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No. 345

TOXICOLOGY AND CARCINOGENESIS STUDIES OF ROXARSONE

(CAS NO. 121-19-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF ROXARSONE

(CAS NO. 121-19-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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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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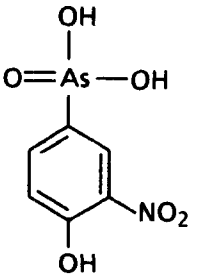
CONTENTS

APPENDIXES



ROXARSONE

CAS No. 121-19-7

$C_6H_6AsNO_6$ Molecular weight 263

Synonyms: 4-hydroxy-3-nitrophenylarsonic acid; 4-hydroxy-3-nitrobenzenearsonic acid; 2-nitro-1-hydroxybenzene-4-arsonic acid; nitrophenolarsonic acid; 3-nitro-4-hydroxybenzenearsonic acid; 3-nitro-4-hydroxyphenylarsonic acid
Trade names: Ristat; Ren-O-sal; 3-nitro; 3-nitro-10; 3-nitro-20; 3-nitro-50; 3-nitro-80

ABSTRACT

Roxarsone is a veterinary drug used as a growth promoter and as an anticoccidial agent and for treatment of swine dysentery. Toxicology and carcinogenesis studies were conducted by administering roxarsone (greater than 99.4% pure) in feed to groups of F344/N rats and B6C3F$_1$ mice of each sex for 14 days, 13 weeks, or 2 years.

Fourteen-Day and Thirteen-Week Studies: In the 14-day studies, the diets fed to rats contained 0 or 100-1,600 ppm roxarsone, and those fed to mice contained 0 or 60-1,000 ppm. Deaths occurred in rats and mice that received the highest doses. Rats that received 800 or 1,600 ppm lost weight. Male mice that received 1,000 ppm and female mice that received 500 ppm lost weight.

In the first 13-week studies, roxarsone was fed to rats and mice at dietary concentrations of 0 or 50-800 ppm. Decreases (more than 10%) in final mean body weights of dosed rats relative to those of controls were observed for males that received 200, 400, or 800 ppm and for females that received 400 or 800 ppm. Deaths occurred in groups that received 800 ppm. Clinical signs of toxicity (trembling, ataxia, and pale skin) were seen primarily in rats that received 800 ppm. Kidney lesions were observed in rats that received 800 ppm. These lesions were characterized by tubular necrosis and mineralization in the rats that died during the studies and by tubular dilatation and casts, interstitial inflammation, and tubular epithelial cell regeneration in the rats that lived to the end of the studies.

Additional 13-week studies were conducted in rats at dietary concentrations of 0, 100, or 400 ppm to demonstrate the absorption of roxarsone from the gastrointestinal tract; to determine its distribution in liver, kidney, and blood; and to study its effects on various hematologic and clinical chemical values. No deaths occurred. Renal lesions of minimal severity observed in male rats that received 400 ppm were characterized by tubular epithelial cell degeneration and regeneration, tubular casts, and mineralization. Arsenic levels in urine, blood, kidney, and liver of dosed rats increased (140%-300%) with time on study and were proportional to the dietary concentrations of roxarsone. No compound-related hematologic or clinical chemical effects were observed in rats.

In the first 13-week studies, final mean body weights of mice that received 800 ppm were 11%-18% lower than those of controls. Deaths occurred in males and females receiving 400 and 800 ppm. No compound-related gross or histopathologic lesions were observed.

In the second 13-week studies in mice, no compound-related hematologic or clinical chemical effects were observed. At the end of the studies, arsenic concentrations in dosed mice ranged from 0.45 to 0.99 µg/g of liver and from 0.85 to 2.98 µg/g of kidney. No arsenic was detected in the liver or kidney of control mice.

Because of kidney lesions, lower body weight gain, and increased mortality in rats and lower body weight gain and increased mortality in mice in the short-term studies, dietary concentrations of roxarsone selected for the 2-year studies were 0, 50, or 100 ppm for rats and 0, 100, or 200 ppm for mice.

Body Weight and Survival in the Two-Year Studies: Mean body weights of dosed rats were generally within 5% of those of controls. No significant differences in survival were observed between any groups of rats of either sex, although survival in males was lower than usual (final survival--male: control, 24/50; low dose, 18/50; high dose, 18/50; female: 27/50; 35/50; 32/50). The average feed consumption by high dose rats was 95% that of controls for males and 88% for females. The average amount of roxarsone consumed per day was approximately 2 mg/kg for low dose rats and 4 mg/kg for high dose rats. Mean body weights of high dose male mice were generally 5%-8% higher than those of the controls, whereas those of female mice were generally 6%-15% lower than those of the controls. The survival of the control group of male mice was lower than that of the low dose group after month 22; survival for females was low (final survival--male: 27/50; 40/50; 33/50; female: 14/50; 18/50; 17/50). The low survival in females was due in part to utero-ovarian infection, with more than 50% of the animals in each dose group having suppurative inflammation at this site. The average daily feed consumption by dosed mice was 105%-111% that by the controls. The average amount of roxarsone consumed per day was approximately 21 or 43 mg/kg for low dose or high dose male mice and 27 or 54 mg/kg for low dose or high dose female mice.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Although the incidence of adenomas of the exocrine pancreas in high dose male rats was not statistically greater than that in the controls (control, 1/50; low dose, 1/50; high dose, 5/50), it was greater than that seen in any historical control group of male F344/N rats. The historical rate is 1/437 (0.2%) for the study laboratory and 5/1,871 (0.3%) throughout the Program. The incidences of hyperplasia were 2/50; 0/50; 3/50. No hyperplasia or adenomas were observed in the exocrine pancreas of female rats.

Clitoral gland adenomas in female rats occurred with a marginally positive trend (1/44; 3/47; 6/48; $P=0.049$). One carcinoma was also observed in each of the groups. The incidences of adenomas or of adenomas or carcinomas (combined) in the dosed groups were not significantly different from those in the controls. This marginal effect was not considered to be related to roxarsone administration.

No chemical-related increases in neoplastic or nonneoplastic lesions occurred in male or female mice. Lymphomas in female mice occurred with a negative trend; the incidences in the dosed groups were lower than that in the controls (13/50; 2/50; 3/50; $P \leq 0.01$).

Genetic Toxicology: Roxarsone was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation. Roxarsone induced trifluorothymidine (Tft) resistance in mouse lymphoma L5178Y cells in the absence of metabolic activation; it was not tested with activation. Exposure of adult male *Drosophila melanogaster* to roxarsone by injection or by feeding did not cause an increase in sex-linked recessive lethal mutations.

Audit: The data, documents, and pathology materials from the 2-year studies of roxarsone have been audited. 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 roxarsone for male F344/N rats, as indicated by a marginally increased incidence of adenomas of the exocrine pancreas. There was *no evidence of carcinogenic activity* for female F344/N rats fed diets containing 50 or 100 ppm roxarsone for 2 years. There was *no evidence of carcinogenic activity* for male or female $B6C3F_1$ mice fed diets containing 100 or 200 ppm roxarsone for 2 years.

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

Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Dietary concentration			
0, 50, or 100 ppm roxarsone	0, 50, or 100 ppm roxarsone	0, 100, or 200 ppm roxarsone	0, 100, or 200 ppm roxarsone
Body weights in the 2-year study			
Dosed comparable to those of controls	Dosed comparable to those of controls	Dosed slightly lower than those of controls	Dosed lower than those of controls
Survival rates in the 2-year study			
24/50; 18/50; 18/50	27/50; 35/50, 32/50	27/50, 40/50 33/50	14/50; 18/50, 17/50
Nonneoplastic effects			
None	None	None	None
Neoplastic effects			
Adenomas of the exocrine pancreas (1/50; 1/50; 5/50)	None	None	None
Level of evidence of carcinogenic activity			
Equivocal evidence	No evidence	No evidence	No evidence
Other considerations			
Kidney lesions at 400 ppm or more in the 13-week studies	Kidney lesions at 800 ppm in the 13-week studies	None	None
Genetic toxicology assays			
Salmonella Gene Mutation: Negative with and without S9	Mouse L5178Y/TK Tft Resistance: Positive with S9, no test without S9	Drosophila Sex-Linked Rec. Lethals: Negative	

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

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

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 Roxarsone is based on the 13-week studies that began in August 1980 and ended in November 1980 and on the 2-year studies that began in June 1981 and ended in June 1983 at Southern Research Institute (Birmingham, Alabama).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on roxarsone on November 6, 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 ROXARSONE

On November 6, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of roxarsone 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. K.M. Abdo, NIEHS/NTP, began the discussion by reviewing the experimental design, results, and proposed conclusions (equivocal evidence of carcinogenic activity for male rats, no evidence of carcinogenic activity for female rats, no evidence of carcinogenic activity for male or female mice).

Dr. Hooper, a principal reviewer, agreed with the conclusions. He asked for discussion as to why a dose-related increase of clitoral gland adenomas in female rats was considered unrelated to chemical administration.

Dr. Capen, a second principal reviewer, agreed with the conclusions. He suggested that comment be added as to whether neoplastic or nonneoplastic lesions were observed in the pancreas of rodents in a previous study with roxarsone. Dr. Abdo said that there was no mention in the earlier study that the pancreas was one of the organs examined.

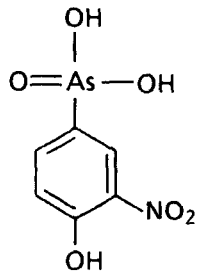
As a third principal reviewer, Dr. Sivak agreed in principle with the conclusions, although he considered the occurrence of clitoral gland adenomas in female rats supportive of equivocal evidence of carcinogenic activity, especially in view of increased hyperplasia in exposed groups. In response to Dr. Hooper and Dr. Sivak, Dr. Abdo said that the incidences of clitoral gland lesions were not significantly different from that in controls even when hyperplasia was included. Dr. S. Eustis, NIEHS, reported that greater emphasis was placed on the pancreatic lesions than on the clitoral gland lesions because of comparisons with their respective historical control rates. Further, the historical control data for clitoral gland tumors given in the Technical Report are based on microscopic examination of tumors only observed grossly. In this study, all clitoral glands were evaluated histopathologically; he said that direct comparisons with contemporary historical controls are therefore inappropriate [see page 57].

Dr. Hooper moved that the Technical Report on roxarsone be accepted with the revisions discussed and with the conclusions as written for male rats, equivocal evidence of carcinogenic activity, and for female rats and male and female mice, no evidence of carcinogenic activity. Dr. Sivak seconded the motion, which was approved unanimously with nine votes.

I. INTRODUCTION

Physical and Chemical Properties
Production and Use
Toxicity
Metabolism
Carcinogenicity
Genetic Toxicity
Study Rationale

I. INTRODUCTION



ROXARSONE

CAS No. 121-19-7

$C_6H_6AsNO_6$ Molecular weight 263

Synonyms: 4-hydroxy-3-nitrophenylarsonic acid; 4-hydroxy-3-nitrobenzenearsonic acid; 2-nitro-1-hydroxybenzene-4-arsonic acid; nitrophenolarsonic acid; 3-nitro-4-hydroxybenzenearsonic acid; 3-nitro-4-hydroxyphenylarsonic acid
Trade names: Ristat; Ren-O-sal; 3-nitro; 3-nitro-10; 3-nitro-20; 3-nitro-50; 3-nitro-80

Roxarsone is an organic arsenical widely used as a growth promoter for swine and poultry, as an anticoccidial compound for poultry, and as a drug for treatment of swine dysentery (Merck Vet. Manual, 1979). Roxarsone is prepared by treating sodium *p*-hydroxyphenylarsonate with a mixture of nitric and sulfuric acids at 0° C (Merck, 1983).

Physical and Chemical Properties

The pure compound is pale yellow (Merck, 1983). It is slightly soluble in cold water; soluble in 30 parts of boiling water; freely soluble in methanol, ethanol, acetic acid, acetone, and alkalies; sparingly soluble in dilute mineral acids; and insoluble in ether and ethyl acetate.

Production and Use

Production of roxarsone in the United States was greater than 2,270 kg in 1979, and imports for the same year were estimated at 19,200 kg (TOXNET, 1987). Recommended levels of roxarsone in feed for growth promotion are 25-50 ppm for poultry and 25-37.5 ppm for swine. It also is recommended that it be fed at a concentration of 200 ppm for 6 days to control dysentery in swine (USCFR, 1987a).

Toxicity

Oral LD_{50} values (milligrams per kilogram body weight) for roxarsone are 155 for rats, 100-123 for chickens, 61 for turkeys, and 50 for dogs (Kerr et al., 1963). The oral LD_{50} values determined by the NTP for roxarsone are 81 for female F344/N rats and 244 for female $B6C3F_1$ mice. Chickens and turkeys that died after short-term exposure showed marked enteritis, hepatitis, and hemorrhage in the gallbladder, spleen, and kidneys. Hemorrhagic nephritis was observed in rats. Icterus and hemorrhage of the stomach, duodenum, colon, and cecum were observed in dogs that died after acute exposure. The kidneys of these dogs were congested, and hematuria was observed.

In 13-week studies, administration of 400 ppm roxarsone in feed caused death in Holtzman rats, and administration of 200 ppm or more caused weight gain depression (Kerr et al., 1963). Rats receiving 400 ppm developed transitory tremors. Leg weakness and ataxia were observed in turkey poults fed diets containing roxarsone at 100-400 ppm (Sullivan and Al-Tammimi, 1972; Wise et al., 1974). Pigs that were accidentally administered feed containing more than 30 ppm arsenic (due to a roxarsone concentration five times the therapeutic concentration) developed

central nervous system signs such as trembling of the muscles of the shoulders, hams, and back followed by extreme agitation (Rice et al., 1980). Histologic responses attributed to roxarsone administration were noted in the sciatic nerve of turkeys given 400 ppm roxarsone in feed (Wise et al., 1974). The nerve fibers showed the lesions characteristic of wallerian degeneration. Myelinic and axonal degeneration was observed in the white matter of the spinal cord of pigs fed diets containing 187.5 ppm roxarsone for 29 days (Kennedy et al., 1986); peripheral and optic neuropathologic effects were observed 3 days after the feed containing roxarsone was withdrawn. Hypoplastic anemia was observed in chickens administered large amounts of oxytetracycline for 18 days with concurrent administration of roxarsone in drinking water for 9 days and administration of sulfaquinoxaline for an additional 3 days (Sadek et al., 1955). Arsanilic acid, an organic arsenical structurally similar to roxarsone, caused increased prothrombin time in chickens (Sweet et al., 1954).

Metabolism

Orally administered roxarsone is excreted slowly: 9-11 days are required for clearance of a single dose of 75 mg/kg in hens (Moody and Williams, 1964). 3-Amino-4-hydroxyphenylarsonic acid was a transformation product found in the urine of hens. A study of residue levels in chickens fed diets containing 500 ppm roxarsone showed that the highest residues are found in the liver (0.71-2.60 ppm arsenic) and kidneys (0.7 ppm arsenic) (Kerr et al., 1969). Five days after withdrawal of feed containing roxarsone, residue levels (expressed as arsenic) in the liver dropped to below the tolerance level of 2 ppm established by the Food and Drug Administration (USCFR, 1987b).

Carcinogenicity

Roxarsone was administered at a concentration of 50 or 100 ppm in the diet for up to 2 years to groups of 50 male and 50 female Swiss Webster mice and at 50 or 200 ppm to groups of 50 male and 50 female Sprague Dawley rats (Prier et al., 1963). No adverse effects on body weight gain, survival, or the incidence of spontaneous tumors were observed in mice. No effects were seen in rats administered 50 ppm roxarsone, and only body weight depression was seen in rats at 200 ppm. In these studies, only 9 organs in mice and 19 organs in rats were examined histologically.

Genetic Toxicity

Roxarsone did not induce gene reversion in streptomycin-dependent *Escherichia coli* strain Sd-4-73 (Szybalski, 1958). In NTP studies, roxarsone was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Zeiger et al., 1987; Table E1). However, roxarsone induced trifluorothymidine resistance in mouse L5178Y lymphoma cells in the absence of metabolic activation; it was not tested with metabolic activation (Table E2). No significant increase in sex-linked recessive lethal mutations was observed in the offspring of adult male *Drosophila melanogaster* injected with 6,800 ppm or fed 7,000 ppm roxarsone (Table E3).

Study Rationale

Roxarsone was nominated for toxicology and carcinogenesis studies by the Food and Drug Administration because of widespread human exposure resulting from its use as a growth promoter and as a therapeutic agent for poultry and swine. Roxarsone was administered in the diet because the most likely route for general human exposure is in food.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF ROXARSONE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES AND FORMULATED DIETS

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

PROCUREMENT AND CHARACTERIZATION OF ROXARSONE

Roxarsone (99.41% pure according to the manufacturer's specifications) was obtained as a yellow powder in one lot (lot no. 8268-F4) from Rhone-Poulenc, Inc., Hess and Clark Division (Ashland, Ohio). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on analyses performed in support of the studies on roxarsone are on file at NIEHS.

The study chemical was identified as roxarsone by its physical properties and by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Infrared and nuclear magnetic resonance spectra were consistent with spectra in the literature (Sadtler Standard Spectra). Representative spectra are presented in Figures 1 and 2. The ultraviolet/visible spectrum was consistent with the structure of roxarsone.

The purity of roxarsone lot no. 8268-F4 was determined by elemental analyses; weight loss on drying to determine water content; nonaqueous titration in pyridine of the acidic groups with 0.1 N tetrabutylammonium hydroxide dissolved in methanol:2-propanol (1:9); thin-layer chromatography with silica gel plates and solvent systems of methanol:acetic acid:water (50:40:10) and propionic acid:95% ethanol (80:20) with ultraviolet visualization; and high-performance liquid chromatography with a Waters μBondapak C_{18} column, a solvent system of aqueous 1% (v/v) acetic acid:methanol containing 1% (v/v) acetic acid (95:5) isocratic, and ultraviolet detection at 254 nm. Results of elemental analyses for carbon, hydrogen, nitrogen, and arsenic agreed with the theoretical values. The water content, determined by weight loss on drying, was 0.076%. Titration of the acidic groups with tetrabutylammonium hydroxide indicated a purity of 100.5%. Thin-layer chromatography showed only one spot with either solvent system. High-performance liquid chromatography indicated two impurities, both with peak areas less than 0.2% that of the major peak. Cumulative data indicated that lot no. 8268-F4 was 100.4% pure.

Stability studies performed with the high-performance liquid chromatographic system described previously indicated that roxarsone was stable when stored in amber vials with Teflon septa for 2 weeks at temperatures up to 60° C. The bulk chemical was stored at room temperature. Reanalysis of lot no. 8268-F4 by MRI was conducted in September 1983 by titration with an aqueous 0.1 N sodium hydroxide titrant, a solvent of 95% ethanol, and potentiometric monitoring; by the titration procedure described previously; and by high-performance liquid chromatography. No degradation of the study material was detected. Results of periodic analysis of the bulk chemical at the study laboratory by infrared spectroscopy, titration with tetrabutylammonium hydroxide, and high-performance liquid chromatography indicated that no notable degradation occurred throughout the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES AND FORMULATED DIETS

For the single-administration gavage studies, appropriate amounts of roxarsone and corn oil were mixed to give the desired concentrations (Table 1). During sampling and dosing, the suspensions were stirred continuously with a magnetic stirrer to ensure homogeneity. For all subsequent studies, formulated diets were prepared by adding a dry premix of feed and roxarsone to the appropriate amount of feed and blending for 15 minutes. The homogeneity of formulated diet mixtures was determined for samples taken from three locations within the blender by spectrophotometric analysis at 408 nm after extraction with aqueous 2% dibasic potassium phosphate, addition of dilute hydrochloric acid to the extract, centrifugation, addition of sodium hydroxide and activated charcoal to the clarified extract, and filtration. Mean concentrations of roxarsone differed by less than 1.5%. The stability of roxarsone at 300 ppm in feed was determined by high-performance liquid chromatography with a Waters μBondapak C_{18} column and a mobile phase of aqueous citric acid/phosphate buffer, pH 2.2:methanol (90:10). Formulated diets containing roxarsone were stable when

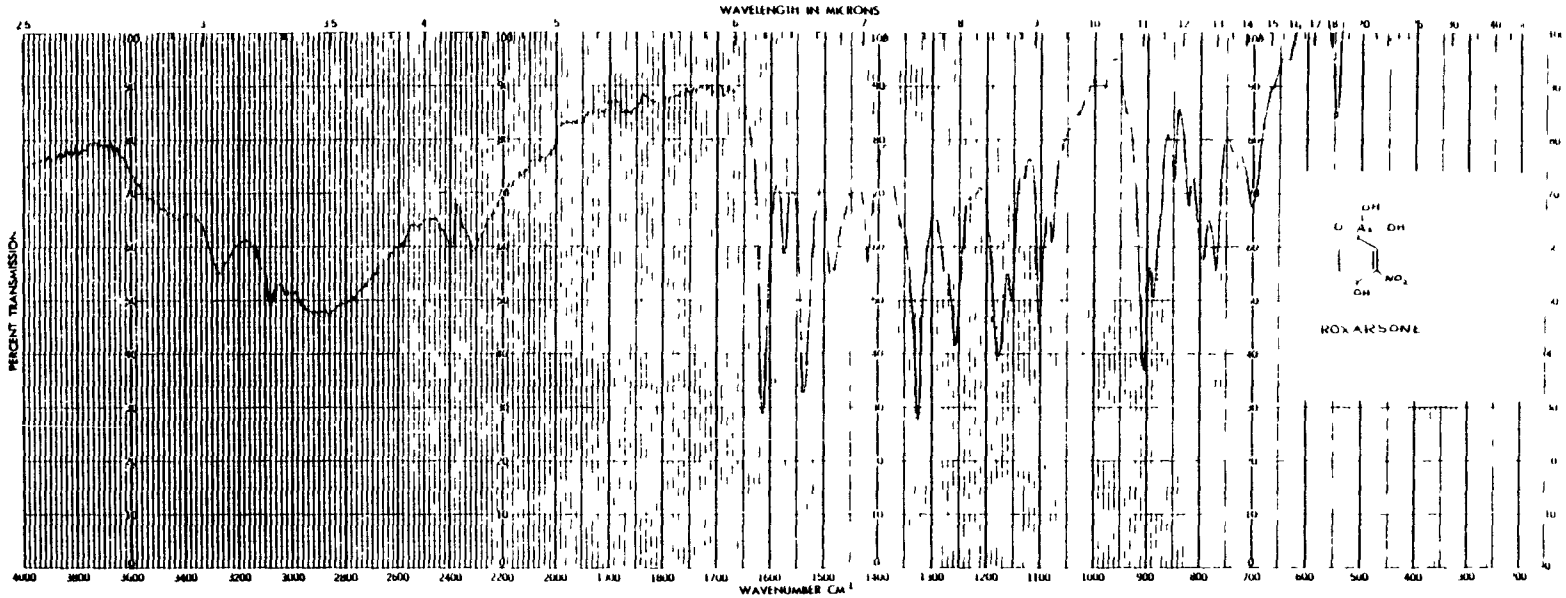


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF ROXARSONE (LOT NO. 8268-F4)

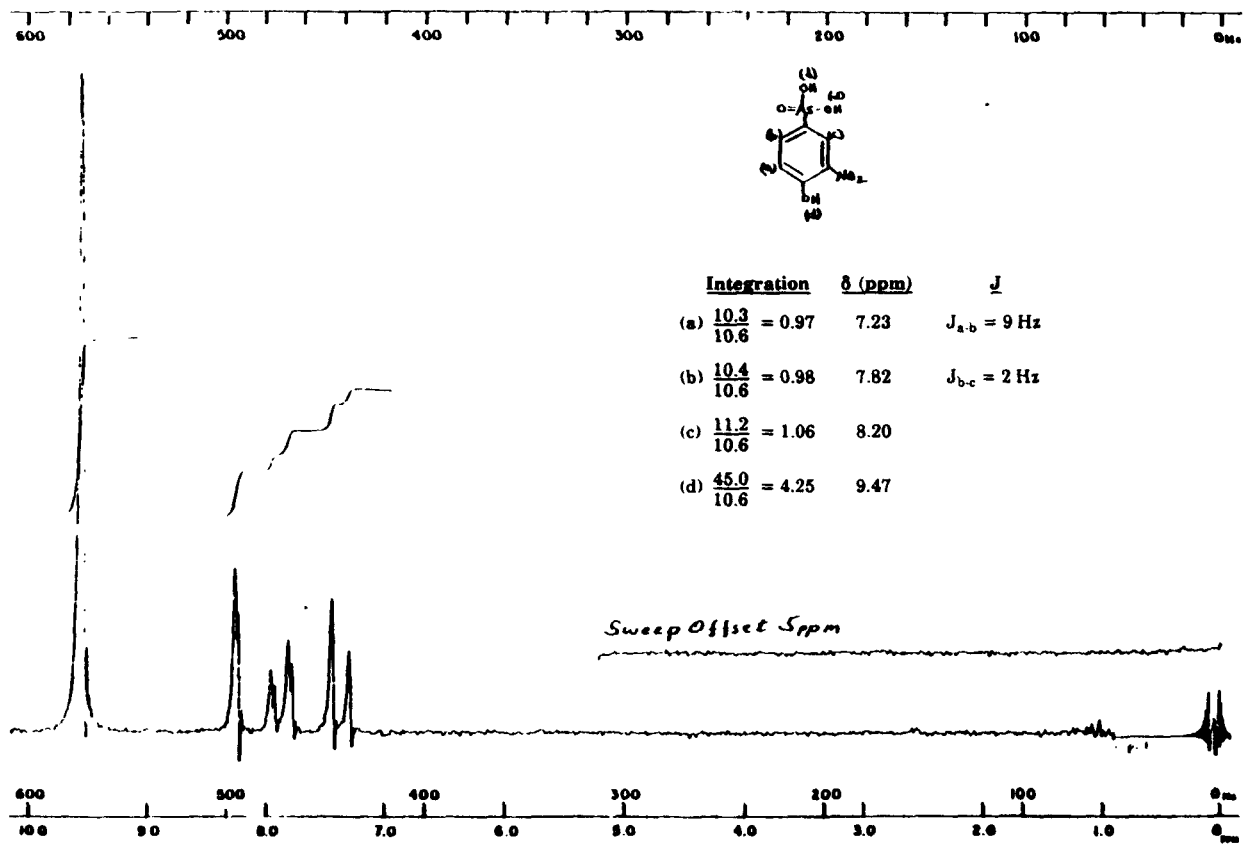


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF ROXARSONE (LOT NO. 8268-F4)

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES AND FORMULATED DIETS IN THE STUDIES OF ROXARSONE

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation			
Chemical placed in amber serum bottle with stir bar; corn oil added to volume and mixture stirred for at least 5 min	Premix of chemical and feed blended with additional feed for 15 min in 16-qt Patterson-Kelly Twin-Shell® blender with intensifier bar	Same as 14-d studies	Same as 14-d studies except intensifier bar on for 5 min
Maximum Storage Time			
Used on day mixed	2 wk	2 wk	2 wk
Storage Conditions			
Used on day mixed	5° C	5° C	Room temperature

stored for 2 weeks in the dark at temperatures up to 45° C. In the 13-week studies, formulated diets were stored at 5° C for no longer than 2 weeks. In the 2-year studies, formulated diets were stored at room temperature for no longer than 2 weeks.

Periodic analyses performed with the extraction procedure described previously were conducted to determine the concentration of roxarsone in formulated diet mixtures. Spectrophotometric analysis (405 nm) was used by the study laboratory in the 13-week studies and for the initial analyses of the 2-year studies, whereas high-performance liquid chromatography (HPLC) was used by the analytical chemistry laboratory for all of the studies. In the 13-week studies, formulated diets were analyzed on three different days by the study laboratory (Table 2). Concentrations of roxarsone in diets mixed on August 12, 1980, ranged from 76% to 95% of the target concentrations. Incomplete extraction after mechanical shaking caused results to be out of specifications in 7/14 mixes prepared on August 12, 1980. Mixes prepared on September 3 and September 17, 1980, and triturated with a Polytron® homogenizer were all determined to be within ±10% of specifications. Results of a referee analysis performed on September 17, 1980, did not agree with the study laboratory's results Since the analytical chemistry laboratory used the HPLC method that was later determined to be the more reliable method, the analytical chemistry laboratory's results are considered more accurate

During the 2-year studies, the formulated diets were analyzed at approximately 8-week intervals. Preliminary ultraviolet spectroscopic analysis for homogeneity of formulated feed mixtures indicated that the low concentrations of roxarsone and the high level of interference from the feed made this method of analysis unacceptable For the remainder of the studies, formulated diets were analyzed by HPLC. The homogeneity of formulated feed mixtures at the 100-ppm level was confirmed later in the study with the HPLC method

Four results of regularly scheduled dose analyses were not reported because of procedural problems. Because 59/73 formulated diets analyzed in the 2-year studies were within ±10% of the target concentrations, it is estimated that the feed mixtures were prepared within specifications approximately 81% of the time (Table 3) Referee analyses were performed periodically by the analytical chemistry laboratory Good agreement was generally found between laboratories (Table 4)

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

Date Mixed	Concentration of Roxarsone in Feed (ppm)		Determined as a Percent of Target
	Target	Determined (a)	
8/12/80	50	(b) 38	76.0
	50	(b) 40	80.0
	50	(b) 42	84.0
	100	(b) 84	84.0
	100	(b) 83	83.0
	100	(b) 86	86.0
	200	(b) 170	85.0
	400	360	90.0
	400	360	90.0
	400	360	90.0
	400	380	95.0
	800	740	92.5
	800	720	90.0
	800	720	90.0
9/03/80	100	90	90.0
9/17/80	50	54	108.0
	50	(c) 64	128.0
	100	98	98.0
	200	220	110.0
	400	390	97.5
	800	860	107.5

(a) Results of duplicate analysis
(b) Out of specifications
(c) Referee sample, triplicate analysis

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

Date Mixed	Concentration of Roxarsone in Feed for Target Concentration (ppm) (a)		
	50	100	200
06/09/81	46 6	105 0	205
	48 0	111 0	
		103 0	
07/07/81	55 0	104 0	
		102 0	
08/04/81	(b) 56 4	92 6	194
	(c) 54 2		
09/08/81	(d) 57 6	(d) 88 8	
		106 0	
09/29/81	47 6	97 7	(d,e) 167
10/01/81			(f) 198
10/27/81	53 3	98 8	
		102 0	
11/24/81	48 4	90 3	207
12/15/81	52 7	93 9	
		93 7	
02/23/82	49 5	101 0	187
	55 0	110 0	
		97 2	
04/20/82	(d,e) 67 0	(d,e) 122 0	
	(d,e) 68 9	106 0	
		(d,e) 112 0	(d,e) 220
04/26/82	(f) 47 6	(f) 89 9	(f) 217
	(f) 51 7	(f) 110 0	
06/22/82		(g)	
08/10/82	46 2	97 2	(d) 222
	46 3	105 0	
		105 0	
10/05/82	46 5	94 8	212
	46 4	99 1	
		101 0	
11/30/82	52 7	96 9	210
	51 8	102 0	
		102 0	
01/25/83	52 2	92 7	192
	(d,e) 43 4	(d,e) 85 3	
		(d,e) 81 6	
01/31/83	(f) 45 0	(f) 96 9	
		(f) 93 5	
03/25/83	(d,e) 40 4	98 6	197
	(d,e) 36 0	99 7	
		98 2	
03/30/83	(e,f) 56 0		
	(f) 53 7		
05/20/83	(h) 53 3	(h) 90 3	
	(h) 49 5	(h) 96 7	
Mean (ppm)	50 7	99 5	201
Standard deviation	7 10	7 75	16 0
Coefficient of variation (percent)	14 0	7 9	8 0
Range (ppm)	36 0 68 9	81 6 122 0	167 222
Number of samples	25	37	11

(a) Results of duplicate analysis unless otherwise specified
(b) Sample subsequently reanalyzed, this value not included in the mean
(c) Concentration obtained on reanalysis, value included in the mean
(d) Out of specifications
(e) Not used in the studies
(f) Remix, not included in the mean
(g) Failure of analytical procedure, results not reported
(h) Analyzed in triplicate

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

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory (a)	Referee Laboratory (b)
06/09/81	50	46.6	50.4
11/24/81	200	207	200
06/22/82	100	(c)	97
11/30/82	50	52.7	52
03/25/83	100	98.6	100

(a) Results of duplicate analysis
(b) Results of triplicate analysis
(c) Failure of analytical procedure; results not reported.

SINGLE-ADMINISTRATION STUDIES

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

Groups of five rats of each sex were administered a single dose of 19, 38, 75, 150, or 300 mg/kg roxarsone in corn oil by gavage. Groups of five mice of each sex were administered 38, 75, 150, 300, or 600 mg/kg. Animals were observed two times per day for 2 weeks. Controls were not used. Details of animal maintenance are presented in Table 5.

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 19 days before the studies began. The rats were 7-8 weeks old when placed on study, and the mice were 8-9 weeks old.

Groups of five rats of each sex were fed diets containing 0, 100, 200, 400, 800, or 1,600 ppm roxarsone for 14 consecutive days. Groups of five mice of each sex were fed diets containing 0, 60, 120, 250, 500, or 1,000 ppm on the same schedule. Animals were housed five per cage. Water and feed were available ad libitum. Further experimental details are summarized in Table 5. Rats and mice were observed two times per day and were weighed on days 1, 8, and 15 and at necropsy. A necropsy was performed on all animals.

THIRTEEN-WEEK STUDIES

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

Five-week-old male and female F344/N rats were obtained from Charles River Breeding Laboratories. Six-week-old male and female B6C3F$_1$ mice were obtained from Harlan Industries. The rats and mice were observed for 15 days, distributed to weight classes, and then assigned to cages according to a table of random numbers. Cages were assigned to dosed and control groups according to another table of random numbers. Two control female mice in the first 13-week studies and 10 control female mice in the second 13-week studies were pregnant. Weights of pregnant mice were not included in the weight classes for randomization.

Groups of 10 rats and 10 mice of each sex were given diets containing 0, 50, 100, 200, 400, or 800 ppm roxarsone for 13 weeks. In the second 13-week studies, groups of 30 rats and 30 mice of each sex were given diets containing 0, 100, or 400 ppm roxarsone for up to 13 weeks. Control diets consisted of NIH 07 Rat and Mouse Ration. Formulated or control diets and water were available ad libitum. Feed consumption was measured once per day by cage for 1 week per

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

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 males and 5 females of each species	First--10 males and 10 females of each species; second--30 males and 30 females of each species	50 males and 50 females of each species
Doses			
Rats--19, 38, 75, 150, or 300 mg/kg roxarsone in corn oil by gavage; mice--38, 75, 150, 300, or 600 mg/kg	Rats 0, 100, 200, 400, 800, or 1,600 ppm roxarsone in feed; mice--0, 60, 120, 250, 500, or 1,000 ppm	First--0, 50, 100, 200, 400, or 800 ppm roxarsone in feed, second--0, 100, or 400 ppm	Rats--0, 50, or 100 ppm roxarsone in feed, mice--0, 100, or 200 ppm
Date of First Dose			
4/8/80	6/2/80	8/13/80	Rats--6/17/81, mice--6/2/81
Date of Last Dose			
N/A	6/15/80	First--11/11/80, second--rats 8/22/80, 9/12/80, 11/10/80, mice· 8/21/80, 9/10/80, 11/11/80	Rats 6/7/83, mice--5/24/83
Duration of Dosing			
Single dose	14 consecutive d	First--13 wk, second--rats: 10, 31, or 90 d, mice. 9, 29, or 91 d	103 wk
Type and Frequency of Observation			
Observed 2 × d on d 2-15; weighed on d 0	Observed 2 × d, weighed on d 1, 8, and 15 and at necropsy, feed consumption measured 1 × d	First--observed 2 × d; weighed initially and 1 × wk thereafter; feed consumption measured 1 × d; second--weighed at necropsy	Observed 2 × d; rats weighed initially, 1 × wk for 12 wk, and then 1 × mo, mice weighed initially 1 × wk for 12 wk, at 14 wk, and then 1 × mo, feed consumption measured 1 × d per cage for 1 wk in each month
Necropsy, Histologic Examination, and Supplemental Studies			
No necropsy or histologic exam performed	Necropsy performed on all animals; histologic exam not performed	Necropsy performed on all animals, histologic exam performed on all control and 800-ppm animals and on mice in the 400 ppm group Kidneys examined for all rats, liver weighed at necropsy for all animals Tissues examined include adrenal glands, brain, colon, esophagus, femur including marrow, gallbladder (mice), heart, kidneys, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, pancreas, parathyroid glands, pituitary gland, salivary glands, seminal vesicles/prostate/testes or ovaries/uterus, skin, small intestine, spleen, stomach, thigh muscle, thymus, thyroid gland, trachea, and urinary bladder. Second studies--biochemical and hematologic analyses. total arsenic concentration in the blood and urine and roxarsone in urine determined before necropsy; kidneys	Necropsy and histologic exam performed on al animals, the following tissues were examined· adrenal glands, brain, cecum, colon, esophagus, femur including marrow, gallbladder (mice), gross lesions, heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, nasal cavity and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland (rats), rectum, salivary glands, sciatic (peripheral) nerve, skin, small intestine (including ileum, jejunum, and duodenum), spinal cord, spleen, stomach, testes/prostate/epididymis or ovaries/uterus, thymus, thyroid gland, tissue masses, trachea, and urinary bladder Blood smear, eyes, pharynx, and regional lymph nodes examined selectively

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

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Necropsy and Histologic Examination (Continued)			
		and liver weighed for mice killed on d 91 and for rats killed on d 90	
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	F344/N rats; $B6C3F_1$ mice
Animal Source			
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Rats--Charles River Breeding Laboratories (Portage, MI); mice--Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory			
Southern Research Institute	Southern Research Institute	Southern Research Institute	Southern Research Institute
Method of Animal Identification			
Ear mark	Ear mark	Ear mark	Ear mark
Time Held Before Study			
14 d	19 d	15 d	Rats--20 d, mice--19 d
Age When Placed on Study			
Rats--6 wk; mice--7-8 wk	Rats--7-8 wk, mice--8-9 wk	Rats--7 wk, mice--8 wk	Rats--7-8 wk; mice--8-9 wk
Age When Killed			
Rats--8 wk; mice--9-10 wk	Rats--9-11 wk; mice--10-12 wk	First--rats: 20-21 wk; mice: 21-22 wk; second--rats. 8, 11, or 20 wk; mice: 9, 12, or 21 wk	Rats -111 112 wk; mice--112 113 wk
Necropsy or Kill Dates			
4/23/80	6/17/80-6/25/80	First--11/12/80-11/19/80; second--rats· 8/22/80, 9/12/80, 11/10/80, mice: 8/21/80, 9/10/80, 11/11/80	Rats -6/15/83 6/17/83, mice -5/31/83-6/3/83
Method of Animal Distribution			
Animals distributed to weight classes and then assigned to cages by one table of random numbers and to groups by another table of random numbers	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Feed			
NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA), available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Bedding			
Beta Chips (Northeastern Products, Inc., Warrensburg, NY)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies

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

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Water			
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages			
Polycarbonate (Lab Products, Garfield, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cage Filters			
Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage			
5	5	5	5
Other Chemicals on Study in the Same Room			
None	None	None	None
Animal Room Environment			
Temp--22°-23° C; hum--42%-49%; fluorescent light 12 h/d; at least 15 room air changes/h	Temp--22°-24° C; hum--47%-55%; fluorescent light 12 h/d; at least 15 room air changes/h	Temp--72°-75° F; hum--42%-62%; fluorescent light 12 h/d, at least 15 room air changes/h	Temp--average: 72.9° F; range: 60°-96° F; hum--average: 53 5%, range: 27%-72%; fluorescent light 12 h/d except on 6/25/81 when lights were on continuously; at least 10-15 room air changes/h

month. Animals were observed two times per day; moribund animals were killed. 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.

In the second 13-week studies, individual animal weights were recorded at necropsy Ten male and 10 female rats per group were killed after 10, 31, or 90 days of roxarsone administration, and 10 male and 10 female mice per group were killed after 9, 29, or 91 days. At each scheduled-kill period, blood from rats and mice was analyzed for erythrocyte, platelet, reticulocyte, and total and differential leukocyte counts; hematocrit values; and hemoglobin concentration. Blood from rats was analyzed for cholinesterase, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), and total arsenic. Three or four days before each scheduled kill, urine from rats was collected for 16 hours and analyzed for roxarsone and total arsenic content. The liver and kidneys from rats and mice killed at day 90 or 91 were weighed, analyzed for total arsenic, and examined histologically. The methods of analysis are described in Appendix I

TWO-YEAR STUDIES

Study Design

Diets containing 0, 50, or 100 ppm roxarsone were fed to groups of 50 rats of each sex. Diets containing 0, 100, or 200 ppm were fed to groups of 50 mice of each sex.

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 animals were quarantined at the study laboratory for 19-20 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7-8 weeks of age and the mice at 8-9 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

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

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

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded when animals were weighed. Body weights were recorded once per week for the first 12 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 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. Tissues examined are listed in Table 5.

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

Representative slides selected by the Chairperson were reviewed by the PWG, which 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: Body weight and feed consumption data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). Other data were recorded in the Toxicology Data Management System. The data elements include descriptive information on the chemicals, animals, experimental design, survival, 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, logistic regression, 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--This method of analysis assumes that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These

results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method (1959) to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Logistic Regression Analyses--This method of analysis assumes that all tumors of a given type were "incidental"; i.e., they did not alter the risk of death and were discovered merely as the result of death from an unrelated cause. According to this approach, tumor prevalence was modeled as a logistic function of dose and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). If the tumor type is nonlethal, this comparison of the time-specific tumor prevalence also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

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

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

FIRST THIRTEEN-WEEK STUDIES

SECOND THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

FIRST THIRTEEN-WEEK STUDIES

SECOND THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SINGLE-ADMINISTRATION STUDIES

All rats that received 150 or 300 mg/kg and 2/5 females that received 75 mg/kg died before the end of the studies (Table 6). Final body weights were not recorded. The incidences of diarrhea and ataxia were greater at higher doses than at lower doses.

FOURTEEN-DAY STUDIES

Three of five male rats and 5/5 female rats that received 1,600 ppm died before the end of the studies (Table 7). Rats that received 800 or 1,600 ppm roxarsone lost weight. The final mean body weights of rats that received 400 ppm were 22% lower than that of the controls for males and 5% lower for females. Feed consumption by male rats that received 1,600 ppm and by females that received 800 ppm was notably lower than that by the controls.

Compound-related effects included slight inactivity for all males and females receiving 400, 800, and 1,600 ppm, cyanotic eyes for males and females receiving 1,600 ppm, and droopy eyelids and ruffled fur for males receiving 800 ppm.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF ROXARSONE

Dose (mg/kg)	Survival (a)	Initial Mean Body Weight (grams) (b)
MALE		
19	5/5	117 ± 4
38	5/5	115 ± 3
75	5/5	109 ± 5
150	(c) 0/5	110 ± 4
300	(d) 0/5	113 ± 3
FEMALE (e)		
19	5/5	107 ± 7
38	5/5	109 ± 4
75	(f) 3/5	105 ± 4
150	(g) 0/5	102 ± 4
300	(h) 0/5	106 ± 4

(a) Number surviving/number in group
(b) Initial group mean body weight ± standard error of the mean; final body weights were not recorded.
(c) Day of death: 1,2,2,2,2
(d) Day of death: 2,2,2,3,3
(e) LD_{50} value by the Spearman-Karber method (95% confidence interval): 81 mg/kg (58-112 mg/kg)
(f) Day of death: 4,5
(g) Day of death: 2,2,2,2,3
(h) Day of death: 2,4,4,4,5

TABLE 7. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE FOURTEEN-DAY FEED STUDIES OF ROXARSONE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Day 7	Day 13
MALE							
0	5/5	159 ± 7	229 ± 7	+70 ± 2		16	17
100	5/5	166 ± 7	226 ± 5	+60 ± 2	99	15	17
200	5/5	167 ± 4	226 ± 1	+59 ± 5	99	17	16
400	5/5	149 ± 3	179 ± 5	+30 ± 2	78	14	15
800	5/5	171 ± 5	153 ± 2	−18 ± 4	67	1	14
1,600	(e) 2/5	157 ± 7	99 ± 15	−65 ± 1	43	1	3
FEMALE							
0	5/5	139 ± 3	162 ± 4	+23 ± 1		12	10
100	5/5	135 ± 4	158 ± 4	+23 ± 1	98	12	12
200	5/5	135 ± 3	153 ± 3	+18 ± 2	94	11	11
400	5/5	138 ± 2	154 ± 3	+16 ± 2	95	14	12
800	5/5	136 ± 3	118 ± 5	−18 ± 6	73	2	7
1,600	(f) 0/5	138 ± 2	(g)	(g)	(g)	(g)	(g)

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; not corrected for scatter.
(e) Day of death: 5,11,15
(f) Day of death: 5,5,5,6,6
(g) No data are reported due to 100% mortality in this group.

FIRST THIRTEEN-WEEK STUDIES

Three of 10 male rats and 2/10 female rats that received 800 ppm died before the end of the studies (Table 8). The final mean body weights of rats that received 200, 400, or 800 ppm were 14%, 26%, or 50% lower than that of controls for males and 8%, 11%, or 33% lower for females. The data on increased feed consumption at 800 ppm suggest that the feed was scattered Compound-related clinical signs observed at 800 ppm included ruffled fur, hyperexcitability, ataxia, trembling, pale skin, and slight inactivity The liver weight to body weight ratios for male rats that received 50, 100, 200, or 400 ppm and female rats that received 800 ppm were significantly greater than those of controls (Table 9).

Compound-related histopathologic lesions in the kidney were noted in male and female rats Moderate to severe tubular cell necrosis, hemorrhage, and mineralization in the outer medulla were seen in the kidney of rats that died before the end of the studies. Interstitial inflammation, focal regenerative hyperplasia of tubular cell epithelium, and mineralization within tubules were seen in the kidney of rats that survived until the end of the studies. The interstitial inflammation was most prominent in the inner stripe of the outer medulla and was characterized by fibrosis and mononuclear cell infiltration between the tubules. There was a mild dilatation of the tubules within areas of inflammation and fibrosis in the outer medulla. In the more severely affected kidneys, the fibrosis extended into the outer stripe of the outer medulla and into the medullary rays and the cortex.

TABLE 8. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE FIRST THIRTEEN-WEEK FEED STUDIES OF ROXARSONE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 4	Week 13
MALE							
0	10/10	117 ± 3	357 ± 6	+240 ± 5		18	16
50	10/10	119 ± 3	320 ± 7	+201 ± 6	90	18	15
100	10/10	123 ± 3	339 ± 7	+216 ± 6	95	18	16
200	10/10	114 ± 4	307 ± 6	+193 ± 5	86	18	15
400	10/10	119 ± 3	263 ± 5	+144 ± 5	74	19	17
800	(e) 7/10	121 ± 3	179 ± 8	+60 ± 6	50	31	30
FEMALE							
0	10/10	102 ± 2	206 ± 3	+104 ± 3		13	11
50	10/10	102 ± 2	202 ± 4	+100 ± 3	98	12	10
100	10/10	103 ± 2	200 ± 2	+97 ± 1	97	13	11
200	10/10	102 ± 2	190 ± 4	+88 ± 3	92	13	9
400	10/10	104 ± 2	184 ± 2	+80 ± 2	89	13	9
800	(f) 8/10	102 ± 1	139 ± 2	+37 ± 3	67	21	18

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; not corrected for scatter.
(e) Week of death: 1,1,3
(f) Week of death: 1,1

TABLE 9. ANALYSIS OF LIVER WEIGHTS OF RATS IN THE FIRST THIRTEEN-WEEK FEED STUDIES OF ROXARSONE (a)

Concentration (ppm)	Number Examined	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Necropsy Body Weight (mg/g)
MALE				
0	10	362 ± 5.8	12,627 ± 663	34.8 ± 1 63
50	10	(b) 326 ± 8.1	13,375 ± 263	(b) 41.2 ± 1.14
100	10	346 ± 7.5	(b) 14,712 ± 424	(b) 42.5 ± 0.71
200	10	(b) 314 ± 5.5	12,663 ± 352	(b) 40.3 ± 0.80
400	10	(b) 272 ± 5.1	11,340 ± 272	(b) 41.7 ± 0.75
800	7	(b) 176 ± 7.5	(b) 6,301 ± 466	35.5 ± 1.32
FEMALE				
0	10	208 ± 3.0	6,711 ± 185	32 4 ± 1 01
50	10	203 ± 3.5	6,576 ± 131	32.5 ± 0 85
100	10	203 ± 2.0	7,004 ± 117	34 6 ± 0.46
200	(c) 10	(b) 189 ± 4.0	6,198 ± 195	32.4 ± 1 08
400	10	(b) 186 ± 1.9	6,551 ± 170	35.3 ± 0 69
800	8	(b) 138 ± 1.8	(b) 5,524 ± 377	(b) 40.0 ± 2 73

(a) Mean ± standard error of the mean, P values vs the controls by Dunnett's test (Dunnett, 1955).
(b) $P<0.01$
(c) One liver not weighed; ratio based on remaining nine animals.

SECOND THIRTEEN-WEEK STUDIES

None of the rats died before the end of the second 13-week studies. The relative liver weight of female rats that received 400 ppm was significantly lower than that of controls (Table 10). The relative kidney weight of male rats that received 400 ppm was significantly greater than that of controls. Minimal nephrotoxicity characterized by minimal tubular epithelial cell degeneration and regeneration, tubular casts, and focal mineralization was observed in male rats that received 400 ppm. No compound-related lesions were observed in female rats. None of the differences in the results of hematologic or biochemical analyses observed between dosed and control rats was considered biologically meaningful (Table 11). The concentration of arsenic in the kidney and liver was significantly increased over that of controls at 100 and 400 ppm roxarsone on day 90. At 100 and 400 ppm, the concentrations of roxarsone and arsenic in the urine and of arsenic in the blood were significantly increased over those of controls on all days measured. Arsenic concentrations in blood and urine increased with time across all dose groups, including controls. This increase could be related to the reduced rate of elimination of arsenic by aging rats. The presence of arsenic at low levels in the blood and urine of control animals is not surprising, since the NIH 07 Rat and Mouse Ration used in these feed studies contains greater than 0.5 ppm of arsenic.

Dose Selection Rationale: Because of the incidence of deaths at 800 ppm, lower body weight gain at 200 ppm, and the incidence of renal lesions at 400 ppm or more, dietary concentrations of roxarsone selected for rats for the 2-year studies were 50 and 100 ppm.

TABLE 10. ANALYSIS OF LIVER AND KIDNEY WEIGHTS OF RATS IN THE SECOND THIRTEEN-WEEK FEED STUDIES OF ROXARSONE (a)

Concentration (ppm)	Number Examined	Final Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Final Body Weight (mg/g)	Kidney Weight (mg)	Kidney Weight/ Final Body Weight (mg/g)
MALE						
0	10	352 ± 6.6	11,536 ± 299	32.7 ± 0.43	2,180 ± 45	6.2 ± 0.07
100	10	(b) 330 ± 6.6	10,950 ± 384	33.2 ± 0.70	(b) 1,978 ± 68	6.0 ± 0.14
400	10	(c) 258 ± 5.7	(c) 8,169 ± 243	31.7 ± 0.67	(c) 1,747 ± 46	(c) 6.8 ± 0.16
FEMALE						
0	10	203 ± 4.2	5,789 ± 169	28.4 ± 0.42	1,244 ± 39	6.1 ± 0.12
100	10	196 ± 3.5	5,452 ± 103	27.8 ± 0.36	1,175 ± 22	6.0 ± 0.09
400	10	(c) 181 ± 2.5	(c) 4,789 ± 130	(c) 26.5 ± 0.50	1,155 ± 23	6.4 ± 0.08

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

TABLE 11. RESULTS OF HEMATOLOGIC, BIOCHEMICAL, AND ARSENIC ANALYSES FOR RATS IN THE SECOND THIRTEEN-WEEK FEED STUDIES OF ROXARSONE (a)

Analysis	Day	Male			Female		
		Control	100 ppm	400 ppm	Control	100 ppm	400 ppm
Erythrocyte count (10^6/mm^3)	10	7 67 ± 0 17	7 58 ± 0 14	7 59 ± 0 09	7 64 ± 0 17	(b) 8 15 ± 0 14	8 02 ± 0 18
	31	8 66 ± 0 14	8 38 ± 0 16	(c) 7 73 ± 0 15	8 27 ± 0 11	8 49 ± 0 12	8 28 ± 0 15
	90	8 96 ± 0 20	9 09 ± 0 13	(c) 8 04 ± 0 21	8 00 ± 0 23	8 13 ± 0 14	(b) 7 74 ± 0 12
Hematocrit value (percent)	10	39 10 ± 0 80	40 00 ± 0 54	39 10 ± 1 10	39 20 ± 0 68	(c) 42 10 ± 0 57	(b) 41 90 ± 0 60
	31	43 10 ± 0 53	43 10 ± 0 87	42 30 ± 0 79	40 70 ± 0 72	42 00 ± 0 33	42 20 ± 0 94
	90	44 15 ± 1 00	(c) 40 75 ± 0 45	(c) 40 50 ± 0 79	39 45 ± 0 86	39 15 ± 0 59	37 90 ± 0 32
Hemoglobin concentration (g/dl)	10	14 55 ± 0 30	14 77 ± 0 23	15 01 ± 0 20	15 14 ± 0 35	(b) 16 24 ± 0 18	15 69 ± 0 22
	31	16 61 ± 0 32	17 08 ± 0 34	(b) 15 56 ± 0 30	16 06 ± 0 28	16 58 ± 0 14	16 41 ± 0 25
	90	15 94 ± 0 34	15 93 ± 0 16	16 45 ± 0 51	15 89 ± 0 51	15 19 ± 0 24	(b) 14 74 ± 0 22
Leukocyte count (1,000/mm^3)	10	7 39 ± 0 58	8 41 ± 0 39	7 45 ± 0 76	6 68 ± 0 27	(c) 8 91 ± 0 48	(b) 8 20 ± 0 49
	31	8 64 ± 0 41	9 90 ± 0 44	8 63 ± 0 37	8 95 ± 0 28	(b) 11 16 ± 0 66	(c) 10 76 ± 0 64
	90	8 57 ± 0 62	7 74 ± 0 29	8 13 ± 0 97	6 36 ± 0 28	(c) 7 56 ± 0 32	(c) 4 96 ± 0 16
Platelet count (1,000/mm^3)	10	191 ± 24 0	249 ± 22 7	(b,d) 262 ± 15 7	284 ± 14 4	268 ± 19 0	234 ± 11 9
	31	271 ± 13 2	277 ± 13 7	270 ± 17 1	250 ± 10 9	(b) 324 ± 20 4	271 ± 20 4
	90	320 ± 22 5	321 ± 34 0	(c) 212 ± 11 6	251 ± 23 7	215 ± 29 6	292 ± 20 0
Lymphocyte count (1,000/mm^3)	10	6 29 ± 0 44	7 61 ± 0 35	6 03 ± 0 58	5 95 ± 0 21	(c) 7 98 ± 0 44	(b) 7 36 ± 0 47
	31	7 52 ± 0 45	(b) 8 93 ± 0 39	7 50 ± 0 38	8 09 ± 0 23	(b) 10 15 ± 0 66	(b) 9 67 ± 0 60
	90	7 37 ± 0 48	6 62 ± 0 26	6 44 ± 0 70	5 52 ± 0 23	(b) 6 40 ± 0 32	(c) 4 01 ± 0 08
Segmented neutrophil count (1,000/mm^3)	10	1 08 ± 0 15	0 77 ± 0 09	1 36 ± 0 35	0 67 ± 0 09	0 88 ± 0 10	0 77 ± 0 08
	31	1 04 ± 0 16	0 93 ± 0 08	1 10 ± 0 11	0 78 ± 0 09	0 91 ± 0 13	1 05 ± 0 11
	90	1 02 ± 0 12	1 07 ± 0 09	1 59 ± 0 50	0 83 ± 0 07	1 06 ± 0 12	0 92 ± 0 10
Eosinophil count (1,000/mm^3)	10	0 02 ± 0 02	0 03 ± 0 02	0 05 ± 0 03	0 06 ± 0 02	0 05 ± 0 02	0 07 ± 0 03
	31	0 05 ± 0 03	0 05 ± 0 03	0 04 ± 0 02	0 08 ± 0 02	0 11 ± 0 03	0 03 ± 0 02
	90	0 06 ± 0 02	0 05 ± 0 03	0 10 ± 0 03	0 01 ± 0 01	(c) 0 09 ± 0 02	0 03 ± 0 01
Reticulocyte count (10^6/mm^3)	10	0 20 ± 0 02	0 27 ± 0 03	(c) 0 10 ± 0 02	0 07 ± 0 01	(c) 0 14 ± 0 02	0 10 ± 0 02
	31	0 17 ± 0 02	(c) 0 08 ± 0 01	(c) 0 10 ± 0 01	0 16 ± 0 02	(c) 0 07 ± 0 01	(c) 0 07 ± 0 01
	90	0 15 ± 0 02	0 11 ± 0 01	(c) 0 09 ± 0 01	0 18 ± 0 02	(c) 0 09 ± 0 01	0 16 ± 0 02
SGOT activity (e) (IU/liter)	10	46 0 ± 3 2	41 3 ± 0 9	40 7 ± 2 0	43 0 ± 0 6	42 0 ± 0 0	(b) 47 7 ± 1 2
	31	46 7 ± 2 7	(b) 38 0 ± 0 6	(b) 33 0 ± 1 7	38 7 ± 0 3	40 3 ± 1 7	38 3 ± 0 7
	90	67 7 ± 6 5	55 3 ± 5 1	(c) 48 6 ± 4 6	43 9 ± 2 6	40 7 ± 3 1	41 6 ± 2 2
SGPT activity (f) (IU/liter)	10	17 3 ± 0 7	17 3 ± 0 9	17 3 ± 0 3	13 7 ± 0 3	13 7 ± 0 3	(b) 16 7 ± 0 7
	31	21 0 ± 2 5	17 3 ± 0 3	15 0 ± 0 6	12 0 ± 0 6	14 0 ± 0 6	(b) 16 0 ± 0 6
	90	35 1 ± 4 2	28 7 ± 4 4	27 8 ± 5 4	17 7 ± 1 8	(c) 12 6 ± 1 2	15 9 ± 1 3
Cholinesterase activity (IU/liter)	10	640 ± 31	591 ± 19	614 ± 22	1,324 ± 93	1,359 ± 70	1 201 ± 22
	31	545 ± 71	518 ± 23	671 ± 10	1 958 ± 76	1 755 ± 141	(b) 1 458 ± 116
	90	662 ± 22	693 ± 15	(c) 832 ± 19	3,598 ± 162	3 272 ± 168	(c) 1 975 ± 36
Arsenic in blood (micrograms/ml)	10	3 8 ± 0 07	(b) 15 3 ± 0 67	(b) 39 3 ± 5 84	4 4 ± 0 03	(b) 11 7 ± 0 33	(b) 25 3 ± 0 67
	31	8 3 ± 0 3	(b) 31 0 ± 1 2	(b) 122 7 ± 12 7	9 6 ± 0 4	(b) 23 0 ± 0 6	(b) 68 0 ± 3 5
	90	9 0 ± 0 2	(c,d) 50 1 ± 1 6	(c) 220 0 ± 6 3	11 1 ± 0 8	(c d) 43 0 ± 2 0	(c) 148 0 ± 5 5
Arsenic in urine (16 h) (micrograms)	7	0 2 ± 0 2	(b) 19 1 ± 2 0	(b) 25 1 ± 3 1	0 0 ± 0 0	(b) 11 8 ± 0 9	(b) 24 8 ± 2 0
	27	0 5 ± 0 3	(b) 24 5 ± 1 7	(b) 59 0 ± 3 8	0 0 ± 0 0	(b) 9 3 ± 1 1	(b) 28 2 ± 4 1
	87	1 3 ± 0 4	(c) 22 3 ± 3 9	(c) 81 7 ± 10 8	0 6 ± 0 3	(c) 14 5 ± 2 4	(c) 45 9 ± 11 5
Roxarsone in urine (16 h) (micrograms)	7	0 0 ± 0 0	(b) 13 6 ± 1 6	(b) 43 3 ± 10 3	0 0 ± 0 0	(b) 15 0 ± 2 2	(b) 33 3 ± 4 0
	27	0 0 ± 0 0	(b) 27 4 ± 0 9	(b) 115 0 ± 4 2	0 0 ± 0 0	(b) 12 0 ± 3 4	(b) 34 3 ± 4 4
	87	0 0 ± 0 0	(c,d) 19 2 ± 2 8	(c) 108 4 ± 21 1	0 0 ± 0 0	(c) 26 4 ± 6 9	(c,d) 113 8 ± 39 7
Arsenic in liver (g)	90	0 43 ± 0 03	(c,d) 3 53 ± 0 10	(c) 10 01 ± 0 60	0 70 ± 0 06	(c) 2 73 ± 0 14	(c) 6 88 ± 0 43
Arsenic in kidney (g)	90	0 78 ± 0 03	(c) 6 40 ± 0 26	(c) 27 67 ± 1 66	1 18 ± 0 06	(c) 7 04 ± 0 37	(c) 19 77 ± 1 14

(a) Values are mean ± standard error except as noted data are for 10 animals in all hematologic and tissue concentration studies and for 87 and 90-day biochemical and urinalysis studies, all 7 to 31-day clinical chemical and urinalysis studies represent three pooled samples P values are vs the controls by the Wilcoxon rank sum test (Hollander and Wolfe, 1973)
(b) P<0 05
(c) P<0 01
(d) Nine animals were examined
(e) Serum glutamic-oxaloacetic transaminase
(f) Serum glutamic pyruvic transaminase
(g) Micrograms arsenic/gram of tissue

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of dosed rats were generally within 5% of those of the controls (Table 12 and Figure 3). The average daily feed consumption per animal by low dose and high dose rats was 98% and 95% that by controls for males and 96% and 88% for females (Tables G1 and G2). The average amount of roxarsone consumed per day was approximately 2.1 mg/kg or 4 mg/kg for low dose or high dose rats. No compound-related clinical signs were observed.

TABLE 12. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF ROXARSONE

Weeks on Study	Control		50 ppm			100 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	146	50	148	101	50	145	99	50
1	190	50	191	101	50	188	99	50
2	214	50	213	100	50	213	100	50
3	237	50	232	98	50	227	96	50
4	254	50	256	101	50	252	99	50
5	270	50	272	101	50	263	97	50
6	278	50	279	100	50	270	97	50
7	286	50	288	101	50	277	97	50
8	293	50	290	99	50	281	96	50
9	299	50	294	98	50	284	95	50
10	311	50	304	98	50	296	95	50
11	320	50	315	98	50	306	96	50
12	329	50	325	99	50	316	96	50
17	368	50	365	99	50	356	97	50
21	392	50	393	100	50	378	96	50
26	411	50	412	100	50	396	96	50
31	423	50	425	100	50	406	96	50
34	433	50	437	101	50	415	96	50
39	443	50	449	101	50	433	98	50
44	458	49	461	101	50	443	97	50
48	467	49	471	101	50	451	97	50
52	465	49	470	101	50	451	97	50
58	469	49	478	102	50	458	98	50
63	469	49	475	101	50	457	97	50
67	472	49	481	102	50	463	98	50
71	465	49	480	103	48	462	99	50
75	463	49	474	102	48	458	99	50
79	471	48	479	102	47	463	98	49
83	466	47	471	101	47	457	98	48
88	459	44	467	102	43	454	99	45
92	449	40	462	103	35	441	98	41
96	450	34	455	101	32	427	95	34
100	430	29	459	107	25	430	100	24
104	445	24	439	99	19	402	90	19
FEMALE								
0	122	50	122	100	50	121	99	50
1	144	50	146	101	50	142	99	50
2	152	50	155	102	50	155	102	50
3	160	50	160	100	50	156	98	50
4	170	50	173	102	50	168	99	50
5	177	50	178	101	50	172	97	50
6	178	50	181	102	50	176	99	50
7	183	50	185	101	50	181	99	50
8	186	50	188	101	50	182	98	50
9	187	50	191	102	50	185	99	50
10	193	50	196	102	50	191	99	50
11	195	50	199	102	50	192	98	50
12	198	50	201	102	50	193	97	50
17	209	50	215	103	50	207	99	50
21	218	50	223	102	50	213	98	50
26	225	50	230	102	50	220	98	50
31	234	50	238	102	50	228	97	50
34	239	50	242	101	50	232	97	50
39	246	50	253	103	50	242	98	50
44	260	50	264	102	50	251	97	50
48	267	50	271	101	50	258	97	50
52	272	50	277	102	50	261	96	50
58	287	49	288	100	50	271	94	49
63	296	49	298	101	50	280	95	48
67	309	49	310	100	50	288	93	48
71	314	48	316	101	47	300	96	48
75	320	48	324	101	47	310	97	47
79	335	46	337	101	44	322	96	46
83	342	46	348	102	43	328	96	46
88	347	43	355	102	40	338	97	46
92	350	39	360	103	40	340	97	45
96	355	36	363	102	40	343	97	44
100	352	32	360	102	37	344	98	39
104	355	28	345	97	36	342	96	32

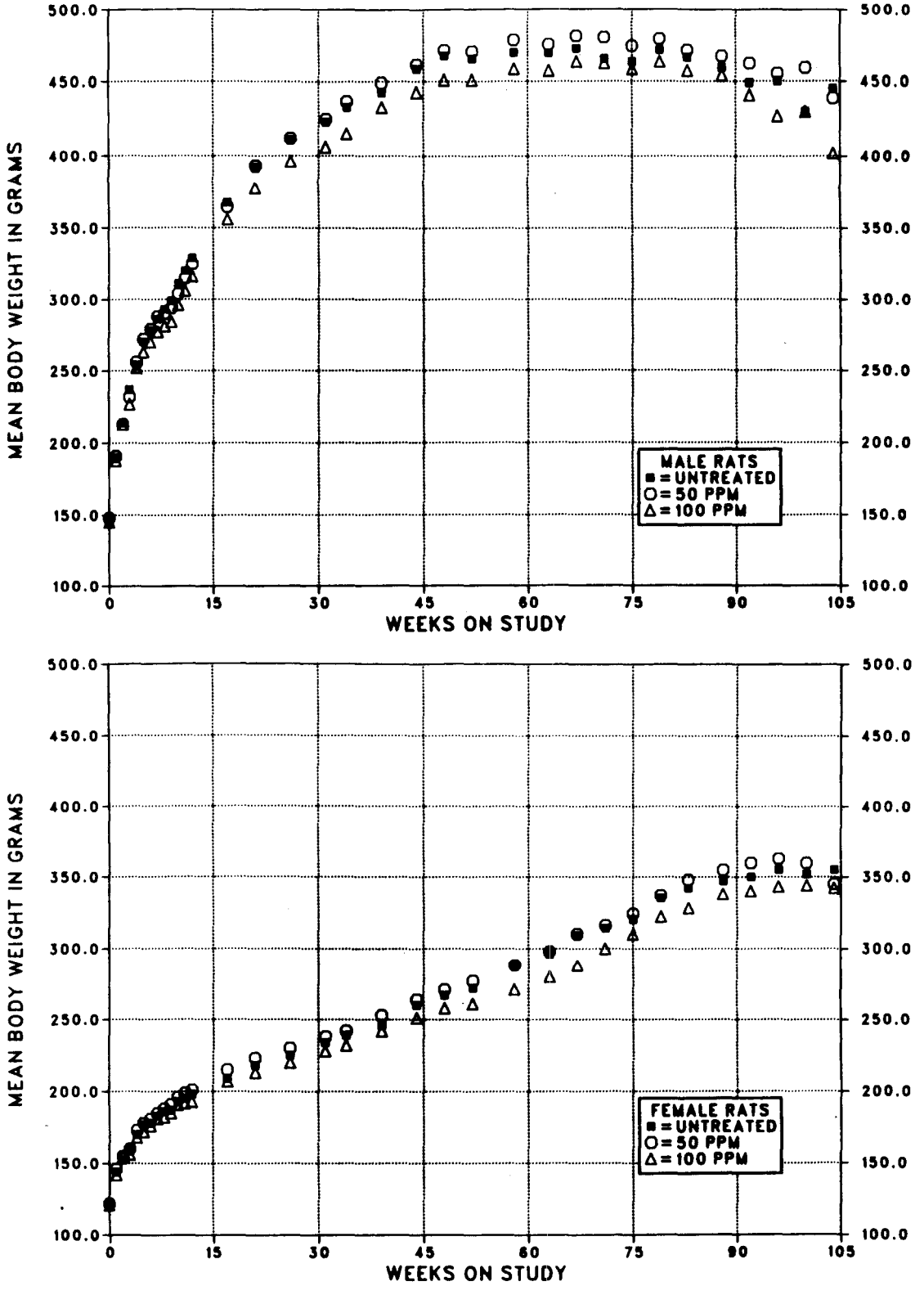


FIGURE 3. GROWTH CURVES FOR RATS FED DIETS CONTAINING ROXARSONE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing roxarsone at the concentrations used in these studies and for controls are shown in Table 13 and in the Kaplan and Meier curves in Figure 4 No 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 pancreas, pancreatic islets, anterior pituitary gland, clitoral gland, jejunum, adrenal gland, and eye

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 13. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF ROXARSONE

	Control	50 ppm	100 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	26	32	32
Killed at termination	24	18	18
Survival P values (c)	0.378	0.333	0.398
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	23	15	18
Killed at termination	27	35	32
Survival P values (c)	0.284	0.205	0.300

(a) First day of terminal-kill period: 729
(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.

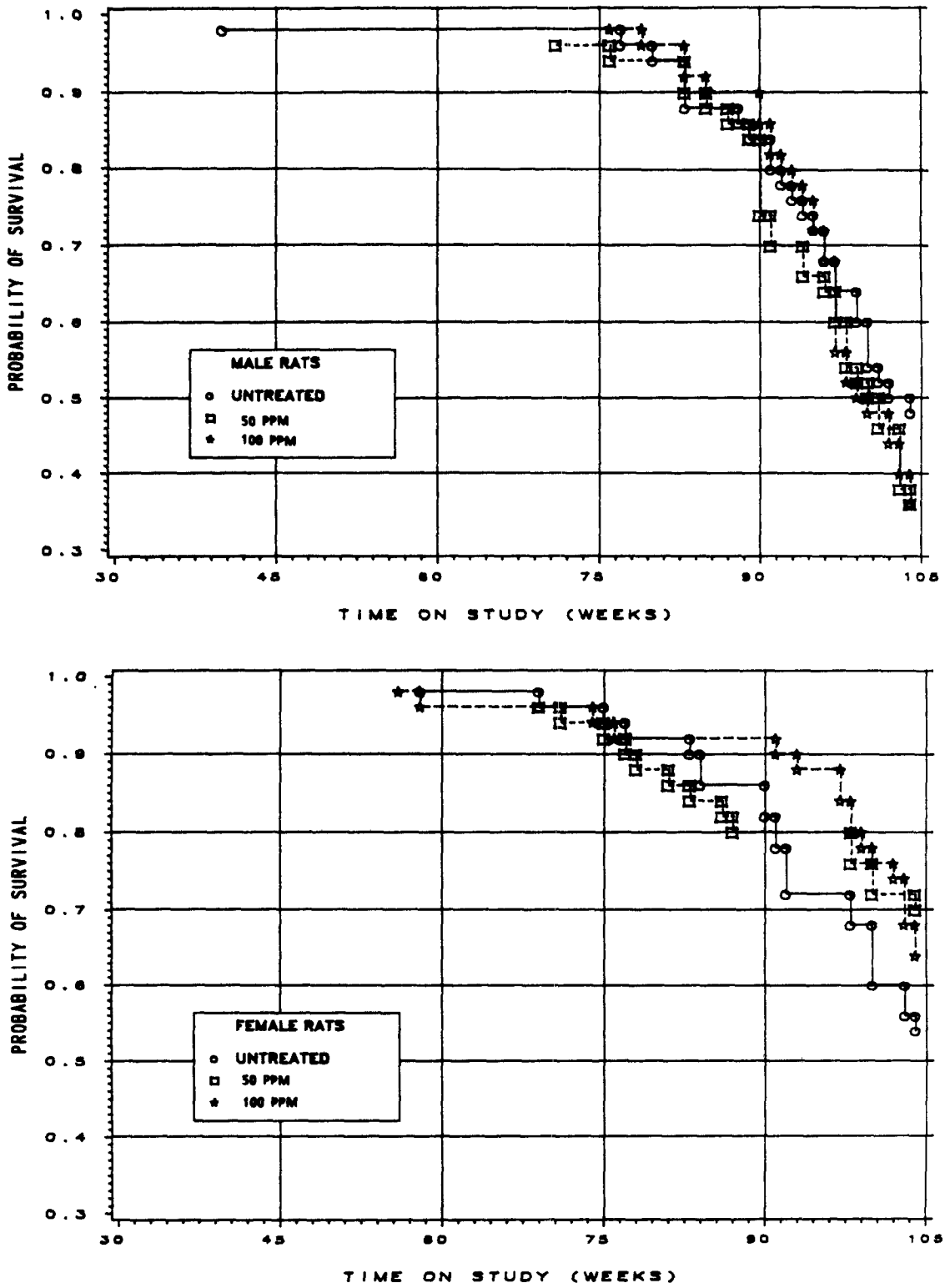


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING ROXARSONE FOR TWO YEARS

Pancreas: Although the incidence of adenomas of the exocrine pancreas in high dose male rats was not significantly greater than that in the controls (Table 14), it was greater than that seen in any historical control group of male F344/N rats. Focal hyperplasia occurred in two control and three high dose male rats. Focal hyperplasia and adenomas are part of a morphologic spectrum, and adenomas are distinguished from hyperplasia on the basis of size and the degree of alteration of the acinar structure. Adenomas were not observed in any female rats.

Pancreatic Islets: Adenomas in male rats occurred with a significant positive trend (control, 0/50; low dose, 3/50; high dose, 4/50; $P<0.05$); the incidences in the dosed groups were not significantly different from that in the controls. The incidences of adenomas or carcinomas (combined) in dosed groups were not significantly different from that in the controls (2/50; 4/50; 4/50).

TABLE 14. ANALYSIS OF LESIONS OF THE EXOCRINE PANCREAS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ROXARSONE (a)

	Control	50 ppm (b)	100 ppm (b)
Focal Hyperplasia			
Overall Rates	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adenoma (c)			
Overall Rates	1/50 (2%)	1/50 (2%)	5/50 (10%)
Adjusted Rates	4.2%	5.6%	18.8%
Terminal Rates	1/24 (4%)	1/18 (6%)	1/18 (6%)
Day of First Observation	729	729	664
Life Table Tests	P=0.035	P=0.697	P=0.075
Logistic Regression Tests	P=0.046	P=0.697	P=0.099

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (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 pancreatic acinar cell adenomas or carcinomas (combined) at study laboratory (mean ± SD): 1/437 (0.2% ± 0.7%); historical incidence in NTP studies: 5/1,871 (0.3% ± 0.9%)

Anterior Pituitary Gland: The incidence of adenomas of the pars distalis in low dose male rats was significantly greater than that in the controls (Table 15). The incidences of adenomas and adenomas or carcinomas (combined) of the pars distalis in female rats occurred with significant negative trends; the incidence of adenomas or carcinomas (combined) in the high dose group was significantly lower than that in the controls.

TABLE 15. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF ROXARSONE

	Control	50 ppm	100 ppm
MALE			
Focal Hyperplasia			
Overall Rates	8/50 (16%)	11/48 (23%)	6/48 (13%)
Adenoma (a)			
Overall Rates	6/50 (12%)	13/48 (27%)	8/48 (17%)
Adjusted Rates	21.4%	49 3%	34.4%
Terminal Rates	4/24 (17%)	7/18 (39%)	4/17 (24%)
Day of First Observation	616	495	671
Life Table Tests	P=0.188	P=0.026	P=0.224
Logistic Regression Tests	P=0.307	P=0.049	P=0.325
FEMALE			
Focal Hyperplasia			
Overall Rates	9/50 (18%)	6/49 (12%)	13/48 (27%)
Adenoma			
Overall Rates	27/50 (54%)	28/49 (57%)	18/48 (38%)
Adjusted Rates	69.5%	67.7%	46.5%
Terminal Rates	16/27 (59%)	21/34 (62%)	11/31 (35%)
Day of First Observation	485	486	678
Life Table Tests	P=0.019N	P=0.320N	P=0.025N
Logistic Regression Tests	P=0 049N	P=0.463	P=0.059N
Carcinoma			
Overall Rates	1/50 (2%)	0/49 (0%)	0/48 (0%)
Adenoma or Carcinoma (b)			
Overall Rates	28/50 (56%)	28/49 (57%)	18/48 (38%)
Adjusted Rates	70.4%	67 7%	46.5%
Terminal Rates	16/27 (59%)	21/34 (62%)	11/31 (35%)
Day of First Observation	485	486	678
Life Table Tests	P=0 013N	P=0 260N	P=0 017N
Logistic Regression Tests	P=0.032N	P=0.544	P=0.039N

(a) Historical incidence of adenomas or carcinomas (combined) at study laboratory (mean ± SD): 86/428 (20% ± 9%), historical incidence in NTP studies: 449/1,825 (25% ± 11%)
(b) Historical incidence at study laboratory (mean ± SD): 167/436 (38% ± 13%); historical incidence in NTP studies: 942/1,922 (49% ± 11%)

Clitoral Gland: The incidences of adenomas in female rats occurred with a significant positive trend by logistic regression analysis (Table 16). The incidences of adenomas or carcinomas (combined) in the dosed groups were not significantly different from that in the controls.

Jejunum: Leiomyosarcomas were observed in 2/50 low dose male rats. The historical incidence of leiomyosarcomas in the small intestine of untreated male F344/N rats is 2/1,865 (0.1%); both neoplasms were observed at this study laboratory.

Adrenal Gland: Fatty degeneration of the adrenal cortex was seen at increased incidences in high dose female rats (male: control, 10/50; low dose, 10/50; high dose, 15/50; female: 6/50; 8/50; 17/50).

Eye: Cataracts and retinal degeneration were observed at increased incidences in high dose male and low dose female rats (cataracts--male: control, 2/4; low dose, 1/6; high dose, 21/25; female: 2/3; 19/20; 3/5; retinal degeneration--male: 3/4; 2/6; 23/25; female: 2/3; 20/20; 4/5). All animals were examined grossly for eye lesions. The denominator denotes the number of animals with gross eye lesions that were subjected to microscopic evaluation. These changes are believed to be related not to the administration of roxarsone but rather to the proximity of animal cages to the light source in the animal room. These studies were conducted before initiation of routine animal cage rotation, a procedure instituted for the purpose of randomizing animals with respect to light. High dose males and low dose females (groups with the greatest incidences of eye lesions) were housed in the top tiers of their respective cage racks. Control males and high dose females were housed in intermediate tiers and control females and low dose males in the bottom tiers.

TABLE 16. ANALYSIS OF CLITORAL GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ROXARSONE

	Control	50 ppm	100 ppm
Hyperplasia			
Overall Rates	2/44 (5%)	7/47 (15%)	4/48 (8%)
Adenoma			
Overall Rates	1/44 (2%)	3/47 (6%)	6/48 (13%)
Adjusted Rates	4.2%	8.9%	16.8%
Terminal Rates	1/24 (4%)	2/32 (6%)	3/30 (10%)
Day of First Observation	729	728	530
Life Table Tests	P=0.057	P=0.410	P=0.100
Logistic Regression Tests	P=0.049	P=0.393	P=0.074
Carcinoma			
Overall Rates	1/44 (2%)	1/47 (2%)	1/48 (2%)
Adenoma or Carcinoma (a)			
Overall Rates	2/44 (5%)	4/47 (9%)	7/48 (15%)
Adjusted Rates	7.1%	10.7%	19.9%
Terminal Rates	1/24 (4%)	2/32 (6%)	4/30 (13%)
Day of First Observation	701	486	530
Life Table Tests	P=0 091	P=0.438	P=0.142
Logistic Regression Tests	P=0 070	P=0.370	P=0.106

(a) Historical incidence of adenomas, adenocarcinomas, or carcinomas (combined) at study laboratory (mean ± SD): 17/439 (4% ± 4%); historical incidence in NTP studies: 96/1,984 (5% ± 3%)

SINGLE-ADMINISTRATION STUDIES

All mice that received 600 mg/kg and 5/5 male mice and 4/5 female mice that received 300 mg/kg died before the end of the studies (Table 17). Diarrhea and ataxia were considered to be compound related. Final body weights were not recorded.

FOURTEEN-DAY STUDIES

Two of five males and 5/5 females that received 1,000 ppm died before the end of the studies (Table 18). Males that received 1,000 ppm and females that received 500 ppm lost weight during the studies. Feed consumption by mice at 1,000 ppm was lower than that by controls. Slight to moderate inactivity was observed for male and female mice that received 250, 500, or 1,000 ppm. Pale skin and ruffled fur were also considered to be compound related.

TABLE 17. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF ROXARSONE

Dose (mg/kg)	Survival (a)	Initial Mean Body Weight (grams) (b)
MALE		
38	5/5	22.2 ± 0.6
75	5/5	22.6 ± 0.5
150	5/5	22.0 ± 0.4
300	(c) 0/5	21.6 ± 0.5
600	(d) 0/5	23.0 ± 0.5
FEMALE (e)		
38	5/5	19.0 ± 0.4
75	5/5	19.4 ± 0.6
150	5/5	19.6 ± 0.5
300	(f) 1/5	19.6 ± 0.4
600	(g) 0/5	19.6 ± 0.4

(a) Number surviving/number in group
(b) Initial group mean body weight ± standard error of the mean; final body weights were not recorded.
(c) Day of death: 4,5,5,5,5
(d) Day of death: 2,2,3,3,4
(e) LD_{50} value by the Spearman-Karber method (95% confidence interval): 244 mg/kg (186-320 mg/kg)
(f) Day of death: 5,5,5,6
(g) Day of death: 3,4,4,5,5

TABLE 18. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF ROXARSONE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Day 7	Day 13
MALE							
0	5/5	24.2 ± 0.4	26.2 ± 0.4	+2.0 ± 0.0		6	5
60	5/5	24.8 ± 0.7	26.0 ± 0.8	+1.2 ± 0.2	99.2	9	9
120	5/5	25.2 ± 1.4	28.0 ± 1.5	+2.8 ± 0.4	106.9	9	5
250	5/5	23.2 ± 1.0	25.2 ± 1.2	+2.0 ± 0.3	96.2	9	4
500	5/5	24.2 ± 0.5	25.2 ± 1.2	+1.0 ± 0.8	96.2	9	6
1,000	(e) 3/5	23.6 ± 0.5	17.3 ± 0.3	−5.7 ± 0.7	66.0	4	3
FEMALE							
0	5/5	20.2 ± 0.4	22.0 ± 0.5	+1.8 ± 0.4		6	8
60	5/5	21.0 ± 0.6	22.4 ± 0.2	+1.4 ± 0.5	101.8	7	9
120	5/5	19.4 ± 0.5	20.6 ± 0.9	+1.2 ± 0.6	93.6	12	9
250	5/5	19.6 ± 0.2	20.8 ± 0.4	+1.2 ± 0.2	94.5	12	8
500	5/5	21.0 ± 0.7	19.8 ± 0.9	−1.2 ± 0.5	90.0	9	6
1,000	(f) 0/5	19.8 ± 0.6	(g)	(g)	(g)	5	(g)

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; not corrected for scatter.
(e) Day of death: 13,14
(f) Day of death: 10,10,10,11,12
(g) No data are reported due to 100% mortality in this group.

FIRST THIRTEEN-WEEK STUDIES

Six of 10 males and 8/10 females that received 800 ppm and 1/10 males and 1/10 females that received 400 ppm died before the end of the studies (Table 19). The final mean body weight of mice that received 800 ppm roxarsone was 18% lower than that of controls for males and 11% lower for females. Feed consumption data for the 800-ppm groups suggest that the feed was scattered. The mean liver weight of male mice that received 800 ppm was significantly lower than that of controls (Table 20). No compound-related lesions were observed. Severe interstitial pneumonia with peribronchiolar epithelial hyperplasia was observed in the 800-ppm mice that died before the end of the studies. The lesions were characteristic of morphologic changes seen in early-stage Sendai infection. The survivors at 800 ppm had lesions characteristic of late-stage Sendai infection.

TABLE 19. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE FIRST THIRTEEN-WEEK FEED STUDIES OF ROXARSONE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 4	Week 13
MALE							
0	10/10	20.3 ± 0.4	27.9 ± 0.6	+7.6 ± 0.3		7	9
50	10/10	20.0 ± 0.4	30.6 ± 0.5	+10.6 ± 0.5	109.7	8	11
100	10/10	20.0 ± 0.4	31.8 ± 0.8	+11.8 ± 0.6	114.0	9	11
200	10/10	20.2 ± 0.6	31.5 ± 0.5	+11.3 ± 0.5	112.9	8	10
400	(e) 9/10	20.4 ± 0.6	29.6 ± 1.1	+9.0 ± 0.6	106.1	9	10
800	(f) 4/10	20.8 ± 0.6	23.0 ± 0.6	+2.0 ± 1.0	82.4	18	16
FEMALE							
0	9/10	17.9 ± 0.6	24.7 ± 0.4	+6.8 ± 0.6		9	9
50	10/10	16.4 ± 0.3	24.7 ± 0.5	+8.3 ± 0.3	100.0	7	10
100	10/10	16.7 ± 0.6	24.4 ± 0.3	+7.7 ± 0.5	98.8	8	9
200	10/10	16.8 ± 0.7	24.4 ± 0.7	+7.6 ± 0.6	98.8	8	10
400	(e) 9/10	16.9 ± 0.5	24.0 ± 0.9	+7.0 ± 0.6	97.2	9	10
800	(g) 2/10	17.1 ± 0.6	22.0 ± 1.0	+4.0 ± 0.0	89.1	20	14

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; not corrected for scatter.
(e) Week of death: 1
(f) Week of death: 2,2,2,2,3,3
(g) Week of death: 2,2,2,3,3,3,3,3

TABLE 20. ANALYSIS OF LIVER WEIGHTS OF MICE IN THE FIRST THIRTEEN-WEEK FEED STUDIES OF ROXARSONE (a)

Concentration (ppm)	Number Examined	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Necropsy Body Weight (mg/g)
MALE				
0	10	28.6 ± 0.54	1,233 ± 41	43.2 ± 1.63
50	10	30.9 ± 0.43	(b) 1,427 ± 43	46.3 ± 1.69
100	10	(c) 31.9 ± 0.67	1,328 ± 53	41.7 ± 1.49
200	10	(b) 31.5 ± 0.60	1,313 ± 40	41.7 ± 1.05
400	9	29.1 ± 1.02	1,303 ± 43	44.8 ± 0.57
800	4	(c) 23.3 ± 0.48	(c) 868 ± 42	37.3 ± 1.26
FEMALE				
0	9	26.2 ± 0.55	1,152 ± 50	43.9 ± 1.34
50	10	25.4 ± 0.69	1,099 ± 28	43.3 ± 0.62
100	10	25.8 ± 0.65	1,154 ± 45	44.8 ± 1.38
200	10	24.6 ± 0.45	1,060 ± 29	43.1 ± 0.64
400	9	24.2 ± 0.78	1,106 ± 53	45.5 ± 1.30
800	2	(b) 22.0 ± 1.00	940 ± 60	42.7 ± 0.78

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

SECOND THIRTEEN-WEEK STUDIES

None of the results of hematologic tests indicated any biologically significant differences between dosed and control mice (Table 21). Arsenic was detected at significantly increased concentrations in the liver and kidney of male and female mice that received 100 or 400 ppm. Relative kidney and liver weights of dosed mice were not significantly different from those of controls (Table 22). No compound-related histopathologic lesions were observed.

Dose Selection Rationale: Because of the incidence of deaths at 400 ppm and above and the lower mean body weight gain at 800 ppm, dietary concentrations of roxarsone selected for mice for the 2-year studies were 100 and 200 ppm.

TABLE 21. RESULTS OF HEMATOLOGIC, BIOCHEMICAL, AND ARSENIC ANALYSES FOR MICE IN THE SECOND THIRTEEN-WEEK FEED STUDIES OF ROXARSONE (a)

Analysis	Day	Male			Female		
		Control	100 ppm	400 ppm	Control	100 ppm	400 ppm
Erythrocyte count (10^6/mm^3)	9	(b) 10 55 ± 0 24	10.76 ± 0 46	(c) 9 54 ± 0 31	9 39 ± 0 17	(c) 10 22 ± 0 30	9 39 ± 0 24
	29	8 22 ± 0 09	(d) 8 95 ± 0 17	8 26 ± 0 09	(b) 8 27 ± 0 16	8 50 ± 0 20	8 09 ± 0 11
	91	8 62 ± 0 15	8 66 ± 0 10	(b) 8 47 ± 0 20	8 82 ± 0 19	(b) 8 84 ± 0 17	(b c) 7 92 ± 0 29
Hematocrit value (percent)	9	(b) 43 78 ± 1 06	41 00 ± 1 11	(c) 40 00 ± 0 99	39 70 ± 1 14	39 10 ± 0 67	40 20 ± 0 98
	29	38 05 ± 0 39	39 65 ± 0 78	38 55 ± 0 52	(b) 37 22 ± 0 72	39 15 ± 1 09	37 25 ± 0 76
	91	35 00 ± 0 67	35 95 ± 0 79	(b) 34 56 ± 0 82	35 30 ± 0 90	(b) 35 28 ± 0 98	(b,d) 30 72 ± 1 06
Hemoglobin concentration (g/dl)	9	(b) 16 79 ± 0 35	17 60 ± 0 66	15 54 ± 0 48	15 22 ± 0 36	(c) 16 59 ± 0 48	15 32 ± 0 37
	29	13 27 ± 0 14	(d) 14 03 ± 0 21	13 40 ± 0 14	(b) 13 47 ± 0 30	13 89 ± 0 36	13 20 ± 0 17
	91	13 61 ± 0 23	14 01 ± 0 18	(b) 13 52 ± 0 30	14 19 ± 0 30	(b) 14 21 ± 0 30	(b,d) 12 54 ± 0 45
Leukocyte count (1,000/mm^3)	9	(b) 4 58 ± 0 62	4 14 ± 0 35	3 58 ± 0 34	5 38 ± 0 32	5 29 ± 0 27	4 90 ± 0 61
	29	5 98 ± 0 66	6 19 ± 0 61	4 53 ± 0 71	(b) 6 29 ± 0 80	5 80 ± 0 64	5 49 ± 0 76
	91	5 23 ± 0 65	6 40 ± 0 66	(b) 4 86 ± 0 79	7 35 ± 2 36	(b) 6 42 ± 0 76	(b) 5 10 ± 0 57
Platelet count (1,000/mm^3)	9	(b) 119 ± 13 6	(c) 148 ± 21 1	147 ± 16 6	90 ± 10 7	84 4 ± 24 6	86 3 ± 12 7
	29	211 ± 33 4	210 ± 20 1	180 ± 27 3	(b) 219 ± 36 2	213 ± 36 1	196 ± 23 3
	91	197 ± 14 3	(d) 126 ± 9 5	(b,d) 124 ± 14 2	164 ± 11 4	(b) 133 ± 12 7	(b d) 106 ± 9 7
Segmented neutrophil count (1,000/mm^3)	9	(b) 1 46 ± 0 19	(c) 0 96 ± 0 13	(c) 0 93 ± 0 13	0 78 ± 0 08	(d) 1 40 ± 0 15	1 13 ± 0 17
	29	1 76 ± 0 25	1 42 ± 0 16	1 15 ± 0 19	(b) 1 30 ± 0 17	1 07 ± 0 09	1 03 ± 0 18
	91	2 02 ± 0 28	2 90 ± 0 49	(b) 2 02 ± 0 72	2 02 ± 0 69	(b) 1 57 ± 0 21	(b) 1 08 ± 0 17
Lymphocyte count (1,000/mm^3)	9	(b) 3 10 ± 0 46	3 17 ± 0 25	2 64 ± 0 26	4 58 ± 0 36	3 85 ± 0 34	3 74 ± 0 48
	29	4 13 ± 0 43	4 74 ± 0 49	3 33 ± 0 61	(b) 4 87 ± 0 66	4 68 ± 0 60	4 40 ± 0 59
	91	3 18 ± 0 47	3 44 ± 0 61	(b) 2 78 ± 0 44	5 30 ± 1 66	(b) 4 83 ± 0 69	(b) 3 97 ± 0 42
Eosinophil count (1,000/mm^3)	9	(b) 0 015 ± 0 010	0 004 ± 0 004	0 015 ± 0 010	0 025 ± 0 010	0 029 ± 0 010	0 029 ± 0 013
	29	0 096 ± 0 029	(c) 0 030 ± 0 015	0 052 ± 0 014	(b) 0 113 ± 0 022	(c) 0 048 ± 0 027	0 064 ± 0 015
	91	0 032 ± 0 014	0 064 ± 0 025	(b) 0 049 ± 0 023	0 030 ± 0 022	(b) 0 019 ± 0 013	(b) 0 052 ± 0 027
Reticulocyte count (10^6/mm^3)	9	(b) 0 09 ± 0 01	(d) 0 17 ± 0 02	(c) 0 15 ± 0 02	0 18 ± 0 02	0 14 ± 0 01	(c) 0 12 ± 0 02
	29	0 13 ± 0 01	(d) 0 29 ± 0 03	(d) 0 22 ± 0 01	(b) 0 18 ± 0 01	0 22 ± 0 03	0 17 ± 0 01
	91	0 16 ± 0 02	0 17 ± 0 02	(b,c) 0 20 ± 0 02	0 16 ± 0 01	(b) 0 18 ± 0 02	(c e) 0 23 ± 0 02
Arsenic in liver (f)	91	0 00 ± 0 00	(d) 0 45 ± 0 04	(d) 0 73 ± 0 02	0 00 ± 0 00	(b,d) 0 50 ± 0 02	(b,d) 0 99 ± 0 04
Arsenic in kidney (f)	91	0 00 ± 0 00	(d) 0 85 ± 0 04	(b,d) 1 85 ± 0 15	0 00 ± 0 00	(d,e) 0 86 ± 0 10	(b,d) 2 98 ± 0 30

(a) Values are mean ± standard error; except as noted, data are for 10 animals P values are vs the controls by the Wilcoxon rank sum test (Hollander and Wolfe, 1973).
(b) Nine animals were examined
(c) $P<0.05$
(d) $P<0.01$
(e) Eight animals were examined
(f) Micrograms arsenic/gram of tissue

TABLE 22. ANALYSIS OF LIVER AND KIDNEY WEIGHTS OF MICE IN THE SECOND THIRTEEN-WEEK FEED STUDIES OF ROXARSONE (a)

Concentration (ppm)	Number Examined	Final Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Final Body Weight (mg/g)	Kidney Weight (mg)	Kidney Weight/ Final Body Weight (mg/g)
MALE						
0	10	28.9 ± 1.34	1,209 ± 54	42.1 ± 1.45	420 ± 22	14.6 ± 0.56
100	10	30.0 ± 0.67	1,272 ± 30	42.4 ± 0.72	449 ± 15	15.0 ± 0.35
400	9	28.8 ± 0.70	1,225 ± 18	42.7 ± 0.87	418 ± 16	14.5 ± 0.32
FEMALE						
0	10	24.6 ± 0.31	1,064 ± 21	43.2 ± 0.53	318 ± 6	12.9 ± 0.20
100	9	26.1 ± 0.77	1,115 ± 36	42.7 ± 0.92	318 ± 13	12.2 ± 0.30
400	9	23.7 ± 0.50	969 ± 38	40.9 ± 1.05	306 ± 19	12.9 ± 1.63

(a) Mean ± standard error; P values vs. the controls by Dunnett's test (Dunnett, 1955).

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of high dose male mice were generally 5%-8% higher than those of the controls after week 24 (Table 23 and Figure 5). Mean body weights of low dose male mice were generally 3%-5% higher than those of the controls after week 24. Mean body weights of high dose female mice were generally 6%-15% lower than those of the controls after week 68. Mean body weights of low dose female mice were generally 6%-11% lower than those of the controls after week 93. The average daily feed consumption by low dose and high dose male mice was 105% and 111% that by the controls and by low dose and high dose female mice, 106% that by the controls (Tables G3 and G4). The average amount of roxarsone consumed per day was approximately 21 or 43 mg/kg for low dose or high dose male mice and 27 or 54 mg/kg for low dose or high dose female mice. No compound-related clinical signs were observed.

TABLE 23. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF ROXARSONE

Weeks on Study	Control		100 ppm			200 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	22 3	50	22 6	101	50	22 4	100	50
1	24 7	50	23 2	94	50	25 3	102	50
2	26 4	50	24 2	92	50	26 2	99	50
3	27 2	50	27 5	101	50	27 6	101	50
4	28 5	50	29 1	102	50	28 4	100	50
5	29 2	50	29 4	101	50	28 8	99	50
6	29 2	50	29 7	102	50	29 3	100	50
7	29 9	50	30 8	103	50	30 5	102	50
8	30 9	50	31 0	100	50	30 8	100	50
9	31 0	50	32 0	103	50	31 8	103	50
10	31 0	50	31 5	102	50	31 2	101	50
11	32 5	50	33 3	102	50	33 0	102	50
12	32 8	50	32 3	98	50	32 9	100	50
14	33 3	50	32 4	97	50	32 7	98	50
19	34 7	50	34 6	100	49	35 1	101	49
24	35 0	50	36 2	103	49	37 1	106	48
28	35 5	50	36 6	103	49	37 8	106	48
33	36 0	49	36 4	101	49	38 5	107	48
37	36 7	49	38 0	104	49	38 8	106	48
40	38 0	49	38 7	102	49	39 9	105	48
46	37 4	48	38 9	104	49	40 1	107	48
50	38 3	48	39 8	104	49	41 3	108	48
55	37 7	48	39 1	104	49	40 1	106	48
60	37 6	48	39 7	106	49	40 6	108	48
65	37 6	48	39 3	105	49	39 9	106	47
68	37 9	46	39 1	103	49	39 9	105	47
72	37 9	46	39 5	104	49	40 1	106	46
76	37 6	45	39 6	105	49	40 3	107	46
80	37 5	43	38 0	101	48	40 4	108	46
84	37 8	43	39 5	104	47	40 7	108	46
89	37 9	40	38 9	103	47	40 2	106	44
93	37 6	37	38 9	103	45	39 6	105	40
97	38 0	34	39 7	104	43	39 1	103	37
101	37 8	32	38 9	103	43	39 3	104	35
103	37 3	27	39 1	105	40	39 4	106	33
FEMALE								
0	17 4	50	17 1	98	50	17 1	98	50
1	19 1	50	18 8	98	50	18 8	98	50
2	19 9	50	19 6	98	50	20 0	101	50
3	20 9	50	21 0	100	50	20 7	99	50
4	21 3	50	21 6	101	50	21 1	99	50
5	22 0	50	22 0	100	50	22 0	100	50
6	22 3	49	22 8	102	50	22 8	102	50
7	23 2	49	23 5	101	50	23 2	100	50
8	23 4	49	23 3	100	50	23 0	98	50
9	23 3	49	23 8	102	50	23 8	102	50
10	23 0	49	23 2	101	50	22 8	99	50
11	24 5	49	25 0	102	50	24 7	101	50
12	24 5	49	23 9	98	50	24 2	99	50
14	25 5	49	24 6	96	50	25 1	98	50
19	27 1	49	27 0	100	50	26 4	97	50
24	27 7	49	27 9	101	50	27 7	100	50
28	28 1	48	28 9	103	50	28 4	101	50
33	29 9	48	29 8	100	50	29 9	100	50
37	30 2	48	30 8	102	50	29 9	99	50
40	31 0	48	31 5	102	50	31 5	102	50
46	31 7	48	32 2	102	50	31 8	100	50
50	32 6	48	32 7	100	50	31 9	98	50
55	32 8	48	31 5	96	50	31 5	96	50
60	33 1	47	32 5	98	50	31 6	95	50
65	32 8	46	32 2	98	50	31 2	95	49
68	34 3	45	32 9	96	50	32 1	94	48
72	35 1	42	33 8	96	44	32 7	93	41
76	35 4	38	35 3	100	35	33 1	94	37
80	37 4	34	35 5	95	35	33 5	90	34
84	38 6	34	37 2	96	34	34 3	89	32
89	39 4	32	37 3	95	30	36 2	92	24
93	39 7	28	37 5	94	24	35 8	90	24
97	42 0	23	38 4	91	20	36 9	88	21
101	41 4	19	36 9	89	18	36 2	87	20
103	42 0	14	37 3	89	18	35 8	85	17

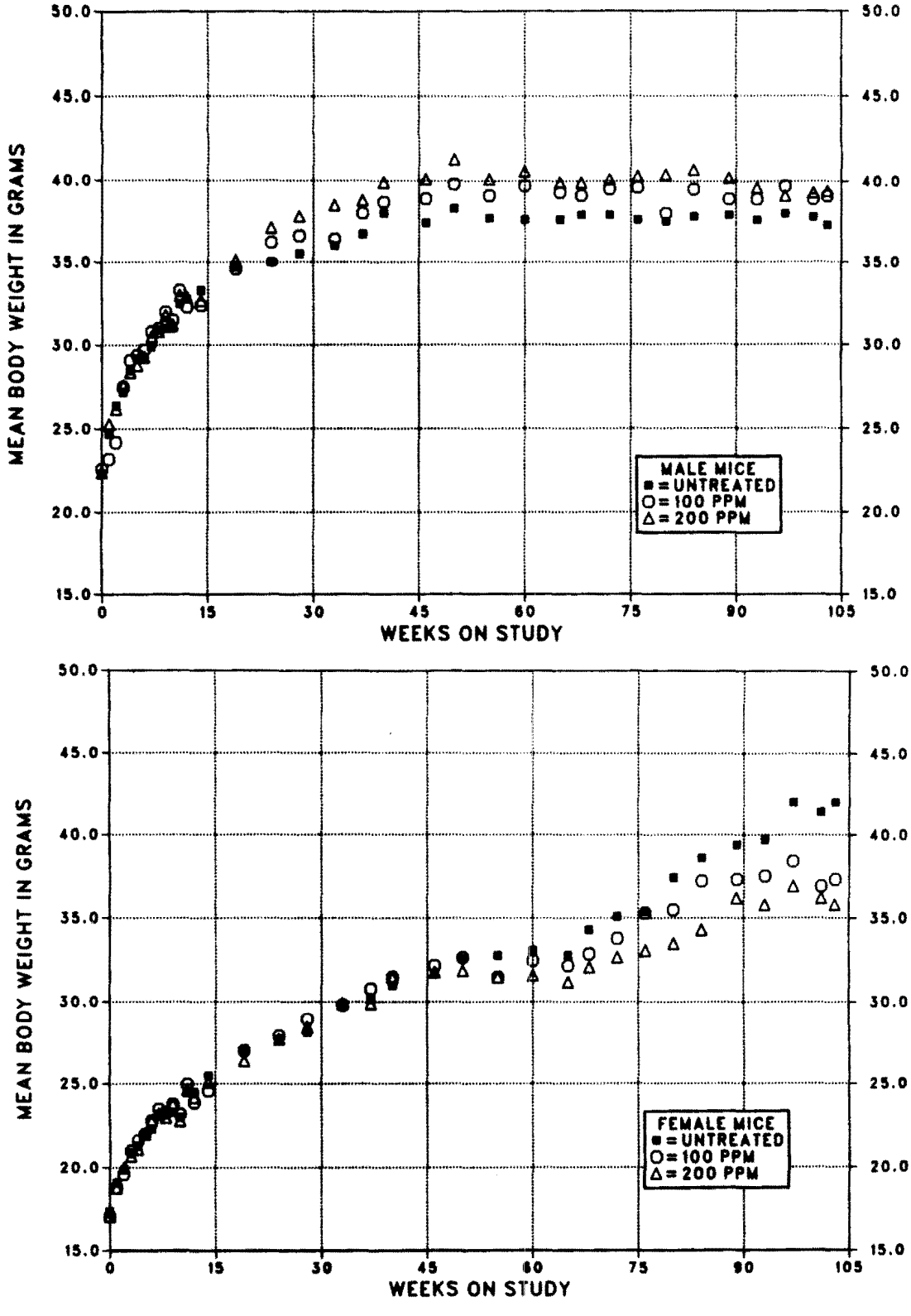


FIGURE 5. GROWTH CURVES FOR MICE FED DIETS CONTAINING ROXARSONE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing roxarsone at the concentrations used in these studies and for controls are shown in Table 24 and in the Kaplan and Meier curves in Figure 6. The survival of the control group of male mice was significantly lower than that of the low dose group after day 665. 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 mice with neoplastic or nonneoplastic lesions of the adrenal gland, hematopoietic system, lung, ovary, and uterus.

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.

TABLE 24. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF ROXARSONE

	Control	100 ppm	200 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	23	10	17
Killed at termination	27	40	33
Survival P values (c)	0.248	0.009	0 319
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	35	32	33
Accidentally killed	1	0	0
Killed at termination	14	18	17
Survival P values (c)	1.000	0.902	1.000

(a) First day of terminal-kill period: 729
(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.

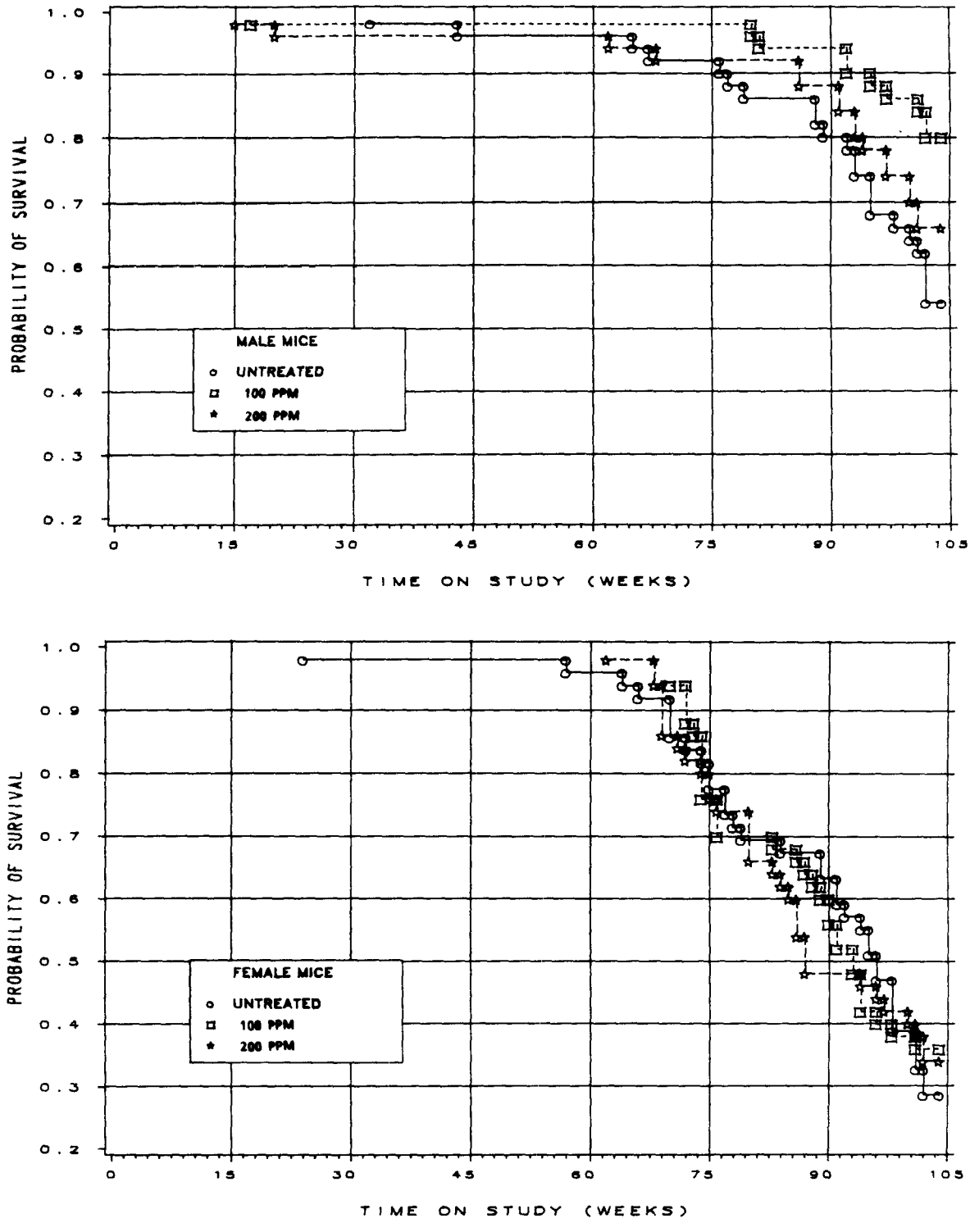


FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING ROXARSONE FOR TWO YEARS

Adrenal Gland: Adenomas of the adrenal cortex in male mice occurred with a significant positive trend; the incidences in the dosed groups were not significantly different from that in the controls (control, 0/50; low dose, 2/50; high dose, 4/49).

Although the pathologist at the study laboratory diagnosed hyperplasia in only 2/50 low dose and 1/49 high dose male mice, this change is present in nearly all aged mice. A review of the adrenal glands for the incidence and severity of hyperplasia by a pathologist at the NTP Archives showed similar results among the dosed groups and the controls (Table 25).

Hematopoietic System: Lymphomas in female mice occurred with a significant negative trend; the incidences in the dosed groups were significantly lower than that in the controls (Table 26).

Lung: Adenomatosis and inflammation were observed at increased incidences in dosed male mice (adenomatosis--male: control, 14/50; low dose, 28/50; high dose, 24/50; female: 19/50; 23/50; 13/50; inflammation--male: 21/50; 31/50; 26/50; female: 19/50; 25/50; 16/50). The lesions were characteristic of those seen with Sendai virus infection, which was confirmed in mice by serologic determination (Table F1). They were located in the alveoli surrounding the terminal bronchioles and consisted of hyperplasia of type II alveolar epithelial cells, ciliated epithelial metaplasia, and accumulation of alveolar macrophages and other mononuclear inflammatory cells in the interstitium. The incidences of alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas or carcinomas (combined) in low dose male mice were significantly lower than those in the controls (Table 27).

Ovary and Uterus: Suppurative inflammation was observed in more than 50% of female mice in the control and dosed groups. Utero-ovarian infections in aged $B6C3F_1$ mice in NTP studies are most likely caused by Klebsiella sp. infections (Rao et al., 1987).

TABLE 25. SEVERITY OF SUBCAPSULAR HYPERPLASIA OF THE ADRENAL GLAND IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ROXARSONE (a)

	Control	100 ppm	200 ppm
None	6	6	5
Minimal	15	9	12
Mild	29	32	27
Moderate	0	3	3
Severe	0	0	2
TOTAL	50	50	49

(a) Number of animals with indicated severity

TABLE 26. ANALYSIS OF LYMPHOMAS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ROXARSONE (a,b)

	Control	100 ppm (c)	200 ppm (c)
Overall Rates	13/50 (26%)	2/50 (4%)	3/50 (6%)
Adjusted Rates	52 0%	9 3%	9 6%
Terminal Rates	5/14 (36%)	0/18 (0%)	0/17 (0%)
Day of First Observation	170	662	534
Life Table Tests	P=0 003N	P=0 003N	P=0 010N
Logistic Regression Tests	P=0 002N	P=0 002N	P=0 007N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table D3 (footnotes)
(b) Historical incidence of lymphomas or leukemia (combined) at study laboratory (mean ± SD) 104/448 (23% ± 7%), historical incidence in NTP studies 616/2,041 (30% ± 12%)
(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 27. ANALYSIS OF ALVEOLAR/BRONCHIOLAR LESIONS IN MALE MICE IN THE TWO YEAR FEED STUDY OF ROXARSONE

	Control	100 ppm	200 ppm
Alveolar Epithelial Hyperplasia			
Overall Rates	6/50 (12%)	3/50 (6%)	2/50 (4%)
Alveolar Epithelial Metaplasia			
Overall Rates	4/50 (8%)	4/50 (8%)	3/50 (6%)
Adenoma			
Overall Rates	5/50 (10%)	3/50 (6%)	9/50 (18%)
Carcinoma			
Overall Rates	6/50 (12%)	2/50 (4%)	1/50 (2%)
Adjusted Rates	20 8%	5 0%	3 0%
Terminal Rates	5/27 (19%)	2/40 (5%)	1/33 (3%)
Day of First Observation	668	729	729
Life Table Tests	P=0 013N	P=0 047N	P=0 033N
Logistic Regression Tests	P=0 018N	P=0 074N	P=0 043N
Adenoma or Carcinoma (a)			
Overall Rates	11/50 (22%)	5/50 (10%)	10/50 (20%)
Adjusted Rates	35 7%	12 0%	28 4%
Terminal Rates	8/27 (30%)	4/40 (10%)	8/33 (24%)
Day of First Observation	665	678	702
Life Table Tests	P=0 302N	P=0 017N	P=0 326N
Logistic Regression Tests	P=0 372N	P=0 039N	P=0 400N

(a) Historical incidence at study laboratory (mean ± SD) 69/448 (15% ± 7%), historical incidence in NTP studies 353/2,032 (17% ± 7%)

IV. DISCUSSION AND CONCLUSIONS

Results of Short-Term Studies
Results of the Two-Year Studies in Rats
Results of the Two-Year Studies in Mice
Genetic Toxicity Studies
Audit
Conclusions

IV. DISCUSSION AND CONCLUSIONS

Roxarsone, an organic arsenical, was selected for toxicology and carcinogenicity studies because of potential widespread human exposure resulting from its use as a growth promoter in poultry and for treatment of dysentery in swine. Studies of roxarsone were conducted in F344/N rats and B6C3F$_1$ mice for 14 days, 13 weeks, and 2 years. The compound was given in feed because the most likely route for general human exposure is in food.

Results of Short-Term Studies

In the 14-day studies, several male and all female rats that received 1,600 ppm roxarsone died during the studies, and those exposed at 800 or 1,600 ppm lost weight. Final mean body weights of rats that received 800 ppm or more were 20% lower than those of controls. For rats, compound-related effects included slight inactivity, cyanotic eyes, and ruffled fur. All female mice and 2/5 male mice at 1,000 ppm died before the end of the studies. Slight to moderate inactivity and pale skin and ruffled fur were observed for mice.

In the 13-week studies, the major target organs of toxicity for roxarsone in rats were the nervous system and the kidney. Neurotoxic effects (trembling and ataxia) were observed in rats at the highest doses. Although these effects suggest nervous system involvement, no histopathologic changes were noted in the central nervous system of dosed rats. Peripheral nerves such as the sciatic nerve were not examined histopathologically; a peripheral nerve lesion characteristic of wallerian degeneration was reported in turkeys receiving 100 ppm roxarsone in the diet (Wise et al., 1974). Myelinic and axonal degeneration was also observed in the spinal cord of pigs fed diets containing 187.5 ppm roxarsone for 29 days (Kennedy et al., 1986). Neuropathy caused by exposure to arsenicals was observed in chickens, pigs, and humans (Heyman et al., 1956; Sullivan and Al-Tammimi, 1972; Robinson, 1975; Rice et al., 1980). Although the biochemical mechanism of the neurotoxic effects associated with roxarsone was not investigated in the current studies, it is possible that this compound may have been metabolized by rats to inorganic arsenic that in turn may have been responsible for neurotoxic effects. Arsenic is known to interfere with oxidative phosphorylation by preventing the conversion of thiamine to thiamine pyrophosphate, thus inhibiting formation of acetyl CoA and resulting in signs of thiamine deficiency (Sexton and Gowdey, 1963); affected animals may develop leg weakness and an unsteady gait (Scott et al., 1976).

The renal lesions observed in rats from the highest dose groups (mineralization, epithelial cell regeneration) were similar to those caused by a structurally related compound, arsanilic acid (Anniko and Ljungqvist, 1977). The renal lesions observed may also have been caused by arsenic poisoning resulting from the conversion of roxarsone to inorganic arsenic, but evidence for such a conversion was not obtained in this or previous studies (Moody and Williams, 1964).

In the second 13-week studies in rats, evidence was obtained for the absorption of roxarsone from the gastrointestinal tract. This was indicated by the dose-dependent increase in arsenic levels in blood, liver, and kidney for both males and females. Roxarsone at a concentration of up to 400 ppm in the diet did not produce any biologically significant hematologic or clinical chemical effects (see Table 11).

In the 13-week studies in mice, no target organs of toxicity for roxarsone were identified, even though the doses used for mice were similar to those used for rats. The dose-dependent increase in arsenic concentration in liver and kidney for both male and female mice (see Table 21) suggests gastrointestinal absorption of roxarsone.

The results of the 13-week studies indicate that rats were more likely than mice to develop a toxic response to roxarsone. The presence of kidney lesions in dosed rats but not in dosed mice may be due to a difference in the ability of the two species to eliminate the compound in urine. Metabolism of arsenic in rats is different from that in rabbits and dogs (Klaassen, 1974), and whole-body retention of arsenic has been reported to be about 20 times higher in rats than in mice (Vahter, 1981).

Results of the Two-Year Studies in Rats

Mean body weights and average daily feed consumption of dosed rats (except for high dose females) were generally within 5% of those of controls. No significant differences in survival were observed between any groups of either sex, although survival in males was lower than usual, and the cause is not known. Although Sendai infection was detected in rats, it is not considered likely that such an infection is associated with reduced survival. As reported in an abstract, the survival of male and female rats in Sendai virus-positive control groups was not significantly different from that in the groups negative for Sendai virus (Rao et al., 1988).

Adenomas of the exocrine pancreas occurred with a positive trend (control, 1/50; low dose, 1/50; high dose, 5/50) in male rats given roxarsone in the diet for 2 years. Hyperplasia at this site was seen in 2/50 control, 0/50 low dose, and 3/50 high dose male rats. The hyperplasia occurred in rats in which pancreatic neoplasms were not seen. Although it is not statistically significant, the incidence of neoplasms in the high dose group is about 50 times greater than the historical incidence observed in untreated control male F344/N rats at this laboratory (1/437, 0.2%) and about 30 times greater than that observed throughout the Program (5/1,871, 0.3%). Because the incidence of adenomas of the exocrine pancreas occurred with a positive trend and because the incidence in the high dose group exceeded the historical rate, the increased incidence of these neoplasms may have been related to roxarsone exposure. In previous studies in which corn oil was used as the vehicle, there appeared to be an association between increased body weight and adenomas of the pancreas in male F344/N rats (Haseman et al., 1985). In the present 2-year study, corn oil was not used and body weights of dosed male rats were not increased. The marginally increased incidences of acinar cell adenomas in dosed male rats were considered to be related equivocally to roxarsone exposure, both because adenomas and hyperplasia of the exocrine pancreas represent different stages of progression of the same lesion along a morphologic continuum and because there was no corresponding increase in the incidence of hyperplasia. Pancreatic adenomas were not seen in female rats or in mice. Apparently, the pancreas was not evaluated histologically in a previous feed study of roxarsone in Sprague Dawley rats (Prier et al., 1963).

Several other marginal increases occurred in male and female rats. In males, there was a positive trend in the incidence of pancreatic islet adenomas (Table A3) as well as an increase in the incidence of pituitary gland adenomas in the low dose group (see Table 15); leiomyosarcomas of the jejunum occurred in two low dose rats (Table A1). In the females, a positive trend was observed in the incidence of clitoral gland adenomas (see Table 16). NTP historical control data for this particular tumor are of limited value because historical control rates were based only on gross lesions examined microscopically and not on complete sampling of clitoral glands in each control group. (In three recent studies in which nearly all clitoral glands were examined microscopically, the incidences of tumors in controls ranged from 7% to 17%.) Because the small increases were observed in common tumors or incidences were increased in low dose groups only, none of these effects was considered to be related to administration of roxarsone.

Results of the Two-Year Studies in Mice

Final mean body weights of dosed male mice were somewhat higher than that of the controls, whereas those of dosed female mice were lower than that of controls. The survival of the low dose group of male mice was greater than that of the controls. The reason for this response is not known. The survival in all groups of female mice was unusually low (less than 40%), probably because of a utero-ovarian infection characterized by overt suppurative inflammation in the majority of the females. The poor survival of the female mice reduced the power of the study to detect a carcinogenic event; however, because more than one-half of the females in each group were alive until week 87 of the study and because no hint of carcinogenicity was observed, the study is considered adequate.

Adenomatosis of the lung occurred at increased incidences in dosed male mice. This lesion is characteristic of a Sendai infection. Because results of the serologic determinations for mice in

these 2-year studies were positive for Sendai virus (Table F1), the lung lesions are thought to be related to this infection.

Genetic Toxicity Studies

Based on short-term mutagenicity tests conducted by the NTP, roxarsone does not appear to be genotoxic (Appendix E). It did not induce gene mutations in in vitro tests with bacteria, nor did it induce sex-linked recessive lethal mutations in germ cells of *Drosophila melanogaster*. An increase in trifluorothymidine resistance in cultured mouse L5178Y cells at doses just below those that caused lethality was the only positive genotoxic effect noted for roxarsone. There are no in vivo data to assess its mutagenicity in mammals.

Audit

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

Conclusions

Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity** of roxarsone for male F344/N rats, as indicated by a marginally increased incidence of adenomas of the exocrine pancreas. There was *no evidence of carcinogenic activity* for female F344/N rats fed diets containing 50 or 100 ppm roxarsone for 2 years. There was *no evidence of carcinogenic activity* for male or female $B6C3F_1$ mice fed diets containing 100 or 200 ppm roxarsone for 2 years.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

V. REFERENCES

V. REFERENCES

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APPENDIX A

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

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS REMOVED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
ALIMENTARY SYSTEM			
Intestine small, jejunum	(50)	(50)	(50)
Adenocarcinoma		1 (2%)	
Leiomyosarcoma		2 (4%)	
Liver	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland		1 (2%)	
Hepatocellular carcinoma	2 (4%)		1 (2%)
Leukemia mononuclear	25 (50%)	27 (54%)	25 (50%)
Neoplastic nodule		2 (4%)	
Mesentery	*(50)	*(50)	*(50)
Mesothelioma malignant		1 (2%)	2 (4%)
Pancreas	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)	5 (10%)
Leukemia mononuclear	1 (2%)		
Pharynx	*(50)	*(50)	*(50)
Papilloma squamous	2 (4%)		1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Papilloma squamous		1 (2%)	
Squamous cell carcinoma		1 (2%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Leukemia mononuclear		3 (6%)	2 (4%)
Osteosarcoma, metastatic, bone	1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal gland			1 (2%)
Atrium, leukemia mononuclear		1 (2%)	
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma			1 (2%)
Leukemia mononuclear	6 (12%)	10 (20%)	4 (8%)
Adrenal gland, medulla	(50)	(49)	(50)
Leukemia mononuclear	7 (14%)	10 (20%)	4 (8%)
Pheochromocytoma malignant	4 (8%)	4 (8%)	3 (6%)
Pheochromocytoma malignant, multiple	1 (2%)		1 (2%)
Pheochromocytoma benign	15 (30%)	9 (18%)	10 (20%)
Pheochromocytoma benign, multiple		5 (10%)	6 (12%)
Islets, pancreatic	(50)	(50)	(50)
Adenoma		3 (6%)	4 (8%)
Carcinoma	2 (4%)	1 (2%)	
Parathyroid gland	(46)	(47)	(45)
Adenoma	1 (2%)		
Pituitary gland	(50)	(48)	(48)
Craniopharyngioma			1 (2%)
Leukemia mononuclear		2 (4%)	1 (2%)
Pars distalis, adenoma	6 (12%)	13 (27%)	8 (17%)
Pars distalis, leukemia mononuclear		5 (10%)	
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	4 (8%)	2 (4%)	3 (6%)
C-cell, carcinoma	1 (2%)	2 (4%)	2 (4%)
Follicular cell, adenoma			1 (2%)
Follicular cell, carcinoma			1 (2%)

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

	Untreated Control	Low Dose	High Dose
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(50)	(50)	(50)
Mesothelioma malignant			1 (2%)
Preputial gland	(49)	(48)	(48)
Adenoma	7 (14%)	3 (6%)	2 (4%)
Carcinoma		4 (8%)	
Prostate	(50)	(50)	(50)
Leukemia mononuclear		2 (4%)	
Osteosarcoma, metastatic, bone	1 (2%)		
Seminal vesicle	*(50)	*(50)	*(50)
Leukemia mononuclear		2 (4%)	
Testes	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)		
Interstitial cell, adenoma	4 (8%)	1 (2%)	9 (18%)
Interstitial cell, adenoma, multiple	42 (84%)	47 (94%)	34 (68%)
Tunic, mesothelioma malignant	1 (2%)		
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	1 (2%)
Bone marrow	(50)	(50)	(50)
Leukemia mononuclear	3 (6%)	14 (28%)	9 (18%)
Lymph node	(50)	(50)	(50)
Bronchial, leukemia mononuclear		2 (4%)	
Deep cervical, leukemia mononuclear		1 (2%)	
Iliac, leukemia mononuclear			1 (2%)
Mediastinal, leukemia mononuclear	2 (4%)	6 (12%)	6 (12%)
Mediastinal, sarcoma		1 (2%)	
Pancreatic, leukemia mononuclear	3 (6%)	4 (8%)	5 (10%)
Popliteal, leukemia mononuclear			1 (2%)
Renal, leukemia mononuclear	1 (2%)		1 (2%)
Lymph node, mandibular	(50)	(50)	(48)
Carcinoma, metastatic, thyroid gland		1 (2%)	
Leukemia mononuclear	12 (24%)	15 (30%)	10 (21%)
Lymph node, mesenteric	(50)	(49)	(48)
Leukemia mononuclear	5 (10%)	8 (16%)	7 (15%)
Spleen	(50)	(50)	(50)
Leukemia mononuclear	26 (52%)	27 (54%)	25 (50%)
Sarcoma			1 (2%)
Thymus	(49)	(49)	(47)
Leukemia mononuclear	2 (4%)	5 (10%)	1 (2%)
Osteosarcoma, metastatic, bone	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(47)	(49)	(49)
Fibroadenoma	2 (4%)		3 (6%)
Skin	(50)	(50)	(50)
Basal cell carcinoma		1 (2%)	
Fibroma			1 (2%)
Hemangioma	1 (2%)		
Keratoacanthoma	4 (8%)	4 (8%)	4 (8%)
Papilloma squamous			2 (4%)
Squamous cell carcinoma	1 (2%)		
Sebaceous gland, adenoma	1 (2%)		
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	3 (6%)
Subcutaneous tissue, fibrosarcoma	2 (4%)	1 (2%)	1 (2%)

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

	Untreated Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Osteosarcoma	3 (6%)		
Skeletal muscle	*(50)	*(50)	*(50)
Osteosarcoma, metastatic, bone	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	(50)	(49)
Astrocytoma malignant		1 (2%)	
Leukemia mononuclear	1 (2%)	3 (6%)	3 (6%)
Schwannoma malignant		1 (2%)	
Squamous cell carcinoma, metastatic, skin	1 (2%)		
Cerebellum, granular cell tumor, NOS			1 (2%)
Spinal cord	(50)	(50)	(50)
Leukemia mononuclear		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	2 (4%)	
Carcinoma, metastatic, thyroid gland		1 (2%)	
Carcinoma, metastatic, Zymbal gland		1 (2%)	
Leukemia mononuclear	18 (36%)	24 (48%)	20 (40%)
Osteosarcoma, metastatic, bone	2 (4%)		
Squamous cell carcinoma, metastatic, skin	1 (2%)		
Nose	(49)	(50)	(49)
Respiratory epithelium, adenoma			1 (2%)
SPECIAL SENSES SYSTEM			
Zymbal gland	*(50)	*(50)	*(50)
Adenoma	1 (2%)		1 (2%)
Carcinoma	1 (2%)	1 (2%)	
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)	5 (10%)	2 (4%)
Renal tubule, adenoma	1 (2%)	2 (4%)	1 (2%)
Renal tubule, carcinoma	1 (2%)		
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	27 (54%)	28 (56%)	25 (50%)
Mesothelioma malignant	1 (2%)	1 (2%)	2 (4%)
Hemangioma	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	24	18	18
Moribund sacrifice	22	25	27
Natural death	4	7	5

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

	Untreated Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary neoplasms **	50	50	50
Total primary neoplasms	141	146	139
Total animals with benign neoplasms	47	50	50
Total benign neoplasms	95	96	101
Total animals with malignant neoplasms	36	35	33
Total malignant neoplasms	46	50	37
Total animals with secondary neoplasms ***	4	2	1
Total secondary neoplasms	8	4	1
Total animals with neoplasms-- uncertain benign or malignant			1
Total uncertain neoplasms			1

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

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

WEEKS ON STUDY	041	077	081	083	084	084	088	090	091	091	093	093	095	096	096	097	097	097	099	100	100	101	101	102	103
CARCASS ID	062	104	091	052	033	065	042	074	031	054	085	084	073	055	082	102	053	081	023	083	092	045	051	063	035
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma														X								X			
Leukemia mononuclear		X			X	X		X	X	X	X	X	X	X			X	X	X	X				X	X
Mesentery															+		+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear		X																							
Pharynx																						+			+
Papilloma squamous																						X			X
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth											+														
CARDIOVASCULAR SYSTEM																									
Blood vessel							+							+		+									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone	X																								
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X						X	X								X							X	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X		X						X			X				X	
Pheochromocytoma malignant																X		X							
Pheochromocytoma malignant, multiple																									X
Pheochromocytoma benign							X	X			X	X	X	X						X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																				X					
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Adenoma																X									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X																X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma																								X	
C cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X			X															X			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																	X								
Seminal vesicle		+																							
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Interstitial cell, adenoma		X																							
Interstitial cell adenoma multiple				X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Tunic, mesothelioma malignant																									

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

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

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

WEEKS ON STUDY	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	041	001	012	013	014	015	021	022	024	025	032	034	043	044	061	064	071	072	075	093	094	095	101	103	105	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										2
Leukemia mononuclear	X								X	X	X				X	X	X	X							X	25
Mesentery																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Leukemia mononuclear																										1
Pharynx																										2
Papilloma squamous																										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
CARDIOVASCULAR SYSTEM																										
Blood vessel																										3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																	X									6
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																									7
Pheochromocytoma malignant							X																		X	4
Pheochromocytoma malignant, multiple																										1
Pheochromocytoma benign	X							X		X	X		X			X				X					X	15
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma					X																					2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	46
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma									X	X							X				X					6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma												X	X						X							4
C-cell, carcinoma																								X		1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X										X								X	X					7
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Seminal vesicle								+																+		3
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Interstitial cell, adenoma									X					X							X					4
Interstitial cell, adenoma, multiple	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	42
Tunic, mesothelioma malignant					X																					1

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

WEEKS ON STUDY	041	077	081	083	084	084	088	090	091	091	093	093	095	096	096	097	097	097	099	100	100	101	101	102	103
CARCASS ID	062	104	091	052	033	065	042	074	031	054	085	084	073	055	082	102	053	081	223	083	092	045	051	063	035
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X				X												
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear													X												
Pancreatic, leukemia mononuclear								X		X			X												
Renal, leukemia mononuclear													X												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X		X	X		X		X					X		X				X	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X			X	X				X												
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X		X	X	X	X	X	X	X			X	X	X	X				X	X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Leukemia mononuclear									X																
Osteosarcoma, metastatic, bone	X																								
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Fibroadenoma		X																							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																					X				
Keratoacanthoma												X					X								
Squamous cell carcinoma			X																						
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																			X						
Subcutaneous tissue, fibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma	X														X		X								
Skeletal muscle	+																								
Osteosarcoma, metastatic, bone	X																								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Squamous cell carcinoma, metastatic, skin			X																						
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Leukemia mononuclear		X			X	X		X	X	X		X	X				X	X		X				X	
Osteosarcoma, metastatic, bone	X														X										
Squamous cell carcinoma, metastatic, skin			X																						
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear							+	+													+				
Eye							+															+	+		
Zymbal gland				+							+														
Adenoma				X																					
Carcinoma											X														
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Renal tubule, adenoma																			X						
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	041	011	012	013	014	015	021	022	024	025	032	034	043	044	061	064	071	072	075	093	094	095	101	103	105	TOTAL TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear	X																									2
Pancreatic, leukemia mononuclear																										3
Renal, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X										X															12
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										5
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X							X	X	X				X	X	X	X				X				26
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear											X															2
Osteosarcoma, metastatic, bone																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibroadenoma										X																2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Keratoacanthoma								X														X				4
Squamous cell carcinoma																										1
Sebaceous gland, adenoma																						X				1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma											X			X												2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										3
Skeletal muscle																										1
Osteosarcoma, metastatic, bone																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Squamous cell carcinoma, metastatic, skin																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X	X																	2
Leukemia mononuclear	X										X				X	X	X								X	18
Osteosarcoma, metastatic, bone																										2
Squamous cell carcinoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear				+														+								5
Eye				+																						4
Zymbal gland																										2
Adenoma																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Renal tubule, adenoma																										1
Renal tubule, carcinoma																						X				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	071	071	077	083	083	085	087	090	090	090	090	091	091	091	091	094	095	097	097	098	098	098	098	099	101
CARCASS ID	211	284	253	303	233	302	293	285	245	273	235	213	115	264	282	241	292	274	263	255	243	252	275	281	232
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma							X																		
Leiomyosarcoma																				X					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland								X																	
Leukemia mononuclear			X	X		X	X			X	X	X	X	X				X	X	X	X	X	X		
Neoplastic nodule				X							X														
Mesentery			+											+									+		
Mesothelioma malignant																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel								+									+	+						+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X														X		
Atrium, leukemia mononuclear																					X				
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X					X							X		X	X	X		
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X					X							X		X	X	X		
Pheochromocytoma malignant														X											
Pheochromocytoma benign									X				X	X			X								
Pheochromocytoma benign, multiple																		X						X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X		X			
Carcinoma																									
Parathyroid gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Pars distalis, adenoma	X					X									X				X	X					
Pars distalis, leukemia mononuclear									X										X		X	X	X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma															X										
C cell, carcinoma								X																	
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ductus deferens																		+						+	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X			X								
Carcinoma					X													X			X				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Seminal vesicle														+	+						+				
Leukemia mononuclear																					X				
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																			X						
Interstitial cell, adenoma, multiple	X	X	X	X	X		X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X

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

WEEKS ON STUDY	101	102	103	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	272	224	261	221	305	262	225	212	214	222	223	231	234	242	244	251	254	265	271	283	291	294	295	301	304	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Leiomyosarcoma																					X					2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Leukemia mononuclear	X		X	X	X		X	X		X		X		X	X				X			X				27
Neoplastic nodule																										2
Mesentery		+																								4
Mesothelioma malignant		X																								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous							X																			1
Squamous cell carcinoma							X																			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel																	+									5
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																									3
Atrium, leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X	X			X																		10
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X			X	X			X																		10
Pheochromocytoma malignant												X			X			X								4
Pheochromocytoma benign				X					X			X					X			X						9
Pheochromocytoma benign, multiple			X				X				X															5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										3
Carcinoma						X																				1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear	X																									2
Pars distalis, adenoma						X			X	X							X	X				X	X		X	13
Pars distalis, leukemia mononuclear																										5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell, adenoma							X																			2
C cell, carcinoma																		X								2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ductus deferens																										2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma										X																3
Carcinoma								X																		4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X																			2
Seminal vesicle			+				+																			5
Leukemia mononuclear							X																			2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1
Interstitial cell, adenoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	47

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

WEEKS ON STUDY	071	071	077	083	083	085	087	090	090	090	090	090	091	091	091	091	094	095	097	097	098	098	098	098	099	101
CARCASS ID	211	284	253	303	233	302	293	285	245	273	235	213	215	264	282	241	292	274	263	255	243	252	275	281	232
HEMATOPOIETIC SYSTEM																										
Blood											+				+											
Leukemia mononuclear											X															
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X		X	X	X						X		X				
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, leukemia mononuclear										X			X													
Deep cervical, leukemia mononuclear																			X							
Mediastinal, leukemia mononuclear										X									X					X		
Mediastinal, sarcoma				X																						
Pancreatic, leukemia mononuclear												X										X		X		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland								X																		
Leukemia mononuclear			X							X		X	X	X					X			X	X	X		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X							X				X								X	X	X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X	X			X	X	X	X	X					X	X	X	X	X	X		
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X				X												
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																										
Keratoacanthoma													X							X	X					
Subcutaneous tissue, fibroma																										
Subcutaneous tissue, fibrosarcoma																										
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									M	
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																										X
Leukemia mononuclear														X										X		
Schwannoma malignant		X																								
Peripheral nerve	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																										
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X														
Carcinoma, metastatic, Zymbal gland																					X					
Carcinoma, metastatic, thyroid gland								X																		
Leukemia mononuclear			X	X		X	X			X	X	X	X	X					X	X		X	X	X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																										
Ear		+							+						+					+						
Eye															+						+				+	
Zymbal gland																					+					
Carcinoma																					X					
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X												X	X	X		
Renal tubule, adenoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	1 0 1	1 0 2	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	
CARCASS ID	2 7 2	2 2 4	2 6 1	2 2 1	3 0 5	2 6 2	2 2 5	2 1 2	2 1 4	2 2 2	2 2 3	2 3 1	2 3 4	2 4 2	2 4 4	2 5 1	2 5 4	2 6 5	2 7 1	2 8 3	2 9 1	2 9 4	2 9 5	3 0 1	3 0 4	TOTAL TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										2
Leukemia mononuclear																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X	X			X		X												X				14
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, leukemia mononuclear																										2
Deep cervical, leukemia mononuclear																										1
Mediastinal, leukemia mononuclear							X	X		X																6
Mediastinal, sarcoma																										1
Pancreatic, leukemia mononuclear					X																					4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Leukemia mononuclear	X			X				X		X				X	X											15
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X			X																						8
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X	X		X	X		X		X		X	X				X		X	X				27
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X						X								X											5
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																			X							1
Keratoacanthoma										X																4
Subcutaneous tissue, fibroma													X													1
Subcutaneous tissue fibrosarcoma																			X							1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Leukemia mononuclear	X																									3
Schwannoma malignant																										1
Peripheral nerve	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																									1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X														2
Carcinoma, metastatic, Zymbal gland																										1
Carcinoma, metastatic, thyroid gland																										1
Leukemia mononuclear	X		X	X	X			X		X				X	X						X	X				24
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear								+												+		+				7
Eye								+	+														+			6
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										5
Renal tubule, adenoma																		X					X			2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	07 7	07 9	08 3	08 3	08 5	09 0	09 1	09 1	09 2	09 3	09 3	09 4	09 5	09 6	09 6	09 6	09 7	09 7	09 7	09 8	09 8	09 8	09 8	09 9	10 0
CARCASS ID	17 4	13 4	15 1	20 3	12 1	11 4	17 5	20 1	16 4	13 1	22 2	17 2	19 1	14 3	15 2	18 5	13 3	18 1	17 1	15 4	15 5	20 5	12 3	13 2	20 2
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Leukemia mononuclear	X		X	X	X		X		X	X		X		X			X	X			X		X		X
Mesentery				+			+				+					+		+		+					
Mesothelioma malignant											X									X					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X							X				X	
Pharynx																+									
Papilloma squamous																X									
Salivary glands	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue									+																
Tooth										+															
CARDIOVASCULAR SYSTEM																									
Blood vessel								+					+						+			+		+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X																		
Pheochromocytoma malignant, metastatic, adrenal gland																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear																		X			X		X		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X			X		X		
Pheochromocytoma malignant																X									
Pheochromocytoma malignant, multiple																			X						
Pheochromocytoma benign								X											X					X	
Pheochromocytoma benign, multiple													X			X									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X		X								X						
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Craniopharyngioma																									
Leukemia mononuclear																									
Pars distalis, adenoma															X										X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma																			X			X			
C cell, carcinoma										X						X									
Follicular cell, adenoma																									
Follicular cell, carcinoma							X																		
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ductus deferens								+					+												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																				X					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle								+																	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma		X					X					X			X				X						
Interstitial cell, adenoma, multiple	X		X	X	X	X		X	X	X	X		X	X			X	X		X	X	X	X	X	

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

WEEKS ON STUDY	101	102	103	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	173	141	145	142	163	192	113	111	112	115	124	125	135	144	153	161	162	165	182	183	184	193	194	195	204	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma				X																						1
Leukemia mononuclear	X			X							X	X	X	X	X	X	X					X		X		25
Mesentery																										6
Mesothelioma malignant																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X									X										5
Pharynx																										1
Papilloma squamous																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue												+		+												3
Tooth		+																								2
CARDIOVASCULAR SYSTEM																										
Blood vessel							+																			6
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Pheochromocytoma malignant, metastatic, adrenal gland					X																					1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					1
Leukemia mononuclear	X																									4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																									4
Pheochromocytoma malignant		X			X																					3
Pheochromocytoma malignant, multiple																										1
Pheochromocytoma benign					X					X		X	X	X		X						X				10
Pheochromocytoma benign, multiple							X								X		X							X		6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Craniopharyngioma													X													1
Leukemia mononuclear				X																						1
Pars distalis, adenoma	X		X								X					X							X	X		8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell, adenoma								X																		3
C cell, carcinoma																										2
Follicular cell, adenoma																X										1
Follicular cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ductus deferens																										2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Adenoma																				X						2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle																						+	+			3
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																	X	X				X	X			9
Interstitial cell, adenoma, multiple		X		X	X	X	X	X	X	X			X	X	X	X			X	X				X	X	34

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

WEEKS ON STUDY	077	079	083	083	085	090	091	091	092	093	093	094	095	096	096	096	097	097	097	098	098	098	098	099	100
CARCASS ID	174	134	151	203	121	114	175	201	164	131	122	172	191	143	152	185	133	181	171	154	155	205	123	132	202
HEMATOPOIETIC SYSTEM																									
Blood									+																
Leukemia mononuclear									X																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X	X	X																X		X		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, leukemia mononuclear					X																				
Mediastinal, leukemia mononuclear	X			X	X													X							X
Pancreatic, leukemia mononuclear	X			X	X																				X
Popliteal, leukemia mononuclear																	X								
Renal, leukemia mononuclear					X																				
Lymph node, mandibular	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X	X							X					X						X		X
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Leukemia mononuclear	X			X	X													X							X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X	X	X		X		X	X		X		X			X	X			X		X		X
Sarcoma		X																							
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma					X																				
Keratoacanthoma											X								X	X					
Papilloma squamous																									
Subcutaneous tissue, fibroma			X																						
Subcutaneous tissue, fibrosarcoma						X																			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+																+	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X						X																		
Cerebellum, granular cell tumor, NOS																									
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X	X	X		X		X	X		X		X			X	X			X		X		X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, adenoma			X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear			+	+		+	+			+				+	+		+			+				+	
Eye			+			+	+	+		+	+		+	+	+		+			+	+		+	+	
Harderian gland		+																							
Zymbal gland								+																	
Adenoma								X																	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X																								
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	101	102	103	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	173	141	145	142	163	192	113	111	112	115	124	125	135	144	153	161	162	165	182	183	184	193	194	195	204	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Leukemia mononuclear																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X													X									9
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Iliac, leukemia mononuclear																										1
Mediastinal, leukemia mononuclear	X																									6
Pancreatic, leukemia mononuclear	X																									5
Popliteal, leukemia mononuclear																										1
Renal, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear	X																X							X		10
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear	X			X																						7
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X							X	X	X	X	X	X	X					X		X		25
Sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Leukemia mononuclear	X																									1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma			X							X																3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Keratoacanthoma									X																	4
Papilloma squamous																	X			X						2
Subcutaneous tissue, fibroma						X															X					3
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear				X																						3
Cerebellum, granular cell tumor, NOS								X																		1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X										X		X	X							X		20
Nose	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory epithelium, adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear	+	+						+		+	+	M			+			+				+				18
Eye		+	+	+			+	+	+		+	+	+	+	+											25
Harderian gland																										1
Zymbal gland																										1
Adenoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																									2
Renal tubule, adenoma								X																		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

	Control	50 ppm	100 ppm
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	15/50 (30%)	14/49 (29%)	16/50 (32%)
Adjusted Rates (b)	43.5%	47.6%	61.1%
Terminal Rates (c)	7/24 (29%)	5/18 (28%)	9/18 (50%)
Day of First Observation	616	629	637
Life Table Tests (d)	P=0.274	P=0.449	P=0.295
Logistic Regression Tests (d)	P=0.449	P=0.546N	P=0.491
Cochran-Armitage Trend Test (d)	P=0.457		
Fisher Exact Test (d)		P=0.526N	P=0.500
Adrenal Medulla: Malignant Pheochromocytoma			
Overall Rates (a)	5/50 (10%)	4/49 (8%)	4/50 (8%)
Adjusted Rates (b)	17.1%	18.9%	14.0%
Terminal Rates (c)	2/24 (8%)	3/18 (17%)	0/18 (0%)
Day of First Observation	675	637	671
Life Table Tests (d)	P=0.530N	P=0.628N	P=0.586N
Logistic Regression Tests (d)	P=0.441N	P=0.545N	P=0.508N
Cochran-Armitage Trend Test (d)	P=0.430N		
Fisher Exact Test (d)		P=0.513N	P=0.500N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	19/50 (38%)	16/49 (33%)	17/50 (34%)
Adjusted Rates (b)	51.9%	55.7%	62.7%
Terminal Rates (c)	8/24 (33%)	7/18 (39%)	9/18 (50%)
Day of First Observation	616	629	637
Life Table Tests (d)	P=0.461	P=0.553	P=0.494
Logistic Regression Tests (d)	P=0.385N	P=0.393N	P=0.426N
Cochran-Armitage Trend Test (d)	P=0.376N		
Fisher Exact Test (d)		P=0.365N	P=0.418N
Bone: Osteosarcoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	7.5%	0.0%	0.0%
Terminal Rates (c)	0/24 (0%)	0/18 (0%)	0/18 (0%)
Day of First Observation	283		
Life Table Tests (d)	P=0.041N	P=0.133N	P=0.130N
Logistic Regression Tests (d)	P=0.061N	P=0.146N	P=0.196N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Preputial Gland: Adenoma			
Overall Rates (a)	7/49 (14%)	3/48 (6%)	2/48 (4%)
Adjusted Rates (b)	23.0%	11.1%	8.0%
Terminal Rates (c)	4/24 (17%)	1/17 (6%)	1/17 (6%)
Day of First Observation	581	637	630
Life Table Tests (d)	P=0.089N	P=0.261N	P=0.141N
Logistic Regression Tests (d)	P=0.051N	P=0.166N	P=0.084N
Cochran-Armitage Trend Test (d)	P=0.052N		
Fisher Exact Test (d)		P=0.167N	P=0.084N
Preputial Gland: Carcinoma			
Overall Rates (a)	0/49 (0%)	4/48 (8%)	0/48 (0%)
Adjusted Rates (b)	0.0%	13.7%	0.0%
Terminal Rates (c)	0/24 (0%)	1/17 (6%)	0/17 (0%)
Day of First Observation		581	
Life Table Tests (d)	P=0.580	P=0.052	(e)
Logistic Regression Tests (d)	P=0.623N	P=0.067	(e)
Cochran-Armitage Trend Test (d)	P=0.615		
Fisher Exact Test (d)		P=0.056	(e)

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

	Control	50 ppm	100 ppm
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	7/49 (14%)	7/48 (15%)	2/48 (4%)
Adjusted Rates (b)	23.0%	23.6%	8.0%
Terminal Rates (c)	4/24 (17%)	2/17 (12%)	1/17 (6%)
Day of First Observation	581	581	630
Life Table Tests (d)	P=0.132N	P=0.469	P=0.141N
Logistic Regression Tests (d)	P=0.075N	P=0.613	P=0.084N
Cochran-Armitage Trend Test (d)	P=0.077N		
Fisher Exact Test (d)		P=0.597	P=0.084N
Pancreatic Islets: Adenoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	0.0%	11.6%	11.9%
Terminal Rates (c)	0/24 (0%)	1/18 (6%)	0/18 (0%)
Day of First Observation		681	638
Life Table Tests (d)	P=0.046	P=0.102	P=0.063
Logistic Regression Tests (d)	P=0.049	P=0.114	P=0.060
Cochran-Armitage Trend Test (d)	P=0.049		
Fisher Exact Test (d)		P=0.121	P=0.059
Pancreatic Islets: Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	7.3%	16.1%	11.9%
Terminal Rates (c)	1/24 (4%)	1/18 (6%)	0/18 (0%)
Day of First Observation	695	681	638
Life Table Tests (d)	P=0.234	P=0.264	P=0.299
Logistic Regression Tests (d)	P=0.274	P=0.306	P=0.337
Cochran-Armitage Trend Test (d)	P=0.274		
Fisher Exact Test (d)		P=0.339	P=0.339
Mammary Gland: Fibroadenoma			
Overall Rates (a)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	6.1%	0.0%	13.1%
Terminal Rates (c)	1/24 (4%)	0/18 (0%)	1/18 (6%)
Day of First Observation	538		695
Life Table Tests (d)	P=0.332	P=0.276N	P=0.422
Logistic Regression Tests (d)	P=0.390	P=0.244N	P=0.498
Cochran-Armitage Trend Test (d)	P=0.390		
Fisher Exact Test (d)		P=0.247N	P=0.500
Pancreas: Adenoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	5/50 (10%)
Adjusted Rates (b)	4.2%	5.6%	18.8%
Terminal Rates (c)	1/24 (4%)	1/18 (6%)	1/18 (6%)
Day of First Observation	729	729	664
Life Table Tests (d)	P=0.035	P=0.697	P=0.075
Logistic Regression Tests (d)	P=0.046	P=0.697	P=0.099
Cochran-Armitage Trend Test (d)	P=0.049		
Fisher Exact Test (d)		P=0.753	P=0.102
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	6/50 (12%)	13/48 (27%)	8/48 (17%)
Adjusted Rates (b)	21.4%	49.3%	34.4%
Terminal Rates (c)	4/24 (17%)	7/18 (39%)	4/17 (24%)
Day of First Observation	616	495	671
Life Table Tests (d)	P=0.188	P=0.026	P=0.224
Logistic Regression Tests (d)	P=0.307	P=0.049	P=0.325
Cochran-Armitage Trend Test (d)	P=0.313		
Fisher Exact Test (d)		P=0.051	P=0.355

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

	Control	50 ppm	100 ppm
Skin: Keratoacanthoma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	13.3%	13.7%	13.7%
Terminal Rates (c)	2/24 (8%)	1/18 (6%)	1/18 (6%)
Day of First Observation	651	633	651
Life Table Tests (d)	P=0.504	P=0.558	P=0.572
Logistic Regression Tests (d)	P=0.571N	P=0.637	P=0.642N
Cochran-Armitage Trend Test (d)	P=0.573		
Fisher Exact Test (d)		P=0.643N	P=0.643N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	3.1%	5.6%	12.1%
Terminal Rates (c)	0/24 (0%)	1/18 (6%)	1/18 (6%)
Day of First Observation	693	729	581
Life Table Tests (d)	P=0.159	P=0.709	P=0.249
Logistic Regression Tests (d)	P=0.203	P=0.746	P=0.304
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test (d)		P=0.753N	P=0.309
Integumentary System: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	11.2%	11.1%	16.0%
Terminal Rates (c)	2/24 (8%)	2/18 (11%)	1/18 (6%)
Day of First Observation	693	729	581
Life Table Tests (d)	P=0.207	P=0.620N	P=0.286
Logistic Regression Tests (d)	P=0.275	P=0.558N	P=0.350
Cochran-Armitage Trend Test (d)	P=0.274		
Fisher Exact Test (d)		P=0.500N	P=0.357
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	46/50 (92%)	48/50 (96%)	43/50 (86%)
Adjusted Rates (b)	100.0%	100.0%	93.0%
Terminal Rates (c)	24/24 (100%)	18/18 (100%)	15/18 (83%)
Day of First Observation	538	495	534
Life Table Tests (d)	P=0.322	P=0.099	P=0.352
Logistic Regression Tests (d)	P=0.138N	P=0.332	P=0.212N
Cochran-Armitage Trend Test (d)	P=0.187N		
Fisher Exact Test (d)		P=0.339	P=0.262N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	15.7%	7.8%	11.6%
Terminal Rates (c)	3/24 (13%)	0/18 (0%)	1/18 (6%)
Day of First Observation	710	637	678
Life Table Tests (d)	P=0.506N	P=0.441N	P=0.606N
Logistic Regression Tests (d)	P=0.429N	P=0.371N	P=0.525N
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test (d)		P=0.339N	P=0.500N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	19.8%	15.0%	16.1%
Terminal Rates (c)	4/24 (17%)	1/18 (6%)	1/18 (6%)
Day of First Observation	710	625	647
Life Table Tests (d)	P=0.472	P=0.626N	P=0.523
Logistic Regression Tests (d)	P=0.566	P=0.536N	P=0.623
Cochran-Armitage Trend Test (d)	P=0.568		
Fisher Exact Test (d)		P=0.500N	P=0.630N

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

	Control	50 ppm	100 ppm
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	27/50 (54%)	28/50 (56%)	25/50 (50%)
Adjusted Rates (b)	64.1%	71.1%	68.7%
Terminal Rates (c)	10/24 (42%)	8/18 (44%)	9/18 (50%)
Day of First Observation	538	535	534
Life Table Tests (d)	P=0.445	P=0.274	P=0.478
Logistic Regression Tests (d)	P=0.387N	P=0.500	P=0.428N
Cochran-Armitage Trend Test (d)	P=0.382N		
Fisher Exact Test (d)		P=0.500	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 logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 100-ppm and control groups.

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

Study	Incidence of Adenomas in Controls (b)
Historical Incidence at Southern Research Institute	
HC Blue No. 2	0/50
C.I. Disperse Blue 1	0/49
Eugenol	0/40
Stannous chloride	0/50
D-Mannitol	0/50
Ziram	0/50
Propyl gallate	1/50
Zearalenone	0/49
HC Blue No. 1	0/49
TOTAL	1/437 (0.2%)
SD (c)	0.67%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	5/1,871 (0.3%)
SD (c)	0.87%
Range (d)	
High	2/46
Low	0/50

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

TABLE A4b. HISTORICAL INCIDENCE OF PANCREATIC ISLET CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
HC Blue No. 2	1/50	1/50	2/50
C.I. Disperse Blue 1	1/49	0/49	1/49
Eugenol	0/40	1/40	1/40
Stannous chloride	2/50	3/50	5/50
D-Mannitol	3/50	0/50	3/50
Ziram	2/50	1/50	2/50
Propyl gallate	0/50	2/50	2/50
Zearalenone	2/49	1/49	3/49
HC Blue No. 1	5/49	0/49	5/49
TOTAL	16/437 (3.7%)	9/437 (2.1%)	24/437 (5.5%)
SD (b)	3.18%	2.01%	2.97%
Range (c)			
High	5/49	3/50	5/49
Low	0/50	0/50	1/49
Overall Historical Incidence			
TOTAL	64/1,871 (3.4%)	37/1,871 (2.0%)	100/1,871 (5.3%)
SD (b)	3.31%	2.56%	3.61%
Range (c)			
High	6/49	4/49	7/49
Low	0/50	0/50	0/50

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

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

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
HC Blue No. 2	(b) 10/50	0/50	(b) 10/50
C.I. Disperse Blue 1	13/49	3/49	16/49
Eugenol	2/39	0/39	2/39
Stannous chloride	11/50	1/50	12/50
D-Mannitol	9/46	0/46	9/46
Ziram	13/50	2/50	15/50
Propyl gallate	5/49	0/49	5/49
Zearalenone	5/46	1/46	6/46
HC Blue No. 1	9/49	2/49	11/49
TOTAL	(b) 77/428 (18.0%)	9/428 (2.1%)	(b) 86/428 (20.1%)
SD (c)	7.38%	2.27%	8.99%
Range (d)			
High	13/49	3/49	16/49
Low	2/39	0/50	2/39
Overall Historical Incidence			
TOTAL	(e) 408/1,825 (22.4%)	(f) 41/1,825 (2.2%)	(e,f) 449/1,825 (24.6%)
SD (c)	11.02%	2.88%	10.67%
Range (d)			
High	24/46	5/45	25/46
Low	2/39	0/50	2/39

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Includes one acidophil adenoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes 1 acidophil adenoma and 35 chromophobe adenomas
(f) Includes one adenocarcinoma, NOS, and seven chromophobe carcinomas

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

Study	Incidence of Leiomyosarcomas in Controls (b)
Historical Incidence at Southern Research Institute	
HC Blue No. 2	1/50
Propyl gallate	1/50
All others	0/335
TOTAL	2/435 (0.5%)
SD (c)	0.88%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	2/1,865 (0.1%)
SD (c)	0.45%
Range (d)	
High	1/50
Low	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) No leiomyomas have been observed.
(c) Standard deviation
(d) 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 ROXARSONE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS REMOVED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(48)	(49)	(49)
Inflammation, chronic			1 (2%)
Intestine large, colon	(50)	(49)	(49)
Inflammation, chronic, focal			1 (2%)
Mineralization, multifocal	1 (2%)	2 (4%)	2 (4%)
Parasite metazoan	3 (6%)	1 (2%)	
Artery, mineralization	1 (2%)		
Intestine large, rectum	(48)	(50)	(49)
Mineralization, multifocal			1 (2%)
Parasite metazoan	3 (6%)	3 (6%)	3 (6%)
Intestine small, jejunum	(50)	(50)	(50)
Thrombus	1 (2%)		
Liver	(50)	(50)	(50)
Angiectasis, focal	11 (22%)	4 (8%)	6 (12%)
Angiectasis, multifocal	2 (4%)	1 (2%)	
Basophilic focus	5 (10%)		1 (2%)
Basophilic focus, multiple	2 (4%)	5 (10%)	1 (2%)
Clear cell focus	5 (10%)	1 (2%)	4 (8%)
Clear cell focus, multiple	1 (2%)		
Degeneration, cystic	4 (8%)	5 (10%)	1 (2%)
Developmental malformation	7 (14%)	3 (6%)	2 (4%)
Eosinophilic focus			1 (2%)
Granuloma, multifocal	1 (2%)	5 (10%)	6 (12%)
Mixed cell focus	1 (2%)		2 (4%)
Necrosis, multifocal	1 (2%)		1 (2%)
Regeneration		1 (2%)	1 (2%)
Vacuolization cytoplasmic, diffuse	1 (2%)		2 (4%)
Vacuolization cytoplasmic, focal		4 (8%)	1 (2%)
Artery, mineralization	1 (2%)		
Biliary tract, proliferation	40 (80%)	33 (66%)	40 (80%)
Centrilobular, necrosis	14 (28%)	20 (40%)	16 (32%)
Serosa, inflammation, suppurative, acute, focal	1 (2%)		
Mesentery	(2)	(4)	(6)
Mineralization, multifocal	1 (50%)		
Fat, necrosis, focal	2 (100%)	2 (50%)	4 (67%)
Fat, necrosis, multifocal		1 (25%)	
Pancreas	(50)	(50)	(50)
Atrophy, focal	22 (44%)	27 (54%)	22 (44%)
Basophilic focus	3 (6%)		
Fibrosis, focal	1 (2%)		
Hyperplasia, focal	2 (4%)		3 (6%)
Artery, inflammation, chronic			1 (2%)
Artery, mineralization, multifocal	1 (2%)	1 (2%)	1 (2%)
Artery, thrombus		1 (2%)	1 (2%)
Stomach	(50)	(50)	(50)
Artery, inflammation, chronic			1 (2%)
Artery, mineralization, diffuse	1 (2%)		
Stomach, forestomach	(50)	(50)	(50)
Edema	1 (2%)		1 (2%)
Hyperkeratosis		3 (6%)	3 (6%)
Hyperplasia	1 (2%)	4 (8%)	3 (6%)
Inflammation, chronic	1 (2%)	1 (2%)	2 (4%)
Inflammation, suppurative, acute	1 (2%)	2 (4%)	
Mineralization, diffuse	3 (6%)	4 (8%)	5 (10%)
Perforation	1 (2%)	2 (4%)	
Ulcer	2 (4%)	2 (4%)	2 (4%)
Ulcer, multiple		1 (2%)	

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

	Untreated Control	Low Dose	High Dose
ALIMENTARY SYSTEM (Continued)			
Stomach, glandular	(50)	(50)	(50)
Edema	1 (2%)	4 (8%)	1 (2%)
Erosion	1 (2%)		2 (4%)
Inflammation, chronic, diffuse			2 (4%)
Mineralization, diffuse	4 (8%)	6 (12%)	8 (16%)
Ulcer	1 (2%)		
Ulcer, multiple	1 (2%)		1 (2%)
Tongue			(3)
Hyperkeratosis, focal			1 (33%)
CARDIOVASCULAR SYSTEM			
Blood vessel	(3)	(5)	(6)
Aorta, mineralization, diffuse	3 (100%)	5 (100%)	6 (100%)
Heart	(50)	(50)	(50)
Cardiomyopathy	44 (88%)	46 (92%)	45 (90%)
Mineralization, multifocal	2 (4%)	4 (8%)	5 (10%)
Atrium, thrombus	2 (4%)	3 (6%)	4 (8%)
Endocardium, inflammation, chronic, focal			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	3 (6%)		
Degeneration, fatty, focal	9 (18%)	10 (20%)	15 (30%)
Degeneration, fatty, multifocal	1 (2%)		
Hyperplasia, focal	1 (2%)		2 (4%)
Adrenal gland, medulla	(50)	(49)	(50)
Hyperplasia, focal	10 (20%)	1 (2%)	10 (20%)
Mineralization, multifocal	1 (2%)		
Islets, pancreatic	(50)	(50)	(50)
Hyperplasia, focal		1 (2%)	
Parathyroid gland	(46)	(47)	(45)
Hyperplasia	3 (7%)	9 (19%)	9 (20%)
Pituitary gland	(50)	(48)	(48)
Pars distalis, angiectasis	9 (18%)	12 (25%)	7 (15%)
Pars distalis, cyst	4 (8%)	1 (2%)	1 (2%)
Pars distalis, hemorrhage		1 (2%)	
Pars distalis, hyperplasia, focal	8 (16%)	11 (23%)	6 (13%)
Pars distalis, pigmentation, hemosiderin	1 (2%)	1 (2%)	
Thyroid gland	(50)	(50)	(50)
C-cell, hyperplasia	3 (6%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ductus deferens		(2)	(2)
Mineralization, diffuse		2 (100%)	2 (100%)
Preputial gland	(49)	(48)	(48)
Foreign body		1 (2%)	
Hyperplasia	1 (2%)		1 (2%)
Inflammation, chronic	2 (4%)	1 (2%)	
Inflammation, suppurative, acute	9 (18%)	5 (10%)	2 (4%)
Duct, cyst	8 (16%)	4 (8%)	3 (6%)

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

	Untreated Control	Low Dose	High Dose
GENITAL SYSTEM (Continued)			
Prostate	(50)	(50)	(50)
Cyst	1 (2%)		
Inflammation, suppurative, acute	17 (34%)	13 (26%)	17 (34%)
Seminal vesicle	(3)	(5)	(3)
Dilatation			1 (33%)
Hyperplasia			1 (33%)
Testes	(50)	(50)	(50)
Atrophy	16 (32%)	16 (32%)	17 (34%)
Hemorrhage			1 (2%)
Mineralization, focal	1 (2%)		
Arteriole, inflammation, chronic			1 (2%)
Artery, mineralization	1 (2%)		
Interstitial cell, hyperplasia	3 (6%)		5 (10%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Hyperplasia		1 (2%)	
Hypoplasia		1 (2%)	1 (2%)
Lymph node	(50)	(50)	(50)
Iliac, hyperplasia	1 (2%)		
Inguinal, hyperplasia		2 (4%)	1 (2%)
Mediastinal, ectasia	3 (6%)		
Mediastinal, pigmentation		1 (2%)	1 (2%)
Pancreatic, ectasia	1 (2%)	1 (2%)	
Renal, congestion		1 (2%)	
Renal, ectasia		1 (2%)	1 (2%)
Lymph node, mandibular	(50)	(50)	(48)
Ectasia	14 (28%)	5 (10%)	4 (8%)
Hyperplasia	3 (6%)	1 (2%)	1 (2%)
Lymph node, mesenteric	(50)	(49)	(48)
Congestion	1 (2%)	1 (2%)	
Ectasia	1 (2%)	2 (4%)	2 (4%)
Spleen	(50)	(50)	(50)
Atrophy	1 (2%)		
Developmental malformation	2 (4%)		
Fibrosis, diffuse		1 (2%)	
Fibrosis, focal	2 (4%)	6 (12%)	6 (12%)
Hematopoietic cell proliferation	9 (18%)	6 (12%)	6 (12%)
Hyperplasia, focal			2 (4%)
Mineralization, focal			1 (2%)
Necrosis, focal		1 (2%)	
Necrosis, multifocal			1 (2%)
Capsule, fibrosis, multifocal	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(47)	(49)	(49)
Duct, cyst	12 (26%)	14 (29%)	10 (20%)
Skin	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)	2 (4%)	
Foreign body	2 (4%)		2 (4%)
Hyperkeratosis, focal	2 (4%)		1 (2%)
Hyperplasia, focal	2 (4%)		1 (2%)
Inflammation, chronic, focal	2 (4%)	1 (2%)	
Inflammation, granulomatous, focal	3 (6%)	1 (2%)	2 (4%)
Inflammation, suppurative, acute, focal		1 (2%)	3 (6%)
Inflammation, suppurative, acute, multifocal			1 (2%)

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

	Untreated Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Fibrous osteodystrophy	3 (6%)	5 (10%)	8 (16%)
Hypertrophy, focal		1 (2%)	
Skeletal muscle	(1)		(2)
Mineralization, multifocal			2 (100%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(49)
Compression		2 (4%)	2 (4%)
Hemorrhage, focal	1 (2%)		
Hemorrhage, multifocal	1 (2%)	1 (2%)	2 (4%)
Spinal cord	(50)	(50)	(50)
Hemorrhage, multifocal		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Congestion	2 (4%)		
Foreign body			1 (2%)
Granuloma, multifocal			1 (2%)
Hemorrhage, multifocal	1 (2%)	1 (2%)	4 (8%)
Infiltration cellular, histiocytic, multifocal	2 (4%)	1 (2%)	3 (6%)
Inflammation, suppurative, acute, multifocal		1 (2%)	
Mineralization, multifocal	3 (6%)	5 (10%)	5 (10%)
Alveolar epithelium, hyperplasia, focal	1 (2%)	2 (4%)	1 (2%)
Nose	(49)	(50)	(49)
Foreign body	5 (10%)		3 (6%)
Fungus	6 (12%)	2 (4%)	4 (8%)
Inflammation, suppurative, acute	6 (12%)	2 (4%)	6 (12%)
Mucosa, cyst	1 (2%)		
Nasolacrimal duct, foreign body	2 (4%)	1 (2%)	1 (2%)
Nasolacrimal duct, inflammation, suppurative, acute	3 (6%)	2 (4%)	1 (2%)
Respiratory epithelium, metaplasia, squamous			2 (4%)
SPECIAL SENSES SYSTEM			
Eye	(4)	(6)	(25)
Cataract	2 (50%)	1 (17%)	21 (84%)
Hemorrhage			2 (8%)
Hyperplasia			1 (4%)
Cornea, inflammation, suppurative, acute		1 (17%)	
Retina, degeneration	3 (75%)	2 (33%)	23 (92%)
Harderian gland			(1)
Inflammation, chronic, focal			1 (100%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Mineralization, diffuse	3 (6%)	4 (8%)	4 (8%)
Nephropathy, chronic	50 (100%)	49 (98%)	49 (98%)
Cortex, cyst	5 (10%)	9 (18%)	8 (16%)
Renal tubule, pigmentation, multifocal			1 (2%)
Urinary bladder	(50)	(50)	(50)
Hemorrhage, multifocal			1 (2%)

APPENDIX B

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

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS REMOVED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
ALIMENTARY SYSTEM			
Liver	(50)	(50)	(50)
Fibrous histiocytoma	1 (2%)		
Leukemia mononuclear	14 (28%)	11 (22%)	11 (22%)
Neoplastic nodule		1 (2%)	
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)	2 (4%)	
Pancreas	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)		1 (2%)
Pharynx	*(50)	*(50)	*(50)
Papilloma squamous	1 (2%)		
Salivary glands	(50)	(47)	(48)
Leukemia mononuclear	1 (2%)		
Stomach, forestomach	(50)	(50)	(50)
Papilloma squamous	1 (2%)		
Tongue	*(50)	*(50)	*(50)
Papilloma squamous			1 (2%)
Tooth	*(50)	*(50)	*(50)
Gingiva, basosquamous tumor malignant			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)	1 (2%)	2 (4%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma	1 (2%)		
Leukemia mononuclear	10 (20%)	6 (12%)	6 (12%)
Adrenal gland, medulla	(49)	(48)	(50)
Leukemia mononuclear	9 (18%)	6 (13%)	6 (12%)
Pheochromocytoma benign		1 (2%)	2 (4%)
Islets, pancreatic	(50)	(50)	(50)
Adenoma	1 (2%)	2 (4%)	
Pituitary gland	(50)	(49)	(48)
Pars distalis, adenoma	27 (54%)	28 (57%)	18 (38%)
Pars distalis, carcinoma	1 (2%)		
Pars distalis, leukemia mononuclear	1 (2%)	3 (6%)	1 (2%)
Thyroid gland	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)		1 (2%)
C-cell, adenoma	8 (16%)	5 (10%)	8 (16%)
C-cell, adenoma, multiple		1 (2%)	1 (2%)
C-cell, carcinoma	2 (4%)	4 (8%)	1 (2%)
Follicular cell, adenoma	1 (2%)		1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(44)	(47)	(48)
Adenoma	1 (2%)	3 (6%)	5 (10%)
Carcinoma	1 (2%)	1 (2%)	1 (2%)
Bilateral, adenoma			1 (2%)

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

	Untreated Control	Low Dose	High Dose
GENITAL SYSTEM (Continued)			
Ovary	(50)	(47)	(50)
Leukemia mononuclear	2 (4%)	2 (4%)	1 (2%)
Uterus	(50)	(49)	(50)
Adenocarcinoma	1 (2%)	2 (4%)	1 (2%)
Leukemia mononuclear	1 (2%)		1 (2%)
Polyp stromal	8 (16%)	18 (37%)	12 (24%)
Polyp stromal, multiple	2 (4%)		
Sarcoma stromal			1 (2%)
Schwannoma malignant			1 (2%)
Cervix, leukemia mononuclear	1 (2%)		
Cervix, polyp			1 (2%)
Cervix, squamous cell carcinoma			1 (2%)
Vagina	*(50)	*(50)	*(50)
Polyp			1 (2%)
Sarcoma			1 (2%)
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		2 (4%)
Bone marrow	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)	2 (4%)	2 (4%)
Lymph node	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin	1 (2%)		
Axillary, leukemia mononuclear			1 (2%)
Bronchial, leukemia mononuclear		1 (2%)	
Deep cervical, leukemia mononuclear			1 (2%)
Iliac, leukemia mononuclear			1 (2%)
Inguinal, leukemia mononuclear			1 (2%)
Mediastinal, leukemia mononuclear	4 (8%)	2 (4%)	1 (2%)
Pancreatic, leukemia mononuclear	2 (4%)	1 (2%)	4 (8%)
Popliteal, leukemia mononuclear			1 (2%)
Renal, leukemia mononuclear			1 (2%)
Lymph node, mandibular	(49)	(46)	(49)
Leukemia mononuclear	6 (12%)	7 (15%)	4 (8%)
Lymph node, mesenteric	(50)	(50)	(46)
Leukemia mononuclear	4 (8%)	3 (6%)	5 (11%)
Spleen	(50)	(50)	(50)
Leukemia mononuclear	14 (28%)	12 (24%)	11 (22%)
Thymus	(50)	(42)	(48)
Leukemia mononuclear	1 (2%)	2 (5%)	1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(49)	(50)
Adenocarcinoma	4 (8%)		1 (2%)
Fibroadenoma	16 (32%)	16 (33%)	17 (34%)
Fibroadenoma, multiple	5 (10%)	1 (2%)	4 (8%)
Fibrosarcoma, metastatic, skin	1 (2%)		
Skin	(50)	(50)	(50)
Basal cell adenoma		1 (2%)	
Basal cell adenoma, multiple			1 (2%)
Papilloma squamous			1 (2%)
Subcutaneous tissue, fibroma			1 (2%)
Subcutaneous tissue, fibroma, multiple	1 (2%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	
Subcutaneous tissue, sarcoma	1 (2%)		
Subcutaneous tissue, schwannoma benign	1 (2%)		1 (2%)

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

	Untreated Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Osteosarcoma			2 (4%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Leukemia mononuclear	2 (4%)	2 (4%)	
Spinal cord	(50)	(50)	(49)
Leukemia mononuclear		1 (2%)	
Osteosarcoma, metastatic, bone			1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			1 (2%)
Fibrosarcoma, metastatic, skin	1 (2%)		
Fibrous histiocytoma, metastatic, liver	1 (2%)		
Leukemia mononuclear	14 (28%)	10 (20%)	7 (14%)
SPECIAL SENSES SYSTEM			
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma		1 (2%)	1 (2%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Leukemia mononuclear	2 (4%)	4 (8%)	3 (6%)
Urinary bladder	(50)	(50)	(50)
Leukemia mononuclear		1 (2%)	
Squamous cell carcinoma, metastatic			1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	14 (28%)	12 (24%)	11 (22%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Moribund sacrifice	22	12	16
Terminal sacrifice	27	35	32
Natural death	1	3	2
TUMOR SUMMARY			
Total animals with primary neoplasms **	48	47	46
Total primary neoplasms	100	98	100
Total animals with benign neoplasms	44	44	42
Total benign neoplasms	74	77	77
Total animals with malignant neoplasms	21	20	20
Total malignant neoplasms	26	21	23
Total animals with secondary neoplasms ***	2		2
Total secondary neoplasms	4		2

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

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

WEEKS ON STUDY	058	070	076	077	084	085	085	090	091	091	091	093	093	093	098	099	100	101	101	101	104	104	104	105	105
CARCASS ID	32 3	36 4	34 1	35 3	31 5	37 3	31 2	33 5	32 5	39 2	36 5	31 3	37 2	38 3	40 3	33 3	33 4	40 2	32 4	31 1	32 2	35 5	39 5	31 4	32 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																									
Leukemia mononuclear					X	X	X	X			X	X			X			X	X	X	X			X	
Mesentery								+											+	+					
Leukemia mononuclear																			X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Pharynx																	+								
Papilloma squamous																	X								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear					X	X	X	X				X						X	X	X					
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X	X	X				X						X	X	X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X	X	X							X	X		X				X	X	X			X
Pars distalis, carcinoma																	X								
Pars distalis, leukemia mononuclear																			X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
C cell, adenoma								X								X							X		
C cell, carcinoma					X																X				
Follicular cell, adenoma															X										
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																		X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X												X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma															X										
Leukemia mononuclear																			X						
Polyp stromal	X								X	X															
Polyp stromal, multiple								X														Y			
Cervix, leukemia mononuclear																			X						

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

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

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	331	332	342	343	344	345	351	352	354	361	362	363	371	374	375	381	382	384	385	391	393	394	401	404	405	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma		X																								1
Leukemia mononuclear														X	X											14
Mesentery	+		+		+						+		+										+	+		10
Leukemia mononuclear																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Pharynx				+																						2
Papilloma squamous																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous						X																				1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Leukemia mononuclear														X	X											10
Adrenal gland, medulla	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear															X											9
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X	X	X					X			X	X	X	X		X		X			27
Pars distalis, carcinoma																										1
Pars distalis, leukemia mononuclear																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
C cell, adenoma								X					X	X								X		X		8
C-cell, carcinoma																										2
Follicular cell, adenoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	44
Adenoma	X																									1
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Leukemia mononuclear																										1
Polyp stromal							X				X	X					X		X							8
Polyp stromal, multiple																										2
Cervix, leukemia mononuclear																										1

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

WEEKS ON STUDY	058	070	076	077	084	085	085	090	091	091	091	093	093	093	098	099	100	101	101	101	104	104	104	105	105
CARCASS ID	323	364	341	353	315	373	312	335	325	392	365	131	372	383	403	333	334	402	324	311	322	355	395	314	321
HEMATOPOIETIC SYSTEM																									
Blood																			+						
Leukemia mononuclear																			X						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin	X																								
Mediastinal, leukemia mononuclear					X						X								X		X				
Pancreatic, leukemia mononuclear												X									X				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Leukemia mononuclear					X														X	X	X			X	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X														X	X	X				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X	X	X			X	X		X				X	X	X	X			X	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																				X					
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma	X	X											X												
Fibroadenoma			X	X					X							X	X		X			X			
Fibroadenoma, multiple																		X							
Fibrosarcoma, metastatic, skin	X																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, fibrosarcoma	X																								
Subcutaneous tissue, sarcoma																									
Subcutaneous tissue, schwannoma benign																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X												X						
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin	X																								
Fibrous histiocytoma, metastatic, liver																									
Leukemia mononuclear					X	X	X	X			X	X			X			X	X	X	X			X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear										+															+
Eye							+																		+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X												X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	331	332	342	343	344	345	351	352	354	361	362	363	371	374	375	381	382	384	385	391	393	394	401	404	405	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Leukemia mononuclear																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Mediastinal, leukemia mononuclear																										4
Pancreatic, leukemia mononuclear																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear															X											6
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear														X	X											14
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma					X																					4
Fibroadenoma		X			X	X				X		X	X					X						X	X	16
Fibroadenoma, multiple	X		X					X													X					5
Fibrosarcoma, metastatic, skin																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma, multiple												X														1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, sarcoma													X													1
Subcutan. tissue, schwannoma benign	X																									1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Fibrous histiocytoma, metastatic, liver		X																								1
Leukemia mononuclear														X	X											14
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										2
Eye											+															3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	069	070	072	076	077	078	081	083	086	087	098	098	100	101	104	105	105	105	105	105	105	105	105	105	105
CARCASS ID	514	563	585	553	601	613	603	532	591	534	523	571	554	605	544	511	512	515	521	522	524	525	531	533	535
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X	X		X		X	X		X											
Neoplastic nodule																	X								
Mesentery			+		+							+	+											+	+
Leukemia mononuclear			X									X													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth										+															
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X	X		X		X														
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X	X		X		X														
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X		X	X			X				X	X		X		X			X	X	X			X
Pars distalis, leukemia mononuclear	X										X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma																					X				
C cell, adenoma, multiple											X														
C cell, carcinoma																	X								
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Carcinoma		X																							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X								X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																X								X	
Polyp stromal	X		X				X	X							X						X	X		X	X

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	5411	5412	5413	5415	5511	5512	5515	5611	5612	5614	5615	5712	5713	5714	5715	5811	5812	5813	5814	5912	5913	5914	5915	6012	6014	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X														X								X			11
Neoplastic nodule																										1
Mesentery																										6
Leukemia mononuclear																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																					+					2
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										6
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										6
Pheochromocytoma benign						X																				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X				X				2
Parathyroid gland	+	+	+	+	M	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X		X	X	X				X		X			X	X	X	X		X	X		X	X	X	28
Pars distalis, leukemia mononuclear																							X			3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell, adenoma										X	X											X	X			5
C-cell, adenoma, multiple																										1
C cell, carcinoma					X							X							X							4
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Adenoma	X													X												3
Carcinoma																										1
Ovary	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										2
Uterus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										2
Polyp stromal						X	X				X		X			X	X		X	X		X				18

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

WEEKS ON STUDY	069	070	072	076	077	078	081	083	086	087	098	098	100	101	104	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	51 4	56 3	58 5	55 3	60 1	51 3	60 3	53 2	59 1	53 4	52 3	57 1	55 4	60 5	54 4	51 1	51 2	51 5	52 1	52 2	52 4	52 5	53 1	53 3	53 5
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, leukemia mononuclear																									
Mediastinal, leukemia mononuclear									X																
Pancreatic, leukemia mononuclear			X																						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X			X	X		X		X	X													
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X					X	X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X	X		X		X	X		X										X	
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Leukemia mononuclear						X					X														
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Fibroadenoma											X	X	X	X	X	X	X		X			X			
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																						X			
Subcutaneous tissue, fibrosarcoma								X																	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X					X																			
Peripheral nerve	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X																			
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X	X		X		X	X		X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear										+	+						+							+	
Eye										+	+	+	+		+	+	+	+	+	+		+	+	+	+
Zymbal gland										+															
Carcinoma										X															
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X			X																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	54 1	54 2	54 3	54 5	55 1	55 2	55 5	56 1	56 2	56 4	56 5	57 2	57 3	57 4	57 5	58 1	58 2	58 3	58 4	59 2	59 3	59 4	59 5	60 2	60 4	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																							X			2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, leukemia mononuclear																							X			1
Mediastinal, leukemia mononuclear																							X			2
Pancreatic, leukemia mononuclear																										1
Lymph node, mandibular	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leukemia mononuclear																							X			7
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X														X								X			12
Thymus	M	M	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	42
Leukemia mononuclear																										2
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma			X									X				X	X	X				X		X		16
Fibroadenoma, multiple																			X							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear															X								X			10
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear					+						+			+							+					8
Eye	+	+	+		+	+	+																			20
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1

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

WEEKS ON STUDY	057	059	074	076	091	093	097	097	098	098	100	101	102	104	104	104	104	104	105	105	105	105	105	105	105
CARCASS ID	445	412	492	413	481	495	434	483	453	435	482	504	502	424	415	474	411	443	414	421	422	423	425	431	432
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X	X	X								X		X				X				
Mesentery					+																	+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Pharynx																					+				
Salivary glands	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue														+											
Papilloma squamous														X											
Tooth																					+				
Gingiva, basosquamous tumor malignant																					X				
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X																		
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X		X							X											
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X		X							X											
Pheochromocytoma benign							X				X														
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X			X	X	X	X		X	X					X			X
Pars distalis, leukemia mononuclear							X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
C-cell, adenoma																					X	X			X
C-cell, adenoma, multiple																									
C-cell, carcinoma																									
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X														X							
Carcinoma																				X					
Bilateral, adenoma														X											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																		X							
Leukemia mononuclear							X																		
Polyp stromal			X	X		X							X							X		X			X
Sarcoma stromal												X													
Schwannoma malignant																	X								
Cervix, polyp																									
Cervix, squamous cell carcinoma								X																	
Vagina																	+								
Polyp																									
Sarcoma																									

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	433	441	442	444	451	452	454	455	461	462	463	464	465	471	472	473	475	484	485	491	505	493	494	501	503	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear										X											X			X		11
Mesentery																					+					3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Pharynx																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																	+									2
Papilloma squamous																										1
Tooth																										1
Gingiva, basosquamous tumor malignant																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																					X					6
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																					X					6
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Pars distalis, adenoma	X	X					X		X	X	X							X				X	X			18
Pars distalis, leukemia mononuclear																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
C cell, adenoma	X								X				X			X					X					8
C cell, adenoma, multiple																			X							1
C cell, carcinoma							X																			1
Follicular cell, adenoma							X																			1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Adenoma								X	X								X									5
Carcinoma																										1
Bilateral, adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Leukemia mononuclear																										1
Polyp stromal											X				X	X								X	X	12
Sarcoma stromal																										1
Schwannoma malignant																										1
Cervix, polyp					X																					1
Cervix, squamous cell carcinoma																										1
Vagina					+								+													3
Polyp													X													1
Sarcoma					X																					1

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

WEEKS ON STUDY	05 57	05 59	07 04	07 06	09 01	09 03	09 07	09 07	09 08	09 08	10 00	10 01	10 02	10 04	10 04	10 04	10 04	10 04	10 05	10 05	10 05	10 05	10 05	10 05
CARCASS ID	44 45	41 02	49 02	41 03	48 01	49 05	43 04	48 03	45 03	43 05	48 02	50 04	50 02	42 04	41 05	47 04	41 01	44 03	41 04	42 01	42 02	42 03	42 05	43 01	43 02
HEMATOPOIETIC SYSTEM																									
Blood					+																				
Leukemia mononuclear					X																				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X										X								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, leukemia mononuclear							X																		
Deep cervical, leukemia mononuclear							X																		
Iliac, leukemia mononuclear							X																		
Inguinal, leukemia mononuclear							X																		
Mediastinal, leukemia mononuclear							X																		
Pancreatic, leukemia mononuclear							X								X		X								
Popliteal, leukemia mononuclear							X																		
Renal, leukemia mononuclear							X																		
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X								X										
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Leukemia mononuclear				X	X		X								X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X	X	X								X		X				X				
Thymus	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma								X																	
Fibroadenoma									X	X		X	X					X	X						
Fibroadenoma, multiple																									X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma, multiple																									
Papilloma squamous																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, schwannoma benign																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																X									
Skeletal muscle																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Osteosarcoma, metastatic, bone																X									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Leukemia mononuclear			X	X	X		X								X		X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear		+							+		+							+					+		
Eye		+																+					+		
Harderian gland																									
Zymbal gland		+																							
Carcinoma		X																							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X	X																		
Urethra	+																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic								X																	

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	433	441	442	444	451	452	454	455	461	462	463	464	465	471	472	473	475	484	485	491	505	493	494	501	503	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																					+					2
Leukemia mononuclear																					X					2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, leukemia mononuclear																										1
Deep cervical, leukemia mononuclear																										1
Iliac, leukemia mononuclear																										1
Inguinal, leukemia mononuclear																										1
Mediastinal, leukemia mononuclear																										1
Pancreatic, leukemia mononuclear																					X					4
Popliteal, leukemia mononuclear																										1
Renal, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																					X					4
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	46
Leukemia mononuclear																					X					5
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear										X											X			X		11
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Fibroadenoma		X		X			X		X					X	X	X		X		X	X		X			17
Fibroadenoma, multiple										X	X	X														4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma, multiple									X																	1
Papilloma squamous																									X	1
Subcutaneous tissue, fibroma													X													1
Subcutan tissue, schwannoma benign														X												1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma			X																							2
Skeletal muscle													+													1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma, metastatic, bone																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X										1
Leukemia mononuclear																					X					7
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear		+						+						+				+						+		10
Eye		+																						+		5
Harderian gland																						+				1
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1

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

	Control	50 ppm	100 ppm
Clitoral Gland: Adenoma			
Overall Rates (a)	1/44 (2%)	3/47 (6%)	6/48 (13%)
Adjusted Rates (b)	4.2%	8.9%	16.8%
Terminal Rates (c)	1/24 (4%)	2/32 (6%)	3/30 (10%)
Day of First Observation	729	728	530
Life Table Tests (d)	P=0.057	P=0.410	P=0.100
Logistic Regression Tests (d)	P=0.049	P=0.393	P=0.074
Cochran-Armitage Trend Test (d)	P=0.045		
Fisher Exact Test (d)		P=0.334	P=0.070
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	2/44 (5%)	4/47 (9%)	7/48 (15%)
Adjusted Rates (b)	7.1%	10.7%	19.9%
Terminal Rates (c)	1/24 (4%)	2/32 (6%)	4/30 (13%)
Day of First Observation	701	486	530
Life Table Tests (d)	P=0.091	P=0.438	P=0.142
Logistic Regression Tests (d)	P=0.070	P=0.370	P=0.106
Cochran-Armitage Trend Test (d)	P=0.070		
Fisher Exact Test (d)		P=0.371	P=0.101
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	4/50 (8%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	9.9%	0.0%	2.3%
Terminal Rates (c)	1/27 (4%)	0/35 (0%)	0/32 (0%)
Day of First Observation	404		678
Life Table Tests (d)	P=0.072N	P=0.058N	P=0.159N
Logistic Regression Tests (d)	P=0.078N	P=0.054N	P=0.183N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.059N	P=0.181N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	21/50 (42%)	17/50 (34%)	21/50 (42%)
Adjusted Rates (b)	58.5%	42.5%	56.2%
Terminal Rates (c)	13/27 (48%)	12/35 (34%)	16/32 (50%)
Day of First Observation	526	685	685
Life Table Tests (d)	P=0.311N	P=0.097N	P=0.326N
Logistic Regression Tests (d)	P=0.405N	P=0.230N	P=0.463N
Cochran-Armitage Trend Test (d)	P=0.541		
Fisher Exact Test (d)		P=0.268N	P=0.580N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	27/50 (54%)	28/49 (57%)	18/48 (38%)
Adjusted Rates (b)	69.5%	67.7%	46.5%
Terminal Rates (c)	16/27 (59%)	21/34 (62%)	11/31 (35%)
Day of First Observation	485	486	678
Life Table Tests (d)	P=0.019N	P=0.320N	P=0.025N
Logistic Regression Tests (d)	P=0.049N	P=0.463	P=0.059N
Cochran-Armitage Trend Test (d)	P=0.065N		
Fisher Exact Test (d)		P=0.455	P=0.075N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	28/50 (56%)	28/49 (57%)	18/48 (38%)
Adjusted Rates (b)	70.4%	67.7%	46.5%
Terminal Rates (c)	16/27 (59%)	21/34 (62%)	11/31 (35%)
Day of First Observation	485	486	678
Life Table Tests (d)	P=0.013N	P=0.260N	P=0.017N
Logistic Regression Tests (d)	P=0.032N	P=0.544	P=0.039N
Cochran-Armitage Trend Test (d)	P=0.043N		
Fisher Exact Test (d)		P=0.535	P=0.051N

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

	Control	50 ppm	100 ppm
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	9.3%	2.3%	3.1%
Terminal Rates (c)	2/27 (7%)	0/35 (0%)	1/32 (3%)
Day of First Observation	404	581	729
Life Table Tests (d)	P=0.177N	P=0.269N	P=0.264N
Logistic Regression Tests (d)	P=0.215N	P=0.242N	P=0.324N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.309N	P=0.309N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	8/50 (16%)	6/50 (12%)	9/50 (18%)
Adjusted Rates (b)	25.4%	16.4%	28.1%
Terminal Rates (c)	5/27 (19%)	5/35 (14%)	9/32 (28%)
Day of First Observation	630	685	729
Life Table Tests (d)	P=0.538N	P=0.241N	P=0.569N
Logistic Regression Tests (d)	P=0.553N	P=0.344N	P=0.587N
Cochran-Armitage Trend Test (d)	P=0.445		
Fisher Exact Test (d)		P=0.387N	P=0.500
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	5.4%	11.4%	3.1%
Terminal Rates (c)	0/27 (0%)	4/35 (11%)	1/32 (3%)
Day of First Observation	582	729	729
Life Table Tests (d)	P=0.344N	P=0.427	P=0.456N
Logistic Regression Tests (d)	P=0.383N	P=0.346	P=0.510N
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.339	P=0.500N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	10/50 (20%)	10/50 (20%)
Adjusted Rates (b)	29.5%	27.6%	31.3%
Terminal Rates (c)	5/27 (19%)	9/35 (26%)	10/32 (31%)
Day of First Observation	582	685	729
Life Table Tests (d)	P=0.399N	P=0.400N	P=0.446N
Logistic Regression Tests (d)	P=0.439N	P=0.563N	P=0.509N
Cochran-Armitage Trend Test (d)	P=0.550		
Fisher Exact Test (d)		P=0.598	P=0.598
Uterus: Stromal Polyp			
Overall Rates (a)	10/50 (20%)	18/49 (37%)	13/50 (26%)
Adjusted Rates (b)	28.3%	45.0%	34.4%
Terminal Rates (c)	5/27 (19%)	13/34 (38%)	9/32 (28%)
Day of First Observation	404	481	517
Life Table Tests (d)	P=0.442	P=0.157	P=0.471
Logistic Regression Tests (d)	P=0.267	P=0.050	P=0.291
Cochran-Armitage Trend Test (d)	P=0.288		
Fisher Exact Test (d)		P=0.052	P=0.318
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	14/50 (28%)	12/50 (24%)	11/50 (22%)
Adjusted Rates (b)	34.1%	26.7%	26.0%
Terminal Rates (c)	3/27 (11%)	4/35 (11%)	4/32 (13%)
Day of First Observation	582	481	517
Life Table Tests (d)	P=0.201N	P=0.325N	P=0.221N
Logistic Regression Tests (d)	P=0.343N	P=0.426N	P=0.370N
Cochran-Armitage Trend Test (d)	P=0.281N		
Fisher Exact Test (d)		P=0.410N	P=0.322N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ROXARSONE (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 logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

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

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
HC Blue No. 2	19/49	1/49	20/49
C.I. Disperse Blue 1	10/49	2/49	12/49
Eugenol	7/39	2/39	9/39
Stannous chloride	17/50	0/50	17/50
D-Mannitol	24/50	1/50	25/50
Ziram	19/50	3/50	22/50
Propyl gallate	16/50	1/50	17/50
Zearalenone	13/49	1/49	14/49
HC Blue No. 1	25/50	6/50	31/50
TOTAL	150/436 (34.4%)	17/436 (3.9%)	167/436 (38.3%)
SD (b)	11.14%	3.55%	12.70%
Range (c)			
High	25/50	6/50	31/50
Low	7/39	0/50	9/39
Overall Historical Incidence			
TOTAL	(d) 875/1,922 (45.5%)	(e) 69/1,922 (3.6%)	(d,e) 942/1,922 (49.0%)
SD (b)	11.63%	4.02%	11.20%
Range (c)			
High	33/47	8/49	33/47
Low	7/39	0/50	9/39

(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 123 chromophobe adenomas
(e) Includes two adenocarcinomas, NOS, and six chromophobe carcinomas

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

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

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

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS REMOVED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(49)	(47)	(50)
Parasite metazoan	1 (2%)		
Intestine large, colon	(49)	(48)	(49)
Cyst		1 (2%)	
Parasite metazoan	1 (2%)	1 (2%)	2 (4%)
Intestine large, rectum	(49)	(50)	(48)
Parasite metazoan	1 (2%)	3 (6%)	2 (4%)
Liver	(50)	(50)	(50)
Angiectasis, focal	1 (2%)	1 (2%)	4 (8%)
Basophilic focus	2 (4%)	2 (4%)	4 (8%)
Basophilic focus, multiple	23 (46%)	30 (60%)	27 (54%)
Clear cell focus	1 (2%)	1 (2%)	1 (2%)
Congestion		1 (2%)	
Degeneration, cystic		1 (2%)	1 (2%)
Degeneration, fatty, multifocal	1 (2%)		
Developmental malformation	6 (12%)	6 (12%)	8 (16%)
Eosinophilic focus	2 (4%)		
Granuloma, multifocal	25 (50%)	29 (58%)	31 (62%)
Hematopoietic cell proliferation	1 (2%)		
Hepatodiaphragmatic nodule		3 (6%)	1 (2%)
Hyperplasia, focal	1 (2%)		
Mixed cell focus	3 (6%)		1 (2%)
Necrosis, multifocal	1 (2%)		2 (4%)
Regeneration	1 (2%)		
Vacuolization cytoplasmic, diffuse		4 (8%)	2 (4%)
Vacuolization cytoplasmic, focal		3 (6%)	
Biliary tract, proliferation	17 (34%)	12 (24%)	16 (32%)
Centrilobular, necrosis	11 (22%)	9 (18%)	8 (16%)
Mesentery	(10)	(6)	(3)
Cyst		1 (17%)	
Mineralization, multifocal	1 (10%)		
Fat, necrosis, focal	8 (80%)	3 (50%)	3 (100%)
Fat, necrosis, multifocal	1 (10%)		
Pancreas	(50)	(50)	(50)
Atrophy, focal	11 (22%)	11 (22%)	14 (28%)
Basophilic focus		1 (2%)	1 (2%)
Pharynx	(2)		(1)
Cyst	1 (50%)		
Inflammation, suppurative, acute, focal			1 (100%)
Salivary glands	(50)	(47)	(48)
Atrophy, focal	1 (2%)		
Stomach, forestomach	(50)	(50)	(50)
Cyst			1 (2%)
Edema			1 (2%)
Erosion			1 (2%)
Hyperkeratosis		3 (6%)	2 (4%)
Hyperplasia	1 (2%)	3 (6%)	2 (4%)
Inflammation; chronic		1 (2%)	1 (2%)
Ulcer	1 (2%)	3 (6%)	2 (4%)
Stomach, glandular	(50)	(50)	(50)
Edema			3 (6%)
Erosion			1 (2%)
Inflammation, chronic, diffuse		1 (2%)	
Ulcer		1 (2%)	1 (2%)
Tooth		(2)	(1)
Dysplasia		1 (50%)	

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

	Untreated Control	Low Dose	High Dose
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Cardiomyopathy	35 (70%)	30 (60%)	32 (64%)
Artery, inflammation, chronic	1 (2%)		
Atrium, thrombus		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Cyst	1 (2%)		
Degeneration, fatty, focal	6 (12%)	8 (16%)	13 (26%)
Degeneration, fatty, multifocal			4 (8%)
Hematopoietic cell proliferation	1 (2%)		
Hyperplasia, focal		1 (2%)	3 (6%)
Necrosis, multifocal			1 (2%)
Adrenal gland, medulla	(49)	(48)	(50)
Hematopoietic cell proliferation	2 (4%)		
Hyperplasia, focal	2 (4%)		1 (2%)
Necrosis, multifocal			1 (2%)
Pituitary gland	(50)	(49)	(48)
Pars distalis, angiectasis	28 (56%)	29 (59%)	24 (50%)
Pars distalis, cyst	11 (22%)	6 (12%)	10 (21%)
Pars distalis, hemorrhage	1 (2%)	1 (2%)	
Pars distalis, hyperplasia, focal	9 (18%)	6 (12%)	13 (27%)
Pars distalis, pigmentation, hemosiderin	9 (18%)	1 (2%)	4 (8%)
Pars distalis, thrombus	1 (2%)		
Thyroid gland	(50)	(50)	(50)
C-cell, hyperplasia	2 (4%)		
C-cell, hyperplasia, focal			1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(44)	(47)	(48)
Abscess	2 (5%)		1 (2%)
Hyperplasia	2 (5%)	7 (15%)	3 (6%)
Inflammation, chronic	1 (2%)		
Inflammation, suppurative, acute		1 (2%)	
Duct, cyst	4 (9%)	1 (2%)	5 (10%)
Duct, hyperplasia			1 (2%)
Ovary	(50)	(47)	(50)
Cyst	1 (2%)	2 (4%)	2 (4%)
Uterus	(50)	(49)	(50)
Cyst			2 (4%)
Hemorrhage	1 (2%)	1 (2%)	
Hydrometria			3 (6%)
Hyperplasia, cystic		1 (2%)	1 (2%)
Inflammation, suppurative, acute		1 (2%)	
Cervix, abscess	6 (12%)	6 (12%)	3 (6%)
Cervix, abscess, multiple			1 (2%)
Cervix, cyst	5 (10%)	7 (14%)	5 (10%)
Cervix, cyst, multiple		1 (2%)	1 (2%)

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

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node	(50)	(50)	(50)
Mediastinal, congestion			1 (2%)
Mediastinal, ectasia			1 (2%)
Lymph node, mandibular	(49)	(46)	(49)
Congestion			1 (2%)
Ectasia	1 (2%)		2 (4%)
Spleen	(50)	(50)	(50)
Fibrosis			1 (2%)
Hematopoietic cell proliferation	3 (6%)	2 (4%)	3 (6%)
Hyperplasia, lymphoid		2 (4%)	
Necrosis, focal	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(49)	(50)
Duct, cyst	44 (88%)	47 (96%)	39 (78%)
Skin	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Hypertrophy, focal			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Compression	7 (14%)	1 (2%)	1 (2%)
Hemorrhage, multifocal	2 (4%)	1 (2%)	
Lateral ventricle, dilatation	1 (2%)		
Peripheral nerve	(50)	(47)	(50)
Infiltration cellular, mononuclear cell			2 (4%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Congestion			1 (2%)
Fungus	1 (2%)		
Granuloma, multifocal			1 (2%)
Hemorrhage, multifocal		1 (2%)	
Infiltration cellular, histiocytic, multifocal		1 (2%)	1 (2%)
Necrosis, focal	1 (2%)		
Alveolar epithelium, hyperplasia, focal	1 (2%)	1 (2%)	4 (8%)
Nose	(50)	(50)	(50)
Foreign body	2 (4%)		
Fungus	3 (6%)		1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, suppurative, acute	3 (6%)		1 (2%)
Nasolacrimal duct, inflammation, suppurative, acute	1 (2%)	1 (2%)	2 (4%)
Olfactory epithelium, erosion			1 (2%)
SPECIAL SENSES SYSTEM			
Eye	(3)	(20)	(5)
Cataract	2 (67%)	19 (95%)	3 (60%)
Anterior chamber, fibrosis			1 (20%)
Retina, degeneration	2 (67%)	20 (100%)	4 (80%)
Harderian gland			(1)
Inflammation, chronic			1 (100%)

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

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Fibrosis, focal	1 (2%)		1 (2%)
Hydronephrosis			1 (2%)
Nephropathy, chronic	36 (72%)	36 (72%)	28 (56%)
Papilla, necrosis			1 (2%)
Renal tubule, degeneration, multifocal			1 (2%)
Renal tubule, dilatation, multifocal			1 (2%)
Urethra			(1)
Calculus gross observation			1 (100%)
Inflammation, suppurative, acute			1 (100%)
Urinary bladder	(50)	(50)	(50)
Hemorrhage, multifocal			1 (2%)
Transitional epithelium, hyperplasia	1 (2%)		1 (2%)

APPENDIX C

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

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS REMOVED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(42)	(42)	(48)
Adenocarcinoma, metastatic			1 (2%)
Lymphoma malignant mixed	1 (2%)		1 (2%)
Intestine large, cecum	(50)	(49)	(49)
Lymphoma malignant mixed			1 (2%)
Intestine small, duodenum	(49)	(45)	(47)
Lymphoma malignant mixed	1 (2%)		
Intestine small, jejunum	(49)	(49)	(48)
Lymphoid tissue, lymphoma malignant mixed	1 (2%)		
Liver	(50)	(50)	(50)
Adenocarcinoma, metastatic			1 (2%)
Adenoma, multiple			1 (2%)
Hemangiosarcoma, multiple	1 (2%)		
Hepatocellular carcinoma	3 (6%)	8 (16%)	5 (10%)
Hepatocellular carcinoma, multiple	1 (2%)		
Hepatocellular adenoma	9 (18%)	8 (16%)	2 (4%)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant mixed	2 (4%)		2 (4%)
Mesentery	*(50)	*(50)	*(50)
Adenocarcinoma, metastatic			1 (2%)
Lymphoma malignant mixed	2 (4%)		1 (2%)
Pancreas	(49)	(50)	(50)
Lymphoma malignant mixed	1 (2%)		1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Lymphoma malignant mixed	1 (2%)		
Papilloma squamous	1 (2%)		
Stomach, glandular	(50)	(50)	(50)
Lymphoma malignant mixed	1 (2%)		
CARDIOVASCULAR SYSTEM			
None			
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(49)
Adenoma		1 (2%)	1 (2%)
Extra adrenal tissue, lymphoma malignant mixed	1 (2%)		
Subcapsular, adenoma		1 (2%)	3 (6%)
Adrenal gland, medulla	(50)	(50)	(49)
Pheochromocytoma, NOS			1 (2%)
Pheochromocytoma benign	3 (6%)		
Thyroid gland	(50)	(48)	(50)
Follicular cell, adenoma		2 (4%)	2 (4%)
Follicular cell, carcinoma			1 (2%)
GENERAL BODY SYSTEM			
None			

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

	Untreated Control	Low Dose	High Dose
GENITAL SYSTEM			
Ductus deferens	*(50)	*(50)	*(50)
Lymphoma malignant mixed	1 (2%)		
Preputial gland	*(50)	*(50)	*(50)
Carcinoma	1 (2%)		
Prostate	(50)	(50)	(49)
Lymphoma malignant mixed	1 (2%)		1 (2%)
Seminal vesicle	*(50)	*(50)	*(50)
Lymphoma malignant mixed	1 (2%)		1 (2%)
Testes	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
Interstitial cell, adenoma			1 (2%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Lymphoma malignant mixed			1 (2%)
Lymph node	(50)	(49)	(50)
Axillary, lymphoma malignant histiocytic	1 (2%)		
Axillary, sarcoma, metastatic, skin	1 (2%)		
Bronchial, lymphoma malignant mixed	1 (2%)		
Inguinal, lymphoma malignant mixed	1 (2%)		2 (4%)
Inguinal, sarcoma, metastatic, skin		1 (2%)	
Inguinal, lumbar, sarcoma, metastatic, skin		1 (2%)	
Mediastinal, adenocarcinoma, metastatic			1 (2%)
Mediastinal, lymphoma malignant histiocytic	1 (2%)		
Mediastinal, lymphoma malignant mixed	2 (4%)		2 (4%)
Lymph node, mandibular	(48)	(42)	(43)
Lymphoma malignant mixed	2 (4%)		2 (5%)
Lymph node, mesenteric	(43)	(48)	(47)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant mixed	3 (7%)	1 (2%)	2 (4%)
Spleen	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)		
Lymphoma malignant mixed	2 (4%)	1 (2%)	3 (6%)
INTEGUMENTARY SYSTEM			
Skin	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		
Abdominal, axillary, subcutaneous tissue, sarcoma, metastatic, multiple, skin		1 (2%)	
Hindlimb, subcutaneous tissue, sarcoma		1 (2%)	
Subcutaneous tissue, fibroma	4 (8%)	4 (8%)	4 (8%)
Subcutaneous tissue, fibrosarcoma	6 (12%)	3 (6%)	7 (14%)
Subcutaneous tissue, hemangioma		1 (2%)	
Subcutaneous tissue, lipoma		1 (2%)	
Subcutaneous tissue, sarcoma	4 (8%)	4 (8%)	5 (10%)
Subcutaneous tissue, sarcoma, multiple	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, schwannoma, NOS	2 (4%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Pelvis, osteoma		1 (2%)	
Skeletal muscle	*(50)	*(50)	*(50)
Lymphoma malignant mixed			1 (2%)
Abdominal, thoracic, adenocarcinoma, metastatic, multiple			1 (2%)

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

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM			
Peripheral nerve	(50)	(50)	(50)
Sciatic, sarcoma, metastatic, skin		1 (2%)	
Spinal cord	(50)	(50)	(50)
Dura, lymphoma malignant mixed	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Adenocarcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	4 (8%)	2 (4%)	9 (18%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)	
Alveolar/bronchiolar carcinoma	6 (12%)	2 (4%)	1 (2%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)		1 (2%)
Hepatocellular carcinoma, metastatic, multiple, liver	1 (2%)		
Lymphoma malignant mixed	2 (4%)		2 (4%)
Sarcoma, metastatic, skin		1 (2%)	1 (2%)
Sarcoma, metastatic, skeletal muscle	1 (2%)		
Squamous cell carcinoma, metastatic, multiple, skin	1 (2%)		
Nose	(48)	(49)	(48)
Lymphoma malignant mixed			1 (2%)
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenoma	1 (2%)	2 (4%)	3 (6%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Adenocarcinoma, metastatic			1 (2%)
Lymphoma malignant mixed	2 (4%)		2 (4%)
Ureter	*(50)	*(50)	*(50)
Transitional epithelium, carcinoma		1 (2%)	
Urinary bladder	(50)	(50)	(50)
Lymphoma malignant mixed	1 (2%)		1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Hemangiosarcoma	3 (6%)		
Lymphoma malignant mixed	3 (6%)	1 (2%)	3 (6%)
Lymphoma malignant histiocytic	2 (4%)		
Hemangioma		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	27	40	33
Moribund sacrifice	17	9	11
Natural death	6	1	6

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

	Untreated Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary neoplasms **	35	30	34
Total primary neoplasms	56	45	51
Total animals with benign neoplasms	18	20	20
Total benign neoplasms	23	24	26
Total animals with malignant neoplasms	26	18	21
Total malignant neoplasms	31	21	23
Total animals with secondary neoplasms ***	6	2	2
Total secondary neoplasms	6	5	9
Total animals with neoplasms-- uncertain benign or malignant	2		2
Total uncertain neoplasms	2		2

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

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

WEEKS ON STUDY	03 3	04 3	06 6	06 8	07 7	07 7	07 9	08 9	08 9	08 9	09 3	09 4	09 4	09 5	09 6	09 6	09 8	10 1	10 2	10 2	10 3	10 3	10 3	10 5	10 5
CARCASS ID	10 4	08 5	08 2	09 3	09 1	03 4	03 1	04 1	04 3	04 2	08 1	06 4	08 3	10 2	02 3	07 1	02 5	06 5	10 5	05 5	05 2	09 5	04 4	04 1	01 2
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+
Lymphoma malignant mixed											X														
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine small	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed											X														
Intestine small, ileum	M	+	+	M	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoid tissue, lymphoma malignant mixed																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple					X																				
Hepatocellular carcinoma										X								X			X				
Hepatocellular carcinoma, multiple												X													
Hepatocellular adenoma								X				X				X			X						
Lymphoma malignant histiocytic													X												
Lymphoma malignant mixed											X														
Mesentery	+										+							+							
Lymphoma malignant mixed											X														
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed											X														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed											X														
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed											X														
Tooth							+	+	+																+
CARDIOVASCULAR SYSTEM																									
Blood vessel		+																							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Extra adrenal tissue, lymphoma malignant mixed											X														
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign								X													X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ductus deferens	+										+														
Lymphoma malignant mixed											X														
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis							+																		
Preputial gland		+			+							+	+		+	+					+	+		+
Carcinoma																					X				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed											X														
Seminal vesicle				+																					
Lymphoma malignant mixed																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X																				

WEEKS ON STUDY	10 5	10 5	10 5	11 0	11 2
CARCASS ID	01 2	07 1	02 5	06 5	05 5	05 2	09 5	04 4	04 1	01 2
ALIMENTARY SYSTEM										
Esophagus	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed										
Intestine large	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	M	+
Intestine small	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed										
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+
Lymphoid tissue, lymphoma malignant mixed										
Liver	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple										
Hepatocellular carcinoma				X			X			
Hepatocellular carcinoma, multiple										
Hepatocellular adenoma		X			X					
Lymphoma malignant histiocytic										
Lymphoma malignant mixed										
Mesentery				+						
Lymphoma malignant mixed										
Pancreas	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed										
Salivary glands	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed										
Papilloma squamous										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed										
Tooth										+
CARDIOVASCULAR SYSTEM										
Blood vessel										
Heart	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM										
Adrenal gland	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+
Extra adrenal tissue, lymphoma malignant mixed										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign						X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM										
None										
GENITAL SYSTEM										
Ductus deferens										
Lymphoma malignant mixed										
Epididymis	+	+	+	+	+	+	+	+	+	+
Penis										
Preputial gland		+				+	+		+	
Carcinoma						X				
Prostate	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed										
Seminal vesicle										
Lymphoma malignant mixed										
Testes	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										

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

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

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	013	014	015	021	022	024	032	033	035	045	051	053	054	061	062	063	072	073	074	075	084	092	094	101	103	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	42
Lymphoma malignant mixed																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoid tissue, lymphoma malignant mixed																						X				1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple																										1
Hepatocellular carcinoma																										3
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma			X						X			X							X	X						9
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed										X																2
Mesentery										+																4
Lymphoma malignant mixed										X																2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Papilloma squamous			X																							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Tooth	+			+				+	+						+	+			+	+	+	+				14
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Extra adrenal tissue, lymphoma malignant mixed																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign						X																				3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	45
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ductus deferens																										2
Lymphoma malignant mixed																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland														+										+		11
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Seminal vesicle										+																2
Lymphoma malignant mixed										X																1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1

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

WEEKS ON STUDY	033	043	066	068	077	077	079	089	089	089	093	094	094	095	096	097	098	101	102	102	103	103	103	105	105
CARCASS ID	104	085	082	093	091	034	031	041	043	042	081	064	083	102	223	071	225	065	105	555	252	095	444	111	112
HEMATOPOIETIC SYSTEM																									
Blood													+												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, lymphoma malignant histiocytic																									
Axillary, sarcoma, metastatic, skin																							X		
Bronchial, lymphoma malignant mixed																									
Inguinal, lymphoma malignant mixed											X														
Mediastinal, lymphoma malignant histiocytic																									
Mediastinal, lymphoma malignant mixed											X														
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed											X														
Lymph node, mesenteric	+	+	M	M	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed											X														
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Lymphoma malignant mixed											X														
Thymus	M	+	M	M	+	M	+	M	+	M	M	+	+	+	M	+	M	M	+	M	+	+	M	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma			X																						
Subcutaneous tissue, fibroma																				X					
Subcutaneous tissue, fibrosarcoma								X	X	X					X						X				
Subcutaneous tissue, sarcoma														X			X			X			X		
Subcutaneous tissue, sarcoma, multiple												X													
Subcutaneous tissue, schwannoma, NOS																			X						
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Dura, lymphoma malignant mixed											X														
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X		X		
Alveolar/bronchiolar adenoma, multiple														X											
Alveolar/bronchiolar carcinoma																X									X
Hepatocellular carcinoma, metastatic, liver										X											X				
Hepatocellular carcinoma, metastatic, multiple, liver																		X							
Lymphoma malignant mixed											X														
Sarcoma, metastatic, skeletal muscle												X													
Squamous cell carcinoma, metastatic, multiple, skin			X																						
Nose	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																+			+						
Adenoma																X									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed											X														
Urethra													+												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	013	014	015	021	022	024	032	033	035	045	051	053	054	061	062	063	072	073	074	075	084	092	094	101	103	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, lymphoma malignant histiocytic																					X					1
Axillary, sarcoma, metastatic, skin																										1
Bronchial, lymphoma malignant mixed										X																1
Inguinal, lymphoma malignant mixed																										1
Mediastinal, lymphoma malignant histiocytic																					X					1
Mediastinal, lymphoma malig mixed										X																2
Lymph node, mandibular	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed										X																2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymphoma malignant histiocytic																					X					1
Lymphoma malignant mixed										X												X				3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X																	2
Lymphoma malignant mixed										X																2
Thymus	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma								X						X						X						4
Subcutaneous tissue, fibrosarcoma											X															6
Subcutaneous tissue, sarcoma																										4
Subcutaneous tissue, sarcoma, multiple																										1
Subcutaneous tissue, schwannoma, NOS													X													2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Dura, lymphoma malignant mixed																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X							X																4
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma	X											X						X			X					6
Hepatocellular carcinoma, metastatic, liver																										2
Hepatocellular carcinoma, metastatic, multiple, liver																										1
Lymphoma malignant mixed										X																2
Sarcoma, metastatic, skeletal muscle																										1
Squamous cell carcinoma, metastatic, multiple, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland		+																					+		+	5
Adenoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed										X																2
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed										X																1

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

WEEKS ON STUDY	017	080	081	093	093	096	097	102	102	102	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	303	244	245	222	224	294	304	221	293	282	211	212	213	214	215	223	225	231	232	233	234	235	241	242	243
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+
Intestine large	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	+	+	+	+	A	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X	X				X		X		X				X		X								
Hepatocellular adenoma				X			X			X									X			X			X
Mesentery						+							+										+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth						+									+			+		+					+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Subcapsular, adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+
Pituitary gland	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								X	
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland							+				+					+			+						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle													+							+					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	251	252	253	254	255	261	262	263	264	265	271	272	273	274	275	281	283	284	285	291	292	295	301	302	305	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	48
Gallbladder	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	42
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X																									8
Hepatocellular adenoma							X																X			8
Mesentery		+																								4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth										+				+									+			8
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
Subcapsular, adenoma													X													1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma													X													2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland							+																			1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis				+																	+					2
Preputial gland	+				+								+		+				+	+	+	+	+			13
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle							+																			3
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	017	080	081	093	093	096	097	102	102	102	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	303	244	245	222	224	294	304	221	293	282	211	212	213	214	215	223	225	231	232	233	234	235	241	242	243
HEMATOPOIETIC SYSTEM																									
Blood				+																					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, sarcoma, metastatic, skin						X																			
Inguinal, lumbar, sarcoma, metastatic, skin				X																					
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																			X						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																			X						
Thymus	+	M	+	+	+	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Abdominal, axillary, subcutaneous tissue, sarcoma, metastatic, multiple, skin				X																					
Hindlimb, subcutaneous tissue, sarcoma				X																					
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma									X																
Subcutaneous tissue, hemangioma																				X					
Subcutaneous tissue, lipoma																								X	
Subcutaneous tissue, sarcoma								X		X		X													
Subcutaneous tissue, sarcoma, multiple						X																			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, osteoma												X													
Skeletal muscle							+						+												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sciatic, sarcoma, metastatic, skin				X																					
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X																		
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma											X														
Sarcoma, metastatic, skin				X																					
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland								+					+	+			+								
Adenoma													X												
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter					+																				
Transitional epithelium, carcinoma					X																				
Urethra										+															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	251	252	253	254	255	261	262	263	264	265	271	272	273	274	275	281	283	284	285	291	292	295	301	302	305	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Inguinal, sarcoma, metastatic, skin																										1
Inguinal, lumbar, sarcoma, metastatic, skin																										1
Lymph node, mandibular	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	M	+	+	+	42
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Thymus	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	40
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Abdominal, axillary, subcutaneous tissue, sarcoma, metastatic, multiple, skin																										1
Hindlimb, subcutaneous tissue, sarcoma																										1
Subcutaneous tissue, fibroma			X												X						X			X		4
Subcutaneous tissue, fibrosarcoma																	X	X								3
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, lipoma																										1
Subcutaneous tissue, sarcoma				X																						4
Subcutaneous tissue, sarcoma, multiple																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pelvis, osteoma																										1
Skeletal muscle																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sciatic, sarcoma, metastatic, skin																										1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																									2
Alveolar/bronchiolar adenoma, multiple													X													1
Alveolar/bronchiolar carcinoma																		X								2
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland																	+							+		6
Adenoma																	X									2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																										1
Transitional epithelium, carcinoma																										1
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	016	020	062	069	087	087	092	092	094	094	095	098	098	101	101	102	102	105	105	105	105	105	105	105	105
CARCASS ID	144	143	142	162	171	174	203	173	134	191	182	131	154	192	194	201	183	111	112	113	114	115	121	122	123
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenocarcinoma, metastatic									X																
Lymphoma malignant mixed															X										
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X										
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+
Intestine small	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine small, ileum	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic									X																
Adenoma, multiple									X																
Hepatocellular carcinoma								X	X			X		X											
Hepatocellular adenoma																					X				
Lymphoma malignant mixed															X										
Mesentery								+		+					+								+		
Adenocarcinoma, metastatic										X															
Lymphoma malignant mixed															X										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth						+																			
CARDIOVASCULAR SYSTEM																									
Blood vessel														+											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Subcapsular, adenoma																									
Adrenal gland, medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, NOS								X																	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis														+											
Preputial gland								+		+				+											
Prostate	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X										
Seminal vesicle							+								+										
Lymphoma malignant mixed															X										
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma														X											

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	1244	1255	1332	1333	1335	1441	1445	1551	1552	1553	1555	1561	1663	1664	1665	1772	1775	1881	1884	1885	1893	1995	2002	2004	2005	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		48
Adenocarcinoma, metastatic																										1
Lymphoma malignant mixed																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic																										1
Adenoma, multiple																										1
Hepatocellular carcinoma							X																			5
Hepatocellular adenoma											X															2
Lymphoma malignant mixed																	X									2
Mesentery													+												+	6
Adenocarcinoma, metastatic																										1
Lymphoma malignant mixed																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth		+			+		+						+		+					+						7
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma										X																1
Subcapsular, adenoma			X												X	X										3
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma, NOS																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																X					X					2
Follicular cell, carcinoma									X																	1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland		+									+										+	+				7
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																										1
Seminal vesicle																										2
Lymphoma malignant mixed																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

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

WEEKS ON STUDY	016	020	062	069	087	087	092	092	094	094	095	098	098	101	101	102	102	105	105	105	105	105	105	105
CARCASS ID	14 4	14 3	14 2	16 2	17 1	17 4	20 3	17 3	13 4	19 1	18 2	13 1	15 4	19 2	19 4	20 1	18 3	11 1	11 2	11 3	11 4	11 5	12 1	12 2	12 3
HEMATOPOIETIC SYSTEM																									
Blood						+	+		+																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																X									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, lymphoma malignant mixed																X									
Mediastinal, adenocarcinoma, metastatic										X															
Mediastinal, lymphoma malignant mixed																X									
Lymph node, mandibular	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M
Lymphoma malignant mixed																X									
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X	X									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X	X									
Thymus	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																	X	X							
Subcutaneous tissue, fibrosarcoma					X	X			X		X	X											X		
Subcutaneous tissue, sarcoma							X	X						X				X							
Subcutaneous tissue, sarcoma, multiple			X																						
Subcutaneous tissue, schwannoma, NOS				X																					
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+						+									
Lymphoma malignant mixed																X									
Abdominal, thoracic, adenocarcinoma, metastatic, multiple										X															
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic										X															
Alveolar/bronchiolar adenoma															X	X			X					X	
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver										X															
Lymphoma malignant mixed																X									
Sarcoma, metastatic, skin			X																						
Nose	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																X									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland											+														
Adenoma											X														
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic										X															
Lymphoma malignant mixed																X									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																X									

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	124	125	132	133	135	141	145	151	152	153	155	161	163	164	165	172	175	181	184	185	193	195	202	204	205	TOTAL TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										3
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Inguinal, lymphoma malignant mixed																	X									2
Mediastinal, adenocarcinoma, metastatic																										1
Mediastinal, lymphoma malig mixed																	X									2
Lymph node, mandibular	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymphoma malignant mixed																	X									2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	47
Lymphoma malignant mixed																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																	X									3
Thymus	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	43
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	+	M	+	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma								X	X																	4
Subcutaneous tissue, fibrosarcoma																		X								7
Subcutaneous tissue, sarcoma															X											5
Subcutaneous tissue, sarcoma, multiple																										1
Subcutaneous tissue, schwannoma, NOS																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Lymphoma malignant mixed																										1
Abdominal, thoracic, adenocarcinoma, metastatic, multiple																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic																										1
Alveolar/bronchiolar adenoma					X							X				X		X				X				9
Alveolar/bronchiolar carcinoma																				X						1
Hepatocellular carcinoma, metastatic, liver																										1
Lymphoma malignant mixed																	X									2
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland											+	+				+										4
Adenoma											X					X										3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic																										1
Lymphoma malignant mixed																	X									2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1

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

	Control	100 ppm	200 ppm
Adrenal Cortex: Subcapsular Adenoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/49 (6%)
Adjusted Rates (b)	0.0%	2.5%	9.1%
Terminal Rates (c)	0/27 (0%)	1/40 (3%)	3/33 (9%)
Day of First Observation		729	729
Life Table Tests (d)	P=0.069	P=0.578	P=0.158
Logistic Regression Tests (d)	P=0.069	P=0.578	P=0.158
Cochran-Armitage Trend Test (d)	P=0.058		
Fisher Exact Test (d)		P=0.500	P=0.117
Adrenal Cortex: Adenoma or Subcapsular Adenoma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	4/49 (8%)
Adjusted Rates (b)	0.0%	5.0%	12.1%
Terminal Rates (c)	0/27 (0%)	2/40 (5%)	4/33 (12%)
Day of First Observation		729	729
Life Table Tests (d)	P=0.044	P=0.328	P=0.090
Logistic Regression Tests (d)	P=0.043	P=0.328	P=0.090
Cochran-Armitage Trend Test (d)	P=0.035		
Fisher Exact Test (d)		P=0.247	P=0.056
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/49 (2%)
Adjusted Rates (b)	9.1%	0.0%	2.3%
Terminal Rates (c)	1/27 (4%)	0/40 (0%)	0/33 (0%)
Day of First Observation	618		641
Life Table Tests (d)	P=0.153N	P=0.082N	P=0.275N
Logistic Regression Tests (d)	P=0.182N	P=0.117N	P=0.312N
Cochran-Armitage Trend Test (d)	P=0.180N		
Fisher Exact Test (d)		P=0.121N	P=0.316N
Harderian Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	2.9%	5.0%	8.4%
Terminal Rates (c)	0/27 (0%)	2/40 (5%)	2/33 (6%)
Day of First Observation	668	729	659
Life Table Tests (d)	P=0.262	P=0.616	P=0.361
Logistic Regression Tests (d)	P=0.228	P=0.535	P=0.312
Cochran-Armitage Trend Test (d)	P=0.222		
Fisher Exact Test (d)		P=0.500	P=0.309
Liver: Hepatocellular Adenoma			
Overall Rates (a)	9/50 (18%)	8/50 (16%)	3/50 (6%)
Adjusted Rates (b)	27.0%	18.3%	8.3%
Terminal Rates (c)	5/27 (19%)	5/40 (13%)	2/33 (6%)
Day of First Observation	618	645	653
Life Table Tests (d)	P=0.029N	P=0.247N	P=0.039N
Logistic Regression Tests (d)	P=0.046N	P=0.435N	P=0.054N
Cochran-Armitage Trend Test (d)	P=0.053N		
Fisher Exact Test (d)		P=0.500N	P=0.061N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	4/50 (8%)	8/50 (16%)	5/50 (10%)
Adjusted Rates (b)	10.9%	17.6%	12.3%
Terminal Rates (c)	0/27 (0%)	4/40 (10%)	1/33 (3%)
Day of First Observation	623	560	641
Life Table Tests (d)	P=0.519	P=0.339	P=0.565
Logistic Regression Tests (d)	P=0.436	P=0.161	P=0.501
Cochran-Armitage Trend Test (d)	P=0.437		
Fisher Exact Test (d)		P=0.178	P=0.500

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

	Control	100 ppm	200 ppm
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	12/50 (24%)	15/50 (30%)	7/50 (14%)
Adjusted Rates (b)	33.3%	32.3%	17.8%
Terminal Rates (c)	5/27 (19%)	9/40 (23%)	3/33 (9%)
Day of First Observation	618	560	641
Life Table Tests (d)	P=0.086N	P=0.496N	P=0.105N
Logistic Regression Tests (d)	P=0.134N	P=0.356	P=0.142N
Cochran-Armitage Trend Test (d)	P=0.141N		
Fisher Exact Test (d)		P=0.326	P=0.154N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	9/50 (18%)
Adjusted Rates (b)	16.4%	7.2%	25.5%
Terminal Rates (c)	3/27 (11%)	2/40 (5%)	7/33 (21%)
Day of First Observation	665	678	702
Life Table Tests (d)	P=0.197	P=0.196N	P=0.304
Logistic Regression Tests (d)	P=0.157	P=0.285N	P=0.246
Cochran-Armitage Trend Test (d)	P=0.135		
Fisher Exact Test (d)		P=0.357N	P=0.194
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	6/50 (12%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	20.8%	5.0%	3.0%
Terminal Rates (c)	5/27 (19%)	2/40 (5%)	1/33 (3%)
Day of First Observation	668	729	729
Life Table Tests (d)	P=0.013N	P=0.047N	P=0.033N
Logistic Regression Tests (d)	P=0.018N	P=0.074N	P=0.043N
Cochran-Armitage Trend Test (d)	P=0.029N		
Fisher Exact Test (d)		P=0.134N	P=0.056N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	11/50 (22%)	5/50 (10%)	10/50 (20%)
Adjusted Rates (b)	35.7%	12.0%	28.4%
Terminal Rates (c)	8/27 (30%)	4/40 (10%)	8/33 (24%)
Day of First Observation	665	678	702
Life Table Tests (d)	P=0.302N	P=0.017N	P=0.326N
Logistic Regression Tests (d)	P=0.372N	P=0.039N	P=0.400N
Cochran-Armitage Trend Test (d)	P=0.447N		
Fisher Exact Test (d)		P=0.086N	P=0.500N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	14.0%	10.0%	11.8%
Terminal Rates (c)	3/27 (11%)	4/40 (10%)	3/33 (9%)
Day of First Observation	714	729	711
Life Table Tests (d)	P=0.477N	P=0.426N	P=0.547N
Logistic Regression Tests (d)	P=0.506N	P=0.467N	P=0.577N
Cochran-Armitage Trend Test (d)	P=0.573		
Fisher Exact Test (d)		P=0.643N	P=0.643N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	6/50 (12%)	3/50 (6%)	7/50 (14%)
Adjusted Rates (b)	15.8%	7.3%	16.7%
Terminal Rates (c)	1/27 (4%)	2/40 (5%)	2/33 (6%)
Day of First Observation	618	712	603
Life Table Tests (d)	P=0.507	P=0.143N	P=0.574
Logistic Regression Tests (d)	P=0.434	P=0.247N	P=0.497
Cochran-Armitage Trend Test (d)	P=0.436		
Fisher Exact Test (d)		P=0.243N	P=0.500

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

	Control	100 ppm	200 ppm
Subcutaneous Tissue: Sarcoma			
Overall Rates (a)	5/50 (10%)	6/50 (12%)	6/50 (12%)
Adjusted Rates (b)	14.1%	13.4%	14.6%
Terminal Rates (c)	0/27 (0%)	2/40 (5%)	2/33 (6%)
Day of First Observation	653	645	432
Life Table Tests (d)	P=0.508	P=0.563N	P=0.569
Logistic Regression Tests (d)	P=0.435	P=0.516	P=0.498
Cochran-Armitage Trend Test (d)	P=0.437		
Fisher Exact Test (d)		P=0.500	P=0.500
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	10/50 (20%)	7/50 (14%)	11/50 (22%)
Adjusted Rates (b)	27.9%	17.0%	26.9%
Terminal Rates (c)	4/27 (15%)	6/40 (15%)	5/33 (15%)
Day of First Observation	618	712	603
Life Table Tests (d)	P=0.530N	P=0.117N	P=0.559N
Logistic Regression Tests (d)	P=0.459	P=0.244N	P=0.509
Cochran-Armitage Trend Test (d)	P=0.449		
Fisher Exact Test (d)		P=0.298N	P=0.500
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	11/50 (22%)	9/50 (18%)	13/50 (26%)
Adjusted Rates (b)	27.7%	19.9%	29.1%
Terminal Rates (c)	1/27 (4%)	4/40 (10%)	4/33 (12%)
Day of First Observation	618	645	432
Life Table Tests (d)	P=0.466	P=0.204N	P=0.520
Logistic Regression Tests (d)	P=0.356	P=0.396N	P=0.403
Cochran-Armitage Trend Test (d)	P=0.359		
Fisher Exact Test (d)		P=0.402N	P=0.408
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	14/50 (28%)	13/50 (26%)	16/50 (32%)
Adjusted Rates (b)	36.1%	28.8%	35.9%
Terminal Rates (c)	4/27 (15%)	8/40 (20%)	6/33 (18%)
Day of First Observation	618	645	432
Life Table Tests (d)	P=0.515	P=0.209N	P=0.559
Logistic Regression Tests (d)	P=0.373	P=0.446N	P=0.415
Cochran-Armitage Trend Test (d)	P=0.370		
Fisher Exact Test (d)		P=0.500N	P=0.414
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	2/48 (4%)	3/50 (6%)
Adjusted Rates (b)	0.0%	5.3%	9.1%
Terminal Rates (c)	0/27 (0%)	2/38 (5%)	3/33 (9%)
Day of First Observation		729	729
Life Table Tests (d)	P=0.099	P=0.316	P=0.158
Logistic Regression Tests (d)	P=0.099	P=0.316	P=0.158
Cochran-Armitage Trend Test (d)	P=0.083		
Fisher Exact Test (d)		P=0.237	P=0.121
All Sites: Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	9.4%	0.0%	0.0%
Terminal Rates (c)	2/27 (7%)	0/40 (0%)	0/33 (0%)
Day of First Observation	535		
Life Table Tests (d)	P=0.026N	P=0.077N	P=0.100N
Logistic Regression Tests (d)	P=0.038N	P=0.128N	P=0.121N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N

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

	Control	100 ppm	200 ppm
All Sites: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	9.4%	2 5%	0.0%
Terminal Rates (c)	2/27 (7%)	1/40 (3%)	0/33 (0%)
Day of First Observation	535	729	
Life Table Tests (d)	P=0 042N	P=0.204N	P=0.100N
Logistic Regression Tests (d)	P=0.061N	P=0.310N	P=0.121N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	5/50 (10%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	15.6%	2 5%	8 3%
Terminal Rates (c)	3/27 (11%)	1/40 (3%)	1/33 (3%)
Day of First Observation	647	729	702
Life Table Tests (d)	P=0.205N	P=0 050N	P=0 285N
Logistic Regression Tests (d)	P=0.249N	P=0.086N	P=0 336N
Cochran-Armitage Trend Test (d)	P=0.264N		
Fisher Exact Test (d)		P=0 102N	P=0 357N

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

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

Study	Incidence in Controls	
	Adenoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute		
HC Blue No. 2	0/50	0/50
C.I. Disperse Blue 1	0/49	0/49
D-Mannitol	0/49	0/49
Ziram	1/49	1/49
Eugenol	0/43	0/43
Propyl gallate	0/49	0/49
Zearalenone	2/50	2/50
HC Blue No. 1	0/49	0/49
Stannous chloride	0/49	0/49
TOTAL	3/437 (0.7%)	3/437 (0.7%)
SD (b)	1.42%	1.42%
Range (c)		
High	2/50	2/50
Low	0/50	0/50
Overall Historical Incidence		
TOTAL	(d) 43/1,962 (2.2%)	(d,e) 45/1,962 (2.3%)
SD (b)	2.97%	3.03%
Range (c)		
High	7/50	7/50
Low	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 eight adenomas, NOS
(e) Two cortical carcinomas were observed, both in the same control group.

TABLE C4b. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
HC Blue No. 2	3/50	2/50	5/50
C.I. Disperse Blue 1	1/50	3/50	4/50
D-Mannitol	6/50	3/50	9/50
Ziram	6/49	3/49	8/49
Eugenol	9/49	5/49	13/49
Propyl gallate	3/50	1/50	4/50
Zearalenone	7/50	4/50	11/50
HC Blue No. 1	3/50	3/50	5/50
Stannous chloride	7/50	3/50	10/50
TOTAL	45/448 (10.0%)	27/448 (6.0%)	69/448 (15.4%)
SD (b)	5.28%	2.28%	6.75%
Range (c)			
High	9/49	5/49	13/49
Low	1/50	1/50	4/50
Overall Historical Incidence			
TOTAL	259/2,032 (12.7%)	103/2,032 (5.1%)	353/2,032 (17.4%)
SD (b)	6.62%	3.49%	7.46%
Range (c)			
High	14/50	8/50	17/50
Low	1/50	0/50	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 C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ROXARSONE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS REMOVED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(42)	(42)	(48)
Hyperplasia, papillary			1 (2%)
Intestine large, rectum	(47)	(49)	(46)
Dysplasia		2 (4%)	
Inflammation, chronic		2 (4%)	
Prolapse		2 (4%)	
Ulcer		2 (4%)	
Intestine small, duodenum	(49)	(45)	(47)
Submucosa, degeneration, focal			1 (2%)
Intestine small, jejunum	(49)	(49)	(48)
Lymphoid tissue, hyperplasia, lymphoid		1 (2%)	
Liver	(50)	(50)	(50)
Angiectasis	1 (2%)		2 (4%)
Atrophy		1 (2%)	
Basophilic focus	1 (2%)		
Cyst	1 (2%)		
Cyst multilocular			1 (2%)
Developmental malformation	1 (2%)		
Eosinophilic focus			1 (2%)
Fibrosis, focal	2 (4%)	2 (4%)	
Focal cellular change			1 (2%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	
Hemorrhage			1 (2%)
Infarct	1 (2%)	1 (2%)	
Infiltration cellular, polymorphonuclear	1 (2%)		
Inflammation, focal			2 (4%)
Mineralization, focal	1 (2%)	2 (4%)	
Necrosis, focal	2 (4%)	2 (4%)	1 (2%)
Necrosis, multifocal	1 (2%)	1 (2%)	
Nuclear alteration	1 (2%)		
Pigmentation		1 (2%)	
Thrombus	1 (2%)		
Vacuolization cytoplasmic		1 (2%)	
Bile duct, dilatation		2 (4%)	
Bile duct, hyperplasia		2 (4%)	
Centrilobular, necrosis	1 (2%)		1 (2%)
Mesentery	(4)	(4)	(6)
Hemorrhage	1 (25%)		
Hyperplasia, lymphoid		1 (25%)	
Inflammation, suppurative		1 (25%)	1 (17%)
Fat, necrosis		2 (50%)	4 (67%)
Pancreas	(49)	(50)	(50)
Accessory spleen			1 (2%)
Atrophy, focal	1 (2%)		
Edema	1 (2%)		
Stomach, forestomach	(50)	(50)	(50)
Hyperplasia, papillary	1 (2%)	2 (4%)	
Inflammation, focal	1 (2%)	3 (6%)	
Pigmentation, focal			1 (2%)
Stomach, glandular	(50)	(50)	(50)
Degeneration, hyaline		1 (2%)	
Mineralization	1 (2%)	2 (4%)	2 (4%)
Tooth	(14)	(8)	(7)
Incisor, dysplasia	12 (86%)	8 (100%)	4 (57%)
Incisor, inflammation, suppurative	8 (57%)	2 (25%)	5 (71%)
Molar, inflammation, suppurative			1 (14%)

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

	Untreated Control	Low Dose	High Dose
CARDIOVASCULAR SYSTEM			
Blood vessel	(1)		(1)
Abdominal, inflammation, chronic			1 (100%)
Mesenteric artery, inflammation, chronic	1 (100%)		
Heart	(50)	(50)	(50)
Infiltration cellular, polymorphonuclear	1 (2%)		
Inflammation, focal			1 (2%)
Mineralization			1 (2%)
Artery, inflammation, chronic	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(49)
Cyst	1 (2%)		
Infiltration cellular, polymorphonuclear	1 (2%)		
Vacuolization cytoplasmic, focal	2 (4%)		
Subcapsular, hyperplasia, focal		2 (4%)	1 (2%)
Adrenal gland, medulla	(50)	(50)	(49)
Hyperplasia, focal	1 (2%)	1 (2%)	2 (4%)
Infiltration cellular, polymorphonuclear	1 (2%)		
Parathyroid gland	(47)	(44)	(50)
Cyst	3 (6%)		2 (4%)
Cyst, multiple		1 (2%)	
Degeneration, cystic	1 (2%)		
Pituitary gland	(45)	(46)	(45)
Cyst	1 (2%)	1 (2%)	
Infiltration cellular, polymorphonuclear	1 (2%)		
Pars distalis, cytoplasmic alteration, focal		1 (2%)	
Pars intermedia, cytomegaly	1 (2%)		
Thyroid gland	(50)	(48)	(50)
Degeneration, cystic	5 (10%)	10 (21%)	11 (22%)
Inflammation, focal		1 (2%)	1 (2%)
Pigmentation			2 (4%)
Follicular cell, hyperplasia	1 (2%)	1 (2%)	3 (6%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ductus deferens	(2)		
Serosa, foreign body	1 (50%)		
Serosa, inflammation, chronic	1 (50%)		
Penis	(1)	(2)	(1)
Foreign body	1 (100%)		
Inflammation, chronic	1 (100%)		1 (100%)
Necrosis	1 (100%)		
Preputial gland	(11)	(13)	(7)
Degeneration, cystic	4 (36%)	8 (62%)	5 (71%)
Inflammation, suppurative	8 (73%)	8 (62%)	4 (57%)
Prostate	(50)	(50)	(49)
Inflammation, suppurative	3 (6%)		1 (2%)
Seminal vesicle	(2)	(3)	(2)
Atrophy		1 (33%)	
Dilatation	1 (50%)	1 (33%)	
Fibrosis, focal	1 (50%)		
Lumen, crystals		1 (33%)	
Testes	(50)	(50)	(50)
Angiectasis	1 (2%)		
Artery, mineralization		2 (4%)	

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

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Hyperplasia, neutrophil	1 (2%)		
Lymph node	(50)	(49)	(50)
Axillary, hyperplasia			1 (2%)
Axillary, inflammation, suppurative	1 (2%)		
Inguinal, angiectasis			2 (4%)
Inguinal, hyperplasia	6 (12%)	2 (4%)	3 (6%)
Inguinal, hyperplasia, lymphoid		1 (2%)	
Inguinal, inflammation, chronic	2 (4%)		
Inguinal, pigmentation		1 (2%)	
Mediastinal, hyperplasia, lymphoid	1 (2%)		
Lymph node, mandibular	(48)	(42)	(43)
Hyperplasia			1 (2%)
Lymph node, mesenteric	(43)	(48)	(47)
Angiectasis	8 (19%)	11 (23%)	11 (23%)
Hematopoietic cell proliferation	2 (5%)		
Pigmentation			1 (2%)
Spleen	(50)	(50)	(50)
Depletion lymphoid		1 (2%)	
Hematopoietic cell proliferation	16 (32%)	12 (24%)	12 (24%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)
Infiltration cellular, polymorphonuclear	1 (2%)		
Red pulp, depletion	1 (2%)	1 (2%)	
Thymus	(36)	(40)	(43)
Cyst	2 (6%)		
Depletion lymphoid		1 (3%)	
Inflammation, granulomatous			1 (2%)
INTEGUMENTARY SYSTEM			
Skin	(50)	(50)	(50)
Cyst		1 (2%)	
Exudate	2 (4%)		
Fibrosis	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, basal cell		1 (2%)	
Inflammation, chronic	19 (38%)	28 (56%)	15 (30%)
Mineralization	1 (2%)	2 (4%)	
Ulcer	13 (26%)	6 (12%)	3 (6%)
Ulcer, multiple	1 (2%)		
Lip, inflammation, suppurative		1 (2%)	
Prepuce, inflammation, chronic	1 (2%)		
Subcutaneous tissue, angiectasis		1 (2%)	1 (2%)
Subcutaneous tissue, edema	2 (4%)		
Subcutaneous tissue, inflammation, chronic			1 (2%)
Subcutaneous tissue, inflammation, suppurative	2 (4%)	1 (2%)	
Subcutaneous tissue, mineralization			1 (2%)
Subcutaneous tissue, ulcer			1 (2%)
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	(1)	(2)	(2)
Artery, head, inflammation, chronic	1 (100%)		
Thigh, mineralization		1 (50%)	

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

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Infiltration cellular, polymorphonuclear	1 (2%)		
Mineralization	25 (50%)	31 (62%)	26 (52%)
Artery, meninges, inflammation, chronic	1 (2%)		
Meninges, hyperplasia, lymphoid			1 (2%)
Peripheral nerve	(50)	(50)	(50)
Sciatic, hyperplasia, lymphoid	2 (4%)	1 (2%)	
Spinal cord	(50)	(50)	(50)
Meninges, hyperplasia, lymphoid		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Adenomatosis	14 (28%)	28 (56%)	24 (48%)
Congestion	1 (2%)		2 (4%)
Hemorrhage, focal	1 (2%)	1 (2%)	
Hyperplasia, lymphoid	1 (2%)		1 (2%)
Hyperplasia, macrophage	3 (6%)	3 (6%)	2 (4%)
Infiltration cellular, polymorphonuclear	4 (8%)	2 (4%)	5 (10%)
Inflammation, focal	21 (42%)	31 (62%)	25 (50%)
Inflammation, suppurative			1 (2%)
Pigmentation	2 (4%)		
Alveolar epithelium, hyperplasia	1 (2%)		
Alveolar epithelium, hyperplasia, focal	5 (10%)	3 (6%)	2 (4%)
Alveolar epithelium, metaplasia, focal	4 (8%)	4 (8%)	3 (6%)
Nose	(48)	(49)	(48)
Infiltration cellular, polymorphonuclear	1 (2%)		
Adventitia, inflammation, focal	1 (2%)		1 (2%)
Adventitia, inflammation, suppurative		1 (2%)	
Lumen, exudate	4 (8%)	17 (35%)	2 (4%)
Lumen, foreign body	1 (2%)	13 (27%)	1 (2%)
Mucosa, inflammation, suppurative	1 (2%)	1 (2%)	4 (8%)
Nasolacrimal duct, foreign body	1 (2%)	2 (4%)	
Nasolacrimal duct, inflammation		2 (4%)	
SPECIAL SENSES SYSTEM			
Harderian gland	(5)	(6)	(4)
Hyperplasia	1 (20%)		
Hyperplasia, focal	2 (40%)		
Duct, dilatation, focal	1 (20%)	3 (50%)	1 (25%)

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

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Autolysis			1 (2%)
Congestion			1 (2%)
Cyst			1 (2%)
Hydronephrosis		1 (2%)	
Hyperplasia, lymphoid	13 (26%)	10 (20%)	2 (4%)
Infiltration cellular, polymorphonuclear	1 (2%)		
Inflammation, focal	1 (2%)		
Mineralization	7 (14%)	9 (18%)	17 (34%)
Nephropathy	19 (38%)	29 (58%)	25 (50%)
Pigmentation		1 (2%)	
Artery, inflammation, chronic	2 (4%)		
Capsule, fibrosis, focal		1 (2%)	
Renal tubule, degeneration, hyaline	1 (2%)		
Renal tubule, dilatation	1 (2%)		1 (2%)
Renal tubule, hyperplasia, focal	1 (2%)		
Renal tubule, vacuolization cytoplasmic			1 (2%)
Urethra	(1)	(1)	
Bulbourethral gland, degeneration, cystic		1 (100%)	
Bulbourethral gland, fibrosis, focal		1 (100%)	
Bulbourethral gland, proliferation connective tissue	1 (100%)		

APPENDIX D

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

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS REMOVED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(45)	(45)	(47)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed		1 (2%)	
Intestine small, duodenum	(47)	(50)	(46)
Adenoma	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		
Intestine small, ileum	(46)	(49)	(47)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	1 (2%)		
Intestine small, jejunum	(49)	(50)	(46)
Lymphoma malignant mixed		1 (2%)	1 (2%)
Liver	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
Hepatocellular carcinoma	1 (2%)		
Hepatocellular carcinoma, multiple	1 (2%)		
Hepatocellular adenoma	1 (2%)		
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant mixed	5 (10%)	1 (2%)	
Sarcoma			1 (2%)
Mesentery	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	3 (6%)		
Sarcoma			1 (2%)
Pancreas	(50)	(50)	(49)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	1 (2%)		
Salivary glands	(48)	(49)	(47)
Lymphoma malignant mixed	1 (2%)		
Stomach, glandular	(50)	(50)	(49)
Lymphoma malignant lymphocytic	1 (2%)		
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(49)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	1 (2%)	1 (2%)	
Extra adrenal tissue, lymphoma malignant mixed	1 (2%)		
Adrenal gland, medulla	(50)	(49)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Islets, pancreatic	(50)	(50)	(49)
Adenoma	1 (2%)		
Parathyroid gland	(46)	(44)	(47)
Lymphoma malignant mixed	1 (2%)		
Pituitary gland	(49)	(46)	(49)
Lymphoma malignant lymphocytic	1 (2%)		
Pars distalis, adenoma	6 (12%)	3 (7%)	4 (8%)
Pars intermedia, adenoma			2 (4%)
Thyroid gland	(49)	(49)	(49)
Lymphoma malignant mixed	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(49)	(49)	(50)
Luteoma	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	1 (2%)		
Sarcoma			1 (2%)
Uterus	(50)	(50)	(50)
Adenocarcinoma		1 (2%)	
Hemangioma, multiple		1 (2%)	
Leiomyoma			1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	1 (2%)		
Sarcoma			1 (2%)
Cervix, polyp stromal		1 (2%)	
Endometrium, polyp stromal	1 (2%)		1 (2%)
Vagina	*(50)	*(50)	*(50)
Lymphoma malignant histiocytic			1 (2%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	1 (2%)		
Lymph node	(50)	(50)	(50)
Axillary, lymphoma malignant mixed		1 (2%)	
Bronchial, lymphoma malignant mixed	4 (8%)		
Iliac, lymphoma malignant mixed	1 (2%)		
Inguinal, lymphoma malignant mixed	4 (8%)		
Mediastinal, lymphoma malignant lymphocytic	1 (2%)		
Mediastinal, lymphoma malignant mixed	9 (18%)	1 (2%)	
Pancreatic, lymphoma malignant mixed	1 (2%)		
Popliteal, lymphoma malignant mixed	1 (2%)		
Renal, lymphoma malignant mixed	2 (4%)		
Renal, sarcoma			1 (2%)
Lymph node, mandibular	(40)	(48)	(42)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	1 (3%)		1 (2%)
Lymphoma malignant mixed	5 (13%)	1 (2%)	
Lymph node, mesenteric	(48)	(48)	(46)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Lymphoma malignant mixed	9 (19%)	1 (2%)	
Spleen	(50)	(50)	(49)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Lymphoma malignant mixed	11 (22%)	1 (2%)	
Thymus	(39)	(42)	(44)
Lymphoma malignant lymphocytic	1 (3%)		
Lymphoma malignant mixed	2 (5%)		

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

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(50)	(50)
Adenocarcinoma	1 (2%)		
Adenocarcinoma, multiple	1 (2%)		
Skin	(50)	(50)	(50)
Papilloma squamous			1 (2%)
Trichoepithelioma		1 (2%)	
Subcutaneous tissue, hemangioma		1 (2%)	
Subcutaneous tissue, lymphoma malignant lymphocytic	1 (2%)		
Subcutaneous tissue, lymphoma malignant mixed	2 (4%)		
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	(49)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Spinal cord	(50)	(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Adventitia, lymphoma malignant mixed		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	3 (6%)	3 (6%)
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	2 (4%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant mixed	7 (14%)	1 (2%)	
Sarcoma, metastatic, uncertain primary site			1 (2%)
Mediastinum, lymphoma malignant lymphocytic	1 (2%)		
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenoma	1 (2%)	2 (4%)	1 (2%)
URINARY SYSTEM			
Kidney	(50)	(50)	(49)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant mixed	9 (18%)		
Sarcoma			1 (2%)
Urinary bladder	(49)	(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	4 (8%)		

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

	Untreated Control	Low Dose	High Dose
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant mixed	12 (24%)	1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	1 (2%)
Hemangioma		2 (4%)	
Lymphoma malignant histiocytic			1 (2%)
Hemangiosarcoma			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	14	15	12
Moribund sacrifice	21	17	21
Terminal sacrifice	14	18	17
Accidently killed	1		
TUMOR SUMMARY			
Total animals with primary neoplasms **	24	11	18
Total primary neoplasms	32	16	25
Total animals with benign neoplasms	11	9	13
Total benign neoplasms	13	12	13
Total animals with malignant neoplasms	18	3	5
Total malignant neoplasms	19	4	12
Total animals with secondary neoplasms ***			1
Total secondary neoplasms			1
Total animals with malignant neoplasms			1

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

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

WEEKS ON STUDY	0 0 6	0 2 5	0 5 8	0 6 5	0 6 7	0 7 1	0 7 1	0 7 1	0 7 3	0 7 5	0 7 5	0 7 6	0 7 8	0 7 8	0 7 9	0 8 0	0 8 5	0 8 9	0 9 0	0 9 1	0 9 2	0 9 3	0 9 4	0 9 6	0 9 6
CARCASS ID	3 5 2	3 5 1	3 1 1	4 0 3	3 8 3	3 8 5	3 4 4	3 6 1	3 8 4	3 1 4	3 6 4	3 2 5	3 1 2	3 5 5	3 1 3	4 0 2	3 1 5	3 7 2	3 9 5	3 2 3	4 0 1	3 4 1	3 5 4	3 9 4	3 3 4
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymphoma malignant lymphocytic		X																							
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Lymphoma malignant lymphocytic		X																							
Intestine small, ileum	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																							X		
Hepatocellular carcinoma, multiple																				X					
Hepatocellular adenoma																						X			
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed							X															X			
Mesentery			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+		+
Lymphoma malignant mixed							X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+
Lymphoma malignant mixed							X																		
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed							X																		
Extra adrenal tissue, lymphoma malignant mixed																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Parathyroid gland	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymphoma malignant mixed																									
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed							X																		
GENERAL BODY SYSTEM																									
Tissue NOS																							+		
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma																									
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed							X																		
Oviduct				+				+	+	+	+		+												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed							X																		
Endometrium, polyp stromal																									

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

M Missing
A Autolysis precludes examination
X Incidence of listed morphology

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

WEEKS ON STUDY	097	097	098	098	098	099	102	102	102	103	103	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	362	375	454	391	404	242	335	342	374	382	405	321	322	311	332	333	343	353	363	651	1	373	381	392	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Lymphoma malignant lymphocytic																									1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	47
Adenoma							X																		1
Lymphoma malignant lymphocytic																									1
Intestine small, ileum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant lymphocytic																									1
Lymphoma malignant mixed	X																								1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																									1
Hepatocellular carcinoma, multiple																									1
Hepatocellular adenoma																									1
Lymphoma malignant lymphocytic																									1
Lymphoma malignant mixed	X	X											X												5
Mesentery		+	+	+					+		+						+								27
Lymphoma malignant mixed		X	X																						3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																									1
Lymphoma malignant mixed			X																						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																									1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																									1
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																									1
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																									1
Lymphoma malignant mixed																									1
Extra adrenal tissue, lymphoma malignant mixed	X																								1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant mixed								X																	1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																									1
Pars distalis, adenoma		X				X		X								X	X						X		6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																									1
GENERAL BODY SYSTEM																									
Tissue, NOS																									1
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Luteoma										X															1
Lymphoma malignant lymphocytic																									1
Lymphoma malignant mixed																									1
Oviduct																					+				7
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																									1
Lymphoma malignant mixed																									1
Endometrium, polyp stromal		X																							1

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

WEEKS ON STUDY	0 0 6	0 2 5	0 5 8	0 6 5	0 6 7	0 7 1	0 7 1	0 7 1	0 7 3	0 7 5	0 7 5	0 7 6	0 7 8	0 7 8	0 7 9	0 8 0	0 8 5	0 8 9	0 9 0	0 9 1	0 9 2	0 9 3	0 9 4	0 9 6	0 9 6
CARCASS ID	3 5 2	3 5 1	3 1 1	4 0 3	3 8 3	3 8 5	3 4 4	3 6 1	3 8 4	3 1 4	3 6 4	3 2 5	3 1 2	3 5 5	3 1 3	4 0 2	3 1 5	3 7 2	3 9 5	3 2 3	4 0 1	3 4 1	3 5 4	3 9 4	3 3 4
HEMATOPOIETIC SYSTEM																									
Blood																			+						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed							X																		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, lymphoma malignant mixed							X												X						
Iliac, lymphoma malignant mixed							X																		
Inguinal, lymphoma malignant mixed							X												X						
Mediastinal, lymphoma malignant lymphocytic		X																							
Mediastinal, lymphoma malignant mixed							X												X			X			
Pancreatic, lymphoma malignant mixed																						X			
Popliteal, lymphoma malignant mixed																									
Renal, lymphoma malignant mixed																						X			
Lymph node, mandibular	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed							X												X						
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed							X												X			X			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed							X												X			X			
Thymus	+	+	+	M	M	+	M	+	M	M	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenocarcinoma multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue lymphoma malignant lymphocytic		X																							
Subcutaneous tissue lymphoma malignant mixed							X																		
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+					+					+			+		+								
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed							X																		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed							X															X			
Mediastinum, lymphoma malignant lymphocytic		X																							
Nose	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed							X															X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed							X																		

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

WEEKS ON STUDY	0 9 7	0 9 7	0 9 8	0 9 8	0 9 8	0 9 9	1 0 2	1 0 2	1 0 2	1 0 3	1 0 3	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL
CARCASS ID	3 6 2	3 7 5	3 4 5	3 9 1	4 0 4	3 2 4	3 3 5	3 4 2	3 7 4	3 8 2	4 0 5	3 2 1	3 2 2	3 3 1	3 3 2	3 3 3	3 4 3	3 5 3	3 6 3	3 6 5	3 7 1	3 7 3	3 8 1	3 9 2	3 9 3	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, lymphoma malignant mixed	X																	X								4
Iliac, lymphoma malignant mixed																										1
Inguinal, lymphoma malignant mixed	X		X																							4
Mediastinal, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malig mixed	X	X	X					X							X										X	9
Pancreatic, lymphoma malignant mixed																										1
Popliteal, lymphoma malignant mixed			X																							1
Renal, lymphoma malignant mixed	X																									2
Lymph node, mandibular	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	40
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed		X	X																						X	5
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed	X	X	X					X										X							X	9
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed	X	X	X					X							X			X			X				X	11
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	39
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed	X														X											2
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																			X							1
Adenocarcinoma, multiple										X																1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, lymphoma malignant lymphocytic																										1
Subcutaneous tissue, lymphoma malignant mixed	X																									2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle										+																6
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																						1
Alveolar/bronchiolar carcinoma							X																		X	2
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed		X	X					X							X			X								7
Mediastinum, lymphoma malignant lymphocytic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Harderian gland				+																				+		2
Adenoma																								X		1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed	X	X	X					X							X			X			X					9
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed		X						X										X								4

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

WEEKS ON STUDY	070	071	071	072	072	073	074	074	074	075	075	075	076	076	076	084	086	088	088	090	091	091	091	092	093
CARCASS ID	563	523	591	581	582	532	541	522	575	544	601	585	551	553	584	524	564	645	603	594	533	593	535	613	525
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	M	+
Lymphoma malignant mixed																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Mesentery		+	+	+	+		+	+	+	+		+	+	+		+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct	+												+	+											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Hemangioma, multiple																									
Cervix, polyp stromal																									

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

WEEKS ON STUDY	093	094	094	095	096	099	101	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	595	531	573	572	604	555	534	511	512	513	514	515	521	542	543	552	554	562	565	571	574	583	592	602	605	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant mixed				X																						1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed				X																						1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic						X																				1
Lymphoma malignant mixed				X																						1
Mesentery	+	+			+	+	+						+													27
Lymphoma malignant lymphocytic						X																				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed				X																						1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	44
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma													X								X	X				3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland																+										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Oviduct																										3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma				X																						1
Hemangioma, multiple																						X				1
Cervix, polyp stromal																					X					1

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

WEEKS ON STUDY	0 7 0	0 7 1	0 7 1	0 7 2	0 7 2	0 7 3	0 7 4	0 7 4	0 7 4	0 7 5	0 7 5	0 7 5	0 7 6	0 7 6	0 7 6	0 8 4	0 8 6	0 8 8	0 8 8	0 9 0	0 9 1	0 9 1	0 9 1	0 9 2	0 9 3
CARCASS ID	5 6 3	5 2 3	5 9 1	5 8 1	5 8 2	5 3 2	5 4 1	5 2 2	5 7 5	5 4 4	6 0 1	5 8 5	5 5 1	5 5 3	5 8 4	5 2 4	5 6 4	5 4 5	6 0 3	5 9 4	5 3 3	5 9 3	5 3 5	5 6 1	5 2 5
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant mixed																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Thymus	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma																					X				
Subcutaneous tissue, hemangioma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																							+	+	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adventitia, lymphoma malignant mixed																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma											X														
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland													+												
Adenoma													X												
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	0 9 3	0 9 4	0 9 4	0 9 5	0 9 6	0 9 9	1 0 1	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL TISSUES TUMORS
CARCASS ID	5 9 5	5 3 1	5 7 3	5 7 2	6 0 4	5 5 5	5 3 4	5 1 1	5 1 2	5 1 3	5 1 4	5 1 5	5 2 1	5 4 2	5 4 3	5 5 2	5 5 4	5 6 2	5 6 5	5 7 1	5 7 4	5 8 3	5 9 2	6 0 2	6 0 5	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, lymphoma malignant mixed				X																					1
Mediastinal, lymphoma malig mixed				X																					1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed				X																					1
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic						X																			1
Lymphoma malignant mixed				X																					1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic						X																			1
Lymphoma malignant mixed				X																					1
Thymus	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	42
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trichoepithelioma																									1
Subcutaneous tissue, hemangioma				X																					1
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																									2
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adventitia, lymphoma malignant mixed				X																					1
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X				X	X						3
Alveolar/bronchiolar carcinoma																									1
Lymphoma malignant lymphocytic						X																			1
Lymphoma malignant mixed				X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																									
Harderian gland														+				+							3
Adenoma														X											2
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic						X																			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	063	069	069	069	070	070	070	072	073	075	075	076	077	081	081	081	083	085	085	086	086	087	088	088
CARCASS ID	461	442	425	453	481	502	463	421	471	433	434	444	472	501	504	464	422	503	492	505	445	484	462	435	451
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	A	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	A	+	A	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	M	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+
Lymphoma malignant mixed																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X						
Lymphoma malignant histiocytic													X												
Lymphoma malignant lymphocytic																			X						
Sarcoma						X																			
Mesentery	+	+	+		+	+		+	+	+	+	+		+	+	+	+	+		+	+	+		+	+
Sarcoma						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Salivary glands	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel																					+				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Pars distalis, adenoma				X																					
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma						X																			
Oviduct										+	+			+											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Sarcoma						X																			
Endometrium, polyp stromal																									
Vagina													+												
Lymphoma malignant histiocytic													X												

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

WEEKS ON STUDY	0 8 8	0 9 5	0 9 7	0 9 7	1 0 1	1 0 2	1 0 2	1 0 3	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL TISSUES TUMORS
CARCASS ID	4 5 2	4 1 1	4 5 5	4 1 4	4 2 3	4 9 3	4 1 5	4 8 5	4 1 2	4 1 3	4 2 4	4 3 1	4 3 2	4 3 5	4 4 1	4 5 4	4 6 5	4 7 3	4 7 4	4 7 5	4 8 2	4 8 3	4 9 1	4 9 4	4 9 5	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant mixed		X																								1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Sarcoma																										1
Mesentery	+		+		+	+	+	+								+				+	+	+				30
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma										X				X	X											4
Pars intermedia, adenoma				X																				X		2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Oviduct																										3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																					X					1
Sarcoma																										1
Endometrium, polyp stromal	X																									1
Vagina																										1
Lymphoma malignant histiocytic																										1

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

WEEKS ON STUDY	063	069	069	069	070	070	070	072	073	075	075	076	077	081	081	081	081	083	085	085	086	086	087	088	088
CARCASS ID	461	442	425	453	481	502	463	421	471	433	434	444	472	501	504	464	422	503	492	505	445	484	462	443	451
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal, sarcoma						X																			
Lymph node, mandibular	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Lymphoma malignant histiocytic													X												
Lymphoma malignant lymphocytic																			X						
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																					+				+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar carcinoma																									
Lymphoma malignant lymphocytic																			X						
Sarcoma, metastatic, uncertain primary site						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland				+																		+			
Adenoma																						X			
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Lymphoma malignant histiocytic													X												
Lymphoma malignant lymphocytic																			X						
Sarcoma						X																			
Urethra					+																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	0 8 8	0 9 5	0 9 7	0 9 7	1 0 1	1 0 2	1 0 2	1 0 3	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL:
CARCASS ID	4 5 2	4 1 1	4 5 5	4 1 4	4 2 3	4 9 3	4 1 5	4 8 5	4 1 2	4 1 3	4 2 4	4 3 1	4 3 2	4 3 5	4 4 1	4 5 4	4 6 5	4 7 3	4 7 4	4 7 5	4 8 2	4 8 3	4 9 1	4 9 4	4 9 5	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal, sarcoma																										1
Lymph node, mandibular	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	44
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																			X							1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X	X																X	3
Alveolar/bronchiolar carcinoma		X																								2
Lymphoma malignant lymphocytic																										1
Sarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Harderian gland									+																	3
Adenoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Sarcoma																										1
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

	Control	100 ppm	200 ppm
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	10.1%	0.0%	0.0%
Terminal Rates (c)	0/14 (0%)	0/18 (0%)	0/17 (0%)
Day of First Observation	635		
Life Table Tests (d)	P=0.054N	P=0.158N	P=0.160N
Logistic Regression Tests (d)	P=0.036N	P=0.117N	P=0.120N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	4.3%	16.7%	16.7%
Terminal Rates (c)	0/14 (0%)	3/18 (17%)	2/17 (12%)
Day of First Observation	684	729	718
Life Table Tests (d)	P=0.288	P=0.360	P=0.356
Logistic Regression Tests (d)	P=0.241	P=0.308	P=0.298
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.309	P=0.309
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	15.9%	18.7%	23.0%
Terminal Rates (c)	1/14 (7%)	3/18 (17%)	2/17 (12%)
Day of First Observation	684	521	606
Life Table Tests (d)	P=0.335	P=0.563	P=0.394
Logistic Regression Tests (d)	P=0.272	P=0.499	P=0.336
Cochran-Armitage Trend Test (d)	P=0.290		
Fisher Exact Test (d)		P=0.500	P=0.357
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	6/49 (12%)	3/46 (7%)	4/49 (8%)
Adjusted Rates (b)	32.1%	16.7%	19.4%
Terminal Rates (c)	3/14 (21%)	3/18 (17%)	3/17 (18%)
Day of First Observation	676	729	483
Life Table Tests (d)	P=0.224N	P=0.177N	P=0.295N
Logistic Regression Tests (d)	P=0.315N	P=0.239N	P=0.392N
Cochran-Armitage Trend Test (d)	P=0.298N		
Fisher Exact Test (d)		P=0.276N	P=0.370N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	13/50 (26%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	52.0%	9.3%	9.6%
Terminal Rates (c)	5/14 (36%)	0/18 (0%)	0/17 (0%)
Day of First Observation	170	662	534
Life Table Tests (d)	P=0.003N	P=0.003N	P=0.010N
Logistic Regression Tests (d)	P=0.002N	P=0.002N	P=0.007N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.002N	P=0.006N

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

TABLE D4. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

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

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

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS REMOVED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(45)	(45)	(47)
Epithelium, degeneration, hyaline			1 (2%)
Epithelium, hyperplasia			1 (2%)
Serosa, inflammation, suppurative			1 (2%)
Intestine large, cecum	(48)	(49)	(46)
Edema			1 (2%)
Intestine small, duodenum	(47)	(50)	(46)
Ulcer	1 (2%)		
Intestine small, jejunum	(49)	(50)	(46)
Hyperplasia, lymphoid			1 (2%)
Perforation		1 (2%)	
Liver	(50)	(50)	(50)
Congestion	1 (2%)		1 (2%)
Fibrosis			1 (2%)
Hematopoietic cell proliferation	10 (20%)	20 (40%)	18 (36%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Infarct	1 (2%)		1 (2%)
Infiltration cellular, polymorphonuclear	21 (42%)	24 (48%)	20 (40%)
Inflammation, focal		1 (2%)	1 (2%)
Necrosis, focal		3 (6%)	1 (2%)
Necrosis, multifocal		1 (2%)	
Vacuolization cytoplasmic	1 (2%)	1 (2%)	
Bile duct, degeneration, hyaline			1 (2%)
Bile duct, hyperplasia			1 (2%)
Centrilobular, vacuolization cytoplasmic	1 (2%)		
Serosa, inflammation, suppurative		3 (6%)	
Mesentery	(27)	(27)	(30)
Inflammation, suppurative	23 (85%)	25 (93%)	29 (97%)
Fat, necrosis	2 (7%)	1 (4%)	1 (3%)
Pancreas	(50)	(50)	(49)
Atrophy, focal			2 (4%)
Edema			1 (2%)
Inflammation, suppurative	1 (2%)		
Duct, hyperplasia, cystic			1 (2%)
Stomach, forestomach	(50)	(50)	(49)
Hyperplasia, papillary	1 (2%)	6 (12%)	
Inflammation, focal		3 (6%)	
Inflammation, suppurative, diffuse	1 (2%)		
Ulcer			1 (2%)
Stomach, glandular	(50)	(50)	(49)
Hyperplasia, lymphoid		1 (2%)	
Necrosis, focal		1 (2%)	
Pigmentation		1 (2%)	
CARDIOVASCULAR SYSTEM			
Blood vessel			(1)
Abdominal, thrombus			1 (100%)
Heart	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	2 (4%)	1 (2%)
Artery, inflammation, chronic			1 (2%)
Artery, thrombus	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(49)	(50)
Angiectasis			1 (2%)
Congestion	2 (4%)	1 (2%)	
Hematopoietic cell proliferation	2 (4%)		
Hyperplasia, focal	1 (2%)		
Infiltration cellular, polymorphonuclear	1 (2%)		
Inflammation, suppurative		1 (2%)	
Vacuolization cytoplasmic, focal	1 (2%)		
Capsule, inflammation, suppurative		1 (2%)	1 (2%)
Corticomedullary junction, degeneration, fatty	1 (2%)		
Extra adrenal tissue, inflammation, suppurative	4 (8%)	2 (4%)	
Subcapsular, hyperplasia, focal			1 (2%)
Adrenal gland, medulla	(50)	(49)	(50)
Angiectasis			1 (2%)
Developmental malformation	1 (2%)		1 (2%)
Hyperplasia, focal		1 (2%)	
Parathyroid gland	(46)	(44)	(47)
Cyst		1 (2%)	1 (2%)
Pituitary gland	(49)	(46)	(49)
Pars distalis, angiectasis	1 (2%)		
Pars distalis, hyperplasia	1 (2%)		
Pars distalis, hyperplasia, focal	7 (14%)	5 (11%)	1 (2%)
Thyroid gland	(49)	(49)	(49)
Cyst	1 (2%)	2 (4%)	
Degeneration, cystic	5 (10%)	2 (4%)	8 (16%)
Inflammation, suppurative	1 (2%)		1 (2%)
Follicular cell, hyperplasia	2 (4%)	1 (2%)	
GENERAL BODY SYSTEM			
Tissue, NOS	(1)		
Bacterium	1 (100%)		
Hyperplasia, neutrophil	1 (100%)		
GENITAL SYSTEM			
Clitoral gland		(1)	
Inflammation, suppurative		1 (100%)	
Ovary	(49)	(49)	(50)
Angiectasis			1 (2%)
Granuloma	1 (2%)		
Hemorrhage	1 (2%)		
Hyperplasia, lymphoid	2 (4%)		
Inflammation, suppurative	25 (51%)	29 (59%)	29 (58%)
Follicle, cyst	10 (20%)	18 (37%)	17 (34%)
Oviduct	(7)	(3)	(3)
Dilatation	1 (14%)		
Inflammation, suppurative	6 (86%)	3 (100%)	3 (100%)
Uterus	(50)	(50)	(50)
Angiectasis			1 (2%)
Hydrometria	1 (2%)	1 (2%)	
Inflammation, suppurative	21 (42%)	33 (66%)	23 (46%)
Thrombus			1 (2%)
Endometrium, hyperplasia, cystic	46 (92%)	49 (98%)	48 (96%)

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

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Angiectasis	3 (6%)		1 (2%)
Myelofibrosis			1 (2%)
Lymph node	(50)	(50)	(50)
Bronchial, bacterium	1 (2%)		
Bronchial, hyperplasia	1 (2%)		3 (6%)
Bronchial, inflammation, suppurative	1 (2%)		3 (6%)
Bronchial, mediastinal, hyperplasia		1 (2%)	
Iliac, hyperplasia	1 (2%)	4 (8%)	8 (16%)
Iliac, hyperplasia, lymphoid			1 (2%)
Iliac, inflammation, suppurative			1 (2%)
Inguinal, hyperplasia		1 (2%)	
Inguinal, hyperplasia, lymphoid			1 (2%)
Lumbar, hyperplasia		1 (2%)	3 (6%)
Mediastinal, cyst	1 (2%)		
Mediastinal, hyperplasia	6 (12%)	7 (14%)	7 (14%)
Mediastinal, inflammation, suppurative	4 (8%)		5 (10%)
Pancreatic, hyperplasia			1 (2%)
Pancreatic, hyperplasia, lymphoid			1 (2%)
Renal, angiectasis			1 (2%)
Renal, hyperplasia	13 (26%)	14 (28%)	16 (32%)
Renal, hyperplasia, lymphoid			1 (2%)
Renal, inflammation, suppurative		1 (2%)	1 (2%)
Renal, mediastinal, hyperplasia		1 (2%)	
Lymph node, mandibular	(40)	(48)	(42)
Hyperplasia	1 (3%)		3 (7%)
Hyperplasia, lymphoid	3 (8%)		1 (2%)
Lymph node, mesenteric	(48)	(48)	(46)
Angiectasis	5 (10%)	6 (13%)	10 (22%)
Hematopoietic cell proliferation			2 (4%)
Hyperplasia	3 (6%)	4 (8%)	3 (7%)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	
Spleen	(50)	(50)	(49)
Angiectasis	1 (2%)		
Hematopoietic cell proliferation	29 (58%)	30 (60%)	31 (63%)
Hyperplasia, lymphoid	2 (4%)	2 (4%)	
Infarct	1 (2%)		
Inflammation, suppurative	1 (2%)		
Red pulp, depletion		1 (2%)	
Thymus	(39)	(42)	(44)
Hyperplasia, lymphoid			1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(50)	(50)
Duct, dilatation	2 (4%)	7 (14%)	10 (20%)
Skin	(50)	(50)	(50)
Inflammation, chronic	2 (4%)	2 (4%)	3 (6%)
Inflammation, suppurative	1 (2%)		
Subcutaneous tissue, edema	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibrosis		1 (2%)	
Subcutaneous tissue, inflammation, suppurative			1 (2%)
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	(6)	(2)	(2)
Inflammation, suppurative	3 (50%)	2 (100%)	2 (100%)
Adventitia, inflammation, focal	1 (17%)	1 (50%)	

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

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(50)	(49)	(50)
Compression		1 (2%)	3 (6%)
Hemorrhage, focal	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
Mineralization	26 (52%)	25 (51%)	19 (38%)
Meninges, inflammation, chronic		1 (2%)	
Ventricle, mineralization, focal			1 (2%)
Peripheral nerve	(50)	(50)	(50)
Sciatic, hyperplasia, lymphoid			1 (2%)
Spinal cord	(50)	(50)	(50)
Hemorrhage, focal	1 (2%)		
Necrosis, focal	1 (2%)		
Meninges, hyperplasia, lymphoid	4 (8%)	1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Adenomatosis	19 (38%)	23 (46%)	13 (26%)
Congestion	6 (12%)	2 (4%)	2 (4%)
Hemorrhage, focal	1 (2%)	1 (2%)	
Hyperplasia, lymphoid	4 (8%)	4 (8%)	1 (2%)
Hyperplasia, macrophage	1 (2%)	3 (6%)	2 (4%)
Infiltration cellular, polymorphonuclear	17 (34%)	14 (28%)	15 (30%)
Inflammation, focal	18 (36%)	21 (42%)	12 (24%)
Inflammation, suppurative	1 (2%)	4 (8%)	4 (8%)
Mineralization	2 (4%)		
Thrombus		1 (2%)	
Alveolar epithelium, hyperplasia, focal	3 (6%)	4 (8%)	1 (2%)
Alveolar epithelium, metaplasia, focal	2 (4%)	2 (4%)	1 (2%)
Mediastinum, inflammation, suppurative	8 (16%)	7 (14%)	7 (14%)
Nose	(48)	(50)	(50)
Cyst			1 (2%)
Lumen, exudate		4 (8%)	
Lumen, foreign body		2 (4%)	
Mucosa, inflammation, suppurative		2 (4%)	
Nasolacrimal duct, inflammation			1 (2%)
Trachea	(49)	(50)	(49)
Glands, dilatation			1 (2%)
Glands, exudate			1 (2%)
SPECIAL SENSES SYSTEM			
Harderian gland	(2)	(3)	(3)
Foreign body			1 (33%)
Hyperplasia, focal	1 (50%)		

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

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney	(50)	(50)	(49)
Congestion	1 (2%)		
Cyst		1 (2%)	
Fibrosis			1 (2%)
Hyperplasia, lymphoid	7 (14%)	1 (2%)	1 (2%)
Infarct	1 (2%)		
Infiltration cellular, polymorphonuclear	6 (12%)	2 (4%)	1 (2%)
Infiltration cellular, mixed cell	1 (2%)	4 (8%)	1 (2%)
Inflammation, multifocal			2 (4%)
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)
Metaplasia, osseous			1 (2%)
Mineralization	1 (2%)	4 (8%)	1 (2%)
Nephropathy	7 (14%)	4 (8%)	3 (6%)
Pigmentation	1 (2%)		
Capsule, inflammation, suppurative	3 (6%)	12 (24%)	5 (10%)
Glomerulus, inflammation			3 (6%)
Papilla, necrosis		1 (2%)	1 (2%)
Renal tubule, degeneration, hyaline	1 (2%)		
Renal tubule, vacuolization cytoplasmic		1 (2%)	
Urethra			(1)
Inflammation, suppurative			1 (100%)
Mineralization			1 (100%)

APPENDIX E

GENETIC TOXICOLOGY OF

ROXARSONE

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

Strain	Dose (µg/plate)	Revertants/plate (b)					
TA100		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
	0	98 ± 2.0	76 ± 5.0	145 ± 6.2	174 ± 10.7	144 ± 13.3	150 ± 5.0
	100	97 ± 8.6	72 ± 3.5	148 ± 6.4	170 ± 8.2	142 ± 5.5	143 ± 9.2
	333	95 ± 6.1	73 ± 5.0	135 ± 6.9	158 ± 10.3	135 ± 5.0	127 ± 10.2
	1,000	95 ± 7.0	81 ± 4.2	135 ± 4.4	158 ± 6.7	144 ± 3.8	146 ± 10.3
	3,333	107 ± 2.3	83 ± 5.2	135 ± 6.6	127 ± 4.6	135 ± 4.7	138 ± 10.7
	10,000	116 ± 4.1	(c) 74 ± 6.7	124 ± 5.5	(c) 54 ± 6.1	126 ± 6.8	(c) 45 ± 3.3
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	1,301 ± 14.7	791 ± 38.1	1,546 ± 267.8	1,014 ± 63.5	1,691 ± 108.4	2,719 ± 75.4
TA1535		−S9				+S9 (hamster)	
		Trial 1	Trial 2	Trial 3	Trial 4	Trial 1	Trial 2
	0	13 ± 2.3	7 ± 0.6	11 ± 1.2	8 ± 0.9	12 ± 2.0	10 ± 0.9
	33	--	--	-	--	--	13 ± 0.3
	100	20 ± 0.3	9 ± 2 2	10 ± 1.2	7 ± 1.2	20 ± 2.1	17 ± 4.4
	333	21 ± 1.8	8 ± 2.0	12 ± 3.7	6 ± 1.2	19 ± 2.4	11 ± 1.2
	1,000	21 ± 2.7	16 ± 0.6	8 ± 0.6	5 ± 1.0	17 ± 2.1	11 ± 2.3
	3,333	22 ± 3.3	13 ± 1.7	9 ± 0.9	4 ± 1.5	12 ± 1.0	8 ± 2.3
	10,000	(c) 23 ± 4.1	12 ± 1.2	4 ± 1.0	4 ± 1.2	Toxic	--
	Trial summary	Negative	Equivocal	Negative	Negative	Negative	Negative
	Positive control (d)	914 ± 120.9	821 ± 34.0	319 ± 66.5	1,371 ± 68.8	285 ± 12.4	772 ± 15.1
		+S9 (rat)					
		Trial 1	Trial 2	Trial 3	Trial 4		
	0	15 ± 1.9	10 ± 1.7	11 ± 0.7	6 ± 2.0		
	3	--	--	14 ± 1.2	--		
	10	--	--	14 ± 1.5	7 ± 0.6		
	33	--	20 ± 4.4	27 ± 2.8	7 ± 1.3		
	100	15 ± 1.5	17 ± 0.9	34 ± 1.5	8 ± 1.5		
	333	18 ± 1.2	16 ± 4.1	27 ± 5.9	15 ± 4.3		
	1,000	16 ± 1.5	16 ± 0.9	--	6 ± 0.6		
	3,333	16 ± 2.1	19 ± 1.9	--	--		
	10,000	Toxic	--	--	--		
	Trial summary	Negative	Negative	Positive	Equivocal		
	Positive control (d)	334 ± 45.1	704 ± 42.9	115 ± 13.2	348 ± 17.5		
TA1537		−S9			+S9 (hamster)		
		Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3
	0	6 ± 0.7	7 ± 0.6	8 ± 1.2	9 ± 1 3	8 ± 0.7	18 ± 0.9
	33	--	--	--	--	4 ± 1.2	9 ± 0.6
	100	3 ± 1.3	8 ± 0.9	--	11 ± 0.9	5 ± 0.3	6 ± 1.8
	333	2 ± 0.6	5 ± 1.7	--	15 ± 0.6	5 ± 1.5	9 ± 1.8
	1,000	1 ± 0.7	3 ± 1.3	11 ± 3.5	14 ± 1.5	7 ± 2.3	9 ± 1.2
	1,667	-	--	7 ± 2.4	--	-	--
	3,333	9 ± 2.1	8 ± 1.2	9 ± 0.3	17 ± 2.8	7 ± 2.0	6 ± 2.1
	6,667	--	-	7 ± 2 2	--	--	--
	10,000	(c) 11 ± 1.0	11 ± 1.5	9 ± 0.7	Toxic	--	--
	Trial summary	Negative	Negative	Negative	Equivocal	Negative	Negative
	Positive control (d)	767 ± 202.2	784 ± 147.4	228 ± 35.3	269 ± 11.4	141 ± 25.1	335 ± 42.9

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

Strain	Dose (µg/plate)	Revertants/plate (b)				
TA1537 (Continued)		+S9 (rat)				
		Trial 1	Trial 2	Trial 3		
	0	6 ± 1.2	8 ± 1.7	14 ± 0.7		
	33	--	8 ± 0.9	9 ± 1.7		
	100	8 ± 0.3	5 ± 1.0	10 ± 1.2		
	333	8 ± 2.9	3 ± 0.3	10 ± 1.5		
	1,000	14 ± 1.8	7 ± 0.0	9 ± 1.2		
	3,333	17 ± 5.8	10 ± 1.2	8 ± 0.9		
	10,000	Toxic	--	--		
	Trial summary	Equivocal	Negative	Negative		
	Positive control (d)	278 ± 79.3	161 ± 8.0	323 ± 44.3		
TA98		-S9			+S9 (hamster)	
		Trial 1	Trial 2	Trial 3	Trial 1	Trial 2
	0	10 ± 2.7	18 ± 5.8	42 ± 3.4	7 ± 1.7	36 ± 9.4
	10	--	18 ± 2.3	35 ± 3.3	--	--
	33	--	19 ± 1.5	37 ± 2.4	--	--
	100	6 ± 1.8	18 ± 1.0	39 ± 2.3	6 ± 0.9	29 ± 3.1
	333	9 ± 2.2	19 ± 0.6	35 ± 2.0	4 ± 0.7	26 ± 3.2
	1,000	6 ± 2.4	21 ± 0.9	30 ± 4.1	5 ± 1.2	22 ± 0.7
	3,333	0 ± 0.0	--	--	3 ± 0.9	33 ± 3.5
	10,000	(c) 0 ± 0.0	--	--	(c) 1 ± 0.3	32 ± 2.9
	Trial summary	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	203 ± 12.5	287 ± 9.1	444 ± 30.5	706 ± 74.2	768 ± 56.4
		+S9 (rat)				
		Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
	0	9 ± 3.0	32 ± 2.0	38 ± 3.2	16 ± 2.0	14 ± 0.3
	10	--	24 ± 1.2	23 ± 4.4	--	--
	33	--	27 ± 4.9	29 ± 2.9	--	--
	100	11 ± 3.0	23 ± 2.2	39 ± 2.1	21 ± 2.9	--
	167	--	--	--	24 ± 0.9	13 ± 2.6
	333	9 ± 0.0	23 ± 3.1	46 ± 5.9	26 ± 4.0	20 ± 2.6
	667	--	--	--	34 ± 4.6	23 ± 2.4
	1,000	5 ± 0.7	26 ± 0.9	47 ± 4.8	39 ± 9.0	23 ± 1.8
	1,667	--	--	--	48 ± 1.2	22 ± 3.1
	3,333	0 ± 0.0	--	--	--	--
	10,000	(c) 1 ± 0.3	--	--	--	--
	Trial summary	Negative	Negative	Negative	Positive	Negative
	Positive control (d)	612 ± 68 5	1,790 ± 71 2	1,997 ± 90.0	1,837 ± 135.5	1,793 ± 49.9

(a) Study performed at Case Western Reserve University. The detailed protocol is presented by 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) Precipitate on plate
(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 ROXARSONE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (µg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
Trial 1					
Dimethyl sulfoxide (d)		76 5 ± 2 7	100 0 ± 4 0	74 8 ± 7 0	32 5 ± 2 8
Roxarsone	125	75 7 ± 13 5	115 0 ± 17 5	85 7 ± 10 7	41 3 ± 11 5
	250	66 0 ± 4 4	97 0 ± 11 0	58 7 ± 5 7	29 7 ± 3 2
	500	77 3 ± 3 5	97 0 ± 9 5	59 0 ± 7 4	25 3 ± 1 9
	750	80 3 ± 6 7	67 7 ± 16 4	84 0 ± 4 0	35 3 ± 4 1
	1,000	82 7 ± 5 6	47 7 ± 4 6	84 0 ± 9 3	34 0 ± 2 5
	1,500	Lethal			--
Methyl methanesulfonate	5	70 0 ± 7 5	56 3 ± 1 5	431 7 ± 5 4	(e) 210 7 ± 24 2
Trial 2					
Dimethyl sulfoxide (d)		85 3 ± 3 8	100 0 ± 1 9	66 0 ± 5 0	25 5 ± 0 9
Roxarsone	400	71 3 ± 4 7	81 3 ± 2 3	73 3 ± 4 7	34 7 ± 2 6
	500	79 7 ± 4 7	69 3 ± 4 1	61 3 ± 5 0	25 3 ± 0 7
	600	66 0 ± 5 0	56 3 ± 5 9	53 7 ± 7 7	27 0 ± 3 2
	800	61 3 ± 4 4	29 7 ± 1 2	63 7 ± 2 3	34 7 ± 1 3
	1,000	53 0 ± 8 4	18 7 ± 5 4	69 7 ± 3 9	(e) 45 3 ± 4 9
	1,200	44 3 ± 7 9	8 7 ± 1 7	92 7 ± 9 0	(e) 74 0 ± 13 7
	1,500	Lethal			
Methyl methanesulfonate	5	33 7 ± 3 5	20 7 ± 1 2	254 0 ± 1 5	(e) 259 7 ± 25 4
Trial 3					
Dimethyl sulfoxide (d)		72 8 ± 5 3	100 0 ± 10 5	65 3 ± 1 8	30 5 ± 2 7
Roxarsone	400	63 7 ± 5 9	66 7 ± 3 5	68 7 ± 14 5	35 7 ± 5 4
	500	56 0 ± 5 0	53 3 ± 3 5	70 0 ± 9 1	41 3 ± 2 4
	600	56 0 ± 2 0	43 0 ± 6 7	73 3 ± 14 4	43 7 ± 8 0
	800	56 3 ± 5 5	33 7 ± 5 5	80 0 ± 3 5	(e) 48 3 ± 4 7
	1,000	64 0 ± 4 9	17 0 ± 3 6	136 0 ± 2 3	(e) 71 3 ± 5 0
	1,200	Lethal			
Methyl methanesulfonate	5	32 3 ± 4 4	38 7 ± 5 2	282 0 ± 17 0	(e) 304 0 ± 42 7

(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 unless otherwise specified, the average for the tests is presented in the table Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine 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 Tft resistance to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated), MF = mutant fraction

(d) Data presented are the average of four tests

(e) *Significant positive response, occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1 6*

TABLE E3. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN *DROSOPHILA MELANOGASTER* BY ROXARSONE (a)

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested			Overall Total (b)
				Mating 1	Mating 2	Mating 3	
Injection	6,250	25	16	0/955	2/873	0/767	2/2,595 (0.08%)
	0			0/1,009	0/953	0/902	0/2,864 (0.00%)
				0/1,009	0/953	0/902	0/2,864 (0.00%)
Injection	6,860	25	17	1/965	0/951	0/828	1/2,744 (0.04%)
	0			0/932	1/980	1/958	2/2,870 (0.07%)
				0/932	1/980	1/958	2/2,870 (0.07%)
Feeding	6,982	0	3	1/1,779	0/1,988	4/1,854	5/5,621 (0.09%)
	0			0/1,772	1/2,210	0/1,736	1/5,718 (0.02%)
				0/1,772	1/2,210	0/1,736	1/5,718 (0.02%)

(a) Study performed at Brown University. A detailed protocol of the sex-linked recessive lethal assay is presented in Zimmering et al. (1985). Exposure by feeding was done by allowing 24-hour-old Canton-S males to feed for 3 days on a solution of the study chemical dissolved in 5% sucrose. In the injection experiments, 24-hour-old Canton-S males were treated with a solution of the chemical dissolved in 0.7% saline and allowed 24 hours to recover. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days; sample sperm from successive matings were treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; no clusters were found. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. Results were not significant at the 5% level (Margolin et al., 1983).
(b) Combined total of number of lethal mutations/number of X chromosomes tested for three mating trials

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

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	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus)	MHV (mouse hepatitis virus) *M. pul.* (*Mycoplasma pulmonis*) (24 mo)
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) Sendai (12 mo)	RCV/SDA (sialodacryoadenitis virus) (24 mo) *M. pul.* (24 mo)

II. Results

Results are presented in Table F1.

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

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	10/10	Sendai
12	10/10	Sendai
18	7/10	Sendai
24	9/10	*M. pul.*
	6/9	Sendai
MICE		
6	10/10	Sendai
12	4/5	Sendai
18	5/10	Sendai
24	1/10	*M. pul.*
	5/10	Sendai

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

APPENDIX G

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

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

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)
2	17	214	16	213	0.9	3.8	18	213	1.1	8
6	15	278	16	279	1.1	2.9	15	270	1.0	6
10	16	311	15	304	0.9	2.5	14	296	0.9	5
17	16	368	15	365	0.9	2.1	15	356	0.9	4
21	16	392	17	393	1.1	2.2	16	378	1.0	4
26	18	411	17	412	0.9	2.1	16	396	0.9	4
31	17	423	17	425	1.0	2.0	15	406	0.9	4
34	17	433	17	437	1.0	1.9	15	415	0.9	4
39	17	443	16	449	0.9	1.8	15	433	0.9	3
44	18	458	17	461	0.9	1.8	18	443	1.0	4
48	19	467	18	471	0.9	1.9	17	451	0.9	4
52	18	465	17	470	0.9	1.8	16	451	0.9	4
58	17	469	17	478	1.0	1.8	16	458	0.9	3
63	16	469	17	475	1.1	1.8	16	457	1.0	4
67	18	472	16	481	0.9	1.7	17	463	0.9	4
71	18	465	18	480	1.0	1.9	17	462	0.9	4
75	18	463	17	474	0.9	1.8	17	458	0.9	4
79	18	471	17	479	0.9	1.8	15	463	0.8	3
83	18	466	17	471	0.9	1.8	16	457	0.9	4
88	17	459	17	467	1.0	1.8	17	454	1.0	4
92	15	449	17	462	1.1	1.8	16	441	1.1	4
96	18	450	18	455	1.0	2.0	17	427	0.9	4
100	17	430	17	459	1.0	1.9	18	430	1.1	4
104	22	445	21	439	1.0	2.4	23	402	1.0	6
Mean	17.3	424	17.0	429	1.0	2.1	16.5	412	0.9	4
SD (d)	1.4		1.2		0.1	0.5	1.8		0.1	1
CV(e)	8.1		7.1		10.0	23.8	10.9		11.1	25.0

(a) Grams of feed removed from feeder 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 roxarsone 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 ROXARSONE

	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)
2	13	152	13	155	1 0	4 2	13	155	1 0	8
6	13	178	12	181	0 9	3 3	11	176	0 8	6
10	12	193	11	196	0 9	2 8	11	1[illegible]	0 9	6
17	11	209	10	215	0 9	2 3	9	[illegible]	0 8	4
21	12	218	11	223	0 9	2 5	11	21[illegible]	0 9	5
26	11	225	12	230	1 1	2 6	11	220	1 0	5
31	12	234	11	238	0 9	2 3	10	228	0 8	4
34	12	239	11	242	0 9	2 3	10	232	0 8	4
39	11	246	11	253	1 0	2 2	10	242	0 9	4
44	13	260	13	264	1 0	2 5	11	251	0 8	4
48	12	267	12	271	1 0	2 2	11	258	0 9	4
52	12	272	12	277	1 0	2 2	11	261	0 9	4
58	13	287	12	288	0 9	2 1	11	271	0 8	4
63	13	296	12	298	0 9	2 0	12	280	0 9	4
67	14	309	13	310	0 9	2 1	12	288	0 9	4
71	14	314	14	316	1 0	2 2	13	300	0 9	4
75	15	320	14	324	0 9	2 2	14	310	0 9	5
79	13	335	14	337	1 1	2 1	13	322	1 0	4
83	15	342	14	348	0 9	2 0	10	328	0 7	3
88	14	347	14	355	1 0	2 0	13	338	0 9	4
92	14	350	14	360	1 0	1 9	12	340	0 9	4
96	15	355	14	363	0 9	1 9	13	343	0 9	4
100	14	352	12	360	0 9	1 7	12	344	0 9	3
104	15	355	14	345	0 9	2 0	13	342	0 9	4
Mean	13 0	277	12 5	281	1 0	2 3	11 5	268	0 9	4
SD (d)	1 3		1 3		0 1	0 5	1 3		0 1	1
CV (e)	10 0		10 4		10 0	21 7	11 3		11 1	25 0

(a) Grams of feed removed from feeder 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 roxarsone 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 ROXARSONE

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)
4	5	28.5	6	29.1	1.2	21	6	28.4	1.2	42
9	6	31.0	7	32.0	1.2	22	7	31.8	1.2	44
14	7	33.3	11	32.4	1.6	34	8	32.7	1.1	49
19	7	34.7	8	34.6	1.1	23	8	35.1	1.1	46
24	7	35.0	8	36.2	1.1	22	8	37.1	1.1	43
28	7	35.5	8	36.6	1.1	22	8	37.8	1.1	42
33	7	36.0	7	36.4	1.0	19	8	38.5	1.1	42
37	8	36.7	8	38.0	1.0	21	8	38.8	1.0	41
40	7	38.0	7	38.7	1.0	18	7	39.9	1.0	35
46	7	37.4	7	38.9	1.0	18	8	40.1	1.1	40
50	6	38.3	6	39.8	1.0	15	7	41.3	1.2	34
55	6	37.7	6	39.1	1.0	15	7	40.1	1.2	35
60	7	37.6	7	39.7	1.0	18	8	40.6	1.1	39
65	8	37.6	8	39.3	1.0	20	8	39.9	1.0	40
68	7	37.9	8	39.1	1.1	20	8	39.9	1.1	40
72	8	37.9	8	39.5	1.0	20	8	40.1	1.0	40
76	8	37.6	9	39.6	1.1	23	9	40.3	1.1	45
80	8	37.5	8	38.0	1.0	21	9	40.4	1.1	45
84	8	37.8	8	39.5	1.0	20	9	40.7	1.1	44
89	9	37.9	9	38.9	1.0	23	10	40.2	1.1	50
97	8	38.0	8	39.7	1.0	20	9	39.1	1.1	46
101	10	37.8	9	38.9	0.9	23	10	39.3	1.0	51
103	10	37.3	8	39.1	0.8	20	10	39.4	1.0	51
Mean	7.4	36.4	7.8	37.5	1.1	21	8.2	38.3	1.1	43
SD (d)	1.2		1.1		0.1	4	1.0		0.1	5
CV (e)	16.2		14.1		9.1	19.0	12.2		9.1	11.6

(a) Grams of feed removed from feeder 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 roxarsone 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 ROXARSONE

	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	4	21.3	5	21.6	1.3	23	6	21.1	1.5	57
9	6	23.3	6	23.8	1.0	25	6	23.8	1.0	50
14	7	25.5	7	24.6	1.0	28	7	25.1	1.0	56
19	6	27.1	8	27.0	1.3	30	6	26.4	1.0	45
24	6	27.7	7	27.9	1.2	25	7	27.7	1.2	51
28	7	28.1	7	28.9	1.0	24	7	28.4	1.0	49
33	7	29.9	7	29.8	1.0	23	7	29.9	1.0	47
37	7	30.2	8	30.8	1.1	26	7	29.9	1.0	47
40	7	31.0	7	31.5	1.0	22	7	31.5	1.0	44
46	7	31.7	7	32.2	1.0	22	7	31.8	1.0	44
50	6	32.6	6	32.7	1.0	18	6	31.9	1.0	38
55	7	32.8	6	31.5	0.9	19	7	31.5	1.0	44
60	8	33.1	7	32.5	0.9	22	7	31.6	0.9	44
65	8	32.8	8	32.2	1.0	25	7	31.2	0.9	45
68	8	34.3	8	32.9	1.0	24	8	32.1	1.0	50
72	8	35.1	8	33.8	1.0	24	8	32.7	1.0	49
76	9	35.4	10	35.3	1.1	28	10	33.1	1.1	60
80	10	37.4	11	35.5	1.1	31	11	33.5	1.1	66
84	10	38.6	11	37.2	1.1	30	11	34.3	1.1	64
89	11	39.4	12	37.3	1.1	32	13	36.2	1.2	72
97	10	42.0	11	38.4	1.1	29	12	36.9	1.2	65
101	13	41.4	15	36.9	1.2	41	13	36.2	1.0	72
103	14	42.0	17	37.3	1.2	46	15	35.8	1.1	84
Mean	8.1	32.7	8.7	31.8	1.1	27	8.5	31.0	1.1	54
SD (d)	2.4		3.0		0.1	6.4	2.7		0.1	11.6
CV (e)	29.6		34.4		9.1	23.4	31.8		9.1	21.5

(a) Grams of feed removed from feeder 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 roxarsone 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: April 1981 to April 1983

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

TABLE H1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE H2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

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

Nutrients	Mean ± Standard Deviation	Range	No. of Samples
Crude protein (percent by weight)	24 19 ± 1 07	22 4 26 3	25
Crude fat (percent by weight)	5 02 ± 0 47	4 2 6 0	25
Crude fiber (percent by weight)	3 37 ± 0 37	2 4 4 2	25
Ash (percent by weight)	6 54 ± 0.26	5 97 7 03	25
Amino Acids (percent of total diet)			
Arginine	1 300	1 21 1 38	3
Cystine	0 340	0 23 0 40	3
Glycine	1 137	1 06-1 20	3
Histidine	0 561	0 530-0 578	3
Isoleucine	0 899	0 881 0 934	3
Leucine	1 930	1 85 1 98	3
Lysine	1 243	1 20 1 30	3
Methionine	0 329	0 306 0 368	3
Phenylalanine	0 991	0 960-1 04	3
Threonine	0 851	0 827 0 886	3
Tryptophan	0 187	0 171-0 211	3
Tyrosine	0 647	0 566 0 769	3
Valine	1 090	1 05-1 12	3
Essential Fatty Acids (percent of total diet)			
Linoleic	2 40	2 37 2 44	2
Linolenic	0 284	0 259 0 308	2
Vitamins			
Vitamin A (IU/kg)	11,936 ± 2,547	8,900 22,000	25
Vitamin D (IU/kg)	5,220	4,140-6,300	2
α-Tocopherol (ppm)	39 1	31 1 44 0	3
Thiamine (ppm)	18 7 ± 3 20	14 0 26 0	(b) 24
Riboflavin (ppm)	7 3	6 1 8 1	3
Niacin (ppm)	82	65 97	3
Pantothenic acid (ppm)	30 2	23 0 30 5	3
Pyridoxine (ppm)	7 7	5 6 8 8	3
Folic acid (ppm)	2 5	1 8 3 4	3
Biotin (ppm)	0 27	0 21 0 32	3
Vitamin B_{12} (ppb)	21 2	10 6 38 0	3
Choline (ppm)	3,337	3,200 3,430	3
Minerals			
Calcium (percent)	1 22 ± 0 10	1 10 1 45	25
Phosphorus (percent)	0 96 ± 0 05	0 84 1 10	25
Potassium (percent)	0 809	0 772 0 846	2
Chloride (percent)	0 581	0 479 0 635	3
Sodium (percent)	0 307	0 258-0 349	3
Magnesium (percent)	0 165	0 151 0 177	3
Sulfur (percent)	0 292	0 270 0 290	3
Iron (ppm)	420	409 431	3
Manganese (ppm)	87 7	81 7 95 5	3
Zinc (ppm)	52 1	46 1 56 0	3
Copper (ppm)	11 15	8 09-15 70	3
Iodine (ppm)	2 66	1 52 3 64	3
Chromium (ppm)	1 72	1 44-1 93	3
Cobalt (ppm)	0 64	0 49 0 78	3

(a) Two or three batches of feed analyzed for nutrients reported in this table were manufactured in 1983 or 1984
(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)	0.45 ± 0.11	0.21-0.65	25
Cadmium (ppm) (a)	<0.1		25
Lead (ppm)	0.95 ± 0.78	0.27-2.93	25
Mercury (ppm) (a)	<0.05		25
Selenium (ppm)	0.28 ± 0.06	0.16-0.40	25
Aflatoxins (ppb) (a,b)	<10	<5.0-10.0	25
Nitrate nitrogen (ppm) (c)	9.85 ± 4.55	0.6-19.0	25
Nitrite nitrogen (ppm) (c)	1.92 ± 1.28	0.4-5.3	25
BHA (ppm) (d)	5.67 ± 5.07	1.5-20.0	25
BHT (ppm) (d)	3.35 ± 2.55	<1.0-13.0	25
Aerobic plate count (CFU/g) (e)	121,420 ± 94,844	7,000-420,000	25
Coliform (MPN/g) (f)	965 ± 991	<3-2,400	25
E. coli (MPN/g) (f,g)	6.76 ± 7.06	<3-23	24
E. coli (MPN/g) (f,h)	12.64 ± 29.46	<3-150	25
Total nitrosamines (ppb) (i, j)	4.40 ± 3.16	<1.2-12.9	24
Total nitrosamines (ppb) (i,k)	8.29 ± 19.41	1.2-100.3	25
N-Nitrosodimethylamine (ppb) (i,l)	3.05 ± 3.05	0.6-12.0	24
N-Nitrosodimethylamine (ppb) (i,m)	6.89 ± 19.42	0.6-99.0	25
N-Nitrosopyrrolidine (ppb)	1.20 ± 0.62	<0.3-2.4	25
Pesticides (ppm)			
α-BHC (a,n)	<0.01		25
β-BHC (a)	<0.02		25
γ-BHC-Lindane (a)	<0.01		25
δ-BHC (a)	<0.01		25
Heptachlor (a)	<0.01		25
Aldrin (a)	<0.01		25
Heptachlor epoxide (a)	<0.01		25
DDE (a,o)	<0.01	0.05 (7/14/81)	25
DDD (a)	<0.01		25
DDT (a)	<0.01		25
HCB (a)	<0.01		25
Mirex (a)	<0.01		25
Methoxychlor (a,p)	<0.05	0.13 (8/25/81); 0.6 (6/29/82)	25
Dieldrin (a)	<0.01		25
Endrin (a)	<0.01		25
Telodrin (a)	<0.01		25
Chlordane (a)	<0.05		25
Toxaphene (a)	<0.1		25
Estimated PCBs (a)	<0.2		25
Ronnel (a)	<0.01		25
Ethion (a)	<0.02		25
Trithion (a)	<0.05		25
Diazinon (a)	<0.1		25
Methyl parathion (a)	<0.02		25
Ethyl parathion (a)	<0.02		25
Malathion (q)	0.08 ± 0.05	<0.05-0.25	25
Endosulfan I (a,r)	<0.01		17
Endosulfan II (a,r)	<0.01		17
Endosulfan sulfate (a,r)	<0.03		17

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) CFU = colony-forming unit
(f) MPN = most probable number
(g) Mean, standard deviation, and range exclude one high value of 150 obtained for the batch produced on 8/26/82.
(h) Mean, standard deviation, and range include the high value given in footnote (g).
(i) All values were corrected for percent recovery.
(j) Mean, standard deviation, and range exclude one value of 100.3 obtained for the batch produced on 4/27/81.
(k) Mean, standard deviation, and range include the high value given in footnote (j).
(l) Mean, standard deviation, and range exclude one high value of 99.0 obtained for the batch produced on 4/27/81.
(m) Mean, standard deviation, and range include the high value given in footnote (l).
(n) BHC = hexachlorocyclohexane or benzene hexachloride
(o) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(p) Two observations were above the detection limit. The values and the dates they were obtained are given under the range.
(q) Ten batches contained more than 0.05 ppm.
(r) Analysis for endosulfan I, endosulfan II, and endosulfan sulfate was started on 12/23/81.

APPENDIX I

PROCEDURES FOR CHEMICAL, BIOCHEMICAL, AND HEMATOLOGIC ANALYSES FOR RATS AND MICE IN THE SECOND THIRTEEN-WEEK FEED STUDIES OF ROXARSONE

APPENDIX I. PROCEDURES

I. Collection of Urine Samples

Urine was collected overnight (from 4:00 p.m. to 8:00 a.m.) from fasted animals in individual metabolism cages. Urine was collected from five animals in each dose group either 3 or 4 days before the scheduled kill. Three poolings were made from the urine collected before the 9- to 10-day and 29- to 30-day scheduled-kill periods with one pool consisting of urine collected from two animals on the first day and one animal on the second. Urine samples collected before the 90- to 91-day kill were analyzed individually. All samples were frozen after collection and before analysis.

II. Collection and Analysis of Blood Samples

A. Hematologic Analyses

Blood samples were collected from the inferior vena cava of rats anesthetized with chloroform. As much blood as possible (minimum 3-4 ml for rats) was collected in a heparinized 5-ml syringe with an 18-gauge stainless steel needle. Approximately 0.5 ml of blood was transferred to a 2-ml vacutainer (containing EDTA), placed on ice, and used for the following hematologic analyses on the day of collection. The remaining blood was divided for biochemical and arsenic determinations as indicated below.

Hematocrit--Packed cell volumes were determined manually with heparinized Fischer red-tip capillary tubes and an International Micro-Capillary Centrifuge Model MB.

Hemoglobin--Hemoglobin was determined with a Coulter hemoglobinometer with reagents and procedures recommended by Coulter Electronics.

Erythrocyte and leukocyte counts--These measurements were made with a Coulter Counter Model ZBI with an aperture of 100 µm. Blood dilutions were made automatically with a Coulter Diluter II with Hematall™ azide-free isotonic diluent.

Differential leukocyte counts--Blood films were stained with Camco Quik Stain® (buffered Wright's stain, Scientific Products) and evaluated by light microscopy.

B. Biochemical Analyses

Approximately 1.0 ml of blood from each rat was placed in a 15-ml culture tube. The blood samples from the 9- to 10-day and 29- to 31-day kill periods were placed in three pools (as described above), placed on ice, and used for separation of plasma and biochemical analysis. Blood samples from the 90- to 91-day kill period were analyzed individually.

Cholinesterase, serum glutamic-oxaloacetic transaminase, and serum glutamic-pyruvic transaminase activities were determined with a Centrifichem System 500 with procedures and reagents recommended by Union Carbide Corporation.

C. Arsenic Determinations

The remaining blood from each animal was placed in a 20-ml plastic scintillation vial. The blood samples were pooled (as described above), placed on ice, and used for determination of total arsenic.

III. Collection of Tissue Samples

Before the blood was taken at the 90-day kill period, each animal was dipped in water to remove all roxarsone feed mixture from the fur. The entire liver was removed and weighed. The left lobe was placed in 10% formalin for histologic processing; the remaining liver was placed in a 50-ml plastic container and refrigerated. Both kidneys were removed and weighed. The left kidney was cut in half (transverse cut), and one portion was placed in 10% formalin for histologic processing. The remaining portion of the left kidney and the right kidney were refrigerated. Liver and kidney tissues were stored at −20° C until extracted for arsenic.

IV. Handling of Animals Dying During the Studies

Animals that died during the studies were weighed. The liver and kidneys were removed, weighed, and placed in 10% formalin for histologic processing. The remaining animal carcass was discarded.

V. Extraction of Urine

Urine samples (0.5 ml) were diluted with 1.0 ml water and acidified with 0.5 ml of 2 M perchloric acid at room temperature. After 10 minutes of occasional mixing, precipitated protein in the samples was removed by centrifugation at 2,400 rpm for 15 minutes. The supernatants were collected and the pellets resuspended in 0.5 ml of 0.5 M perchloric acid. After centrifugation, the supernatants were pooled with those previously collected, and enough 5 M potassium hydroxide (approximately 0.5 ml) was added to bring the pH of each sample to greater than 12. Precipitated potassium perchlorate that formed was removed by centrifugation and washed with 0.5 ml of 0.05 M potassium hydroxide. The combined alkaline supernatants were treated with 0.2 g of activated charcoal and vacuum filtered with sintered glass funnels coated with a light layer of diatomaceous earth (Celite). The charcoal residue was washed with 0.5 ml of 0.05 M potassium hydroxide, and the combined filtrates were acidified to pH 3 with 2.4 M hydrochloric acid (approximately 0.2 ml).

VI. Analysis of Urine for Roxarsone

The extracts were analyzed by a reverse-phase high-performance liquid chromatographic (HPLC) system consisting of a 300 × 4.6 mm μBondapak C_{18} column and a Whatman 70 × 2.5 mm CO:PELL ODS guard column with detection at 340 nm. The mobile phase consisted of methanol:acetic acid (5:1) in water (pH 3.2) at a flow rate of 1.0 ml/minute. The retention time for roxarsone was approximately 10 minutes. Samples were quantitated from peak areas with external standards.

VII. Limits of Detection and Correction Factors for Roxarsone Analysis

The lower limit of detection for roxarsone was approximately 2.5 ng. The standard curve was linear from 25 ng to 1.6 μg. If urine roxarsone levels were quite low, the lower limits of detection could be extended by increasing the injection volume or by scaling down the dilutions during the extraction procedure.

The correction factors for roxarsone measurements in urine were determined by measuring the recoveries of roxarsone from spiked samples. The recovery of roxarsone from urine was 84.5%.

VIII. Method for Arsenic (as As^{3+}) Determinations in Liver, Kidney, Blood, and Urine

Approximately 1 g of liver or kidney tissue was chopped into small pieces with a razor blade and transferred into a preweighed 50-ml Pyrex flask; for urine and blood samples, a 1-ml aliquot was transferred to a 50-ml Pyrex flask. Ten milliliters of concentrated nitric acid was added to the flask, and the sample was allowed to digest overnight under a hood. One milliliter of concentrated sulfuric acid plus 2 ml of 60% perchloric acid were then added and gently mixed behind a protective shield. The mixture was heated to a steady boil and allowed to simmer to remove the nitric and perchloric acids until the volume was reduced to approximately 1 ml. The mixture was allowed to cool to room temperature. The entire sample was transferred to a 10-ml volumetric flask; the flask was rinsed with 3 N hydrochloric acid containing 3% potassium iodide and the washings added to the digestate until the final volume was equal to 10 ml. Arsenic content was determined by atomic absorption spectrophotometry.

APPENDIX J

AUDIT SUMMARY

APPENDIX J. AUDIT SUMMARY

The experimental data, documents, pathology materials, and draft Technical Report for the 2-year toxicology and carcinogenesis studies of roxarsone in rats and mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice (GLP) regulations of the Food and Drug Administration (implemented by the NTP beginning on October 1, 1981). The studies were conducted by Southern Research Institute, Birmingham, Alabama. Animal dosing with roxarsone in feed began on June 17, 1981, for rats and June 2, 1981, for mice. The retrospective audit was conducted for the NIEHS at the NTP Archives in May 1987 by Argus Research Laboratories, Inc. The full audit report 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) All inlife records including protocol, correspondence, dosing, environmental conditions, masses, mortality, animal identification, and serology.
(3) Body weight and clinical observation data for a random 10% sample of animals in each study group.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning disposition codes, condition codes, tissue accountability, correlations of masses or clinical signs recorded during the last 3 months of life with gross observations and microscopic diagnoses, and correlations between gross observations and microscopic diagnoses.
(6) All wet tissue bags for inventory, and wet tissues from a random 20% sample of animals from each study group plus other relevant instances to verify animal identity and to examine for untrimmed potential lesions.
(7) Blocks and slides of tissues from a random 20% sample of animals from each study group to examine for proper match and inventory.
(8) Correlation between original microscopic observations and tabulated pathology diagnoses for a random 10% sample of study animals to verify computer data entry.
(9) Data and results pertaining to the 2-year studies of roxarsone in the Preliminary Draft of the NTP Technical Report.

Procedures and events for the studies were documented adequately in the archival records with the exception of records for the disposition of surplus animals and chemical. All pathology specimens were present.

The audit found that 6/150 rats and 13/150 mice had visible masses noted during their last month of life which were not also observed at necropsy; these were distributed uniformly between study groups. Records of the room environment were documented and revealed one high temperature recording of 96° F, but this temperature had no apparent effect on animals.

Inspection of residual tissues for individual animal identifiers showed that 64/65 rats and 69/69 mice were identified correctly; the ears for 1 rat were not present, but its wet tissues matched the necropsy record description. No untrimmed potential lesions were found for any of the animals examined. The tissue accountability for the clitoral gland was 88% in control female, 94% in low dose female, and 94% in high dose female rats.

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.