50	38/50
Low	5/50	6/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE D4c. HISTORICAL INCIDENCE OF UTERINE GLANDULAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence of Adenomas, Adenocarcinomas, or Carcinomas in Controls
Historical Incidence at Southern Research Institute	
HC Blue No. 2	0/50
C.I. Disperse Blue 1	0/50
D-Mannitol	0/47
Ziram	0/50
Eugenol	0/50
Propyl gallate	0/50
Zearalenone	0/50
HC Blue No. 1	(b) 1/50
Stannous chloride	0/49
TOTAL	1/446 (0.2%)
SD (c)	0.67%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 7/2,010 (0.3%)
SD (c)	0.78%
Range (d)	
High	1/47
Low	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Squamous cell carcinoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one adenoma, NOS, one squamous cell carcinoma, and five adenocarcinomas, NOS

TABLE D4d. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
HC Blue No. 2	3/50	4/50	7/50
C.I. Disperse Blue 1	2/50	1/50	3/50
D-Mannitol	0/48	3/48	3/48
Ziram	7/50	2/50	9/50
Eugenol	0/50	2/50	2/50
Propyl gallate	0/50	3/50	3/50
Zearalenone	0/50	3/50	3/50
HC Blue No. 1	2/50	1/50	3/50
Stannous chloride	3/49	0/49	3/49
TOTAL	17/447 (3.8%)	19/447 (4.3%)	36/447 (8.1%)
SD (b)	4.64%	2.56%	4.67%
Range (c)			
High	7/50	4/50	9/50
Low	0/50	0/49	2/50
Overall Historical Incidence			
TOTAL	97/2,033 (4.8%)	(d) 83/2,033 (4.1%)	177/2,033 (8.7%)
SD (b)	4.14%	2.61%	4.75%
Range (c)			
High	9/49	5/50	10/49
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) One hepatoblastoma was also observed.

TABLE D4e. HISTORICAL INCIDENCE OF LIVER ITO CELL TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Diagnosis	Incidence in Controls
Historical Incidence at Southern Research Institute		0/447
Overall Historical Incidence		
	Ito cell tumors	0/2,033
	Lipomas	1/2,033 (0.05%)

(a) Data as of August 7, 1986, for studies of at least 104 weeks

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

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(41)	(39)	(42)
Dilatation	2 (5%)		
Liver	(50)	(50)	(50)
Basophilic focus			1 (2%)
Hematopoietic cell proliferation	1 (2%)		
Necrosis, multifocal	1 (2%)	2 (4%)	2 (4%)
Vacuolization cytoplasmic, focal	1 (2%)		
Kupffer cell, pigmentation	1 (2%)		
Sinusoid, infiltration cellular, polymorphonuclear	17 (34%)		
Mesentery	(21)	(2)	(8)
Cyst	1 (5%)		
Hemorrhage, focal	1 (5%)		
Inflammation, subacute, focal	1 (5%)		
Inflammation, suppurative, acute, multifocal	14 (67%)		
Fat, necrosis, focal	4 (19%)	1 (50%)	3 (38%)
Pancreas	(47)	(50)	(50)
Abscess	1 (2%)		
Atrophy	3 (6%)	1 (2%)	2 (4%)
Inflammation, subacute	1 (2%)		
Duct, cyst	1 (2%)		2 (4%)
Stomach, forestomach	(49)	(49)	(50)
Hyperkeratosis	1 (2%)		
Hyperplasia	1 (2%)		1 (2%)
Inflammation, suppurative, acute, focal	1 (2%)		
Ulcer	1 (2%)	1 (2%)	
Stomach, glandular	(49)	(49)	(49)
Edema			1 (2%)
Mineralization			1 (2%)
Ulcer		1 (2%)	
CARDIOVASCULAR SYSTEM			
None			
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)		1 (2%)
Congestion	1 (2%)		
Cyst			4 (8%)
Degeneration, fatty	1 (2%)		
Spindle cell, hyperplasia	3 (6%)	41 (82%)	45 (90%)
Adrenal gland, medulla	(48)	(49)	(49)
Hyperplasia	1 (2%)	2 (4%)	2 (4%)
Pituitary gland	(48)	(44)	(49)
Pars distalis, angiectasis	1 (2%)	1 (2%)	2 (4%)
Pars distalis, hyperplasia		3 (7%)	2 (4%)
Thyroid gland	(48)	(49)	(50)
Follicle, cyst	2 (4%)		2 (4%)
Follicle, degeneration, cystic	3 (6%)		
Follicle, hyperplasia, cystic			1 (2%)

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

	Untreated Control	Low Dose	High Dose
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(1)		
Cyst	1 (100%)		
Ovary	(50)	(50)	(50)
Abscess	18 (36%)		
Atrophy		48 (96%)	49 (98%)
Cyst	14 (28%)	10 (20%)	15 (30%)
Hemorrhage	1 (2%)	1 (2%)	3 (6%)
Inflammation, chronic	1 (2%)		
Mineralization		2 (4%)	3 (6%)
Uterus	(50)	(50)	(50)
Hydrometria	2 (4%)		1 (2%)
Hyperplasia, cystic	49 (98%)	49 (98%)	49 (98%)
Inflammation, suppurative, acute	11 (22%)		
HEMATOPOIETIC SYSTEM			
Lymph node	(50)	(50)	(49)
Deep cervical, inflammation, suppurative, acute, focal	2 (4%)		
Iliac, hyperplasia	2 (4%)		
Mediastinal, congestion	1 (2%)		
Mediastinal, hyperplasia	1 (2%)		
Renal, congestion		1 (2%)	
Renal, hyperplasia	6 (12%)		
Lymph node, mandibular	(50)	(50)	(45)
Congestion	1 (2%)		
Hyperplasia	1 (2%)		
Inflammation, suppurative, acute, focal	1 (2%)		
Lymph node, mesenteric	(45)	(45)	(48)
Angiectasis	3 (7%)		
Hyperplasia	2 (4%)		
Spleen	(49)	(50)	(50)
Angiectasis	1 (2%)		1 (2%)
Hematopoietic cell proliferation	21 (43%)	4 (8%)	2 (4%)
Hemorrhage		1 (2%)	
Thymus	(47)	(48)	(48)
Cyst		1 (2%)	2 (4%)
Hemorrhage	1 (2%)		
Mediastinum, inflammation, suppurative, acute	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(48)	(48)
Duct, cyst	3 (6%)		3 (6%)
Skin	(50)	(50)	(50)
Alopecia	2 (4%)		1 (2%)
Fibrosis			1 (2%)
Hemorrhage, focal	1 (2%)		
Inflammation, granulomatous, focal		1 (2%)	
Inflammation, suppurative, acute	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	(2)	(1)	(2)
Inflammation, suppurative, acute	1 (50%)		
NERVOUS SYSTEM			
Brain	(49)	(50)	(50)
Compression		1 (2%)	1 (2%)
Hydrocephalus		1 (2%)	
Inflammation, suppurative, acute, multifocal		1 (2%)	
Necrosis		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Congestion	1 (2%)		1 (2%)
Hemorrhage, focal		1 (2%)	1 (2%)
Infiltration cellular, histiocytic, multifocal	1 (2%)		
Inflammation, subacute	1 (2%)		
Inflammation, subacute, multifocal	25 (50%)	19 (38%)	19 (38%)
Inflammation, suppurative, acute	1 (2%)		
Alveolar epithelium, hyperplasia	2 (4%)		3 (6%)
Mediastinum, inflammation, suppurative, acute	2 (4%)		
Nose	(48)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, granulomatous		1 (2%)	
Inflammation, suppurative, acute		1 (2%)	1 (2%)
SPECIAL SENSES SYSTEM			
Harderian gland	(2)	(5)	(1)
Hemorrhage		1 (20%)	
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Cyst		1 (2%)	
Fibrosis, focal	1 (2%)	1 (2%)	
Hydronephrosis		1 (2%)	1 (2%)
Metaplasia, osseous, focal			2 (4%)
Nephropathy		1 (2%)	
Cortex, infarct		3 (6%)	1 (2%)
Cortex, mineralization, diffuse		1 (2%)	
Medulla, mineralization			7 (14%)
Renal tubule, degeneration, multifocal			1 (2%)
Renal tubule, dilatation		1 (2%)	1 (2%)
Renal tubule, necrosis, multifocal	1 (2%)		
Urinary bladder	(50)	(50)	(50)
Inflammation, chronic	3 (6%)	2 (4%)	

APPENDIX E

GENETIC TOXICOLOGY OF NITROFURANTOIN

TABLE E1. MUTAGENICITY OF NITROFURANTOIN IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b) −S9	+S9 (hamster)	+S9 (rat)
TA1535	0	21 ± 3.7	10 ± 1.7	7 ± 2.5
	0.1	17 ± 1.3	5 ± 3.4	14 ± 0.6
	0.3	22 ± 4.8	13 ± 3.5	9 ± 2.0
	1	21 ± 4.2	11 ± 1.7	13 ± 0.3
	3	17 ± 5.7	15 ± 1.5	12 ± 1.7
	10	Toxic	13 ± 2.6	17 ± 1.2
Trial summary		Negative	Negative	Negative
Positive control (c)		384 ± 17.9	429 ± 31.8	255 ± 18.4
TA1537	0	8 ± 0.6	7 ± 3.0	13 ± 2.9
	0.1	10 ± 2.9	13 ± 3.2	11 ± 2.2
	0.3	9 ± 2.8	9 ± 1.5	14 ± 1.9
	1	13 ± 1.9	10 ± 3.3	8 ± 0.9
	3	7 ± 1.2	17 ± 1.9	17 ± 2.0
	10	Toxic	18 ± 4.7	23 ± 2.4
Trial summary		Negative	Negative	Negative
Positive control (c)		99 ± 3.5	479 ± 6.1	238 ± 4.4

Strain	Dose (µg/plate)	Revertants/Plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
TA100	0	145 ± 1.5	120 ± 4.7	160 ± 11.8	126 ± 9.1	154 ± 16.5	117 ± 7.8
	0.03	--	136 ± 13.2	--	156 ± 17.0	--	139 ± 12.5
	0.1	337 ± 7.5	228 ± 16.7	288 ± 16.6	214 ± 23.1	202 ± 7.5	158 ± 7.3
	0.3	860 ± 17.9	528 ± 38.2	501 ± 24.2	440 ± 42.1	297 ± 2.6	216 ± 14.2
	1	1,471 ± 31.2	1,216 ± 34.0	990 ± 30.6	824 ± 64.1	585 ± 25.5	463 ± 20.4
	3	(d) 469 ± 183.2	404 ± 24.0	931 ± 43.9	670 ± 87.9	1,131 ± 53.2	870 ± 38.9
	10	Toxic	--	475 ± 120.2	--	(d) 420 ± 84.4	--
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		321 ± 11.7	424 ± 16.2	2,113 ± 4.8	1,895 ± 83.7	1,055 ± 61.4	900 ± 15.3
TA98	0	25 ± 0.9	22 ± 2.7	24 ± 3.7	28 ± 4.6	38 ± 6.7	24 ± 2.6
	0.03	--	18 ± 2.6	--	29 ± 0.7	--	34 ± 7.1
	0.1	31 ± 3.5	24 ± 2.3	36 ± 2.8	31 ± 2.2	29 ± 3.8	24 ± 3.8
	0.3	39 ± 4.3	53 ± 3.2	39 ± 1.9	39 ± 0.9	33 ± 3.5	29 ± 6.4
	1	75 ± 4.1	89 ± 10.6	50 ± 0.6	41 ± 2.9	40 ± 4.4	38 ± 5.8
	3	41 ± 5.5	24 ± 6.8	90 ± 3.2	60 ± 1.5	59 ± 4.6	56 ± 4.8
	10	(d) 0 ± 0.0	--	33 ± 3.7	--	65 ± 6.1	--
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		830 ± 33.4	760 ± 8.0	1,779 ± 45.1	1,761 ± 147.7	613 ± 12.5	640 ± 8.7

(a) Study performed at SRI International. The detailed protocol is presented in Haworth et al. (1983). Cells and study compound or solvent (dimethylsulfoxide) 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 E2. MUTAGENICITY OF NITROFURANTOIN IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
Trial 1					
Dimethyl sulfoxide (d)		108.0 ± 0.0	100.0 ± 16.0	114.5 ± 4.5	35.5 ± 1.5
Nitrofurantoin	50	90.0 ± 4.6	65.0 ± 3.2	145.0 ± 5.6	53.7 ± 1.8
	100	81.3 ± 5.9	44.7 ± 3.5	245.3 ± 19.6	(e) 101.0 ± 3.6
	150	79.3 ± 11.5	26.7 ± 1.2	472.7 ± 97.1	(e) 196.3 ± 13.7
	200	70.5 ± 4.5	22.5 ± 3.5	417.0 ± 181.0	(e) 194.0 ± 74.0
	(f) 300	67.3 ± 5.2	15.0 ± 1.5	586.7 ± 44.6	(e) 292.0 ± 12.1
	500	54.3 ± 3.9	9.0 ± 0.6	485.7 ± 41.2	(e) 297.7 ± 13.9
Methyl methanesulfonate	5	80.3 ± 5.2	56.3 ± 2.3	684.0 ± 29.0	(e) 285.3 ± 6.1
Trial 2					
Dimethyl sulfoxide (g)		84.0 ± 1.7	100.0 ± 6.1	63.5 ± 8.1	25.3 ± 3.0
Nitrofurantoin	50	84.7 ± 5.6	65.0 ± 2.6	102.7 ± 26.5	(e) 40.0 ± 8.7
	100	75.0 ± 1.2	42.3 ± 3.5	137.3 ± 33.2	(e) 60.7 ± 14.2
	150	61.0 ± 2.6	27.7 ± 0.9	142.3 ± 26.7	(e) 78.3 ± 14.7
	200	59.7 ± 10.7	15.0 ± 2.0	245.3 ± 40.6	(e) 144.0 ± 31.9
	(f) 300	37.3 ± 5.6	6.3 ± 1.2	297.0 ± 38.2	(e) 270.7 ± 29.2
	500	19.3 ± 2.8	2.0 ± 0.0	189.3 ± 61.1	(e) 374.0 ± 141.5
Methyl methanesulfonate	5	56.7 ± 6.1	44.0 ± 3.5	247.7 ± 20.2	(e) 149.0 ± 20.0

(a) Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate; the average for the three 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 for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency. All trials were conducted in the absence of S9.

(b) Mean ± standard error from replicate trials of approximately 1×10^6 cells each, unless otherwise noted. 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 mutagenic. 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 mutant count 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 two 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) Precipitate formed at this and all higher concentrations.

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

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY NITROFURANTOIN (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)								
Trial 1--Summary: Equivocal								
Dimethyl sulfoxide		50	1,023	493	0.48	9.9	26.0	
Nitrofurantoin	3.3	50	1,007	487	0.48	9.7	(d) 32.0	98.0
	10	50	1,026	489	0.48	9.8	(d) 32.0	99.0
	33.3	50	1,011	583	0.58	11.7	(d) 32.0	118.2
	100	0					26.0	
Mitomycin C	0.001	50	1,027	597	0.58	11.9	26.0	120.2
	0.01	5	103	144	1.40	28.8	26.0	290.9
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,012	455	0.45	9.1	26.0	
Nitrofurantoin								
	10	50	1,000	532	0.53	10.6	(d) 31.5	116.5
	25	50	1,006	623	0.62	12.5	(d) 31.5	137.4
	33	50	1,020	774	0.76	15.5	(d) 31.5	170.3
	50	0					26.0	
Mitomycin C	0.001	50	1,013	602	0.59	12.0	26.0	131.9
	0.01	5	101	153	1.51	30.6	26.0	336.3
+S9 (e)								
Trial 1--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,018	483	0.47	9.7	26.0	
Nitrofurantoin	33	50	1,006	483	0.48	9.7	(d) 32.0	100.0
	100	50	1,001	528	0.53	10.6	(d) 32.0	109.3
	333	50	1,016	602	0.59	12.0	(d) 32.0	123.7
	1,000	0					26.0	
Cyclophosphamide	0.4	50	1,033	673	0.65	13.5	26.0	139.2
	2	5	104	178	1.71	35.6	26.0	367.0
Trial 2--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,020	457	0.45	9.1	26.0	
Nitrofurantoin	330	50	1,028	498	0.48	10.0	(d) 31.5	109.9
	500	50	1,017	526	0.52	10.5	(d) 31.5	115.4
	750	50	1,001	634	0.63	12.7	(d) 31.5	139.6
Cyclophosphamide	0.4	50	1,029	649	0.63	13.0	26.0	142.9
	2	5	101	150	1.49	30.0	26.0	329.7

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY NITROFURANTOIN (Continued)

(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 (dimethylsulfoxide) as described in (c) or (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
(b) SCEs/cell in treated culture expressed as a percent of the SCEs/cell in the control culture
(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. Then cells were washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY NITROFURANTOIN (a)

Trial 1					Trial 2				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
-S9 (b)									
Dimethyl sulfoxide									
	200	1	0.01	1.0					
	200	0	0.00	0.0					
Nitrofurantoin									
10	200	4	0.02	2.0					
25	200	5	0.03	3.0					
50	200	9	0.05	5.0					
75	0								
	Summary: Weakly positive								
Mitomycin C									
0.05	200	44	0.22	19.0					
0.08	25	25	1.00	60.0					
+S9 (c)									
Dimethyl sulfoxide					Dimethyl sulfoxide				
	200	4	0.02	2.0		100	0	0.00	0.0
	200	1	0.01	1.0		100	2	0.02	2.0
Nitrofurantoin					Nitrofurantoin				
250	200	4	0.02	2.0	747	100	10	0.10	8.0
500	200	2	0.01	1.0	900	100	23	0.23	17.0
750	200	17	0.09	6.0	950	100	33	0.33	16.0
1,000	0								
	Summary: Weakly positive					Summary: Positive			
Cyclophosphamide					Cyclophosphamide				
6.25	200	10	0.05	4.0	6.25	100	15	0.15	13.0
12.5	25	7	0.28	28.0	12.5	25	12	0.48	40.0

(a) Study performed at Litton Bionetics, Inc. Abs = aberrations. Harvest time--20.0 hours. A detailed presentation of the technique for detecting chromosomal aberrations is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) or (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, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) 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 (dimethyl sulfoxide) 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.

TABLE E5. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA BY NITROFURANTOIN (a)

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested			Overall Total (b)
				Mating 1	Mating 2	Mating 3	
Feeding	2,000	52	25	5/5,063	4/3,279	3/3,400	12/11,742 (0.10%)
	0	--	--	5/4,271	3/2,942	2/2,396	10/9,609 (0.10%)
Injection	10,000	13	1	1/2,822	1/2,856	1/2,591	3/8,269 (0.04%)
	0	--	--	2/1,964	1/1,919	1/1,882	4/5,765 (0.07%)

(a) Study performed at Bowling Green State University. A detailed protocol of the sex-linked recessive lethal assay is presented in Zimmering 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 were not 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

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

Methods

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

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Data from animals surviving 24 months were collected from 5/50 randomly selected 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 viral antibody titers. The following tests were performed:

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

Results

Results are presented in Table F1.

TABLE F1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF NITROFURANTOIN (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	2/10	RCV
	10/10	Sendai
12	1/10	RCV
	9/10	Sendai
18	4/9	Sendai
24	3/10	Sendai
	2/10	KRV
MICE		
6	10/10	Sendai
12	4/10	Sendai
18	9/9	Sendai
24	5/10	Sendai

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX G

FEED AND COMPOUND CONSUMPTION BY RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF NITROFURANTOIN

TABLE G1. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

Week	Control		1,300 ppm			2,500 ppm		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
2	17	190	17	192	115	16	177	226
6	17	264	17	268	82	16	240	167
11	17	321	17	327	68	16	300	133
17	19	363	20	365	71	19	340	140
21	18	381	17	381	58	17	361	118
25	18	393	18	391	60	16	374	107
29	19	404	17	406	54	15	385	97
34	18	416	17	416	53	17	402	106
38	18	422	19	426	58	18	414	109
44	19	430	19	427	58	17	420	101
48	19	443	19	448	55	17	438	97
52	18	449	18	452	52	17	446	95
55	17	445	17	450	49	16	439	91
59	19	452	19	452	55	18	448	100
64	17	455	17	451	49	17	456	93
69	17	454	17	445	50	17	453	94
74	18	442	18	439	53	17	444	96
78	18	446	17	440	50	16	442	90
82	16	441	17	434	51	16	437	92
86	18	440	17	428	52	17	435	98
90	17	440	18	432	54	16	430	93
94	16	436	17	426	52	17	425	100
98	17	435	17	422	52	17	413	103
104	18	412	17	401	55	18	391	115
Mean	17.7	407	17.6	405	59	16.8	396	111
SD (c)	0.9		0.9		14	0.9		30
CV (d)	5.1		5.1		23.7	5.4		27.0

(a) Average grams of feed removed from feeder per animal per day. Not corrected for scatter.
(b) Estimated milligrams of nitrofurantoin consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE G2. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

Week	Control		600 ppm			1,300 ppm		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
2	13	135	13	138	57	13	136	124
6	12	170	14	174	48	12	167	93
11	11	193	11	198	33	11	191	75
17	10	210	12	216	33	11	206	69
21	12	214	11	223	30	11	212	67
25	11	225	11	231	29	11	217	66
29	11	228	11	239	28	11	223	64
34	11	237	11	248	27	11	233	61
38	12	245	12	256	28	11	237	60
44	13	256	13	271	29	11	246	58
48	11	267	11	279	24	10	256	51
52	13	283	13	294	27	12	270	58
55	12	288	13	300	26	13	277	61
59	13	303	13	310	25	13	291	58
64	13	316	12	325	22	12	302	52
69	13	328	13	339	23	12	314	50
74	13	332	13	343	23	13	318	53
78	14	340	13	347	22	13	324	52
82	13	343	14	355	24	13	331	51
86	13	345	14	359	23	14	339	54
90	13	352	14	367	23	14	344	53
94	14	353	14	368	23	14	346	53
98	14	361	14	375	22	13	352	48
104	14	352	13	359	22	14	351	52
Mean	12.5	278	12.6	288	28	12.2	270	62
SD (c)	1.1		1.1		8	1.2		17
CV (d)	8.8		8.7		28.6	9.8		27.4

(a) Average grams of feed removed from feeder per animal per day. Not corrected for scatter.
(b) Estimated milligrams of nitrofurantoin consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE G3. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

Week	Control		1,300 ppm			2,500 ppm		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
4	6	27.6	6	27.6	283	6	25.3	593
8	7	30.9	8	29.7	350	7	28.5	614
13	7	33.4	8	31.7	328	8	31.0	645
18	7	34.9	7	33.9	268	7	32.0	547
22	8	36.0	8	35.0	297	8	33.1	604
26	8	37.2	7	35.3	258	8	34.1	587
30	7	37.4	8	36.4	286	7	34.0	515
35	10	38.0	9	36.8	318	9	34.9	645
40	8	38.1	8	36.2	287	8	35.4	565
45	9	39.1	8	37.9	274	8	36.0	556
49	8	40.0	7	37.6	242	7	36.6	478
53	8	41.4	7	39.0	233	7	37.6	465
57	9	41.5	8	39.6	263	8	37.8	529
61	9	41.3	9	39.1	299	8	37.7	531
65	9	41.4	8	40.2	259	8	37.9	528
69	9	41.1	8	39.6	263	8	37.5	533
74	9	40.7	9	38.0	308	8	36.4	549
78	9	40.4	9	38.2	306	8	36.3	551
82	9	41.0	9	38.6	303	8	37.0	541
86	10	39.6	10	37.2	349	9	36.3	620
90	9	40.0	11	38.6	370	9	36.3	620
94	10	40.1	10	38.5	338	9	36.0	625
98	9	39.9	12	38.9	401	11	36.3	758
104	5	39.6	6	39.1	199	6	36.5	411
Mean	8.3	38.4	8.3	36.8	295	7.9	35.0	567
SD (c)	1.3		1.4		46	1.1		71
CV (d)	15.7		16.9		15.6	13.9		12.5

(a) Average grams of feed removed from feeder per animal per day. Not corrected for scatter.
(b) Estimated milligrams of nitrofurantoin consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE G4. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURANTOIN

Week	Control		1,300 ppm			2,500 ppm		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
4	6	21.0	6	21.4	364	6	21.1	711
8	7	23.5	8	23.9	435	7	23.2	754
13	7	25.4	7	25.0	364	8	24.3	823
18	5	26.6	6	26.2	298	6	25.3	593
22	6	28.4	7	27.3	333	7	26.1	670
26	6	29.2	6	28.2	277	7	27.0	648
30	6	29.6	6	28.8	271	6	26.8	560
35	8	30.8	7	29.6	307	8	27.7	722
40	7	32.1	7	29.8	305	6	28.4	528
45	7	32.7	7	31.0	294	7	28.6	612
49	7	34.3	6	32.4	241	7	29.6	591
53	7	35.4	7	33.8	269	7	31.0	565
57	7	35.2	7	34.6	263	7	31.3	559
61	8	36.1	7	35.1	259	7	32.1	545
65	8	37.0	7	36.5	249	7	34.2	512
69	8	37.1	7	37.1	245	7	34.7	504
74	8	36.4	7	36.7	248	7	34.4	509
78	7	36.8	7	36.9	247	6	34.9	430
82	8	38.1	7	38.7	235	7	36.6	478
86	9	37.7	8	38.7	269	7	35.7	490
90	9	39.0	8	40.2	259	7	36.4	481
94	10	39.8	7	40.5	225	8	36.6	546
98	10	40.5	7	41.0	222	9	37.0	608
104	5	41.7	5	40.5	160	6	37.0	405
Mean	7.3	33.5	6.8	33.1	277	7.0	30.8	577
SD (c)	1.3		0.7		56	0.8		103
CV (d)	17.8		10.3		20.2	11.4		17.9

(a) Average grams of feed removed from feeder per animal per day. Not corrected for scatter.
(b) Estimated milligrams of nitrofurantoin consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX H

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

Meal Diet: December 1980 to January 1983

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

TABLE H1. 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 H2. 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 H3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.25 ± 1.04	22.6-26.3	24
Crude fat (percent by weight)	5.10 ± 0.44	4.4-6.0	24
Crude fiber (percent by weight)	3.38 ± 0.38	2.4-4.2	24
Ash (percent by weight)	6.59 ± 0.34	5.97-7.42	24
Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,188 ± 1,239	8,900-14,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	19.0 ± 3.02	14.0-26.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.23 ± 0.12	1.10-1.53	24
Phosphorus (percent)	0.97 ± 0.06	0.84-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (7/22/81) not analyzed for thiamine

TABLE H4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.44 ± 0.14	<0.21-0.93	24
Cadmium (ppm) (a)	<0.1		24
Lead (ppm)	1.03 ± 0.75	0.27-2.93	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.27 ± 0.05	0.16-0.40	24
Aflatoxins (ppb) (a,b)	<10	<5.0-10.0	24
Nitrate nitrogen (ppm) (c)	9.35 ± 4.35	0.6-18.0	24
Nitrite nitrogen (ppm) (c)	1.97 ± 1.28	0.4-5.3	24
BHA (ppm) (d,e)	5.83 ± 5.12	0.4-20.0	24
BHT (ppm) (d)	3.42 ± 2.57	<1.0-13.0	24
Aerobic plate count (CFU/g)	105,438 ± 75,797	7,000-300,000	24
Coliform (MPN/g) (f)	1,046 ± 973	<3-2,400	24
E. coli (MPN/g) (f,g)	8.0 ± 7.91	<3-23	23
E. coli (MPN/g) (h)	13.92 ± 30.0	<3-150	24
Total nitrosamines (ppb) (i, j)	5.13 ± 4.47	<1.2-18.8	22
Total nitrosamines (ppb) (i,k)	13.11 ± 27.39	<1.2-101.6	24
N-Nitrosodimethylamine (ppb) (i,l)	3.82 ± 4.29	0.6-16.8	22
N-Nitrosodimethylamine (ppb) (i,m)	11.71 ± 27.03	0.6-99	24
N-Nitrosopyrrolidine (ppb)	1.21 ± 0.66	<0.3-2.4	24
Pesticides (ppm)			
α-BHC (a,n)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (o)	<0.01	0.05 (7/14/81)	24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (p)	<0.05	0.13 (8/25/81); 0.06 (6/29/82)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCBs (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (o)	<0.1		24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (q)	0.08 ± 0.05	<0.05-0.25	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

TABLE H4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) One batch contained less than 0.5 ppm. The value was <0.04, and the batch was produced on 4/27/81.
(f) MPN = most probable number
(g) Mean, standard deviation, and range exclude one value of 150 ppm obtained for the batch produced on 8/26/82.
(h) Mean, standard deviation, and range include the high value listed in footnote (g).
(i) All values were corrected for percent recovery.
(j) Mean, standard deviation, and range exclude two very high values of 101.6 and 100.3 ppb obtained for batches produced on 1/26/81 and 4/27/81.
(k) Mean, standard deviation, and range include the high values listed in footnote (j).
(l) Mean, standard deviation, and range exclude two very high values in the range of 97.9 and 99 ppb obtained for batches produced on 1/26/81 and 4/27/81.
(m) Mean, standard deviation, and range include the very high values given in footnote (l).
(n) BHC = hexachlorocyclohexane or benzene hexachloride.
(o) There was one observation above the detection limit; the value and date it was obtained are given under the range.
(p) There were two observations above the detection limit; the values and dates they were obtained are given under the range.
(q) Eleven batches contained more than 0.05 ppm.

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The experimental data, documents, and pathology specimens for the 2-year toxicology and carcinogenesis studies of nitrofurantoin in rats and mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations of the Food and Drug Administration (fully implemented by the National Toxicology Program (NTP) beginning October 1, 1981). The animal studies were conducted for the NTP by Southern Research Institute (Birmingham, AL) under a subcontract with Tracor Jitco, Inc., until May 31, 1982, and then under contract with the National Institute of Environmental Health Sciences (NIEHS). Animal exposure to the chemical in feed began in February 1981. The retrospective audit was conducted for the NIEHS at the NTP Archives in June 1986 by Dynamac Corporation, J.C. Bhandari, D.V.M., Ph.D., Principal Investigator. The other individuals who conducted the audit are listed in the full audit report, which is on file at the NIEHS. The audit included a review of:

1. All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
2. Body weight, feed consumption, and clinical observation data for a random 10% sample of the study animals.
3. All inlife records, including protocol, correspondence, environmental conditions, palpable masses, mortality, animal identification, and correlation of final inlife observation of masses, date of death, and disposition with necropsy records.
4. All chemistry records.
5. All postmortem records for individual animals concerning identification, disposition codes, condition codes, correlations between gross observations and microscopic diagnoses, and tissue accountability.
6. All wet tissue bags for inventory and wet tissues from a random 10% sample of the study animals, plus other relevant cases, to verify animal identification and examine for untrimmed potential lesions.
7. Blocks and slides of tissues from control and high dose groups of study animals to examine for proper match and inventory.
8. Comparison of individual animal data tables.
9. Draft (4/87) of the NTP Technical Report on the 2-year studies of nitrofurantoin.

Inlife procedures and events were documented adequately by the archival records with the exception of analytical data for chemical/vehicle samples in the animal room and bulk chemical reanalysis within 30 days prior to initiation of the study. The relatively few audit findings from review of the inlife records were miscellaneous and minor; for example, four mice (one control male, two control females, and one high dose female) were coded as moribund kill in clinical records and were coded as found dead in necropsy records. No corresponding necropsy descriptions of masses were found for five rats; these discrepancies were resolved by examination of the wet tissues. Animal disposition for one control male rat (animal no. 10) and one high dose male mouse (animal no. 7) was found to be recorded in error in EISRPT01. Because the resulting changes in the statistical analyses did not influence interpretation of the studies, these changes were not incorporated into the Technical Report.

Inspection of wet tissues for individual animal identifiers showed that 42/48 rats and 31/34 mice were identified correctly by their residual tissues. All animals that were cross-checked were correctly identified, with the exception of one control male rat with a torn ear that prevented further verification. The audit identified five untrimmed potential lesions in the wet tissues of 48 rats examined and three untrimmed potential lesions in 34 mice examined. These lesions were in nontarget tissues and were examined by NTP pathologists. The correlation between gross observation and microscopic diagnoses was very good (only one noncorrelation in rats and three in mice). Full details of these and other audit findings are presented in the audit report. In conclusion, the study records at the NTP Archives support the data and results presented in the NTP Technical Report.