NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 337

TOXICOLOGY AND CARCINOGENESIS STUDIES OF NITROFURAZONE

(CAS NO. 59-87-0)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF NITROFURAZONE

(CAS NO. 59-87-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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P.O. Box 12233
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NOTE TO THE READER

This study was performed under the direction of the National Institute of Environmental Health Sciences as a function of the National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for public peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

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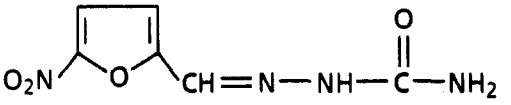

NITROFURAZONE

CAS No. 59-87-0

$C_6H_6N_4O_4$ Molecular weight 198.1

Synonyms or Trade Names: 5-Nitro-2-furaldehyde semicarbazone; 2-[(5-Nitro-2-furanyl)methylene]hydrazine carboxamide; Aldomycin; Amifur; Chemfuran; Coxistat; Furacin; Furacinetten; Furaplast; Furazol W; Furesol; Furracoccid; Mammex; Nefco; Nifuzon; Nitrofural; Vabrocid

ABSTRACT

Nitrofurazone is a synthetic furan derivative, active against a broad spectrum of bacteria, which has been widely used in veterinary and human medicine. Toxicology and carcinogenesis studies were conducted by feeding diets containing nitrofurazone (99% pure) 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: Groups of five males and five females of each species were fed diets containing 0, 630, 1,250, 2,500, 5,000, or 10,000 ppm for 14 consecutive days. Early deaths occurred in all groups of rats receiving 5,000 or 10,000 ppm nitrofurazone. The surviving rats in the lower two dose groups gained weight, but weight gain was decreased as the dose of nitrofurazone was increased. Feed consumption by rats of each sex was decreased at all doses above 630 ppm. In all dosed groups, clinical signs of toxicity included rough hair coats and lethargy. At doses of 2,500 ppm and above, rats of each sex exhibited intermittent episodes of seizures and lethargy.

All mice that received 2,500, 5,000, or 10,000 ppm nitrofurazone and 3/5 males that received 1,250 ppm died before the end of the 14-day studies; the surviving dosed mice (except females at 630 ppm) lost weight. A dose-related decrease in feed consumption was observed at all doses above 630 ppm. Clinical signs included rough hair coats and convulsive seizures.

In the 13-week studies, groups of 10 rats of each sex were given diets containing 0, 150, 310, 620, 1,250, or 2,500 ppm nitrofurazone. No deaths were observed and all animals gained weight, but the magnitude of weight gain was dose dependent with decrements in final mean body weight for the highest dose group reaching 55% in males and 36% in females. Other evidence of chemically related toxicity included convulsive seizures, osteoporosis, degenerative arthropathy, and gonadal hypoplasia in both sexes at the two highest doses.

Groups of 10 mice of each sex were given diets containing 0, 70, 150, 310, 620, or 1,250 ppm nitrofurazone for 13 weeks. Early deaths were observed in the two highest dose groups of each sex. The final mean body weights of male and female mice in the 1,250-ppm groups were about 20% lower than those of the controls; weight gains of the other dosed mice were comparable to those of the controls. Stimulus-induced convulsive seizures were observed for all mice in the two highest dose groups. Testicular hypoplasia was observed in the two highest dose groups of male mice.

Body Weight and Survival in the Two-Year Studies: Dietary concentrations for the 2-year studies were 0, 310, or 620 ppm for rats and 0, 150, or 310 ppm for mice (50 animals per dose group). Mean

body weights of high dose male rats were lower than those of the controls after week 39; mean body weights of low dose male rats and of the controls were comparable throughout the study. Final mean body weights of low and high dose female rats were 9% and 21% lower than those of the controls. Dosed rats consumed less feed than did the controls. The average amount of nitrofurazone consumed per day was approximately 11-12 or 24-26 mg/kg by low or high dose male and female rats. The survival of the high dose group of male rats was lower than that of the controls after week 92 (final survival--male: control, 33/50; low dose, 30/50; high dose, 20/50; female: 28/50; 37/50; 31/50).

Mean body weights of dosed mice were similar to or somewhat greater than those of the controls throughout most of the studies. The average daily feed consumption by dosed mice was similar to that of controls. The average amount of nitrofurazone consumed per day was approximately 14-16 or 29-33 mg/kg for low or high dose male and female mice. The survival of the high dose group of male mice was lower than that of the controls after week 88 (final survival--male: 39/50; 31/50; 27/50; female: 39/50; 40/50; 35/50).

In mice of each sex, nitrofurazone administration induced stimulus-sensitive convulsive seizures beginning at week 4 or 5 for high dose mice and week 24 for low dose female mice. These seizures were observed primarily in the first year of the study.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Degenerative changes involving the vertebral and femoro-tibial (knee) joints were observed at increased incidences in dosed rats. The degenerative changes primarily affected the articular cartilage and were similar to those seen in the 13-week studies. Degeneration of the sternal synchondroses was increased in high dose female rats. The osteoporosis seen in the 13-week studies was not observed in the 2-year studies. Testicular degeneration, characterized by atrophy of the germinal epithelium and aspermatogenesis, was observed at increased incidences in dosed male rats (control, 12/50; low dose, 49/50; high dose, 47/50).

Adenomas of the sebaceous glands and trichoepitheliomas or sebaceous adenomas (combined) of the skin were observed in high dose male rats (0/50; 0/50; 5/50). Carcinomas of the preputial gland were increased in dosed male rats (1/50; 8/50; 5/50). The incidences of preputial gland adenomas or carcinomas (combined) in dosed male rats were not statistically greater than that in the controls (9/50; 16/50; 7/50). However, in the low dose group, the incidence is greater than the highest incidence observed in historical untreated control groups (9/50). In addition, hyperplasia of the preputial gland was observed in six low dose male rats in which neither adenomas nor carcinomas occurred. The incidence of mesotheliomas of the tunica vaginalis in low dose male rats was greater than that in the controls (0/50; 7/50; 2/50).

Fibroadenomas of the mammary gland occurred at markedly increased incidences in dosed female rats (8/49; 36/50; 36/50). Three adenocarcinomas were also observed (1/49; 0/50; 2/50).

Ovarian atrophy (7/47; 44/50; 38/50) and tubular cell hyperplasia of the ovary (1/47; 23/50; 21/50) were observed at markedly increased incidences in dosed female mice. The incidences of benign mixed tumors (0/47; 17/50; 20/50), granulosa cell tumors (1/47; 4/50; 9/50), and granulosa cell tumors or luteomas (combined) (3/47; 6/50; 9/50) of the ovary were increased in exposed female mice.

Mononuclear cell leukemia in rats occurred with negative trends (male: 21/50; 23/50; 6/50; female: 15/49; 2/50; 2/50). In female mice, the incidences of adenomas or carcinomas (combined) of the anterior pituitary gland occurred with a negative trend (10/50; 7/50; 2/49). The incidences of testicular interstitial cell tumors were decreased in dosed male rats (45/50; 30/50; 28/50).

Genetic Toxicology: Nitrofurazone was mutagenic in *Salmonella typhimurium* strains TA98 and TA100 both with and without exogenous metabolic activation. The responses in strains TA1535 and

TA1537 were more varied: nitrofurazone was mutagenic in strain TA1535 only in the presence of S9 and produced no consistent increase in gene reversions in strain TA1537 with or without S9. In the absence of metabolic activation, nitrofurazone induced forward mutations at the $TK^{+/-}$ locus of mouse L5178Y lymphoma cells; the chemical was not tested with S9. Treatment of cultured Chinese hamster ovary cells with nitrofurazone in the absence of S9 produced a dose-related increase in sister chromatid exchanges and chromosomal aberrations; with S9, sister chromatid exchanges were increased, but no induction of chromosomal aberrations was observed.

Audit: The data, documents, and pathology materials from the 2-year studies of nitrofurazone were audited at the NTP Archives. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report.

Conclusions: Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity** of nitrofurazone for male F344/N rats as shown by the occurrence of sebaceous gland adenomas and trichoepitheliomas of the skin, mesotheliomas of the tunica vaginalis, and preputial gland tumors. There was *clear evidence of carcinogenic activity* of nitrofurazone for female F344/N rats as shown by a markedly increased incidence of fibroadenomas of the mammary gland. There was *no evidence of carcinogenic activity* for male $B6C3F_1$ mice fed diets containing nitrofurazone at concentrations of 150 or 310 ppm. There was *clear evidence of carcinogenic activity* of nitrofurazone for female $B6C3F_1$ mice as shown by increased incidences of benign mixed tumors and granulosa cell tumors of the ovary.

Administration of nitrofurazone was associated with decreased incidences of mononuclear cell leukemia in male and female rats, testicular interstitial cell tumors in male rats, and pituitary gland neoplasms in female mice. Convulsive seizures in mice of each sex, ovarian atrophy in female mice, testicular degeneration in rats, and degeneration of articular cartilage in rats were all associated with the administration of nitrofurazone.

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*Explanation of Levels of Evidence of Carcinogenic Activity is on page 9.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 12-13.

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

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Dietary concentrations			
310 or 620 ppm nitrofurazone	310 or 620 ppm nitrofurazone	150 or 310 ppm nitrofurazone	150 or 310 ppm nitrofurazone
Survival rates in the 2-year study			
33/50; 30/50; 20/50	28/50; 37/50; 31/50	39/50; 31/50; 27/50	39/50; 40/50; 35/50
Body weights in the 2-year study			
High dose lower than controls	Dosed lower than controls	Dosed and controls comparable	Dosed and controls comparable
Nonneoplastic effects			
Degeneration of articular cartilage; gonadal atrophy	Degeneration of articular cartilage	Convulsive seizures	Convulsive seizures; gonadal atrophy
Neoplastic effects			
Sebaceous gland adenomas and trichoepitheliomas of the skin; mesotheliomas of the tunica vaginalis; preputial gland tumors	Mammary gland fibroadenomas	None	Ovarian granulosa cell and benign mixed tumors
Level of evidence of carcinogenic activity			
Equivocal evidence	Clear evidence	No evidence	Clear evidence
Other considerations			
Decreased incidences of mononuclear cell leukemia and testicular interstitial cell tumors	Decreased incidence of mononuclear cell leukemia	None	Decreased incidence of anterior pituitary gland neoplasms
Genetic toxicology			
Mutagenic in *S. typhimurium* TA98 and TA100 with and without S9; mutagenic in *S. typhimurium* TA1535 with S9. Mutagenic in L5178Y lymphoma cells without S9; caused increased frequency of sister chromatid exchanges in cultured CHO cells in the absence and presence of S9; caused increase in chromosomal aberrations in CHO cells in the absence but not the presence of S9.			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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.

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. 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 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.

These considerations together with the definitions as written should be used as composite guidelines for selecting one of the five categories. Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the induction by chemicals of more neoplasms than are generally found, or the earlier induction by chemicals of neoplasms that are commonly observed. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Nitrofurazone is based on the 13-week studies that began in July 1980 and ended in October 1980 and on the 2-year studies that began in June 1981 and ended in June 1983 at Physiological Research Laboratories.

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The members of the Peer Review Panel who evaluated the draft Technical Report on nitrofurazone on July 14, 1987, 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 NITROFURAZONE

On July 14, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of nitrofurazone 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, Research Triangle Park, North Carolina.

Dr. F. Kari, NIEHS, introduced the studies by reviewing the experimental design, results, and proposed conclusions (equivocal evidence of carcinogenic activity for male rats; clear evidence of carcinogenic activity for female rats; no evidence of carcinogenic activity for male mice; clear evidence of carcinogenic activity for female mice).

Dr. Chinchilli, a principal reviewer, agreed with the conclusions. He suggested that a sentence might be added to the conclusion for male rats to emphasize the uncertainty as to whether the increased tumor incidences were chemically related. Dr. Kari indicated that the definition of equivocal evidence of carcinogenic activity already emphasized this uncertainty.

As a second principal reviewer, Dr. Hooper agreed with the conclusions for male and female rats and female mice. He stated that the conclusion for male mice should be equivocal evidence of carcinogenic activity, based on marginal increases of subcutaneous tissue fibromas, sarcomas, fibrosarcomas, or neurofibrosarcomas (combined) in high dose animals. Further, he felt that reduced survival in the high dose animals limited the sensitivity of the assay to detect carcinogenic effects. Dr. Kari explained that the large variability in the historical control data base for subcutaneous tumors was a prime reason for not associating these tumors with chemical exposure. Dr. Hooper asked if there was any mechanistic explanation for the decreases in incidence of several tumors in dosed rats and mice. Dr. Kari said he could only speculate that there is some relationship between body weight differences and incidences of certain endocrine-associated tumors.

As a third principal reviewer, Dr. Ashby agreed with the conclusion for male mice. For male rats, he asked whether the incidences of preputial gland adenomas and carcinomas should be analyzed separately, in which case the incidence of carcinomas in exposed groups supported a conclusion of some evidence of carcinogenic activity. Dr. Kari said the progression from adenomas to carcinomas was an established continuum and thus evaluating them combined is more appropriate (although the incidences for benign and malignant tumors are also shown separately). Dr. J. Huff, NIEHS, indicated this was a routine analysis procedure adopted for all tumor sites. Dr. Ashby continued that the conclusion for female rats should be some evidence of carcinogenic activity unless data can be cited that confirm the ability of fibroadenomas to progress to malignancy. Dr. Kari noted that the Discussion section of the Technical Report cited other authors who have shown this progression to occur in a small percentage of observations and that the NTP also has compiled evidence for progression, about which a manuscript is being prepared. Dr. S. Eustis, NIEHS, commented that whether a tumor remains benign or becomes malignant depends on both the intrinsic properties of the tumor and on host factors. He further stated that fibroadenomas have been demonstrated to progress to malignant tumors when transplanted into suitable hosts. Dr. Hooper said that this made it most important that appropriate documentation be provided supporting the potential for progression to malignancy. For female mice, Dr. Ashby thought the conclusion should be some evidence of carcinogenic activity unless progression to malignancy could be shown for the ovarian granuloma cell tumors. Dr. Kari remarked that in the study of nitrofurantoin, malignant granulosa cell tumors were observed. Dr. Ashby emphasized the importance of good data and exact citations in which the distinction between

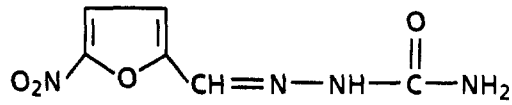
some evidence and clear evidence is supported by evidence of progression from studies of other investigators. Dr. Ashby noted that semicarbazide, a known animal carcinogen which is a substructure of nitrofurazone, was not associated with the carcinogenic effects observed because different site-specific neoplasms occur.

Dr. Chinchilli moved that the Technical Report on nitrofurazone be accepted with revisions as discussed to contain more explanation about progression and with the conclusions as written for male rats, equivocal evidence of carcinogenic activity, for male mice, no evidence of carcinogenic activity, and for female rats and mice, clear evidence of carcinogenic activity. Dr. Hooper seconded the motion, which was approved by seven reviewers with two abstentions (Dr. Capen and Dr. Hughes).

I. INTRODUCTION

Use and Production
Absorption, Metabolism, and Excretion
Toxicity in Animals
Carcinogenicity
Toxicity in Humans
Genetic Toxicology
Study Rationale

I. INTRODUCTION



NITROFURAZONE

CAS No. 59-87-0

$C_6H_6N_4O_4$ Molecular weight 198.1

Synonyms or Trade Names: 5-Nitro-2-furaldehyde semicarbazone; 2-[(5-Nitro-2-furanyl)methylene]hydrazine carboxamide; Aldomycin; Amifur; Chemfuran; Coxistat; Furacin; Furacinetten; Furaplast; Furazol W; Furesol; Furracoccid; Mammex; Nefco; Nifuzon; Nitrofural; Vabrocid

Use and Production

Nitrofurazone, a synthetic furan derivative active against a broad spectrum of bacteria, has been used widely in veterinary and human medicine. The chemical is available as a National Formulary Grade containing not less than 98% nor more than 102% nitrofurazone after drying at 105° C for 1 hour (National Formulary, 1975). It is available as a topical cream containing 0.2% nitrofurazone in a water-miscible base which is applied daily or several times weekly (PDR, 1984). The annual production of nitrofurazone has been estimated to be approximately 1.2×10^4 kg (Chemical Information Services, 1973), most of which is thought to be used in veterinary medicine. Recent marketing surveys indicate that the total quantity of nitrofurazone represented by drug store and hospital purchases averaged about 27 kg in 1985 and 1986 (IMS America Ltd, 1987).

In human medicine, nitrofurazone is used primarily to treat surface infections that have become resistant to antibiotics. The bactericidal activity of nitrofurazone was first described by Dodd and Stillman (1944). The chemical has been used as a topical adjunct for patients who have second- and third-degree burns or who require skin grafts. Nitrofurazone is also used widely in veterinary medicine to treat surface lesions, infectious enteritis in small animals, and skin, eye, ear, and genital tract infections. Nitrofurazone has been used as a coccidiostat in poultry and in the treatment of bovine mastitis (Hayes, 1967).

Absorption, Metabolism, and Excretion

The disposition of nitrofurazone after oral administration to rats has been well studied. Within 24 hours after a single administration of ^{14}C-labeled nitrofurazone (100 mg/kg), about two-thirds of the radioactivity appeared in the urine, 26% in feces, and approximately 1% in the expired carbon dioxide; complete recovery of the administered dose was observed in 96 hours, with less than 15% of the label being recovered as unchanged parent compound (Tatsumi et al., 1971). Major metabolites of nitrofurazone detected and identified in the urine from dosed Donryu rats included hydroxylaminofuraldehyde semicarbazone, aminofuraldehyde semicarbazone, and 4-cyano-2-oxobutyraldehyde semicarbazone (Paul et al., 1960). Nitrofurazone has been shown to bind to nucleic acids and proteins both in vivo and in vitro (Tatsumi et al., 1977).

It has been proposed that the cytotoxicity and DNA damage observed in animals after administration of nitrofurazone may result from the formation of toxic intermediates upon nitroreduction by mammalian and/or bacterial enzymes. For example, a positive correlation exists between the ability of several organs to reduce nitrofurazone and the DNA damage observed in the thymidine-labeled cells incubated with these tissues (Olive and McCalla, 1975; Olive, 1979). Recent research activity has focused on the relative roles of bacterial versus mammalian metabolism of this compound.

Investigations with various in vitro preparations have shown that nitrofurazone can be metabolized by the liver (Mason and Holtzman, 1975; Peterson et al., 1979; Kutcher and McCalla, 1984), kidney (Hoener and Krueger, 1984), and testes (Hollinger and Davis, 1969) under both aerobic and anaerobic conditions. Furthermore, the small intestine has been shown to be a major site of nitrofurazone metabolism in vivo, and this activity is not dependent on enteric bacteria but can be attributed to xanthine oxidase activity located in intestinal mucosal cells (Tatsumi et al., 1973). Finally, reduced metabolites of nitrofurazone have been identified in the urine of germ-free animals (Yeung et al., 1983). Considered together, these findings suggest that microbial metabolism is not obligatory for the observed toxicity of nitrofurazone in animals.

Toxicity in Animals

Oral LD_{50} values of 590 mg/kg body weight for Donryu rats and 640 mg/kg for ICR/JCL mice have been reported (Miyaji, 1971). Clinical signs observed in mice and rats administered nitrofurazone at 300 mg/kg or more included hyperirritability, seizures and tremors, and death from respiratory insufficiency (Krantz and Evans, 1945; Dodd, 1946).

Administration of nitrofurazone in a high fat milk replacer (daily dose, 13.9 mg/kg) to male Holstein calves caused hyperirritability and convulsions after 3-5 weeks, and at higher doses (30.7 mg/kg) all six calves showed evidence of severe limb paralysis after several days (Lister and Fisher, 1970).

In rats, oral administration of nitrofurazone was shown to inhibit spermatogenesis at the spermatocyte or spermatid stage, resulting in testicular atrophy when dosing was prolonged. This was generally reversible when administration of the chemical was stopped. Hypertrophy of the adrenal glands was also reported. A similar effect was demonstrated in mice, and interstitial cell hyperplasia and seminal vesicle hypertrophy were also shown (Prior and Ferguson, 1950; Nissim, 1957; Montemurro, 1969).

Investigations of the mode of action of the antispermatogenic activity of nitrofurazone reveal that under conditions where nitrofurazone completely inhibited spermatogenesis, functional and morphologic parameters of Leydig and Sertoli cells proved to be normal, but marked degeneration of germ cells was noted (Hagenas et al., 1978). These abnormalities were characterized by cell death during meiosis, occurrence of multinucleate spermatocytes and spermatids, and acrosomal derangements. All germ cells except spermatogonia and early primary spermatocytes were affected, and damage was shown to be most severe in cells staged from mid-prophase through meiotic division. Long-term administration of nitrofurazone to rats has been shown to inhibit the testicular oxidation of glucose (Hollinger and Davis, 1969). Spermatogonia are relatively independent of glucose oxidation for energy (Davis and Firlit, 1965), and this may partially explain the refractiveness of the undifferentiated germ cells to the morphologic damage observed in spermatids. However, direct effects of nitrofurazone on DNA in these cells cannot be precluded because nitrofurazone has been shown to be clastogenic toward single-stranded DNA (Olive and McCalla, 1975).

In a study of nitrofurazone conducted by the NTP, timed-pregnant CD-1 mice were fed dietary concentrations of nitrofurazone ranging from 38 to 500 ppm on days 6-15 of gestation, with observations continuing through day 17 (Price et al., 1985). No evidence of teratogenic effects was observed. Selective embryotoxicity, expressed as increased incidence of late fetal death and intrauterine growth retardation, was observed at doses that were only marginally toxic to the exposed dams.

Carcinogenicity

In two separate experiments, nitrofurazone was administered to female Holtzman rats in diets at a concentration of 1,000 ppm for 36 or 44 weeks (Morris et al., 1969). For the first experiment, the control and dosed groups initially contained 20 animals each; in the second experiment, control and dosed groups contained between 30 and 36 animals each. All gross lesions as well as tissue from liver, kidney, and spleen were evaluated histologically. Only mammary gland tumors were observed in these studies; incidences of mammary gland fibroadenomas in the control

groups were 0/5 and 3/16 in the two experiments. The remainder of the animals in these control groups did not survive to 36 weeks, presumably due to respiratory infections. In the dosed groups, the incidences of mammary gland tumors among nitrofurazone-dosed animals surviving to 36 weeks were 11/18 and 24/24. Both experiments were plagued by high mortality, reportedly due to chronic respiratory infections. Strict interpretations of these results must be tempered by the fact that known impurities accounted for at least 3% of the study material. Furthermore, in an effort to retard mortality caused by infections in their laboratory, the investigators treated study animals with various antibiotics and nematocides.

In a subsequent 46-week study, the same oral exposure to nitrofurazone, free of detectable impurities, resulted in an increased incidence of benign mammary gland tumors (Erturk et al., 1970). This same study reported the subcutaneous transplantability of mammary fibroadenoma tissue from nitrofurazone-dosed female rats to untreated male and female rats of the same strain.

In another investigation, 40-day-old female Sprague Dawley rats were given 10 equal doses (one every third day for 30 days) of nitrofurazone by gavage in sesame oil (Griswold et al., 1968). Animals in the three dosed groups received a total of 200, 350, or 500 mg of nitrofurazone per rat, and the initial size of these groups was 10, 10, and 20 rats, respectively. The control group contained 140 rats. After 9 months, all surviving animals were killed, and mammary gland tissue, intestinal tract, pituitary gland, liver, ovaries, and adrenal glands were evaluated, as were all gross lesions in additional tissues. Necropsies were performed on 132/140 control animals, and five of these had mammary gland lesions. (Three carcinomas, one fibroadenoma, and five hyperplastic lesions were characterized in these five animals.) Nine of 10 low dose, 10/10 mid dose, and 5/20 high dose animals survived the 9-month observation period, and one animal in each group was found to contain a mammary gland lesion. The lesions were reported as a carcinoma, a hyperplastic lesion, and a fibroadenomatous change.

Toxicity in Humans

Nitrofurazone causes contact or allergic dermatitis, which may be severe (Shipley and Dodd, 1947). Nitrofurazone is seldom administered orally to humans because of the frequent onset of a severe peripheral polyneuropathy at the doses required for effective therapy (Koch-Weser et al., 1971; Karol, 1960). Hemolytic anemia has also been observed and is thought to be due to decreased activity of glucose-6-phosphate dehydrogenase and to the oxidizing activity of the 5-nitrofurans (Beutler, 1972).

Genetic Toxicology

The mutagenicity of nitrofurazone and other 5-nitrofuran derivatives has been reviewed in comprehensive articles by Klemencic and Wang (1978) and McCalla (1983). In general, nitrofurazone has consistently exhibited mutagenic activity in vitro in a variety of bacterial and mammalian cell assays. It has not demonstrated mutagenic activity in vivo, but the number and variety of such assays in which it has been tested are limited.

Nitrofurazone induced gene reversion in numerous strains of *Escherichia coli* without metabolic activation (Yahagi et al., 1974; McCalla et al., 1975). Differential growth inhibition after exposure of *E. coli* to nitrofurazone was reported (Haveland-Smith et al., 1979; Ebringer and Bencova, 1980). Similarly, both gene reversion and growth inhibition were observed after treatment of *Bacillus subtilis* cultures with nitrofurazone (Tanooka, 1977).

Reverse gene mutation in *Salmonella typhimurium*, without S9 activation, was observed in strains TA98, TA100, TA1535, TA1537, and TA1538 after treatment with nitrofurazone with a variety of experimental configurations including plate incorporation procedures, spot tests, and fluctuation tests (Sugimura et al., 1976; Chin et al., 1978; Bruce and Heddle, 1979; Ebringer and Bencova, 1980). Results from NTP Salmonella studies that used preincubation protocols were generally similar to those reported in the literature. Nitrofurazone was mutagenic in strains TA98 and TA100 with and without

Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9. However, S9 activation was required for a significant increase in revertant colonies with strain TA1535, and no consistent increase in gene reversions was observed in strain TA1537 (Zeiger et al., 1987; Appendix E, Table E1).

Although nitrofurazone consistently causes mutagenicity without mammalian activation in bacterial systems, there is evidence to suggest that this compound is not a direct-acting mutagen in bacteria. In the absence of S9 activation, nitrofurazone is nonmutagenic toward *S. typhimurium* strain TA100-FR1, a nitroreductase-deficient strain. However, this strain is responsive to nitrofurazone-induced mutagenicity if a mammalian source of enzymes is provided (Rosenkranz and Speck, 1976). Similarly, *E. coli* strain 343/113/R-9, which lacks nitroreductase activity and is therefore normally resistant to nitrofurans, can be mutated by nitrofurazone if exposure occurs in the presence of microsome extracts from Drosophila (Baars et al., 1980) or mouse liver (Olive and Durand, 1978). Considered together, these results indicate an obligatory role for metabolism in the nitrofurazone-induced mutagenicity in bacteria and demonstrate that eukaryotic enzyme preparations are able to activate nitrofurazone to a mutagenic form.

Generally, tests with cultured mammalian cells were also positive, but the role of metabolic activation is uncertain. At concentrations of 100-200 µg/ml, nitrofurazone induced 6-thioguanine resistance in Chinese hamster V79 cells in the absence of exogenous metabolic activation (Olive, 1981). Similarly, in an NTP mouse lymphoma assay, nitrofurazone induced forward mutations at the $TK^{+/-}$ locus of L5178Y cells without S9 activation (Table E2).

Tonomura and Sasaki (1973) observed no induction of chromosomal aberrations or unscheduled DNA synthesis after human lymphocytes and fibroblasts were treated with nitrofurazone at concentrations up to 10 mM. Furthermore, no increase in the induction of chromosomal aberrations was observed in Chinese hamster fibroblasts exposed to nitrofurazone over a range of doses that included a 50% growth inhibition response (Ishidate and Odashima, 1977). However, Matsuoka and coworkers (1979) noted an increase in chromosomal aberrations when Chinese hamster fibroblasts were exposed to nitrofurazone at 0.1 mg/ml in the presence of S9. Results from NTP cytogenetic studies revealed that treatment of cultured Chinese hamster ovary cells with nitrofurazone in the absence of S9 produced a dose-related increase in sister chromatid exchanges (Table E3) and chromosomal aberrations (Table E4). With Aroclor 1254-induced male Sprague Dawley rat liver S9, sister chromatid exchanges were increased, but induction of chromosomal aberrations was not observed at doses up to 500 µg/ml.

In vivo assays for genetic damage resulting from exposure to nitrofurazone were uniformly negative. Feeding nitrofurazone (5-mM solution) to adult male Drosophila produced no significant increase in sex-linked recessive lethal mutations in their offspring (Kramers, 1982). No increases in micronuclei, chromosomal aberrations, or morphologically abnormal sperm were observed in rats or mice dosed with up to 60 mg nitrofurazone/kg body weight (Goodman et al., 1977; Bruce and Heddle, 1979).

Study Rationale

The National Toxicology Program undertook evaluation of nitrofurazone to gain insight into the potential carcinogenicity of chemicals representative of the furan class. The class study of furans was initiated by the National Cancer Institute and was predicated on high levels of human exposure or consumption and on structure-function considerations suggesting that furans may be carcinogenic in rodents. The scope of chemicals considered for carcinogenic evaluation included all furans, dihydrofurans, and nitrofurans.

Nitrofurazone was specifically selected for evaluation because of high levels of human exposure (8.5×10^4 g/year) (National Cancer Institute/Stanford Research Institute Mark II Database) and evidence available in the open literature suggesting that long-term administration of nitrofurazone to rodents might cause cancer.

II. MATERIALS AND METHODS

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF NITROFURAZONE

Nitrofurazone was obtained in one lot (lot no. C1206) from Norwich Eaton Pharmaceuticals (Norwich, New York). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). (MRI reports on the analyses performed in support of the nitrofurazone studies are on file at NIEHS.)

The identity of lot no. C1206 was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy; all spectra were consistent with literature spectra (Sadtler Pharmaceutical Spectra; Sadtler Standard Spectra) (Figures 1 and 2). Purity was determined by elemental analysis, Karl Fischer water analysis, thin-layer chromatography, and high-performance liquid chromatography. Cumulative data indicated that lot no. C1206 was approximately 99% pure. Results of elemental analysis agreed with the theoretical values. The water content was 0.69%. A minor impurity was detected by thin-layer chromatography with activated aluminum oxide plates and a chloroform:methanol:acetic acid (90:5:5) solvent system. One impurity with a relative area equal to 0.1% that of the major peak was detected by high-performance liquid chromatography and ultraviolet detection at 365 nm on a Varian Micropak MCH-10 column with a water:methanol (40:60) solvent system. One additional impurity was detected with this same system and a gradient of 0%-10% methanol; the relative area of this impurity was less than 1%, but precise quantitation was difficult under the conditions used.

Nitrofurazone was shown to be stable when stored for 2 weeks at temperatures up to 60° C. The study material was stored at 25° C. Periodic characterization of the bulk chemical by infrared or ultraviolet spectroscopy and high-performance liquid chromatography indicated no deterioration over the course of the studies.

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

Formulated diet mixtures were shown to be homogeneous by both the analytical chemistry and study laboratories. Nitrofurazone at 1,500 ppm in feed was shown to be stable for 2 weeks in the dark at temperatures up to 5° C, whereas a 3% reduction in concentration was observed at 25° C after 2 weeks. No decrease in concentration was observed during storage for 7 days under simulated cage conditions with open beakers maintained at normal animal room temperature and lighting conditions. Formulated diets were prepared by blending a premix of nitrofurazone and feed with the bulk feed; the premix was prepared by mixing the appropriate weight of the study material with feed in a beaker (Table 1). Formulated diets were analyzed for nitrofurazone content at the study and analytical chemistry laboratories by extraction of the feed with methanol and quantitation by high-performance liquid chromatography with a Waters μBondapak C_{18} column, ultraviolet detection at 365 nm,

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

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation Premix layered between equal quantities of feed in a Patterson-Kelly® 8-qt twin-shell blender and mixed with intensifier bar for 5 min and without intensifier bar for 10 min	Same as 14-d studies	Same as 14-d studies
Maximum Storage Time 14 d	10 d	14 d
Storage Conditions 5° C in the dark	4° C	5° C in the dark

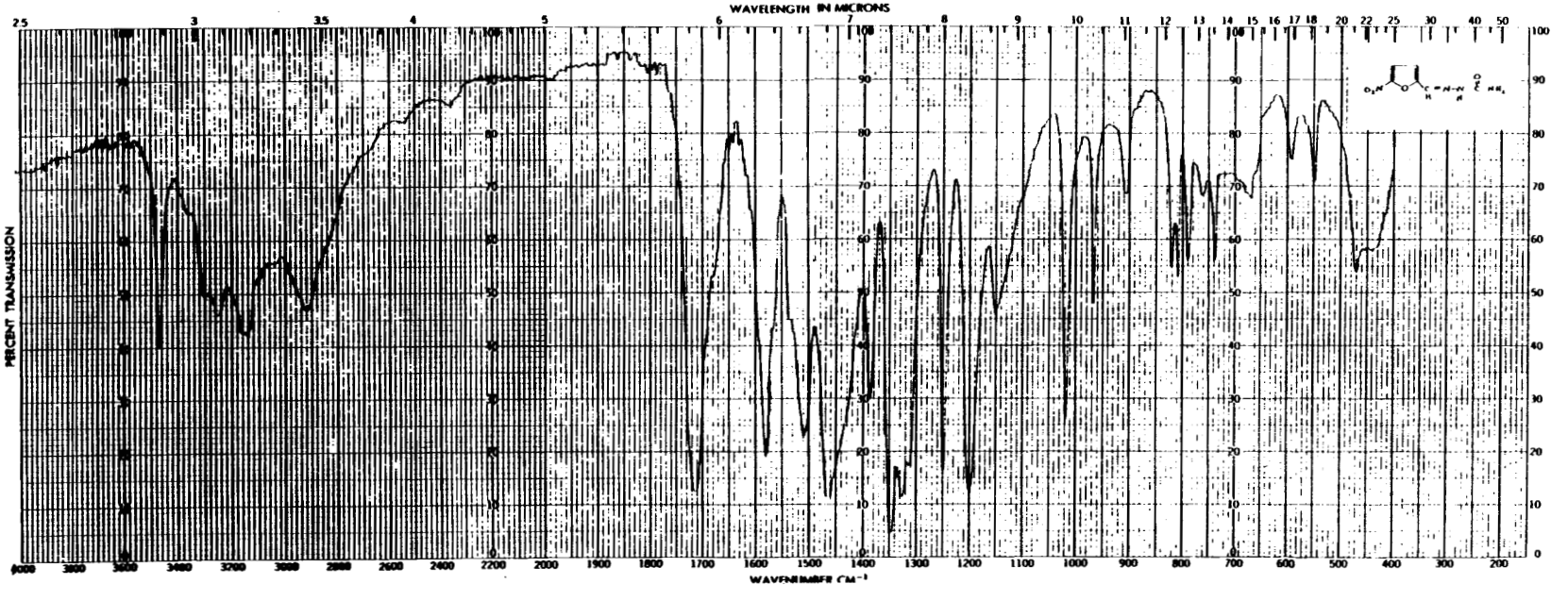


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF NITROFURAZONE (LOT NO. C1206)

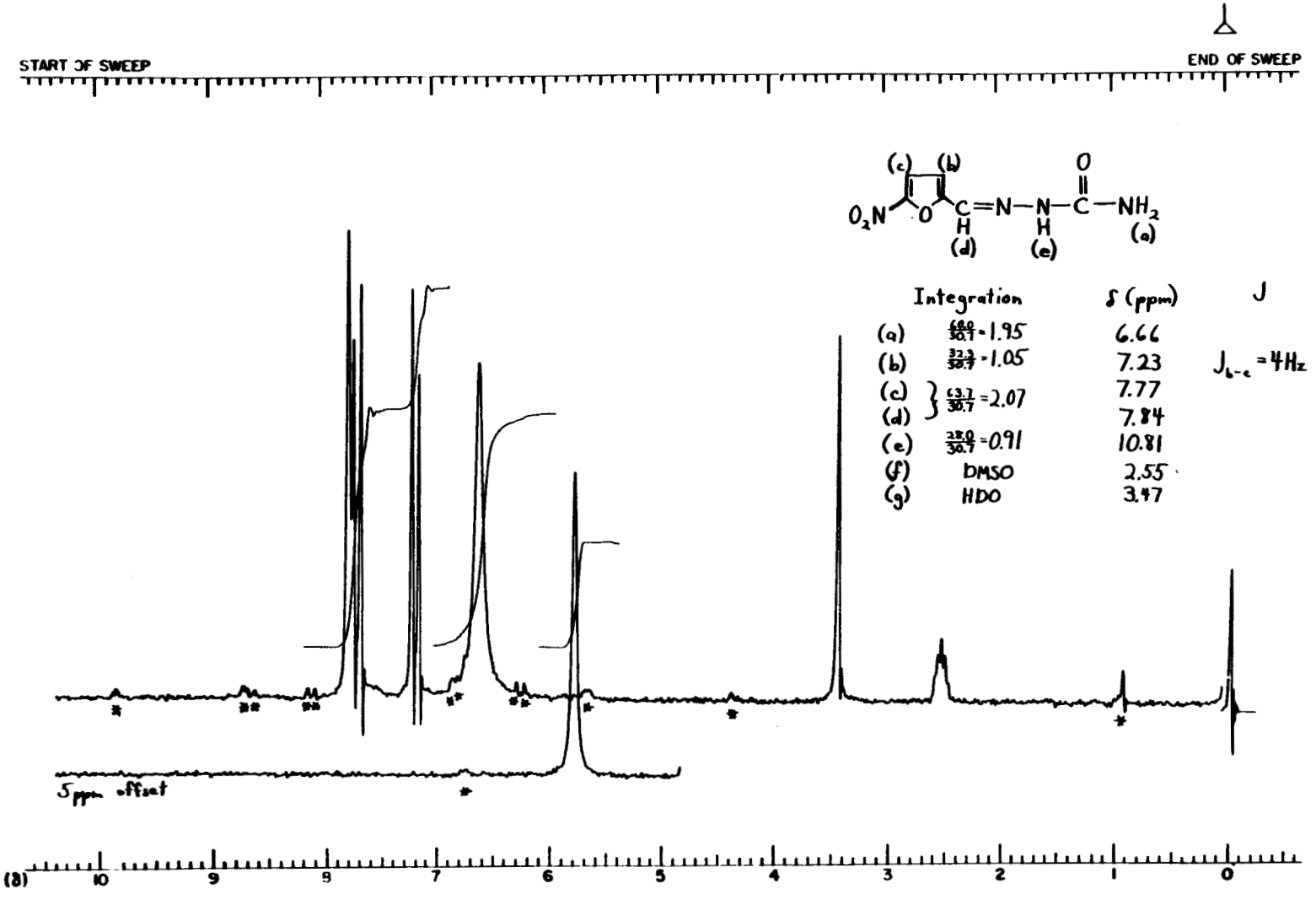


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF NITROFURAZONE (LOT NO. C1206)

and a water:acetonitrile (70:30) solvent system. Formulated diets were analyzed twice during the 13-week studies (Table 2). The nitrofurazone concentrations ranged from 76% to 105% of the target concentrations; results of 9/10 analyses were within specifications. Formulated diets were analyzed periodically during the 2-year studies with nitrofurazone concentrations ranging from 95.5% to 118.0% of the target concentrations (Table 3). Because 40/43 formulated diets analyzed were within ±10% of the target concentrations, the diets were estimated to have been formulated within specifications 93% of the time during the 2-year studies. Referee analyses were also performed periodically by the analytical chemistry laboratory (Table 4). Generally good agreement was found between the results from the two laboratories. In the 2-year studies, the formulated diets were stored at 5° C for no longer than 14 days.

TABLE 2. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE THIRTEEN-WEEK FEED STUDIES OF NITROFURAZONE

Date Mixed	Concentration of Nitrofurazone in Feed (ppm) (a) Target	Determined	Determined as a Percent of Target
08/06/80	70	(b) 65	93
	150	150	100
	310	290	94
	620	580	94
	1,250	1,200	96
	2,500	(c) 2,300	92
09/10/80	70	70	100
	150	140	93
	(d) 150	100	67
	310	280	90
	620	470	(e) 76
	1,250	1,310	105
	2,500	2,570	103

(a) Results of duplicate analysis
(b) Samples taken from three other locations within the blender had concentrations of 65, 65, and 67 ppm.
(c) Three other samples from different locations within the blender all had concentrations of 2,400 ppm.
(d) Referee analysis by MRI; result of triplicate analysis.
(e) Out of specifications; used in the studies.

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

Date Mixed	Concentration of Nitrofurazone in Feed for Target Concentration (ppm) (a)		
	150	310	620
06/05/81	160	320	630
07/03/81	157	331	648
09/11/81	151	303	625
10/09/81	148	302	592
01/01/82	160	317	637
03/05/82	150	309	650
04/02/82	150	300	644
06/25/82	148	307	605
07/16/82	147	324	677
08/27/82	160	309	631
12/03/82	(b) 177	(b) 344	(b) 704
12/07/82	(c) 159	(c) 306	(c) 624
01/28/83	157	309	624
03/29/83	154	300	606
04/12/83	163	303	610
06/01/83		303	
Mean (ppm)	155.9	312.1	634.5
Standard deviation	8.1	12.8	29.7
Coefficient of variation (percent)	5.2	4.1	4.7
Range (ppm)	147-177	300-344	592-704
Number of samples	14	15	14

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

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

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory (a)	Referee Laboratory (b)
06/05/81	150	160	150
10/09/81	620	592	610
03/05/82	310	309	322
12/03/82	150	177	152
01/28/83	620	624	660
06/01/83	310	303	310

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

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 18 days before the studies began. Rats were 6-7 weeks old and mice were 6-8 weeks old when placed on study. Groups of five males and five females of each species were fed diets containing 0, 630, 1,250, 2,500, 5,000, or 10,000 ppm nitrofurazone for 14 consecutive days. Rats and mice were observed twice daily and were weighed once per week. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 5.

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

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		
0, 630, 1,250, 2,500, 5,000, or 10,000 ppm nitrofurazone in feed	Rats--0, 150, 310, 620, 1,250, or 2,500 ppm nitrofurazone in feed; mice--0, 70, 150, 310, 620, or 1,250 ppm	Rats--0, 310, or 620 ppm nitrofurazone in feed; mice--0, 150, or 310 ppm
Date of First Dose		
9/30/79	7/28/80	Rats--6/24/81; mice--6/8/81
Date of Last Dose		
10/13/79	10/25/80	Rats--6/13/83; mice--5/31/83
Duration of Dosing		
14 consecutive d	13 wk	103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and 1 × wk thereafter	Same as 14-d studies	Observed 2 × d; weighed initially, 1 × wk for 12 wk (rats) or 13 wk (mice), and monthly thereafter
Necropsy and Histologic Examination		
Necropsy performed on all animals; histologic exam performed on 10% of rats and mice	Necropsy performed on all animals; histologic exam performed on all controls, all animals in the highest dose group with at least 60% survival at the end of the studies, and all animals with gross lesions. Tissues examined: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), gallbladder (mice), gross lesions, heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroid glands, peripheral nerve, pituitary gland, prostate/testes or ovaries/uterus, regional lymph nodes, salivary glands, small intestine, spinal cord, spleen, sternebrae or femur or vertebrae including marrow, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder. Tissues examined for all rats in the other dose groups: femur, muscles, testes or uterus/ovaries, tibia. Liver weighed at necropsy	Necropsy performed on all animals; histologic exams performed on all controls, all high dose animals, low dose male rats, and low dose male mice. Tissues examined: same as those in the 13-wk studies; tissues examined for low dose female rats: adrenal glands, femur, liver, pituitary gland, spleen, and vertebrae; tissues examined for low dose female mice: liver, lung, ovaries, pituitary gland, and spleen; neurologic exam performed during wk 100 included visual response to threat, righting reflexes, gait, extensor postural thrust, placing response, strength of grasp, flexor reflexes, and muscle atrophy
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory		
Physiological Research Laboratories	Physiological Research Laboratories	Physiological Research Laboratories
Method of Animal Identification		
Rats--tail mark; mice--ear punch	Toe clip	Toe and ear clip

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

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Time Held Before Study 18 d	Rats--14 d; mice--20 d	Rats--14 d; mice--13 d
Age When Placed on Study Rats--6-7 wk; mice--6-8 wk	Rats--6-8 wk; mice--8 wk	Rats--6-7 wk; mice--7-8 wk
Age When Killed Rats--8-9 wk; mice--8-10 wk	Rats--19-21 wk; mice--21-22 wk	Rats--111 wk; mice--112 wk
Necropsy Dates Rats--10/16/79-10/17/79; mice--10/15/79	10/27/80-10/28/80	Rats--6/20/83-6/24/83; mice--6/6/83-6/9/83
Method of Animal Distribution Animals distributed to weight classes and assigned to cages according to a table of random numbers	Same as 14-d studies	According to tables of random numbers
Feed Rodent Laboratory Chow 5001® meal (Ralston Purina Co., St. Louis, MO); available ad libitum	Same as 14-d studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum
Bedding Aspen wood chips (Minnesota Sawdust and Shavings Co., Anoka, MN)	Same as 14-d studies	Same as 14-d studies
Water Automatic watering system (Edstrom Industries, Waterford, WI); softened; available ad libitum	Same as 14-d studies	Same as 14-d studies; softened to <1 grain/gal hardness through sodium zeolite, then filtered
Cages Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Same as 14-d studies	Same as 14-d studies
Cage Filters (Snow Filtration, Cincinnati, OH)	Same as 14-d studies	Spun-bonded polyester, Dupont 2024® (Snow Filtration, Cincinnati, OH)
Animals per Cage 5	5	5
Other Chemicals on Study in the Same Room None	None	None
Animal Room Environment Temp--22.2°-24.4° C; hum--35%-45%; fluorescent light 12 h/d	Temp--21.1°-26.6° C; hum--33%-74%; fluorescent light 12 h/d	Temp--21.7°-26.1° C; hum--30%-74%; fluorescent light 12 h/d; 5-17 room air changes/h

THIRTEEN-WEEK STUDIES

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

Four- to six-week-old male and female F344/N rats and 5-week-old male and female $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories. Animals were observed for 14 days (rats) or 20 days (mice) and then distributed to weight classes. Animals were assigned to cages and groups according to a table of random numbers. Diets containing 0, 150, 310, 620, 1,250, or 2,500 ppm nitrofurazone were fed to groups of 10 rats of each sex. Diets containing 0, 70, 150, 310, 620, or 1,250 ppm nitrofurazone were fed to groups of 10 mice of each sex.

Animals were housed five per cage. Formulated or control diets and water were available ad libitum. Animals were checked two times per day; moribund animals were killed. Feed consumption was measured weekly by cage. Individual animal weights were recorded weekly.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Diets containing 0, 310, or 620 ppm nitrofurazone were fed to groups of 50 male and 50 female rats for 103 weeks. Diets containing 0, 150, or 310 ppm nitrofurazone were fed to groups of 50 male and 50 female mice on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. 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 5-6 weeks of age. The rats were quarantined at the study laboratory for 14 days and the mice, for 13 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were 47 days old and the mice were 51 days old when placed on study. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

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

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

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

Animal Maintenance

Animals were housed five per cage and the cages were not rotated within cage racks during the studies. 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, and clinical signs were recorded at least once per month. Body weights by cage were recorded once per week for the first 12 or 13 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, unless they were excessively autolyzed or cannibalized, missexed, or found missing. 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. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 5) were performed on all high dose and control animals and on low dose animals dying before the end of the study. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose group were examined histopathologically. If mortality in the highest dose group exceeded that in the control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

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 includes 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 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.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements

include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathology 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, incidental tumor analysis, and Fisher exact/Cochran-Armitage trend analyses. Tests of significance include pairwise comparisons of each dosed group 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--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel 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.

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

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

All rats receiving 5,000 or 10,000 ppm nitrofurazone died (Table 6). Surviving animals in the lower two dose groups all gained weight, but the degree of weight gain was dose dependent. Feed consumption was decreased at all doses above 630 ppm. In all dosed groups, clinical signs of toxicity included rough hair coats and evidence of lethargy. At doses of 2,500 ppm and above, rats of each sex exhibited intermittent episodes of seizures and lethargy. Histopathologic examinations indicated that dosed male rats were aspermatogenic.

THIRTEEN-WEEK STUDIES

All rats lived to the end of the studies (Table 7). Final mean body weights of rats that received 620, 1,250, or 2,500 ppm nitrofurazone were 11%, 32%, or 55% lower, respectively, than that of the controls for males and 2%, 12%, or 36% lower for females. With the exception of the highest dose group, feed consumption by dosed and control groups was comparable. Liver weight to body weight ratios for dosed rats were significantly greater than those for the controls (Table 8). Stimulus-induced convulsive seizures were observed in males at 2,500 ppm. Females that received 1,250 or 2,500 ppm and males that received 1,250 ppm were hyperexcitable. Atrophy constricture of the hind quarters was seen in males and females that received 2,500 ppm. Moderate to severe degeneration of the seminiferous epithelium in the testis was observed in all male rats in the four highest dose groups. Testes of males that received 150 ppm were normal.

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

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	136 ± 5	197 ± 5	+61 ± 2	--	16.1	16.2
630	5/5	135 ± 6	200 ± 7	+65 ± 2	102	14.6	16.3
1,250	5/5	135 ± 3	183 ± 5	+48 ± 2	93	11.6	13.3
2,500	(e) 4/5	133 ± 6	140 ± 5	+2 ± 4	71	6.5	7.3
5,000	(f) 0/5	124 ± 9	(g)	(g)	(g)	4.5	2.5
10,000	(h) 0/5	137 ± 6	(g)	(g)	(g)	3.9	0.4
FEMALE							
0	5/5	97 ± 5	133 ± 3	+36 ± 2	--	10.9	13.3
630	5/5	99 ± 4	132 ± 2	+33 ± 3	99	11.6	11.2
1,250	5/5	110 ± 8	132 ± 6	+22 ± 2	99	8.4	5.9
2,500	5/5	103 ± 2	110 ± 4	+7 ± 3	83	5.7	6.0
5,000	(i) 0/5	101 ± 4	(g)	(g)	(g)	3.9	2.8
10,000	(j) 0/5	95 ± 3	(g)	(g)	(g)	1.5	1.6

(a) Number surviving/number initially in the group
(b) Initial mean group 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 per animal per day; not corrected for scatter.
(e) Day of death: 11
(f) Day of death: 10,11,11,11,11
(g) No data are reported due to 100% mortality in this group.
(h) Day of death: 9,10,10,10,11
(i) Day of death: 11,11,12,12,12
(j) Day of death: 7,7,9,9,11

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

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 7	Week 13
MALE							
0	10/10	109 ± 3	349 ± 6	+240 ± 4	--	16	10
150	10/10	105 ± 2	346 ± 5	+241 ± 5	99	16	10
310	10/10	104 ± 2	332 ± 4	+228 ± 4	95	16	10
620	10/10	106 ± 3	310 ± 5	+204 ± 3	89	16	11
1,250	10/10	104 ± 2	239 ± 4	+135 ± 3	68	13	9
2,500	10/10	106 ± 3	158 ± 3	+52 ± 3	45	9	7
FEMALE							
0	10/10	90 ± 2	195 ± 3	+105 ± 2	--	15	10
150	10/10	92 ± 2	200 ± 3	+108 ± 4	103	16	10
310	10/10	89 ± 1	195 ± 3	+106 ± 3	100	15	9
620	10/10	92 ± 2	191 ± 3	+99 ± 2	98	14	10
1,250	10/10	90 ± 2	172 ± 4	+82 ± 3	88	11	9
2,500	10/10	90 ± 2	125 ± 3	+35 ± 2	64	8	6

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

TABLE 8. ANALYSIS OF LIVER WEIGHTS OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF NITROFURAZONE (a)

Concentration (ppm)	No. of Animals Examined	Final Body Weight (grams)	Liver Weight (mg)	Liver Weight/Final Body Weight (mg/g)
MALE				
0	10	348.9 ± 2.95	14,469 ± 814	41.5 ± 2.33
150	10	345.9 ± 4.53	(b) 18,664 ± 303	(b) 54.0 ± 0.63
310	10	332.0 ± 4.41	(c) 16,609 ± 409	(b) 50.1 ± 1.21
620	10	(b) 309.5 ± 4.83	(b) 18,167 ± 536	(b) 58.6 ± 1.23
1,250	10	(b) 238.8 ± 4.13	12,662 ± 405	(b) 53.0 ± 1.33
2,500	10	(b) 158.2 ± 3.30	(b) 9,041 ± 370	(b) 57.0 ± 1.28
FEMALE				
0	10	195.3 ± 2.89	7,272 ± 514	37.2 ± 2.59
150	10	199.9 ± 2.61	(b) 9,578 ± 258	(b) 47.9 ± 1.10
310	10	195.0 ± 3.40	(b) 9,511 ± 312	(b) 48.8 ± 1.42
620	10	191.0 ± 3.02	(b) 9,599 ± 221	(b) 50.3 ± 0.76
1,250	10	(b) 172.1 ± 3.64	(b) 10,148 ± 149	(b) 59.1 ± 1.17
2,500	10	(b) 124.7 ± 2.65	6,743 ± 203	(b) 54.1 ± 1.29

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

Chemical-related histopathologic effects were observed in the long bones of male and female rats and in the testis of males. Male and female rats receiving 1,250 or 2,500 ppm had reduced amounts of trabecular bone in the metaphyseal region (osteoporosis) (Table 9). Subsequent to

TABLE 9. NUMBER OF RATS WITH SELECTED LESIONS IN THE THIRTEEN-WEEK FEED STUDIES OF NITROFURAZONE (a)

Site/Lesion	Concentration (ppm) 0	150	310	620	1,250	2,500
MALE						
Bone						
Osteoporosis (b)	0	--	0	2	5	9
Testis						
Degeneration	0	0	10	10	10	10
Seminal vesicle						
Hypoplasia	0	--	--	--	2	10
FEMALE						
Bone						
Osteoporosis (b)	0	--	--	0	3	10
Uterus						
Hypoplasia	0	--	--	0	2	10

(a) Ten rats were examined for each group.
(b) A study pathologist used the less exact term *osteomalacia* for this lesion.

the completion of the 2-year studies, degenerative changes in the articular cartilage were characterized by the formation of subchondral cysts and irregularly thickened cartilage containing numerous chondrocyte clones (degenerative arthropathy).

Dose Selection Rationale: Based on the lower weight gain and skeletal lesions observed at high doses, dietary concentrations of 310 and 620 ppm nitrofurazone were selected for rats for the 2-year studies.

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of high dose male and female rats were progressively lower than those of the controls throughout the studies (Table 10 and Figure 3). Mean body weights of low dose male and female rats were 4%-9% lower than those of the controls from week 39 to the end of the studies. The average daily feed consumption per rat by low and high dose rats was 95% and 90% that of the controls for males and 92% and 91% for females (Appendix G, Tables G1 and G2). The average amount of nitrofurazone consumed per day was approximately 11 or 24 mg/kg for low or high dose male rats and 12 or 26 mg/kg for low or high dose female rats.

Musculoskeletal impairment of the hind limbs, reported as "bowlegged" or occasionally as "immobile legs," occurred in high dose male and female rats. Rats were subjected to a neurologic evaluation, and in both male and female rats, nitrofurazone was found to cause abnormal posture and pelvic limp gait with atrophy of external pelvic muscles and flexor muscles of the knee. Contracture of the semimembranous and semitendinous muscles, the muscles subserving knee flexion, was also noted. This effect was dose related and by month 21 affected nearly 100% of high dose male and female rats and 44% and 62% of low dose males and females. Further examination revealed preserved strength of grasp of the pelvic limbs with intact sensation to deep painful stimuli and intact position sense. (Full methods and details of these studies are on file at the NTP.)

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF NITROFURAZONE

Weeks on Study	Control		310 ppm			620 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	122	50	123	101	50	124	102	50
1	166	50	164	99	50	167	101	50
2	199	50	186	93	50	190	95	50
3	213	50	209	98	50	202	95	50
4	231	50	227	98	50	220	95	50
5	255	50	253	99	50	241	95	50
6	276	50	271	98	50	260	94	50
7	278	50	276	99	50	264	95	50
8	291	50	292	100	50	278	96	50
9	299	50	303	101	50	286	96	50
10	306	50	310	101	50	292	95	50
11	315	50	318	101	50	302	96	50
12	326	50	328	101	50	308	94	50
17	361	50	357	99	50	334	93	50
21	386	50	372	96	50	355	92	50
25	401	50	387	97	50	365	91	50
30	410	50	396	97	50	370	90	50
34	416	50	405	97	50	376	90	50
39	428	50	412	96	50	377	88	50
43	438	50	417	95	50	385	88	49
47	437	50	412	94	50	381	87	49
52	440	50	415	94	50	378	86	49
56	439	50	414	94	50	380	87	48
61	438	49	419	96	48	376	86	46
66	441	49	422	96	48	381	86	45
70	441	48	419	95	46	377	85	42
74	441	48	412	93	46	374	85	42
78	441	47	417	95	46	370	84	40
82	445	47	422	95	45	369	83	38
87	433	45	410	95	44	353	82	37
91	427	42	407	95	42	346	81	33
96	429	39	407	95	37	340	79	25
100	431	37	404	94	36	323	75	25
103	422	33	398	94	31	319	76	21
FEMALE								
0	111	50	109	98	50	111	100	50
1	135	50	133	99	50	133	99	50
2	145	50	144	99	50	142	98	50
3	151	50	149	99	50	146	97	50
4	162	50	158	98	50	156	96	50
5	170	50	164	96	50	164	96	50
6	178	50	171	96	50	169	95	50
7	176	50	168	95	50	166	94	50
8	179	50	175	98	50	171	96	50
9	182	50	176	97	50	172	95	50
10	183	50	179	98	50	174	95	50
11	188	50	184	98	50	179	95	50
12	190	50	187	98	50	180	95	50
17	204	50	198	97	50	190	93	50
21	218	50	208	95	50	199	91	50
25	222	50	213	96	50	204	92	50
30	229	50	218	95	50	209	91	49
34	234	50	223	95	50	213	91	49
39	239	50	227	95	50	217	91	49
43	246	50	233	95	50	223	91	49
47	253	50	239	94	50	226	89	49
52	263	49	250	95	50	233	89	49
56	269	47	255	95	50	235	87	49
61	280	47	265	95	49	242	86	48
66	290	46	273	94	49	246	85	46
70	293	44	278	95	47	247	84	46
74	302	41	285	94	46	253	84	45
78	313	38	290	93	44	253	81	44
82	318	38	298	94	44	261	82	44
87	319	38	302	95	43	262	82	42
91	325	34	301	93	41	263	81	41
96	329	31	304	92	40	264	80	38
100	333	29	304	91	40	265	80	37
103	331	28	301	91	38	263	79	33

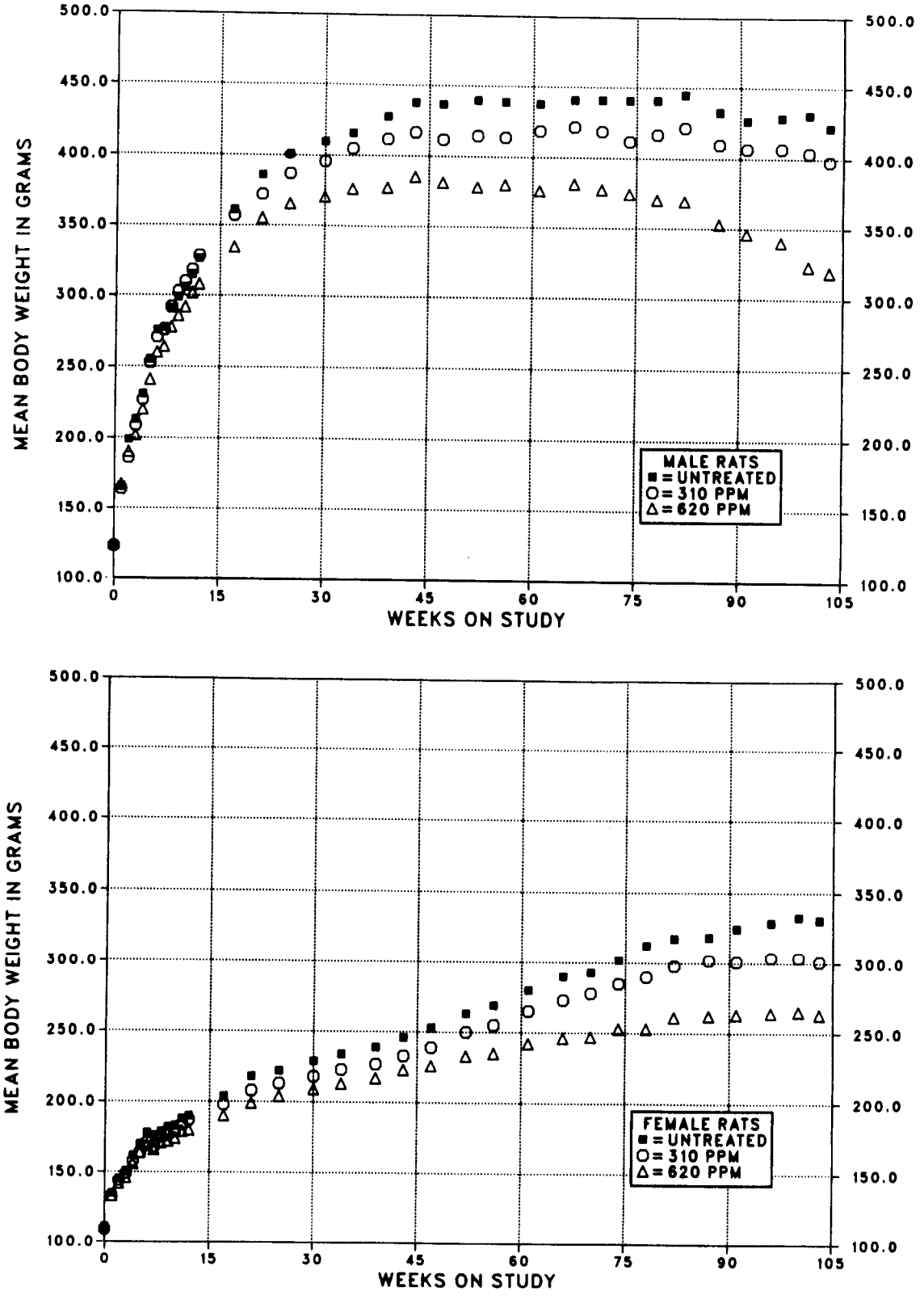


FIGURE 3. GROWTH CURVES FOR RATS FED DIETS CONTAINING NITROFURAZONE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing nitrofurazone at the concentrations used in these studies and for controls are shown in Table 11 and in the Kaplan and Meier curves in Figure 4. The survival of the high dose group of male rats was significantly lower than that of the controls after week 92. No other significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the mammary gland, joints, tunica vaginalis, skin, preputial gland, testis, and hematopoietic system.

Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (footnotes). Historical incidences of tumors in control male rats are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female rats are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female rats. Table B3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table B3 (footnotes). Historical incidences of tumors in control female rats are listed in Table B4. Findings on nonneoplastic lesions are summarized in Table B5.

TABLE 11. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF NITROFURAZONE

	Control	310 ppm	620 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	17	20	30
Killed at termination	33	30	20
Survival P values (c)	0.005	0.672	0.008
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	22	13	19
Killed at termination	28	37	31
Survival P values (c)	0.448	0.078	0.496

(a) Terminal-kill period: week 104
(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.

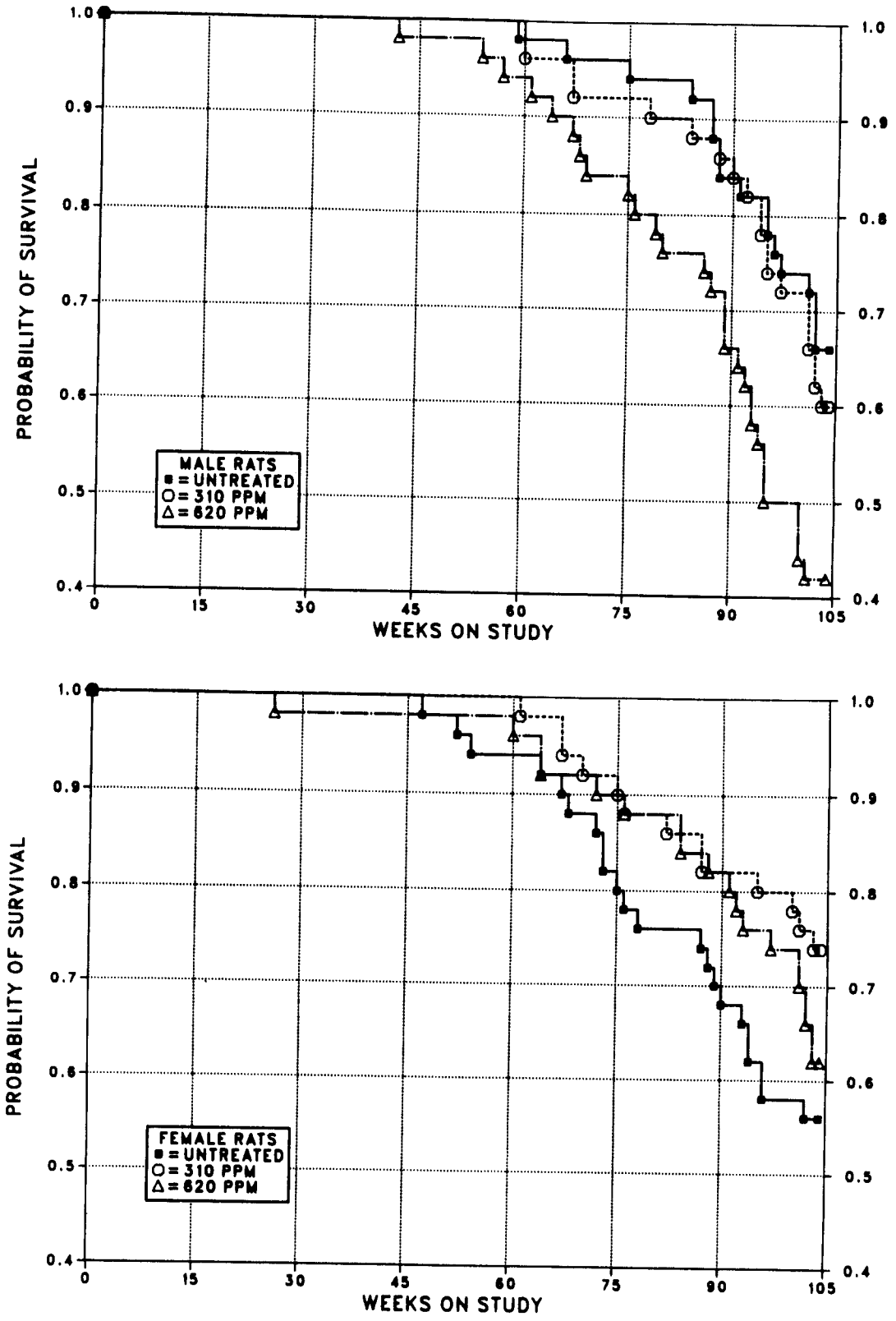


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING NITROFURAZONE FOR TWO YEARS

Mammary Gland: Fibroadenomas in female rats occurred with a significant positive trend; the incidences in the dosed groups were significantly greater than that in the controls (Table 12). Fibroadenomas consisted of varying proportions of epithelium and fibrous connective tissue. In smaller tumors, the epithelial component was quite prominent, whereas in larger tumors, the fibrous connective component almost completely obliterated the epithelium. Three adenocarcinomas were also observed.

Joints (Articular Cartilage): Degenerative changes involving the vertebral and knee (femoro-tibial) joints occurred at increased incidences in dosed rats of each sex relative to those of controls (Table 13). These lesions were characterized by a spectrum of changes that varied in extent and severity from animal to animal. There was fibrillation of the surface cartilage with degeneration of the cartilage matrix. The articular cartilage was irregularly or focally thickened and contained multiple chondrocyte clones or daughter cell nests. Occasional subchondral cysts and exostoses at the edge of the joint were also noted. Degeneration of the sternal synchondrosis was also increased in high dose female rats and was characterized by granular or fibrillar degeneration of the cartilage matrix with proliferation of the cartilage and formation of chondrocyte clones at the margins of the degenerative changes.

TABLE 12. ANALYSIS OF MAMMARY GLAND TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE (a,b)

	Control	310 ppm (c)	620 ppm (c)
Fibroadenoma			
Overall Rates	8/49 (16%)	36/50 (72%)	36/50 (72%)
Adjusted Rates	24.8%	81.6%	85.6%
Terminal Rates	5/28 (18%)	29/37 (78%)	25/31 (81%)
Week of First Observation	67	67	60
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
Adenocarcinoma			
Overall Rates	1/49 (2%)	0/50 (0%)	2/50 (4%)

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix B, Table B3 (footnotes).
(b) Historical incidence at study laboratory (mean ± SD): 42/149 (28% ± 12%); historical incidence in NTP studies: 550/1,984 (28% ± 11%)
(c) The estimated dose in milligrams per kilograms per day is given in Chapter III (Body Weights, Feed Consumption, and Clinical Signs) and in Appendix G.

TABLE 13. NUMBER OF RATS WITH DEGENERATION OF JOINT ARTICULAR CARTILAGE IN THE TWO-YEAR FEED STUDIES OF NITROFURAZONE

	Male			Female		
Site	Control	310 ppm	620 ppm	Control	310 ppm	620 ppm
No. of rats examined grossly	50	50	50	49	50	50
Vertebral joint	10	31	23	3	39	36
Knee joint	5	32	48	4	30	39
Sternal synchondrosis	24	26	21	15	(a) 1	32

(a) There was incomplete histopathologic sampling of the costochondral junction in low dose female rats.

Tunica Vaginalis: The incidence of mesotheliomas in low dose male rats was significantly greater than that in the controls (Table 14). Mesotheliomas are derived from the mesothelium that lines the body cavities and frequently begin in the tunica vaginalis. The more extensive tumors extend into the peritoneal cavity and involve the mesothelium overlying the gastrointestinal tract, mesentery, and urogenital tract. The mesotheliomas consisted of cuboidal to columnar epithelial cells arranged in complex papillary or pseudoglandular formations with an interspersed collagenous stroma. The tumors sometimes invaded the soft tissues underlying the mesothelium.

Skin: The incidence of trichoepitheliomas or sebaceous adenomas (combined) in high dose male rats was significantly greater than that in controls (Table 15). These tumors were observed in 0/50 control, 0/50 low dose, and 2/50 high dose female rats.

Sebaceous adenomas and trichoepitheliomas arise from cells in the epidermis or adnexal structures. Pluripotential cells in the epidermis or adnexa are capable of differentiating into any of several different cell types including sebaceous cells, cells composing hair follicles, and squamous cells. Epithelial tumors of the skin frequently contain varying proportions of basal

TABLE 14. ANALYSIS OF MESOTHELIOMAS IN THE TUNICA VAGINALIS OF MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE (a)

	Control	310 ppm	620 ppm
Overall Rates	0/50 (0%)	7/50 (14%)	2/50 (4%)
Adjusted Rates	0.0%	17.4%	6.6%
Terminal Rates	0/33 (0%)	2/30 (7%)	0/20 (0%)
Week of First Observation		67	93
Life Table Tests	P=0.149	P=0.010	P=0.174
Incidental Tumor Tests	P=0.363	P=0.014	P=0.307

(a) Historical incidence of mesotheliomas (all sites) at study laboratory (mean ± SD): 5/150 (3% ± 3%); historical incidence in NTP studies: 52/1,937 (3% ± 2%)

TABLE 15. ANALYSIS OF SKIN TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE

	Control	310 ppm	620 ppm
Trichoepithelioma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Sebaceous Adenoma			
Overall Rates	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates	0.0%	0.0%	15.2%
Terminal Rates	0/33 (0%)	0/30 (0%)	2/20 (10%)
Week of First Observation			69
Life Table Tests	P=0.006	(a)	P=0.028
Incidental Tumor Tests	P=0.015	(a)	P=0.067
Trichoepithelioma or Sebaceous Adenoma (b)			
Overall Rates	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates	0.0%	0.0%	17.4%
Terminal Rates	0/33 (0%)	0/30 (0%)	2/20 (10%)
Week of First Observation			69
Life Table Tests	P=0.002	(a)	P=0.014
Incidental Tumor Tests	P=0.009	(a)	P=0.044

(a) No P value recorded because no tumors were observed in the 310-ppm and control groups.
(b) Historical incidence of sebaceous adenomas, basal cell tumors, trichoepitheliomas, or adnexal adenomas (combined) at study laboratory (mean ± SD): 2/150 (1% ± 1%); historical incidence in NTP studies: 32/1,937 (2% ± 2%)

cells, sebaceous cells, and hair follicle-like structures; therefore, classification is usually based on the predominant component.

Preputial Gland: The incidence of carcinomas in low dose male rats was significantly greater than that in the controls (Table 16). The incidences of adenomas or carcinomas (combined) in dosed rats were not significantly greater than that in the controls. However, the incidence of adenomas or carcinomas (combined) in low dose rats is greater than the highest incidence observed in historical control groups (9/50). Hyperplasia was observed in six low dose male rats in which neither adenomas nor carcinomas were diagnosed. In females, the incidences of adenomas, adenocarcinomas, or carcinomas (combined) in the clitoral gland were not increased in dosed groups (control, 8/49; low dose, 7/50; high dose, 7/50).

Hyperplasia of the preputial gland consisted of expansile foci of enlarged cells with abundant granular cytoplasm and vesicular nuclei containing prominent nucleoli. The cells retained relatively normal arrangement in small packets or nests separated by a delicate fibrovascular stroma. Ducts present in the hyperplastic foci had increased numbers of cell layers showing variable degrees of squamous differentiation. The adenomas were circumscribed masses exhibiting loss of normal cellular arrangement. The tumor cells were similar to those in foci of hyperplasia but formed large aggregates and solid clusters. Remnants of the duct system were still apparent. Preputial gland carcinomas showed complete effacement of normal architectural features. The tumor cells were arranged in solid clusters or trabecular cords and showed greater pleomorphism and anaplasia than did the adenomas. The carcinomas showed only minimal invasion of adjacent soft tissue. There was a clear morphologic continuum from lesions classified as hyperplasia to those classified as carcinoma.

TABLE 16. ANALYSIS OF PREPUTIAL GLAND LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE

	Control	310 ppm	620 ppm
Hyperplasia			
Overall Rates	0/50 (0)%	6/50 (12%)	1/50 (2%)
Adenoma (a)			
Overall Rates	8/50 (16%)	8/50 (16%)	2/50 (4%)
Carcinoma (b)			
Overall Rates	1/50 (2%)	8/50 (16%)	5/50 (10%)
Adjusted Rates	3.0%	22.2%	16.0%
Terminal Rates	1/33 (3%)	5/30 (17%)	2/20 (10%)
Week of First Observation	104	60	42
Life Table Tests	P=0.041	P=0.016	P=0.053
Incidental Tumor Tests	P=0.171	P=0.018	P=0.166
Adenoma or Carcinoma (c)			
Overall Rates	9/50 (18%)	16/50 (32%)	7/50 (14%)
Adjusted Rates	25.2%	43.6%	22.5%
Terminal Rates	7/33 (21%)	11/30 (37%)	3/20 (15%)
Week of First Observation	95	60	42
Life Table Tests	P=0.356	P=0.062	P=0.496
Incidental Tumor Tests	P=0.366N	P=0.086	P=0.379N

(a) Historical incidence at study laboratory (mean): 2/150 (1%); historical incidence in NTP studies: 57/1,937 (3%)
(b) Historical incidence of carcinomas or adenocarcinomas (combined) at study laboratory (mean): 3/150 (2%); historical incidence in NTP studies: 66/1,937 (3%)
(c) Historical incidence of adenomas, adenocarcinomas, or carcinomas (combined) at study laboratory (mean): 5/150 (3%); historical incidence in NTP studies: 123/1,937 (6%)

Testis: Degeneration was observed at increased incidences in dosed male rats (control, 12/50; low dose, 49/50; high dose, 47/50; $P<0.001$). The lesion was usually bilateral and diffuse in dosed male rats; the lesion in control rats was often unilateral and associated with interstitial cell tumors. The degeneration was characterized by variable atrophy of the germinal epithelium and lack of spermatogenesis within the seminiferous tubules. Multinucleated giant cells were sometimes present in the lumina of seminiferous tubules.

The administration of nitrofurazone was also associated with a significant decrease in the incidence of testicular interstitial cell tumors (Table 17).

Hematopoietic System: Mononuclear cell leukemia in male and female rats occurred with significant negative trends; the incidences of leukemia in high dose males and dosed females were significantly lower than those in controls (Table 18).

TABLE 17. ANALYSIS OF TESTICULAR LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE

	Control	310 ppm	620 ppm
Interstitial Cell Hyperplasia			
Overall Rates	2/50 (4%)	2/50 (4%)	7/50 (14%)
Interstitial Cell Tumor (a)			
Overall Rates	45/50 (90%)	30/50 (60%)	28/50 (56%)
Adjusted Rates	100.0%	74.4%	86.8%
Terminal Rates	33/33 (100%)	20/30 (67%)	16/20 (80%)
Week of First Observation	75	67	75
Life Table Tests	P=0.352N	P=0.022N	P=0.495N
Incidental Tumor Tests	P=0.005N	P<0.001N	P=0.007N

(a) Historical incidence at study laboratory (mean ± SD): 133/150 (89% ± 6%); historical incidence in NTP studies: 1,681/1,909 (88% ± 7%)

TABLE 18. ANALYSIS OF MONONUCLEAR CELL LEUKEMIA IN RATS IN THE TWO-YEAR FEED STUDIES OF NITROFURAZONE

	Control	310 ppm	620 ppm
MALE (a)			
Overall Rates	21/50 (42%)	23/50 (46%)	6/50 (12%)
Adjusted Rates	50.8%	55.5%	21.2%
Terminal Rates	13/33 (39%)	12/30 (40%)	1/20 (5%)
Week of First Observation	88	88	92
Life Table Tests	P=0.068N	P=0.334	P=0.041N
Incidental Tumor Tests	P=0.001N	P=0.388	P=0.001N
FEMALE (b)			
Overall Rates	15/49 (31%)	2/50 (4%)	2/50 (4%)
Adjusted Rates	40.8%	4.5%	6.5%
Terminal Rates	7/28 (25%)	0/37 (0%)	2/31 (6%)
Week of First Observation	87	67	104
Life Table Tests	P<0.001N	P<0.001N	P<0.001N
Incidental Tumor Tests	P<0.001N	P<0.001N	P<0.001N

(a) Historical incidence of leukemia at study laboratory (mean ± SD): 71/150 (47% ± 3%); historical incidence in NTP studies: 586/1,937 (30% ± 12%)
(b) Historical incidence of leukemia at study laboratory (mean ± SD): 41/149 (28% ± 2%); historical incidence in NTP studies: 378/1,984 (19% ± 7%)

FOURTEEN-DAY STUDIES

All mice that received 2,500, 5,000, or 10,000 ppm nitrofurazone and 3/5 males that received 1,250 ppm died before the end of the studies (Table 19). All dosed groups except the 630-ppm female group lost weight. Feed consumption relative to that of the controls was reduced in all but the two lowest dose male groups and the lowest dose female group. All dosed animals had rough hair coats and convulsive seizures. No compound-related histopathologic effects were observed.

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

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	24.5 ± 0.9	25.4 ± 1.0	+0.9 ± 0.3	--	2.9	3.1
630	5/5	25.9 ± 1.2	24.4 ± 1.1	−1.5 ± 1.1	96.1	3.4	3.0
1,250	(e) 2/5	26.3 ± 1.3	24.9 ± 0.4	−2.5 ± 0.2	98.0	2.9	3.3
2,500	(f) 0/5	25.9 ± 0.9	(g)	(g)	(g)	1.9	1.9
5,000	(h) 0/5	26.3 ± 0.3	(g)	(g)	(g)	0.9	0.9
10,000	(i) 0/5	25.2 ± 0.5	(g)	(g)	(g)	0.6	(g)
FEMALE							
0	5/5	20.7 ± 0.7	21.7 ± 0.7	+1.0 ± 0.1	--	3.1	3.0
630	5/5	21.7 ± 0.6	22.1 ± 0.5	+0.4 ± 0.2	101.8	3.1	2.9
1,250	5/5	20.3 ± 0.4	16.7 ± 1.1	−3.6 ± 0.9	77.0	2.7	1.8
2,500	(j) 0/5	21.0 ± 0.5	(g)	(g)	(g)	1.6	1.4
5,000	(k) 0/5	19.9 ± 0.5	(g)	(g)	(g)	0.8	0.3
10,000	(l) 0/5	20.9 ± 0.4	(g)	(g)	(g)	0.3	(g)

(a) Number surviving/number initially in the group
(b) Initial mean group 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 per animal per day; not corrected for scatter.
(e) Day of death: 8,8,12
(f) Day of death: 10,12,12,12,12
(g) No data are reported due to 100% mortality in this group.
(h) Day of death: 7,7,9,10,10
(i) Day of death: all 5
(j) Day of death: 6,7,10,10,11
(k) Day of death: 6,7,7,8,9
(l) Day of death: all 6

THIRTEEN-WEEK STUDIES

Six of 10 males and 9/10 females that received 1,250 ppm and 3/10 males and 5/10 females that received 620 ppm died before the end of the studies (Table 20). The final mean body weight of the 5/20 surviving mice that received 1,250 ppm was 21% lower than that of the controls. The liver weight to body weight ratio for male mice that received 620 or 1,250 mg/kg was significantly greater than that for the controls (Table 21). The liver weight to body weight ratios for male and female mice that received 70 mg/kg and for female mice that received 150 mg/kg were significantly lower than those for controls. Hyperexcitability and convulsive seizures were observed for all mice that received at least 620 ppm nitrofurazone. Testicular hypoplasia of mild to moderate severity was observed in 8/10 males that received 1,250 ppm and in 9/10 that received 620 ppm.

Dose Selection Rationale: Because of the incidence of deaths, lower weight gain, and seizures at higher concentrations, dietary concentrations of nitrofurazone selected for mice for the 2-year studies were 150 and 310 ppm.

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

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 7	Week 13
MALE							
0	10/10	19.5 ± 0.3	31.7 ± 0.8	+12.2 ± 0.6	--	3.4	2.9
70	10/10	19.2 ± 0.3	30.9 ± 1.0	+11.7 ± 1.0	97.5	3.5	3.1
150	10/10	19.8 ± 0.3	30.9 ± 0.6	+11.1 ± 0.5	97.5	3.5	3.1
310	10/10	19.9 ± 0.3	32.8 ± 1.0	+12.9 ± 0.8	103.5	3.8	3.4
620	(e) 7/10	19.9 ± 0.3	29.9 ± 1.1	+10.1 ± 1.2	94.3	3.3	3.6
1,250	(f) 4/10	19.7 ± 0.3	24.9 ± 1.6	+4.7 ± 1.6	78.5	2.9	2.4
FEMALE							
0	10/10	16.3 ± 0.3	25.3 ± 0.6	+9.0 ± 0.4	--	3.2	3.0
70	10/10	16.8 ± 0.3	25.1 ± 0.6	+8.3 ± 0.6	99.2	3.0	3.1
150	10/10	16.2 ± 0.4	25.2 ± 0.7	+9.0 ± 0.9	99.6	2.9	3.1
310	10/10	16.6 ± 0.3	23.3 ± 0.4	+6.7 ± 0.3	92.1	3.4	3.2
620	(g) 5/10	15.9 ± 0.3	25.1 ± 1.3	+9.1 ± 1.4	99.2	2.6	3.2
1,250	(h) 1/10	16.3 ± 0.5	20.1	+2.6	79.4	3.2	3.2

(a) Number surviving/number initially in the group
(b) Initial mean group 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 per animal per day; not corrected for scatter.
(e) Week of death: 3,11,12
(f) Week of death: 3,3,3,3,3,4
(g) Week of death: 4,7,9,10,12
(h) Week of death: 2,3,3,4,4,4,4,6,9

TABLE 21. ANALYSIS OF LIVER WEIGHTS OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF NITROFURAZONE (a)

Concentration (ppm)	No. of Animals Examined	Final Body Weight (grams)	Liver Weight (mg)	Liver Weight/Final Body Weight (mg/g)
MALE				
0	10	31.7 ± 0.8	1,306 ± 74	41.5 ± 2.61
70	10	30.9 ± 1.0	(b) 1,071 ± 34	(b) 34.7 ± 0.61
150	10	30.9 ± 0.6	1,145 ± 28	37.0 ± 0.33
310	10	32.8 ± 1.0	1,488 ± 46	45.4 ± 0.76
620	7	29.9 ± 1.1	(c) 1,647 ± 90	(c) 55.2 ± 2.86
1,250	(d) 4	(c) 24.9 ± 1.6	1,523 ± 29	(c) 57.6 ± 0.44
FEMALE				
0	10	25.3 ± 0.6	1,179 ± 74	46.9 ± 2.97
70	10	25.1 ± 0.6	(c) 891 ± 28	(c) 35.5 ± 1.01
150	10	25.2 ± 0.7	(b) 998 ± 48	(b) 39.5 ± 1.48
310	10	23.3 ± 0.4	1,204 ± 36	51.6 ± 1.25
620	5	25.1 ± 1.3	1,240 ± 50	49.9 ± 2.68
1,250	(e) 1	20.1	1,220	60.7

(a) Mean ± standard error; P values vs. the controls by Dunnett's test (Dunnett, 1955).
(b) $P<0.05$
(c) $P<0.01$
(d) One liver weight not taken; ratio is based on the remaining three animals.
(e) Not included in statistical analysis

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of dosed mice were comparable to or greater than those of the controls throughout most of the studies (Table 22 and Figure 5). The average daily feed consumption by low dose and high dose male mice was 100% and 105% that of the controls and by low dose and high dose female mice, 97% that of the controls (Appendix G, Tables G3 and G4). The average amount of nitrofurazone consumed per day was approximately 16 or 33 mg/kg for low or high dose male mice and 14 or 29 mg/kg for low or high dose female mice.

Stimulus-sensitive seizures of short duration were seen primarily during the first year, beginning at weeks 4 and 5 for high dose male and female mice and at week 24 for low dose female mice. The seizures were usually initiated by the auditory and tactile stimuli created by cage changing and weighing activities. The episodes were characterized by about 10 seconds of convulsive seizures that began with the animal either sitting or lying down and with eyes partially closed. When animals were in the sitting position, some facial preening motions were noted which faded into a steady, tense stance followed by trembling that became severe enough to cause the animal to fall over. Seizure episodes averaged 10 seconds and lasted up to 34 seconds. Episodes ended as the tremulous activity subsided and righting reflexes began. Postseizure signs usually included a lethargic period followed by a prolonged period of hyperexcitability.

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

Weeks on Study	Control		150 ppm			310 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								
1	23.0	50	22.3	97	50	23.2	101	50
2	25.0	50	24.6	98	50	25.1	100	50
3	25.5	50	25.6	100	50	26.1	102	50
4	27.0	50	27.5	102	50	26.9	100	50
5	27.0	50	27.3	101	48	28.2	104	50
6	28.7	50	29.0	101	44	29.2	102	50
7	29.8	50	30.5	102	44	30.9	104	50
8	29.5	50	29.7	101	44	29.8	101	50
9	29.4	50	30.7	104	44	31.0	105	50
10	30.3	49	30.7	101	44	30.8	102	50
11	30.7	49	31.0	101	44	31.5	103	50
12	31.7	49	32.1	101	44	32.3	102	50
13	32.3	49	31.5	98	44	32.1	99	49
20	33.0	49	33.1	100	44	33.1	100	45
23	34.3	49	34.3	100	43	35.2	103	44
28	35.9	49	35.7	99	43	36.8	103	44
33	36.4	49	35.8	98	42	37.0	102	43
37	37.3	49	36.4	98	42	38.2	102	43
42	37.1	49	36.4	98	42	38.3	103	42
46	38.6	49	38.1	99	42	39.6	103	41
49	38.3	49	38.8	101	41	40.4	105	41
54	39.2	49	38.8	99	40	39.5	101	40
58	39.0	49	39.1	100	40	39.9	102	40
64	38.7	49	38.7	100	40	40.0	103	40
68	38.3	47	38.6	101	40	39.1	102	40
72	37.9	47	39.0	103	40	40.2	106	40
77	39.1	47	39.6	101	40	40.2	103	40
80	38.9	46	39.0	100	40	39.2	101	40
84	39.9	45	39.2	98	38	40.0	100	40
89	37.1	45	37.6	101	36	38.0	102	36
93	38.5	44	37.7	98	36	37.6	98	33
98	39.1	42	36.7	94	35	38.2	98	29
102	39.4	40	37.6	95	32	38.6	98	27
104	39.6	39	38.1	96	31	38.6	97	27
FEMALE								
1	17.7	50	17.9	101	50	17.6	99	50
2	19.5	50	19.6	101	50	18.9	97	50
3	19.9	50	19.5	98	50	19.9	100	50
4	20.9	50	20.5	98	50	21.1	101	50
5	21.5	50	21.5	100	50	21.1	98	50
6	22.6	50	22.8	101	50	22.5	100	50
7	23.3	50	23.1	99	50	22.8	98	50
8	23.5	50	23.9	102	50	23.2	99	50
9	23.7	50	24.3	103	50	23.9	101	50
10	23.4	50	24.5	105	50	23.9	102	49
11	24.2	50	24.4	101	50	24.2	100	49
12	24.8	50	25.0	101	50	24.4	98	49
13	25.7	50	25.8	100	50	25.3	98	49
20	27.3	50	27.1	99	50	26.5	97	49
23	28.6	50	28.1	98	50	27.7	97	49
28	31.0	50	29.6	95	50	29.4	95	47
33	31.1	50	29.8	96	50	29.4	95	47
37	32.3	50	30.7	95	50	31.4	97	47
42	33.6	50	32.6	97	50	32.8	98	46
46	34.9	50	32.8	94	49	34.1	98	46
49	35.7	50	34.8	97	49	35.9	101	46
54	37.1	50	35.7	96	49	37.2	100	46
58	37.3	49	36.6	98	49	38.4	103	46
64	37.9	49	37.4	99	49	39.7	105	46
68	38.2	49	38.6	101	49	40.5	106	46
72	39.0	49	39.3	101	49	41.5	106	46
77	39.6	49	41.1	104	49	42.1	106	46
80	39.2	49	41.5	106	49	42.3	108	46
84	40.4	49	42.1	104	48	43.5	108	44
89	39.6	47	41.3	104	48	41.9	106	42
93	40.3	44	41.8	104	45	42.5	105	41
98	41.7	42	42.5	102	42	44.1	106	36
102	42.7	39	43.0	101	40	43.5	102	36
104	42.7	39	42.6	100	40	43.3	101	35

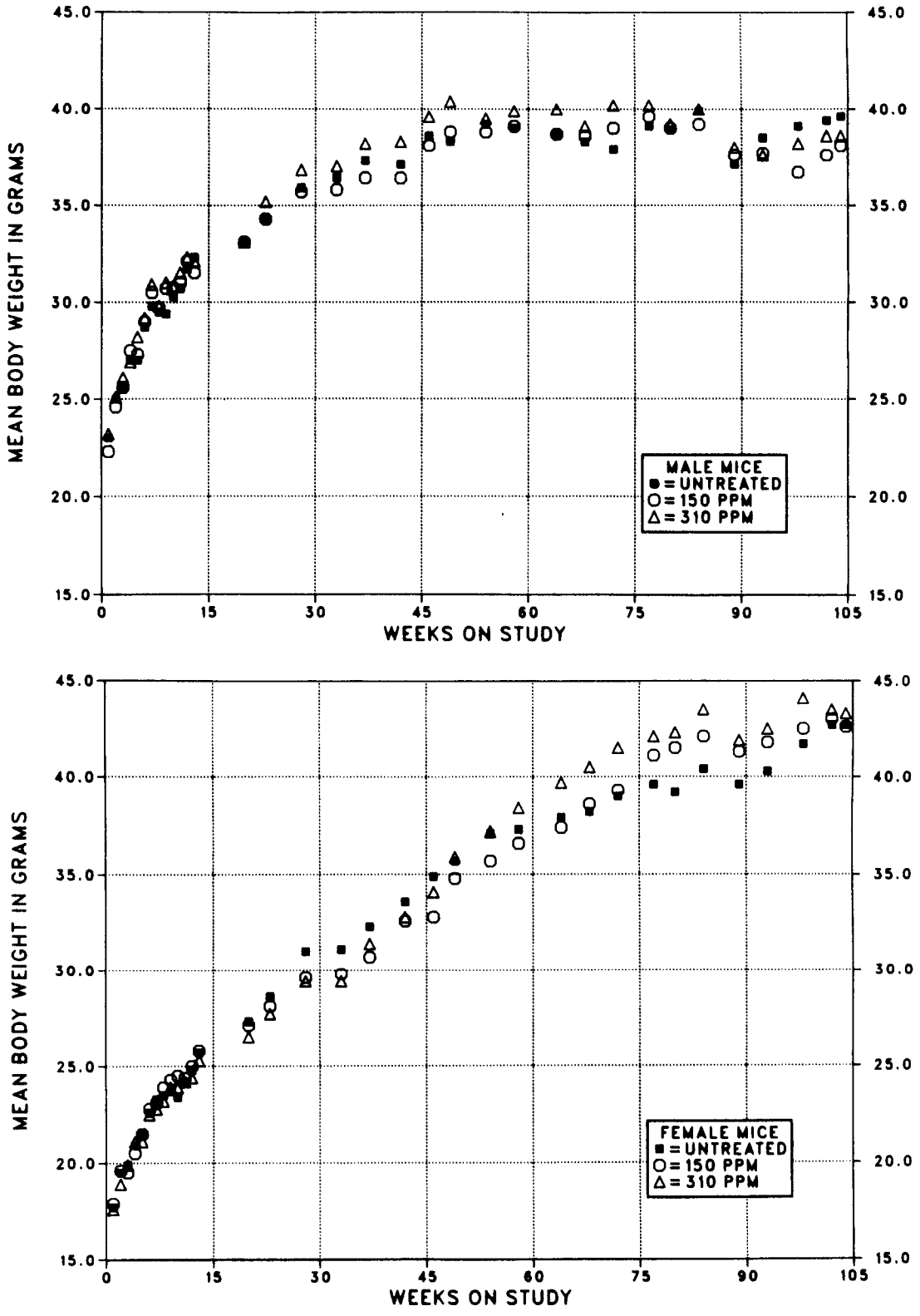


FIGURE 5. GROWTH CURVES FOR MICE FED DIETS CONTAINING NITROFURAZONE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing nitrofurazone at the concentrations used in these studies and for controls are shown in Table 23 and in the Kaplan and Meier curves in Figure 6.

The survival of the high dose group of male mice was significantly lower than that of the controls after week 88. No other significant differences in survival were observed between any groups of either sex. Three low dose males in each of two separate cages died during weeks 5 and 6, probably as a result of fighting.

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

	Control	150 ppm	310 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	10	19	23
Accidentally killed	1	0	0
Killed at termination	39	31	27
Survival P values (c)	0.008	0.057	0.007
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	11	10	14
Accidentally killed	0	0	1
Killed at termination	39	40	35
Survival P values (c)	0.448	0.974	0.529

(a) Terminal-kill period: week 104
(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.

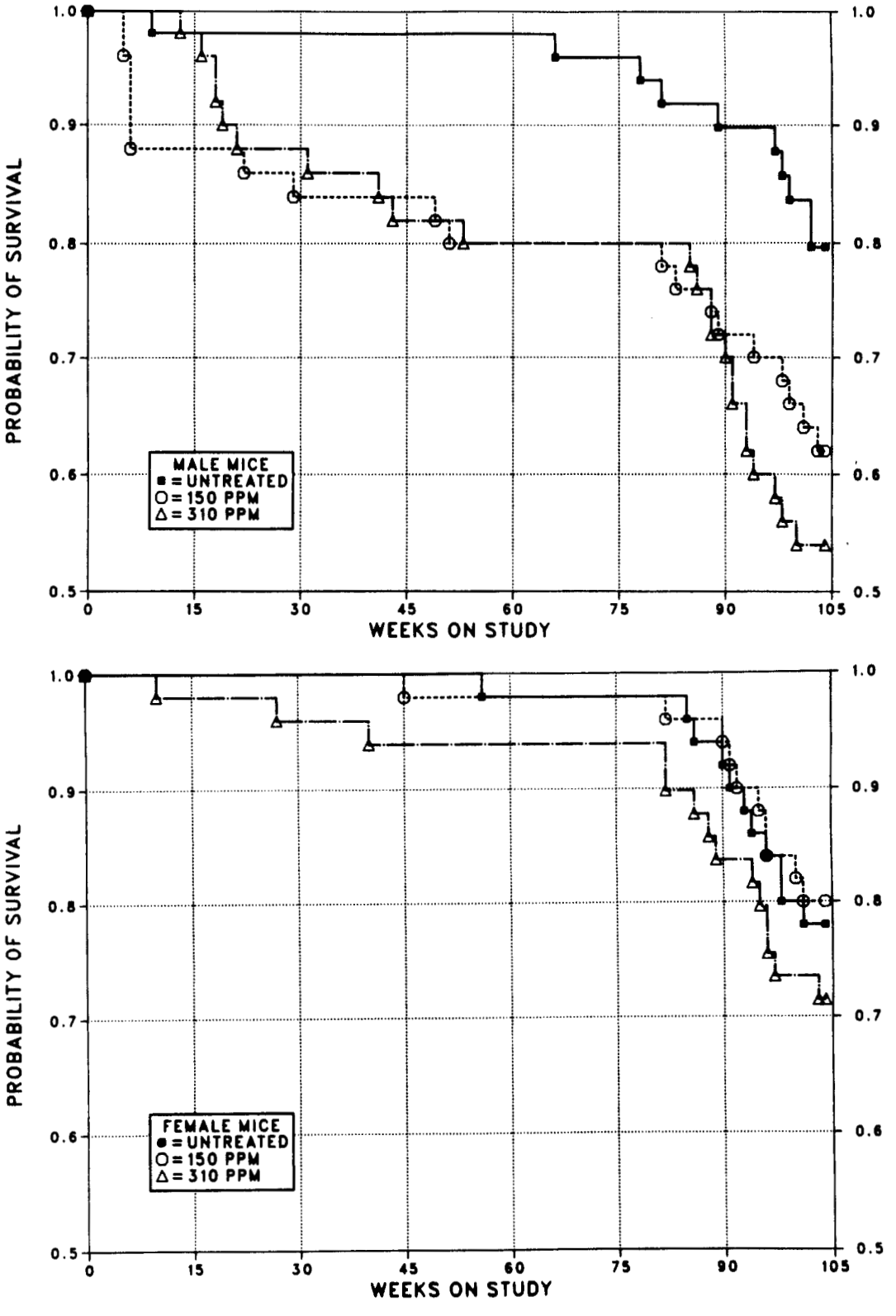


FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING NITROFURAZONE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the ovary, circulatory system, integumentary system, liver, anterior pituitary gland, and kidney.

Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table C3 (footnotes). Historical incidences of tumors in control male mice are listed in Table C4. Findings on nonneoplastic lesions are summarized in Table C5.

Lesions in female mice are summarized in Appendix D. Histopathologic findings on neoplasms are summarized in Table D1. Table D2 gives the survival and tumor status for individual female mice. Table D3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table D3 (footnotes). Historical incidences of tumors in control female mice are listed in Table D4. Findings on nonneoplastic lesions are summarized in Table D5.

Ovary: Ovarian atrophy and tubular cell hyperplasia were observed at increased incidences ($P<0.001$) in dosed female mice (ovarian atrophy: control, 7/47; low dose, 44/50; high dose, 38/50; tubular cell hyperplasia: 1/47; 23/50; 21/50). Benign mixed tumors, granulosa cell tumors, and granulosa cell tumors or luteomas (combined) occurred with significant positive trends; the incidences of benign mixed tumors in dosed female mice and granulosa cell tumors in high dose female mice were significantly greater than those in the controls (Table 24).

The ovarian atrophy and tubular cell hyperplasia were characterized by variable reduction in size of the ovaries, loss of graafian follicles and associated theca cells, and branching tubular downgrowth of the cuboidal cells lining the surface of the ovary (modified mesothelium).

Tumors classified as benign mixed tumors consisted of variable amounts of cuboidal cells arranged in complex branching tubular structures, apparently arising from the surface mesothelium, and interspersed stroma. The stromal cells had scant cytoplasm and contained fusiform or round nuclei with dense chromatin patterns. In some tumors, the stromal cells contained fine cytoplasmic vacuoles characteristic of lipid accumulation. The few tumors classified as tubular cell adenomas consisted primarily of the branching tubular component seen in the mixed tumors. Mixed tumors and tubular adenomas constitute a morphologic spectrum and are classified according to the extent of stromal proliferation.

The granulosa cell tumors consisted predominantly of granulosa cells arranged in follicular, glandular, or tubular patterns. Enlargement of granulosa cells with the accumulation of pale eosinophilic vacuoles (luteinization) occurred in some tumors. The luteomas were composed primarily of similarly luteinized cells and may be derived from granulosa or theca cells.

Circulatory System: Hemangiomas or hemangiosarcomas (combined) in male mice occurred with a significant positive trend (control, 1/50; low dose, 0/50; high dose, 4/50; $P=0.049$, life table test); the incidences in the dosed groups were not significantly greater than that in the controls.

TABLE 24. ANALYSIS OF OVARIAN LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE (a)

	Control	150 ppm (b)	310 ppm (b)
Granulosa Cell Hyperplasia			
Overall Rates	1/47 (2%)	0/50 (0%)	1/50 (2%)
Granulosa Cell Tumor			
Overall Rates	1/47 (2%)	4/50 (8%)	9/50 (18%)
Adjusted Rates	2.6%	10.0%	23.9%
Terminal Rates	1/39 (3%)	4/40 (10%)	7/35 (20%)
Week of First Observation	104	104	88
Life Table Tests	P=0.003	P=0.187	P=0.007
Incidental Tumor Tests	P=0.004	P=0.187	P=0.009
Luteoma			
Overall Rates	2/47 (4%)	2/50 (4%)	0/50 (0%)
Granulosa Cell Tumor or Luteoma (c)			
Overall Rates	3/47 (6%)	6/50 (12%)	9/50 (18%)
Adjusted Rates	7.7%	14.5%	23.9%
Terminal Rates	3/39 (8%)	5/40 (13%)	7/35 (20%)
Week of First Observation	104	96	88
Life Table Tests	P=0.030	P=0.257	P=0.043
Incidental Tumor Tests	P=0.039	P=0.267	P=0.055
Tubular Cell Hyperplasia			
Overall Rates	1/47 (2%)	23/50 (46%)	21/50 (42%)
Tubular Cell Adenoma			
Overall Rates	0/47 (0%)	2/50 (4%)	0/50 (0%)
Benign Mixed Tumor			
Overall Rates	0/47 (0%)	17/50 (34%)	20/50 (40%)
Adjusted Rates	0.0%	41.4%	55.5%
Terminal Rates	0/39 (0%)	16/40 (40%)	19/35 (54%)
Week of First Observation		96	97
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
Tubular Cell Adenoma or Benign Mixed Tumor (d)			
Overall Rates	0/47 (0%)	18/50 (36%)	20/50 (40%)
Adjusted Rates	0.0%	43.8%	55.5%
Terminal Rates	0/39 (0%)	17/40 (43%)	19/35 (54%)
Week of First Observation		96	97
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix D, Table D3 (footnotes).
(b) The estimated dose in milligrams per kilograms per day is given in Chapter III (Body Weights, Feed Consumption, and Clinical Signs) and in Appendix G.
(c) Historical incidence of granulosa cell tumors or luteomas (combined) at study laboratory (mean): 0/134; historical incidence in NTP studies: 8/1,858 (0.4%)
(d) Historical incidence of benign mixed tumors or tubular cell adenomas (combined) at study laboratory (mean): 0/134; historical incidence in NTP studies: 5/1,858 (0.3%)

Integumentary System: Subcutaneous tissue fibromas, sarcomas, fibrosarcomas, and neurofibrosarcomas in male mice occurred with significant positive trends by the life table test (Table 25). The incidence of fibromas, sarcomas, fibrosarcomas, or neurofibrosarcomas (combined) in high dose male mice was significantly greater than that in the controls by the life table test. However, neither of these increases was significant by the incidental tumor test, which is the more appropriate test for these generally nonfatal neoplasms.

Liver: The incidence of hepatocellular adenomas or carcinomas (combined) in high dose male mice was significantly lower than that in the controls by the incidental tumor test (Table 26).

Anterior Pituitary Gland: Adenomas and adenomas or carcinomas (combined) in female mice occurred with significant negative trends; the incidences in the high dose group were significantly lower than those in the controls (Table 27).

Kidney: Mineralization was observed at increased incidences in dosed male mice (male: control, 1/50; low dose, 3/49; high dose, 8/50; female: 2/50; 0/7; 3/50).

TABLE 25. ANALYSIS OF SUBCUTANEOUS TISSUE TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE

	Control	150 ppm	310 ppm
Fibroma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Fibrosarcoma			
Overall Rates	2/50 (4%)	3/50 (6%)	5/50 (10%)
Fibroma or Fibrosarcoma			
Overall Rates	2/50 (4%)	3/50 (6%)	6/50 (12%)
Adjusted Rates	4.7%	8.9%	18.5%
Terminal Rates	0/39 (0%)	2/31 (6%)	2/27 (7%)
Week of First Observation	97	88	86
Life Table Tests	P=0.039	P=0.402	P=0.057
Incidental Tumor Tests	P=0.119	P=0.519	P=0.159
Sarcoma			
Overall Rates	1/50 (2%)	0/50 (0%)	1/50 (2%)
Neurofibrosarcoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates	3/50 (6%)	3/50 (6%)	7/50 (14%)
Adjusted Rates	6.9%	8.9%	20.8%
Terminal Rates	0/39 (0%)	2/31 (6%)	1/27 (4%)
Week of First Observation	97	88	86
Life Table Tests	P=0.044	P=0.557	P=0.064
Incidental Tumor Tests	P=0.140	P=0.653N	P=0.172
Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma (a)			
Overall Rates	3/50 (6%)	3/50 (6%)	8/50 (16%)
Adjusted Rates	6.9%	8.9%	23.8%
Terminal Rates	0/39 (0%)	2/31 (6%)	2/27 (7%)
Week of First Observation	97	88	86
Life Table Tests	P=0.021	P=0.557	P=0.034
Incidental Tumor Tests	P=0.070	P=0.653N	P=0.084

(a) Historical incidence of fibromas, neurofibromas, sarcomas, fibrosarcomas, or neurofibrosarcomas (combined) at study laboratory (mean ± SD): 16/150 (11% ± 14%); historical incidence in NTP studies: 160/2,040 (8% ± 8%)

TABLE 26. ANALYSIS OF HEPATOCELLULAR TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE

	Control	150 ppm	310 ppm
Adenoma			
Overall Rates	9/50 (18%)	6/49 (12%)	2/50 (4%)
Carcinoma			
Overall Rates	8/50 (16%)	9/49 (18%)	4/50 (8%)
Adenoma or Carcinoma (a)			
Overall Rates	16/50 (32%)	15/49 (31%)	5/50 (10%)
Adjusted Rates	36.8%	43.8%	17.7%
Terminal Rates	12/39 (31%)	12/31 (39%)	4/27 (15%)
Week of First Observation	66	83	97
Life Table Tests	P=0.072N	P=0.380	P=0.062N
Incidental Tumor Tests	P=0.007N	P=0.382	P=0.031N

(a) Historical incidence at study laboratory (mean ± SD): 52/150 (35% ± 4%); historical incidence in NTP studies: 609/2,032 (30% ± 8%)

TABLE 27. ANALYSIS OF ANTERIOR PITUITARY GLAND TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE

	Control	150 ppm	310 ppm
Adenoma			
Overall Rates	9/50 (18%)	5/50 (10%)	2/49 (4%)
Adjusted Rates	22.4%	12.5%	5.7%
Terminal Rates	8/39 (21%)	5/40 (13%)	2/35 (6%)
Week of First Observation	96	104	104
Life Table Tests	P=0.025N	P=0.180N	P=0.041N
Incidental Tumor Tests	P=0.026N	P=0.187N	P=0.043N
Carcinoma			
Overall Rates	1/50 (2%)	2/50 (4%)	0/49 (0%)
Adenoma or Carcinoma (a)			
Overall Rates	10/50 (20%)	7/50 (14%)	2/49 (4%)
Adjusted Rates	24.1%	17.5%	5.7%
Terminal Rates	8/39 (21%)	7/40 (18%)	2/35 (6%)
Week of First Observation	93	104	104
Life Table Tests	P=0.019N	P=0.280N	P=0.026N
Incidental Tumor Tests	P=0.019N	P=0.296N	P=0.027N

(a) Historical incidence at study laboratory (mean ± SD): 26/146 (18% ± 16%); historical incidence in NTP studies: 204/1,764 (12% ± 10%)

IV. DISCUSSION AND CONCLUSIONS

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Studies of the toxicity and carcinogenicity of nitrofurazone were conducted in F344/N rats and B6C3F$_1$ mice of each sex. For the 2-year studies, nitrofurazone was administered in the diet at concentrations of 0, 310, or 620 ppm to rats and 0, 150, or 310 ppm to mice. The selection of these doses was based on results of 14-day and 13-week studies.

In the 13-week studies, doses for rats of each sex were 0, 150, 310, 620, 1,250, or 2,500 ppm. None of the rats died, all animals gained weight, and decreases in weight gain and feed consumption were evident only at the two doses above 620 ppm. At the two highest doses, nitrofurazone produced hyperexcitability and seizures. Thus, for rats of each sex, nitrofurazone at 620 ppm and below had negligible effects on weight gain and feed intake and, with the exception of moderate testicular degeneration, did not show evidence of overt toxicity. Based on these findings, 310 ppm and 620 ppm were chosen as the dietary concentrations for the 2-year evaluation of nitrofurazone in rats of each sex.

The survival of male rats after 103 weeks of exposure to nitrofurazone at 620 ppm was two-thirds that of controls and low dose animals. Feed consumption in the high dose group decreased throughout most of the study, and this was accompanied by lower body weights. The survival among all groups of female rats was comparable, but there was a dose-related decrease in body weight gain. In retrospect, somewhat lower doses might have been chosen for male rats. However, the doses for the 2-year studies were based primarily on chemical-associated convulsive seizures, weight gain, and survival in the 13-week studies. Furthermore, the depressed weight gain of dosed groups in the 2-year studies did not become evident until after 4 months. Since survival of dosed females was not decreased and since 80% of high dose male rats survived for at least 90 weeks of exposure, these studies were considered to be adequate assessments of the long-term toxicity and carcinogenicity of nitrofurazone in male and female rats.

The long bones of male and female rats were observed for histopathologic effects in both the 13-week and 2-year studies. It is uncertain if the osteoporosis observed in the 13-week studies was directly related to the administration of nitrofurazone. Since it was not observed in the 2-year studies in which weight gain was not depressed as severely as in the 13-week studies, it is possible that the osteoporosis occurred secondarily to the severe decrease in weight gain of the high dose groups in the 13-week studies.

Degenerative lesions of articular cartilage were also observed in the 2-year studies in rats. These lesions were microscopically evaluated at three sites: the vertebral and knee joints and the sternal synchondrosis. Although the arthropathy was observed in the control groups, increased incidences of the site-specific lesions of the vertebral and knee joints (see Table 13) indicate that these lesions were the result of nitrofurazone administration. Since examinations did not provide neurologic bases for the observed disturbed gait and muscle atrophy, it is likely that these were secondary to the degenerative lesions in the articular cartilage. The etiology of these lesions is unknown. They have been described as occurring in untreated F344 rats, but not as early as 90 days, and they were not severe enough to cause gait or motor disturbances (Yamasaki and Inui, 1985). Similar arthropathies have been described in young dogs after administration of nalidixic, oxolinic, or pipemidic acids. Although structurally unrelated to nitrofurazone, these three chemicals (fused ring *N*-alkyl-4-pyridone-3-carboxylic acids) are also used as antibiotics (Ingham et al., 1977; Gough et al., 1979).

Gonadal degeneration and atrophy were prominent findings in the 13-week and 2-year studies of nitrofurazone in rats. Testicular degeneration was characteristically bilateral and diffuse and accompanied by a lack of spermatogenesis. These lesions were reported previously by other investigators studying the toxicity of nitrofurazone (Montemurro, 1969; Miyaji, 1971; Hagenas et al., 1978), but the mechanism responsible for these findings is unknown.

The range of nitrofurazone doses used in the 13-week studies in B6C3F$_1$ mice of each sex encompassed a no-apparent-effect level as well as levels that produced overt signs of toxicity, as evidenced by the occurrence of seizures, microscopic evidence of gonadal hypoplasia, and chemically

related deaths. Feed consumption for mice was decreased only at the highest dose in males, and decreases in body weight were observed at the 620-ppm (males only) and 1,250-ppm doses. Gross lesions observed at necropsy did not provide evidence of any chemically affected organs. Testicular hypoplasia, judged not to be life threatening, was observed only at doses above 310 ppm. Although clinical signs of hyperexcitability and convulsive seizures were noted in both sexes at doses of 620 ppm and above, no histopathologic lesions were found which would account for this behavior. Thus, in the 13-week studies, the effects of nitrofurazone on mortality rate, clinical signs, feed consumption, and weight gain depression were comparable for male and female mice. Considered together, these observations indicated that doses of nitrofurazone not exceeding 310 ppm would be appropriate and compatible with long-term survival in the 2-year studies in $B6C3F_1$ mice of each sex.

Throughout most of the 2-year studies in mice, body weights and feed consumption of dosed and control animals were comparable. Convulsive seizures, seen in these studies, were reported in other toxicologic investigations of nitrofurazone in rodents (Krantz and Evans, 1945; Dodd, 1946). Furthermore, peripheral sensorimotor polyneuropathies were observed after administration of nitrofurazone and other nitrofurans to humans and animals (Karol, 1960; Lister and Fisher, 1970; Toole and Parrish, 1973). No histopathologic lesions were found to explain the seizures observed in the studies reported here.

Neoplastic Lesions

Results from the 2-year study provide substantial evidence that administration of nitrofurazone induces mammary gland fibroadenomas in female rats. Marked increases in incidence were seen in both dosed groups, although chemical exposure did not hasten the time to appearance of this neoplasm. The control incidence in this study (16%) was somewhat lower than the historical laboratory and NTP average (28%), but the incidences in both dosed groups were about 50% greater than the highest incidences observed in untreated historical control groups (Appendix B, Table B4a). This interpretation that nitrofurazone induced mammary gland neoplasms is consistent with observations reported by other investigators. Erturk et al. (1970) reported mammary gland fibroadenoma incidences of 2/29 and 22/29 in the control and dosed groups, respectively, in a study in which 30 female Sprague Dawley rats were fed diets containing 1,000 ppm of pure nitrofurazone for 46 weeks followed by 20 weeks of a control diet. Concurrent evaluation of equimolar concentrations of 2-furaldehyde semicarbazone revealed no difference in the incidences of mammary gland fibroadenomas in dosed groups compared with that in controls. Except for the absence of the nitro group, 2-furaldehyde is structurally identical to nitrofurazone. Therefore, this observation leads to the speculation that the nitro group is required for the induction of fibroadenomas by nitrofurazone.

Fibroadenomas are benign tumors that can progress to malignant epithelial or mesenchymal tumors. In observations from at least 1,100 rats of each strain, Van Zwieten (1984) reported carcinomas arising in mammary gland fibroadenomas at rates of 2.3% for WAG/Rij rats, 0.5% for BN/BiRij rats, and 2.1% for Sprague Dawley rats. Furthermore, a low incidence of carcinomas arising from fibroadenomas has also been observed in F344/N rats (Boorman et al., unpublished observations). Evidence of malignancy was also observed in mammary tissue from studies reported here. Therefore, these studies provide strong evidence of a marked increase in the incidence of benign tumors that can progress to malignancy.

Cells showing sebaceous differentiation predominated in four skin neoplasms found in high dose male rats and diagnosed as sebaceous adenomas; an additional neoplasm showing differentiation toward hair follicles was diagnosed as a trichoepithelioma. Because of their similar histogenesis, these were combined for evaluation. Since these neoplasms were not observed in the low dose groups (see Table 15), there was not a clear dose response, but the incidence of these neoplasms in the high dose male rats (5/50) exceeds the highest observed incidence in historical controls for studies at this laboratory (1/50) or at all NTP laboratories (4/50).

The incidence of preputial gland carcinomas in low dose male rats, a group having a survival rate comparable to that of controls, was increased above that of concurrent and historical controls (see Table 16). Furthermore, 3/8 carcinomas were seen in the early-death low dose animals beginning at week 60. In high dose males, 3/5 carcinomas were observed earlier than week 80. In contrast, no preputial gland carcinomas were observed in the 17 early-death control animals. Considered together, these results suggest that nitrofurazone administration may have shortened the time to appearance of this neoplasm. Evidence supporting the conclusion that nitrofurazone caused the preputial gland neoplasms is lessened when the incidence of male rats with adenomas is considered. The combined incidence is the most appropriate value to use when comparing the incidences of preputial gland neoplasms in dosed and control groups because both lesions are derived from the same cell type; adenomas and carcinomas of the preputial gland represent a morphologic continuum, and distinctions between them are not easily quantifiable. The incidence of adenomas in the control group (16%) is well above the mean historical rate (3%) and, when combined with the carcinomas, does not strongly support an association between chemical exposure and these lesions in the dosed groups. Inflammation of the preputial gland was observed at incidences of 75% in all groups (Appendix A, Table A5), but the incidence of hyperplasia was increased above that of controls only in the low dose group. Nitrofurazone administration did not cause a response in the corresponding (clitoral) gland of female rats.

In view of the marginal responses in the sebaceous glands of the skin and preputial glands (modified sebaceous glands) observed in male rats in this study, it is of interest that the toxicologic assessment of a variety of nitrofurans showed an apparent positive correlation between their reported carcinogenicity in rodents (regardless of topography) and their ability to destroy sebaceous glands in mouse skin (Takizawa et al., 1975). Evidence of nitrofurazone-induced neoplasia in sebaceous glands has not been described in the literature.

The incidence of mesotheliomas of the tunica vaginalis in low dose male rats was increased above the control incidence and exceeded the incidence in historical controls. The incidence of this neoplasm was not increased in the high dose group, possibly because of poor survival.

Results of the 2-year studies also included considerable evidence of nitrofurazone-induced atrophy, hyperplasia, and neoplasia in the ovaries of female mice. The incidences in both dosed groups were dose related and markedly above the historical control rates observed in NTP studies (Appendix D, Table D4a). Except for two neoplasms in the high dose group, all of these lesions were observed at week 104. Overall, the results indicate that nitrofurazone increased the incidence of granulosa cell tumors. No evidence of malignancy was observed in ovarian tissue from studies reported here; however, malignant granulosa cell tumors have been observed in this and other strains of mice (NTP, 1988; Beamer et al., 1985).

The ovaries of mice also exhibited a dose-dependent increase in the incidence of benign mixed tumors. This neoplasm has a low (0.3%) incidence in NTP studies and was absent in control animals, but it was observed at rates of 34% and 40% in the low and high dose groups (see Table 24). Most of these neoplasms were found in animals that lived to the end of the study. Tubular cell hyperplasia was observed in ovaries from almost half of the nitrofurazone-exposed mice but was seen in only one control animal. NTP data and observations of others (Lemon and Gubareva, 1979) support the view that tumors of the ovary are comparatively rare in untreated mice.

The ovarian neoplasms were observed at doses that were also associated with ovarian atrophy. Since the biologic behavior of ovarian tumors is thought to be influenced by pituitary gonadotropic hormones (Biskind and Biskind, 1944), it can be questioned whether the ovarian tumors were caused directly by the nitrofurazone or were influenced indirectly by alterations in hormonal status resulting from diminished follicle production. A negative trend in pituitary gland neoplasms was observed in female mice, and this trend may conceivably be an indication of a chemical-related interaction with the ovary/pituitary gland axis. At present, the role for gonadotropin involvement in the causation of

ovarian tumors is unclear. Recent experimental evidence obtained with mice indicates that the presence of gonadotropins is necessary for normal follicular atresia processes including stromal luteinization after oocyte death, but the mere presence of gonadotropins was insufficient to stimulate adenoma formation (Tennent and Beamer, 1986; Beamer and Tennent, 1986).

The incidences of mesenchymal neoplasms (fibromas, fibrosarcomas, sarcomas, or neurofibrosarcomas) of subcutaneous tissue in male mice occurred with a positive trend. These neoplasms are combined for evaluation because of probable similar histogenesis and their common origin from fibroblasts. The incidence in high dose male mice was marginally increased compared with that in concurrent controls, and the incidence was within the range seen in historical controls for studies both at this laboratory and for all NTP studies (Appendix C, Table C4b). For these reasons, the increase in mesenchymal neoplasms of subcutaneous tissue is not considered to be chemical related.

Vascular neoplasms (hemangioma or hemangiosarcoma) in male mice occurred with a positive trend; the lesions were observed at different organ sites (Table C1). The incidence of these neoplasms in the high dose group (4/50) exceeded the highest incidence observed in historical controls from studies conducted by this laboratory but was within the overall range for historical controls at all NTP laboratories (Table C4a). Thus, the increased incidence of vascular neoplasms was not considered to be clearly related to chemical exposure.

The incidences of some neoplasms were decreased in these studies. The incidence of mononuclear cell leukemia was lower in high dose male rats and in dosed female rats than in controls (see Table 18). The decreased incidence in the high dose males is probably not due entirely to the poor survival of this group because a decreased incidence was also observed in high dose females, which had survival rates comparable to control values. The combined incidence of hepatocellular adenomas and carcinomas (10%) in high dose male mice was lower than the concurrent control value (30%) and was below the lowest incidence observed in historical controls (16%). Although the survival rate of the high dose group at week 104 was lower than that of the controls (78% vs. 54%), hepatocellular neoplasms were first observed in the control group 31 weeks earlier than in the high dose group. These findings suggest that the decreased incidence of hepatocellular neoplasms may be related to chemical exposure. The incidences of testicular interstitial cell tumors were decreased in dosed male rats. Although survival was decreased in the high dose group, it is conceivable that the decreased tumor incidences may be chemically related because a similar decrease was also observed in dosed male rats in a study of the structurally related nitrofuran, nitrofurantoin (NTP, 1988). Survival of dosed rats was not decreased in that study.

Nitrofurazone is a gene mutagen in bacteria, requiring metabolism by either a bacterial nitroreductase or a eukaryotic cell enzyme system for expression of this mutagenic activity. In cultured mammalian cells, nitrofurazone is a clastogen as well as a gene mutagen in the absence of exogenous metabolic activation and is, therefore, either direct acting or is activated by enzymes functioning in established cell lines. Nitrofurazone has not been demonstrated to be mutagenic in vivo; however, these negative studies are limited to a sex-linked lethal study in Drosophila, a test for morphologically abnormal sperm in mice, and micronuclei studies in two rodent species (one rat and one mouse). Both micronuclei studies used doses of 30 mg/kg per day; mice were injected on 5 consecutive days (Bruce and Heddle, 1979), and rats were dosed twice (Goodman et al., 1977). In both studies, bone marrow sampling occurred within 6 hours of the final dosing, which effectively decreased the total dose by 30 mg/kg. The in vivo mutagenicity data are insufficient to assess whether the observed carcinogenicity of this chemical is related to its mutagenicity in vitro.

The experimental and tabulated data for the NTP Technical Report on nitrofurazone 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.

Conclusions: Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity** of nitrofurazone for male F344/N rats as shown by the occurrence of sebaceous gland adenomas and trichoepitheliomas of the skin, mesotheliomas of the tunica vaginalis, and preputial gland tumors. There was *clear evidence of carcinogenic activity* of nitrofurazone for female F344/N rats as shown by a markedly increased incidence of fibroadenomas of the mammary gland. There was *no evidence of carcinogenic activity* for male B6C3F$_1$ mice fed diets containing nitrofurazone at concentrations of 150 or 310 ppm. There was *clear evidence of carcinogenic activity* of nitrofurazone for female B6C3F$_1$ mice as shown by increased incidences of benign mixed tumors and granulosa cell tumors of the ovary.

Administration of nitrofurazone was associated with decreased incidences of mononuclear cell leukemia in male and female rats, testicular interstitial cell tumors in male rats, and pituitary gland neoplasms in female mice. Convulsive seizures in mice of each sex, ovarian atrophy in female mice, testicular degeneration in rats, and degeneration of articular cartilage in rats were all associated with the administration of nitrofurazone.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 9.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 12-13.

V. REFERENCES

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APPENDIX A

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

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Papilloma, NOS		1 (2%)	
Trichoepithelioma			1 (2%)
Sebaceous adenoma			4 (8%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	3 (6%)	4 (8%)	6 (12%)
Fibrosarcoma	1 (2%)	2 (4%)	1 (2%)
Fibrous histiocytoma, malignant	1 (2%)		
Neurilemoma, malignant			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(46)	(50)
Alveolar/bronchiolar carcinoma		3 (7%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	21 (42%)	23 (46%)	6 (12%)
#Spleen	(48)	(46)	(50)
Sarcoma, NOS	1 (2%)		
#Thymus	(29)	(28)	(35)
Thymoma, benign			1 (3%)
CIRCULATORY SYSTEM			
#Spleen	(48)	(46)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma			1 (2%)
DIGESTIVE SYSTEM			
*Intestinal tract	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
#Liver	(50)	(49)	(50)
Neoplastic nodule	6 (12%)	4 (8%)	3 (6%)
Hepatocellular carcinoma	1 (2%)		
Fibrosarcoma, metastatic	1 (2%)		
#Pancreas	(48)	(49)	(49)
Adenoma, NOS	1 (2%)		
#Jejunum	(50)	(50)	(49)
Leiomyoma	1 (2%)		
Leiomyosarcoma	1 (2%)		
#Ileum	(50)	(50)	(49)
Mucinous adenocarcinoma	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenocarcinoma			1 (2%)
Nephroblastoma			1 (2%)
#Kidney/cortex	(50)	(50)	(50)
Lipoma		1 (2%)	

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

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(49)	(45)
Adenoma, NOS	11 (23%)	7 (14%)	8 (18%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma	1 (2%)		
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	12 (24%)	15 (30%)	12 (24%)
Pheochromocytoma, malignant	2 (4%)	1 (2%)	2 (4%)
#Thyroid	(49)	(49)	(50)
Follicular cell carcinoma	1 (2%)	1 (2%)	1 (2%)
C-cell adenoma	11 (22%)	7 (14%)	8 (16%)
#Parathyroid	(38)	(38)	(39)
Adenoma, NOS			1 (3%)
#Pancreatic islets	(48)	(49)	(49)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS			2 (4%)
Fibroadenoma	2 (4%)	1 (2%)	1 (2%)
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	8 (16%)	5 (10%)
Adenoma, NOS	8 (16%)	8 (16%)	2 (4%)
#Testis	(50)	(50)	(50)
Interstitial cell tumor	45 (90%)	30 (60%)	28 (56%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Astrocytoma		1 (2%)	
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)	2 (4%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*Vertebra	(50)	(50)	(50)
Chordoma		1 (2%)	
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Fibrosarcoma	1 (2%)		
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS		6 (12%)	
Mesothelioma, malignant		1 (2%)	2 (4%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Fibrosarcoma			1 (2%)
Fibrous histiocytoma, metastatic	1 (2%)		
Mesothelioma, metastatic		1 (2%)	2 (4%)
Osteosarcoma, metastatic			1 (2%)
Shoulder			
Osteosarcoma			1

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

	Untreated Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	1	3
Moribund sacrifice	15	19	27
Terminal sacrifice	33	30	20
TUMOR SUMMARY			
Total animals with primary tumors**	49	47	46
Total primary tumors	135	129	101
Total animals with benign tumors	48	40	40
Total benign tumors	96	75	72
Total animals with malignant tumors	27	34	21
Total malignant tumors	33	44	26
Total animals with secondary tumors##	2	1	3
Total secondary tumors	2	1	3
Total animals with tumors uncertain-- benign or malignant	6	10	3
Total uncertain tumors	6	10	3

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE: UNTREATED CONTROL

ANIMAL NUMBER	1 2 1	1 1 6	1 1 3	1 2 5	1 0 1	1 4 6	1 3 8	1 4 1	1 0 4	1 1 7	1 2 8	1 1 5	1 3 1	1 4 9	1 0 3	1 0 5	1 3 6	1 0 2	1 0 6	1 0 7	1 0 8	1 0 9	1 1 0	1 1 1	1 1 2
WEEKS ON STUDY	0 5 9	0 6 6	0 7 5	0 8 4	0 8 7	0 8 7	0 8 8	0 8 8	0 9 1	0 9 5	0 9 5	0 9 6	0 9 7	1 0 1	1 0 2	1 0 2	1 0 2	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma						X			X																
Fibrosarcoma				X																					
Fibrous histiocytoma, malignant														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Sarcoma, NOS																									
Hemangioma	X																								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	+	–	+	–	–	–	+	+	–	–	–	+	–	+	+	+	+	+	+	–	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule						X			X		X													X	
Hepatocellular carcinoma																									
Fibrosarcoma, metastatic																						X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Esophagus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucinous adenocarcinoma			X																						
Leiomyoma																									
Leiomyosarcoma																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X	X		X	X			X	X	X		X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																		X					X		
Pheochromocytoma, malignant															X										
Thyroid	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C cell adenoma											X	X					X				X				
Parathyroid	+	+	+	+	–	–	+	+	+	–	–	+	–	–	+	+	+	+	+	+	+	–	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									X
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X	X			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS										X			X										X	X	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma		X																							
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma																						X			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrous histiocytoma, metastatic														X											
Leukemia, mononuclear cell							X	X	X		X		X		X	X	X		X	X				X	

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

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

ANIMAL NUMBER	114	118	119	120	122	123	124	126	127	129	130	132	133	134	135	137	139	140	142	143	144	145	147	148	150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma		X																								3
Fibrosarcoma																										1
Fibrous histiocytoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, NOS																	X									1
Hemangioma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	–	–	+	+	+	+	–	+	+	+	+	–	+	+	–	+	–	+	–	–	–	+	–	+	29
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule									X														X			6
Hepatocellular carcinoma						X																				1
Fibrosarcoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																				X						1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucinous adenocarcinoma																										1
Leiomyoma																									X	1
Leiomyosarcoma									X																	1
Large intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS				X																		X				11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma	X																									1
Pheochromocytoma	X	X	X					X	X				X	X	X			X					X			12
Pheochromocytoma, malignant																			X							2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Follicular cell carcinoma																									X	1
C-cell adenoma	X	X				X				X				X		X								X		11
Parathyroid	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	–	+	+	–	+	38
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma													X													2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	45
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																									X	1
Adenoma, NOS							X						X			X							X			8
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrous histiocytoma, metastatic																										1
Leukemia, mononuclear cell						X			X	X	X	X	X	X			X						X		X	21

* Animals necropsied

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

ANIMAL NUMBER	012	016	034	039	007	008	027	046	031	018	037	001	047	015	021	040	041	003	032	028	002	004	005	006	009
WEEKS ON STUDY	060	060	067	087	078	084	088	090	092	094	094	095	095	097	101	101	101	102	102	103	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																							X		
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma														X											
Fibrosarcoma					X														X						X
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+
Alveolar/bronchiolar carcinoma																							X	X	X
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	–	+	–	–	–	–	+	+	+	+	–	+	+	–	+	+	–	–	–	+	+	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule										X							X				X				
Bile duct	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Urinary bladder	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma												X	X	X		X		X							
Pheochromocytoma, malignant													X												
Thyroid	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									X
C-cell adenoma									X		X							X					X		
Parathyroid	–	+	+	+	+	+	+	–	+	–	+	–	+	+	+	–	–	+	–	+	–	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma													X												
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	+	+	+	N	N	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor				X	X						X	X	X	X	X	X	X		X		X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS	X								X		X											X		X	
Adenoma, NOS				X								X									X				X
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma													X												
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Chordoma																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS			X						X			X	X										X		
Mesothelioma, malignant										X															
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, metastatic										X															
Leukemia, mononuclear cell							X	X	X	X		X	X		X	X	X	X		X		X			X
Intestinal tract																									
Sarcoma, NOS			X																						

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

ANIMAL NUMBER	0110	0111	0113	0114	0117	0119	0120	0122	0123	0124	0125	0126	0129	0130	0133	0135	0136	0138	0142	0143	0144	0145	0148	0149	0150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma	X									X																4
Fibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Alveolar/bronchiolar carcinoma																										3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	46
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	–	+	–	+	–	+	–	+	–	–	+	+	+	+	–	–	–	+	+	–	+	–	28
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule				X																						4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma						X																				1
Urinary bladder	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X				X				X				X	X			X								7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X		X			X						X			X			X		X	X	X		X	15
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																										1
C-cell adenoma														X					X		X					7
Parathyroid	+	–	+	–	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	*50
Fibroadenoma																			X							1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor			X	X	X	X	X	X		X	X					X	X	X	X	X			X	X		30
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS													X		X		X									8
Adenoma, NOS		X				X														X				X		8
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma				X																						1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma			X																							2
MUSCULOSKELETAL SYSTEM																										
Bone	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	N	+	+	*50
Chordoma					X																					1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																									X	6
Mesothelioma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, metastatic																										1
Leukemia, mononuclear cell	X			X		X	X		X		X						X	X		X			X			23
Intestinal tract																										
Sarcoma, NOS																										1

* Animals necropsied

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

ANIMAL NUMBER	051	053	064	076	073	062	052	087	083	094	085	085	097	098	059	060	080	074	081	088	089	078	063	068	091
WEEKS ON STUDY	042	054	057	061	064	067	068	069	075	076	079	080	086	087	089	089	089	091	092	093	093	094	095	095	095
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma												X													
Sebaceous adenoma								X															X		
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma														X	X										
Fibrosarcoma																						X			
Neurilemoma, malignant																X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	–	+	+	+	+	+	+	–	–	+	+	+	–	+	+	+	+	+	–	–	+	+	+
Thymoma, benign																									X
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																X									
Nephroblastoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS											X		X					X					X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X								X				
Pheochromocytoma, malignant																									X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																X									
C-cell adenoma									X									X				X		X	
Parathyroid	+	+	–	+	+	–	+	+	+	–	–	+	+	–	+	+	+	+	+	–	+	+	–	–	+
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	N	+	N	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor									X					X	X		X	X			X	X			X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS	X					X						X													
Adenoma, NOS									X																
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	+	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N
Squamous cell carcinoma										X															
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, malignant																					X	X			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma										X															
Mesothelioma, metastatic																					X	X			
Osteosarcoma, metastatic															X										
Leukemia, mononuclear cell																			X	X		X			
Shoulder, NOS																									
Osteosarcoma															X										

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

ANIMAL NUMBER	054	056	066	095	057	055	058	061	067	089	070	071	072	075	077	079	082	084	086	090	092	093	096	099	100	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	100	100	100	101	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Trichoepithelioma																										1
Sebaceous adenoma										X												X				4
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma					X	X							X	X												6
Fibrosarcoma																										1
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	−	−	+	−	+	+	+	−	+	−	+	+	+	−	−	+	+	−	−	+	+	35
Thymoma, benign																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule					X								X						X							3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																										1
Nephroblastoma		X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS							X						X					X								8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma						X				X			X	X		X	X	X	X	X				X		12
Pheochromocytoma, malignant									X																	2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																										1
C-cell adenoma						X				X	X			X												8
Parathyroid	+	+	+	+	+	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Adenoma, NOS																				X						1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS								X		X																2
Fibroadenoma								X																		1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X		X			X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	28
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS						X														X						5
Adenoma, NOS																	X									2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, malignant																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										1
Mesothelioma, metastatic																										2
Osteosarcoma, metastatic																										1
Leukemia, mononuclear cell	X			X		X																				6
Shoulder, NOS																										
Osteosarcoma																										1

* Animals necropsied

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

	Control	310 ppm	620 ppm
Skin: Sebaceous Adenoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	15.2%
Terminal Rates (c)	0/33 (0%)	0/30 (0%)	2/20 (10%)
Week of First Observation			69
Life Table Tests (d)	P=0.006	(e)	P=0.028
Incidental Tumor Tests (d)	P=0.015	(e)	P=0.067
Cochran-Armitage Trend Test (d)	P=0.015		
Fisher Exact Test (d)		(e)	P=0.059
Skin: Trichoepithelioma or Sebaceous Adenoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	0.0%	0.0%	17.4%
Terminal Rates (c)	0/33 (0%)	0/30 (0%)	2/20 (10%)
Week of First Observation			69
Life Table Tests (d)	P=0.002	(e)	P=0.014
Incidental Tumor Tests (d)	P=0.009	(e)	P=0.044
Cochran-Armitage Trend Test (d)	P=0.006		
Fisher Exact Test (d)		(e)	P=0.028
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	6/50 (12%)
Adjusted Rates (b)	7.4%	12.4%	23.4%
Terminal Rates (c)	1/33 (3%)	3/30 (10%)	3/20 (15%)
Week of First Observation	87	97	87
Life Table Tests (d)	P=0.069	P=0.465	P=0.106
Incidental Tumor Tests (d)	P=0.160	P=0.433	P=0.231
Cochran-Armitage Trend Test (d)	P=0.187		
Fisher Exact Test (d)		P=0.500	P=0.243
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	7/50 (14%)
Adjusted Rates (b)	9.4%	16.9%	26.1%
Terminal Rates (c)	1/33 (3%)	3/30 (10%)	3/20 (15%)
Week of First Observation	84	78	87
Life Table Tests (d)	P=0.079	P=0.339	P=0.113
Incidental Tumor Tests (d)	P=0.256	P=0.340	P=0.287
Cochran-Armitage Trend Test (d)	P=0.215		
Fisher Exact Test (d)		P=0.370	P=0.262
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	0/50 (0%)	3/46 (7%)	0/50 (0%)
Adjusted Rates (b)	0.0%	11.1%	0.0%
Terminal Rates (c)	0/33 (0%)	3/27 (11%)	0/20 (0%)
Week of First Observation		104	
Life Table Tests (d)	P=0.504	P=0.087	(e)
Incidental Tumor Tests (d)	P=0.504	P=0.087	(e)
Cochran-Armitage Trend Test (d)	P=0.638		
Fisher Exact Test (d)		P=0.106	(e)
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	21/50 (42%)	23/50 (46%)	6/50 (12%)
Adjusted Rates (b)	50.8%	55.5%	21.2%
Terminal Rates (c)	13/33 (39%)	12/30 (40%)	1/20 (5%)
Week of First Observation	88	88	92
Life Table Tests (d)	P=0.068N	P=0.334	P=0.041N
Incidental Tumor Tests (d)	P=0.001N	P=0.388	P=0.001N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.420	P<0.001N

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

	Control	310 ppm	620 ppm
Liver: Neoplastic Nodule			
Overall Rates (a)	6/50 (12%)	4/49 (8%)	3/50 (6%)
Adjusted Rates (b)	15.3%	11.5%	14.3%
Terminal Rates (c)	3/33 (9%)	2/30 (7%)	2/20 (10%)
Week of First Observation	87	94	103
Life Table Tests (d)	P=0.397N	P=0.411N	P=0.481N
Incidental Tumor Tests (d)	P=0.221N	P=0.424N	P=0.299N
Cochran-Armitage Trend Test (d)	P=0.188N		
Fisher Exact Test (d)		P=0.384N	P=0.244N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	7/50 (14%)	4/49 (8%)	3/50 (6%)
Adjusted Rates (b)	18.1%	11.5%	14.3%
Terminal Rates (c)	4/33 (12%)	2/30 (7%)	2/20 (10%)
Week of First Observation	87	94	103
Life Table Tests (d)	P=0.292N	P=0.305N	P=0.383N
Incidental Tumor Tests (d)	P=0.150N	P=0.312N	P=0.224N
Cochran-Armitage Trend Test (d)	P=0.115N		
Fisher Exact Test (d)		P=0.274N	P=0.159N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	11/48 (23%)	7/49 (14%)	8/45 (18%)
Adjusted Rates (b)	30.0%	23.3%	28.0%
Terminal Rates (c)	7/32 (22%)	7/30 (23%)	3/19 (16%)
Week of First Observation	96	104	79
Life Table Tests (d)	P=0.472	P=0.266N	P=0.483
Incidental Tumor Tests (d)	P=0.443N	P=0.200N	P=0.443N
Cochran-Armitage Trend Test (d)	P=0.300N		
Fisher Exact Test (d)		P=0.203N	P=0.362N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	12/50 (24%)	15/50 (30%)	12/50 (24%)
Adjusted Rates (b)	36.4%	42.0%	52.9%
Terminal Rates (c)	12/33 (36%)	10/30 (33%)	10/20 (50%)
Week of First Observation	104	95	86
Life Table Tests (d)	P=0.094	P=0.236	P=0.110
Incidental Tumor Tests (d)	P=0.175	P=0.299	P=0.142
Cochran-Armitage Trend Test (d)	P=0.545		
Fisher Exact Test (d)		P=0.326	P=0.592N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	14/50 (28%)	15/50 (30%)	14/50 (28%)
Adjusted Rates (b)	41.1%	42.0%	59.1%
Terminal Rates (c)	13/33 (39%)	10/30 (33%)	11/20 (55%)
Week of First Observation	102	95	86
Life Table Tests (d)	P=0.080	P=0.391	P=0.085
Incidental Tumor Tests (d)	P=0.174	P=0.486	P=0.147
Cochran-Armitage Trend Test (d)	P=0.544		
Fisher Exact Test (d)		P=0.500	P=0.588N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	11/49 (22%)	7/49 (14%)	8/50 (16%)
Adjusted Rates (b)	30.0%	20.0%	29.6%
Terminal Rates (c)	8/33 (24%)	4/30 (13%)	4/20 (20%)
Week of First Observation	95	92	75
Life Table Tests (d)	P=0.486	P=0.281N	P=0.484
Incidental Tumor Tests (d)	P=0.340N	P=0.218N	P=0.434N
Cochran-Armitage Trend Test (d)	P=0.240N		
Fisher Exact Test (d)		P=0.217N	P=0.288N

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

	Control	310 ppm	620 ppm
Preputial Gland: Adenoma			
Overall Rates (a)	8/50 (16%)	8/50 (16%)	2/50 (4%)
Adjusted Rates (b)	22.3%	23.7%	7.3%
Terminal Rates (c)	6/33 (18%)	6/30 (20%)	1/20 (5%)
Week of First Observation	95	67	75
Life Table Tests (d)	P=0.169N	P=0.539	P=0.170N
Incidental Tumor Tests (d)	P=0.075N	P=0.592N	P=0.079N
Cochran-Armitage Trend Test (d)	P=0.045N		
Fisher Exact Test (d)		P=0.607N	P=0.046N
Preputial Gland: Carcinoma			
Overall Rates (a)	1/50 (2%)	8/50 (16%)	5/50 (10%)
Adjusted Rates (b)	3.0%	22.2%	16.0%
Terminal Rates (c)	1/33 (3%)	5/30 (17%)	2/20 (10%)
Week of First Observation	104	60	42
Life Table Tests (d)	P=0.041	P=0.016	P=0.053
Incidental Tumor Tests (d)	P=0.171	P=0.018	P=0.166
Cochran-Armitage Trend Test (d)	P=0.114		
Fisher Exact Test (d)		P=0.015	P=0.102
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	9/50 (18%)	16/50 (32%)	7/50 (14%)
Adjusted Rates (b)	25.2%	43.6%	22.5%
Terminal Rates (c)	7/33 (21%)	11/30 (37%)	3/20 (15%)
Week of First Observation	95	60	42
Life Table Tests (d)	P=0.356	P=0.062	P=0.496
Incidental Tumor Tests (d)	P=0.366N	P=0.086	P=0.379N
Cochran-Armitage Trend Test (d)	P=0.357N		
Fisher Exact Test (d)		P=0.083	P=0.393N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	45/50 (90%)	30/50 (60%)	28/50 (56%)
Adjusted Rates (b)	100.0%	74.4%	86.8%
Terminal Rates (c)	33/33 (100%)	20/30 (67%)	16/20 (80%)
Week of First Observation	75	67	75
Life Table Tests (d)	P=0.352N	P=0.022N	P=0.495N
Incidental Tumor Tests (d)	P=0.005N	P<0.001N	P=0.007N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P<0.001N	P<0.001N
All Sites: Mesothelioma			
Overall Rates (a)	0/50 (0%)	7/50 (14%)	2/50 (4%)
Adjusted Rates (b)	0.0%	17.4%	6.6%
Terminal Rates (c)	0/33 (0%)	2/30 (7%)	0/20 (0%)
Week of First Observation		67	93
Life Table Tests (d)	P=0.149	P=0.010	P=0.174
Incidental Tumor Tests (d)	P=0.363	P=0.014	P=0.307
Cochran-Armitage Trend Test (d)	P=0.264		
Fisher Exact Test (d)		P=0.006	P=0.247
All Sites: Benign Tumors			
Overall Rates (a)	48/50 (96%)	40/50 (80%)	40/50 (80%)
Adjusted Rates (b)	100.0%	95.2%	100.0%
Terminal Rates (c)	33/33 (100%)	28/30 (93%)	20/20 (100%)
Week of First Observation	59	67	69
Life Table Tests (d)	P=0.050	P=0.249N	P=0.054
Incidental Tumor Tests (d)	P=0.262N	P=0.012N	P=0.258N
Cochran-Armitage Trend Test (d)	P=0.017N		
Fisher Exact Test (d)		P=0.014N	P=0.014N

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

	Control	310 ppm	620 ppm
All Sites: Malignant Tumors			
Overall Rates (a)	27/50 (54%)	34/50 (68%)	21/50 (42%)
Adjusted Rates (b)	59.6%	73.7%	54.6%
Terminal Rates (c)	15/33 (45%)	18/30 (60%)	5/20 (25%)
Week of First Observation	66	60	42
Life Table Tests (d)	P=0.285	P=0.112	P=0.391
Incidental Tumor Tests (d)	P=0.055N	P=0.138	P=0.057N
Cochran-Armitage Trend Test (d)	P=0.135N		
Fisher Exact Test (d)		P=0.109	P=0.159N
All Sites: All Tumors			
Overall Rates (a)	49/50 (98%)	47/50 (94%)	46/50 (92%)
Adjusted Rates (b)	100.0%	97.9%	100.0%
Terminal Rates (c)	33/33 (100%)	29/30 (97%)	20/20 (100%)
Week of First Observation	59	60	42
Life Table Tests (d)	P=0.008	P=0.469	P=0.010
Incidental Tumor Tests (d)	P=0.390N	P=0.265N	P=0.545N
Cochran-Armitage Trend Test (d)	P=0.133N		
Fisher Exact Test (d)		P=0.309N	P=0.182N

(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 incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the dosed and control groups.

TABLE A4a. HISTORICAL INCIDENCE OF MESOTHELIOMAS IN MALE F344/N RATS RECEIVING NO TREATMENT (a,b)

Study	Incidence in Controls
Historical Incidence at Physiological Research Laboratories	
Ephedrine sulfate	3/50
Phenylephrine hydrochloride	2/50
Oxytetracycline hydrochloride	0/50
TOTAL	5/150 (3.3%)
SD (c)	3.06%
Range (d)	
High	3/50
Low	0/50
Overall Historical Incidence	
TOTAL	52/1,937 (2.7%)
SD (c)	2.39%
Range (d)	
High	5/50
Low	0/50

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

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

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Historical Incidence at Physiological Research Laboratories			
Ephedrine sulfate	1/50	0/50	1/50
Phenylephrine hydrochloride	1/50	0/50	1/50
Oxytetracycline hydrochloride	0/50	0/50	0/50
TOTAL	(b) 2/150 (1.3%)	0/150 (0.0%)	(b) 2/150 (1.3%)
SD (c)	1.15%	0.00%	1.15%
Range (d)			
High	1/50	0/50	1/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	(e) 18/1,937 (0.9%)	(f) 14/1,937 (0.7%)	(e,f) 32/1,937 (1.7%)
SD (c)	1.45%	1.19%	1.90%
Range (d)			
High	3/50	2/50	4/50
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Basal cell tumors
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes nine basal cell tumors, five trichoepitheliomas, one adnexal adenoma, and three sebaceous adenomas
(f) Basal cell carcinomas; no other malignant sebaceous gland tumors have been observed.

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

Study	No. Examined	No. of Tumors	Diagnosis
Historical Incidence at Physiological Research Laboratories			
Ephedrine sulfate	50	2	Adenoma, NOS
Phenylephrine hydrochloride	50	2	Carcinoma, NOS
Oxytetracycline hydrochloride	50	1	Adenocarcinoma, NOS
TOTAL	150	5 (3.3%)	
Overall Historical Incidence			
		55	Adenoma, NOS
		1	Papillary adenoma
		1	Cystadenoma
		55	Carcinoma, NOS
		2	Squamous cell carcinoma
		8	Adenocarcinoma, NOS
		1	Sebaceous adenocarcinoma
TOTAL	1,937	123 (6.4%)	

(a) Data as of August 7, 1986, for studies of at least 104 weeks; greatest incidence observed in any untreated control group is 9/50.

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

Study	Incidence in Controls
Historical Incidence at Physiological Research Laboratories	
Ephedrine sulfate	45/50
Phenylephrine hydrochloride	47/50
Oxytetracycline hydrochloride	41/50
TOTAL	133/150 (88.7%)
SD (b)	6.11%
Range (c)	
High	47/50
Low	41/50
Overall Historical Incidence	
TOTAL	1,681/1,909 (88.1%)
SD (b)	7.32%
Range (c)	
High	49/50
Low	35/49

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

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

Study	Incidence in Controls
Historical Incidence at Physiological Research Laboratories	
Ephedrine sulfate	25/50
Phenylephrine hydrochloride	24/50
Oxytetracycline hydrochloride	22/50
TOTAL	71/150 (47.3%)
SD (b)	3.06%
Range (c)	
High	25/50
Low	22/50
Overall Historical Incidence	
TOTAL	586/1,937 (30.3%)
SD (b)	11.97%
Range (c)	
High	30/50
Low	5/50

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	2 (4%)	3 (6%)	2 (4%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, NOS	8 (16%)	4 (8%)	14 (28%)
Inflammation, suppurative		1 (2%)	
Infection, fungal		1 (2%)	
Foreign material, NOS		2 (4%)	
*Nasal turbinate	(50)	(50)	(50)
Exostosis			1 (2%)
#Tracheal submucosa	(49)	(49)	(49)
Cyst, NOS			1 (2%)
#Tracheal cartilage	(49)	(49)	(49)
Degeneration, NOS			1 (2%)
#Lung	(50)	(46)	(50)
Congestion, NOS	1 (2%)		1 (2%)
Inflammation, NOS	3 (6%)	1 (2%)	5 (10%)
Hyperplasia, alveolar epithelium		2 (4%)	1 (2%)
#Lung/alveoli	(50)	(46)	(50)
Edema, NOS	1 (2%)		1 (2%)
Histiocytosis	1 (2%)		
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(50)
Hypoplasia, NOS	2 (4%)	1 (2%)	5 (10%)
Hyperplasia, NOS	12 (24%)	18 (36%)	6 (12%)
Hyperplasia, reticulum cell	1 (2%)		1 (2%)
#Spleen	(48)	(46)	(50)
Inflammation, acute	1 (2%)		
Fibrosis	1 (2%)		
Scar	2 (4%)	5 (11%)	5 (10%)
Hematopoiesis	1 (2%)		
#Lymph node	(50)	(50)	(50)
Cyst, NOS		1 (2%)	4 (8%)
Hemorrhage	2 (4%)	2 (4%)	1 (2%)
Granulation tissue	1 (2%)		
Hyperplasia, NOS	2 (4%)		2 (4%)
Histiocytosis			2 (4%)
Plasmacytosis		1 (2%)	
*Intestinal tract	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Glandular stomach	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
#Thymus	(29)	(28)	(35)
Cyst, NOS	1 (3%)		
Hyperplasia, lymphoid			1 (3%)
CIRCULATORY SYSTEM			
#Heart/atrium	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	49 (98%)	47 (94%)	50 (100%)

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

	Untreated Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
*Artery	(50)	(50)	(50)
Periarteritis	1 (2%)	2 (4%)	3 (6%)
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(48)	(48)
Cyst, NOS	1 (2%)		
Nuclear alteration	2 (4%)	3 (6%)	2 (4%)
Atrophy, focal	4 (8%)		3 (6%)
Hyperplasia, focal			1 (2%)
Metaplasia, squamous			1 (2%)
#Liver	(50)	(49)	(50)
Accessory structure	3 (6%)	4 (8%)	3 (6%)
Inflammation, NOS		1 (2%)	2 (4%)
Granuloma, NOS	1 (2%)	1 (2%)	2 (4%)
Cystic degeneration	1 (2%)	1 (2%)	1 (2%)
Necrosis, NOS	1 (2%)	1 (2%)	2 (4%)
Angiectasis			1 (2%)
#Intrahepatic bile duct	(50)	(49)	(50)
Hyperplasia, NOS	47 (94%)	47 (96%)	46 (92%)
#Liver/hepatocytes	(50)	(49)	(50)
Degeneration, NOS	1 (2%)		3 (6%)
Focal cellular change	35 (70%)	34 (69%)	29 (58%)
Nodular regeneration	2 (4%)	1 (2%)	1 (2%)
#Pancreas	(48)	(49)	(49)
Atrophy, focal	30 (63%)	30 (61%)	22 (45%)
Atrophy, diffuse	1 (2%)		1 (2%)
#Glandular stomach	(50)	(50)	(50)
Cyst, NOS	8 (16%)	12 (24%)	6 (12%)
Erosion			1 (2%)
#Forestomach	(50)	(50)	(50)
Ulcer, NOS	1 (2%)		
#Colon	(49)	(50)	(47)
Inflammation, chronic focal			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Nephropathy	48 (96%)	50 (100%)	47 (94%)
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS		3 (6%)	2 (4%)
#Kidney/tubule	(50)	(50)	(50)
Hyperplasia, focal	1 (2%)		1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(49)	(45)
Hyperplasia, focal	1 (2%)		
#Anterior pituitary	(48)	(49)	(45)
Hemorrhage	1 (2%)		
Hyperplasia, focal	6 (13%)	13 (27%)	10 (22%)
Hyperplasia, cystic	3 (6%)	2 (4%)	
Angiectasis		1 (2%)	
#Adrenal cortex	(50)	(50)	(50)
Accessory structure	1 (2%)	1 (2%)	1 (2%)
Cytoplasmic vacuolization	4 (8%)	7 (14%)	4 (8%)
Hypertrophy, focal	6 (12%)	4 (8%)	3 (6%)
Hyperplasia, focal	16 (32%)	21 (42%)	10 (20%)
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	10 (20%)	9 (18%)	4 (8%)

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

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(49)	(49)	(50)
Follicular cyst, NOS	2 (4%)		2 (4%)
Hemorrhage			1 (2%)
Inflammation, chronic necrotizing			1 (2%)
Hyperplasia, C-cell	4 (8%)	3 (6%)	5 (10%)
#Thyroid follicle	(49)	(49)	(50)
Mineralization	1 (2%)		
Degeneration, NOS		1 (2%)	1 (2%)
Necrosis, NOS		1 (2%)	
Atrophy, NOS			1 (2%)
Hyperplasia, cystic		1 (2%)	
#Parathyroid	(38)	(38)	(39)
Hyperplasia, NOS		2 (5%)	1 (3%)
#Pancreatic islets	(48)	(49)	(49)
Hypertrophy, NOS	1 (2%)	1 (2%)	
Hyperplasia, NOS	2 (4%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, cystic	7 (14%)	8 (16%)	5 (10%)
*Preputial gland	(50)	(50)	(50)
Inflammation, NOS	37 (74%)	37 (74%)	38 (76%)
Hyperplasia, NOS		6 (12%)	1 (2%)
#Prostate	(49)	(49)	(50)
Cyst, NOS			1 (2%)
Inflammation, NOS	32 (65%)	30 (61%)	30 (60%)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic			1 (2%)
Inflammation, chronic suppurative			1 (2%)
Atrophy, NOS	1 (2%)		2 (4%)
Hyperplasia, cystic	1 (2%)		
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	1 (2%)	1 (2%)	
Cyst, NOS	1 (2%)		
Hemorrhage	1 (2%)		
Inflammation, chronic suppurative	1 (2%)		
Atrophy, NOS	8 (16%)		3 (6%)
Hyperplasia, epithelial		4 (8%)	
Hyperplasia, cystic		1 (2%)	
#Testis	(50)	(50)	(50)
Degeneration, NOS	12 (24%)	49 (98%)	47 (94%)
Hyperplasia, interstitial cell	2 (4%)	2 (4%)	7 (14%)
*Epididymis	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Inflammation, chronic	1 (2%)		
Basophilic cyto change	1 (2%)		
Atrophy, NOS	15 (30%)	14 (28%)	18 (36%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Hemorrhage	1 (2%)		1 (2%)
#Cerebral cortex	(50)	(50)	(50)
Atrophy, focal			1 (2%)
#Brain stem	(50)	(50)	(50)
Atrophy, pressure	3 (6%)		4 (8%)
*Spinal cord	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Atrophy, pressure	1 (2%)		1 (2%)

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

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM (Continued)			
*White matter spinal	(50)	(50)	(50)
Degeneration, NOS	3 (6%)	6 (12%)	4 (8%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Phthisis bulbi		1 (2%)	1 (2%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract			1 (2%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, NOS			1 (2%)
*Harderian gland	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	
*Ear canal	(50)	(50)	(50)
Hemorrhage			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Deformity, NOS			1 (2%)
Fibrous osteodystrophy		1 (2%)	
*Maxilla	(50)	(50)	(50)
Exostosis		1 (2%)	
*Vertebra	(50)	(50)	(50)
Exostosis	1 (2%)		
*Joint	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	3 (6%)
*Vertebral joint	(50)	(50)	(50)
Degeneration, NOS	10 (20%)	31 (62%)	23 (46%)
*Sternal synchondrosis	(50)	(50)	(50)
Degeneration, NOS	24 (48%)	26 (52%)	21 (42%)
*Knee joint	(50)	(50)	(50)
Degeneration, NOS	5 (10%)	32 (64%)	48 (96%)
*Intervertebral disc	(50)	(50)	(50)
Prolapse	1 (2%)		1 (2%)
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Necrosis, fat	5 (10%)	2 (4%)	1 (2%)
*Tunica vaginalis	(50)	(50)	(50)
Hyperplasia, mesothelial	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mineralization			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX B

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

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Trichoepithelioma			2 (4%)
*Subcutaneous tissue	(49)	(50)	(50)
Fibrosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(48)	(15)	(49)
Alveolar/bronchiolar adenoma	1 (2%)		
Alveolar/bronchiolar carcinoma		1 (7%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Leukemia, mononuclear cell	15 (31%)	2 (4%)	2 (4%)
CIRCULATORY SYSTEM			
#Heart/atrium	(48)	(11)	(50)
Neurilemoma, malignant	1 (2%)		
DIGESTIVE SYSTEM			
*Tongue	(49)	(50)	(50)
Squamous cell carcinoma			1 (2%)
#Liver	(49)	(50)	(50)
Neoplastic nodule		2 (4%)	2 (4%)
#Forestomach	(49)	(12)	(50)
Squamous cell papilloma		1 (8%)	
#Duodenum	(49)	(10)	(50)
Leiomyosarcoma		1 (10%)	
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(50)	(48)
Adenoma, NOS	1 (2%)		
#Anterior pituitary	(48)	(50)	(48)
Carcinoma, NOS		4 (8%)	
Adenoma, NOS	18 (38%)	17 (34%)	15 (31%)
#Adrenal	(49)	(50)	(49)
Cortical adenoma	2 (4%)		1 (2%)
#Adrenal medulla	(49)	(50)	(49)
Pheochromocytoma	4 (8%)	1 (2%)	4 (8%)
#Thyroid	(48)	(14)	(49)
C-cell adenoma	6 (13%)	1 (7%)	9 (18%)

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

	Untreated Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)		2 (4%)
Fibroadenoma	8 (16%)	36 (72%)	36 (72%)
*Clitoral gland	(49)	(50)	(50)
Carcinoma, NOS	5 (10%)	6 (12%)	
Adenoma, NOS	3 (6%)		7 (14%)
Adenocarcinoma, NOS		1 (2%)	
#Uterus	(49)	(20)	(50)
Endometrial stromal polyp	11 (22%)	9 (45%)	15 (30%)
Endometrial stromal sarcoma		1 (5%)	
Neurilemoma, malignant			2 (4%)
#Cervix uteri	(49)	(20)	(50)
Neurilemoma, malignant	1 (2%)		
#Ovary	(49)	(12)	(50)
Granulosa cell tumor		1 (8%)	
Granulosa cell carcinoma	1 (2%)		
NERVOUS SYSTEM			
#Brain	(48)	(9)	(50)
Astrocytoma			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(49)	(50)	(50)
Squamous cell carcinoma	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(49)	(50)	(50)
Neurilemoma, invasive			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Granulosa cell carcinoma, metastatic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	1	2
Moribund sacrifice	19	12	17
Terminal sacrifice	28	37	31

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

	Untreated Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	44	47	46
Total primary tumors	80	85	100
Total animals with benign tumors	37	40	43
Total benign tumors	54	65	89
Total animals with malignant tumors	23	17	9
Total malignant tumors	26	17	9
Total animals with secondary tumors##	1		1
Total secondary tumors	1		1
Total animals with tumors uncertain--benign or malignant		3	2
Total uncertain tumors		3	2

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE: UNTREATED CONTROL

ANIMAL NUMBER	1 3 0	1 1 9	1 0 8	1 4 4	1 4 9	1 4 3	1 3 9	1 1 7	1 2 6	1 3 4	1 0 1	1 2 7	1 3 3	1 1 1	1 2 4	1 4 7	1 3 8	1 2 0	1 4 2	1 2 5	1 3 7	1 0 6	1 0 2	1 0 3	1 0 4
WEEKS ON STUDY	0 4 7	0 5 2	0 5 4	0 6 4	0 6 7	0 6 8	0 7 2	0 7 3	0 7 3	0 7 5	0 7 6	0 7 8	0 8 7	0 8 8	0 8 9	0 9 0	0 9 3	0 9 4	0 9 4	0 9 6	0 9 6	1 0 2	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	–	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	–	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	B	+	+	–	+	–	+	+	+	+	–	+	–	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	–	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	–	+	+	+	+	B	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	–	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X				X		X			X		X			X			X		X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									X
Pheochromocytoma																X		X							
Thyroid	+	+	+	+	+	–	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma				X																					
Parathyroid	–	–	+	+	+	–	+	–	+	+	B	+	+	–	–	–	+	+	+	+	+	+	+	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS		X																							
Fibroadenoma					X													X				X	X		
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	B	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS			X						X																
Adenoma, NOS																								X	
Uterus	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp	X			X		X													X	X					
Neurilemoma, malignant										X															
Ovary	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell carcinoma																					X				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	B	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	B	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Granulosa cell carcinoma, metastatic																					X				
Leukemia, mononuclear cell													X	X	X	X	X	X	X	X					

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

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

ANIMAL NUMBER	105	107	109	110	112	113	114	115	116	118	121	122	123	128	129	131	132	135	136	140	141	145	146	148	150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibrosarcoma															X											1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma					X																					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	–	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	+	–	–	+	–	–	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neurilemoma, malignant																							X			1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS			X				X					X					X		X	X	X		X	X		19
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma									X																	2
Pheochromocytoma																			X				X			4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma			X										X		X							X		X		6
Parathyroid	–	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	36
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenocarcinoma, NOS																										1
Fibroadenoma								X							X	X			X							8
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Carcinoma, NOS							X										X				X					5
Adenoma, NOS														X				X								3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp	X			X	X		X													X		X				11
Neurilemoma, malignant																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell carcinoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	*49
Squamous cell carcinoma													X													1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Granulosa cell carcinoma, metastatic																										1
Leukemia, mononuclear cell					X					X			X	X	X		X	X								15

* Animals necropsied

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

ANIMAL NUMBER	0029	0034	0049	0047	0115	0030	0023	0113	0500	0117	0009	0114	0002	0001	0003	0004	0005	0006	0007	0008	0110	0111	0112	0116	0118
WEEKS ON STUDY	0061	0067	0067	0070	0075	0076	0082	0087	0087	0095	1000	1011	1031	1041	1041	1041	1041	1041	1041	1041	1041	1041	1041	1041	1041
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–
Alveolar/bronchiolar carcinoma																				X					
Trachea	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Thymus	+	+	+	+	–	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																					X				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–
Esophagus	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–
Stomach	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Leiomyosarcoma																									
Large intestine	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Urinary bladder	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																	X		X				X		
Adenoma, NOS						X							X	X		X		X		X		X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X												
Thyroid	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–
C-cell adenoma																									
Parathyroid	+	+	–	–	–	–	+	+	+	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N
Fibroadenoma			X	X		X		X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS							X					X	X					X						X	
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	–	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–
Endometrial stromal polyp									X																
Endometrial stromal sarcoma					X																				
Ovary	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SPECIAL SENSE ORGANS																									
Zymbal gland	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma	X																								
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X									X														

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

ANIMAL NUMBER	019	020	021	022	024	025	026	027	028	031	032	033	035	036	037	038	039	040	041	042	043	044	045	046	048	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	-	+	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15
Alveolar/bronchiolar carcinoma																										1
Trachea	-	+	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	14
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	10
Thymus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8
CIRCULATORY SYSTEM																										
Heart	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	11
DIGESTIVE SYSTEM																										
Salivary gland	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	10
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule												X														2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10
Esophagus	-	+	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	14
Stomach	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12
Squamous cell papilloma								X																		1
Small intestine	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10
Leiomyosarcoma							X																			1
Large intestine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	9
URINARY SYSTEM																										
Kidney	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10
Urinary bladder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	9
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS												X														4
Adenoma, NOS	X	X								X	X					X			X			X		X	X	17
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										1
Thyroid	-	+	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	14
C-cell adenoma										X																1
Parathyroid	-	+	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	+	N	N	+	+	+	+	N	+	+	+	+	+	+	+	+	N	N	N	+	+	*50
Fibroadenoma		X	X	X	X			X	X	X	X		X	X	X	X	X	X	X	X				X	X	38
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																							X			6
Adenocarcinoma, NOS											X															1
Uterus	-	+	-	-	-	-	-	-	-	-	+	+	-	+	+	+	+	+	-	+	-	-	-	-	+	21
Endometrial stromal polyp		X									X				X	X	X	X		X					X	9
Endometrial stromal sarcoma																										1
Ovary	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	-	12
Granulosa cell tumor																						X				1
NERVOUS SYSTEM																										
Brain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	9
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell																										2

* Animals necropsied

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

ANIMAL NUMBER	069	057	076	079	085	064	060	087	090	088	052	063	058	081	092	055	074	075	093	051	053	054	056	059	061
WEEKS ON STUDY	026	060	064	064	072	076	084	084	088	091	092	093	097	101	101	102	102	103	103	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma																									X
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	−	+	−	+	−	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma								X																	
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+
Adenoma, NOS													X	X		X		X	X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma				X										X											X
Parathyroid	−	+	−	+	+	+	−	+	−	−	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma		X			X					X		X	X	X	X	X	X	X	X			X	X		
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS														X											X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp			X					X						X					X	X					
Neurilemoma, malignant							X				X														
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma						X																			
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma, invasive							X																		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell																						X			

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

ANIMAL NUMBER	062	065	066	067	068	070	071	072	073	077	078	080	082	083	084	086	089	091	094	095	096	097	098	099	100	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	N	+	+	+	+	+	+	+ X	N	+	+	+	+	+	+	+	+	+	+	*50
Trichoepithelioma														X												2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma										X																1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	−	+	+	−	+	+	−	−	+	−	+	+	−	+	+	−	+	+	+	+	−	+	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule										X								X								2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS							X			X		X	X	X		X	X				X		X	X		15
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma														X												1
Pheochromocytoma			X		X							X								X						4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma		X		X	X	X						X									X					9
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	−	+	−	+	+	−	+	37
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+ X	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS													X	X												2
Fibroadenoma		X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	36
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X					X										X						X	X		7
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp	X	X	X	X			X							X			X	X	X			X				15
Neurilemoma, malignant																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																										1
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurilemoma, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell					X																					2

* Animals necropsied

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

	Control	310 ppm	620 ppm
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	15/49 (31%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	40.8%	4.5%	6.5%
Terminal Rates (c)	7/28 (25%)	0/37 (0%)	2/31 (6%)
Week of First Observation	87	67	104
Life Table Tests (d)	P<0.001N	P<0.001N	P<0.001N
Incidental Tumor Tests (d)	P<0.001N	P<0.001N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P<0.001N	P<0.001N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	18/48 (38%)	17/50 (34%)	15/48 (31%)
Adjusted Rates (b)	51.2%	43.4%	42.4%
Terminal Rates (c)	11/27 (41%)	15/37 (41%)	10/30 (33%)
Week of First Observation	54	76	97
Life Table Tests (d)	P=0.180N	P=0.165N	P=0.212N
Incidental Tumor Tests (d)	P=0.219N	P=0.310N	P=0.253N
Cochran-Armitage Trend Test (d)	P=0.295N		
Fisher Exact Test (d)		P=0.440N	P=0.334N
Anterior Pituitary Gland: Carcinoma			
Overall Rates (a)	0/48 (0%)	4/50 (8%)	0/48 (0%)
Adjusted Rates (b)	0.0%	10.8%	0.0%
Terminal Rates (c)	0/27 (0%)	4/37 (11%)	0/30 (0%)
Week of First Observation		104	
Life Table Tests (d)	P=0.596N	P=0.109	(e)
Incidental Tumor Tests (d)	P=0.596N	P=0.109	(e)
Cochran-Armitage Trend Test (d)	P=0.623		
Fisher Exact Test (d)		P=0.064	(e)
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	18/48 (38%)	21/50 (42%)	15/48 (31%)
Adjusted Rates (b)	51.2%	53.7%	42.4%
Terminal Rates (c)	11/27 (41%)	19/37 (51%)	10/30 (33%)
Week of First Observation	54	76	97
Life Table Tests (d)	P=0.176N	P=0.388N	P=0.212N
Incidental Tumor Tests (d)	P=0.214N	P=0.579	P=0.253N
Cochran-Armitage Trend Test (d)	P=0.299N		
Fisher Exact Test (d)		P=0.402	P=0.334N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	4/49 (8%)	1/50 (2%)	4/49 (8%)
Adjusted Rates (b)	12.5%	2.6%	12.9%
Terminal Rates (c)	2/28 (7%)	0/37 (0%)	4/31 (13%)
Week of First Observation	90	103	104
Life Table Tests (d)	P=0.529N	P=0.118N	P=0.579N
Incidental Tumor Tests (d)	P=0.519N	P=0.210N	P=0.574N
Cochran-Armitage Trend Test (d)	P=0.584		
Fisher Exact Test (d)		P=0.175N	P=0.643
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	6/48 (13%)	(f) 1/14 (7%)	9/49 (18%)
Adjusted Rates (b)	19.6%		26.2%
Terminal Rates (c)	5/28 (18%)		7/31 (23%)
Week of First Observation	64		64
Life Table Test (d)			P=0.363
Incidental Tumor Test (d)			P=0.314
Fisher Exact Test (d)			P=0.303

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

	Control	310 ppm	620 ppm
Mammary Gland: Fibroadenoma			
Overall Rates (a)	8/49 (16%)	36/50 (72%)	36/50 (72%)
Adjusted Rates (b)	24.8%	81.6%	85.6%
Terminal Rates (c)	5/28 (18%)	29/37 (78%)	25/31 (81%)
Week of First Observation	67	67	60
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	11/49 (22%)	9/21 (43%)	15/50 (30%)
Adjusted Rates (b)	30.9%	73.4%	41.8%
Terminal Rates (c)	6/28 (21%)	8/11 (73%)	11/31 (35%)
Week of First Observation	47	87	64
Life Table Tests (d)	P=0.320	P=0.225	P=0.359
Incidental Tumor Tests (d)	P=0.279	P=0.034	P=0.275
Cochran-Armitage Trend Test (d)	P=0.239		
Fisher Exact Test (d)		P=0.076	P=0.266
Clitoral Gland: Adenoma			
Overall Rates (a)	3/49 (6%)	0/50 (0%)	7/50 (14%)
Adjusted Rates (b)	10.7%	0.0%	21.5%
Terminal Rates (c)	3/28 (11%)	0/37 (0%)	6/31 (19%)
Week of First Observation	104		101
Life Table Tests (d)	P=0.094	P=0.076N	P=0.206
Incidental Tumor Tests (d)	P=0.099	P=0.076N	P=0.208
Cochran-Armitage Trend Test (d)	P=0.084		
Fisher Exact Test (d)		P=0.117N	P=0.167
Clitoral Gland: Carcinoma			
Overall Rates (a)	5/49 (10%)	6/50 (12%)	0/50 (0%)
Adjusted Rates (b)	14.6%	14.8%	0.0%
Terminal Rates (c)	3/28 (11%)	3/37 (8%)	0/31 (0%)
Week of First Observation	54	82	
Life Table Tests (d)	P=0.029N	P=0.591N	P=0.029N
Incidental Tumor Tests (d)	P=0.040N	P=0.486	P=0.047N
Cochran-Armitage Trend Test (d)	P=0.039N		
Fisher Exact Test (d)		P=0.514	P=0.027N
Clitoral Gland: Adenocarcinoma or Carcinoma			
Overall Rates (a)	5/49 (10%)	7/50 (14%)	0/50 (0%)
Adjusted Rates (b)	14.6%	17.3%	0.0%
Terminal Rates (c)	3/28 (11%)	4/37 (11%)	0/31 (0%)
Week of First Observation	54	82	
Life Table Tests (d)	P=0.034N	P=0.547	P=0.029N
Incidental Tumor Tests (d)	P=0.045N	P=0.383	P=0.047N
Cochran-Armitage Trend Test (d)	P=0.045N		
Fisher Exact Test (d)		P=0.394	P=0.027N
Clitoral Gland: Adenoma, Adenocarcinoma, or Carcinoma			
Overall Rates (a)	8/49 (16%)	7/50 (14%)	7/50 (14%)
Adjusted Rates (b)	24.9%	17.3%	21.5%
Terminal Rates (c)	6/28 (21%)	4/37 (11%)	6/31 (19%)
Week of First Observation	54	82	101
Life Table Tests (d)	P=0.357N	P=0.310N	P=0.415N
Incidental Tumor Tests (d)	P=0.386N	P=0.451N	P=0.479N
Cochran-Armitage Trend Test (d)	P=0.427N		
Fisher Exact Test (d)		P=0.483N	P=0.483N

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

	Control	310 ppm	620 ppm
All Sites: Malignant Tumors			
Overall Rates (a)	23/49 (47%)	17/50 (34%)	9/50 (18%)
Adjusted Rates (b)	55.2%	38.0%	23.7%
Terminal Rates (c)	10/28 (36%)	10/37 (27%)	5/31 (16%)
Week of First Observation	52	61	76
Life Table Tests (d)	P=0.002N	P=0.053N	P=0.003N
Incidental Tumor Tests (d)	P=0.001N	P=0.238N	P=0.001N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.134N	P=0.002N
All Sites: All Tumors			
Overall Rates (a)	44/49 (90%)	47/50 (94%)	46/50 (92%)
Adjusted Rates (b)	91.6%	95.9%	95.8%
Terminal Rates (c)	24/28 (86%)	35/37 (95%)	29/31 (94%)
Week of First Observation	47	61	60
Life Table Tests (d)	P=0.365N	P=0.150N	P=0.386N
Incidental Tumor Tests (d)	P=0.441	P=0.299	P=0.528
Cochran-Armitage Trend Test (d)	P=0.415		
Fisher Exact Test (d)		P=0.346	P=0.487

(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 incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 620-ppm and control groups.
(f) Incomplete sampling of tissues

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

Study	Incidence of Fibroadenomas in Controls
Historical Incidence at Physiological Research Laboratories	
Ephedrine sulfate	10/49
Phenylephrine hydrochloride	11/50
Oxytetracycline hydrochloride	21/50
TOTAL	42/149 (28.2%)
SD (c)	12.03%
Range (d)	
High	21/50
Low	10/49
Overall Historical Incidence	
TOTAL	(d) 550/1,984 (27.7%)
SD (c)	11.07%
Range (d)	
High	24/49
Low	5/50

(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) Four cystfibroadenomas were also observed.

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

Study	Incidence in Controls
Historical Incidence at Physiological Research Laboratories	
Ephedrine sulfate	13/49
Phenylephrine hydrochloride	15/50
Oxytetracycline hydrochloride	13/50
TOTAL	41/149 (27.5%)
SD (b)	2.17%
Range (c)	
High	15/50
Low	13/50
Overall Historical Incidence	
TOTAL	378/1,984 (19.1%)
SD (b)	6.94%
Range (c)	
High	19/50
Low	3/50

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(50)	(50)
Inflammation, NOS	12 (24%)		8 (16%)
Inflammation, suppurative			1 (2%)
Parasitism	1 (2%)		
Infection, fungal	1 (2%)		
#Lung	(48)	(15)	(49)
Edema, NOS			1 (2%)
Hemorrhage		1 (7%)	
Inflammation, NOS	5 (10%)	2 (13%)	1 (2%)
Inflammation, focal		1 (7%)	
Inflammation, chronic focal	1 (2%)		
Infection, protozoan		1 (7%)	
Hyperplasia, alveolar epithelium	3 (6%)		2 (4%)
#Lung/alveoli	(48)	(15)	(49)
Histiocytosis	1 (2%)		
HEMATOPOIETIC SYSTEM			
#Bone marrow	(48)	(50)	(50)
Fibrosis, diffuse	1 (2%)		
Hypoplasia, NOS	1 (2%)		6 (12%)
Hyperplasia, NOS	12 (25%)	8 (16%)	4 (8%)
Histiocytosis		1 (2%)	
Hyperplasia, reticulum cell	2 (4%)	6 (12%)	5 (10%)
#Megakaryocytes	(48)	(50)	(50)
Hyperplasia, NOS	1 (2%)		
#Spleen	(49)	(50)	(50)
Scar	1 (2%)	1 (2%)	2 (4%)
Metamorphosis, fatty	1 (2%)		
#Lymph node	(49)	(10)	(50)
Cyst, NOS	1 (2%)		
Hemorrhage	1 (2%)		
Inflammation, acute	1 (2%)		
Hyperplasia, NOS			3 (6%)
#Mandibular lymph node	(49)	(10)	(50)
Hemorrhagic cyst			1 (2%)
#Mesenteric lymph node	(49)	(10)	(50)
Inflammation, granulomatous			1 (2%)
Histiocytosis	1 (2%)	2 (20%)	
*Bone	(49)	(50)	(50)
Myelofibrosis		1 (2%)	
#Ileum	(49)	(10)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Thymus	(36)	(8)	(36)
Hyperplasia, epithelial	2 (6%)		
Hyperplasia, lymphoid			1 (3%)

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

	Untreated Control	Low Dose	High Dose
CIRCULATORY SYSTEM			
#Heart/ventricle	(48)	(11)	(50)
Dilatation, NOS			1 (2%)
#Myocardium	(48)	(11)	(50)
Degeneration, NOS	35 (73%)	10 (91%)	37 (74%)
#Mitral valve	(48)	(11)	(50)
Degeneration, mucoid			1 (2%)
*Artery	(49)	(50)	(50)
Inflammation, chronic			1 (2%)
DIGESTIVE SYSTEM			
*Tongue	(49)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	
#Salivary gland	(47)	(10)	(48)
Inflammation, NOS	1 (2%)	1 (10%)	1 (2%)
Atrophy, focal	1 (2%)		2 (4%)
#Liver	(49)	(50)	(50)
Accessory structure	6 (12%)	7 (14%)	4 (8%)
Inflammation, NOS	2 (4%)	1 (2%)	1 (2%)
Granuloma, NOS	13 (27%)	23 (46%)	21 (42%)
Necrosis, NOS	1 (2%)		1 (2%)
Necrosis, coagulative	1 (2%)		
Angiectasis		1 (2%)	
#Intrahepatic bile duct	(49)	(50)	(50)
Hyperplasia, NOS	27 (55%)	34 (68%)	25 (50%)
#Liver/hepatocytes	(49)	(50)	(50)
Cytoplasmic vacuolization	1 (2%)	1 (2%)	1 (2%)
Focal cellular change	38 (78%)	47 (94%)	41 (82%)
#Pancreas	(48)	(10)	(49)
Inflammation, NOS	1 (2%)	1 (10%)	1 (2%)
Atrophy, focal	14 (29%)	1 (10%)	15 (31%)
Atrophy, diffuse	2 (4%)		
Hypertrophy, focal			1 (2%)
#Glandular stomach	(49)	(12)	(50)
Cyst, NOS	14 (29%)	2 (17%)	16 (32%)
Hyperplasia, epithelial		1 (8%)	
#Stomach wall	(49)	(12)	(50)
Granuloma, NOS	1 (2%)		
#Forestomach	(49)	(12)	(50)
Inflammation, chronic			1 (2%)
Hyperkeratosis	1 (2%)		2 (4%)
URINARY SYSTEM			
#Kidney	(49)	(10)	(50)
Mineralization			4 (8%)
Cyst, NOS			1 (2%)
Nephropathy	33 (67%)	9 (90%)	24 (48%)
#Kidney/cortex	(49)	(10)	(50)
Inflammation, chronic focal	1 (2%)		
#Urinary bladder	(48)	(9)	(50)
Hyperplasia, epithelial	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(50)	(48)
Cyst, NOS	1 (2%)		
Multiple cysts	2 (4%)		1 (2%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	7 (15%)	7 (14%)	6 (13%)
Hyperplasia, cystic	16 (33%)	17 (34%)	16 (33%)
#Adrenal/capsule	(49)	(50)	(49)
Accessory structure			2 (4%)
#Adrenal cortex	(49)	(50)	(49)
Accessory structure		1 (2%)	
Cyst, NOS		1 (2%)	
Necrosis, focal	1 (2%)		
Cytoplasmic vacuolization	4 (8%)	5 (10%)	3 (6%)
Hypertrophy, focal	14 (29%)	8 (16%)	1 (2%)
Hyperplasia, focal	15 (31%)	21 (42%)	10 (20%)
Angiectasis	1 (2%)	2 (4%)	
#Adrenal medulla	(49)	(50)	(49)
Hyperplasia, focal		1 (2%)	1 (2%)
#Thyroid	(48)	(14)	(49)
Hyperplasia, C-cell	8 (17%)	1 (7%)	8 (16%)
#Thyroid follicle	(48)	(14)	(49)
Degeneration, NOS			1 (2%)
#Pancreatic islets	(48)	(10)	(49)
Hypertrophy, NOS	2 (4%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Inflammation, NOS	1 (2%)		
Inflammation, chronic	1 (2%)		1 (2%)
Atrophy, NOS		1 (2%)	1 (2%)
Hyperplasia, cystic	21 (43%)	11 (22%)	20 (40%)
*Clitoral gland	(49)	(50)	(50)
Inflammation, NOS	3 (6%)	3 (6%)	7 (14%)
*Vagina	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
Inflammation, chronic suppurative	1 (2%)		
#Uterus	(49)	(21)	(50)
Hydrometra	2 (4%)	4 (19%)	1 (2%)
Inflammation, NOS		2 (10%)	3 (6%)
#Cervix uteri	(49)	(21)	(50)
Cyst, NOS			1 (2%)
Inflammation, NOS			1 (2%)
Fibrosis	1 (2%)		
#Endometrial gland	(49)	(21)	(50)
Cyst, NOS	4 (8%)	2 (10%)	4 (8%)
Hyperplasia, NOS	2 (4%)	1 (5%)	2 (4%)
#Ovary	(49)	(12)	(50)
Cyst, NOS	3 (6%)	2 (17%)	4 (8%)
Parovarian cyst	1 (2%)	1 (8%)	
NERVOUS SYSTEM			
#Brain/meninges	(48)	(9)	(50)
Congestion, NOS	1 (2%)		
Inflammation, acute			1 (2%)
#Cerebral ventricle	(48)	(9)	(50)
Dilatation, NOS		1 (11%)	
#Brain	(48)	(9)	(50)
Gliosis		1 (11%)	2 (4%)

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

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM (Continued)			
#Brain stem	(48)	(9)	(50)
Atrophy, pressure	8 (17%)		7 (14%)
*White matter spinal	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye/iris	(49)	(50)	(50)
Synechia, anterior	1 (2%)		
Synechia, posterior	1 (2%)	1 (2%)	
*Eye/crystalline lens	(49)	(50)	(50)
Cataract	1 (2%)	5 (10%)	
*Nasolacrimal duct	(49)	(50)	(50)
Foreign body, NOS	1 (2%)		
Inflammation, NOS			1 (2%)
*Harderian gland	(49)	(50)	(50)
Inflammation, focal	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Joint	(49)	(50)	(50)
Degeneration, NOS			4 (8%)
*Synovial tissue	(49)	(50)	(50)
Inflammation, chronic			1 (2%)
*Vertebral joint	(49)	(50)	(50)
Degeneration, NOS	3 (6%)	39 (78%)	36 (72%)
*Sternal synchondrosis	(49)	(50)	(50)
Degeneration, NOS	15 (31%)	1 (2%)	32 (64%)
*Knee joint	(49)	(50)	(50)
Degeneration, NOS	4 (8%)	30 (60%)	39 (78%)
*Skeletal muscle	(49)	(50)	(50)
Mineralization			1 (2%)
Hemorrhage		1 (2%)	
*Cartilage, NOS	(49)	(50)	(50)
Necrosis, focal	1 (2%)		
BODY CAVITIES			
*Mesentery	(49)	(50)	(50)
Steatitis	1 (2%)		
Inflammation, chronic			1 (2%)
Necrosis, fat	4 (8%)	6 (12%)	2 (4%)
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Inflammation, granulomatous		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
No necropsy performed	1		

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

APPENDIX C

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

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		1 (2%)
Fibroma			1 (2%)
Fibrosarcoma	2 (4%)	3 (6%)	†5 (10%)
Neurofibrosarcoma			1 (2%)
Neurilemoma			2 (4%)
Neurilemoma, malignant		†1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(50)
Hepatocellular carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	6 (12%)	5 (10%)	4 (8%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	2 (4%)
Sarcoma, NOS, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undifferentiated type		2 (4%)	
Malignant lymphoma, lymphocytic type		1 (2%)	
Malignant lymphoma, mixed type	4 (8%)	1 (2%)	1 (2%)
#Spleen	(49)	(48)	(50)
Malignant lymphoma, undifferentiated type		1 (2%)	
Malignant lymphoma, mixed type		1 (2%)	
#Peyer's patch	(47)	(44)	(45)
Malignant lymphoma, mixed type			1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma			2 (4%)
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Liver	(50)	(49)	(50)
Hemangioma			1 (2%)
*Preputial gland	(50)	(50)	(50)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(50)
Hepatocellular adenoma	9 (18%)	6 (12%)	2 (4%)
Hepatocellular carcinoma	8 (16%)	9 (18%)	4 (8%)
#Forestomach	(49)	(46)	(48)
Squamous cell papilloma	2 (4%)		
Squamous cell carcinoma			1 (2%)
#Duodenum	(47)	(44)	(45)
Carcinoma, NOS	1 (2%)		
#Jejunum	(47)	(44)	(45)
Carcinoma, NOS			1 (2%)
Papillary carcinoma			1 (2%)
URINARY SYSTEM			
None			

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

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary intermedia	(44)	(48)	(49)
Adenoma, NOS	1 (2%)		
#Adrenal	(48)	(49)	(49)
Cortical adenoma	3 (6%)	1 (2%)	1 (2%)
#Adrenal medulla	(48)	(49)	(49)
Pheochromocytoma	2 (4%)		1 (2%)
#Thyroid	(49)	(48)	(50)
Follicular cell adenoma	1 (2%)		
Follicular cell carcinoma			1 (2%)
#Pancreatic islets	(49)	(48)	(48)
Islet cell adenoma	1 (2%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Eye/lacrimal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
*Harderian gland	(50)	(50)	(50)
Carcinoma, NOS		2 (4%)	
Adenoma, NOS			2 (4%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	12	10
Moribund sacrifice	6	7	13
Terminal sacrifice	39	31	27
Accidentally killed, nda	1		

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

	Untreated Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	28	25	26
Total primary tumors	45	39	38
Total animals with benign tumors	17	12	14
Total benign tumors	25	13	16
Total animals with malignant tumors	16	21	17
Total malignant tumors	20	26	22
Total animals with secondary tumors##		1	1
Total secondary tumors		1	1

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
**Primary tumors: all tumors except secondary tumors
Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ
† Multiple occurrence of morphology in same organ; tissue counted only once.

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE: UNTREATED CONTROL

ANIMAL NUMBER	12 7	11 8	10 5	10 1	13 1	14 7	13 3	14 4	14 6	12 4	14 1	10 2	10 3	10 4	10 6	10 7	10 8	10 9	11 0	11 1	11 2	11 3	11 4	11 5	11 6
WEEKS ON STUDY	00 9	06 4	06 6	07 8	08 1	08 9	09 7	09 8	09 9	10 2	10 2	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS								X																	
Fibrosarcoma							X				X														
Hemangiosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X							X					X	
Alveolar/bronchiolar carcinoma																X									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	+	−	−	−	+	+	+	−	+	−	−	+	−	+	+	−	+	+	+	−	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X					X													
Hepatocellular carcinoma			X			X					X			X									X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	+	+	+	+	N	N	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X																		
Small intestine	+	+	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS						X																			
Large intestine	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	−	+	+	−	−	+	+	+	+
Adenoma, NOS																X									
Adrenal	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																						X			
Pheochromocytoma																									
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																					X				
Parathyroid	+	+	−	+	−	−	+	+	+	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS					X																				
Malignant lymphoma, mixed type									X														X		

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

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

ANIMAL NUMBER	117	119	120	121	122	123	125	126	128	129	130	132	134	135	136	137	138	139	140	142	143	145	148	149	150	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibrosarcoma																										2
Hemangiosarcoma																								X		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X					X					X									6
Alveolar/bronchiolar carcinoma																								X		2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	−	+	+	+	+	−	+	+	+	+	+	−	−	+	+	+	−	−	−	+	−	−	+	30
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma										X	X	X			X		X			X				X		9
Hepatocellular carcinoma										X			X								X					8
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma				X																						2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	48
Cortical adenoma			X	X																						3
Pheochromocytoma							X										X									2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																										1
Parathyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma												X														1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Malignant lymphoma, mixed type			X																X							4

* Animals necropsied

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

ANIMAL NUMBER	033	035	013	014	015	034	048	045	028	047	017	008	019	027	031	040	012	018	037	001	002	003	004	005	006
WEEKS ON STUDY	005	005	006	006	006	006	022	029	049	051	081	083	088	089	094	098	099	101	103	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma													X												
Neurilemoma, malignant												@X													
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X	X								
Alveolar/bronchiolar carcinoma																									
Sarcoma, NOS, metastatic											X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	−	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, undifferentiated type																									
Malignant lymphoma, mixed type																							X		
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	−	+	A	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	−	+	−	+	+	+	−	−	A	+	−	−	−	−	+	+	−	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	−	+	+	+	+	+	+	+	+	+	−	+	A	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																				X					X
Hepatocellular carcinoma												X				X			X			X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	N	N	N	N	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	−	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	−	+	+	+	+	+	−	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	−	+	−	+	+	+	+	+	+	+	+	A	+	+	+	+	−	+	+	+	+	+	+
Large intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	A	+	+	+	+	−	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	−	+	−	−	+	+	+	+	+	+	+	+	A	+	+	+	+	−	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																		X							
Thyroid	+	+	+	+	+	+	+	+	+	+	+	−	+	A	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	−	+	−	−	−	+	+	+	+	−	−	+	A	+	+	+	+	+	−	+	−	+	+	+
Pancreatic islets	+	+	+	+	−	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	−	+	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	−	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																		X							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Lacrimal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undifferentiated type															X										
Malignant lymphoma, lymphocytic type																	X								
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	007	009	010	011	016	020	021	022	023	024	025	026	029	030	032	036	038	039	041	042	043	044	046	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma											X										X					3
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma										X	X								X							5
Alveolar/bronchiolar carcinoma						X																		X		2
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, undiffer type											X															1
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	−	+	−	+	−	+	+	+	−	−	−	+	−	−	+	−	+	−	+	+	+	+	+	+	29
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma					X	X			X											X						6
Hepatocellular carcinoma										X					X					X			X	X		9
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Small intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Large intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma					X																					1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Lacrimal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS									X																	1
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS					X														X							2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, undiffer type																								X		2
Malig lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type																	X									1

* Animals necropsied

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

ANIMAL NUMBER	051	094	065	074	053	081	067	054	068	095	100	059	077	086	078	052	069	058	088	089	079	073	062	055	056
WEEKS ON STUDY	013	016	018	018	019	021	031	041	043	053	085	086	088	088	090	091	091	093	093	094	097	098	100	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																							X		
Fibroma																									
Fibrosarcoma												X								X	X	X			
Neurofibrosarcoma																			X						
Neurilemoma																	X					X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	−	+	−	+	+	+	−	+	+	+	−	−	−	+	+	−	−	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																					X				X
Hemangioma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	N	N	N	N	N	+	+	N	+	N	+	+	+	+	+	+	+	+	N	+	+	+
Pancreas	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Small intestine	+	+	+	−	+	+	+	−	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Papillary carcinoma																									
Malignant lymphoma, mixed type																								X	
Large intestine	+	+	+	−	+	+	+	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	−	+	+	+	−	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
Parathyroid	+	+	+	−	+	−	+	−	+	+	+	−	+	−	+	−	+	+	−	−	+	+	+	+	+
Pancreatic islets	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangioma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma												X		X											
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	057	060	061	063	064	066	070	071	072	075	076	080	082	083	084	085	087	090	091	092	093	096	097	098	099	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma		X																								1
Fibrosarcoma																	@X									5
Neurofibrosarcoma																										1
Neurilemoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic										X																1
Alveolar/bronchiolar adenoma		X																							X	3
Alveolar/bronchiolar carcinoma																		X								2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	−	−	+	+	+	−	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	−	−	−	+	33
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma															X	X										2
Hepatocellular carcinoma										X						X										4
Hemangioma		X																								1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma				X																						1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma, NOS																X										1
Papillary carcinoma															X											1
Malignant lymphoma, mixed type																										1
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma					X																					1
Pheochromocytoma																						X				1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																							X			1
Parathyroid	+	+	−	+	+	+	+	+	+	−	+	+	+	−	+	+	−	+	+	+	+	+	−	+	+	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma								X																		1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangioma																		X								1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS			X			X																				2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										2
Malignant lymphoma, mixed type												X														1

* Animals necropsied

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

	Control	150 ppm	310 ppm
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	4.7%	8.9%	15.3%
Terminal Rates (c)	0/39 (0%)	2/31 (6%)	1/27 (4%)
Week of First Observation	97	88	86
Life Table Tests (d)	P=0.080	P=0.402	P=0.109
Incidental Tumor Tests (d)	P=0.224	P=0.519	P=0.293
Cochran-Armitage Trend Test (d)	P=0.159		
Fisher Exact Test (d)		P=0.500	P=0.218
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	7/50 (14%)
Adjusted Rates (b)	6.9%	8.9%	20.8%
Terminal Rates (c)	0/39 (0%)	2/31 (6%)	1/27 (4%)
Week of First Observation	97	88	86
Life Table Tests (d)	P=0.044	P=0.557	P=0.064
Incidental Tumor Tests (d)	P=0.140	P=0.653N	P=0.172
Cochran-Armitage Trend Test (d)	P=0.105		
Fisher Exact Test (d)		P=0.661	P=0.159
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	4.7%	8.9%	18.5%
Terminal Rates (c)	0/39 (0%)	2/31 (6%)	2/27 (7%)
Week of First Observation	97	88	86
Life Table Tests (d)	P=0.039	P=0.402	P=0.057
Incidental Tumor Tests (d)	P=0.119	P=0.519	P=0.159
Cochran-Armitage Trend Test (d)	P=0.089		
Fisher Exact Test (d)		P=0.500	P=0.134
Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	8/50 (16%)
Adjusted Rates (b)	6.9%	8.9%	23.8%
Terminal Rates (c)	0/39 (0%)	2/31 (6%)	2/27 (7%)
Week of First Observation	97	88	86
Life Table Tests (d)	P=0.021	P=0.557	P=0.034
Incidental Tumor Tests (d)	P=0.070	P=0.653N	P=0.084
Cochran-Armitage Trend Test (d)	P=0.059		
Fisher Exact Test (d)		P=0.661	P=0.100
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	6/50 (12%)	5/49 (10%)	4/50 (8%)
Adjusted Rates (b)	15.4%	14.8%	13.5%
Terminal Rates (c)	6/39 (15%)	3/31 (10%)	3/27 (11%)
Week of First Observation	104	98	88
Life Table Tests (d)	P=0.542N	P=0.596	P=0.597N
Incidental Tumor Tests (d)	P=0.427N	P=0.623	P=0.511N
Cochran-Armitage Trend Test (d)	P=0.311N		
Fisher Exact Test (d)		P=0.514N	P=0.371N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	8/50 (16%)	7/49 (14%)	6/50 (12%)
Adjusted Rates (b)	20.5%	20.9%	20.0%
Terminal Rates (c)	8/39 (21%)	5/31 (16%)	4/27 (15%)
Week of First Observation	104	98	88
Life Table Tests (d)	P=0.497	P=0.534	P=0.564
Incidental Tumor Tests (d)	P=0.500N	P=0.558	P=0.563N
Cochran-Armitage Trend Test (d)	P=0.335N		
Fisher Exact Test (d)		P=0.517N	P=0.387N

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

	Control	150 ppm	310 ppm
Hematopoietic System: Malignant Lymphoma, Undifferentiated Type			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	9.1%	0.0%
Terminal Rates (c)	0/39 (0%)	2/31 (6%)	0/27 (0%)
Week of First Observation		94	
Life Table Tests (d)	P=0.561	P=0.087	(e)
Incidental Tumor Tests (d)	P=0.611	P=0.097	(e)
Cochran-Armitage Trend Test (d)	P=0.626N		
Fisher Exact Test (d)		P=0.121	(e)
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	9.9%	6.5%	7.4%
Terminal Rates (c)	3/39 (8%)	2/31 (6%)	2/27 (7%)
Week of First Observation	99	104	104
Life Table Tests (d)	P=0.418N	P=0.446N	P=0.519N
Incidental Tumor Tests (d)	P=0.384N	P=0.428N	P=0.469N
Cochran-Armitage Trend Test (d)	P=0.258N		
Fisher Exact Test (d)		P=0.339N	P=0.339N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	9.9%	17.8%	7.4%
Terminal Rates (c)	3/39 (8%)	4/31 (13%)	2/27 (7%)
Week of First Observation	99	94	104
Life Table Tests (d)	P=0.492N	P=0.244	P=0.519N
Incidental Tumor Tests (d)	P=0.408N	P=0.270	P=0.469N
Cochran-Armitage Trend Test (d)	P=0.284N		
Fisher Exact Test (d)		P=0.370	P=0.339N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	2.6%	0.0%	12.2%
Terminal Rates (c)	1/39 (3%)	0/31 (0%)	2/27 (7%)
Week of First Observation	104		86
Life Table Tests (d)	P=0.049	P=0.546N	P=0.109
Incidental Tumor Tests (d)	P=0.107	P=0.546N	P=0.237
Cochran-Armitage Trend Test (d)	P=0.079		
Fisher Exact Test (d)		P=0.500N	P=0.181
Liver: Hepatocellular Adenoma			
Overall Rates (a)	9/50 (18%)	6/49 (12%)	2/50 (4%)
Adjusted Rates (b)	22.3%	19.4%	7.4%
Terminal Rates (c)	8/39 (21%)	6/31 (19%)	2/27 (7%)
Week of First Observation	97	104	104
Life Table Tests (d)	P=0.078N	P=0.467N	P=0.095N
Incidental Tumor Tests (d)	P=0.070N	P=0.454N	P=0.081N
Cochran-Armitage Trend Test (d)	P=0.021N		
Fisher Exact Test (d)		P=0.303N	P=0.026N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	8/50 (16%)	9/49 (18%)	4/50 (8%)
Adjusted Rates (b)	18.6%	26.1%	14.1%
Terminal Rates (c)	5/39 (13%)	6/31 (19%)	3/27 (11%)
Week of First Observation	66	83	97
Life Table Tests (d)	P=0.376N	P=0.317	P=0.386N
Incidental Tumor Tests (d)	P=0.242N	P=0.304	P=0.288N
Cochran-Armitage Trend Test (d)	P=0.154N		
Fisher Exact Test (d)		P=0.482	P=0.178N

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

	Control	150 ppm	310 ppm
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	16/50 (32%)	15/49 (31%)	5/50 (10%)
Adjusted Rates (b)	36.8%	43.8%	17.7%
Terminal Rates (c)	12/39 (31%)	12/31 (39%)	4/27 (15%)
Week of First Observation	66	83	97
Life Table Tests (d)	P=0.072N	P=0.380	P=0.062N
Incidental Tumor Tests (d)	P=0.032N	P=0.382	P=0.031N
Cochran-Armitage Trend Test (d)	P=0.007N		
Fisher Exact Test (d)		P=0.527N	P=0.007N
Adrenal Gland: Cortical Adenoma			
Overall Rates (a)	3/48 (6%)	1/49 (2%)	1/49 (2%)
Adjusted Rates (b)	7.9%	3.0%	3.7%
Terminal Rates (c)	3/38 (8%)	0/31 (0%)	1/27 (4%)
Week of First Observation	104	101	104
Life Table Tests (d)	P=0.314N	P=0.383N	P=0.433N
Incidental Tumor Tests (d)	P=0.263N	P=0.341N	P=0.433N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.301N	P=0.301N
All Sites: Benign Tumors			
Overall Rates (a)	17/50 (34%)	12/50 (24%)	14/50 (28%)
Adjusted Rates (b)	42.4%	35.1%	45.9%
Terminal Rates (c)	16/39 (41%)	9/31 (29%)	11/27 (41%)
Week of First Observation	97	98	88
Life Table Tests (d)	P=0.343	P=0.437N	P=0.368
Incidental Tumor Tests (d)	P=0.508	P=0.396N	P=0.535
Cochran-Armitage Trend Test (d)	P=0.297N		
Fisher Exact Test (d)		P=0.189N	P=0.333N
All Sites: Malignant Tumors			
Overall Rates (a)	16/50 (32%)	21/50 (42%)	17/50 (34%)
Adjusted Rates (b)	34.5%	55.2%	49.6%
Terminal Rates (c)	9/39 (23%)	14/31 (45%)	10/27 (37%)
Week of First Observation	66	83	86
Life Table Tests (d)	P=0.107	P=0.070	P=0.142
Incidental Tumor Tests (d)	P=0.342	P=0.068	P=0.414
Cochran-Armitage Trend Test (d)	P=0.468		
Fisher Exact Test (d)		P=0.204	P=0.500
All Sites: All Tumors			
Overall Rates (a)	28/50 (56%)	25/50 (50%)	26/50 (52%)
Adjusted Rates (b)	60.7%	65.7%	72.0%
Terminal Rates (c)	21/39 (54%)	18/31 (58%)	17/27 (63%)
Week of First Observation	66	83	86
Life Table Tests (d)	P=0.114	P=0.371	P=0.134
Incidental Tumor Tests (d)	P=0.415	P=0.489	P=0.477
Cochran-Armitage Trend Test (d)	P=0.386N		
Fisher Exact Test (d)		P=0.345N	P=0.421N

(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 incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 310-ppm and control groups.

TABLE C4a. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence at Physiological Research Laboratories			
Ephedrine sulfate	0/50	2/50	2/50
Phenylephrine hydrochloride	0/50	0/50	0/50
Oxytetracycline hydrochloride	1/50	2/50	3/50
TOTAL	1/150 (0.7%)	4/150 (2.7%)	5/150 (3.3%)
SD (b)	1.15%	2.31%	3.06%
Range (c)			
High	1/50	2/50	3/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	26/2,040 (1.3%)	(d) 69/2,040 (3.4%)	(d) 94/2,040 (4.6%)
SD (b)	2.64%	2.58%	4.03%
Range (c)			
High	7/50	5/49	10/50
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 12 angiosarcomas

TABLE C4b. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Fibroma (b)	Fibrosarcoma (c)	Fibroma or Fibrosarcoma (b,c)
Historical Incidence at Physiological Research Laboratories			
Ephedrine sulfate	0/50	0/50	0/50
Phenylephrine hydrochloride	2/50	1/50	3/50
Oxytetracycline hydrochloride	2/50	11/50	13/50
TOTAL	4/150 (2.7%)	12/150 (8.0%)	16/150 (10.7%)
SD (d)	2.31%	12.17%	13.61%
Range (e)			
High	2/50	11/50	13/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	39/2,040 (1.9%)	127/2,040 (6.2%)	160/2,040 (7.8%)
SD (d)	2.79%	6.66%	7.80%
Range (e)			
High	6/50	15/50	19/50
Low	0/50	0/50	0/50

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

TABLE C4c. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Physiological Research Laboratories			
Ephedrine sulfate	10/50	13/50	19/50
Phenylephrine hydrochloride	12/50	4/50	15/50
Oxytetracycline hydrochloride	7/50	11/50	18/50
TOTAL	29/150 (19.3%)	28/150 (18.7%)	52/150 (34.7%)
SD (b)	5.03%	9.45%	4.16%
Range (c)			
High	12/50	13/50	19/50
Low	7/50	4/50	15/50
Overall Historical Incidence			
TOTAL	242/2,032 (11.9%)	394/2,032 (19.4%)	609/2,032 (30.0%)
SD (b)	7.44%	6.84%	7.90%
Range (c)			
High	(d) 22/50	16/50	(e) 29/50
Low	0/49	4/50	8/50

(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) Second highest: 12/50
(e) Second highest: 20/50

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ectopia	7 (14%)	4 (8%)	
Ulcer, NOS	1 (2%)		
Inflammation, acute focal		1 (2%)	1 (2%)
Inflammation, granulomatous			1 (2%)
Necrosis, NOS		3 (6%)	1 (2%)
Hyperkeratosis			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Hematoma, NOS	1 (2%)		
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic	1 (2%)		
Perivascular cuffing			1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Foreign body, NOS		1 (2%)	
Hemorrhage		1 (2%)	2 (4%)
Inflammation, pyogranulomatous		1 (2%)	
*Nasal mucosa	(50)	(50)	(50)
Degeneration, hyaline	1 (2%)	1 (2%)	
#Peritracheal tissue	(50)	(49)	(50)
Multiple cysts	1 (2%)		
#Lung/bronchus	(50)	(49)	(50)
Cyst, NOS			1 (2%)
#Lung/bronchiole	(50)	(49)	(50)
Hyperplasia, epithelial			2 (4%)
#Lung	(50)	(49)	(50)
Congestion, NOS	8 (16%)	11 (22%)	6 (12%)
Hemorrhage	3 (6%)	1 (2%)	4 (8%)
Inflammation, chronic focal	10 (20%)	9 (18%)	8 (16%)
Perivascular cuffing	5 (10%)		
Necrosis, NOS	1 (2%)		
Hemosiderosis		1 (2%)	
Alveolar macrophages	1 (2%)		3 (6%)
Hyperplasia, adenomatous	1 (2%)	1 (2%)	2 (4%)
#Lung/alveoli	(50)	(49)	(50)
Edema, NOS		1 (2%)	
Crystals, NOS		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid	4 (8%)	1 (2%)	2 (4%)
*Anterior mediastinum	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
*Blood	(50)	(50)	(50)
Leukocytosis, NOS		1 (2%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Mastocytosis	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Bone marrow	(50)	(49)	(50)
Congestion, NOS		1 (2%)	
Fibrosis			1 (2%)
Necrosis, NOS	1 (2%)		
Atrophy, NOS			1 (2%)
Hyperplasia, NOS	8 (16%)	1 (2%)	7 (14%)
Angiectasis	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, granulocytic	12 (24%)	12 (24%)	18 (36%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)
#Spleen	(49)	(48)	(50)
Inflammation, suppurative	1 (2%)		
Necrosis, NOS		1 (2%)	
Atrophy, diffuse		1 (2%)	
Angiectasis	5 (10%)	3 (6%)	
Hyperplasia, granulocytic		1 (2%)	
Hyperplasia, reticulum cell	2 (4%)	3 (6%)	7 (14%)
Hyperplasia, lymphoid	25 (51%)	11 (23%)	16 (32%)
Hematopoiesis	9 (18%)	8 (17%)	13 (26%)
#Splenic follicles	(49)	(48)	(50)
Necrosis, NOS		1 (2%)	
#Lymph node	(49)	(47)	(48)
Hemosiderosis			1 (2%)
#Mandibular lymph node	(49)	(47)	(48)
Hemosiderosis			1 (2%)
Plasmacytosis			1 (2%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	1 (2%)
Mastocytosis		1 (2%)	
#Mesenteric lymph node	(49)	(47)	(48)
Hemorrhage	1 (2%)		
Inflammation, acute			2 (4%)
Cytomegaly	1 (2%)	1 (2%)	2 (4%)
Angiectasis	18 (37%)	11 (23%)	13 (27%)
Hyperplasia, lymphoid	4 (8%)	1 (2%)	4 (8%)
#Lung	(50)	(49)	(50)
Leukocytosis, NOS	1 (2%)	3 (6%)	
Leukocytosis, neutrophilic			1 (2%)
Hyperplasia, lymphoid		1 (2%)	
#Salivary gland	(50)	(47)	(50)
Hyperplasia, lymphoid	4 (8%)	2 (4%)	2 (4%)
#Liver	(50)	(49)	(50)
Hematopoiesis	1 (2%)	3 (6%)	1 (2%)
#Pancreas	(49)	(48)	(48)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
#Peyer's patch	(47)	(44)	(45)
Hyperplasia, lymphoid	2 (4%)		
#Duodenum	(47)	(44)	(45)
Hyperplasia, lymphoid	1 (2%)		
#Ileum	(47)	(44)	(45)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
#Cecum	(48)	(46)	(45)
Hyperplasia, lymphoid	3 (6%)	2 (4%)	2 (4%)
#Kidney	(50)	(49)	(50)
Hyperplasia, lymphoid	3 (6%)	2 (4%)	1 (2%)
#Urinary bladder	(48)	(45)	(45)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	3 (7%)
#Prostate	(49)	(46)	(49)
Hyperplasia, lymphoid	3 (6%)		3 (6%)
#Testis	(50)	(49)	(50)
Hyperplasia, lymphoid			1 (2%)
#Thyroid	(49)	(48)	(50)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	

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

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Thymus	(30)	(29)	(33)
Cyst, NOS	2 (7%)		2 (6%)
Multiple cysts	4 (13%)	2 (7%)	6 (18%)
Necrosis, NOS	1 (3%)	4 (14%)	1 (3%)
Atrophy, NOS	1 (3%)	6 (21%)	6 (18%)
Hyperplasia, epithelial	2 (7%)		1 (3%)
Hyperplasia, lymphoid	1 (3%)		
CIRCULATORY SYSTEM			
#Lymph node	(49)	(47)	(48)
Lymphangiectasis		1 (2%)	
#Mandibular lymph node	(49)	(47)	(48)
Lymphangiectasis		1 (2%)	
#Lung	(50)	(49)	(50)
Thrombosis, NOS		1 (2%)	1 (2%)
#Heart	(50)	(49)	(50)
Inflammation, pyogranulomatous	1 (2%)		
#Myocardium	(50)	(49)	(50)
Inflammation, chronic focal	2 (4%)		
Inflammation with fibrosis		1 (2%)	
Necrosis, focal		1 (2%)	
Calcification, NOS	1 (2%)		
Cytomegaly	1 (2%)		
*Artery	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
DIGESTIVE SYSTEM			
*Hard palate	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
*Tongue	(50)	(50)	(50)
Hemoglobin pigment	1 (2%)		
*Tooth	(50)	(50)	(50)
Dysplasia, NOS	4 (8%)	2 (4%)	3 (6%)
*Pulp of tooth	(50)	(50)	(50)
Inflammation, acute	1 (2%)	1 (2%)	
Inflammation, granulomatous			1 (2%)
*Periodontal tissues	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
Granuloma, foreign body	1 (2%)		
Inflammation with fibrosis		2 (4%)	
Fibrosis	2 (4%)		
#Salivary gland	(50)	(47)	(50)
Dilatation/ducts		1 (2%)	
Fibrosis		1 (2%)	
Degeneration, NOS			1 (2%)
Calcification, focal		1 (2%)	
#Liver	(50)	(49)	(50)
Inflammation, chronic focal			1 (2%)
Degeneration, granular			1 (2%)
Necrosis, NOS	1 (2%)		1 (2%)
Necrosis, focal	4 (8%)	4 (8%)	3 (6%)
Necrosis, coagulative	1 (2%)		1 (2%)
Metamorphosis, fatty			1 (2%)
Basophilic cyto change			1 (2%)
Focal cellular change		1 (2%)	
Hepatocytomegaly			1 (2%)
Multinucleate giant cell			1 (2%)
Syncytial alteration			1 (2%)
Hyperplasia, focal			1 (2%)
Angiectasis	1 (2%)	1 (2%)	1 (2%)

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

	Untreated Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver/centrilobular	(50)	(49)	(50)
Congestion, NOS			1 (2%)
#Liver/hepatocytes	(50)	(49)	(50)
Inclusion, nuclear			2 (4%)
*Gallbladder	(50)	(50)	(50)
Calculus, gross observation only			1 (2%)
Cyst, NOS		1 (2%)	
Inflammation, acute/chronic			1 (2%)
Hyperplasia, papillary		1 (2%)	2 (4%)
*Gallbladder/mucosa	(50)	(50)	(50)
Degeneration, hyaline		1 (2%)	
#Bile duct	(50)	(49)	(50)
Multiple cysts		1 (2%)	
#Pancreas	(49)	(48)	(48)
Cyst, NOS			1 (2%)
Multiple cysts		1 (2%)	
Inflammation, chronic		1 (2%)	
Inflammation, granulomatous			1 (2%)
Atrophy, focal	1 (2%)	1 (2%)	
#Pancreatic acinus	(49)	(48)	(48)
Degeneration, NOS		1 (2%)	1 (2%)
Cytoplasmic vacuolization	4 (8%)	2 (4%)	1 (2%)
*Esophageal lumen	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
#Glandular stomach	(49)	(46)	(48)
Cyst, NOS	1 (2%)		2 (4%)
Multiple cysts			2 (4%)
Inflammation, acute	2 (4%)		
Inflammation, acute/chronic	2 (4%)		
Degeneration, hyaline			1 (2%)
Dysplasia, NOS		2 (4%)	
#Forestomach	(49)	(46)	(48)
Cyst, NOS	1 (2%)		
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic			2 (4%)
Inflammation, chronic focal		1 (2%)	
Hyperplasia, epithelial	1 (2%)		1 (2%)
Hyperkeratosis		1 (2%)	1 (2%)
#Peyer's patch	(47)	(44)	(45)
Inflammation, acute	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Mineralization	1 (2%)	3 (6%)	8 (16%)
Cyst, NOS	1 (2%)	3 (6%)	4 (8%)
Multiple cysts	2 (4%)		
Congestion, NOS	2 (4%)		2 (4%)
Hemorrhage	1 (2%)		
Inflammation, acute necrotizing		1 (2%)	
Nephropathy	8 (16%)	8 (16%)	13 (26%)
Nephrosis, NOS			1 (2%)
Infarct, NOS	1 (2%)		
Amyloidosis			2 (4%)
Atrophy, NOS	1 (2%)		
Metaplasia, osseous	3 (6%)		1 (2%)
#Kidney/cortex	(50)	(49)	(50)
Necrosis, NOS		1 (2%)	
#Renal papilla	(50)	(49)	(50)
Necrosis, NOS		2 (4%)	

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

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
#Perirenal tissue	(50)	(49)	(50)
Inflammation, acute			1 (2%)
Calcification, NOS		1 (2%)	
#Kidney/tubule	(50)	(49)	(50)
Dilatation, NOS			1 (2%)
Degeneration, NOS			1 (2%)
#Convoluted tubules	(50)	(49)	(50)
Dilatation, NOS		1 (2%)	
Metamorphosis, fatty			1 (2%)
*Ureter	(50)	(50)	(50)
Inflammation, acute			1 (2%)
#Urinary bladder	(48)	(45)	(45)
Calculus, gross observation only	1 (2%)		1 (2%)
Edema, NOS	1 (2%)		
Hemorrhage		1 (2%)	
Inflammation, acute		1 (2%)	1 (2%)
Calcification, NOS		1 (2%)	
Hyperplasia, epithelial	1 (2%)	1 (2%)	1 (2%)
Angiectasis			2 (4%)
ENDOCRINE SYSTEM			
#Pituitary	(44)	(48)	(49)
Congestion, NOS		3 (6%)	1 (2%)
#Anterior pituitary	(44)	(48)	(49)
Cyst, NOS	2 (5%)	1 (2%)	2 (4%)
Multiple cysts		2 (4%)	1 (2%)
Angiectasis			1 (2%)
#Adrenal/capsule	(48)	(49)	(49)
Hyperplasia, stromal	24 (50%)	16 (33%)	17 (35%)
#Adrenal cortex	(48)	(49)	(49)
Ectopia	1 (2%)	1 (2%)	
Cyst, NOS	1 (2%)	1 (2%)	
Degeneration, lipoid		1 (2%)	
Necrosis, focal			1 (2%)
Metamorphosis, fatty			1 (2%)
Focal cellular change	3 (6%)	3 (6%)	
Hypertrophy, focal	9 (19%)	9 (18%)	8 (16%)
Hyperplasia, focal	2 (4%)	1 (2%)	6 (12%)
#Adrenal medulla	(48)	(49)	(49)
Hyperplasia, focal	3 (6%)	4 (8%)	4 (8%)
#Thyroid	(49)	(48)	(50)
Follicular cyst, NOS	1 (2%)	2 (4%)	
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, granulomatous		1 (2%)	
Inflammation with fibrosis		1 (2%)	
Cholesterol deposit		1 (2%)	
Calcification, NOS		1 (2%)	
Hyperplasia, follicular cell	2 (4%)	1 (2%)	1 (2%)
#Thyroid follicle	(49)	(48)	(50)
Crystals, NOS		1 (2%)	
#Parathyroid	(43)	(38)	(37)
Cyst, NOS		2 (5%)	1 (3%)
#Pancreatic islets	(49)	(48)	(48)
Hypertrophy, NOS	1 (2%)		
Hyperplasia, NOS	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Penis	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
*Prepuce	(50)	(50)	(50)
Ulcer, NOS	1 (2%)		1 (2%)
Inflammation, suppurative		2 (4%)	
Abscess, NOS			1 (2%)
Inflammation, acute/chronic			1 (2%)
Necrosis, NOS		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Inflammation, acute	1 (2%)		
Abscess, NOS		1 (2%)	
Inflammation, acute/chronic	5 (10%)	2 (4%)	5 (10%)
Inflammation, chronic	3 (6%)	1 (2%)	2 (4%)
Inflammation, pyogranulomatous			1 (2%)
Inflammation with fibrosis	1 (2%)		
Metaplasia, squamous	9 (18%)	9 (18%)	9 (18%)
#Prostate	(49)	(46)	(49)
Cyst, NOS	1 (2%)		
Inflammation, suppurative		2 (4%)	1 (2%)
Inflammation, acute			1 (2%)
Amyloidosis		1 (2%)	
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Inflammation, suppurative			1 (2%)
#Testis	(50)	(49)	(50)
Degeneration, NOS		1 (2%)	1 (2%)
Necrosis, NOS		1 (2%)	
Calcification, NOS	4 (8%)		2 (4%)
Atrophy, NOS	3 (6%)	1 (2%)	4 (8%)
Atrophy, focal	2 (4%)		
Hyperplasia, interstitial cell	1 (2%)		
*Epididymis	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal	1 (2%)		1 (2%)
Perivascular cuffing	1 (2%)		1 (2%)
Calcification, NOS	1 (2%)		1 (2%)
NERVOUS SYSTEM			
#Brain	(48)	(49)	(50)
Congestion, NOS		5 (10%)	2 (4%)
Hemorrhage	1 (2%)		1 (2%)
#Brain/thalamus	(48)	(49)	(50)
Calcification, NOS	28 (58%)	26 (53%)	27 (54%)
*Spinal cord	(50)	(50)	(50)
Epidermal inclusion cyst			1 (2%)
Perivascular cuffing			1 (2%)
Demyelinization	1 (2%)		
SPECIAL SENSE ORGANS			
*Nasolacrimal duct	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, suppurative	1 (2%)		
Inflammation, chronic	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Dyschondroplasia	1 (2%)	1 (2%)	1 (2%)
Atrophy, NOS			1 (2%)
Osteosclerosis	1 (2%)		
*Mandible	(50)	(50)	(50)
Osteosclerosis			1 (2%)
*Ankle joint	(50)	(50)	(50)
Ankylosis	15 (30%)	4 (8%)	4 (8%)
Fibrosis		1 (2%)	
*Skeletal muscle	(50)	(50)	(50)
Fibrosis			1 (2%)
BODY CAVITIES			
*Pericardial cavity	(50)	(50)	(50)
Hemorrhage			1 (2%)
ALL OTHER SYSTEMS			
Periorbital region			
Inflammation, pyogranulomatous		1	
Knee			
Dyschondroplasia	16	9	10
Ankle			
Dyschondroplasia	1		
Adipose tissue			
Necrosis, fat	5	3	1
Renal pelvic cavity			
Inflammation, suppurative			1
SPECIAL MORPHOLOGY SUMMARY			
Auto/necropsy/no histo		1	

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

APPENDIX D

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

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibrosarcoma	1 (2%)	1 (2%)	
Neurilemoma, malignant			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(49)
Alveolar/bronchiolar adenoma	2 (4%)	6 (12%)	6 (12%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	
Osteosarcoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	2 (4%)		1 (2%)
Malignant lymphoma, undifferentiated type			1 (2%)
Malignant lymphoma, lymphocytic type	1 (2%)		2 (4%)
Malignant lymphoma, histiocytic type		3 (6%)	
Malignant lymphoma, mixed type	16 (32%)	13 (26%)	9 (18%)
Plasma cell tumor		1 (2%)	
#Spleen	(49)	(50)	(50)
Malignant lymphoma, lymphocytic type	1 (2%)		
Malignant lymphoma, mixed type	2 (4%)	3 (6%)	
#Mandibular lymph node	(49)	(12)	(49)
Squamous cell carcinoma, metastatic		1 (8%)	
#Peyer's patch	(48)	(8)	(44)
Malignant lymphoma, mixed type		1 (13%)	
#Duodenum	(48)	(8)	(44)
Malignant lymphoma, mixed type			1 (2%)
#Jejunum	(48)	(8)	(44)
Malignant lymphoma, mixed type		1 (13%)	
#Uterus	(50)	(40)	(50)
Malignant lymphoma, histiocytic type		1 (3%)	
CIRCULATORY SYSTEM			
*Abdominal cavity	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
#Liver	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
*Mesentery	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Urinary bladder	(48)	(3)	(47)
Hemangioma	1 (2%)		
#Ovary	(47)	(50)	(50)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	2 (4%)	1 (2%)	1 (2%)
Hepatocellular carcinoma	1 (2%)	2 (4%)	
#Glandular stomach	(48)	(9)	(47)
Adenomatous polyp, NOS			1 (2%)

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

	Untreated Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(48)	(9)	(47)
Papilloma, NOS		1 (11%)	2 (4%)
Squamous cell carcinoma		1 (11%)	
URINARY SYSTEM			
#Kidney	(50)	(7)	(50)
Tubular cell adenoma	1 (2%)		
Tubular cell adenocarcinoma			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(49)
Carcinoma, NOS	1 (2%)	2 (4%)	
Adenoma, NOS	9 (18%)	5 (10%)	2 (4%)
Sarcoma, NOS	1 (2%)		
#Adrenal	(49)	(6)	(48)
Sarcoma, NOS		1 (17%)	
#Adrenal/capsule	(49)	(6)	(48)
Adenoma, NOS			2 (4%)
#Adrenal medulla	(49)	(6)	(48)
Pheochromocytoma	1 (2%)		2 (4%)
#Thyroid	(50)	(4)	(50)
Follicular cell adenoma			2 (4%)
Fibrosarcoma, metastatic		1 (25%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	2 (4%)
#Uterus	(50)	(42)	(50)
Adenocarcinoma, NOS			1 (2%)
Endometrial stromal polyp	3 (6%)	3 (7%)	
#Ovary	(47)	(50)	(50)
Cystadenoma, NOS	2 (4%)	2 (4%)	2 (4%)
Luteoma	2 (4%)	2 (4%)	
Granulosa cell tumor	1 (2%)	4 (8%)	9 (18%)
Tubular adenoma		2 (4%)	
Mixed tumor, benign		17 (34%)	20 (40%)
Teratoma, NOS			1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Eyelid	(50)	(50)	(50)
Papilloma, NOS			1 (2%)
*Harderian gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	3 (6%)	1 (2%)
*Ear	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			

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

	Untreated Control	Low Dose	High Dose
BODY CAVITIES			
*Pleura	(50)	(50)	(50)
Osteosarcoma	1 (2%)		
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	3	6
Moribund sacrifice	7	7	8
Terminal sacrifice	39	40	35
Accidentally killed, nda			1
TUMOR SUMMARY			
Total animals with primary tumors**	36	43	42
Total primary tumors	55	80	72
Total animals with benign tumors	20	29	33
Total benign tumors	24	39	41
Total animals with malignant tumors	24	30	19
Total malignant tumors	30	36	21
Total animals with secondary tumors##	1	2	
Total secondary tumors	1	2	
Total animals with tumors uncertain--benign or malignant	1	5	10
Total uncertain tumors	1	5	10

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF NITROFURAZONE: UNTREATED CONTROL

ANIMAL NUMBER	121	131	118	130	116	115	141	108	112	139	104	101	102	103	105	106	107	109	110	111	113	114	117	119	120
WEEKS ON STUDY	056	085	086	090	091	093	094	096	098	098	101	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X					
Alveolar/bronchiolar carcinoma						X																			
Osteosarcoma, metastatic																			X						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type														X											
Malignant lymphoma, mixed type																									X
Lymph nodes	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	−	+	+	+	−	−	−	−	+	+	+	+	+	−	+	+	+	+	+	−	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																X					X				
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	N	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS						X																			
Adenoma, NOS								X								X				X					X
Sarcoma, NOS																									
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma							X																		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	+	−	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																						X	X		
Ovary	−	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS							X																		
Luteoma																X									
Granulosa cell tumor																									
Hemangioma				X																					
NERVOUS SYSTEM																									
Brain	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																						X			
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																			X						
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																									X
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS	X					X																			
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type			X	X				X	X	X												X		X	

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

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

ANIMAL NUMBER	122	123	124	125	126	127	128	129	132	133	134	135	136	137	138	140	142	143	144	145	146	147	148	149	150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X																		2
Alveolar/bronchiolar carcinoma																										1
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type																				X						2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										2
Hepatocellular carcinoma		X																								1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma															X											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	48
Hemangioma						X																				1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Adenoma, NOS			X								X	X		X		X										9
Sarcoma, NOS																							X			1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	−	+	+	+	+	+	−	−	−	−	−	+	−	+	+	+	+	+	+	+	+	−	+	36
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp										X																3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma, NOS				X																						2
Luteoma	X																									2
Granulosa cell tumor						X																				1
Hemangioma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										2
Malignant lymphoma, lymphocytic type																					X					1
Malignant lymphoma, mixed type		X	X	X			X					X		X			X	X					X			16

* Animals necropsied

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

ANIMAL NUMBER	0010	0042	0050	0025	0004	0001	0005	0047	0014	0017	0002	0003	0006	0007	0008	0009	0011	0012	0013	0015	0016	0018	0019	0020	0021
WEEKS ON STUDY	045	082	090	091	092	095	096	096	100	101	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma				X																					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X							X				X								X		
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type											X														
Lymph nodes	+	+	+	+	−	+	−	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−
Squamous cell carcinoma, metastatic										X															
Thymus	−	+	+	+	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma												X													
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Esophagus	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Papilloma, NOS																					X				
Squamous cell carcinoma																									
Small intestine	+	+	+	+	−	−	−	−	−	+	−	−	+	−	−	−	−	−	+	−	−	−	−	−	−
Malignant lymphoma, mixed type													X												
Large intestine	+	+	+	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−
Urinary bladder	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																						X			
Adenoma, NOS																			X						
Adrenal	+	+	+	+	−	−	−	−	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−
Sarcoma, NOS									X																
Thyroid	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Fibrosarcoma, metastatic				X																					
Parathyroid	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	−	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+
Endometrial stromal polyp			X																						
Malignant lymphoma, histiocytic type												X						X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS																									
Luteoma								X															X		
Granulosa cell tumor																		X							
Tubular adenoma																									
Mixed tumor, benign								X								X			X		X				
NERVOUS SYSTEM																									
Brain	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																							X		
Ear	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma										X															
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma					X																				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, histiocytic type										X															
Malignant lymphoma, mixed type						X	X	X							X						X		X	X	
Plasma cell tumor	X																								

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

ANIMAL NUMBER	022	023	024	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	043	044	045	046	048	049	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma		X																	X							6
Alveolar/bronchiolar carcinoma										X																1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type										X						X										3
Lymph nodes	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	12
Squamous cell carcinoma, metastatic																										1
Thymus	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																X										1
Hepatocellular carcinoma																				X						2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Stomach	–	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	9
Papilloma, NOS																										1
Squamous cell carcinoma														X												1
Small intestine	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Malignant lymphoma, mixed type					X																					2
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
URINARY SYSTEM																										
Kidney	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–		7
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		3
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS	X																									2
Adenoma, NOS						X										X			X		X					5
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
Sarcoma, NOS																										1
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Fibrosarcoma, metastatic																										1
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	*50
Adenocarcinoma, NOS										X																1
Uterus	–	+	–	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Endometrial stromal polyp																						X				3
Malignant lymphoma, histiocytic type																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma, NOS	X																X									2
Luteoma																										2
Granulosa cell tumor									X									X						X		4
Tubular adenoma			X															X								2
Mixed tumor, benign	X		X	X		X	X		X			X		X	X					X	X	X	X			17
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS	X		X																							3
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, histiocytic type								X	X																	3
Malignant lymphoma, mixed type		X		X		X													X					X	X	13
Plasma cell tumor																										1

* Animals necropsied

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

ANIMAL NUMBER	077	054	059	064	078	098	073	076	080	090	092	072	084	088	091	051	052	053	055	056	057	058	060	061	062
WEEKS ON STUDY	010	024	027	040	082	082	086	088	089	094	095	096	096	097	103	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Alveolar/bronchiolar adenoma															X							X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Thymus	+	+	−	+	+	+	−	−	+	+	−	−	−	+	−	+	+	−	+	+	−	+	−	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X																
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	+	+	+	+	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Adematous polyp, NOS																									
Small intestine	−	+	−	+	−	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									X
Large intestine	−	+	−	+	−	+	+	+	−	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma													X												
Urinary bladder	−	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma							X																		
Parathyroid	+	+	+	+	−	+	−	−	−	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	+	+	N	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS					X						X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS																						X			
Granulosa cell tumor								X				X											X		
Mixed tumor, benign														X			X	X	X	X	X			X	X
Teratoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N
Carcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS															X										
Malignant lymphoma, undifferentiated type				X																					
Malignant lymphoma, lymphocytic type										X				X											
Malignant lymphoma, mixed type							X						X				X		X				X	X	

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

ANIMAL NUMBER	063	065	066	067	068	069	070	071	074	075	079	081	082	083	085	086	087	089	093	094	095	096	097	099	100	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Neurilemoma, malignant																				X						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma			X				X		X						X											6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	−	+	+	+	+	+	+	−	−	+	+	−	+	+	−	+	+	+	+	+	−	+	33
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Hemangiosarcoma																					X					1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papilloma, NOS					X								X													2
Adematous polyp, NOS														X												1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Malignant lymphoma, mixed type																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS					X																		X			2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS									X													X				2
Pheochromocytoma														X							X					2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma														X												2
Parathyroid	+	+	+	+	+	+	+	+	+	+	−	−	+	−	+	+	+	+	+	+	+	−	+	+	+	40
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma, NOS						X																				2
Granulosa cell tumor		X					X						X	X			X						X			9
Mixed tumor, benign						X		X	X		X	X			X	X		X	X		X			X	X	20
Teratoma, NOS																		X								1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS																									X	1
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										1
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, lymphocytic type																										2
Malignant lymphoma, mixed type															X			X					X			9

* Animals necropsied

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

	Control	150 ppm	310 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/50 (4%)	6/49 (12%)	6/49 (12%)
Adjusted Rates (b)	5.1%	14.7%	17.1%
Terminal Rates (c)	2/39 (5%)	5/39 (13%)	5/34 (15%)
Week of First Observation	104	91	103
Life Table Tests (d)	P=0.056	P=0.137N	P=0.098
Incidental Tumor Tests (d)	P=0.064	P=0.136	P=0.100
Cochran-Armitage Trend Test (d)	P=0.075		
Fisher Exact Test (d)		P=0.128	P=0.128
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	7/49 (14%)	6/49 (12%)
Adjusted Rates (b)	7.2%	17.2%	17.1%
Terminal Rates (c)	2/39 (5%)	6/39 (15%)	5/34 (15%)
Week of First Observation	93	91	103
Life Table Tests (d)	P=0.133	P=0.163N	P=0.188
Incidental Tumor Tests (d)	P=0.149	P=0.155	P=0.193
Cochran-Armitage Trend Test (d)	P=0.170		
Fisher Exact Test (d)		P=0.151	P=0.233
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	0.0%	9.8%	0.0%
Terminal Rates (c)	0/39 (0%)	3/40 (7%)	0/35 (0%)
Week of First Observation		101	
Life Table Tests (d)	P=0.613	P=0.068	(e)
Incidental Tumor Tests (d)	P=0.621	P=0.061	(e)
Cochran-Armitage Trend Test (d)	P=0.605N		
Fisher Exact Test (d)		P=0.059	(e)
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	18/50 (36%)	18/50 (36%)	10/50 (20%)
Adjusted Rates (b)	40.6%	41.7%	26.5%
Terminal Rates (c)	13/39 (33%)	15/40 (38%)	8/35 (23%)
Week of First Observation	86	95	86
Life Table Tests (d)	P=0.106N	P=0.545N	P=0.123N
Incidental Tumor Tests (d)	P=0.077N	P=0.567	P=0.085N
Cochran-Armitage Trend Test (d)	P=0.050N		
Fisher Exact Test (d)		P=0.583N	P=0.059N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	22/50 (44%)	22/50 (44%)	14/50 (28%)
Adjusted Rates (b)	47.4%	49.9%	33.7%
Terminal Rates (c)	15/39 (38%)	18/40 (45%)	8/35 (23%)
Week of First Observation	56	95	40
Life Table Tests (d)	P=0.148N	P=0.537N	P=0.172N
Incidental Tumor Tests (d)	P=0.093N	P=0.475	P=0.093N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.580N	P=0.072N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	7.1%	2.2%	2.9%
Terminal Rates (c)	2/39 (5%)	0/40 (0%)	1/35 (3%)
Week of First Observation	90	92	104
Life Table Tests (d)	P=0.237N	P=0.300N	P=0.348N
Incidental Tumor Tests (d)	P=0.198N	P=0.297N	P=0.315N
Cochran-Armitage Trend Test (d)	P=0.208N		
Fisher Exact Test (d)		P=0.309N	P=0.309N

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

	Control	150 ppm	310 ppm
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	7.7%	7.5%	2.4%
Terminal Rates (c)	3/39 (8%)	3/40 (7%)	0/35 (0%)
Week of First Observation	104	104	89
Life Table Tests (d)	P=0.274N	P=0.652N	P=0.346N
Incidental Tumor Tests (d)	P=0.257N	P=0.652N	P=0.315N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.661	P=0.309N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	9/50 (18%)	5/50 (10%)	2/49 (4%)
Adjusted Rates (b)	22.4%	12.5%	5.7%
Terminal Rates (c)	8/39 (21%)	5/40 (13%)	2/35 (6%)
Week of First Observation	96	104	104
Life Table Tests (d)	P=0.025N	P=0.180N	P=0.041N
Incidental Tumor Tests (d)	P=0.026N	P=0.187N	P=0.043N
Cochran-Armitage Trend Test (d)	P=0.019N		
Fisher Exact Test (d)		P=0.194N	P=0.028N
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	7/50 (14%)	2/49 (4%)
Adjusted Rates (b)	24.1%	17.5%	5.7%
Terminal Rates (c)	8/39 (21%)	7/40 (18%)	2/35 (6%)
Week of First Observation	93	104	104
Life Table Tests (d)	P=0.019N	P=0.280N	P=0.026N
Incidental Tumor Tests (d)	P=0.019N	P=0.296N	P=0.027N
Cochran-Armitage Trend Test (d)	P=0.013N		
Fisher Exact Test (d)		P=0.298N	P=0.015N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	3/50 (6%)	3/42 (7%)	0/50 (0%)
Adjusted Rates (b)	7.7%	7.8%	0.0%
Terminal Rates (c)	3/39 (8%)	2/34 (6%)	0/35 (0%)
Week of First Observation	104	90	
Life Table Tests (d)	P=0.124N	P=0.610	P=0.141N
Incidental Tumor Tests (d)	P=0.114N	P=0.585	P=0.141N
Cochran-Armitage Trend Test (d)	P=0.105N		
Fisher Exact Test (d)		P=0.575	P=0.121N
Ovary: Granulosa Cell Tumor			
Overall Rates (a)	1/47 (2%)	4/50 (8%)	9/50 (18%)
Adjusted Rates (b)	2.6%	10.0%	23.9%
Terminal Rates (c)	1/39 (3%)	4/40 (10%)	7/35 (20%)
Week of First Observation	104	104	88
Life Table Tests (d)	P=0.003	P=0.187	P=0.007
Incidental Tumor Tests (d)	P=0.004	P=0.187	P=0.009
Cochran-Armitage Trend Test (d)	P=0.006		
Fisher Exact Test (d)		P=0.201	P=0.010
Ovary: Granulosa Cell Tumor or Luteoma			
Overall Rates (a)	3/47 (6%)	6/50 (12%)	9/50 (18%)
Adjusted Rates (b)	7.7%	14.5%	23.9%
Terminal Rates (c)	3/39 (8%)	5/40 (13%)	7/35 (20%)
Week of First Observation	104	96	88
Life Table Tests (d)	P=0.030	P=0.257	P=0.043
Incidental Tumor Tests (d)	P=0.039	P=0.267	P=0.055
Cochran-Armitage Trend Test (d)	P=0.056		
Fisher Exact Test (d)		P=0.275	P=0.075

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

	Control	150 ppm	310 ppm
Ovary: Mixed Tumor, Benign			
Overall Rates (a)	0/47 (0%)	17/50 (34%)	20/50 (40%)
Adjusted Rates (b)	0.0%	41.4%	55.5%
Terminal Rates (c)	0/39 (0%)	16/40 (40%)	19/35 (54%)
Week of First Observation		96	97
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Ovary: Tubular Cell Adenoma or Mixed Tumor, Benign			
Overall Rates (a)	0/47 (0%)	18/50 (36%)	20/50 (40%)
Adjusted Rates (b)	0.0%	43.8%	55.5%
Terminal Rates (c)	0/39 (0%)	17/40 (43%)	19/35 (54%)
Week of First Observation		96	97
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Harderian Gland: Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	2.6%	7.5%	2.9%
Terminal Rates (c)	1/39 (3%)	3/40 (7%)	1/35 (3%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.585	P=0.314	P=0.738
Incidental Tumor Tests (d)	P=0.585	P=0.314	P=0.738
Cochran-Armitage Trend Test (d)	P=0.604N		
Fisher Exact Test (d)		P=0.309	P=0.753
All Sites: Benign Tumors			
Overall Rates (a)	20/50 (40%)	29/50 (58%)	33/50 (66%)
Adjusted Rates (b)	47.3%	67.2%	84.5%
Terminal Rates (c)	17/39 (44%)	26/40 (65%)	29/35 (83%)
Week of First Observation	90	90	86
Life Table Tests (d)	P<0.001	P=0.073	P=0.001
Incidental Tumor Tests (d)	P<0.001	P=0.059	P=0.001
Cochran-Armitage Trend Test (d)	P=0.006		
Fisher Exact Test (d)		P=0.055	P=0.008
All Sites: Malignant Tumors			
Overall Rates (a)	24/50 (48%)	30/50 (60%)	19/50 (38%)
Adjusted Rates (b)	50.7%	63.8%	43.7%
Terminal Rates (c)	16/39 (41%)	23/40 (58%)	11/35 (31%)
Week of First Observation	56	91	40
Life Table Tests (d)	P=0.355N	P=0.229	P=0.381N
Incidental Tumor Tests (d)	P=0.247N	P=0.098	P=0.256N
Cochran-Armitage Trend Test (d)	P=0.175N		
Fisher Exact Test (d)		P=0.158	P=0.210N
All Sites: All Tumors			
Overall Rates (a)	36/50 (72%)	43/50 (86%)	42/50 (84%)
Adjusted Rates (b)	74.9%	87.8%	91.3%
Terminal Rates (c)	27/39 (69%)	34/40 (85%)	31/35 (89%)
Week of First Observation	56	45	40
Life Table Tests (d)	P=0.040	P=0.184	P=0.055
Incidental Tumor Tests (d)	P=0.027	P=0.067	P=0.030
Cochran-Armitage Trend Test (d)	P=0.086		
Fisher Exact Test (d)		P=0.070	P=0.113

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

(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 *incidental tumor test* regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 310-ppm and control groups

TABLE D4a. HISTORICAL INCIDENCE OF OVARIAN TUMORS IN FEMALE B6C3F1$_1$ MICE RECEIVING NO TREATMENT (a)

Study	No. Examined	No. of Tumors	Diagnosis
Historical Incidence at Physiological Research Laboratories			
Ephedrine sulfate	41	0	
Phenylephrine hydrochloride	49	0	
Oxytetracycline hydrochloride	44	2	Cystadenoma, NOS
TOTAL	134	2 (1.5%)	
Overall Historical Incidence			
		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	1,858	8 (0.4%)	Granulosa cell tumor or luteoma
		1 (<0.1%)	Mixed tumor, benign
		4 (0.2%)	Tubular cell adenoma
		32 (1.7%)	All tumors

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

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

Study	Incidence in Controls		
	Adenoma (b)	Carcinoma (c)	Adenoma or Carcinoma (b,c)
Historical Incidence at Physiological Research Laboratories			
Ephedrine sulfate	8/48	2/48	10/48
Phenylephrine hydrochloride	0/48	0/48	0/48
Oxytetracycline hydrochloride	13/50	3/50	16/50
TOTAL	21/146 (14.4%)	5/146 (3.4%)	26/146 (17.8%)
SD (d)	13.17%	3.07%	16.24%
Range (e)			
High	13/50	3/50	16/50
Low	0/48	0/48	0/48
Overall Historical Incidence			
TOTAL	192/1,764 (10.9%)	12/1,764 (0.7%)	204/1,764 (11.6%)
SD (d)	9.47%	1.44%	9.67%
Range (e)			
High	12/40	3/50	16/50
Low	0/48	0/49	0/48

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

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ectopia	2 (4%)		2 (4%)
Epidermal inclusion cyst	1 (2%)		
Ulcer, NOS	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Necrosis, fat		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Dermal inclusion cyst	1 (2%)		
Hemorrhage	2 (4%)		1 (2%)
Inflammation, acute			1 (2%)
*Nasal mucosa	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Multiple cysts	1 (2%)		
Degeneration, hyaline	29 (58%)		16 (32%)
#Lung/bronchus	(50)	(49)	(49)
Hyperplasia, epithelial			1 (2%)
#Lung/bronchiole	(50)	(49)	(49)
Crystals, NOS			1 (2%)
#Lung	(50)	(49)	(49)
Mineralization	2 (4%)		1 (2%)
Congestion, NOS	4 (8%)		2 (4%)
Hemorrhage	3 (6%)	2 (4%)	2 (4%)
Pneumonia, aspiration			1 (2%)
Inflammation, chronic focal	6 (12%)	8 (16%)	6 (12%)
Perivascular cuffing	5 (10%)	2 (4%)	1 (2%)
Calcification, NOS	1 (2%)		
Crystals, NOS		1 (2%)	
Alveolar macrophages	1 (2%)	3 (6%)	3 (6%)
Hyperplasia, adenomatous			1 (2%)
HEMATOPOIETIC SYSTEM			
#Brain/thalamus	(49)	(4)	(50)
Hyperplasia, lymphoid			1 (2%)
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid	9 (18%)		5 (10%)
*Blood	(50)	(50)	(50)
Leukocytosis, NOS	1 (2%)		1 (2%)
#Bone marrow	(50)	(4)	(49)
Fibrosis, focal	1 (2%)		1 (2%)
Atrophy, NOS			1 (2%)
Hyperplasia, NOS	4 (8%)		
Hyperplasia, granulocytic	4 (8%)	2 (50%)	3 (6%)

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

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Spleen	(49)	(50)	(50)
Dilatation, NOS		1 (2%)	
Infarct, healed			1 (2%)
Amyloidosis	1 (2%)		
Hemosiderosis			4 (8%)
Hyperplasia, reticulum cell	3 (6%)	5 (10%)	3 (6%)
Hyperplasia, lymphoid	16 (33%)	24 (48%)	19 (38%)
Hematopoiesis	5 (10%)	7 (14%)	4 (8%)
#Mandibular lymph node	(49)	(12)	(49)
Hyperplasia, lymphoid	2 (4%)		1 (2%)
#Mesenteric lymph node	(49)	(12)	(49)
Angiectasis	2 (4%)	1 (8%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)		1 (2%)
#Renal lymph node	(49)	(12)	(49)
Hyperplasia, lymphoid	1 (2%)		
#Lung	(50)	(49)	(49)
Leukocytosis, NOS			1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)
#Salivary gland	(49)	(5)	(49)
Hyperplasia, lymphoid	3 (6%)		
#Liver	(50)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	6 (12%)
Hematopoiesis	1 (2%)	3 (6%)	
#Pancreas	(48)	(4)	(48)
Hyperplasia, lymphoid			1 (2%)
#Stomach	(48)	(9)	(47)
Hyperplasia, lymphoid		1 (11%)	
#Cecum	(49)	(6)	(44)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
#Kidney	(50)	(7)	(50)
Hyperplasia, lymphoid	2 (4%)	1 (14%)	9 (18%)
#Urinary bladder	(48)	(3)	(47)
Hyperplasia, lymphoid	3 (6%)		7 (15%)
#Thymus	(37)	(5)	(33)
Cyst, NOS	2 (5%)		1 (3%)
Multiple cysts	2 (5%)		1 (3%)
Hemorrhage	1 (3%)		
Atrophy, NOS	2 (5%)		
Angiectasis	1 (3%)		
Hyperplasia, lymphoid	4 (11%)		1 (3%)
CIRCULATORY SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Perivasculitis			1 (2%)
#Heart	(50)	(4)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Myocardium	(50)	(4)	(50)
Fibrosis, focal	1 (2%)		
Calcification, NOS	3 (6%)		1 (2%)
*Pulmonary vein	(50)	(50)	(50)
Mineralization	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Dysplasia, NOS			1 (2%)
#Salivary gland	(49)	(5)	(49)
Degeneration, NOS	1 (2%)		
#Liver	(50)	(50)	(50)
Hemorrhage	1 (2%)		2 (4%)
Fibrosis, focal	1 (2%)		
Necrosis, focal	5 (10%)	11 (22%)	12 (24%)
Necrosis, cytodegenerative			1 (2%)
Necrosis, coagulative	2 (4%)	1 (2%)	1 (2%)
Metamorphosis, fatty	1 (2%)	2 (4%)	3 (6%)
Basophilic cyto change	1 (2%)	1 (2%)	1 (2%)
Clear cell change			1 (2%)
Hepatocytomegaly			1 (2%)
Angiectasis	1 (2%)		1 (2%)
#Hepatic capsule	(50)	(50)	(50)
Calcification, NOS		1 (2%)	1 (2%)
#Liver/centrilobular	(50)	(50)	(50)
Pigmentation, NOS		1 (2%)	
Cytoplasmic vacuolization	1 (2%)		
#Liver/Kupffer cell	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)		2 (4%)
*Gallbladder	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Degeneration, hyaline			1 (2%)
#Pancreas	(48)	(4)	(48)
Cyst, NOS	1 (2%)		1 (2%)
Inflammation, acute		1 (25%)	
Inflammation, chronic focal	2 (4%)		
Fibrosis, focal	1 (2%)		
Atrophy, NOS	2 (4%)		4 (8%)
#Pancreatic duct	(48)	(4)	(48)
Multiple cysts			1 (2%)
#Pancreatic acinus	(48)	(4)	(48)
Cytoplasmic vacuolization	3 (6%)		6 (13%)
#Esophageal submucosa	(50)	(4)	(50)
Inflammation, chronic focal	1 (2%)		
#Stomach	(48)	(9)	(47)
Inflammation, acute		1 (11%)	
#Gastric mucosa	(48)	(9)	(47)
Calcification, NOS			1 (2%)
#Glandular stomach	(48)	(9)	(47)
Cyst, NOS	1 (2%)		
Multiple cysts	3 (6%)		5 (11%)
Inflammation, acute/chronic	2 (4%)		
Inflammation, chronic focal	2 (4%)		
Calcification, NOS	3 (6%)		
Hyperplasia, epithelial	1 (2%)		
Dysplasia, NOS	1 (2%)		
#Forestomach	(48)	(9)	(47)
Mineralization			1 (2%)
Inflammation, acute/chronic		2 (22%)	1 (2%)
Hyperplasia, epithelial	1 (2%)	2 (22%)	
Hyperkeratosis		1 (11%)	

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

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(7)	(50)
Mineralization	2 (4%)		3 (6%)
Cyst, NOS	1 (2%)		1 (2%)
Inflammation, suppurative			1 (2%)
Glomerulonephritis, chronic	1 (2%)		
Nephropathy	7 (14%)		10 (20%)
Nephrosis, NOS		1 (14%)	
Nephrosis, toxic		1 (14%)	
Amyloidosis			1 (2%)
#Perirenal tissue	(50)	(7)	(50)
Hemorrhage	1 (2%)		
#Kidney/glomerulus	(50)	(7)	(50)
Amyloidosis			1 (2%)
#Convoluted tubules	(50)	(7)	(50)
Dilatation, NOS		1 (14%)	1 (2%)
Degeneration, hyaline	1 (2%)	1 (14%)	
Necrosis, focal			1 (2%)
Metamorphosis, fatty		1 (14%)	
#Kidney/pelvis	(50)	(7)	(50)
Mineralization			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary	(50)	(50)	(49)
Hemorrhage			1 (2%)
#Pituitary intermedia	(50)	(50)	(49)
Hyperplasia, focal	1 (2%)		
#Anterior pituitary	(50)	(50)	(49)
Cyst, NOS			1 (2%)
Multiple cysts	2 (4%)		
Focal cellular change			1 (2%)
Hyperplasia, focal	8 (16%)	4 (8%)	8 (16%)
Angiectasis		1 (2%)	
#Adrenal/capsule	(49)	(6)	(48)
Hyperplasia, stromal	46 (94%)	5 (83%)	42 (88%)
#Adrenal cortex	(49)	(6)	(48)
Ectopia	1 (2%)		2 (4%)
Degeneration, lipoid	1 (2%)		
Hypertrophy, focal	1 (2%)	1 (17%)	2 (4%)
Hyperplasia, focal	1 (2%)		1 (2%)
Angiectasis	1 (2%)		
#Adrenal medulla	(49)	(6)	(48)
Hyperplasia, focal	3 (6%)		1 (2%)
#Thyroid	(50)	(4)	(50)
Multiple cysts			1 (2%)
Granuloma, NOS	1 (2%)		
Inflammation, pyogranulomatous			1 (2%)
Hyperplasia, follicular cell	2 (4%)		1 (2%)
#Parathyroid	(36)	(2)	(40)
Multiple cysts			1 (3%)
#Pancreatic islets	(48)	(4)	(48)
Hyperplasia, focal	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	1 (2%)	1 (2%)	2 (4%)
Cyst, NOS			1 (2%)
*Clitoral gland	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
Metaplasia, squamous		1 (2%)	
#Uterus	(50)	(42)	(50)
Dilatation, NOS	1 (2%)	2 (5%)	2 (4%)
#Uterus/endometrium	(50)	(42)	(50)
Multiple cysts	3 (6%)	1 (2%)	1 (2%)
Inflammation, suppurative			1 (2%)
Inflammation, acute/chronic			1 (2%)
Hyperplasia, cystic	44 (88%)	36 (86%)	44 (88%)
Hyperplasia, stromal	1 (2%)		
Angiectasis		2 (5%)	2 (4%)
Metaplasia, squamous	1 (2%)		
#Fallopian tube	(50)	(40)	(50)
Multiple cysts			1 (2%)
#Ovary	(47)	(50)	(50)
Cyst, NOS	13 (28%)	11 (22%)	7 (14%)
Multiple cysts	3 (6%)	3 (6%)	3 (6%)
Hemorrhagic cyst	10 (21%)	1 (2%)	
Inflammation, acute		1 (2%)	
Abscess, NOS	1 (2%)	1 (2%)	
Calcification, NOS	6 (13%)	4 (8%)	3 (6%)
Atrophy, NOS	7 (15%)	44 (88%)	38 (76%)
Hyperplasia, tubular cell	1 (2%)	23 (46%)	21 (42%)
Hyperplasia, granulosa cell	1 (2%)		1 (2%)
Angiectasis		2 (4%)	1 (2%)
#Germinal epithelium	(47)	(50)	(50)
Hyperplasia, NOS		3 (6%)	
#Mesovarium	(47)	(50)	(50)
Necrosis, fat		1 (2%)	
NERVOUS SYSTEM			
*Nerve tract	(50)	(50)	(50)
Demyelinization		1 (2%)	
*Choroid plexus	(50)	(50)	(50)
Calcification, NOS			1 (2%)
#Brain	(49)	(4)	(50)
Hemorrhage			2 (4%)
Perivascular cuffing	1 (2%)		
#Brain/thalamus	(49)	(4)	(50)
Calcification, NOS	25 (51%)	1 (25%)	25 (50%)
Cell shape alteration	1 (2%)		
#Cerebellum	(49)	(4)	(50)
Hemorrhage	1 (2%)		
SPECIAL SENSE ORGANS			
*Nasolacrimal duct	(50)	(50)	(50)
Cyst, NOS	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Malocclusion	1 (2%)		
Fibrous osteodystrophy	1 (2%)		
Osteosclerosis	13 (26%)		17 (34%)
BODY CAVITIES			
*Pericardium	(50)	(50)	(50)
Mineralization	1 (2%)		
*Epicardium	(50)	(50)	(50)
Mineralization			1 (2%)
*Mesentery	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Perivascular cuffing	1 (2%)		
Necrosis, fat		1 (2%)	
ALL OTHER SYSTEMS			
Knee			
Dyschondroplasia	6		6
Adipose tissue			
Inflammation, acute		1	
Necrosis, fat	1	3	2
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX E

GENETIC TOXICOLOGY OF NITROFURAZONE

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

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	85 ± 3.7	150 ± 0.3	99 ± 13.0	133 ± 5.0	110 ± 9.9	128 ± 3.5
	0.03	--	171 ± 8.5	--	--	--	--
	0.10	163 ± 12.2	212 ± 5.0	--	175 ± 5.5	--	164 ± 6.9
	0.30	383 ± 20.1	344 ± 34.1	--	241 ± 16.2	--	204 ± 16.1
	1	1,091 ± 43.2	902 ± 28.8	302 ± 16.1	406 ± 6.6	253 ± 9.1	297 ± 3.8
	3	1,791 ± 26.0	1,650 ± 85.8	650 ± 103.5	787 ± 51.1	419 ± 7.5	555 ± 37.1
	10	(c) 257 ± 53.7	--	1,239 ± 106.0	1,418 ± 38.5	868 ± 30.9	1,008 ± 19.6
	33	--	--	(c) 58 ± 21.8	--	1,242 ± 71.3	--
	100	--	--	Toxic	--	(c) 101 ± 27.2	--
	Trial summary	Positive	Positive	Positive	Positive	Positive	Positive
	Positive control (d)	233 ± 6.2	507 ± 0.3	2,649 ± 40.4	1,901 ± 61.3	1,938 ± 66.0	820 ± 32.1
TA1535	0	5 ± 0.3	24 ± 1.5	5 ± 0.0	8 ± 2.0	9 ± 2.3	10 ± 2.2
	0.10	10 ± 2.8	--	--	--	--	--
	0.30	11 ± 3.4	18 ± 3.1	--	--	--	--
	1	16 ± 1.9	19 ± 0.3	6 ± 1.2	14 ± 0.9	8 ± 0.6	--
	1.6	--	23 ± 4.0	--	--	--	--
	3	34 ± 2.4	29 ± 2.2	9 ± 3.0	17 ± 2.2	10 ± 3.0	13 ± 2.3
	6	--	37 ± 3.5	--	23 ± 2.7	--	--
	10	(c) 24 ± 3.2	--	25 ± 4.4	31 ± 1.9	13 ± 2.7	17 ± 1.2
	16	--	--	--	38 ± 11.1	--	20 ± 4.7
	33	--	--	(c) 3 ± 3.0	--	23 ± 3.8	26 ± 2.8
	66	--	--	--	--	--	45 ± 4.4
	100	--	--	Toxic	--	(c) 24 ± 2.2	--
	Trial summary	Positive	Negative	Equivocal	Positive	Equivocal	Positive
	Positive control (d)	154 ± 2.8	407 ± 1.2	530 ± 29.1	464 ± 22.8	542 ± 39.0	506 ± 17.9
TA1537	0	3 ± 0.6	6 ± 1.0	5 ± 1.2	7 ± 0.9	4 ± 0.6	5 ± 0.7
	0.10	5 ± 1.9	--	--	--	--	--
	0.30	5 ± 1.2	8 ± 1.9	--	--	--	--
	1	6 ± 2.4	4 ± 0.3	5 ± 1.2	6 ± 1.2	5 ± 0.9	--
	1.6	--	8 ± 3.2	--	--	--	--
	3	17 ± 2.4	7 ± 0.6	4 ± 0.3	13 ± 2.6	3 ± 0.3	6 ± 0.6
	6	--	16 ± 0.6	--	11 ± 1.5	--	--
	10	(c) 3 ± 0.0	--	12 ± 2.6	10 ± 2.0	6 ± 1.0	15 ± 3.8
	16	--	--	--	22 ± 3.1	--	11 ± 2.5
	33	--	--	(c) 5 ± 4.0	--	20 ± 0.9	11 ± 2.2
	66	--	--	--	--	--	9 ± 2.3
	100	--	--	Toxic	--	(c) 3 ± 0.9	--
	Trial summary	Equivocal	Negative	Negative	Equivocal	Negative	Negative
	Positive control (d)	216 ± 54.9	106 ± 16.8	89 ± 8.9	479 ± 40.9	231 ± 3.2	356 ± 8.3
TA98	0	25 ± 4.2	22 ± 2.1	29 ± 3.5	28 ± 2.1	25 ± 2.6	29 ± 2.3
	0.10	21 ± 3.4	--	--	--	--	--
	0.30	23 ± 4.3	24 ± 4.0	--	--	--	--
	1	35 ± 2.7	24 ± 4.0	27 ± 6.0	32 ± 7.8	25 ± 2.0	--
	1.6	--	32 ± 4.7	--	--	--	--
	3	80 ± 2.3	58 ± 2.3	34 ± 2.9	46 ± 3.0	24 ± 1.7	31 ± 3.5
	6	--	126 ± 10.1	--	53 ± 5.2	--	--
	10	96 ± 14.0	--	63 ± 5.5	76 ± 2.6	40 ± 5.6	42 ± 5.5
	16	--	--	--	104 ± 1.3	--	64 ± 0.3
	33	--	--	(c) 20 ± 7.5	--	83 ± 7.2	103 ± 7.8
	66	--	--	--	--	--	131 ± 2.1
	100	--	--	Toxic	--	(c) 17 ± 4.6	--
	Trial summary	Positive	Positive	Positive	Positive	Positive	Positive
	Positive control (d)	619 ± 20.5	943 ± 78.7	2,152 ± 45.1	1,551 ±162.2	1,465 ± 18.5	612 ± 9.1

TABLE E1. MUTAGENICITY OF NITROFURAZONE IN *SALMONELLA TYPHIMURIUM* (Continued)

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

TABLE E2. MUTAGENICITY OF NITROFURAZONE 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)	--	86.5 ± 3.9	99.8 ± 6.1	136.0 ± 7.1	52.8 ± 3.6
Nitrofurazone	25	61.3 ± 4.1	61.0 ± 8.1	62.3 ± 2.7	34.0 ± 3.8
	50	88.7 ± 10.5	58.0 ± 2.1	104.7 ± 3.5	40.3 ± 4.1
	(e) 100	91.5 ± 9.5	40.0 ± 2.0	171.5 ± 26.5	62.5 ± 3.5
	150	81.0 ± 7.1	34.0 ± 4.0	235.7 ± 12.0	(f) 98.7 ± 10.7
	200	77.3 ± 2.8	28.3 ± 0.9	294.0 ± 9.0	(f) 127.3 ± 7.2
	300	49.3 ± 9.8	5.3 ± 2.0	460.0 ± 51.6	(f) 323.0 ± 36.5
Methyl methanesulfonate	5 nl/ml	66.3 ± 3.9	58.3 ± 5.2	582.0 ± 23.1	(f) 294.7 ± 21.9
Trial 2					
Dimethyl sulfoxide (d)	--	85.0 ± 4.6	100.3 ± 1.3	72.3 ± 1.4	28.5 ± 1.6
Nitrofurazone	25	74.7 ± 0.9	57.3 ± 7.3	82.3 ± 7.7	37.0 ± 3.2
	50	72.3 ± 5.2	43.3 ± 3.2	100.0 ± 3.1	(f) 46.3 ± 2.7
	100	96.0 ± 11.7	38.3 ± 1.2	189.7 ± 41.7	(f) 64.7 ± 6.7
	200	73.7 ± 3.4	14.3 ± 5.8	349.7 ± 47.4	(f) 160.0 ± 24.5
	(g) 300	48	4	352	247
	400	Lethal	--	--	--
Methyl methanesulfonate	5	81.3 ± 5.9	67.3 ± 9.8	312.0 ± 39.5	(f) 128.3 ± 13.6

(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 (unless otherwise specified) 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.

(b) Mean ± standard error of replicate trials for approximately 3×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered mutagenic. If only one of these responses is significant, the call is "questionable"; 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) Results presented are the average of four tests.

(e) Results presented are the average of two tests.

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

(g) Data presented are the results of one test; doses were lethal in two tests.

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

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
-S9 (c)								
Trial 1--Summary: Positive								
Dimethyl sulfoxide	--	50	1,048	554	0.53	11.1	26.0	--
Nitrofurazone	0.25	50	1,049	667	0.64	13.3	26.0	119.8
	0.83	50	1,043	717	0.69	14.3	26.0	128.8
	2.50	50	1,048	713	0.68	14.3	26.0	128.8
	8.33	0	--	--	--	--	26.0	--
Mitomycin C	0.001	50	1,048	810	0.77	16.2	26.0	145.9
	0.010	5	105	249	2.37	49.8	26.0	448.6
Trial 2--Summary: Positive								
Dimethyl sulfoxide	--	50	1,048	544	0.52	10.9	26.0	--
Nitrofurazone	10	50	1,049	864	0.82	17.3	(d) 34.3	158.7
	12.5	50	1,046	1,033	0.99	20.7	(d) 34.3	189.9
	15	50	1,047	1,052	1.00	21.0	(d) 34.3	192.7
Mitomycin C	0.001	50	1,047	844	0.81	16.9	26.0	155.0
	0.010	5	105	309	2.94	61.8	26.0	567.0
+S9 (e)								
Trial 1--Summary: Positive								
Dimethyl sulfoxide	--	50	1,040	497	0.48	9.9	26.0	--
Nitrofurazone	25	50	1,043	558	0.53	11.2	26.0	113.1
	83.3	50	1,047	610	0.58	12.2	26.0	123.2
	250	50	1,045	697	0.67	13.9	26.0	140.4
	833	0	--	--	--	--	26.0	--
Cyclophosphamide	0.4	50	1,047	732	0.70	14.6	26.0	147.5
	2	5	105	158	1.50	31.6	26.0	319.2

(a) Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) 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 NITROFURAZONE (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)					**−S9 (b)**				
Dimethyl sulfoxide					Dimethyl sulfoxide				
--	100	3	0.03	3	--	100	2	0.02	2
Nitrofurazone					Nitrofurazone				
20	100	3	0.03	3	25	100	19	0.19	17
23	100	21	0.21	17	30	100	22	0.22	19
25	25	13	0.52	24	40	50	56	1.12	44
30	25	9	0.36	28					
Summary: Positive					Summary: Positive				
Mitomycin C					Mitomycin C				
0.040	100	16	0.16	14	0.040	100	33	0.33	24
0.063	100	31	0.31	21	0.063	25	14	0.56	40
+S9 (c)									
Dimethylsulfoxide									
--	100	0	0.00	0					
Nitrofurazone									
300	100	5	0.05	4					
400	100	5	0.05	5					
500	100	4	0.04	2					
600	0								
Summary: Negative									
Cyclophosphamide									
3.80	100	5	0.05	5					
12.50	25	7	0.28	16					

(a) Study performed at Litton Bionetics, Inc. Abs = aberrations. Harvest time--18.5 hours; because of chemical-induced cell cycle delay, incubation time before addition of colcemid was lengthened to provide sufficient metaphases at harvest. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) 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.

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

I. Methods

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

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests are 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, 18, 24 mo)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (12 mo)	MHV (mouse hepatitis virus) *M. pul.* (*Mycoplasma pulmonis*)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6, 18, 24 mo)	RCV (rat coronavirus) (6, 12, 18 mo)	RCV (24 mo) Sendai (12 mo) *M. pul.*

II. Results

Results are presented in Table F1.

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

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	10/10	PVM
	10/10	Sendai
12	10/10	Sendai
18	10/10	PVM
	9/10	Sendai
24	10/10	PVM
	6/10	Sendai
	4/10	(b) *M. pul.*
MICE		
6	5/10	PVM
	6/10	Sendai
12	2/10	PVM
	8/9	Sendai
18	9/9	PVM
	8/9	Sendai
24	5/10	PVM
	10/10	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 determination of antibody titers.
(b) Further evaluation of this assay indicated that it was not specific for *M. pulmonis*, and these results were considered to be false positive.

APPENDIX G

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

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

	Control		Low Dose				High Dose			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
4	16.9	231	15.9	227	0.9	22	14.8	220	0.9	42
8	14.3	291	14.7	292	1.0	16	14.4	278	1.0	32
12	16.6	326	12.6	328	0.8	12	12.4	308	0.7	25
17	15.8	361	15.2	357	1.0	13	15.0	334	0.9	28
21	14.5	386	14.6	372	1.0	12	14.1	355	1.0	25
25	15.9	401	15.6	387	1.0	12	15.2	365	1.0	26
30	14.1	410	13.6	396	1.0	11	13.5	370	1.0	23
34	14.5	416	14.5	405	1.0	11	14.2	376	1.0	23
39	15.1	428	13.9	412	0.9	10	13.7	377	0.9	23
43	15.2	438	14.0	417	0.9	10	13.9	385	0.9	22
47	15.1	437	13.3	412	0.9	10	13.6	381	0.9	22
52	13.9	440	13.9	415	1.0	10	12.5	378	0.9	21
56	13.7	439	16.4	414	1.2	12	13.7	380	1.0	22
61	14.2	438	14.6	419	1.0	11	12.6	376	0.9	21
66	14.8	441	13.7	422	0.9	10	13.3	381	0.9	22
70	14.8	441	13.9	419	0.9	10	13.0	377	0.9	21
74	13.8	441	12.8	412	0.9	10	12.4	374	0.9	21
78	14.5	441	13.7	417	0.9	10	12.8	370	0.9	21
82	13.9	445	13.1	422	0.9	10	11.7	369	0.8	20
87	13.0	433	12.0	410	0.9	9	11.2	353	0.9	20
91	13.2	427	12.5	407	0.9	10	11.1	346	0.8	20
96	13.4	429	13.2	407	1.0	10	13.1	340	1.0	24
100	13.7	431	12.9	404	0.9	10	10.4	323	0.8	20
Mean	14.6	407	13.9	390	1.0	11	13.2	353	0.9	24
SD (d)	1.0		1.1		0.1	3	1.3		0.1	5
CV (e)	6.8		7.9		10.0	27.3	9.8		11.1	20.8

(a) Grams of feed removed from feed per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of nitrofurazone consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

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

	Control		Low Dose				High Dose			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
4	10.9	162	10.0	158	0.9	20	10.9	156	1.0	43
8	9.8	179	9.4	175	1.0	17	9.4	171	1.0	34
12	8.1	190	7.6	187	0.9	13	7.3	180	0.9	25
17	10.4	204	9.9	198	1.0	16	9.8	190	0.9	32
21	9.9	218	9.2	208	0.9	14	9.0	199	0.9	28
25	9.8	222	9.6	213	1.0	14	9.4	204	1.0	29
30	9.8	229	9.2	218	0.9	13	9.1	209	0.9	27
34	9.8	234	8.9	223	0.9	12	9.1	213	0.9	26
39	10.1	239	9.2	227	0.9	13	8.8	217	0.9	25
43	9.7	246	8.4	233	0.9	11	8.3	223	0.9	23
47	10.8	253	10.1	239	0.9	13	9.8	226	0.9	27
52	10.5	263	10.2	250	1.0	13	9.6	233	0.9	26
56	11.0	269	10.5	255	1.0	13	9.8	235	0.9	26
61	9.4	280	10.0	265	1.1	12	9.6	242	1.0	25
66	11.1	290	9.7	273	0.9	11	9.9	246	0.9	25
70	11.3	293	10.5	278	0.9	12	10.0	247	0.9	25
74	11.6	302	9.7	285	0.8	11	9.8	253	0.8	24
78	11.2	313	10.0	290	0.9	11	9.3	253	0.8	23
82	11.0	318	10.4	298	0.9	11	9.5	261	0.9	23
87	10.8	319	10.1	302	0.9	10	9.1	262	0.8	22
91	11.0	325	9.5	301	0.9	10	10.6	263	1.0	25
96	11.0	329	9.9	304	0.9	10	9.2	264	0.8	22
100	11.1	333	9.5	304	0.9	10	8.9	265	0.8	21
Mean	10.4	261	9.6	247	0.9	12	9.4	227	0.9	26
SD (d)	0.8		0.7		0.0	2	0.7		0.1	5
CV (e)	7.7		7.3		0.0	16.7	7.4		11.1	19.2

(a) Grams of feed removed from feed per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of nitrofurazone consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

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

Week	Control		Low Dose				High Dose			
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
6	3.4	28.7	3.5	29.0	1.0	18	3.6	29.2	1.1	38
10	3.6	30.3	3.6	30.7	1.0	18	2.8	30.8	0.8	28
20	4.1	33.0	3.9	33.1	1.0	18	4.4	33.1	1.1	41
23	3.8	34.3	5.0	34.3	1.3	22	6.3	35.2	1.7	55
28	4.0	35.9	3.9	35.7	1.0	16	4.2	36.8	1.1	35
33	4.0	36.4	4.0	35.8	1.0	17	4.0	37.0	1.0	34
37	3.8	37.3	3.7	36.4	1.0	15	4.0	38.2	1.1	32
42	3.6	37.1	3.7	36.4	1.0	15	3.8	38.3	1.1	31
46	4.1	38.6	3.8	38.1	0.9	15	4.2	39.6	1.0	33
49	3.9	38.3	4.3	38.8	1.1	17	3.7	40.4	0.9	28
54	3.8	39.2	3.8	38.8	1.0	15	3.9	39.5	1.0	31
58	3.7	39.0	3.7	39.1	1.0	14	3.9	39.9	1.1	30
64	5.0	38.7	3.5	38.7	0.7	14	3.8	40.0	0.8	29
68	3.6	38.3	4.1	38.6	1.1	16	4.4	39.1	1.2	35
72	3.9	37.9	3.8	39.0	1.0	15	3.9	40.2	1.0	30
77	3.8	39.1	3.7	39.6	1.0	14	4.0	40.2	1.1	31
80	3.9	38.9	3.5	39.0	0.9	13	3.5	39.2	0.9	28
84	3.7	39.9	3.7	39.2	1.0	14	3.6	40.0	1.0	28
89	3.6	37.1	3.7	37.6	1.0	15	3.9	38.0	1.1	32
93	3.8	38.5	3.4	37.7	0.9	14	3.9	37.6	1.0	32
98	3.7	39.1	3.4	36.7	0.9	14	3.8	38.2	1.0	31
102	3.7	39.4	3.5	37.6	0.9	14	3.9	38.6	1.1	31
Mean	3.8	37.0	3.8	36.8	1.0	16	4.0	37.7	1.0	33
SD (d)	0.3		0.4		0.1	2	0.6		0.2	6
CV (e)	7.9		10.5		10.0	12.5	15.0		20.0	18.2

(a) Grams of feed removed from feed per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of nitrofurazone consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

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

	Control		Low Dose				High Dose			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
6	3.3	22.6	2.9	22.8	0.9	19	3.3	22.5	1.0	45
10	2.9	23.4	3.1	24.5	1.1	19	2.8	23.9	1.0	36
20	3.2	27.3	3.1	27.1	1.0	17	3.3	26.5	1.0	39
23	3.2	28.6	3.3	28.1	1.0	18	3.4	27.7	1.1	38
28	3.5	31.0	3.4	29.6	1.0	17	3.5	29.4	1.0	37
33	3.3	31.1	3.4	29.8	1.0	17	3.4	29.4	1.0	36
37	3.2	32.3	3.2	30.7	1.0	16	3.1	31.4	1.0	31
42	3.5	33.6	3.3	32.6	0.9	15	3.3	32.8	0.9	31
46	3.7	34.9	3.6	32.8	1.0	16	3.5	34.1	0.9	32
49	3.6	35.7	3.5	34.8	1.0	15	3.4	35.9	0.9	29
54	3.3	37.1	2.8	35.7	0.8	12	3.2	37.2	1.0	27
58	3.5	37.3	3.3	36.6	0.9	14	3.3	38.4	0.9	27
64	3.7	37.9	3.7	37.4	1.0	15	3.5	39.7	0.9	27
68	3.9	38.2	3.5	38.6	0.9	14	3.5	40.5	0.9	27
72	3.1	39.0	3.7	39.3	1.2	14	3.2	41.5	1.0	24
77	3.4	39.6	3.5	41.1	1.0	13	3.3	42.1	1.0	24
80	3.1	39.2	3.0	41.5	1.0	11	2.9	42.3	0.9	21
84	3.2	40.4	2.9	42.1	0.9	10	3.1	43.5	1.0	22
89	3.3	39.6	3.1	41.3	0.9	11	3.0	41.9	0.9	22
93	3.7	40.3	3.2	41.8	0.9	11	3.4	42.5	0.9	25
98	3.8	41.7	3.2	42.5	0.8	11	3.4	44.1	0.9	24
102	3.9	42.7	3.3	43.0	0.8	12	3.2	43.5	0.8	23
Mean	3.4	35.2	3.3	35.2	1.0	14	3.3	35.9	1.0	29
SD (d)	0.3		0.3		0.1	3	0.2		0.1	7
CV (e)	8.8		9.1		10.0	21.4	6.1		10.0	24.1

(a) Grams of feed removed from feed per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of nitrofurazone consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX H

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

Meal Diet: June 1981 to July 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) NIH, 1978; NCI, 1976
(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	No. of Samples
Crude protein (percent by weight)	23.97 ± 1.16	21.7-26.3	27
Crude fat (percent by weight)	5.00 ± 0.46	4.2-6.0	27
Crude fiber (percent by weight)	3.38 ± 0.36	2.4-4.2	27
Ash (percent by weight)	6.56 ± 0.27	5.97-7.11	27
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)	12,163 ± 3,045	7,800-22,000	27
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	1.82 ± 0.34	1.2-2.6	(b) 26
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)	1.24 ± 0.10	1.10-1.45	27
Phosphorus (percent)	0.97 ± 0.05	0.84-1.1	27
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	No. of Samples
Arsenic (ppm)	0.48 ± 0.13	0.21-0.74	27
Cadmium (ppm) (a)	<0.01	<0.01-0.01	27
Lead (ppm)	0.91 ± 0.75	0.27-2.93	27
Mercury (ppm) (a)	<0.05		27
Selenium (ppm)	0.28 ± 0.06	0.16-0.40	27
Aflatoxins (ppb) (b)	<5	<5.0-<10.0	27
Nitrate nitrogen (ppm) (c)	9.97 ± 4.64	0.6-19.0	27
Nitrite nitrogen (ppm) (c)	1.99 ± 1.23	0.4-5.3	27
BHA (ppm) (d)	5.42 ± 4.94	<2.0-20.0	27
BHT (ppm) (d)	3.19 ± 2.52	<1.0-13.0	27
Aerobic plate count (CFU/g) (e)	110,956 ± 82,794	7,000-310,000	25
Aerobic plate count (CFU/g) (f)	133,848 ± 114,587	7,000-420,000	27
Coliform (MPN/g) (g)	931.1 ± 973.4	<3->2,400	27
E. coli (MPN/g) (h)	6.89 ± 7.46	<3-23	26
E. coli (MPN/g) (i)	12.15 ± 28.51	<3-150	27
Total nitrosamines (ppb) (j)	3.73 ± 3.26	0.9-12.9	27
N-Nitrosodimethylamine (ppb) (j)	2.93 ± 2.89	0.7-12.9	27
N-Nitrosopyrrolidine (ppb) (k)	1.24 ± 0.60	<0.9-3.2	24
Pesticides (ppm)			
α-BHC (a,l)	<0.01		27
β-BHC (a)	<0.02		27
γ-BHC-Lindane (a)	<0.01		27
δ-BHC (a)	<0.01		27
Heptachlor (a)	<0.01		27
Aldrin (a)	<0.01		27
Heptachlor epoxide (a)	<0.01		27
DDE (a)	<0.01		27
DDD (m)	<0.01	0.05 (7/14/81)	27
DDT (a)	<0.01		27
HCB (a)	<0.01		27
Mirex (a)	<0.01		27
Methoxychlor (n)	<0.05	0.13 (8/25/81); 0.6 (6/24/82)	27
Dieldrin (m)	<0.01	0.02 (7/27/82)	27
Endrin (a)	<0.01		27
Telodrin (a)	<0.01		27
Chlordane (a)	<0.05		27
Toxaphene (a)	<0.1		27
Estimated PCBs (a)	<0.2		27
Ronnel (a)	<0.01		27
Ethion (a)	<0.02		27
Trithion (a)	<0.05		27
Diazinon (a)	<0.1		27
Methyl parathion (a)	<0.02		27
Ethyl parathion (a)	<0.02		27
Malathion (o)	0.10 ± 0.07	<0.05-0.34	27
Endosulfan I (a,p)	<0.01		25
Endosulfan II (a,p)	<0.01		25
Endosulfan sulfate (a,p)	<0.03		25

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) Mean, standard deviation, and range exclude the very high value of 420,000 obtained for the batches produced on 3/23/83 and 7/12/83; CFU = colony-forming unit.
(f) Mean, standard deviation, and range include the very high value given in footnote (e).
(g) MPN = most probable number
(h) Mean, standard deviation, and range exclude the high value of 150 obtained for the batch produced on 8/26/82.
(i) Mean, standard deviation, and range include the high value given in footnote (h).
(j) All values were corrected for percent recovery.
(k) Values not detected for batches produced on 6/24/82, 6/22/83, and 7/12/83.
(l) BHC = hexachlorocyclohexane or benzene hexachloride
(m) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(n) Two observations were above the detection limit. The values and the dates they were obtained are given under the range.
(o) Twelve batches contained more than 0.05 ppm.
(p) Two batches produced on 5/26/81 and 7/14/81 were not analyzed for endosulfan I, endosulfan II, and endosulfan sulfate.

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The experimental data, documents, and pathology materials for the 2-year studies of nitrofurazone in rats and mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice (GLP) regulations of the Food and Drug Administration (fully implemented by the NTP beginning on October 1, 1981). The laboratory studies were conducted for the NTP by Physiological Research Laboratories, Minneapolis, Minnesota, under a subcontract with Tracor Jitco, Inc., until February 28, 1983, and then under contract with the NIEHS. Animal exposures to the chemical in feed began in June 1981 for rats and mice. The retrospective audit was conducted for the NIEHS at the NTP Archives in January and February 1987 by the Dynamac Corporation (J.C. Bhandri, D.V.M., Ph.D., Principal Investigator). 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 20% sample of the study animals plus other relevant material to verify animal identification and to examine for untrimmed potential lesions.
(7) Blocks and slides of tissues from a random 20% sample of study animals to examine for proper match and inventory.
(8) Tabulated pathology diagnoses for a random 10% sample of study animals to verify computer data entry.
(9) The preliminary draft Technical Report (February 1987).

Inlife procedures and events were documented adequately by the archival records, with the exception of the receipt of female rats and female mice, disposition of surplus animals, release of mice from quarantine, cage and rack changes, sanitation procedures, light cycle, and twice daily cage checks. The relatively few audit findings from the review of the inlife records were miscellaneous and minor in nature. Also, the mode of death entered into separate records maintained for animal census and clinical observations was either not internally consistent or sometimes not listed in both records for 29 rats and 14 mice; however, one of the two records was always in agreement with the disposition code listed on the necropsy record form. Minor errors in computing feed consumption were reported and corrected.

Inspection of wet tissues for individual animal identifiers showed that 63/76 rats and 57/68 mice were identified correctly by their residual tissues and that tissues were either partially present and correct or absent for the remaining animals. The audit identified 26 untrimmed potential lesions in the wet tissues of 22/76 rats examined and 15 untrimmed potential lesions in 12/68 mice examined. As a result, all wet tissues were reviewed for untrimmed lesions. This review resulted in the identification of the following neoplastic lesions: hepatic nodules in two control male rats, an adenoma of the pancreas in one control male rat, a squamous cell papilloma in a low dose female rat, a trichoepithelioma in the skin of a high dose male rat, several alveolar/bronchiolar adenomas or carcinomas in mice of each sex, and three forestomach papillomas in control and dosed mice. These diagnoses have been incorporated into the tables of the final version of this report and did not alter the interpretations. The

correlation between gross observations and microscopic diagnoses was very good (four noncorrelations each in rats and mice). Full details about 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.

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PUBLISHED AS OF APRIL 1988

TR No.	CHEMICAL
200	2,6-Toluenediamine Dihydrochloride
201	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dermal)
202	1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin and 1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (Dermal)
203	Phenol
204	Benzoin
205	4,4'-Oxydianiline
206	Dibromochloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane (Inhalation)
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butylbenzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-*p*-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	D-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos
250	Benzyl Acetate
251	Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
267	Propylene Oxide
269	Telone II®
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four strains of rats)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
281	H.C. Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethy)phosphonium Sulfate and Tetrakis(hydroxymethy)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol

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