TRADE SECRET

Study Title

H-24616: Subchronic Toxicity
90-Day Gavage Study in Rats
with One-Generation Reproduction Evaluations

Volume 1 of 5

Laboratory Project ID: DuPont-4739

TEST GUIDELINES: U.S. EPA Health Effects Test Guidelines
OPPTS 870.3100 (1998)

AUTHOR: Don A. Delker, Ph.D.

STUDY COMPLETED ON: October 23, 2001

PERFORMING LABORATORY: E.I. du Pont de Nemours and Company
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WORK REQUEST NUMBER: [redacted]

SERVICE CODE NUMBER: [redacted]

SPONSOR STUDY NUMBER: [redacted]

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards except for the items documented below. None of the items listed impact the validity of the study.

1. The characterization of the test substance that was conducted prior to the initiation of the study provided the percentage of solids in the test substance. This information was used to calculate the dose levels, based on percent active ingredient, for the study. Additional chemical characterization of the test substance was conducted after the completion of the study and provided analysis of the solids in the test substance. Samples of the test substance were collected on the first day of dosing, during the 90-day dosing period, and on the last day of dosing and were analyzed; these analyses provided confirmation of the percentage of solids and documented the test substance stability and uniformity over the course of the study. None of the aforementioned analyses were performed under Good Laboratory Practice Standards; however, the analyses were conducted in compliance with ISO9002 regulations. All of the analyses are considered valid and sufficient for the purposes of this study.

2. Gross observations on five F_1 weanlings, not more than two from any treatment group, were inadvertently not documented at the time of necropsy. Due to the large number of pups that received gross observations on postnatal day 21, this lack of data will not affect the validity of the study.

Submitter / Sponsor: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

Study Director: Don A. Delker 23 Oct 2001
Don A. Delker, Ph.D. Date
Research Scientist

QUALITY ASSURANCE STATEMENT

Haskell Sample Number(s):

24616

Dates of Inspections:

Conduct: September 6, 2000; November 13, 15, 22, 2000; December 6, 14, 18, 2000

Records, Reports: March 5-9, 2001; April 10-12, 15, 16, 27, 30, 31, 2001; May 1-4, 6-10, 13-14, 17-18, 21-25, 28-31, 2001; June 1,4, 2001; August 6-10, 13, 30, 2001; September 11-14, 17, 2001

Dates Findings Reported to:

Study Director: November 14, 2000; March 12, 2001; April 16, 2001; May 14, 2001; June 18, 2001; August 30, 31, 2001; September 17, 2001

Management: December 3, 2000; March 12, 2001; April 16, 2001; June 18, 2001; August 30, 31, 2001; September 17, 25, 2001; October 18, 2001

Reported by: Joseph C Hamill — 23-Oct-2001

Joseph C. Hamill
Sr. Quality Assurance Auditor

Date

CERTIFICATION

We, the undersigned, declare that this report provides an accurate evaluation of data obtained from this study.

Neurological Evaluations Reported by: Linda A. Malley — 23-Oct-2001
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Clinical Pathology Evaluations Reported by: 23 Oct 2001
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Pathological Evaluations Reported by: G. Tracy Makovec — 23-Oct-2001
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TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

Page

TABLE OF CONTENTS (Continued)

Page

LIST OF TABLES

Page

LIST OF TABLES (Continued)

Page

LIST OF TABLES (Continued)

Page

LIST OF FIGURES

Page

LIST OF APPENDICES

LIST OF APPENDICES (Continued)

Page

STUDY INFORMATION

Substance Tested: [redacted]

Synonyms/Codes: • H-24616
• [redacted]

Haskell Number: 24616

Composition [redacted]

Known Impurities: [redacted]

[redacted]

Physical Characteristics: [redacted]

Sponsor: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
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Study Initiated/Completed: September 14, 2000/ (see report cover page)

In-Life Initiated/Completed: September 18, 2000 / March 19, 2001

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SUMMARY

Four groups of young adult male and female Crl:CD®(SD)IGS BR rats were administered neat H-24616 by gavage at dosages of 0, 50, 250, or 1000 mg/kg/day based on the active ingredient. Selected animals from each group were designated for subchronic toxicity or reproductive evaluations.

In the subchronic study, body weights, food consumption, and clinical signs were evaluated weekly. Clinical pathology endpoints were evaluated during weeks 7 and 13 of the 90-day exposure period and 1-month postdosing. Neurobehavioral assessments were also performed prior to dosing, during week 12, and near the end of the 1-month recovery period. After 90 days of dosing, ten rats/sex/dose were sacrificed and given a gross and microscopic pathological examination. One month after the 90-day dosing period, 10 animals/sex in the control and high dose group were examined for recovery of toxic effects. An additional five animals/sex/dose were evaluated for recovery 3 months following the end of the dosing period.

The average daily volumes of H-24616 given to male rats over the 90-day exposure period were 0.09, 0.45, and 1.74 mL H-24616 for the 50, 250, and 1000 mg/kg/day dosage groups, respectively. The average daily volume given to female rats over the 90-day exposure period were 0.05, 0.28, and 1.08 mL H-24616 for the 50, 250, and 1000 mg/kg/day dosage groups, respectively.

In-Life and Neurotoxicology Parameters: No test substance-related mortality occurred in the study. No adverse clinical signs of toxicity or changes in neurobehavioral parameters were observed in male or female rats in any dose group. Statistically significant lower body weight, body weight gain, food consumption, and food efficiency were observed in male rats administered 1000 mg/kg/day when compared to controls. There were no adverse effects on these parameters at any dose level in female rats at 90 days and no adverse effects in males and females dosed with 1000 mg/kg/day by the end of the one-month recovery period.

Clinical Pathology: Potentially adverse findings of elevated liver enzymes (ALKP, AST, ALT, and/or SDH) were observed after treatment and/or a one month recovery in males and/or females dosed with 250 or 1000 mg/kg/day. Other changes in clinical pathology parameters, during treatment or after a one-month recovery, were considered treatment-related but non-adverse because the magnitude of change was small, transient, and/or in a direction not associated with toxicity. The noteworthy parameters thus affected were red cell mass, red cell shape, urea nitrogen, cholesterol, triglycerides, bilirubin, albumin, globulin, and urine fluoride.

Anatomical Pathology (Subchronic Toxicity): Test-substance related and statistically significant increases in liver weight parameters occurred in male rats of all dose groups and female rats in the high-dose group after the 90-day exposure period. Histopathologically, hepatocellular hypertrophy was also observed in male rats of all dose levels but not in female rats. Nasal olfactory epithelium degeneration/necrosis was observed in male and female rats at all dose levels and inflammation of the olfactory epithelium in male rats in the 250 and 1000 mg/kg/day dose level. Thyroid hypertrophy and increased alterations in colloid were observed in male and

female rats in the 250 and 1000 mg/kg/day dose groups. No thyroid hypertrophy was observed in rats dosed with 50 mg/kg/day.

After one month of recovery, rats dosed with 1000 mg/kg/day showed some reversibility of effects. Hepatocellular hypertrophy was present in male rats (less severe than at 90 days) and nasal epithelium degeneration/necrosis also persisted in male rats at a lower incidence and severity than observed at the end of the dosing period. Inflammation of the nasal epithelium was no longer seen in male rats and nasal epithelium degeneration/necrosis was not observed in female rats. Treatment-related thyroid hypertrophy and increased colloid alterations persisted in male and female rats.

After the 3-month recovery period, hepatocellular hypertrophy was observed only in male rats in the 250 and 1000 mg/kg/day dose groups. Nasal epithelium degeneration/necrosis or inflammation was not observed in male or female rats at any dose level. Thyroid hypertrophy occurred in one female rat in the 1000 mg/kg/day dose group and increased colloid alterations were observed in male rats in the 250 and 1000 mg/kg/day dose groups.

Reproduction: Twenty male and female rats from each dose group were designated for reproductive evaluations. Parental rats (P_1 generation) were dosed daily for 70 days prior to cohabitation, during the cohabitation period (mating), during gestation, and during lactation, until the weaning of the F_1 offspring. The following parameters were conducted on P_1 rats: body weights, food consumption, clinical signs, gross pathology, sperm parameters, estrous cyclicity and reproductive performance. The F_1 offspring were evaluated during the lactation period for growth and survival and given a gross pathological examination at weaning. A subset of F_1 rats (F_1 generation) were retained at weaning, and the following parameters evaluated for 6 weeks: body weights, food consumption, clinical signs, and age at onset of vaginal opening and preputial separation. After 6 weeks, the F_1 generation rats were given a gross pathological examination, selected reproductive organs were weighed and histopathology evaluation of the thyroid was conducted.

No test substance-related effects on reproductive parameters were observed. There were no adverse effects at any dose level on estrous cycle or sperm parameters, or reproductive indices. There were no test substance-related changes in F_1 litter size, pup weights or survival during lactation. There were no test substance-related changes in body weights, food consumption, or developmental landmarks in the F_1 generation.

Mean thyroid organ weight was significantly lower in the 250 and 1000 mg/kg/day dose groups in the F_1 generation, but not in the P_1 generation. However, there were no histopathological changes in the thyroid of the F_1 generation rats. There were no other test substance-related gross pathology findings in P_1 or F_1 generation rats.

NOEL for Subchronic Toxicity and Recovery: Target organs identified in this 90-day subchronic toxicity study included liver, nose and thyroid. Based on the olfactory nasal epithelium necrosis observed after 90 days of treatment in male and female rats at all dose levels, a no-observed-effect level (NOEL)[a] cannot be determined for the subchronic toxicity evaluation. However, the nasal olfactory epithelium effects observed after the 90-day exposure period were completely reversible by the end of the 3-month recovery period.

NOEL for Reproductive Evaluations: Although there were no test substance-related effects observed on reproductive function, a NOEL of 50 mg/kg/day was determined for reproductive evaluations based on decreased thyroid weights in both male and female F_1 adults at dosages of 250 mg/kg/day and above.

[a] The NOEL for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Thus, for this study, the NOEL is equivalent to the NOEL as defined by the United States Environmental Protection Agency (1985) and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union (1994).

INTRODUCTION

The test substance, H-24616, contains an [redacted] In a 2-week range-finding study conducted with H-24616 in rats, there was no observable systemic toxicity observed up to the limit dosage of 1000 mg/kg/day active ingredient. Dosages of 50, 250 and 1000 mg/kg/day were selected for this 90-day subchronic toxicity with one generation reproduction study based on the ability of rats to tolerate the upper limit dosage of 1000 mg/kg/day in the range-finding study.

OBJECTIVE

The objective of this study was to evaluate the potential subchronic and reproductive toxicity of H-24616 when administered by gavage to male and female rats. The oral route of administration was selected as the most efficient way to deliver an accurate dosage.

MATERIALS AND METHODS

A. Test Guidelines

The subchronic toxicity study design complies with the United States Environmental Protection Agency (EPA), Office of Prevention, Pesticides, and Toxic Substances (OPPTS) Health Effects Test Guidelines, OPPTS 870.3100 90-Day Oral Toxicity in Rodents (AUG-1998). The one-generation reproduction study includes many endpoints of reproductive function but does not comply with a specific guideline.

B. Test Substance

The test substance, H-24616, was supplied by the sponsor as an [redacted] The test substance is a [redacted] The stability analysis of the test substance before and during the study was conducted by Regional Analytical Services (RAS), Jackson Laboratories, Deepwater, New Jersey. A reserve sample of the test substance was collected and retained by Haskell Laboratory.

C. Test Species

On August 31, 2000, 176 male and 176 female Crl:CD®(SD)IGS BR rats, with an assigned birth date of July 31, 2000, were received from Charles River Laboratories, Inc., Raleigh, North Carolina for use on this study.

The rat was selected because it is the recommended species specified in the subchronic toxicity guidelines and is extensively used in reproduction studies. The Crl:CD®(SD)IGS BR strain was chosen because extensive background information is available from the literature, the supplier, and previous studies at Haskell Laboratory. This species/strain also is considered suitable relative to longevity, hardiness, sensitivity to the test substance, and low incidence of spontaneous diseases.

D. Animal Husbandry

1. Housing

With the exception of some portions of the reproductive study, all rats were housed one per cage, sexes separate, in stainless steel, wire-mesh cages suspended above cage boards. Animal rooms were maintained on a 12-hour light/dark cycle (fluorescent light) and at a temperature of 23 ± 3°C and a relative humidity of 50% ± 20%. Occasional excursions outside the accepted ranges were minor and did not affect the study.

Rats designated for reproductive toxicity evaluations were housed as breeding pairs during the cohabitation period. During the gestation period, female rats designated for reproductive toxicity evaluations were housed individually until gestation day 20. Beginning on gestation day 20 for mated females, or at the end of the cohabitation period for females without evidence of copulation, female rats were housed individually in polycarbonate pans with bedding. During the lactation period, adult female rats were housed with their litters in polycarbonate pans.

During the 70-day premating period for P_1 adults and the 42-day postweaning period for F_1 weanlings, cage racks were relocated within the animal room each week and cages were repositioned on the racks every 2 weeks.

2. Feed and Water

Tap water was provided *ad libitum*. All rats were fed PMI Nutrition International, Inc. Certified Rodent LabDiet® 5002 *ad libitum*.

3. Identification

Prior to assignment to groups, each rat was temporarily identified by either the presence or absence of a colored tail mark and cage identification. After assignment to groups, an individual identification number was tattooed on the tail of each rat. The information on the cage labels included the unique 6-digit Haskell animal number and the individual identification number assigned to each rat.

4. Health Monitoring Program

As specified in the Haskell Laboratory animal health and environmental monitoring program, the following procedures are performed periodically to ensure that contaminant levels are below those that would be expected to impact the scientific integrity of the study:

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Feed samples are analyzed for total bacterial, spore and fungal counts.
- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

Certified animal feed is used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates. The presence of these contaminants below the maximum concentration stated by the manufacturer would not be expected to impact the integrity of the study.

The animal health and environmental monitoring program is administered by the attending laboratory animal veterinarian. Evaluation of these data did not indicate any conditions that affected the validity of the study.

E. Quarantine and Pretest Period

Upon arrival at Haskell Laboratory, the rats were quarantined for 10 days of the 17-day pretest period. The rats were observed daily for any clinically apparent signs of disease or injury, weighed 4 times, and examined by a veterinary ophthalmologist to identify animals with preexisting ocular lesions.

Prior to study start, one female rat (animal no. 641270) was found dead prior to grouping and was necropsied to check for the presence of disease. No disease was found; death was due to spontaneous urinary obstruction.

On the basis of acceptable body weight gains and clinical observations, all surviving rats were released from quarantine on test day -7 by the laboratory animal veterinarian.

F. Study Design

Groups		No./ Group		Dietary Dosage[a]
Male	Female	Male	Female	(mg/kg/day)
I	II	45	45	0 (Control)
III	IV	35	35	50
V	VI	35	35	250
VII	VIII	45	45	1000

a Weight of test substance (adjusted for [redacted] active ingredient)/kg animal body weight.

The first ten rats in each group were designated for the 90-day exposure evaluation. The next five rats in each group were designated as a satellite subset for serial blood collection and evaluation of selected tissues following a 3-month recovery period. The next 20 animals in each group were designated for reproductive evaluations. The last 10 male and female rats in the control and high dose groups were designated for 1-month recovery evaluations.

Male and female rats designated for the 90-day exposure evaluation were dosed for 91 and 92 days, respectively, and necropsied the following day. Male and female rats designated for the one- and three- month recovery evaluations were dosed for 90 days and necropsied 33-34 days and 92 days postdosing, respectively.

Neurobehavioral evaluations were conducted on control and high dose animals designated for the one-month recovery (predose, week 13, one-month post dose) and on male and female animals designated for the 90-day exposure evaluation (predose and week 13). Clinical pathology evaluations were conducted on animals designated for the 90-day exposure evaluation on weeks 7 and 13 and on animals designated for the one-month recovery evaluation immediately prior to necropsy.

G. Assignment to Groups and Study Start

Rats were selected for study use on the basis of adequate body weight gain, freedom from any ophthalmological abnormalities or clinical signs of disease or injury, and a body weight within ± 20% of the mean within a sex. The selected rats were distributed by computerized, stratified randomization so that there were no statistically significant differences among group body weight means within a sex.

Oral administration of H-24616 began on test day 0. The rats were approximately 49 days of age on test day 0. Prior to the start of the test substance administration, rats with body weights that were not within ± 20% of the mean within a sex, were replaced and discarded without gross or microscopic evaluations. Replacement rats were selected on the basis of freedom from any clinical signs of disease or injury and a body weight ± 20% of the mean within a sex.

H. Test Substance Administration and Sampling

The test substance as received from the sponsor was administered to the study animals by oral gavage to achieve dosage levels of 50, 250, or 1000 mg active ingredient/kg body weight/day, based on the most recently recorded body weight. The neat liquid was not diluted prior to dosing but was given to the animals in varying volumes depending on the targeted dose and amount (grams) of active ingredient in the test substance preparation. Dose volumes did not exceed 20 mL/kg. Animals designated for subchronic toxicity were dosed daily by gavage for 90 days. Animals designated for reproductive evaluations were dosed daily by gavage for 70 days, and then daily during cohabitation until evidence of copulation was found or until the 14-day cohabitation period ended. Pregnant females were dosed during the 3-week gestation period. From gestation day 18 until delivery, dose volumes were based on the gestation day 18 body weights. Pregnant females in the process of delivery or showing signs of delivery were not dosed. Lactating females were dosed until pups were weaned on day 21. P_1 females with no evidence of copulation continued to be dosed until sacrifice. Following the cohabitation period, P_1 males were dosed until sacrifice.

The test substance was supplied by the sponsor in multiple-gallon containers. To determine the stability of the test substance over the 90-day exposure period, an analytical sample was taken from gallon container #1 on test day 0 and from gallon container # 6 on test day 91. Analytical samples for homogeneity and concentration verification were also taken. To verify proper mixing and homogeneity of the test substance over the course of the daily dosing period, an additional analytical sample was taken from the dosing container after dosing on test day 0. To verify proper mixing and homogeneity of the test substance in gallon container #1, an additional analytical sample was taken from gallon container # 1 prior to the last day of use on test day 17.

All male and female control animals were treated with deionized water at the same dose volume as used in the high-dosage groups, respectively.

I. Body Weights

All rats were weighed once per week during the 90-day feeding phase of the study. In addition, the rats designated for neurobehavioral evaluations, undergoing functional observational battery and motor activity assessments, were weighed on the days of those observations. During the reproduction substudy, male rats were weighed on a weekly schedule and female rats were weighed during gestation on days 0, 7, 14, and 21, and lactation days 0, 7, 14, and 21. P_1 female rats with no evidence of copulation or that did not deliver a litter continued to be weighed weekly. Weaned F_1 rats were weighed weekly until postnatal day 63.

J. Food Consumption and Food Efficiency

The amount of food consumed by each rat over each weighing interval was determined throughout the study. Each rat's feeder was weighed at the beginning and end of the interval and the final weight of the feeder and the amount of spillage from the feeder during the interval was subtracted from the initial feeder weight. From these measurements, mean daily food

consumption over the interval was determined. From the food consumption and body weight data, the mean daily food efficiency was calculated.

Mean daily food consumption was determined for all animals designated for subchronic toxicity evaluations during the 90-day exposure period. Food consumption was also determined for one-month postdosing for animals designated for one- and three-month recovery evaluations. The only exception is that food consumption was not determined for animals designated for 3-month recovery during the urine and feces collection period on test days 84-91.

During the reproductive assessment, food consumption was determined for each female rat designated for reproductive assessment as follows:

- Premating Dosing period – individual food consumption was determined weekly, ending test day 69.
- Cohabitation period, beginning test day 69 – food consumption was not determined.
- Gestation period – individual food consumption was determined on gestation days 0, 7, 14, and 21 (not reported).
- Lactation period – food consumption was not determined.
- Postweaning F_1 rats – individual food consumption was determined weekly, ending on postnatal day 63.

K. Detailed Clinical Observations and Mortality

During the test period, cage-site examinations to detect moribund or dead rats and abnormal behavior and/or appearance among rats were conducted at least twice daily throughout the study, except for test day 36 when the rats were checked only once. One male animal in the 250 mg/kg/day dosage group was euthanized on test day 51 due to a large open wound under the neck. At every weighing, each rat was individually handled and examined for abnormal behavior and appearance. Detailed clinical observations in a standardized arena were also evaluated on rats designated for the 90-day exposure and one-month recovery periods. The detailed clinical observations included (but were not limited to) evaluation of fur, skin, eyes, mucous membranes, occurrence of secretions and excretions, autonomic nervous system activity (lacrimation, piloerection, and unusual respiratory pattern), changes in gait, posture, response to handling, presence of clonic, tonic, stereotypical, or bizarre behavior.

L. Ophthalmological Evaluations

Three ophthalmological examinations were conducted by a veterinary ophthalmologist. Both eyes were examined by focal illumination and indirect ophthalmoscopy. The examinations were conducted under subdued lighting after mydriasis had been produced with a 1% tropicamide solution.

On test day -10, the initial examination was performed on all rats received for the study, prior to selection and grouping. On test day 88, all surviving rats designated for the 90-day exposure and one-month recovery were examined again. On test day 116, all surviving rats designated for recovery evaluation were given a final examination.

M. Neurotoxicity Evaluations

1. Sensory Function Evaluation

Prior to test substance administration, during week 12 of test substance administration, and following an approximately one-month recovery period, assessments of responses to approach/touch, sharp auditory stimulus, and tail pinch were made while the animal was in a standard arena. These assessments were conducted on 10 animals per group for the baseline and week 12 evaluations. The recovery evaluation was conducted on the 10 animals per group designated for recovery (control and high-dose groups only). Fore- and hindlimb grip strength were measured by a strain gauge device (Chatillon® Digital Force gauge). Pupillary constriction was measured immediately prior to removing the rats from the motor activity chambers (Section 2. below) because the darkened room in which the apparatus was located facilitated observing the response. The presence or absence of pupillary constriction was assessed after a beam of light was directed into each eye. For all these assessments, the experimenter was unaware of the group designation of the animal.

2. Motor Activity (MA)

Following the evaluation of grip strength and sensory function, assessment of motor activity (MA) was conducted. Rats were individually tested in 1 of 30 nominally identical, automated activity monitors (Coulbourn® Infrared Motor Activity System). Group and gender were counterbalanced across the monitors and time of day to the fullest extent possible. The infrared monitoring device enables measurement of 2 dependent variables: duration of movement and number of movements. A continuous movement was counted as 1 movement regardless of duration. Each test session was 60 minutes in duration, and the results were expressed for the total session as well as for 6 successive 10-minute blocks.

Presence of defecation and urination on the cageboards below the motor activity monitor were also recorded following each motor activity session.

3. Test Facility Positive Control Data

Data on the effects of acrylamide, carbaryl, d-amphetamine, and trimethyltin are described in four separate reports.[1,2,3,4] These positive control studies are the basis of training certification for the individuals making judgments in the neurobehavioral and neuropathology tests. The data also document that the equipment and procedures are capable of detecting effects that may be seen in neurotoxicity studies of this type.

N. Clinical Pathology

Clinical pathology evaluations were conducted on the first 10 male and 10 female rats per group in all groups on test days 45 (male) or 44 (female) and either 91 (male) or 92 (female). The rats were fasted overnight (approximately 16 hours) and urine was collected during this interval. Blood samples for hematology and clinical chemistry measurements were collected from the orbital sinus of each fasted rat while the rat was under light carbon dioxide anesthesia. Blood samples for coagulation (end of dosing only) were collected from the abdominal vena cava while

the rat was under carbon dioxide anesthesia, immediately prior to sacrifice. All blood samples were examined visually and observations recorded. A clinical pathology evaluation (hematology, clinical chemistry, and urinalysis, but not coagulation) was also conducted on all recovery rats (control and rats dosed with 1000 mg/kg/day) from blood and urine collected after a month of recovery (test day 123, male, or 124, female).

1. Hematology/Coagulation

Complete blood counts (including reticulocytes) were determined on a Bayer® Advia 120 hematology analyzer and determined from microscopic evaluation of the blood smear. Wright-stained blood smears from all rats were examined microscopically for confirmation of automated results and evaluation of cellular morphology. Coagulation times were determined on a BCS Behring Coagulation Analyzer. New methylene blue-stained blood smears were prepared from each rat undergoing hematology evaluation but were not needed for evaluation.

The following hematology and coagulation parameters were determined:

Erythrocyte count (RBC)
Hemoglobin concentration (HGB)
Hematocrit (HCT)
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)

Red cell distribution width (RDW)
Absolute reticulocyte counts (ARET)
Total leukocyte count (WBC)
Differential leukocyte count
Platelet count (PLT)
Microscopic blood smear examination

Prothrombin time (PT)
Activated partial thromboplastin time (APTT)

2. Clinical Chemistry

Clinical chemistry parameters were measured or calculated on a Roche Diagnostics (BMC)/Hitachi® 917 clinical chemistry analyzer. Plasma fluoride concentration was determined using a phi/12 pH meter with a fluoride-selective electrode.

The following serum chemistry parameters were determined:

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Sorbitol dehydrogenase (SDH)
Alkaline phosphatase (ALKP)
Total bilirubin (BILI)
Urea nitrogen (BUN)
Creatinine (CREA)
Cholesterol (CHOL)
Triglyceride (TRIG)
Glucose (GLUC)

Total protein (TP)
Albumin (ALB)
Globulin (GLOB)
Calcium (CALC)
Inorganic phosphorus (IPHS)
Sodium (NA)
Potassium (K)
Chloride (CL)
Plasma fluoride (PFLU)

3. Urinalysis

The following urinalysis parameters were determined:

Appearance (quality, clarity, and color)
Volume (VOL)
Osmolality (OSMO)
Specific gravity (SG)
pH
Glucose (UGLU)
Ketones (KET)
Bilirubin (UBIL)
Blood (BLD)
Urobilinogen (URO)
Urine fluoride (UFLU)
Protein (UMTP)
Microscopic examination of sediment

Urine volume and appearance were measured and evaluated visually, respectively. Urine constituents were semi-quantitatively measured on a Bayer Clinitek® Atlas™ Automated Urine Chemistry analyzer. Urine volume and appearance were measured and evaluated visually, respectively. Urine constituents were semi-quantitatively measured on a Bayer Clinitek® Atlas™ Automated Urine Chemistry analyzer. Urine protein was measured on a Roche Diagnostics (BMC)/Hitachi® 717 clinical chemistry analyzer. Urine osmolality was determined using an Advanced Osmometer 3900. Urine fluorides were determined by multiplication of measured urine volume by urine fluoride concentration (measured using a phi/12pH meter and a fluoride selective electrode). Sediments from all urine specimens were evaluated microscopically.

O. Serial Blood Collection (Satellite Group)

On test day 1 (males only), and test days 4, 10, 21, 36, 57, 78, and 90 (males and females) blood (approximately 0.5 – 1 mL) was collected from the orbital sinus of designated animals (5 rats/sex/dose) while the animals were under light carbon dioxide anesthesia. On the day of blood collection, blood was collected from the animals prior to dosing. The blood was collected in glass tubes containing EDTA while the tubes were on ice and then stored frozen. For each bleeding, blood was collected at approximately the same time of day. During the last week of the 90-day exposure period urine and feces were collected daily at 24-hour intervals from each animal. The animals were placed in metabolism cages for collection of feces and urine. The exact time period of collection of urine and feces was documented along with the total volume of urine obtained. Urine and feces were stored frozen. Blood was also collected 3, 9, 16, 29, 43, 64, and 85 days postdosing for both male and female animals of each dose group. Animals were sacrificed at the end of the 3-month recovery period. Blood, urine, and feces samples were not analyzed during the course of this study but may be analyzed, if needed, at a later date. Any data generated from these analyses will be archived in the study records and reported separately.

P. Anatomic Pathology – Rats Designated for Subchronic Toxicity and Recovery

On test days 91/92, the first 10 male/female rats from the 0, 50, 250, and 1000 mg/kg/day groups were sacrificed and necropsied. Thirty-day recovery rats from 0 and 1000 mg/kg/day were sacrificed and necropsied on test days 122 and 123 for males and females, respectively. Male and female satellite animals (90-day recovery) from each group were sacrificed and necropsied on test day 182. Rats were euthanatized by carbon dioxide anesthesia and exsanguination. Rats

scheduled for sacrifice were fasted overnight on the afternoon before their scheduled sacrifice. Gross examinations were performed on all male and female rats.

The following tissues were collected from rats designated for the 90-day exposure and one-month recovery that were found dead, accidentally killed, or sacrificed by design.

Digestive System
- Liver
- Esophagus
- Stomach
- Duodenum
- Jejunum
- Ileum
- Cecum
- Colon
- Rectum
- Salivary glands
- Pancreas

Urinary System
- Kidneys
- Urinary bladder

Respiratory System
- Lungs
- Trachea
- Nose
- Larynx
- Pharynx

Cardiovascular System
- Heart
- Aorta

Hematopoietic System
- Spleen
- Thymus
- Mandibular lymph node
- Mesenteric lymph node
- Bone Marrow[a]

Endocrine System
- Pituitary gland
- Thyroid gland
- Parathyroid glands
- Adrenal glands

Nervous System
- Brain (including cerebrum, cerebellum, medulla/pons)
- Spinal Cord (3 levels: cervical, mid-thoracic, lumbar)
- Sciatic Nerve

Musculoskeletal System
- Skeletal Muscle
- Femur/Knee Joint
- Sternum

Reproductive System
- Male
  - Testes
  - Epididymides
  - Prostate
  - Seminal Vesicles
- Female
  - Ovaries
  - Uterus
  - Mammary Gland

Miscellaneous
- Skin
- Eyes (including optic nerve)
- gross observations

a Bone marrow was collected with the femur and sternum.

The liver, kidneys, adrenal glands, brain, spleen, thymus, heart, ovaries, uterus, epididymides, and testes were weighed at necropsy, and organ weight/final body weight and organ weight/brain weight ratios were calculated. Due to elevated liver weights observed at the one-month recovery sacrifice, liver was also collected and weighed from 3-month recovery animals designated for blood collection.

Gross lesions which were diagnosed at necropsy and for which microscopic examination was not appropriate (e.g., fluid accumulation, ruffled fur, missing anatomic parts) were generally not collected. Gross lesions for which a microscopic diagnosis would not be additive (e.g., osteoarthritis, pododermatitis, chronic dermatitis of the tail, urinary calculi, and deformity of the teeth, toe, tail, or pinna) were saved but were generally not processed for microscopic evaluation.

Testes, epididymides, and eyes were fixed in Bouin's solution. All other tissues were fixed in 10% neutral buffered formalin. Processed tissues were embedded in paraffin, cut at a nominal thickness of 5 micrometers, stained with hematoxylin and eosin (H&E), and examined microscopically.

All collected tissues from rats sacrificed on test days 91/92 from control, and 1000 mg/kg/day rats and all found dead or accidentally killed rats were processed and received a full histopathological examination. Liver, thyroid gland, and nose were collected and processed from 50 and 250 mg/kg/day 90-day exposure rats and from all one-month and 3-month recovery (satellite) rats and were examined microscopically. The key to Appendix G describes the lesion grading system used in this study.

Liver, kidney, testes, and approximately one gram of fat were collected from all satellite animals designated for blood collection (90-day recovery) and placed in plastic freezer bags and stored in the freezer for future analysis.

Q. Reproductive Assessment

1. Breeding

After approximately 10 weeks of exposure to the test substance, on test day 69, each female was continually housed on a 1:1 basis with a randomly selected male of the same dose concentration level in the male's cage. On the day copulation was confirmed, the female was transferred back to individual cage housing. Mating pairs were cohoused until evidence of copulation was observed (designated as day 0 of gestation), or until 2 weeks elapsed. The presence of an intravaginal or extruded copulation plug was considered evidence of copulation.

2. Estrous Cycle Evaluation

Vaginal smears were collected from all P_1 female rats in order to determine the stages of the estrous cycle. Vaginal smears were collected daily beginning 3 weeks prior to mating, and continuing until copulation was confirmed, or the cohabitation period ended.

Vaginal smears were also collected from all P_1 parental female rats at the time of sacrifice to determine the stage of estrous cycle.

3. Gestation Procedures

Female rats were transferred to polycarbonate pans (on day 20 of gestation for mated females or at the end of the cohabitation period for female rats without evidence of copulation), and were observed at least twice daily for signs of delivery and pups.

4. Lactation Procedures

The day when delivery was complete was designated day 0 postpartum. At each examination period, pups were individually handled and examined for abnormal behavior and appearance; any dead, missing, or abnormal pups were recorded.

a. Day 0 Postpartum

Live and dead pups in each litter were counted as soon as possible after delivery was completed. Live pups in each litter were individually weighed.

b. Day 4 Postpartum

Litters were culled randomly to 8 (4/sex when possible). Extra pups were euthanatized (by decapitation) and discarded without pathological examination. Litters of 8 pups or less were not reduced. Litter counts were determined prior to and after culling, and individual pup weights were determined prior to culling.

c. Days 7 and 14 Postpartum

Pups in each litter were counted by sex and individually weighed.

d. Day 21 Postpartum (Weaning)

Pups in each litter were counted by sex and individually weighed (3 of 4/sex/litter were then sacrificed and grossly examined on postnatal day 21). Randomly selected weanlings (one/sex/litter) were placed in individual cages, monitored for attainment of developmental landmarks, and weighed and food consumption determined weekly until developmental landmark criteria were met.

At each examination period, offspring were individually handled and examined for abnormal behavior and appearance; any dead, missing, or abnormal pups were recorded.

5. Post Weaning and Developmental Landmarks

Developmental landmarks in the F_1 generation male and female rats (one/sex/litter) were monitored on a daily basis until criterion was achieved. Body weight and food consumption were determined until postnatal day 63.

a. Vaginal Patency

Female rats were examined beginning on test day 0 (postpartum day 21).

b. Preputial Separation

Male rats were examined beginning on test day 14 (postpartum day 35).

R. Anatomical Pathology - Rats Designated for Reproductive Evaluations

1. P_1 Adults

All P_1 parental rats were sacrificed by carbon dioxide asphyxiation and exsanguination, and subjected to gross pathological examination, including the females that died and those for which mating did not result in a production of offspring. The sacrifices were on test days 107 through 110 for male rats and on test days 113 through 118 for female rats.

The uteri of all cohabited females were examined for the presence and number of implantation sites.

The testes of each male rat were weighed. Sperm parameters for the first 10 male animals sacrificed by design in each treatment group were evaluated. The right cauda epididymis was weighed. Sperm was collected from the right cauda epididymis and percent motility and morphology was determined. The left epididymis and testis were frozen in liquid nitrogen and stored between –65 and –85° C for sperm and spermatid counts, respectively. The right testis and epididymis from these 10 rats were saved and placed in fixative.

The following table lists tissues that were collected:

Tissues Collected from P_1 Adults

Male	Female	Both Sexes
Testes/Testis[a]	Ovaries	Thyroid Gland[b]
Epididymides/Epididymis[a]	Uterus (with oviducts)	Gross Observations[c]
Prostate	Vagina	Pituitary Gland
Seminal Vesicles		
Coagulating Gland		

a The testes/testis and epididymides/epididymis collected from male rats were placed in Bouin's solution. All other tissues (reproductive and non-reproductive) collected from male and female rats were placed in formalin.
b Thyroid glands were weighed after fixation.
c Gross lesions observed at necropsy for which histopathology was not appropriate or would not be additive were generally not collected.

Reproductive organs from animals with impaired reproductive performance were evaluated microscopically.

2. Offspring

Offspring that were found dead during the lactation period underwent a gross pathological evaluation.

3. F_1 Weanlings

Three F_1 weanlings/sex/litter (randomly selected), litter size permitting, were sacrificed by carbon dioxide asphyxiation and underwent a gross pathological evaluation on postnatal day 21. Gross lesions were preserved.

4. F_1 Adults

All F_1 generation rats were sacrificed by carbon dioxide asphyxiation and exsanguination, and subjected to a gross pathological examination. Selected tissues and gross lesions were preserved.

The following table lists tissues that were collected and/or weighed:

Tissues Collected from F_1 Adults

Male	Female	Both Sexes
Testes	Ovaries	Thyroid Gland
Epididymides	Uterus (with oviducts)	Gross Observations
Prostate	Vagina	Pituitary
Seminal Vesicles		
Coagulating Gland		

Tissues Weighed from F_1 Adults

Male	Female	Both Sexes
Testes	Uterus (with oviducts and cervix)	Thyroid Gland (after fixation)
Epididymides		Liver
Seminal Vesicles (with coagulating glands)		Brain
Prostate		

Processed tissues for histopathological examination were embedded in paraffin, cut at a nominal thickness of 5 micrometers, and stained with hematoxylin and eosin (H&E). Selected gross lesions were evaluated microscopically. Selected gross observations for which a microscopic diagnosis would not be additive (e.g., osteoarthritis, pododermatitis, tail chronic dermatitis, calculus, and deformities of the teeth, toe, tail, or ear pinnae) were saved, but not processed for microscopic evaluation.

Thyroid glands from all F_1 adults were processed for microscopic examination. Thyroid glands from F_1 control and 1000 mg/kg/day males and females were examined microscopically.

S. Statistical Analyses

Except for Bartlett's test ($p < 0.005$), significance was judged at $p < 0.05$. Separate analyses were performed on the data for each gender.

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Food Efficiency Organ Weight	Test for lack of trend[5]	Sequential application[6] of the Jonckheere-Terpstra trend test[7]	Preliminary tests for pairwise comparison
	OR[a]		
	Levene's test for homogeneity[8] and Shapiro-Wilk test[9] for normality[b]	One-way analysis of variance[10] followed with Dunnett's test[11]	Kruskall-Wallis test[12] followed with Dunn's test[13]
Motor Activity[c]	Levene's test for homogeneity[8] and Shapiro-Wilk test[9] for normality[b]	Repeated measures analysis of variance[14] followed by contrasts[15]	Sequential application[6] of the Jonckheere-Terpstra trend test[7]
Grip Strength	Bartlett's test[16] for homogeneity of variances	One-way analysis of variance[10] followed with Dunnett's test[11]	Kruskall-Wallis test[12] followed with Dunn's test[13]
Clinical Pathology[d]	Levene's test for homogeneity[8] and Shapiro-Wilk test[9] for normality[b]	One-way analysis of variance[10] followed with Dunnett's test[7]	Kruskall-Wallis test[12] followed with Dunn's test[13]
Survival Incidence of Clinical Observations Incidence of FOB Descriptive Parameters	None	Cochran-Armitage test for trend[10][e]	
Incidence of Microscopic Lesions	None	None	

a Pairwise comparisons and associated preliminary tests were only conducted if the test for lack of trend was significant.

b If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used.

c Test day and block (10-minute EPOCH) was used as repeated-measure factors.

d When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that bilirubin data.

e If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test[17] with a Bonferroni correction was used.

The following table lists the indices of reproductive function that were calculated for the P_1 and F_1 adults.

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Mean Number of Pups Per Litter Percent Born Alive Vaginal Patency Preputial Separation	Test for lack of trend[5]	Sequential application[6] of the Jonckheere-Terpstra trend test[7]	Preliminary tests for pairwise comparison
	OR[a]		
	Levene's test for homogeneity[8] and Shapiro-Wilk test [9]for normality[b]	One-way analysis of variance[10] followed with Dunnett's test[11]	Kruskall-Wallis test [12]followed with Dunn's test[13]
Body Weight Body Weight Gain Food Consumption Food Efficiency Gestation Length	None	One-way analysis of variance[10] followed with Dunnett's test[11]	
Implantation Site Numbers Implantation Efficiency Precoital Interval Estrous Cycle Length Sperm Parameters	None	Jonckheere-Terpstra trend test[7]	
Incidence of Clinical Observations Mating Index Fertility Index Gestation Index Viability Index Lactation Index	None	Cochran-Armitage test for trend[10]c	
Sex Ratio Mean Pup Weights (Covariates: litter size, sex ratio)	None	Linear contrast of least squares means[18]	Dunn's test[13]

a Pairwise comparisons and associated preliminary tests were only conducted if the test for lack of trend was significant.

b If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used.

c If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test[17] with a Bonferroni correction was used.

For each parameter analyzed with a trend test, the test was applied to the data sequentially. If a significant dose-response was detected, data from the top dose group were excluded and the test repeated until no significant trend was detected.[6] For litter parameters, the proportion of affected fetuses per litter or the litter mean was used as the experimental unit for statistical evaluation.[19] The level of significance selected was $p < 0.05$.

Where the data are tied and the standard large sample version of Jonckheere's test is not applicable, exact p values were calculated using permutation methodology.[20]

RECORDS AND SAMPLE STORAGE

Laboratory-specific or site-specific raw data, such as personnel files and equipment records will be retained by the facility where the work was done.

A sample of the test substance was collected for archive purposes and retained at Haskell Laboratory. Specimens (if applicable), raw data, and the final report will be retained at Haskell Laboratory, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware. Clinical pathology slides and raw data will be retained at Haskell Laboratory, Newark, Delaware. Characterization data will be stored at Regional Analytical Services (RAS), Jackson Laboratories, Deepwater, New Jersey

RESULTS AND DISCUSSION

ANALYTICAL EVALUATIONS

A. Test Substance Stability

To determine the stability of the test substance over the duration of the study, H-24616 (Lot # 436) was analyzed on the first and last day of dosing of the 90-day exposure period. The percent solids of the test substance on test day 0 (predose) and test day 91 were [redacted] respectively. [redacted] between test day 0 and test day 91 analytical samples may be due to analytical variability. However, independent of analytical variability [redacted] would not significantly impact the targeted dose given to the test animals. Therefore, under the conditions of this study, the test substance was considered stable over the course of the study.

B. Test Substance Uniformity Analyses

H-24616 was administered neat to the test animals. No dosing preparations were made. However, uniformity of the test substance was determined in the daily dosing container, the first gallon container used for the study, and across multiple gallon containers.

1. Daily Dosing Container

On test day 0, percent solids prior to dosing (predose) and after dosing (postdose) were [redacted] respectively. This [redacted] over the course of the daily dosing period may be due to evaporation of water from the test substance. This [redacted] would not significantly impact the targeted dose given to the test animals. Therefore, the test substance was considered uniform during the daily dosing period.

2. First Gallon Container

On test day 0 and on test day 17 analytical samples were taken from the first gallon container used for the study. The percent solids of the test substance taken from the first gallon container on test day 0 (predose) and test day 17 were [redacted] respectively. Based on these results, the test substance was considered uniform in the first gallon container used for the study.

3. Across Gallon Containers

Analytical samples were taken from the first and last gallon container used for the 90-day study. The percent solids of the test substance from gallon container #1 (test day 0, predose) and gallon container #6 (test day 91) were [redacted] respectively. Other test substance analyses of percent solids from a concurrently run developmental study with H-24616, showed percent solids from gallon container #3 to be [redacted] The

maximum difference in percent solids from samples from each of the three gallon containers was [redacted] Based on these results, the test substance was considered uniform across containers supplied by the sponsor.

Test Day	Container	% Solids
0 (Predose)	# 1	[redacted]
0 (Postdose)	# 1	
17	# 1	
91	# 6	

a represents average of two analyses [redacted]

C. Analytical Conclusions

Data from the stability and uniformity checks of the test substance, H-24616 [redacted], during the study, suggest that the test substance was stable and uniform throughout the 90-day exposure period.

SUBCHRONIC TOXICITY EVALUATIONS

IN-LIFE TOXICOLOGY

A. Dosage Data
(Tables1-2, Appendix A)

The amount of test substance administered to each animal was calculated using individual body weights, the density of the test substance and the design dosage (50, 250, and 1000 mg/kg/day). Tables 1 and 2 depict the average amount of test substance (mL) administered by gavage for a given test day. The average daily amounts given to male rats over the 90-day exposure period were 0.09, 0.45, and 1.74 mL H-24616 for the 50, 250, and 1000 mg/kg/day dosage groups, respectively. Based on individual body weights, these amounts equated to dose ranges of 46-55, 236-255, and 932-1036 mg/kg/day for the 50, 250, and 1000 mg/kg/day dosage groups, respectively. The average daily amounts given to female rats over the 90-day exposure period were 0.05, 0.28, and 1.08 mL H-24616 for the 50, 250, and 1000 mg/kg/day dosage groups, respectively. Based on individual body weights, these amounts equated to dose ranges of 43-57, 241-258, and 934-1044 mg/kg/day for the 50, 250, and 1000 mg/kg/day dosage groups, respectively.

On test day 28, 1.18 mL (4 times the correct amount of 0.29 mL) of test material was inadvertently administered to one female rat in the 250 mg/kg/day dosage group. On test day 45, 0.5 mL (10 times the correct amount of 0.05 mL) of test material was inadvertently administered to two female rats in the 50 mg/kg/day dosage group. These errors in dosing will not affect the validity of the study.

B. Mean Body Weights and Body Weight Gains
(Tables 3-6, Figures 1-2, Appendices B-C)

Body weight and weight gain in male rats fed 1000 mg/kg/day were statistically lower than control rats after week 4 and throughout the remainder of the 90-day exposure period. At the end of the 90-day exposure period, mean body weights were approximately 20 % (day 90, exposure animals) and 8 % (day 91, recovery animals) lower in male rats given 1000 mg/kg/day compared to control rats. The overall weight gains were approximately 34 and 15 % lower, respectively. This reduction in body weight gain was considered toxicologically adverse.

After a 30-day recovery period, the mean body weights of male rats that received 1000 mg/kg/day H-24616 were similar to controls (± 2%) indicating that the effects on body weight were reversible.

There were no adverse, test substance-related effects on body weight or body weight gain in female rats.

C. Food Consumption and Food Efficiency
(Tables 7-10, Appendix D)

Compared to male control rats overall, food consumption and food efficiency was statistically lower in male rats that received 1000 mg/kg/day H-24616 after week 4 and throughout the remainder of the 90-day exposure period. At the end of the 90 day exposure period, food consumption was approximately 16 % (day 90, exposure animals) and 2 % (day 91, recovery animals) lower in male rats given 1000 mg/kg/day compared to control rats. The overall food efficiency was 21 and 20 % lower, respectively. Based on the parallel reduction in body weight gain in male rats given 1000 mg/kg/day, this reduction in food efficiency was considered toxicologically adverse.

After a 30-day recovery period, food consumption and food efficiency in male rats given 1000 mg/kg/day H-24616 were similar to or greater than that observed in control rats. Therefore, the test substance-related effects on food consumption and food efficiency were reversible.

There were no adverse, test substance-related effects on food consumption or food efficiency in female rats.

D. Clinical Observations, Ophthalmology Evaluations, and Survival
(Tables 11-16, Appendix E-F)

No test substance-related clinical or ophthalmological signs of toxicity were observed in male or female rats. Clinical signs observed were incidental, i.e., hair loss, exo/enophthalmus as the result of orbital sinus bleeding, etc.

One male rat in the 250 mg/kg/day group was sacrificed *in extremis* on test day 51 due to a large, open wound under the neck of the animal. One female rat in the 1000 mg/kg/day dose group was found dead on test day 121. These deaths were considered not to be treatment related but of a spontaneous nature.

E. In-Life Toxicology Conclusions

Based on the decrements in body weight gain and food efficiency in males dosed with 1000 mg/kg/day H-24616 for 90 days, the NOEL for in-life parameters for male rats is 250 mg/kg/day. The NOEL for female rats is 1000 mg/kg/day since no adverse in-life effects were observed in female rats during the 90-day dosing period.

NEUROBEHAVIORAL TOXICOLOGY

A. Functional Observational Battery (FOB)

1. Forelimb Grip Strength
(Table 17, Figures 3-4, Appendix G)

There were no test substance-related effects or statistically significant differences on forelimb grip strength in males or females administered any dosage of H-24616. Males administered 250 or 1000 mg/kg/day had slightly lower (14% and 13% lower than the control value, respectively) forelimb grip strength at week 12, however, a linear dose response-relationship was not present, and the values were within the range of normal variation for this measurement. In addition, there were no effects in females for forelimb grip strength, and no effects on hindlimb grip strength. Therefore, this slight difference was not considered to be test substance-related.

2. Hindlimb Grip Strength
(Table 18, Figures 5-6, Appendix G)

There were no test substance-related effects or statistically significant differences in hindlimb grip strength for either males or females administered any dosage of H-24616.

3. Sensory Function Observation
(Table 19-20, Figures 7-8, Appendix H)

There were no test substance-related changes in neurobehavioral parameters in males or females administered any dosage of H-24616. During the baseline evaluation, females assigned to the 1000 mg/kg/day group had a significantly lower incidence of defecation in the motor activity monitor compared to control. However, since test substance administration had not been initiated, this statistical difference was considered to be spurious. During the week 12 evaluation, females administered 50, 250 or 1000 mg/kg/day had a significantly higher incidence of defecation in the motor activity monitor compared to the control value. However, a dose response-relationship was not present, and the incidences of the females treated with 50, 250, or 1000 mg/kg/day were similar to the control incidence during the baseline evaluation. Therefore, these statistically significant differences were considered to be spurious. There were no statistically significant differences in males for any parameter.

B. Motor Activity (MA)
(Tables 21-24, Appendices I-J)

There were no test substance-related effects on duration of movement or number of movements for males or females for any dosage concentration tested. Males assigned to the 1000 mg/kg/day group had significantly lower total duration of movement during the baseline evaluation and during the week 12 evaluation (20% and 26% lower, respectively, compared to control). In addition, mean total number of movements was significantly lower for 1000 mg/kg/day males compared to control during the week 12 evaluation. However, the values for total duration of

movement and total number of movements for 1000 mg/kg/day males were similar between their baseline, week 12, and recovery evaluations. Since there was no increase or decrease from their baseline performance with respect to either duration of movement or number of movements, the statistically significant differences compared to control were not considered to be test substance related. In addition, total duration of movement for males in the 1000 mg/kg/day group was 20% lower compared to control during the baseline evaluation and 26% lower compared to control during the week 12 evaluation. Therefore the percentage change from control between baseline and week 12 for the 1000 mg/kg/day males was not biologically relevant. Duration of movement and number of movements for males in the 1000 mg/kg/day group was also significantly lower compared to control during the third 10-minute interval for the week 12 evaluation. These statistical differences contributed to the significantly lower total duration of movement and total number of movements; however, as discussed above, they are not considered to be test substance related.

There were no statistically significant differences in either duration of movement or number of movements for females administered any dosage of the test substance.

C. Neurobehavioral Toxicity Conclusions

Under the conditions of the study, the NOEL for neurobehavioral parameters was 1000 mg/kg/day in males and females, the highest concentration tested.

CLINICAL PATHOLOGY

A. Hematology/Coagulation
(Tables 25-28, Appendix K)

There were no toxicologically significant changes in hematology parameters in rats dosed with 50, 250, or 1000 mg/kg/day

All statistically significant changes in hematology parameters were considered unrelated to treatment and/or non-adverse (not toxicologically significant). These changes are detailed below.

- Hemoglobin and hematocrit were transiently decreased in males dosed with 1000 mg/kg/day at test day 44. These decreases were considered to be non-adverse because the changes were minor (96% and 95% of control group mean, respectively) and transient.

- Acanthocytes were minimally increased in some males dosed with 1000 mg/kg/day at test day 44. Although this change was possibly related to treatment, acanthocytes were not considered adverse because the effect was mild, variable, transient, and in affected individual animals was not associated with any other measured changes in red blood cells.

- Absolute reticulocytes were mildly decreased (77% of control group mean) in males dosed with 1000 mg/kg/day at test day 91. For individual animals, there was no correlation between decreased reticulocytes and decreased RBC mass. Decreased reticulocytes were considered to be unrelated to treatment, because mildly decreased reticulocytes in the absence of relevant alterations in red cell mass have no significance. After one month of recovery, reticulocytes of rats previously dosed with 1000 mg/kg/day were similar to control group values.

- Platelets were minimally decreased (82% of control group mean) in males dosed with 1000 mg/kg/day at test day 91 only. This change was considered unrelated to treatment and non-adverse, because the change was very minor (clinically insignificant) and individual counts did not follow a dose relationship. After one month of recovery, platelet counts in rats previously dosed with 1000 mg/kg/day were statistically similar to control group values.

- White blood cells were transiently increased due to increased lymphocytes in male rats dosed with 1000 mg/kg/day at test day 44. This change was considered unrelated to treatment. The increases were minimal for both white blood cell counts and lymphocytes compared to the normal variability of these cell counts. Additionally, although the cell counts were increased, individual values for rats dosed with 1000 mg/kg/day were both above and below the minimum and maximum values for individual control animals. Due to the magnitude and transient nature of the responses, these changes were not considered adverse.

The following statistically significant changes in hematology parameters were considered to be unrelated to treatment because they did not occur in a dose-related manner:

- Minimally decreased red cell mass parameters (red blood cell, hemoglobin, and hematocrit) in females dosed with 50, 250, or 1000 mg/kg/day at test days 44 and 92. The decreases were variable and unrelated to dose (varying from 93-97% of control group means; variable statistical significance). Therefore, these changes were considered to be unrelated to treatment, and therefore non-adverse. After one month of recovery, red cell mass parameters in rats previously dosed with 1000 mg/kg/day were similar to control values.

- Increased MCHC in females dosed with 250 mg/kg/day at test day 44

- Increased monocytes in males (day 44) and decreased eosinophils in females (day 92) dosed with 50 mg/kg/day

At the end of treatment (test days 91/92), there were no alterations in coagulation parameters; therefore, coagulation parameters were not measured at the end of recovery (test days 123/124).

B. Clinical Chemistry
(Tables 29-30, Appendix K)

Rats dosed with 250 (males only) or 1000 mg/kg/day (males and females) had changes in liver enzymes indicating possible adverse effects. Males dosed with 1000 mg/kg/day had increased ALKP (an indicator of cholestasis or enzyme induction) at mid-study, at the end of treatment, and after one month of recovery. Most males and some females previously dosed with 1000 mg/kg/day had increased enzyme activity indicating hepatocellular injury (AST, ALT, SDH) after one month of recovery. Although many of these changes, in isolation, could likely be considered non-adverse, the constellation of changes and the persistence of changes into the recovery period suggest potential adverse effects in light of continued liver weight changes even after recovery. Thus the NOEL for liver effects was conservatively determined to be 50 mg/kg/day in males and 250 mg/kg/day in females.

- ALT activity was minimally increased (137% of control group means) in males dosed with 1000 mg/kg/day at test day 91. The increase was consistent among all animals in the group. ALT activity was also minimally increased in males dosed with 250 mg/kg/day and possibly 50 mg/kg/day.

  After one month of recovery, mean ALT (males and females), and AST and SDH (females only) activities were increased in rats previously dosed with 1000 mg/kg/day. The increased mean activities were primarily due to toxicologically significant increases in the enzymes of 3 animals (Animal No. 641203 - male, Animal No. 641366 - female, and Animal No. 641399 - female). Histologically, 2 of these rats (Animal No. 641203 - male and Animal No. 641366 - female) had minimal to multiple small areas of hepatic necrosis. Excluding the outliers, the remainder of the recovery males still had minimally increased AST and ALT. The remainder of the females actually had decreased AST, ALT, and SDH activities (of no toxicologic significance). The fact that 3 of 20 rats had toxicologically significant increases in hepatocellular injury enzymes after one month of recovery suggests an ongoing process and is potentially adverse.

- ALKP activity was minimally to mildly increased (124-229% of control group mean) in male rats dosed with 1000 mg/kg/day at mid-study and at the end of dosing. The changes were more prominent at test day 91 compared to test day 44. Anatomic pathology changes included increased liver weights and hepatocellular hypertrophy; these changes might have contributed to the ALKP increase. After recovery, ALKP activity was still minimally increased. Excluding rat Animal No. 641203 (see discussion under ALT above), mean ALKP activity after one month of recovery was 126 U/L (158% of control group mean).

  Statistically significant increased ALKP in male rats dosed with 250 mg/kg/day was considered to be of equivocal relationship to treatment because the difference from control was very slight.

The following statistically significant changes were considered unrelated to treatment and/or non-adverse (not toxicologically significant):

- Urea nitrogen was mildly increased in males (250 or 1000 mg/kg/day) and in females (1000 mg/kg/day) at test days 91/92. The magnitude of change was similar in both dose groups. Increased urea nitrogen was probably related to treatment. The cause of increased urea nitrogen was not determined. Generally, increased urea nitrogen indicates decreased glomerular filtration due to dehydration or renal damage. However, individual animals with increased urea nitrogen did not have indicators of dehydration (increased sodium, chloride, or albumin). Additionally, individual rats with increased serum urea nitrogen maintained urinary concentrating ability (as indicated by urine osmolality and specific gravity) indicating normal functioning kidneys. There were no changes in other markers of decreased renal function (phosphorus or creatinine) and no renal histologic lesions were observed in rats dosed with H-24616 at any dose. After one month of recovery, urea nitrogen values in treated animals were similar to controls. For the above reasons, the change in urea nitrogen was not considered to be adverse.

- Cholesterol and triglyceride concentrations were mildly decreased in rats dosed with 250 or 1000 mg/kg/day (variable statistical significance, variable across sexes and time-points).

  Cholesterol was decreased in males and females dosed with 250 or 1000 mg/kg/day (Clinical Pathology Text Table). The changes were generally similar at test days 44 and 91/92, and were more pronounced in males. After one month of recovery (test days123/124), cholesterol concentrations in rats previously dosed with 1000 mg/kg/day were only minimally less than those in control group rats.

  Triglyceride concentrations were decreased in rats dosed with 1000 mg/kg/day. Triglyceride concentrations in males were decreased at all time-points, including recovery, but were only decreased at test day 44 in females.

- The above decreases in cholesterol and triglycerides were considered to be treatment-related because they are part of a dose-response and are consistent within treatment groups. The changes in cholesterol and triglycerides indicate alteration of lipid processing. However, changes of this magnitude in cholesterol and triglycerides are not associated with adverse effects.

Clinical Pathology Text Table:
Cholesterol and Triglyceride changes
(expressed as percent of control group mean)

				Males
TEST	Dose (mg/kg/day)	50	250	1000
CHOL (mg/dL)	Day 44	87%	***73%***	***63%***
	Day 91	87%	***70%***	***64%***
	Day 123	ND	ND	81%
TRIG (mg/dL)	Day 44	119%	76%	***56%***
	Day 91	127%	88%	***54%***
	Day 123	ND	ND	***55%***
				Females
CHOL (mg/dL)	Day 44	86%	***82%***	*74%*
	Day 92	90%	***80%***	*75%*
	Day 124	ND	ND	94%
TRIG (mg/dL)	Day 44	85%	74%	***63%***
	Day 92	93%	102%	82%
	Day 124	ND	ND	90%

Statistical significance indicated by bold italicized font
ND: Not done

- Decreased bilirubin concentrations in females dosed with 1000 mg/kg/day at test days 44, 92, and 124 were considered treatment-related, but were not considered adverse because decreased bilirubin is not an indicator of disease. The persistence of this change during recovery is correlated with persistence of increased liver weights.

- Mildly increased albumin and decreased globulins occurred in males dosed with 250 or 1000 mg/kg/day at all time-points, including recovery (except albumin at test day 44 in rats dosed with 250 mg/kg/day). The changes compared to controls were similar at all time-points. These changes were probably treatment-related, but were not considered adverse because the magnitude of change was small compared to the normal variability of the parameter. Additionally, mild changes in these parameters are not associated with adverse effects.

- Calcium was minimally decreased in males dosed with 1000 mg/kg/day at test day 91. This change is possibly treatment-related, but was considered non-adverse because of the extremely small change in the parameter.

- Chloride was minimally and transiently increased in females dosed with 1000 mg/kg/day at test day 44. This change was possibly treatment-related, but was considered non-adverse because of the transient nature of the change and the extremely small magnitude of the change (103% of control group mean).

The following statistically significant changes in clinical chemistry parameters were considered to be unrelated to treatment because they did not occur in a dose-related manner, or only occurred after one month of recovery:

- Decreased creatinine in males dosed with 50 mg/kg/day at test day 91, and in females dosed with 250 mg/kg/day at day 44

- Decreased total protein in males and females dosed with 250 mg/kg/day at test day 44

- Decreased globulins in females dosed with 250 mg/kg/day at test day 44

- Decreased calcium in females dosed with 250 mg/kg/day at test day 44

- Increased sodium in females previously dosed with 1000 mg/kg/day at test day 124

- Increased inorganic phosphorus in males previously dosed with 1000 mg/kg/day at test day 123

C. Urinalysis
(Tables 32-32, Appendix K)

There were no toxicologically significant changes in urinalysis parameters in rats dosed with 50, 250, or 1000 mg/kg/day. All statistically significant changes were considered unrelated to treatment and/or non-adverse. These changes are detailed below.

- Urine volume was decreased in females dosed with 50 mg/kg/day (test day 92) or 1000 mg/kg/day (test days 44 and 92). These changes were considered to be unrelated to treatment because they did not occur in a dose-related manner. Additionally, decreased urine volume in animals with normal hydration is of no biologic or toxicologic significance.

- Urine fluoride was increased in males and females dosed with 250 or 1000 mg/kg/day at test days 91/92. The change occurred in a dose-related manner, and males were minimally more affected than females. After one month of recovery (test days 123/124), urine fluoride was still mildly increased in males and females previously dosed with 1000 mg/kg/day (not statistically significant in females). Although increased urine fluoride was treatment-related, it was not considered adverse because there were no adverse effects on any parameters relating to renal glomerular or tubular function.

- Decreased urine protein concentration in males dosed with 1000 mg/kg/day at test day 91 is possibly treatment-related, but was not considered adverse because increased urine protein, rather than decreased urine protein, is indicative of toxicity.

D. Clinical Pathology Conclusions

Under the conditions of this study, the NOEL for males was 50 mg/kg/day and the NOEL for females was 250 mg/kg/day. These were based on the findings of elevated liver enzymes at 90 days and/or recovery in males dosed with 250 or 1000 mg/kg/day and females dosed with 1000 mg/kg/day. There were no adverse findings for hematologic, coagulation or urinalysis parameters at any dose.

ANATOMICAL PATHOLOGY

A. Subchronic Toxicity and Recovery

1. Organ Weight Data
(Tables 33-34, Appendix L)

Test substance-related and statistically significant increases, compared to controls, in liver weight parameters occurred in male rats sacrificed on test day 91. Liver weight relative to body weight was increased in 50, 250, and 1000 mg/kg/day males. Absolute and relative to body weight liver weights were increased in one-month recovery and 3-month recovery (satellite) males at 1000 mg/kg/day. At all dose levels, the increased liver weights in males correlated with microscopic hepatocellular hypertrophy (see discussion under Microscopic Findings).

Liver weight relative to body weight was statistically significantly increased in 1000 mg/kg/day females on test day 92. This increased weight was most likely test substance-related, however, there were no correlative microscopic findings present in female livers.

Increased absolute spleen weights (not statistically significant) and statistically significant relative to body weight and relative to brain weight spleen weights were present in 250 and 1000 mg/kg/day females on test day 92. There were no microscopic findings in spleens from 1000 mg/kg/day females, male spleen weights were not affected, and clinical pathology parameters were within normal limits. Therefore, the increased spleen weights were considered to be test substance-related but not toxicologically significant.

There were no other test substance-related organ weight effects. All other statistically significant organ weight changes in subchronic and recovery groups were secondary to decreases in body weight. In 1000 mg/kg/day male rats, these included decreases in absolute organ weight and/or organ weight relative to brain weight for heart, spleen (90-day exposure and one-month recovery groups), thymus and adrenal glands. There were no weight changes in these organs when adjusted to final body weight, and no test substance-related microscopic changes were present. Also in 1000 mg/kg/day male rats, organ weights relative to body weight were increased in brain, testes (90-day exposure and one-month recovery groups), epididymides and kidney (250 and 1000 mg/kg/day exposure groups) without correlative effects in other weight parameters or microscopic changes in these organs. Weights for these latter organs are generally maintained despite body weight loss, and thus this pattern of organ weight change is also consistent with effects occurring secondary to decrements in body weight.

2. Gross Observations
(Tables 35-36, Appendix M)

Gross observations noted were sporadic across groups and were not test substance-related.

3. Microscopic Findings
(Tables 37-42, Appendix M)

Test substance-related microscopic findings were present in nose and thyroid gland from male and female rats and in liver from male rats.

Summary of Test substance-Related Microscopic Findings

	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
Males 90-day Exposure (Day 91)				
Nose:				
Degeneration/necrosis, olfactory epithelium	0/10[a]	8/10 (0.9)[b]	10/10 (1.7)	10/10 (2.1)
Inflammation, subacute/chronic	0/10	0/10	5/10 (0.5)	6/10 (0.6)
Thyroid gland:				
Hypertrophy, follicular	0/10	0/10	5/10 (0.5)	10/10 (1.8)
Alteration, colloid	8/10 (0.8)	8/10 (1.1)	10/10 (1.4)	10/10 (2.8)
Liver:				
Hypertrophy, hepatocellular	0/10	1/10 (0.1)	10/10 (1.8)	10/10 (2.0)
Males One-Month Recovery (Day 122)				
Nose:				
Degeneration/necrosis, olfactory epithelium	0/10	NA	NA	3/10 (0.3)
Thyroid gland:				
Hypertrophy, follicular	0/10	NA	NA	8/10 (1.1)
Alteration, colloid	6/10 (0.7)	NA	NA	10/10 (2.9)
Liver:				
Hypertrophy, hepatocellular	0/10	NA	NA	10/10 (1.0)
Males Three-Month Recovery (Satellite) (Day 182)				
Thyroid gland:				
Alteration, colloid	5/5 (1.2)	4/5 (1.2)	4/4 (2.3)	5/5 (2.6)
Liver:				
Hypertrophy, hepatocellular	0/5	0/5	3/4 (0.8)	4/5 (0.8)

Summary of Test substance-Related Microscopic Findings

	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
Females 90-day Exposure (Day 92)				
Nose:				
Degeneration/necrosis, olfactory epithelium	0/10	2/10 (0.2)	4/10(0.5)	8/10 (1.0)
Thyroid gland:				
Hypertrophy, follicular	0/10	0/10	2/10 (0.2)	7/10 (1.0)
Alteration, colloid	3/10 (0.3)	5/10 (0.5)	6/10 (0.6)	10/10 (1.1)
Females One-Month Recovery (Day 123)				
Thyroid gland:				
Hypertrophy, follicular	0/10	NA	NA	5/10 (0.6)
Alteration, colloid	6/10 (0.6)	NA	NA	7/10 (1.0)
Females Three-Month Recovery (Satellite) (Day 182)				
Thyroid gland:				
Hypertrophy, follicular	0/5	0/5	0/5	1/5 (0.2)
Alteration, colloid	3/5 (0.6)	5/5 (1.0)	4/5 (0.8)	3/5 (0.8)

a Numerator indicates incidence of rats with microscopic lesion.
Denominator indicates number of rats in group.
b Number in parentheses indicates group average severity of lesion.
NA Tissue not available

Test substance-related nose lesions in 50, 250, and 1000 mg/kg/day test day 91 male and female rats consisted of degeneration and or necrosis of olfactory epithelium, which was most prominent along the endoturbinates and nasal septum of levels 3 and 4. Incidence and severity of this lesion increased in a dose dependent manner. Subacute to chronic inflammation was also present in male noses at 250 and 1000 mg/kg/day. In male one-month recovery rats the nasal degeneration/necrosis of olfactory epithelium was still present, however, the incidence and severity were decreased. Test substance-related nose lesions were not present in female one-month recovery rats or in male and female 3-month recovery (satellite) rats.

Follicular hypertrophy was present in thyroid glands of male and female rats in the 250 and 1000 mg/kg/day 90-day exposure and one-month recovery groups, and in 1 female rat in the 1000 mg/kg/day 3-month recovery (satellite) group. Follicular hypertrophy was characterized by tall columnar follicular epithelium with a finely granular or vacuolated cytoplasm. Thyroid hypertrophy was minimal and unassociated with proliferative thyroid lesions. However, this hypertrophy indicates possible disruption of thyroid homeostasis and thus was considered potentially adverse.

Follicles containing altered colloid were found in thyroids from controls as well as treated, one-month recovery, and 3-month recovery (satellite) rats. However, an increase in the number of affected follicles, and thus grade, was treatment related. The diagnosis of "alteration, colloid" was used to diagnose stippled, granular, clumped, and/or diffusely basophilic colloid. A 4 level grading scheme was applied based on an estimate of the percentage of follicles that contained altered colloid. A grade of 1 was applied when 1 follicle to about 25% of the follicles were involved, with grades 2,3, and 4 applied for each 25% increase in follicular involvement. The size, density, or staining intensity of stipples, granules, clumps, or diffuse basophilia within individual follicles did not impact the grading. In this study, there was only a treatment-related increase in grade and not an appreciable increase in the overall incidence of the observation. There was no apparent association between the presence or absence of altered colloid with follicles that were lined by hypertrophic or non-hypertrophic follicular cells.

Altered colloid described as clumped or granular has been reported to occur spontaneously in Sprague-Dawley rats with increasing incidence correlating to increasing age.[21] Because altered colloid occurs spontaneously in healthy Sprague-Dawley rats, and since increases in its grading score did not consistently correlate with other morphologic alterations, altered colloid was interpreted in the present study as not biologically meaningful and not adverse.

There was minimal to mild diffuse hepatocellular hypertrophy in 50, 250, and 1000 mg/kg/day male 90-day exposure rats, the male 1000 mg/kg/day one-month recovery group, and 250 and 1000 mg/kg/day male 3-month recovery (satellite) group. Microscopically, hepatocellular hypertrophy was characterized by an increased amount of finely granular eosinophilic cytoplasm within hepatocytes. There was no histomorphologic evidence of hepatocellular damage. The severity of hepatocellular hypertrophy was less in one-month recovery and three-month recovery (satellite) rats then in 90-day exposure rats, however, complete reversibility of the hypertrophy was not evident by test day 182. The hepatocellular hypertrophy (and the associated increase in liver weights) was considered a test substance-related physiologic response to a xenobiotic and not toxicologically adverse.[22,23,24]

All other microscopic observations noted are known to occur spontaneously in rats of this strain and age and were not present in a dose response fashion in either incidence or severity.

4. Cause of Death
   (Appendix M)

There were no test substance-related deaths. One male 250 mg/kg/day rat (Animal No. 641090) was sacrificed *in extremis* on test day 51 due to a large, open wound under the neck of the animal. One female 1000 mg/kg one-month recovery rat (Animal No. 641356) was found dead on test day 121. Cause of death was a brain tumor (mixed glioma).

B. Anatomical Pathology Conclusions for Subchronic Toxicity Evaluation

Exposure to 50, 250, and 1000 mg/kg/day of the test substance for up to 91/92 days produced degeneration/necrosis of olfactory epithelium in the noses of male and female rats and thyroid gland hypertrophy in 250 and 1000 mg/kg/day males and females. Increased liver weights and microscopic hepatocellular hypertrophy were also present in males in the 50, 250, and 1000 mg/kg/day groups. These liver changes were considered to represent a physiologic response to metabolism of a xenobiotic and thus were not considered to be toxicologically significant. The severity of altered colloid in thyroid glands increased beyond control level as the dose increased, however, it was not consistently correlated with any morphologic alterations and was not considered biologically adverse. Under the conditions of this study, the NOEL for pathology for male and female rats could not be determined based on nose lesions at the lowest dose tested (50 mg/kg/day).

REPRODUCTIVE TOXICOLOGY EVALUATIONS

REPRODUCTIVE FUNCTION

A. P_1 Generation

1. Mean Body Weights and Body Weight Gains
   (Table 43-45, Appendices O-T)

Body weights of P_1 adult male rats administered 1000 mg/kg/day H-24616 were statistically lower (10-11% of control mean) than male control body weights during and after the cohabitation period. Although this finding was test substance-related, it was not considered toxicologically significant since there was no concomitant reduction in body weight gain in P_1 males during that period. There were no test substance-related effects on body weight or body weight gain in P_1 female rats during gestation or lactation.

2. Food Consumption and Food Efficiency During Gestation
   (Table 46, Appendix U)

There were no test substance-related effects on food consumption and food efficiency in P_1 female rats during gestation.

3. Clinical Observations
   (Tables 47, Appendices V-X)

There were no test substance-related clinical signs in P_1 male rats during or after the cohabitation period, or in P_1 female rats during cohabitation, gestation or lactation.

4. Reproductive Indices
   (Tables 48-50, Appendices Y-EE)

There were no test substance-related effects on estrous cycle or sperm parameters, or reproductive indices in the P_1 generation.

B. Offspring Data

1. Litter Size, and Pup Weights, and Survival
   (Table 51-52; Appendix FF-HH)

Mean number of pups per litter, pup weights at birth, and pup weights and survival during the lactation period were not affected by test substance administration. There were no test substance-related clinical signs in pups during lactation.

C. F_1 Generation

1. Mean Body Weights and Body Weight Gains
(Table 54-55, Appendices II-JJ)

There were no test substance-related effects on body weight or body weight gain during the post-weaning period.

2. Food Consumption and Food Efficiency
(Table 56-57, Appendix KK)

There were no test substance-related effects on food consumption or food efficiency during the post-weaning period.

3. Clinical Observations
(Tables 58, Appendices LL)

There were no test substance-related clinical signs during the post-weaning period.

4. Developmental Landmarks
(Tables 59, Appendices LL)

The age at onset of vaginal opening in F_1 female rats was similar across groups. The age at onset of preputial separation in F_1 male rats was similar across groups. However, the mean day of preputial separation for the control group in this study (48.8) was outside the range for other studies at Haskell Laboratory.[a] Thus, some of the sensitivity of the assay may have been lost because the criteria for preputial separation was more rigid in this study compared to previous studies.

D. Reproductive Function Conclusions

For the reproductive toxicity parameters evaluated under the condition of this study, the NOEL was 1000 mg/kg/day, the highest dose tested. The NOEL was based upon the absence of test substance-related effects on reproductive function.

[a] Historical control data for preputial separation was collected between April and August, 1999. For these studies, the mean day of preputial separation ranged from 42.2-43.9 days.

REPRODUCTIVE TOXICOLOGY EVALUATIONS

ANATOMICAL PATHOLOGY

A. Organ Weight Data

Parental P_1 Adults and F_1 Adults
(Tables 60-63; Appendix MM)

There were no test substance-related weight effects on the thyroid gland of P_1 adults. Thyroid gland absolute weight, relative to body weight, and relative to brain weight were decreased in F_1 males and females at 250 and 1000 mg/kg/day dose levels. There were no correlating microscopic changes seen in males or females at 1000 mg/kg/day.

B. Gross Observations

Parental P_1 Adults (Tables 64-65, Appendix NN)
F_1 Pups, Weanlings, and Adults (Tables 66-70, Appendix OO-QQ)

There were no test substance-related gross observations. Observations occurred in low incidences and were randomly distributed across control and treatment groups.

C. Microscopic Observations

Parental P_1 Adults (Tables 71-72, Appendix NN)
F_1 Adults (Tables 73-74, Appendix QQ)

There were no test substance-related microscopic findings. Lesions occurred in low incidences without a relevant dose-response relationship and were considered incidental occurrences of spontaneous lesions in rats of this strain and age.

D. Mortality

Parental P_1 Adults and F_1 Adults
(Appendices NN and QQ)

There were no test substance-related effects on mortality. One P_1 female rat (Animal No. 641392) from the 250 mg/kg/day dose group was found dead. The cause of death was urinary calculi and obstruction. There were no test substance-related effects on mortality in F_1 adults.

E. Anatomical Pathology Conclusions for Reproductive Toxicity

For pathology, the NOEL, based upon the decreased thyroid gland weights in F_1 adults, was 50 mg/kg/day for both male and female rats.

CONCLUSIONS

No test substance-related mortality or clinical signs of toxicity were observed in male or female rats. Statistically significant and toxicologically adverse lower body weights, weight gain, and food efficiency were observed in male rats administered 1000 mg/kg/day compared to controls. Food consumption was also significantly lower in male rats administered 1000 mg/kg/day. After a 30-day recovery period these parameters were similar to controls. No effects on body weight, weight gain, food consumption, or food efficiency were observed in female rats at any dose level.

Potentially adverse findings of elevated liver enzymes (ALKP, AST, ALT and/or SDH) were observed after the 90-day exposure period and/or after one month of recovery in some male rats dosed with 250 and 1000 mg/kg/day and some female rats dosed with 1000 mg/kg/day.

Increased liver weights and/or hepatocellular hypertrophy were observed in male rats of all dose levels and female rats administered 1000 mg/kg/day. These latter changes were considered a test substance-related physiologic response to a xenobiotic and not toxicologically adverse. After three months of recovery, hepatocellular hypertrophy was observed only in male rats administered 250 and 1000 mg/kg/day and not in female rats.

Thyroid hypertrophy was observed after 90 days in male and female rats administered 250 and 1000 mg/kg/day. These changes were considered test substance-related and toxicologically adverse. After three months of recovery, thyroid hypertrophy was not observed in male rats and seen in only one female rat in the 1000 mg/kg/day dose group.

Test substance-related and toxicologically adverse olfactory epithelium degeneration / necrosis was observed in male and female rats in all dose groups. Incidence and severity of the lesion occurred in a dose dependent manner. Incidence and severity of the lesions decreased after one month of recovery. Nose lesions were not observed in male or female rats at any dose level after a 3-month recovery period.

There were no test substance-related effects on reproductive function. However, the F_1 offspring of P_1 adults administered 250 and 1000 mg/kg/day had statistically significant lower thyroid weights compared to control F_1 rats. These effects on F1 thyroid organ weight were considered toxicologically adverse.

Based on the nasal epithelium necrosis observed in male and female rats of all dose levels, a no-observed-effect-level (NOEL)[a] cannot be determined for the 90-day exposure period. Although there were no test-substance related effects observed on reproductive function, a NOEL of 50 mg/kg/day was determined for reproductive evaluations based on decreased thyroid weight observed in both male and female F_1 adults at dosages of 250 mg/kg/day and above.

[a] The NOEL for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Thus, for this study, the NOEL is equivalent to the NOEL as defined by the United States Environmental Protection Agency [25] and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union [26].

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TABLES

TABLES

EXPLANATORY NOTES

Critical Dates

Day 69 Male and female rats designated for reproduction evaluations were co-housed. Body weight and clinical observation data recorded during the cohabitation and post-mating periods are reported in the Reproductive Toxicology section. Dose volumes administered during the cohabitation and post-mating periods are documented in study records.

Day 90
- Last day of test substance administration for male rats designated for the 90-day exposure and one-month and 3-month recovery periods, and female rats designated for one-month and 3-month recovery periods.
- Last day of non-fasted body weight and food consumption data collection for male rats designated for the 90-day exposure period.

Day 91
- Last day of test substance administration for female rats designated for the 90-day exposure period.
- Last day of non-fasted body weight and food consumption data collection for female rats designated for the 90-day exposure period.
- Male rats designated for the 90-day exposure period were sacrificed.
- Recovery period begins for rats designated for the one-month and 3-month recovery periods.

Days 84-91 Rats designated for the 3-month recovery period were temporarily housed in metabolism cages for urine and feces collection. Food consumption data was not collected for these animals during this period.

Day 92 Female rats designated for 90-day exposure period were sacrificed.

Day 119 Last day of food consumption data collection for animals designated for the one-month and 3-month recovery periods.

Days 122 and 123 Male and female rats designated for the one-month recovery period were sacrificed, respectively.

Days 126-182 Body weight and clinical observation data for rats designated for the 3-month recovery period are provided in the appendix.

Day 182 Male and female rats designated for the 3-month recovery period were sacrificed.

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

Summary of Hematology Values

RBC - red blood cell count
HGB - hemoglobin
HCT - hematocrit
MCV - mean corpuscular volume
MCH - mean corpuscular hemoglobin
MCHC - mean corpuscular hemoglobin concentration
RDW - red cell distribution width
ARET - absolute reticulocyte count
WBC - white blood cell count
ANEU - absolute neutrophil (all forms)
ANPR - absolute neutrophil precursor
ALYM - absolute lymphocyte
AMON - absolute monocyte
AEOS - absolute eosinophil
ABAS - absolute basophil
ALUC - absolute large unstained cell
ABLT - absolute blast leukocyte
AMSC - absolute miscellaneous leukocyte
PLT - platelet count

Summary of Coagulation Values

PT - prothrombin time
APTT - activated partial thromboplastin time

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

Summary of Serum and Plasma Chemistry Values

AST - aspartate aminotransferase
ALT - alanine aminotransferase
SDH - sorbitol dehydrogenase
ALKP - alkaline phosphatase
BILI - total bilirubin
BUN - urea nitrogen
CREA - creatinine
CHOL - cholesterol
TRIG - triglycerides
GLUC - glucose
TP - total protein
ALB - albumin
GLOB - globulin
CALC - calcium
IPHS - inorganic phosphorous
NA - sodium
K - potassium
CL - chloride
PFLU - plasma fluoride

Summary of Urinalysis Values

VOL - volume
UOSM - urine osmolality
SG - specific gravity
pH - the logarithm of the reciprocal of the hydrogen ion concentration
URO - urobilinogen
UFLU - urine fluoride
UMTP - urine protein

Notes for Clinical Pathology data:

When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that bilirubin data.

TABLE 1

MEAN DAILY DOSE VOLUMES (mL) FOR MALE RATS

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
DAY 0 - DAY 6	1.04 0.08 (45)	0.05 0.00 (35)	0.26 0.02 (35)	1.03 0.08 (45)
DAY 7 - DAY 13	1.26 0.10 (45)	0.06 0.00 (35)	0.31 0.02 (35)	1.23 0.09 (45)
DAY 14 - DAY 20	1.45 0.12 (45)	0.07 0.01 (35)	0.36 0.02 (35)	1.42 0.12 (45)
DAY 21 - DAY 27	1.62 0.14 (45)	0.08 0.01 (35)	0.40 0.03 (35)	1.57 0.14 (45)
DAY 28 - DAY 34	1.77 0.16 (45)	0.09 0.01 (35)	0.43 0.03 (35)	1.67 0.17 (45)
DAY 35 - DAY 41	1.88 0.16 (45)	0.09 0.01 (35)	0.46 0.03 (35)	1.77 0.19 (45)
DAY 42 - DAY 48	1.97 0.18 (45)	0.10 0.01 (35)	0.47 0.04 (35)	1.84 0.20 (45)
DAY 49 - DAY 55	2.05 0.19 (45)	0.10 0.01 (35)	0.49 0.04 (35)	1.90 0.22 (45)
DAY 56 - DAY 62	2.13 0.21 (45)	0.10 0.01 (35)	0.52 0.04 (34)	1.95 0.22 (45)
DAY 63 - DAY 69	2.18 0.22 (45)	0.11 0.01 (35)	0.53 0.04 (34)	2.00 0.23 (45)
DAY 70 - DAY 76	2.25 0.21 (25)	0.11 0.01 (15)	0.54 0.04 (14)	2.06 0.27 (25)
DAY 77 - DAY 83	2.32 0.22 (25)	0.11 0.01 (15)	0.55 0.04 (14)	2.10 0.27 (25)
DAY 84 - DAY 89	2.36 0.25 (25)	0.11 0.02 (15)	0.55 0.04 (14)	2.05 0.28 (25)
DAY 90	2.37 0.24 (25)	0.11 0.02 (15)	0.55 0.04 (14)	2.05 0.28 (25)

Data summarized as: Mean
Standard Deviation (n)

TABLE 2

MEAN DAILY DOSE VOLUMES (mL) FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
DAY 0 - DAY 6	0.76 0.04 (45)	0.04 0.00 (35)	0.19 0.01 (35)	0.76 0.05 (45)
DAY 7 - DAY 13	0.85 0.05 (45)	0.04 0.00 (35)	0.21 0.02 (35)	0.85 0.06 (45)
DAY 14 - DAY 20	0.92 0.06 (45)	0.04 0.01 (35)	0.23 0.02 (35)	0.93 0.07 (45)
DAY 21 - DAY 27	0.99 0.08 (45)	0.05 0.00 (35)	0.25 0.02 (35)	0.99 0.09 (45)
DAY 28 - DAY 34	1.08 0.09 (45)	0.05 0.01 (35)	0.27 0.03 (35)	1.05 0.09 (45)
DAY 35 - DAY 41	1.10 0.09 (45)	0.05 0.01 (35)	0.28 0.03 (35)	1.08 0.10 (45)
DAY 42 - DAY 48	1.14 0.10 (45)	0.06 0.01 (35)	0.29 0.03 (35)	1.12 0.11 (45)
DAY 49 - DAY 55	1.17 0.10 (45)	0.06 0.01 (35)	0.30 0.03 (35)	1.15 0.12 (45)
DAY 56 - DAY 62	1.20 0.10 (45)	0.06 0.01 (35)	0.30 0.03 (35)	1.17 0.11 (45)
DAY 63 - DAY 69	1.24 0.10 (45)	0.06 0.01 (35)	0.31 0.03 (35)	1.21 0.12 (45)
DAY 70 - DAY 76	1.27 0.11 (25)	0.06 0.00 (15)	0.30 0.03 (15)	1.25 0.14 (25)
DAY 77 - DAY 83	1.28 0.11 (25)	0.06 0.01 (15)	0.32 0.04 (15)	1.26 0.15 (25)
DAY 84 - DAY 90	1.30 0.13 (25)	0.06 0.01 (15)	0.33 0.04 (15)	1.28 0.15 (25)
DAY 91	1.37 0.15 (10)	0.06 0.00 (10)	0.34 0.04 (10)	1.26 0.20 (10)

Data summarized as: Mean
Standard Deviation (n)

TABLE 3

MEAN BODY WEIGHTS (g) OF MALE RATS

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity and Reproduction Evaluations				
DAY 0	255.1 16.9(45)	254.7 15.6(35)	253.0 15.6(35)	252.9 16.9(45)
DAY 7	308.5 22.2(45)	305.6 21.5(35)	305.9 20.3(35)	300.5 20.6(45)
DAY 14	352.8 27.0(45)	353.2 28.2(35)	352.5 24.0(35)	344.8 26.8(45)
DAY 21	394.2 31.9(45)	396.6 34.4(35)	392.2 28.0(35)	382.7 35.2(45)
DAY 28	431.7 37.6(45)	427.1 39.8(35)	421.2 32.5(35)	407.1# 40.9(45)
DAY 35	457.5 40.3(45)	459.9 41.4(35)	446.4 33.2(35)	431.9# 44.4(45)
DAY 42	481.4 44.5(45)	482.3 43.8(35)	464.7 41.5(35)	448.5# 46.3(45)
DAY 49	499.6 46.5(45)	505.0 45.1(35)	483.8 43.8(35)	465.1# 50.9(45)
DAY 56	520.7 51.1(45)	520.6 47.9(35)	508.0 40.4(34)	476.5# 51.8(45)
DAY 63	532.7 53.3(45)	533.0 47.9(35)	520.1 41.5(34)	487.4# 56.5(45)
DAY 69 [a]	551.2 60.1(20)	551.7 39.6(20)	540.4 43.3(20)	498.6# 51.2(20)

TABLE 3 (CONTINUED)

MEAN BODY WEIGHTS (g) OF MALE RATS

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity Evaluation (Continued)				
DAY 70	548.5 52.5(25)	542.0 60.5(15)	524.5 37.3(14)	503.1# 63.4(25)
DAY 77	565.1 55.5(25)	552.9 66.3(15)	536.3 39.9(14)	513.0# 65.9(25)
DAY 84	574.2 60.2(25)	562.8 68.7(15)	538.9 42.3(14)	500.7# 69.0(25)
DAY 90 [b]	592.9 57.3(10)	577.0 66.1(10)	549.6 35.0(10)	474.7# 27.4(10)
Recovery Period for Subchronic Toxicity Evaluation				
DAY 91 [c]	571.6 61.1(15)	559.1 87.7(5)	521.5 54.7(4)	527.6 85.0(15)
DAY 99	573.9 62.5(15)	562.5 84.2(5)	528.6 61.0(4)	542.9 82.6(15)
DAY 106	580.9 64.2(15)	570.1 89.6(5)	545.4 61.3(4)	560.3 79.2(15)
DAY 112	592.4 71.8(15)	581.1 87.3(5)	561.7 67.2(4)	572.1 85.0(15)
DAY 119	601.5 73.4(15)	588.9 91.6(5)	573.8 64.8(4)	588.2 85.9(15)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).
Statistically significant difference at $p < 0.05$.

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 69; subsequent data are reported as part of the reproduction evaluation.
b. Rats designated for the 90-day sacrifice (10 rats/group) only; rats were sacrificed on test day 91.
c. Rats designated for recovery evaluation. Recovery period began on test day 91.

TABLE 4

MEAN BODY WEIGHTS (g) OF FEMALE RATS

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity and Reproduction Evaluations				
DAY 0	187.3 10.1(45)	184.7 11.8(35)	187.2 13.6(35)	186.7 11.6(45)
DAY 7	208.4 12.0(45)	205.5 14.8(35)	208.7 16.9(35)	208.5 14.0(45)
DAY 14	227.5 15.5(45)	227.8 15.7(35)	229.5 19.1(35)	227.0 16.4(45)
DAY 21	244.0 18.0(45)	244.5 18.7(35)	249.8 24.4(35)	241.6 20.6(45)
DAY 28	265.2 20.2(45)	265.2 22.5(35)	265.1 25.1(35)	258.8 21.7(45)
DAY 35	272.3 21.8(45)	271.7 21.6(35)	274.2 25.8(35)	266.3 22.5(45)
DAY 42	281.9 23.5(45)	285.0 23.0(35)	283.4 26.3(35)	277.4 26.0(45)
DAY 49	289.2 22.8(45)	289.4 24.3(35)	290.5 27.5(35)	284.2 26.4(45)
DAY 56	296.4 23.6(45)	297.8 24.7(35)	298.7 28.6(35)	288.9 26.9(45)
DAY 63	300.1 24.6(45)	301.3 26.5(35)	303.0 27.8(35)	294.2 29.1(45)
DAY 69 [a]	304.2 22.9(20)	312.9 29.4(20)	306.1 27.2(20)	296.7 28.4(20)

TABLE 4 (CONTINUED)

MEAN BODY WEIGHTS (g) OF FEMALE RATS

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity Evaluation (Continued)				
DAY 70	307.7 27.4(25)	299.5 19.2(15)	309.0 32.9(15)	303.6 33.5(25)
DAY 77	311.0 27.1(25)	304.6 18.9(15)	312.2 37.4(15)	309.3 36.9(25)
DAY 84	316.6 30.1(25)	306.2 18.0(15)	320.0 40.5(15)	312.7 36.5(25)
DAY 91 [b]	330.8 37.2(10)	309.3 17.5(10)	328.2 41.0(10)	308.0 45.7(10)
Recovery Period for Subchronic Toxicity Evaluation				
DAY 91 [c]	308.6 24.9(15)	301.7 15.9(5)	304.8 40.0(5)	318.6 31.2(15)
DAY 99	317.5 22.1(15)	307.7 16.7(5)	313.6 42.9(5)	328.1 31.9(15)
DAY 106	322.2 24.6(15)	313.0 15.7(5)	316.6 44.9(5)	337.8 33.5(15)
DAY 112	326.2 23.4(15)	316.3 13.2(5)	323.4 44.1(5)	337.7 34.5(15)
DAY 119	327.5 26.1(15)	320.2 10.1(5)	331.8 45.6(5)	341.7 34.3(15)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).
There were no statistically significant differences at $p < 0.05$.

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 69; subsequent data are reported as part of the reproduction evaluation.
b. Rats designated for the 90-day sacrifice (10 rats/group) only; rats were sacrificed on test day 92.
c. Rats designated for recovery evaluation. Recovery period began on test day 91.

TABLE 5

MEAN BODY WEIGHT GAINS (g) OF MALE RATS

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity and Reproduction Evaluations				
DAY 0 - DAY 7	53.4 8.7(45)	50.9 10.0(35)	52.9 9.9(35)	47.5# 8.7(45)
DAY 7 - DAY 14	44.3 8.3(45)	47.7 9.5(35)	46.5 6.6(35)	44.3 9.4(45)
DAY 14 - DAY 21	41.4 8.9(45)	43.3 9.1(35)	39.7 10.4(35)	37.9 11.6(45)
DAY 21 - DAY 28	37.5 9.0(45)	30.5# 10.4(35)	29.1# 12.3(35)	24.4# 11.7(45)
DAY 28 - DAY 35	25.8 8.1(45)	32.8 12.6(35)	25.2 6.9(35)	24.9 9.1(45)
DAY 35 - DAY 42	23.9 8.8(45)	22.4 7.9(35)	18.3 19.9(35)	16.6# 8.1(45)
DAY 42 - DAY 49	18.2 7.6(45)	22.7 10.5(35)	19.1 13.4(35)	16.6 11.6(45)
DAY 49 - DAY 56	21.1 8.9(45)	15.6 9.1(35)	20.5 9.6(34)	11.4# 8.5(45)
DAY 56 - DAY 63	12.0 11.5(45)	12.4 9.7(35)	12.0 8.7(34)	10.8 8.4(45)
DAY 63 - DAY 69 [a]	12.8 4.9(20)	11.3 6.8(20)	10.7 8.4(20)	9.8 9.8(20)
DAY 0 - DAY 69 [a]	294.6 46.4(20)	295.8 37.7(20)	285.0 36.2(20)	246.8# 41.7(20)

TABLE 5 (CONTINUED)

MEAN BODY WEIGHT GAINS (g) OF MALE RATS

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity Evaluation (Continued)				
DAY 63 - DAY 70	20.4 14.1(25)	18.9 6.1(15)	18.0 6.9(14)	16.9 8.1(25)
DAY 70 - DAY 77	16.6 6.2(25)	10.9 8.5(15)	11.8 6.7(14)	9.9# 10.8(25)
DAY 77 - DAY 84	9.1 9.5(25)	9.9 7.5(15)	2.7# 9.4(14)	-12.3# 17.0(25)
DAY 84 - DAY 90 [b]	6.9 6.1(10)	10.0 4.0(10)	5.1 6.7(10)	2.5 7.8(10)
DAY 84 - DAY 91 [c]	5.3 15.8(15)	4.4 8.3(5)	-3.6 8.1(4)	7.9 10.6(15)
DAY 0 - DAY 90 [b]	338.2 52.3(10)	322.5 62.8(10)	297.5 30.5(10)	224.2# 28.7(10)
DAY 0 - DAY 91 [c]	318.2 51.6(15)	308.8 76.6(5)	273.1 36.8(4)	271.6# 73.7(15)
Recovery Period for Subchronic Toxicity Evaluation				
DAY 91 - DAY 99	2.2 8.0(15)	3.4 8.6(5)	7.1 13.4(4)	15.2# 14.2(15)
DAY 99 - DAY 106	7.0 7.7(15)	7.6 7.0(5)	16.7# 2.6(4)	17.5# 12.3(15)
DAY 106 - DAY 112	11.5 11.6(15)	11.0 5.0(5)	16.3 6.4(4)	11.8 12.0(15)
DAY 112 - DAY 119	9.1 6.3(15)	7.7 7.8(5)	12.2 4.3(4)	16.1# 5.1(15)
DAY 91 - DAY 119 [c]	29.9 20.4(15)	29.8 10.8(5)	52.3 19.9(4)	60.6# 22.5(15)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).
Statistically significant difference at $p < 0.05$.

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 69; subsequent data are reported as part of the reproduction evaluation.
b. Rats designated for the 90-day sacrifice (10 rats/group) only; rats were sacrificed on test day 91.
c. Rats designated for recovery evaluation. Recovery period began on test day 91.

TABLE 6

MEAN BODY WEIGHT GAINS (g) OF FEMALE RATS

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity and Reproduction Evaluations				
DAY 0 - DAY 7	21.2 6.5(45)	20.9 9.4(35)	21.5 8.0(35)	21.7 6.6(45)
DAY 7 - DAY 14	19.1 9.3(45)	22.3 7.6(35)	20.9 8.3(35)	18.6 6.3(45)
DAY 14 - DAY 21	16.5 7.3(45)	16.7 6.7(35)	20.2 9.8(35)	14.6 7.9(45)
DAY 21 - DAY 28	21.3 9.2(45)	20.6 8.7(35)	15.3# 8.9(35)	17.2# 8.2(45)
DAY 28 - DAY 35	7.0 10.8(45)	6.5 7.8(35)	9.1 7.1(35)	7.4 7.7(45)
DAY 35 - DAY 42	9.6 8.5(45)	13.3 7.3(35)	9.2 6.7(35)	11.2 9.4(45)
DAY 42 - DAY 49	7.3 10.5(45)	4.3 6.2(35)	7.1 7.7(35)	6.8 8.1(45)
DAY 49 - DAY 56	7.2 9.0(45)	8.4 8.8(35)	8.2 6.5(35)	4.6 7.9(45)
DAY 56 - DAY 63	3.7 8.0(45)	3.5 8.0(35)	4.3 6.1(35)	5.3 7.0(45)
DAY 63 - DAY 69 [a]	4.0 6.7(20)	4.4 5.7(20)	2.3 5.3(20)	5.6 6.8(20)
DAY 0 - DAY 69 [a]	116.6 20.6(20)	125.7 23.5(20)	117.8 22.3(20)	109.8 24.1(20)

TABLE 6 (CONTINUED)

MEAN BODY WEIGHT GAINS (g) OF FEMALE RATS

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity Evaluation (Continued)				
DAY 63 - DAY 70	7.5 5.3(25)	7.7 8.1(15)	7.0 9.9(15)	6.9 7.2(25)
DAY 70 - DAY 77	3.4 7.4(25)	5.1 10.2(15)	3.3 9.5(15)	5.7 8.3(25)
DAY 77 - DAY 84	5.6 6.6(25)	1.6 7.7(15)	7.7 10.2(15)	3.4 8.2(25)
DAY 84 - DAY 91 [b]	0.2 9.7(10)	-0.8 6.9(10)	1.6 3.8(10)	0.7 9.4(10)
DAY 84 - DAY 91 [c]	1.3 5.1(15)	3.3 10.2(5)	-1.9 8.4(5)	2.3 6.7(15)
DAY 0 - DAY 91	130.4 28.5(25)	125.5 16.2(15)	134.7 28.4(15)	127.7 28.8(25)
Recovery Period for Subchronic Toxicity Evaluation				
DAY 91 - DAY 99	8.9 7.2(15)	6.0 11.7(5)	8.8 7.5(5)	9.5 4.2(15)
DAY 99 - DAY 106	4.7 7.6(15)	5.3 5.5(5)	3.0 3.4(5)	9.7 6.8(15)
DAY 106 - DAY 112	4.0 5.9(15)	3.4 7.3(5)	6.8 5.5(5)	-0.0 21.2(15)
DAY 112 - DAY 119	1.3 11.9(15)	3.9 5.8(5)	8.4 5.9(5)	4.0 6.9(15)
DAY 91 - DAY 119 [c]	18.9 11.7(15)	18.5 18.5(5)	27.0 9.2(5)	23.2 17.0(15)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).
Statistically significant difference at $p < 0.05$.

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 69; subsequent data are reported as part of the reproduction evaluation.
b. Rats designated for the 90-day sacrifice (10 rats/group) only; rats were sacrificed on test day 92.
c. Rats designated for recovery evaluation. Recovery period began on test day 91.

TABLE 7

MEAN DAILY FOOD CONSUMPTION (g) BY MALE RATS

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity and Reproduction Evaluations				
DAY 0 - DAY 7	28.7 3.0(44)	28.7 2.3(35)	27.6 2.5(35)	27.9 2.9(45)
DAY 7 - DAY 14	30.4 3.1(45)	30.7 3.2(35)	30.5 2.7(35)	29.8 3.2(45)
DAY 14 - DAY 21	32.1 3.3(45)	32.4 3.3(35)	31.6 2.6(35)	31.2 4.1(45)
DAY 21 - DAY 28	32.6 3.5(45)	32.6 3.5(35)	30.5# 2.6(35)	29.2# 4.0(45)
DAY 28 - DAY 35	31.2 3.4(45)	31.5 3.4(35)	30.2 2.3(35)	29.5# 3.9(45)
DAY 35 - DAY 42	32.1 3.5(45)	31.4 3.3(35)	29.1# 4.6(35)	28.7# 3.5(45)
DAY 42 - DAY 49	31.3 3.4(45)	31.1 3.3(35)	29.3# 3.5(35)	28.8# 3.9(45)
DAY 49 - DAY 56	32.8 3.7(45)	31.6 2.9(35)	31.5 3.1(34)	29.5# 3.5(45)
DAY 56 - DAY 63	32.4 4.3(45)	31.3 3.1(35)	31.2 2.9(34)	29.8# 3.7(45)
DAY 63 - DAY 69 [a]	33.2 4.5(20)	33.4 3.0(20)	31.8 2.7(20)	31.1 4.2(20)
DAY 0 - DAY 69 [a]	32.03 3.651(19)	31.75 2.444(20)	30.80 2.391(20)	29.62# 2.788(20)

TABLE 7 (CONTINUED)

MEAN DAILY FOOD CONSUMPTION (g) BY MALE RATS

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity Evaluation (Continued)				
DAY 63 - DAY 70	32.5 3.6(25)	32.0 2.7(15)	30.1 2.2(14)	30.5 4.1(25)
DAY 70 - DAY 77	32.3 3.5(25)	32.0 3.4(15)	30.2 2.2(14)	30.1# 4.2(25)
DAY 77 - DAY 84 [b]	31.7 3.4(20)	32.2 2.8(10)	29.1# 2.6(10)	27.6# 3.7(20)
DAY 84 - DAY 90 [b,c]	32.4 4.2(10)	31.7 3.1(10)	28.3# 2.3(10)	25.5# 2.1(10)
DAY 84 - DAY 91 [b,d]	30.9 2.3(10)	-	-	26.4# 6.2(10)
DAY 0 - DAY 90 [b,c]	32.43 3.296(10)	31.35 2.627(10)	29.99 1.674(10)	27.34# 0.890(10)
DAY 0 - DAY 91 [b,d]	31.28 1.517(10)	-	-	30.70 3.117(10)
Recovery Period for Subchronic Toxicity Evaluation				
DAY 91 - DAY 99	29.2 2.6(15)	29.7 3.1(5)	27.6 3.6(4)	31.3 4.7(15)
DAY 99 - DAY 106	30.3 3.6(15)	30.3 4.2(5)	29.5 4.0(4)	31.9 4.5(15)
DAY 106 - DAY 112	29.6 4.0(15)	29.0 4.1(5)	30.9 3.4(4)	31.4 4.2(15)
DAY 112 - DAY 119	31.2 3.8(15)	30.4 3.7(5)	32.3 2.8(4)	32.5 3.8(15)
DAY 91 - DAY 119 [d]	30.06 3.313(15)	29.88 3.704(5)	29.94 3.422(4)	31.79 4.120(15)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).
Statistically significant difference at $p < 0.05$.

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 69; food consumption data were not collected during the cohabitation and postmating periods.
b. Food consumption data for rats designated for the 3-month recovery (5 rats/group) were not determined for test days 84 through 91.
c. Rats designated for the 90-day sacrifice (10 rats/group) only; rats were sacrificed on test day 91.
d. Rats designated for recovery only. Recovery period began on test day 91.

TABLE 8

MEAN DAILY FOOD CONSUMPTION (g) BY FEMALE RATS

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity and Reproduction Evaluations				
DAY 0 - DAY 7	20.4 2.5(45)	19.9 1.7(35)	20.3 2.0(35)	20.1 1.8(45)
DAY 7 - DAY 14	22.5 5.7(45)	21.8 2.0(35)	21.6 2.5(35)	21.5 2.1(45)
DAY 14 - DAY 21	22.4 2.5(45)	21.9 1.9(35)	22.3 2.4(35)	21.6 2.6(45)
DAY 21 - DAY 28	23.3 2.5(45)	23.9 2.4(35)	23.6 2.6(33)	22.7 2.7(44)
DAY 28 - DAY 35	22.3 2.4(45)	22.5 2.0(35)	22.1 2.1(35)	21.1# 2.8(45)
DAY 35 - DAY 42	23.1 2.5(45)	23.7 2.0(34)	23.3 2.2(35)	22.6 2.4(45)
DAY 42 - DAY 49	21.2 2.4(45)	22.8 2.1(35)	21.5 2.6(35)	21.9 2.4(45)
DAY 49 - DAY 56	21.9 2.3(45)	21.8 3.0(35)	22.3 2.4(35)	21.2 2.7(45)
DAY 56 - DAY 63	22.3 2.4(45)	23.1 2.6(35)	22.0 2.3(35)	22.0# 5.3(45)
DAY 63 - DAY 69 [a]	22.65 1.717(20)	23.50 2.278(20)	22.16 2.109(20)	21.66 2.450(20)
DAY 0 - DAY 69 [a]	21.79 1.299(20)	22.93 1.802(20)	22.53 1.682(18)	21.46 1.742(20)

TABLE 8 (CONTINUED)

MEAN DAILY FOOD CONSUMPTION (g) BY FEMALE RATS

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity Evaluation (Continued)				
DAY 63 - DAY 70	22.8 2.3(25)	22.3 1.8(15)	22.6 2.6(15)	22.5 2.6(25)
DAY 70 - DAY 77	22.1 2.4(25)	22.8 1.9(15)	22.8 2.8(15)	22.8 3.2(25)
DAY 77 - DAY 84 [b,c]	23.0 2.1(20)	22.3 1.4(10)	22.1 3.2(10)	22.6 3.4(20)
DAY 84 - DAY 91 [b,c]	22.4 3.4(10)	21.2 1.2(10)	21.5 3.0(10)	22.4 2.5(10)
DAY 84 - DAY 91 [b,d]	21.6 1.6(10)	- -	- -	21.6 2.3(10)
DAY 0 - DAY 91 [b,c]	22.77 2.404(20)	21.83 0.884(9)	21.94 2.386(10)	21.62 2.146(19)
Recovery Period for Subchronic Toxicity Evaluation				
DAY 91 - DAY 99	23.2 2.2(15)	22.2 2.6(5)	21.9 3.3(5)	24.7 3.3(15)
DAY 99 - DAY 106	22.9 2.0(15)	20.8 3.0(5)	23.1 1.6(5)	24.1 3.2(15)
DAY 106 - DAY 112	22.6 1.9(15)	21.5 3.7(5)	23.8 1.6(5)	22.5 4.9(15)
DAY 112 - DAY 119	22.3 2.6(15)	21.6 2.1(5)	24.4 2.0(5)	23.3 3.8(15)
DAY 91 - DAY 119 [d]	22.80 1.571(15)	21.55 2.364(5)	23.25 1.735(5)	23.70 2.988(15)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).
Statistically significant difference at $p < 0.05$.

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 69; data were not collected during the cohabitation and postmating periods.
b. Food consumption data for rats designated for the 3-month recovery (5 rats/group) were not determined for test days 84 through 91.
c. Rats designated for the 90-day sacrifice (10 rats/group) only; rats were sacrificed on test day 92.
d. Rats designated for recovery only. Recovery period began on test day 91.

TABLE 9

MEAN DAILY FOOD EFFICIENCY OF MALE RATS
(g body weight gain/g food consumed)

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity and Reproduction Evaluations				
DAY 0 - DAY 7	0.265 0.029(44)	0.252 0.038(35)	0.272 0.036(35)	0.243# 0.034(45)
DAY 7 - DAY 14	0.207 0.028(45)	0.221 0.031(35)	0.217 0.023(35)	0.211 0.029(45)
DAY 14 - DAY 21	0.184 0.029(45)	0.190 0.028(35)	0.179 0.041(35)	0.171 0.039(45)
DAY 21 - DAY 28	0.163 0.034(45)	0.133# 0.038(35)	0.133# 0.053(35)	0.116# 0.048(45)
DAY 28 - DAY 35	0.118 0.034(45)	0.148 0.061(35)	0.119 0.033(35)	0.120 0.040(45)
DAY 35 - DAY 42	0.105 0.032(45)	0.102 0.035(35)	0.054 0.276(35)	0.082# 0.036(45)
DAY 42 - DAY 49	0.082 0.032(45)	0.104 0.047(35)	0.091 0.064(35)	0.079 0.050(45)
DAY 49 - DAY 56	0.090 0.033(45)	0.070 0.040(35)	0.092 0.039(34)	0.054# 0.039(45)
DAY 56 - DAY 63	0.052 0.048(45)	0.055 0.042(35)	0.054 0.037(34)	0.049 0.038(45)
DAY 63 - DAY 69 [a]	0.064 0.025(20)	0.056 0.032(20)	0.056 0.041(20)	0.049 0.048(20)
DAY 0 - DAY 69 [a]	0.134 0.009(19)	0.135 0.013(20)	0.134 0.013(20)	0.120# 0.012(20)

TABLE 9 (CONTINUED)

MEAN DAILY FOOD EFFICIENCY OF MALE RATS
(g body weight gain/g food consumed)

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity Evaluation (Continued)				
DAY 63 - DAY 70	0.087 0.047(25)	0.084 0.025(15)	0.085 0.031(14)	0.079 0.034(25)
DAY 70 - DAY 77	0.073 0.025(25)	0.047 0.036(15)	0.055 0.030(14)	0.044# 0.047(25)
DAY 77 - DAY 84 [b]	0.046 0.040(20)	0.043 0.034(10)	0.011# 0.032(10)	-0.077# 0.106(20)
DAY 84 - DAY 90 [b,c]	0.035 0.032(10)	0.052 0.019(10)	0.029 0.040(10)	0.018 0.049(10)
DAY 84 - DAY 91 [b,d]	0.043 0.039(10)	-	-	0.044 0.063(10)
DAY 0 - DAY 90 [b,c]	0.115 0.009(10)	0.114 0.016(10)	0.110 0.006(10)	0.091# 0.010(10)
DAY 0 - DAY 91 [b,d]	0.119 0.008(10)	-	-	0.095# 0.015(10)
One-Month Recovery Period for Subchronic Toxicity Evaluation				
DAY 91 - DAY 99	0.008 0.032(15)	0.015 0.037(5)	0.028 0.051(4)	0.058# 0.051(15)
DAY 99 - DAY 106	0.032 0.037(15)	0.033 0.032(5)	0.082# 0.016(4)	0.080# 0.066(15)
DAY 106 - DAY 112	0.060 0.050(15)	0.066 0.036(5)	0.086 0.024(4)	0.057 0.066(15)
DAY 112 - DAY 119	0.041 0.028(15)	0.034 0.035(5)	0.054 0.020(4)	0.072# 0.023(15)
DAY 91 - DAY 119 [d]	0.034 0.021(15)	0.035 0.011(5)	0.061 0.017(4)	0.068# 0.021(15)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).
Statistically significant difference at $p < 0.05$.

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 69; data were not collected during the cohabitation and postmating periods.
b. Food consumption data for rats designated for the 3-month recovery (5 rats/group) were not determined for test days 84 through 91.
c. Rats designated for the 90-day sacrifice (10 rats/group) only; rats were sacrificed on test day 91.
d. Rats designated for recovery only. Recovery period began on test day 91.

TABLE 10

MEAN DAILY FOOD EFFICIENCY OF FEMALE RATS
(g body weight gain/g food consumed)

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity and Reproduction Evaluations				
DAY 0 - DAY 7	0.148 0.042(45)	0.147 0.059(35)	0.149 0.048(35)	0.153 0.041(45)
DAY 7 - DAY 14	0.121 0.052(45)	0.145 0.046(35)	0.137 0.054(35)	0.122 0.036(45)
DAY 14 - DAY 21	0.103 0.042(45)	0.108 0.040(35)	0.127 0.056(35)	0.095 0.048(45)
DAY 21 - DAY 28	0.132 0.058(45)	0.122 0.047(35)	0.091# 0.052(33)	0.106# 0.050(44)
DAY 28 - DAY 35	0.042 0.065(45)	0.041 0.048(35)	0.058 0.044(35)	0.046 0.060(45)
DAY 35 - DAY 42	0.058 0.050(45)	0.080 0.040(34)	0.055 0.041(35)	0.068 0.057(45)
DAY 42 - DAY 49	0.047 0.070(45)	0.026 0.038(35)	0.046 0.049(35)	0.043 0.052(45)
DAY 49 - DAY 56	0.045 0.058(45)	0.055 0.054(35)	0.052 0.040(35)	0.029 0.051(45)
DAY 56 - DAY 63	0.023 0.052(45)	0.019 0.050(35)	0.028 0.041(35)	0.034 0.043(45)
DAY 63 - DAY 69 [a]	0.028 0.049(20)	0.032 0.038(20)	0.015 0.038(20)	0.041 0.052(20)
DAY 0 - DAY 69 [a]	0.077 0.012(20)	0.079 0.009(20)	0.077 0.010(18)	0.074 0.012(20)

TABLE 10 (CONTINUED)

MEAN DAILY FOOD EFFICIENCY OF FEMALE RATS
(g body weight gain/g food consumed)

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
Dosing Period for Subchronic Toxicity Evaluation (Continued)				
DAY 63 - DAY 70	0.048 0.035(25)	0.048 0.053(15)	0.042 0.062(15)	0.042 0.043(25)
DAY 70 - DAY 77	0.020 0.048(25)	0.030 0.062(15)	0.018 0.060(15)	0.033 0.054(25)
DAY 77 - DAY 84 [b]	0.041 0.038(20)	0.006 0.038(10)	0.046 0.056(10)	0.025 0.043(20)
DAY 84 - DAY 91 [b,c]	-0.001 0.051(20)	-0.006 0.047(10)	0.009 0.025(10)	0.009 0.050(20)
DAY 84 - DAY 91 [b,d]	-0.004 0.067(10)	-0.006 0.047(10)	0.009 0.025(10)	0.005 0.060(10)
DAY 0 - DAY 91 [b,c]	0.064 0.009(20)	0.062 0.004(9)	0.069 0.007(10)	0.062 0.011(19)
One-Month Recovery Period for Subchronic Toxicity Evaluation				
DAY 91 - DAY 99	0.046 0.037(15)	0.029 0.071(5)	0.048 0.038(5)	0.048 0.020(15)
DAY 99 - DAY 106	0.028 0.047(15)	0.035 0.035(5)	0.017 0.021(5)	0.056 0.037(15)
DAY 106 - DAY 112	0.028 0.045(15)	0.022 0.053(5)	0.047 0.041(5)	-0.055 0.351(15)
DAY 112 - DAY 119	-0.000 0.093(15)	0.027 0.037(5)	0.048 0.033(5)	0.026 0.050(15)
DAY 91 - DAY 119 [d]	0.029 0.018(15)	0.029 0.031(5)	0.041 0.013(5)	0.034 0.023(15)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).
Statistically significant difference at $p < 0.05$.

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 69; data were not collected during the cohabitation and postmating periods.
b. Food consumption data for rats designated for the 3-month recovery (5 rats/group) were not determined for test days 84 through 91.
c. Rats designated for the 90-day sacrifice (10 rats/group) only; rats were sacrificed on test day 92.
d. Rats designated for recovery only. Recovery period began on test day 91.

TABLE 11

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group	I	III	V	VII
Dose	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
Number Animals at Study Start	45	35	35	45
Eye Observations				
Corneal Opacity				
Incidence	2	0	0	0
Mean onset (Days)	103	-	-	-
Exophthalmus				
Incidence	1	0	0	0
Mean onset (Days)	91	-	-	-
Enophthalmus				
Incidence	1	0	0	0
Mean onset (Days)	106	-	-	-
General Teeth Observations				
Absent				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	85
Breathing Observations				
Noise				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	84

TABLE 11 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group	I	III	V	VII
Dose	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
Number Animals at Study Start	45	35	35	45
Discharge				
Eyes				
Incidence	2	0	1	1
Mean onset (Days)	77	-	63	112
Nose				
Incidence	1		0	2
Mean onset (Days)	77	-	-	81
Hair Loss				
Incidence	5	4	4	8
Mean onset (Days)	44	35	26	34
Wound				
Deep (Neck, Tail)				
Incidence	1	0	1	0
Mean onset (Days)	69	-	51	-
Superficial (Nose, Neck, Lumbar, Forepaw)				
Incidence	3	0	1	1
Mean onset (Days)	47	-	21	21

TABLE 11 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group	I	III	V	VII
Dose	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
Number Animals at Study Start	45	35	35	45
Hyperreactive				
Incidence	1	0	0	1
Mean onset (Days)	49	-	-	99
Vocalization				
Incidence	1	0	0	1
Mean onset (Days)	14	-	-	14

Incidence - The number of animals for which an observation was recorded.
Mean onset (Days) - The mean of the first test day an observation was recorded for that group.

Statistical Methods: Trend test (Cochran-Armitage).
There were no statistically significant differences at $p < 0.05$.

TABLE 12

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II	IV	VI	VIII
Dose	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
Number Animals at Study Start	45	35	35	45
Mass Side				
Right				
Mass #1				
Not Ulcerated				
Incidence	1	0	0	0
Mean onset (Days)	63	-	-	-
Eye Observations				
Corneal Opacity				
Incidence	0	1	0	0
Mean onset (Days)	-	106	-	-
Exophthalmus				
Incidence	0	1	1	0
Mean onset (Days)	-	99	106	-
Enophthalmus				
Incidence	0	1	0	0
Mean onset (Days)	-	119	-	-

TABLE 12 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II	IV	VI	VIII
Dose	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
Number Animals at Study Start	45	35	35	45
Abnormal Gait				
Hindlimb				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	119
Breathing Observations				
Noise				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	77
Discharge				
Eyes				
Incidence	1	4	1	1
Mean onset (Days)	77	90	14	112
Nose				
Incidence	0	1	0	1
Mean onset (Days)	-	84	-	112

TABLE 12 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II	IV	VI	VIII
Dose	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
Number Animals at Study Start	45	35	35	45
Hair Loss				
Incidence	8	7	6	11
Mean onset (Days)	51	41	39	40
Wound				
Superficial (Neck, Side, Forelimb)				
Incidence	1	0	1	2
Mean onset (Days)	99	-	49	35

Incidence - The number of animals for which an observation was recorded.
Mean onset (Days) - The mean of the first test day an observation was recorded for that group.

Statistical Methods: Trend test (Cochran-Armitage).
There were no statistically significant differences at $p < 0.05$.

TABLE 13

SUMMARY OF OPHTHALMOLOGICAL OBSERVATIONS FOR MALE RATS

Treatment Group Dose	I 0 mg/kg/day	III 50 mg/kg/day	V 250 mg/kg/day	VII 1000 mg/kg/day
Examination Day: Test Day 88 Number of Rats Examined	20	10	10	20
Retina Retinal Degeneration Focal				
Incidence	0 (0%)	1 (10%)	0 (0%)	0 (0%)
Examination Day: Test Day 116 Number of Rats Examined	10	0	0	10
Retina Retinal Degeneration Focal				
Incidence	1 (10%)	-	-	1 (10%)

Incidence - The number of animals (percent of animals examined) for which an observation was recorded.

Statistical Methods: Trend test (Cochran-Armitage).
There were no statistically significant differences at $p < 0.05$.

TABLE 14

SUMMARY OF OPHTHALMOLOGICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II	IV	VI	VIII
Dose	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
Number of Rats Examined	25	15	14	25
Examination Day: Test Day 88				
Number of Rats Examined	20	10	10	20
There were no ophthalmological abnormalities detected.				
Examination Day: Test Day 116				
Number of Rats Examined	10	0	0	10
There were no ophthalmological abnormalities detected.				

TABLE 15

PERCENT SURVIVAL OF MALE RATS

Treatment Group	I	III	V	VII
Dose (mg/kg/day)	0	50	250	1000
Animal Count at Study Start	45	35	35	45
DAYS ON TEST				
0	100	100	100	100
7	100	100	100	100
14	100	100	100	100
21	100	100	100	100
28	100	100	100	100
35	100	100	100	100
42	100	100	100	100
49	100	100	100	100
56	100	100	97	100
63	100	100	97	100
70[a]	100	100	93	100
77	100	100	93	100
84	100	100	93	100
91[b]	100	100	93	100
99	100	100	80	100
106	100	100	80	100
112	100	100	80	100
119	100	100	80	100
Number at study start	45	35	35	45
Sacrificed in extremis	0	0	1	0
Removed from study (test day 69)[a]	20	20	20	20
Sacrificed by design (test day 91)	10	10	10	10
Alive on test day 119	15	5	4	15

Percent Survival = (AE/Number of rats at risk)*100
Number of rats at risk = Number at study start - number of rats removed from study - number sacrificed by design.

a. Rats designated for reproduction evaluation were cohoused on test day 69.
b. Recovery period began on test day 91.

Statistical Method: Cochran-Armitage trend test.
There were no statistically significant decreases in survival at $p < 0.05$.

TABLE 16

PERCENT SURVIVAL OF FEMALE RATS

Treatment Group	II	IV	VI	VIII
Dose (mg/kg/day)	0	50	250	1000
Number Animals at Study Start	45	35	35	35
DAYS ON TEST				
0	100	100	100	100
7	100	100	100	100
14	100	100	100	100
21	100	100	100	100
28	100	100	100	100
35	100	100	100	100
42	100	100	100	100
49	100	100	100	100
56	100	100	100	100
63	100	100	100	100
70[a]	100	100	100	100
77	100	100	100	100
84	100	100	100	100
91[b]	100	100	100	100
99	100	100	100	100
106	100	100	100	100
112	100	100	100	100
119	100	100	100	100
Number at study start	45	35	35	45
Accidentally killed	1	0	0	0
Removed from study (test day 69)[a]	20	20	20	20
Sacrificed by design (test day 92)	9	10	10	10
Alive on test day 119	15	5	5	15

Percent Survival = (AE/Number of rats at risk)*100
Number of rats at risk = Number at study start - number of rats removed from study - number sacrificed by design - accidentally killed.

a. Rats designated for reproduction evaluation were cohoused on test day 69.
b. Recovery period began on test day 91.

Statistical Method: Cochran-Armitage trend test.
There were no statistically significant decreases in survival at $p < 0.05$.

TABLE 17

MEAN FORELIMB GRIP STRENGTH (kg): MEAN OF THREE TRIALS

Male Rats

Group:	I	III	V	VII
Concentration:	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
N:	10	10	10	10
Baseline	0.71 (0.14)	0.65 (0.06)	0.73 (0.10)	0.67 (0.12)
Week 12	1.42 (0.33)	1.32 (0.36)	1.22 (0.39)	1.24 (0.34)
Recovery	1.49 (0.43)	NM	NM	1.42 (0.26)

Female Rats

Group:	II	IV	VI	VIII
Concentration:	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
N:	10	10	10	10
Baseline	0.66 (0.08)	0.63 (0.11)	0.70 (0.16)	0.68 (0.13)
Week 12	1.09 (0.26)	0.94 (0.24)	1.01 (0.41)	1.06 (0.31)
Recovery	1.01 (0.34)	NM	NM	0.93 (0.24)

Data arranged as: Mean (Standard Deviation).

NM = Not measured.

Statistical Methods: Bartlett's test for homogeneity, followed by Analysis of Variance and Dunnett's test.

There were no statistically significant differences from control at $p<0.05$.

TABLE 18

MEAN HINDLIMB GRIP STRENGTH (kg): MEAN OF THREE TRIALS

Male Rats

Group:	I	III	V	VII
Concentration:	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
N:	10	10	10	10
Baseline	0.32 (0.07)	0.28 (0.06)	0.36 (0.05)	0.32 (0.07)
Week 12	0.57 (0.14)	0.54 (0.13)	0.69 (0.16)	0.60 (0.12)
Recovery	0.78 (0.15)	NM	NM	0.66 (0.07)

Female Rats

Group:	II	IV	VI	VIII
Concentration:	0 mg/kg/day	50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day
N:	10	10	10	10
Baseline	0.31 (0.06)	0.30 (0.05)	0.35 (0.07)	0.33 (0.06)
Week 12	0.51 (0.07)	0.46 (0.09)	0.52 (0.11)	0.47 (0.09)
Recovery	0.58 (0.12)	NM	NM	0.60 (0.14)

Data arranged as: Mean (Standard Deviation).

NM = Not measured.

Statistical Methods: Bartlett's test for homogeneity, followed by Analysis of Variance and Dunnett's test.

There were no statistically significant differences from control at $p<0.05$.

TABLE 19

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY FINDINGS FOR MALE RATS

	BASELINE				WEEK 12				RECOVERY	
GROUP:	I	III	V	VII	I	III	V	VII	I	VII
CONCENTRATION (mg/kg/day):	0	50	250	1000	0	50	250	1000	0	1000
NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
APPROACH & TOUCH:										
-1 no reaction	0	0	0	0	0	0	0	0	0	0
0 normal	10	10	9	9	10	10	10	10	10	10
1 increased reaction (jumps away or attacks)	0	0	1	1	0	0	0	0	0	0
AUDITORY STIMULUS:										
-1 no reaction	0	0	0	0	0	2	1	0	0	0
0 normal reaction (rat flinches or flicks ear)	10	10	10	9	10	8	9	10	10	10
1 exaggerated reaction (rat jumps, flips)	0	0	0	1	0	0	0	0	0	0
TAIL PINCH:										
-1 no response	0	0	0	0	2	1	2	2	0	0
0 normal (turns toward site)	10	10	10	9	8	9	8	8	9	10
1 exaggerated response	0	0	0	1	0	0	0	0	1	0
PUPILLARY RESPONSE:										
1 absent	0	0	0	0	0	0	0	0	0	0
0 present	10	10	10	10	10	10	10	10	10	10
DEFECATION IN MOTOR ACTIVITY MONITOR:										
0 absent	4	3	3	1	4	6	5	4	2	2
1 present	6	7	7	9	6	4	5	6	8	8
D diarrhea	0	0	0	0	0	0	0	0	0	0

TABLE 19 (CONTINUED)

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY FINDINGS FOR MALE RATS

	BASELINE				WEEK 12				RECOVERY	
GROUP:	I	III	V	VII	I	III	V	VII	I	VII
CONCENTRATION (mg/kg/day):	0	50	250	1000	0	50	250	1000	0	1000
NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
URINATION IN MOTOR ACTIVITY MONITOR:										
0 absent	0	0	1	0	1	1	0	1	0	1
1 present	10	10	9	10	9	9	10	9	10	9

There were no statistically significant differences by Cochran-Armitage test for trend at $p < 0.05$.

TABLE 20

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY FINDINGS FOR FEMALE RATS

	BASELINE				WEEK 12				RECOVERY	
GROUP:	II	IV	VI	VIII	II	IV	VI	VIII	II	VIII
CONCENTRATION (mg/kg/day):	0	50	250	1000	0	50	250	1000	0	1000
NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
APPROACH & TOUCH:										
-1 no reaction	0	0	0	0	0	0	0	0	0	0
0 normal	10	9	10	10	10	9	10	10	10	9
1 increased reaction (jumps away or attacks)	0	1	0	0	0	1	0	0	0	0
AUDITORY STIMULUS:										
-1 no reaction	0	0	0	0	0	0	0	0	0	0
0 normal reaction (rat flinches or flicks ear)	10	8	10	9	10	9	10	10	10	9
1 exaggerated reaction (rat jumps, flips)	0	2	0	1	0	1	0	0	0	0
TAIL PINCH:										
-1 no response	1	0	1	0	1	1	1	0	0	0
0 normal (turns toward site)	9	9	9	10	9	9	9	10	10	10
1 exaggerated response	0	1	0	0	0	0	0	0	0	0
PUPILLARY RESPONSE:										
1 absent	0	0	0	0	0	0	0	0	0	0
0 present	10	10	10	10	10	10	10	10	10	10
DEFECATION IN MOTOR ACTIVITY MONITOR:										
0 absent	7	7	5	3 *	1	9 #	6 *	7 *	6	5
1 present	3	3	5	7	9	1	4	3	4	4
D diarrhea	0	0	0	0	0	0	0	0	0	0

TABLE 20 (CONTINUED)

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY FINDINGS FOR FEMALE RATS

	BASELINE				WEEK 12				RECOVERY	
GROUP:	II	IV	VI	VIII	II	IV	VI	VIII	II	VIII
CONCENTRATION (mg/kg/day):	0	50	250	1000	0	50	250	1000	0	1000
NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
URINATION IN MOTOR ACTIVITY MONITOR:										
0 absent	0	0	0	1	0	1	1	1	0	0
1 present	10	10	10	9	10	9	9	9	10	9

\# Statistically significant difference by Fisher's exact test at $p < 0.05$.
* Statistically significant difference by Cochran-Armitage test for trend at $p < 0.05$.

TABLE 21

MOTOR ACTIVITY ASSESSMENT: DURATION OF MOVEMENTS (sec) FOR MALE RATS

BASELINE

GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
		1	2	3	4	5	6	TOTAL
I	0	397 (54)	349 (87)	262 (95)	173 (115)	57 (99)	23 (37)	1261 (396)
III	50	408 (33)	332 (56)	170 (101)	77 (102)	43 (77)	7 (13)	1037 (202)
V	250	373 (33)	287 (50)	166 (137)	101 (115)	74 (99)	40 (95)	1041 (444)
VII	1000	378 (57)	293 (69)	227 (74)	65 (93)	35 (93)	16 (46)	1014 (327) *

WEEK 12

GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
		1	2	3	4	5	6	TOTAL
I	0	415 (57)	344 (70)	288 (81)	220 (92)	152 (127)	120 (83)	1539 (402)
III	50	409 (37)	343 (67)	265 (107)	208 (119)	133 (117)	89 (76)	1447 (348)
V	250	390 (53)	293 (78)	243 (90)	126 (106)	80 (92)	84 (87)	1216 (347)
VII	1000	417 (58)	271 (93)	152 (139) *	135 (135)	106 (138)	62 (102)	1143 (499) *

TABLE 21 (CONTINUED)

MOTOR ACTIVITY ASSESSMENT: DURATION OF MOVEMENTS (sec) FOR MALE RATS

RECOVERY

GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
		1	2	3	4	5	6	TOTAL
I	0	393 (74)	283 (69)	215 (86)	151 (76)	129 (141)	98 (107)	1268 (432)
VII	1000	351 (48)	233 (79)	161 (59)	131 (36)	114 (77)	89 (54)	1077 (227)

Data arranged as: Mean (Standard Deviation).

Statistical Methods: Shapiro-Wilk's and Levene's tests were performed. Jonckheere's trend test or repeated measures analysis of variance with linear contrasts was used to identify which dosage groups, if any, were significantly different from the control group. These tests were applied to bin data and total data.

* Statistically significant difference from control at $p < 0.05$.

TABLE 22

MOTOR ACTIVITY ASSESSMENT: DURATION OF MOVEMENTS (sec) FOR FEMALE RATS

BASELINE

GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
		1	2	3	4	5	6	TOTAL
II	0	379 (63)	284 (52)	146 (83)	91 (86)	77 (73)	46 (76)	1023 (249)
IV	50	384 (85)	323 (94)	274 (106)	193 (140)	170 (145)	119 (140)	1464 (597)
VI	250	391 (50)	258 (121)	167 (119)	192 (140)	141 (123)	75 (114)	1223 (537)
VIII	1000	373 (48)	257 (54)	184 (115)	105 (85)	95 (126)	53 (78)	1066 (321)

WEEK 12

GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
		1	2	3	4	5	6	TOTAL
II	0	392 (43)	312 (67)	207 (70)	138 (94)	132 (105)	99 (77)	1280 (224)
IV	50	391 (46)	322 (64)	226 (96)	184 (97)	105 (88)	63 (84)	1291 (244)
VI	250	380 (74)	274 (71)	158 (81)	176 (124)	114 (95)	43 (44)	1145 (352)
VIII	1000	378 (43)	266 (92)	133 (99)	112 (103)	115 (90)	86 (95)	1088 (319)

TABLE 22 (CONTINUED)

MOTOR ACTIVITY ASSESSMENT: DURATION OF MOVEMENTS (sec) FOR FEMALE RATS

RECOVERY

GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
		1	2	3	4	5	6	TOTAL
II	0	351 (46)	203 (56)	136 (45)	172 (70)	104 (71)	107 (54)	1073 (218)
VIII	1000	361 (61)	172 (45)	128 (51)	106 (52)	93 (61)	114 (87)	974 (206)

Data arranged as: Mean (Standard Deviation).

Statistical Methods: Shapiro-Wilk's and Levene's tests were performed. Jonckheere's trend test or repeated measures analysis of variance with linear contrasts was used to identify which dosage groups, if any, were significantly different from the control group. These tests were applied to bin data and total data.

There were no statistically significant differences from control at $p < 0.05$.

TABLE 23

MOTOR ACTIVITY ASSESSMENT: NUMBER OF MOVEMENTS FOR MALE RATS

BASELINE

GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
		1	2	3	4	5	6	TOTAL
I	0	119 (20)	117 (20)	119 (27)	85 (36)	27 (37)	17 (24)	484 (91)
III	50	122 (19)	125 (21)	95 (42)	47 (59)	30 (43)	8 (12)	427 (136)
V	250	128 (11)	136 (10)	89 (56)	67 (60)	47 (54)	26 (46)	493 (181)
VII	1000	133 (14)	132 (19)	120 (19)	42 (36)	25 (53)	16 (41)	468 (134)

WEEK 12

GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
		1	2	3	4	5	6	TOTAL
I	0	130 (19)	128 (20)	125 (17)	110 (33)	78 (59)	68 (41)	638 (78)
III	50	124 (9)	129 (14)	119 (45)	94 (39)	66 (55)	59 (41)	591 (132)
V	250	133 (17)	136 (24)	118 (30)	74 (57)	59 (53)	55 (44)	574 (124)
VII	1000	130 (22)	118 (24)	71 (58) *	67 (54)	58 (62)	38 (46)	482 (179) *

TABLE 23 (CONTINUED)

MOTOR ACTIVITY ASSESSMENT: NUMBER OF MOVEMENTS FOR MALE RATS

RECOVERY

GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
		1	2	3	4	5	6	TOTAL
I	0	122 (25)	126 (25)	99 (36)	80 (40)	54 (45)	49 (37)	531 (118)
VII	1000	136 (14)	122 (33)	100 (31)	81 (19)	72 (37)	71 (36)	581 (109)

Data arranged as: Mean (Standard Deviation).

Statistical Methods: Shapiro-Wilk's and Levene's tests were performed. Repeated measures analysis of variance with linear contrasts was used to identify which dosage groups, if any, were significantly different from the control group. These tests were applied to bin data and total data.

* Statistically significant difference from control at $p < 0.05$.

TABLE 24

MOTOR ACTIVITY ASSESSMENT: NUMBER OF MOVEMENTS FOR FEMALE RATS

BASELINE

GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
		1	2	3	4	5	6	TOTAL
II	0	130 (18)	136 (14)	91 (37)	62 (49)	56 (45)	36 (51)	511 (151)
IV	50	120 (24)	124 (23)	118 (25)	92 (49)	80 (60)	61 (55)	595 (179)
VI	250	129 (22)	109 (41)	85 (47)	89 (60)	78 (53)	45 (49)	534 (191)
VIII	1000	132 (18)	129 (13)	100 (53)	76 (51)	59 (67)	48 (63)	544 (181)

WEEK 12

GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
		1	2	3	4	5	6	TOTAL
II	0	134 (14)	140 (14)	119 (25)	96 (52)	89 (56)	71 (51)	649 (128)
IV	50	133 (16)	137 (16)	119 (33)	108 (42)	73 (53)	48 (60)	618 (106)
VI	250	134 (19)	129 (15)	101 (40)	100 (47)	79 (47)	36 (28)	579 (107)
VIII	1000	141 (12)	132 (26)	88 (46)	73 (50)	79 (54)	57 (49)	569 (149)

TABLE 24 (CONTINUED)

MOTOR ACTIVITY ASSESSMENT: NUMBER OF MOVEMENTS FOR FEMALE RATS

RECOVERY

GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
		1	2	3	4	5	6	TOTAL
II	0	143 (15)	126 (11)	93 (21)	112 (30)	84 (32)	84 (30)	642 (80)
VIII	1000	144 (14)	121 (20)	91 (30)	82 (32)	77 (41)	82 (48)	596 (113)

Data arranged as: Mean (Standard Deviation).

Statistical Methods: Shapiro-Wilk's and Levene's tests were performed. Repeated measures analysis of variance with linear contrasts was used to identify which dosage groups, if any, were significantly different from the control group. These tests were applied to bin data and total data.

There were no statistically significant differences from control at $p < 0.05$.

TABLE 25

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 50 mg/kg	Group V 250 mg/kg	Group VII 1000 mg/kg
RBC ($x10^6/\mu L$)				
DAY 45	8.18 0.27(9)	8.07 0.32(10)	7.83 0.33(10)	7.86 0.31(10)
DAY 91	8.74 0.23(10)	8.84 0.57(10)	8.73 0.37(10)	8.50 0.44(10)
DAY 123	8.65 0.29(10)	[a]	[a]	8.47 0.35(10)
HGB (g/dL)				
DAY 45	15.0 0.5(9)	14.9 0.4(10)	14.7 0.6(10)	14.4* 0.4(10)
DAY 91	15.8 0.5(10)	15.8 0.9(10)	15.8 0.6(10)	15.2 0.6(10)
DAY 123	15.0 0.5(10)	[a]	[a]	14.6 0.7(10)
HCT (%)				
DAY 45	48.9 1.5(9)	48.0 1.6(10)	47.4 2.5(10)	46.5* 1.1(10)
DAY 91	49.5 1.3(10)	49.5 3.1(10)	49.7 2.5(10)	47.8 2.1(10)
DAY 123	46.3 1.3(10)	[a]	[a]	45.5 2.3(10)
MCV (fl)				
DAY 45	59.8 1.2(9)	59.6 1.3(10)	60.5 2.1(10)	59.2 1.6(10)
DAY 91	56.7 1.2(10)	56.0 1.4(10)	56.9 1.9(10)	56.2 1.4(10)
DAY 123	53.6 1.5(10)	[a]	[a]	53.7 2.1(10)
MCH (pg)				
DAY 45	18.4 0.6(9)	18.5 0.9(10)	18.7 0.7(10)	18.3 0.6(10)
DAY 91	18.1 0.6(10)	17.9 0.7(10)	18.1 0.6(10)	17.9 0.6(10)
DAY 123	17.3 0.6(10)	[a]	[a]	17.3 0.5(10)

TABLE 25 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 50 mg/kg	Group V 250 mg/kg	Group VII 1000 mg/kg
MCHC (g/dL)				
DAY 45	30.7 0.5(9)	31.1 1.0(10)	31.0 0.7(10)	30.9 0.6(10)
DAY 91	31.8 0.5(10)	31.9 0.8(10)	31.8 0.5(10)	31.8 0.5(10)
DAY 123	32.3 0.5(10)	[a]	[a]	32.2 0.4(10)
RDW (%)				
DAY 45	11.5 0.5(9)	11.5 0.5(10)	11.5 0.5(10)	12.1 0.8(10)
DAY 91	12.3 0.7(10)	12.3 0.6(10)	12.1 0.5(10)	12.6 0.8(10)
DAY 123	13.4 0.4(10)	[a]	[a]	13.7 0.8(10)
ARET (x10³/μL)				
DAY 45	223 33(9)	216 27(10)	208 33(10)	219 50(10)
DAY 91	192 36(10)	205 27(10)	159 33(10)	147* 40(10)
DAY 123	183 21(10)	[a]	[a]	177 24(10)
WBC (x10³/μL)				
DAY 45	14.08 2.83(9)	16.84 2.73(10)	16.43 2.68(10)	18.67* 5.47(10)
DAY 91	11.26 1.97(10)	13.05 1.39(10)	12.72 2.62(10)	13.54 3.41(10)
DAY 123	13.85 2.80(10)	[a]	[a]	13.35 1.52(10)
ANEU (x10³/μL)				
DAY 45	1.73 0.54(9)	2.02 0.36(10)	1.85 0.64(10)	2.04 0.76(10)
DAY 91	1.45 0.27(10)	1.93 0.49(10)	1.45 0.29(10)	1.62 0.68(10)
DAY 123	1.84 0.55(10)	[a]	[a]	2.16 0.79(10)

TABLE 25 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 50 mg/kg	Group V 250 mg/kg	Group VII 1000 mg/kg
ANPR (x10³/μL)				
DAY 45	[b]	[b]	[b]	[b]
DAY 91	[b]	[b]	[b]	[b]
DAY 123	[b]	[a]	[a]	[b]
ALYM (x10³/μL)				
DAY 45	11.55	13.95	13.84	15.68*
	3.00(9)	2.82(10)	2.28(10)	4.78(10)
DAY 91	9.18	10.36	10.63	11.23
	2.00(10)	1.48(10)	2.43(10)	2.99(10)
DAY 123	11.16	[a]	[a]	10.34
	2.29(10)			1.93(10)
AMON (x10³/μL)				
DAY 45	0.26	0.38@	0.32	0.36
	0.09(9)	0.11(10)	0.08(10)	0.17(10)
DAY 91	0.31	0.37	0.30	0.32
	0.08(10)	0.11(10)	0.06(10)	0.08(10)
DAY 123	0.32	[a]	[a]	0.33
	0.11(10)			0.04(10)
AEOS (x10³/μL)				
DAY 45	0.18	0.15	0.10	0.15
	0.15(9)	0.05(10)	0.04(10)	0.13(10)
DAY 91	0.14	0.17	0.15	0.12
	0.06(10)	0.05(10)	0.09(10)	0.04(10)
DAY 123	0.15	[a]	[a]	0.15
	0.09(10)			0.08(10)
ABAS (x10³/μL)				
DAY 45	0.12	0.10	0.12	0.15
	0.04(9)	0.05(10)	0.04(10)	0.07(10)
DAY 91	0.08	0.09	0.08	0.11
	0.03(10)	0.04(10)	0.04(10)	0.05(10)
DAY 123	0.14	[a]	[a]	0.20
	0.06(10)			0.12(10)

TABLE 25 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 50 mg/kg	Group V 250 mg/kg	Group VII 1000 mg/kg
ALUC ($x10^3/\mu L$)				
DAY 45	0.24	0.24	0.20	0.31
	0.14(9)	0.07(10)	0.06(10)	0.27(10)
DAY 91	0.11	0.12	0.10	0.15
	0.05(10)	0.03(10)	0.04(10)	0.06(10)
DAY 123	0.23	a	a	0.17
	0.15(10)			0.08(10)
ABLT ($x10^3/\mu L$)				
DAY 45	b	b	b	b
DAY 91	b	b	b	b
DAY 123	b	a	a	b
AMSC ($x10^3/\mu L$)				
DAY 45	b	b	b	b
DAY 91	b	b	b	b
DAY 123	b	a	a	b
PLT ($x10^3/\mu L$)				
DAY 45	1158	1186	1002	1068
	76(5)	99(6)	144(8)	116(9)
DAY 91	1131	1056	972	929*
	117(8)	55(7)	188(9)	122(8)
DAY 123	1060	a	a	926
	128(7)			132(9)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a Measurements for this group at this timepoint were not taken or not performed.
b Measurements for these cells are determined either by instrument or microscopic examination. Microscopic slide review indicated no cells of this type; therefore, the instrument count was accepted and no manual count was performed. Individual data are reported in the Clinical Pathology appendix.

* Statistically significant difference from control at $p < 0.05$ by parametric test (Dunnett/Tamhane-Dunnett).
@ Statistically significant difference from control at $p < 0.05$ by nonparametric test (Dunn's).

TABLE 26

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 50 mg/kg	Group VI 250 mg/kg	Group VIII 1000 mg/kg
RBC ($x10^6/\mu L$)				
DAY 44	8.12	7.83	7.71*	7.70*
	0.34(10)	0.27(10)	0.41(10)	0.18(10)
DAY 92	8.51	8.23*	8.29	8.15*
	0.22(10)	0.16(10)	0.45(10)	0.15(10)
DAY 124	8.12	[a]	[a]	8.11
	0.37(10)			0.46(9)
HGB (g/dL)				
DAY 44	15.3	14.7*	14.6*	14.9
	0.3(10)	0.7(10)	0.5(10)	0.4(10)
DAY 92	15.9	15.4	15.4	15.7
	0.4(10)	0.6(10)	0.5(10)	0.5(10)
DAY 124	15.0	[a]	[a]	15.1
	0.4(10)			0.7(9)
HCT (%)				
DAY 44	49.4	47.2*	45.7*	47.0*
	1.4(10)	2.0(10)	1.9(10)	1.5(10)
DAY 92	50.0	48.1*	48.5	48.4
	1.4(10)	1.6(10)	2.3(10)	1.4(10)
DAY 124	45.8	[a]	[a]	46.0
	1.3(10)			2.4(9)
MCV (fl)				
DAY 44	60.9	60.4	59.4	61.1
	2.0(10)	1.5(10)	1.4(10)	1.5(10)
DAY 92	58.8	58.5	58.6	59.3
	1.5(10)	1.5(10)	1.0(10)	1.1(10)
DAY 124	56.5	[a]	[a]	56.8
	2.1(10)			2.0(9)
MCH (pg)				
DAY 44	18.9	18.8	18.9	19.3
	0.5(10)	0.6(10)	0.6(10)	0.5(10)
DAY 92	18.7	18.8	18.6	19.2
	0.5(10)	0.6(10)	0.5(10)	0.5(10)
DAY 124	18.5	[a]	[a]	18.6
	0.7(10)			0.6(9)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 50 mg/kg	Group VI 250 mg/kg	Group VIII 1000 mg/kg
MCHC (g/dL)				
DAY 44	31.1	31.2	31.8*	31.6
	0.7(10)	0.6(10)	0.8(10)	0.6(10)
DAY 92	31.8	32.1	31.7	32.3
	0.4(10)	0.6(10)	0.5(10)	0.6(10)
DAY 124	32.8	[a]	[a]	32.7
	0.4(10)			0.3(9)
RDW (%)				
DAY 44	11.0	11.4	11.2	11.3
	0.3(10)	0.6(10)	0.8(10)	0.3(10)
DAY 92	10.8	10.6	10.6	10.7
	0.4(10)	0.4(10)	0.4(10)	0.3(10)
DAY 124	12.0	[a]	[a]	11.9
	0.5(10)			0.3(9)
ARET (x10³/μL)				
DAY 44	212	222	226	241
	47(10)	43(10)	29(10)	37(10)
DAY 92	153	146	173	173
	41(10)	29(10)	13(10)	34(10)
DAY 124	176	[a]	[a]	167
	20(10)			31(9)
WBC (x10³/μL)				
DAY 44	13.87	13.20	13.32	13.70
	2.94(10)	2.48(10)	3.68(10)	3.63(10)
DAY 92	8.68	8.84	10.29	10.14
	1.26(10)	1.49(10)	2.21(10)	3.04(10)
DAY 124	11.10	[a]	[a]	10.83
	2.66(10)			2.50(9)
ANEU (x10³/μL)				
DAY 44	1.39	1.13	1.50	1.58
	0.49(10)	0.48(10)	0.32(10)	0.63(10)
DAY 92	0.93	0.93	1.33	1.15
	0.36(10)	0.31(10)	1.23(10)	0.41(10)
DAY 124	1.00	[a]	[a]	1.11
	0.24(10)			0.42(9)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 50 mg/kg	Group VI 250 mg/kg	Group VIII 1000 mg/kg
ANPR ($x10^3/\mu L$)				
DAY 44	b	b	b	b
DAY 92	b	c	c	c
DAY 124	c	a	a	c
ALYM ($x10^3/\mu L$)				
DAY 44	11.68	11.41	11.11	11.43
	2.71(10)	2.54(10)	3.50(10)	3.17(10)
DAY 92	7.20	7.51	8.35	8.44
	1.25(10)	1.46(10)	2.01(10)	2.65(10)
DAY 124	9.35	a	a	9.04
	2.48(10)			2.24(9)
AMON ($x10^3/\mu L$)				
DAY 44	0.28	0.27	0.25	0.22
	0.05(10)	0.12(10)	0.10(10)	0.09(10)
DAY 92	0.23	0.19	0.25	0.21
	0.07(10)	0.04(10)	0.10(10)	0.08(10)
DAY 124	0.31	a	a	0.31
	0.08(10)			0.13(9)
AEOS ($x10^3/\mu L$)				
DAY 44	0.17	0.12	0.18	0.19
	0.06(10)	0.06(10)	0.09(10)	0.23(10)
DAY 92	0.16	0.09*	0.13	0.13
	0.05(10)	0.04(10)	0.04(10)	0.04(10)
DAY 124	0.16	a	a	0.12
	0.12(10)			0.03(9)
ABAS ($x10^3/\mu L$)				
DAY 44	0.11	0.09	0.09	0.10
	0.03(10)	0.05(10)	0.05(10)	0.05(10)
DAY 92	0.08	0.05	0.10	0.08
	0.03(10)	0.03(10)	0.07(10)	0.05(10)
DAY 124	0.09	a	a	0.09
	0.05(10)			0.07(9)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 50 mg/kg	Group VI 250 mg/kg	Group VIII 1000 mg/kg
ALUC ($x10^3/\mu L$)				
DAY 44	0.25	0.18	0.19	0.20
	0.14(10)	0.09(10)	0.12(10)	0.08(10)
DAY 92	0.09	0.08	0.13	0.13
	0.03(10)	0.05(10)	0.09(10)	0.12(10)
DAY 124	0.19	[a]	[a]	0.16
	0.10(10)			0.10(9)
ABLT ($x10^3/\mu L$)				
DAY 44	[b]	[b]	[b]	[b]
DAY 92	[b]	[c]	[c]	[c]
DAY 124	[c]	[a]	[a]	[c]
AMSC ($x10^3/\mu L$)				
DAY 44	[b]	[b]	[b]	[b]
DAY 92	[b]	[c]	[c]	[c]
DAY 124	[c]	[a]	[a]	[c]
PLT ($x10^3/\mu L$)				
DAY 44	1055	1084	1054	1161
	259(5)	153(8)	129(6)	218(7)
DAY 92	1123	1050	1043	1050
	164(7)	69(6)	107(9)	152(9)
DAY 124	954	[a]	[a]	985
	138(7)			111(9)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a Measurements for this group at this timepoint were not taken or not performed.

b Measurements for these cells are determined either by instrument or microscopic examination. Microscopic slide review indicated no cells of this type; therefore, the instrument count was accepted and no manual count was performed. Individual data are reported in the Clinical Pathology appendix.

c When this analysis was performed, valid measurements were taken on only 1 animal from the group. Data from this small sample size did not add value to this summary table. Individual data are reported in the Clinical Pathology appendix.

* Statistically significant difference from control at $p < 0.05$ by parametric test (Dunnett/Tamhane-Dunnett).

TABLE 27

SUMMARY OF COAGULATION VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 50 mg/kg	Group V 250 mg/kg	Group VII 1000 mg/kg
PT (seconds)				
DAY 91	15.1	15.1	15.7	15.7
	0.4(10)	0.5(10)	0.7(9)	0.6(10)
APTT (seconds)				
DAY 91	20.1	19.9	19.8	19.5
	3.8(10)	3.0(10)	1.7(9)	2.6(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

There were no statistically significant differences from control at $p < 0.05$.

TABLE 28

SUMMARY OF COAGULATION VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 50 mg/kg	Group VI 250 mg/kg	Group VIII 1000 mg/kg
PT (seconds)				
DAY 92	15.3	15.2	15.2	15.2
	0.3(9)	0.7(10)	0.7(10)	0.5(10)
APTT (seconds)				
DAY 92	19.8	19.6	18.3	18.3
	1.2(9)	1.9(10)	1.1(10)	1.5(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

There were no statistically significant differences from control at $p < 0.05$.

TABLE 29

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 50 mg/kg	Group V 250 mg/kg	Group VII 1000 mg/kg
AST (U/L)				
DAY 45	91	86	85	88
	17(10)	19(10)	14(10)	11(10)
DAY 91	84	92	91	94
	10(10)	22(10)	27(10)	17(10)
		[a]	[a]	
DAY 123	79			131
	10(10)			116(10)
ALT (U/L)				
DAY 45	38	39	37	44
	6(10)	7(10)	7(10)	10(10)
DAY 91	35	46	50	48@
	5(10)	17(10)	26(10)	9(10)
		[a]	[a]	
DAY 123	34			98@
	7(10)			158(9)
SDH (U/L)				
DAY 45	20.4	24.2	23.7	20.5
	3.5(10)	6.4(10)	5.0(10)	3.7(10)
DAY 91	23.4	27.1	24.0	22.4
	5.6(10)	8.4(10)	7.1(10)	4.4(10)
		[a]	[a]	
DAY 123	19.4			32.7
	3.8(10)			36.2(10)
ALKP (U/L)				
DAY 45	127	130	115	158*
	17(10)	24(10)	20(10)	31(10)
DAY 91	80	100	110*	183*
	13(10)	24(10)	26(10)	28(10)
		[a]	[a]	
DAY 123	80			135*
	15(10)			37(10)
BILI (mg/dL)				
DAY 45	0.09	0.07	0.06	0.06
	0.04(10)	0.03(10)	0.02(10)	0.02(10)
DAY 91	0.14	0.14	0.12	0.12
	0.01(10)	0.04(10)	0.04(10)	0.02(10)
		[a]	[a]	
DAY 123	0.08			0.06
	0.03(10)			0.02(10)

TABLE 29 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 50 mg/kg	Group V 250 mg/kg	Group VII 1000 mg/kg
BUN (mg/dL)				
DAY 45	15 2(10)	15 2(10)	15 3(10)	16 2(10)
DAY 91	15 1(10)	16 2(10)	19* 2(10)	19* 2(10)
DAY 123	14 1(10)	[a]	[a]	15 2(10)
CREA (mg/dL)				
DAY 45	0.37 0.02(10)	0.36 0.05(10)	0.33 0.06(10)	0.34 0.06(10)
DAY 91	0.42 0.04(10)	0.37* 0.05(10)	0.42 0.03(10)	0.40 0.05(10)
DAY 123	0.30 0.06(10)	[a]	[a]	0.30 0.05(10)
CHOL (mg/dL)				
DAY 45	75 16(10)	65 12(10)	55* 12(10)	47* 13(10)
DAY 91	77 19(10)	67 19(10)	54* 14(10)	49* 15(10)
DAY 123	79 24(10)	[a]	[a]	64 16(10)
TRIG (mg/dL)				
DAY 45	75 28(10)	89 47(10)	57 41(10)	42@ 22(10)
DAY 91	81 29(10)	103 43(10)	71 25(10)	44@ 11(10)
DAY 123	210 62(10)	[a]	[a]	115* 53(10)
GLUC (mg/dL)				
DAY 45	104 7(10)	104 6(10)	100 6(10)	109 10(10)
DAY 91	113 6(10)	118 13(10)	117 6(10)	121 8(10)
DAY 123	122 11(10)	[a]	[a]	122 8(10)

TABLE 29 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 50 mg/kg	Group V 250 mg/kg	Group VII 1000 mg/kg
TP (g/dL)				
DAY 45	6.7	6.8	6.4*	6.8
	0.2(10)	0.2(10)	0.3(10)	0.3(10)
DAY 91	7.2	7.2	7.2	7.1
	0.2(10)	0.2(10)	0.4(10)	0.3(10)
DAY 123	6.9	[a]	[a]	7.0
	0.2(10)			0.3(10)
ALB (g/dL)				
DAY 45	4.2	4.3	4.2	4.6*
	0.1(10)	0.1(10)	0.2(10)	0.2(10)
DAY 91	4.3	4.3	4.5*	4.7*
	0.2(10)	0.2(10)	0.2(10)	0.2(10)
DAY 123	4.2	[a]	[a]	4.5*
	0.1(10)			0.2(10)
GLOB (g/dL)				
DAY 45	2.5	2.5	2.2*	2.2*
	0.2(10)	0.2(10)	0.3(10)	0.1(10)
DAY 91	3.0	2.9	2.7*	2.4*
	0.2(10)	0.2(10)	0.3(10)	0.2(10)
DAY 123	2.7	[a]	[a]	2.5@
	0.2(10)			0.2(10)
CALC (mg/dL)				
DAY 45	10.7	10.8	10.7	10.7
	0.3(10)	0.3(10)	0.4(10)	0.2(10)
DAY 91	10.7	10.7	10.8	10.3@
	0.2(10)	0.3(10)	0.3(10)	0.2(10)
DAY 123	11.1	[a]	[a]	11.0
	0.3(10)			0.3(10)
IPHS (mg/dL)				
DAY 45	8.6	8.7	8.9	9.1
	0.6(10)	0.5(10)	0.7(10)	0.5(10)
DAY 91	7.4	7.2	7.7	7.7
	0.2(10)	0.5(10)	0.5(10)	0.9(10)
DAY 123	7.0	[a]	[a]	7.5*
	0.3(10)			0.4(10)

TABLE 29 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 50 mg/kg	Group V 250 mg/kg	Group VII 1000 mg/kg
NA (mmol/L)				
DAY 45	148.0	148.1	148.5	147.8
	1.6(10)	0.9(10)	0.7(10)	0.7(10)
DAY 91	146.5	146.6	147.3	145.4
	0.9(10)	0.9(10)	1.0(10)	1.5(10)
DAY 123	146.5	[a]	[a]	147.0
	1.0(10)			0.9(10)
K (mmol/L)				
DAY 45	6.45	6.29	6.31	6.54
	0.35(10)	0.18(10)	0.23(10)	0.43(10)
DAY 91	6.25	5.97	6.07	6.15
	0.34(10)	0.31(10)	0.30(10)	0.45(10)
DAY 123	6.05	[a]	[a]	6.19
	0.24(10)			0.28(10)
CL (mmol/L)				
DAY 45	99.3	98.1	98.9	99.7
	1.1(10)	0.9(10)	1.0(10)	1.9(10)
DAY 91	101.6	100.5	100.9	101.7
	1.2(10)	1.7(10)	1.1(10)	1.0(10)
DAY 123	98.9	[a]	[a]	99.5
	1.2(10)			1.3(10)
PFLU (μg/mL)				
DAY 45	[a]	[a]	[a]	[a]
DAY 91	0.1	0.1	0.1	0.1
	0.0(10)	0.0(9)	0.0(8)	0.0(10)
DAY 123	[a]	[a]	[a]	[a]

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a Measurements for this group at this timepoint were not taken or not performed.

\# Statistically significant difference from control at $p < 0.05$ by trend test (Jonckheere-Terpstra).
* Statistically significant difference from control at $p < 0.05$ by parametric test (Dunnett/Tamhane-Dunnett).

TABLE 30

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 50 mg/kg	Group VI 250 mg/kg	Group VIII 1000 mg/kg
AST (U/L)				
DAY 44	82 7(10)	107 47(9)	82 6(10)	91 20(10)
DAY 92	88 19(9)	113 40(10)[a]	87 23(10)[a]	91 30(10)
DAY 124	101 19(10)			152 176(9)
ALT (U/L)				
DAY 44	35 3(10)	49 29(9)	36 5(10)	39 9(10)
DAY 92	36 14(9)	62 38(10)[a]	45 23(10)[a]	39 12(10)
DAY 124	64 30(10)			124 192(9)
SDH (U/L)				
DAY 44	22.4 5.9(10)	24.1 12.9(10)	18.6 5.0(10)	20.3 6.1(10)
DAY 92	21.8 4.8(9)	26.4 11.1(10)[a]	22.0 4.5(10)[a]	20.1 3.3(10)
DAY 124	26.1 5.4(10)			45.4 68.7(9)
ALKP (U/L)				
DAY 44	81 25(10)	91 14(9)	81 17(10)	82 20(10)
DAY 92	51 21(9)	58 22(10)[a]	50 12(10)[a]	58 17(10)
DAY 124	40 13(10)			44 15(9)
BILI (mg/dL)				
DAY 44	0.12 0.03(10)	0.09 0.04(9)	0.08 0.04(10)	0.06* 0.03(10)
DAY 92	0.18 0.03(9)	0.16 0.04(10)[a]	0.16 0.03(10)[a]	0.10* 0.03(10)
DAY 124	0.15 0.04(10)			0.09@ 0.04(9)

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 50 mg/kg	Group VI 250 mg/kg	Group VIII 1000 mg/kg
BUN (mg/dL)				
DAY 44	16 2(10)	16 1(10)	16 2(10)	17 2(10)
DAY 92	15 2(9)	17 3(10)	16 2(10)	18* 2(10)
DAY 124	15 2(10)	[a]	[a]	15 2(9)
CREA (mg/dL)				
DAY 44	0.44 0.04(10)	0.39 0.04(10)	0.37* 0.05(10)	0.39 0.04(10)
DAY 92	0.46 0.08(9)	0.47 0.06(10)	0.47 0.05(10)	0.46 0.05(10)
DAY 124	0.41 0.03(10)	[a]	[a]	0.45 0.07(9)
CHOL (mg/dL)				
DAY 44	102 18(10)	88 12(10)	84* 18(10)	75* 9(10)
DAY 92	104 12(9)	94 15(10)	83@ 29(10)	78@ 11(10)
DAY 124	105 29(10)	[a]	[a]	99 32(9)
TRIG (mg/dL)				
DAY 44	46 11(10)	39 16(9)	34 12(10)	29* 9(10)
DAY 92	57 27(9)	53 21(10)	58 47(10)	47 15(10)
DAY 124	62 20(10)	[a]	[a]	56 22(9)
GLUC (mg/dL)				
DAY 44	97 12(10)	99 10(10)	104 9(10)	103 12(10)
DAY 92	117 18(9)	111 13(10)	109 9(10)	133 26(10)
DAY 124	107 10(10)	[a]	[a]	104 11(9)

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 50 mg/kg	Group VI 250 mg/kg	Group VIII 1000 mg/kg
TP (g/dL)				
DAY 44	7.4	7.2	7.0*	7.5
	0.3(10)	0.5(9)	0.3(10)	0.4(10)
DAY 92	8.0	8.0	7.7	8.1
	0.3(9)	0.5(10)	0.6(10)	0.6(10)
DAY 124	8.3	[a]	[a]	8.2
	0.6(10)			0.3(9)
ALB (g/dL)				
DAY 44	5.0	4.9	4.8	5.3
	0.2(10)	0.3(9)	0.3(10)	0.4(10)
DAY 92	5.2	5.3	5.2	5.5
	0.3(9)	0.4(10)	0.3(10)	0.4(10)
DAY 124	5.6	[a]	[a]	5.5
	0.5(10)			0.3(9)
GLOB (g/dL)				
DAY 44	2.4	2.3	2.1*	2.2
	0.1(10)	0.3(9)	0.2(10)	0.2(10)
DAY 92	2.8	2.6	2.5	2.6
	0.1(9)	0.2(10)	0.3(10)	0.3(10)
DAY 124	2.7	[a]	[a]	2.6
	0.2(10)			0.3(9)
CALC (mg/dL)				
DAY 44	11.0	10.7	10.5*	10.7
	0.3(10)	0.3(10)	0.4(10)	0.4(9)
DAY 92	11.1	11.2	11.2	11.2
	0.4(9)	0.3(10)	0.5(10)	0.4(10)
DAY 124	11.7	[a]	[a]	11.6
	0.5(10)			0.3(9)
IPHS (mg/dL)				
DAY 44	8.0	7.8	7.5	7.9
	0.6(10)	0.8(9)	1.1(10)	0.5(10)
DAY 92	5.1	5.4	5.7	5.6
	0.9(8)	0.6(10)	0.7(10)	0.5(10)
DAY 124	6.3	[a]	[a]	6.5
	0.6(10)			0.4(9)

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 50 mg/kg	Group VI 250 mg/kg	Group VIII 1000 mg/kg
NA (mmol/L)				
DAY 44	146.2	146.2	145.9	146.2
	1.6(10)	1.4(9)	1.4(10)	1.4(10)
DAY 92	147.7	147.6	148.1	147.6
	1.2(9)	1.0(10)	1.7(10)	1.1(10)
DAY 124	145.7	[a]	[a]	146.9*
	0.7(10)			1.1(9)
K (mmol/L)				
DAY 44	6.25	6.01	6.01	6.13
	0.38(10)	0.34(9)	0.31(10)	0.33(10)
DAY 92	5.67	5.67	5.67	5.82
	0.26(9)	0.27(10)	0.46(10)	0.41(10)
DAY 124	5.67	[a]	[a]	5.41
	0.56(10)			0.24(9)
CL (mmol/L)				
DAY 44	98.6	99.6	100.6	101.4@
	2.1(10)	1.7(9)	1.7(10)	1.3(10)
DAY 92	103.1	103.8	103.7	104.2
	1.7(9)	1.2(10)	1.8(10)	1.9(10)
DAY 124	97.8	[a]	[a]	98.4
	1.8(10)			2.2(9)
PFLU (μg/mL)				
DAY 44	[a]	[a]	[a]	[a]
DAY 92	0.2	0.2	0.2	0.2
	0.1(8)	0.0(10)	0.1(10)	0.0(10)
DAY 124	[a]	[a]	[a]	[a]

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a Measurements for this group at this timepoint were not taken or not performed.

* Statistically significant difference from control at $p < 0.05$ by parametric test (Dunnett/Tamhane-Dunnett).

@ Statistically significant difference from control at $p < 0.05$ by nonparametric test (Dunn's).

TABLE 31

SUMMARY OF URINALYSIS VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 50 mg/kg	Group V 250 mg/kg	Group VII 1000 mg/kg
VOL (mL)				
DAY 45	9.4	11.9	8.5	12.1
	5.3(10)	4.6(10)	5.4(9)	9.3(10)
DAY 91	8.5	11.4	5.7	9.4
	7.8(10)	5.6(10)[a]	2.9(10)[a]	5.5(10)
DAY 123	4.4			5.4
	2.0(10)			2.9(10)
UOSM (mOsm)				
DAY 45	1143	945	1435	1277
	380(9)	333(10)	873(9)	882(10)
DAY 91	1275	990	1848	1075
	384(10)	464(10)[a]	741(10)[a]	472(10)
DAY 123	1823			1891
	723(10)			795(10)
SG				
DAY 45	1.035	1.030	1.043	1.039
	0.012(10)	0.010(10)	0.024(9)	0.025(10)
DAY 91	1.040	1.031	1.051	1.036
	0.011(10)	0.013(10)[a]	0.019(10)[a]	0.015(10)
DAY 123	1.054			1.055
	0.018(10)			0.020(10)
pH				
DAY 45	6.6	6.9	6.7	6.9
	0.6(10)	0.2(10)	0.4(9)	0.3(10)
DAY 91	6.7	6.4	6.6	6.6
	0.3(10)	0.5(10)[a]	0.5(10)[a]	0.6(10)
DAY 123	6.5			7.1
	0.9(10)			0.8(10)
URO (EU/dL)				
DAY 45	0.2	0.2	0.4	0.4
	0.0(10)	0.0(10)	0.4(9)	0.3(10)
DAY 91	0.4	0.3	0.4	0.4
	0.3(10)	0.3(10)[a]	0.4(10)[a]	0.3(10)
DAY 123	0.3			0.4
	0.3(10)			0.3(10)

TABLE 31 (Continued)

SUMMARY OF URINALYSIS VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 50 mg/kg	Group V 250 mg/kg	Group VII 1000 mg/kg
UFLU (μg)				
DAY 45	a	a	a	a
DAY 91	12.2	14.1	24.9@	42.7@
	3.5(9)	3.4(10)	4.3(9)	14.1(10)
DAY 123	10.3	a	a	14.8*
	4.9(10)			4.4(10)
UMTP (mg/dL)				
DAY 45	89	60	83	79
	48(10)	38(10)	68(9)	71(10)
DAY 91	93	57	86	45*
	36(10)	38(10)	34(9)	21(10)
DAY 123	141	a	a	129
	64(10)			66(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a Measurements for this group at this timepoint were not taken or not performed.

* Statistically significant difference from control at $p < 0.05$ by parametric test (Dunnett/Tamhane-Dunnett).

@ Statistically significant difference from control at $p < 0.05$ by nonparametric test (Dunn's).

TABLE 32

SUMMARY OF URINALYSIS VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 50 mg/kg	Group VI 250 mg/kg	Group VIII 1000 mg/kg
VOL (mL)				
DAY 44	12.6	9.7	6.9	6.8*
	6.3(9)	5.2(9)	4.9(9)	3.3(10)
DAY 92	8.6	4.3@	5.8	5.8@
	3.6(10)	1.3(10)[a]	3.1(10)[a]	5.4(9)
DAY 124	6.5			5.2
	3.9(10)			1.7(9)
UOSM (mOsm)				
DAY 44	713	763	1038	1066
	265(9)	338(8)	515(8)	455(10)
DAY 92	860	1255	1168	1354
	303(10)	419(10)[a]	572(10)[a]	662(9)
DAY 124	1291			1227
	699(10)			376(9)
SG				
DAY 44	1.022	1.027	1.035	1.032
	0.008(9)	0.015(9)	0.018(9)	0.013(10)
DAY 92	1.026	1.038	1.035	1.041
	0.009(10)	0.012(10)[a]	0.016(10)[a]	0.019(9)
DAY 124	1.040			1.039
	0.019(10)			0.011(9)
pH				
DAY 44	6.4	6.4	6.3	6.3
	0.4(9)	0.2(9)	0.4(9)	0.4(10)
DAY 92	6.1	5.9	6.0	5.9
	0.6(10)	0.2(10)[a]	0.4(10)[a]	0.3(9)
DAY 124	5.7			5.8
	0.7(10)			0.3(9)
URO (EU/dL)				
DAY 44	0.2	0.2	0.2	0.2
	0.0(9)	0.0(9)	0.0(9)	0.0(10)
DAY 92	0.2	0.3	0.3	0.4
	0.0(10)	0.3(10)[a]	0.3(10)[a]	0.4(9)
DAY 124	0.2			0.2
	0.0(10)			0.0(9)

TABLE 32 (Continued)

SUMMARY OF URINALYSIS VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 50 mg/kg	Group VI 250 mg/kg	Group VIII 1000 mg/kg
UFLU (μg)				
DAY 44	[a]	[a]	[a]	[a]
DAY 92	9.5	8.2	14.0*	23.7*
	2.2(10)	2.4(10)	4.4(9)	8.1(7)
DAY 124	9.2	[a]	[a]	10.7
	3.6(9)			2.3(9)
UMTP (mg/dL)				
DAY 44	12	18	22	21
	7(9)	16(9)	14(9)	12(10)
DAY 92	19	25	57	33
	10(10)	8(10)	124(10)	27(9)
DAY 124	35	[a]	[a]	30
	21(10)			13(9)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a Measurements for this group at this timepoint were not taken or not performed.

* Statistically significant difference from control at $p < 0.05$ by parametric test (Dunnett/Tamhane-Dunnett).
@ Statistically significant difference from control at $p < 0.05$ by nonparametric test (Dunn's).

TABLE 33

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
(90-DAY EXPOSURE EVALUATION)

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
LIVER	16.29990 2.37854(10)	16.87220 2.61074(10)	17.17570 1.42650(10)	17.73860 1.69212(10)
KIDNEYS	4.11790 0.46383(10)	4.07140 0.44324(10)	4.29670 0.30710(10)	4.14600 0.50094(10)
HEART	1.72150 0.18011(10)	1.63930 0.09797(10)	1.60160 0.15360(10)	1.45190# 0.15909(10)
SPLEEN	0.81060 0.13297(10)	0.81960 0.13467(10)	0.75140 0.04046(10)	0.62300# 0.06573(10)
BRAIN	2.11630 0.11666(10)	2.09420 0.05678(10)	2.10710 0.07523(10)	2.08770 0.10561(10)
THYMUS	0.39550 0.10511(10)	0.35220 0.10652(10)	0.35900 0.07574(10)	0.29070# 0.08475(10)
ADRENAL GLANDS	0.05420 0.00819(10)	0.05070 0.00766(10)	0.05590 0.00565(10)	0.04540 0.00759(10)
TESTES	3.55240 0.26647(10)	3.44250 0.28401(10)	3.47420 0.21284(10)	3.63750 0.46281(10)
EPIDIDYMIDES	1.52290 0.13239(10)	1.46590 0.10031(10)	1.44610 0.07824(10)	1.44300 0.12745(10)
FINAL BODY WEIGHT	571.20001 54.34041(10)	553.88000 64.04053(10)	525.24000 32.58446(10)	453.54000# 27.10724(10)

TABLE 33 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS (90-DAY EXPOSURE EVALUATION)

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
LIVER/ FINAL BODY * 100	2.84282 0.18604(10)	3.03802# 0.21348(10)	3.26805# 0.13073(10)	3.90847# 0.24375(10)
KIDNEYS/ FINAL BODY * 100	0.72142 0.04767(10)	0.73746 0.05458(10)	0.81838# 0.03911(10)	0.91438# 0.09585(10)
HEART/ FINAL BODY * 100	0.30162 0.01735(10)	0.29831 0.02690(10)	0.30476 0.02003(10)	0.32005 0.02896(10)
SPLEEN/ FINAL BODY * 100	0.14146 0.01571(10)	0.14759 0.01234(10)	0.14355 0.01190(10)	0.13746 0.01303(10)
BRAIN/ FINAL BODY * 100	0.37329 0.03801(10)	0.38195 0.03860(10)	0.40251 0.02774(10)	0.46124# 0.02746(10)
THYMUS/ FINAL BODY * 100	0.06894 0.01543(10)	0.06381 0.01967(10)	0.06850 0.01460(10)	0.06376 0.01674(10)
ADRENAL GLANDS/ FINAL BODY * 100	0.00952 0.00147(10)	0.00919 0.00117(10)	0.01066 0.00100(10)	0.01000 0.00146(10)
TESTES/ FINAL BODY * 100	0.62419 0.04177(10)	0.62763 0.07394(10)	0.66300 0.04622(10)	0.80306# 0.10131(10)
EPIDIDYMIDES/ FINAL BODY * 100	0.26700 0.01067(10)	0.26813 0.03744(10)	0.27582 0.01536(10)	0.31857# 0.02711(10)

TABLE 33 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
(90-DAY EXPOSURE EVALUATION)

MEAN RELATIVE ORGAN WEIGHTS (% organ to brain weight ratio)

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
LIVER/ BRAIN * 100	770.15709 104.54656(10)	805.01169 115.90201(10)	815.55517 67.73836(10)	849.17608 61.67427(10)
KIDNEYS/ BRAIN * 100	194.75542 20.46963(10)	194.18409 17.86388(10)	203.90854 12.59494(10)	198.79654 23.95776(10)
HEART/ BRAIN * 100	81.49513 9.02494(10)	78.26848 3.91573(10)	76.02567 6.96468(10)	69.57323# 7.11744(10)
SPLEEN/ BRAIN * 100	38.35205 6.39417(10)	39.03931 5.59356(10)	35.69114 2.14067(10)	29.85103# 2.88927(10)
THYMUS/ BRAIN * 100	18.75573 5.19498(10)	16.85615 5.23759(10)	17.02594 3.49770(10)	13.92191# 3.97262(10)
ADRENAL GLANDS/ BRAIN * 100	2.57297 0.43823(10)	2.41939 0.34590(10)	2.65955 0.32621(10)	2.16774# 0.29613(10)
TESTES/ BRAIN * 100	168.21509 14.61825(10)	164.39229 12.67559(10)	165.02970 10.88670(10)	174.03435 18.18484(10)
EPIDIDYMIDES/ BRAIN * 100	72.06007 6.34437(10)	70.09865 5.95636(10)	68.65294 3.39848(10)	69.12080 5.03411(10)

TABLE 33 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS (ONE-MONTH RECOVERY EVALUATION)

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

	Group I 0 mg/kg/day	Group VII 1000 mg/kg/day
LIVER	18.08270 1.47750(10)	21.60940# 3.55199(10)
KIDNEYS	4.45450 0.47991(10)	4.36820 0.56393(10)
HEART	1.79860 0.16518(10)	1.71710 0.17531(10)
SPLEEN	0.85170 0.09574(10)	0.77160# 0.07517(10)
BRAIN	2.21690 0.08271(10)	2.12510 0.14088(10)
THYMUS	0.40740 0.08460(10)	0.33660 0.06047(10)
ADRENAL GLANDS	0.05500 0.00790(10)	0.05570 0.00983(10)
TESTES	3.50310 0.15626(10)	3.62410 0.34573(10)
EPIDIDYMIDES	1.56120 0.11432(10)	1.53520 0.13761(10)
FINAL BODY WEIGHT	614.23000 31.93733(10)	575.99000 75.57794(10)

TABLE 33 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS (ONE-MONTH RECOVERY EVALUATION)

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

	Group I 0 mg/kg/day	Group VII 1000 mg/kg/day
LIVER/ FINAL BODY * 100	2.94443 0.19349(10)	3.74065# 0.17971(10)
KIDNEYS/ FINAL BODY * 100	0.72426 0.05939(10)	0.76003 0.06052(10)
HEART/ FINAL BODY * 100	0.29257 0.01864(10)	0.29998 0.02662(10)
SPLEEN/ FINAL BODY * 100	0.13879 0.01514(10)	0.13549 0.01764(10)
BRAIN/ FINAL BODY * 100	0.36188 0.02412(10)	0.37309 0.04080(10)
THYMUS/ FINAL BODY * 100	0.06621 0.01259(10)	0.05842 0.00695(10)
ADRENAL GLANDS/ FINAL BODY * 100	0.00896 0.00130(10)	0.00974 0.00167(10)
TESTES/ FINAL BODY * 100	0.57159 0.03732(10)	0.63583# 0.07408(10)
EPIDIDYMIDES/ FINAL BODY * 100	0.25424 0.01435(10)	0.26847 0.02279(10)

TABLE 33 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

MEAN RELATIVE ORGAN WEIGHTS (% organ to brain weight ratio)

	Group I 0 mg/kg/day	Group VII 1000 mg/kg/day
LIVER/ BRAIN*100	816.87669 76.65974(10)	1015.9066# 144.74869(10)
KIDNEYS/ BRAIN*100	200.98135 21.27432(10)	205.35810 21.95910(10)
HEART/ BRAIN*100	81.24372 8.38089(10)	80.73190 5.51430(10)
SPLEEN/ BRAIN*100	38.41308 3.88576(10)	36.51872 4.85835(10)
THYMUS/ BRAIN*100	18.39074 3.84886(10)	15.82333 2.53299(10)
ADRENAL GLANDS/ BRAIN * 100	2.47677 0.31243(10)	2.63760 0.52852(10)
TESTES/ BRAIN*100	158.21602 9.14123(10)	170.75088 14.77783(10)
EPIDIDYMIDES/ BRAIN * 100	70.55650 6.38733(10)	72.33118 6.05327(10)

TABLE 33 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
(3-MONTH RECOVERY EVALUATION)

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

	Group I 0 mg/kg/day	Group III 50 mg/kg/day	Group V 250 mg/kg/day	Group VII 1000 mg/kg/day
LIVER	16.02880 3.59419(5)	17.89020 5.71336(5)	17.80925 2.72291(4)	19.89400 4.91210(5)
FINAL BODY WEIGHT	570.94001 115.89048(5)	613.46000 90.47218(5)	614.80000 66.22251(4)	628.34000 122.14361(5)
MEAN RELATIVE ORGAN WEIGHT (% organ to body weight)				
LIVER/ FINAL BODY * 100	2.80261 0.13585(5)	2.86633 0.46688(5)	2.88670 0.16631(4)	3.15405 0.33800(5)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).
Statistically significant difference at p < 0.05.

TABLE 34

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
LIVER	8.84878 0.88178(9)	8.70190 0.37828(10)	9.13210 1.55337(10)	9.61140 1.45116(10)
KIDNEYS	2.32156 0.13554(9)	2.37890 0.13760(10)	2.43270 0.32086(10)	2.41310 0.20469(10)
HEART	1.13467 0.11533(9)	1.03470 0.09322(10)	1.08350 0.12105(10)	1.05610 0.15199(10)
SPLEEN	0.47933 0.06135(9)	0.51200 0.08004(10)	0.54790 0.08040(10)	0.54350 0.11346(10)
BRAIN	1.95533 0.04179(9)	1.93720 0.05827(10)	1.94880 0.04951(10)	1.94110 0.11203(10)
THYMUS	0.30811 0.06008(9)	0.27820 0.05904(10)	0.32100 0.08173(10)	0.32000 0.07946(10)
ADRENAL GLANDS	0.06756 0.01454(9)	0.07030 0.01046(10)	0.07790 0.02075(10)	0.07380 0.00860(10)
OVARIES	0.13444 0.03048(9)	0.12380 0.02466(10)	0.11550 0.01848(10)	0.12490 0.02469(10)
UTERUS	0.48856 0.08202(9)	0.62250 0.14580(10)	0.64920 0.10251(10)	0.61880 0.16651(10)
FINAL BODY WEIGHT	313.86000 33.38430(10)	294.51000 17.61934(10)	311.33000 38.77024(10)	293.62000 46.15103(10)

TABLE 34 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS (90-DAY EXPOSURE EVALUATION)

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
LIVER/ FINAL BODY * 100	2.87266 0.19054(9)	2.96392 0.21436(10)	2.92590 0.20524(10)	3.28260# 0.18650(10)
KIDNEYS/ FINAL BODY * 100	0.75624 0.05892(9)	0.80964 0.05663(10)	0.78343 0.06553(10)	0.83304 0.09834(10)
HEART/ FINAL BODY * 100	0.36786 0.01744(9)	0.35204 0.03400(10)	0.34870 0.01585(10)	0.36162 0.03160(10)
SPLEEN/ FINAL BODY * 100	0.15582 0.01949(9)	0.17458 0.03057(10)	0.17637# 0.01806(10)	0.18582# 0.03162(10)
BRAIN/ FINAL BODY * 100	0.63885 0.06119(9)	0.66028 0.04991(10)	0.63323 0.06670(10)	0.67437 0.09883(10)
THYMUS/ FINAL BODY * 100	0.10020 0.01888(9)	0.09442 0.01909(10)	0.10210 0.01577(10)	0.10923 0.02110(10)
ADRENAL GLANDS/ FINAL BODY * 100	0.02200 0.00471(9)	0.02391 0.00358(10)	0.02509 0.00590(10)	0.02573 0.00502(10)
OVARIES/ FINAL BODY * 100	0.04364 0.00931(9)	0.04227 0.00945(10)	0.03746 0.00667(10)	0.04275 0.00772(10)
UTERUS/ FINAL BODY * 100	0.15839 0.02151(9)	0.21128 0.04737(10)	0.21164 0.04491(10)	0.21888 0.08174(10)

TABLE 34 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

MEAN RELATIVE ORGAN WEIGHTS (% organ to brain weight ratio)

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
LIVER/ BRAIN * 100	453.16871 51.53255(9)	449.40303 19.98274(10)	467.75182 70.86370(10)	496.43390 79.13478(10)
KIDNEYS/ BRAIN * 100	118.82351 8.13654(9)	122.86286 7.29982(10)	124.72456 14.96060(10)	124.65330 12.56924(10)
HEART/ BRAIN * 100	58.04840 6.01775(9)	53.39885 4.26402(10)	55.56214 5.64538(10)	54.52115 8.21116(10)
SPLEEN/ BRAIN * 100	24.52604 3.19572(9)	26.43428 4.08542(10)	28.06953# 3.72366(10)	27.90773# 4.88065(10)
THYMUS/ BRAIN * 100	15.78026 3.20325(9)	14.37108 3.07053(10)	16.43012 3.95870(10)	16.50275 4.12823(10)
ADRENAL GLANDS/ BRAIN * 100	3.45494 0.72733(9)	3.62641 0.50714(10)	3.98493 0.98532(10)	3.81032 0.47299(10)
OVARIES/ BRAIN * 100	6.88661 1.60341(9)	6.40432 1.30463(10)	5.92383 0.91033(10)	6.41872 1.17561(10)
UTERUS/ BRAIN * 100	24.99779 4.19207(9)	32.08705 7.23638(10)	33.35351 5.50293(10)	32.04322 9.03999(10)

TABLE 34 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS (ONE-MONTH RECOVERY EVALUATION)

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

	Group II 0 mg/kg/day	Group VIII 1000 mg/kg/day
LIVER	9.28370 1.09118(10)	9.81700 1.02818(9)
KIDNEYS	2.49660 0.13680(10)	2.49433 0.25909(9)
HEART	1.18130 0.12273(10)	1.16611 0.06908(9)
SPLEEN	0.53490 0.06089(10)	0.53133 0.06821(9)
BRAIN	1.92700 0.06756(10)	1.90700 0.07682(9)
THYMUS	0.27040 0.06344(10)	0.26578 0.08276(9)
ADRENAL GLANDS	0.06720 0.00930(10)	0.07433 0.01158(9)
OVARIES	0.11380 0.01923(10)	0.13044 0.03080(9)
UTERUS	0.69240 0.15493(10)	0.64000 0.14365(9)
FINAL BODY WEIGHT	319.89000 29.45560(10)	319.46667 39.20315(9)

TABLE 34 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

	Group II 0 mg/kg/day	Group VIII 1000 mg/kg/day
LIVER/ FINAL BODY * 100	2.90965 0.31572(10)	3.08176 0.17865(9)
KIDNEYS/ FINAL BODY * 100	0.78454 0.06459(10)	0.78462 0.07204(9)
HEART/ FINAL BODY * 100	0.37077 0.04110(10)	0.36727 0.02209(9)
SPLEEN/ FINAL BODY * 100	0.16798 0.02111(10)	0.16684 0.01593(9)
THYMUS/ FINAL BODY * 100	0.08434 0.01769(10)	0.08194 0.01357(9)
BRAIN/ FINAL BODY * 100	0.60627 0.05176(10)	0.60309 0.06179(9)
ADRENAL GLANDS/ FINAL BODY * 100	0.02115 0.00335(10)	0.02332 0.00303(9)
OVARIES/ FINAL BODY * 100	0.03554 0.00488(10)	0.04080 0.00830(9)
UTERUS/ FINAL BODY * 100	0.21976 0.05912(10)	0.20282 0.05408(9)

TABLE 34 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS (ONE-MONTH RECOVERY EVALUATION)

MEAN RELATIVE ORGAN WEIGHTS (% of organ to brain weight ratio)

	Group II 0 mg/kg/day	Group VIII 1000 mg/kg/day
LIVER/ BRAIN*100	481.41153 51.16500(10)	514.77685 48.35577(9)
KIDNEYS/ BRAIN*100	129.58552 6.03970(10)	130.84378 12.62861(9)
HEART/ BRAIN*100	61.30509 6.13495(10)	61.16895 3.06644(9)
SPLEEN/ BRAIN*100	27.72580 2.69809(10)	27.85508 3.32437(9)
THYMUS/ BRAIN*100	14.02984 3.15456(10)	13.92129 4.13240(9)
ADRENAL GLANDS/ BRAIN * 100	3.47982 0.39498(10)	3.90318 0.63048(9)
OVARIES/ BRAIN*100	5.90446 0.97360(10)	6.83405 1.57365(9)
UTERUS/ BRAIN*100	35.91140 7.83175(10)	33.68099 8.06631(9)

TABLE 34 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS (3-MONTH RECOVERY EVALUATION)

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHT (grams)

	Group II 0 mg/kg/day	Group IV 50 mg/kg/day	Group VI 250 mg/kg/day	Group VIII 1000 mg/kg/day
LIVER	9.78580	9.09420	10.15800	10.94320
	1.03445(5)	1.03757(5)	1.14344(5)	1.05921(5)
FINAL BODY WEIGHT	321.19999	329.13999	345.69999	371.77999#
	15.12316(5)	14.29032(5)	45.08364(5)	33.74221(5)

MEAN RELATIVE ORGAN WEIGHT (% organ to body weight)

LIVER/ FINAL BODY * 100	3.05923	2.75646	2.95270	2.95638
	0.42653(5)	0.19747(5)	0.25319(5)	0.33569(5)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).
Statistically significant difference at p < 0.05.

TABLE 35

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0	50	250	1000
		I	III	V	VII
LIVER		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
KIDNEYS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
LUNGS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
HEART		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SKELETAL MUSCLE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SPLEEN		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
AORTA		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
BRAIN		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0	50	250	1000
		I	III	V	VII
SPINAL CORD		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
STOMACH		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
DUODENUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
JEJUNUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
ILEUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
PANCREAS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
CECUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
COLON		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0	50	250	1000
		I	III	V	VII
RECTUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
MESENTERIC LYMPH NODE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SALIVARY GLANDS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
MANDIBULAR LYMPH NODE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
THYMUS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
ADRENAL GLANDS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SCIATIC NERVE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
PITUITARY GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0	50	250	1000
		I	III	V	VII
THYROID GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
PARATHYROID GLANDS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
TRACHEA		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
ESOPHAGUS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
PHARYNX/LARYNX		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
EYE(S) WITH OPTIC NERVE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SKIN		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
PROSTATE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0	50	250	1000
		I	III	V	VII
SEMINAL VESICLES		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
URINARY BLADDER		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
TESTES		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	9
LARGE, RIGHT.					1
EPIDIDYMIDES		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
FEMUR/KNEE JOINT		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
STERNUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
NOSE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric) Males			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
LIVER	(10)			(10)
NO ABNORMALITY DETECTED	10			10
KIDNEYS	(10)			(10)
NO ABNORMALITY DETECTED	10			10
LUNGS	(10)			(10)
NO ABNORMALITY DETECTED	10			10
HEART	(10)			(10)
NO ABNORMALITY DETECTED	10			10
SKELETAL MUSCLE	(10)			(10)
NO ABNORMALITY DETECTED	10			10
SPLEEN	(10)			(10)
NO ABNORMALITY DETECTED	10			10
AORTA	(10)			(10)
NO ABNORMALITY DETECTED	10			10
BRAIN	(10)			(10)
NO ABNORMALITY DETECTED	10			10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0	50	250	1000
		I	III	V	VII
SPINAL CORD		(10)			(10)
NO ABNORMALITY DETECTED		10			10
STOMACH		(10)			(10)
NO ABNORMALITY DETECTED		10			10
DUODENUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
JEJUNUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
ILEUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
PANCREAS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
CECUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
COLON		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0 I	50 III	250 V	1000 VII
RECTUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MESENTERIC LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SALIVARY GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MANDIBULAR LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
THYMUS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
ADRENAL GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SCIATIC NERVE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
PITUITARY GLAND		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0	50	250	1000
		I	III	V	VII
THYROID GLAND		(10)			(10)
NO ABNORMALITY DETECTED		10			10
PARATHYROID GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
TRACHEA		(10)			(10)
NO ABNORMALITY DETECTED		10			10
ESOPHAGUS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
PHARYNX/LARYNX		(10)			(10)
NO ABNORMALITY DETECTED		10			10
EYE(S) WITH OPTIC NERVE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SKIN		(10)			(10)
NO ABNORMALITY DETECTED		10			10
PROSTATE		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0	50	250	1000
		I	III	V	VII
SEMINAL VESICLES		(10)			(10)
NO ABNORMALITY DETECTED		10			10
URINARY BLADDER		(10)			(10)
NO ABNORMALITY DETECTED		10			10
TESTES		(10)			(10)
NO ABNORMALITY DETECTED		10			10
EPIDIDYMIDES		(10)			(10)
NO ABNORMALITY DETECTED		10			10
FEMUR/KNEE JOINT		(10)			(10)
NO ABNORMALITY DETECTED		10			10
STERNUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
NOSE		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0 I	50 III	250 V	1000 VII
LIVER		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	4	4	5
DISCOLORATION, TAN, MANY.			1		
KIDNEYS		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
LUNGS		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
HEART		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
SKELETAL MUSCLE		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
SPLEEN		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
AORTA		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
BRAIN		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(3-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric) Males			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
SPINAL CORD	(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED	5	5	4	5
STOMACH	(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED	5	5	4	5
DUODENUM	(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED	5	5	4	5
JEJUNUM	(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED	5	5	4	5
ILEUM	(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED	5	5	4	5
PANCREAS	(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED	5	5	4	5
CECUM	(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED	5	5	4	5
COLON	(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED	5	5	4	5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0 I	50 III	250 V	1000 VII
RECTUM		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
MESENTERIC LYMPH NODE		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
SALIVARY GLANDS		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
MANDIBULAR LYMPH NODE		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
THYMUS		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
ADRENAL GLANDS		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
SCIATIC NERVE		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
PITUITARY GLAND		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0 I	50 III	250 V	1000 VII
THYROID GLAND		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
PARATHYROID GLANDS		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
TRACHEA		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
ESOPHAGUS		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
PHARYNX/LARYNX		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
EYE(S) WITH OPTIC NERVE		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
SKIN		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5
PROSTATE		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

Company Sanitized. Does not contain TSCA CBI

TABLE 35 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Males 0 I	50 III	250 V	1000 VII
SEMINAL VESICLES NO ABNORMALITY DETECTED		(5) 5	(5) 5	(4) 4	(5) 5
URINARY BLADDER NO ABNORMALITY DETECTED		(5) 5	(5) 5	(4) 4	(5) 5
TESTES NO ABNORMALITY DETECTED		(5) 5	(5) 5	(4) 4	(5) 5
EPIDIDYMIDES NO ABNORMALITY DETECTED		(5) 5	(5) 5	(4) 4	(5) 5
FEMUR/KNEE JOINT NO ABNORMALITY DETECTED		(5) 5	(5) 5	(4) 4	(5) 5
STERNUM NO ABNORMALITY DETECTED		(5) 5	(5) 5	(4) 4	(5) 5
NOSE NO ABNORMALITY DETECTED		(5) 5	(5) 5	(4) 4	(5) 5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0	50	250	1000
		II	IV	VI	VIII
LIVER		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
KIDNEYS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
LUNGS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		9	10	10	10
DISCOLORATION, DARK, DIFFUSE.		1			
HEART		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SKELETAL MUSCLE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SPLEEN		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	9

Figures in parentheses is the number of animals grossly examined for this tissue.
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0 II	50 IV	250 VI	1000 VIII
SPLEEN		(10)	(10)	(10)	(10)
DISCOLORATION, BROWN.					1
AORTA		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
BRAIN		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SPINAL CORD		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
STOMACH		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
DUODENUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0	50	250	1000
		II	IV	VI	VIII
JEJUNUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
ILEUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
PANCREAS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
CECUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
COLON		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
RECTUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0	50	250	1000
		II	IV	VI	VIII
MESENTERIC LYMPH NODE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SALIVARY GLANDS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
MANDIBULAR LYMPH NODE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
THYMUS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
ADRENAL GLANDS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SCIATIC NERVE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0	50	250	1000
		II	IV	VI	VIII
PITUITARY GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
THYROID GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
PARATHYROID GLANDS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
TRACHEA		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
ESOPHAGUS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
PHARYNX/LARYNX		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0 II	50 IV	250 VI	1000 VIII
EYE(S) WITH OPTIC NERVE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SKIN		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
MAMMARY GLAND (FEMALE)		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
OVARIES		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
UTERUS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
URINARY BLADDER		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(90-DAY EXPOSURE EVALUATION)

	LESION INCIDENCE (Numeric)			
	Females			
LESIONS / TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
FEMUR/KNEE JOINT	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10
STERNUM	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10
NOSE	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

	LESION INCIDENCE (Numeric)			
	Females			
LESIONS / TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
LIVER	(10)			(10)
NO ABNORMALITY DETECTED	9			10
HERNIA.	1			
KIDNEYS	(10)			(10)
NO ABNORMALITY DETECTED	10			10
LUNGS	(10)			(10)
NO ABNORMALITY DETECTED	10			10
HEART	(10)			(10)
NO ABNORMALITY DETECTED	10			10
SKELETAL MUSCLE	(10)			(10)
NO ABNORMALITY DETECTED	10			10
SPLEEN	(10)			(10)
NO ABNORMALITY DETECTED	10			10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

		LESION INCIDENCE (Numeric)			
		Females			
LESIONS	TREATMENT (mg/kg/day)	0	50	250	1000
		II	IV	VI	VIII
AORTA		(10)			(10)
NO ABNORMALITY DETECTED		10			10
BRAIN		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SPINAL CORD		(10)			(10)
NO ABNORMALITY DETECTED		10			10
STOMACH		(10)			(10)
NO ABNORMALITY DETECTED		10			10
DUODENUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
JEJUNUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric) Females			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
ILEUM	(10)			(10)
NO ABNORMALITY DETECTED	10			10
PANCREAS	(10)			(10)
NO ABNORMALITY DETECTED	10			10
CECUM	(10)			(10)
NO ABNORMALITY DETECTED	10			10
COLON	(10)			(10)
NO ABNORMALITY DETECTED	10			10
RECTUM	(10)			(10)
NO ABNORMALITY DETECTED	10			10
MESENTERIC LYMPH NODE	(10)			(10)
NO ABNORMALITY DETECTED	10			10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0	50	250	1000
		II	IV	VI	VIII
SALIVARY GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MANDIBULAR LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
THYMUS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
ADRENAL GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SCIATIC NERVE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
PITUITARY GLAND		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric) Females			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
THYROID GLAND	(10)			(10)
NO ABNORMALITY DETECTED	10			10
PARATHYROID GLANDS	(10)			(10)
NO ABNORMALITY DETECTED	10			10
TRACHEA	(10)			(10)
NO ABNORMALITY DETECTED	10			10
ESOPHAGUS	(10)			(10)
NO ABNORMALITY DETECTED	10			10
PHARYNX/LARYNX	(10)			(10)
NO ABNORMALITY DETECTED	10			10
EYE(S) WITH OPTIC NERVE	(10)			(10)
NO ABNORMALITY DETECTED	10			10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric) Females			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
SKIN	(10)			(10)
NO ABNORMALITY DETECTED	10			10
MAMMARY GLAND (FEMALE)	(10)			(10)
NO ABNORMALITY DETECTED	10			10
OVARIES	(10)			(10)
NO ABNORMALITY DETECTED	10			10
UTERUS	(10)			(10)
NO ABNORMALITY DETECTED	10			10
URINARY BLADDER	(10)			(10)
NO ABNORMALITY DETECTED	10			10
FEMUR/KNEE JOINT	(10)			(10)
NO ABNORMALITY DETECTED	10			10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric) Females			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
STERNUM	(10)			(10)
NO ABNORMALITY DETECTED	10			10
NOSE	(10)			(10)
NO ABNORMALITY DETECTED	10			10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0 II	50 IV	250 VI	1000 VIII
LIVER		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
KIDNEYS		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
LUNGS		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
HEART		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
SKELETAL MUSCLE		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
SPLEEN		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0 II	50 IV	250 VI	1000 VIII
AORTA		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
BRAIN		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
SPINAL CORD		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
STOMACH		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
DUODENUM		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
JEJUNUM		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0 II	50 IV	250 VI	1000 VIII
ILEUM		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
PANCREAS		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
CECUM		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
COLON		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
RECTUM		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
MESENTERIC LYMPH NODE		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0 II	50 IV	250 VI	1000 VIII
SALIVARY GLANDS		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
MANDIBULAR LYMPH NODE		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
THYMUS		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
ADRENAL GLANDS		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
SCIATIC NERVE		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
PITUITARY GLAND		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(3-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)			
	Females			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
THYROID GLAND	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5
PARATHYROID GLANDS	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5
TRACHEA	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5
ESOPHAGUS	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5
PHARYNX/LARYNX	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5
EYE(S) WITH OPTIC NERVE	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0 II	50 IV	250 VI	1000 VIII
SKIN		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
MAMMARY GLAND (FEMALE)		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
OVARIES		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
UTERUS		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
URINARY BLADDER		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
FEMUR/KNEE JOINT		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 36 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric) Females 0	50	250	1000
		II	IV	VI	VIII
STERNUM		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5
NOSE		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 37

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
DIGESTIVE SYSTEM				
LIVER	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	1			
NECROSIS, FOCAL.	2	2		1
INFLAMMATION, SUBACUTE/CHRONIC.	9	10	10	10
HYPERTROPHY, HEPATOCELLULAR.		1	10	10
HYPERPLASIA, BILE DUCT.	1	1		
FATTY CHANGE, PERIPORTAL.		3		
FATTY CHANGE, MEDIAN CLEFT.		1	1	1
FATTY CHANGE, CENTRILOBULAR.			1	
PANCREAS	(10)			(10)
NO ABNORMALITY DETECTED	6			8
INFLAMMATION, SUBACUTE/CHRONIC.	4			
ATROPHY.	1			2
ESOPHAGUS	(10)			(10)
NO ABNORMALITY DETECTED	9			9
FIBROSIS.	1			1
STOMACH	(10)			(10)
NO ABNORMALITY DETECTED	10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 37 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
DUODENUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
JEJUNUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
ILEUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
CECUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
COLON		(10)			(10)
NO ABNORMALITY DETECTED		10			10
RECTUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SALIVARY GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		10			9
INFLAMMATION, SUBACUTE/CHRONIC.					1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 37 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
URINARY SYSTEM				
KIDNEYS	(10)			(10)
NO ABNORMALITY DETECTED	5			5
NEPHROPATHY, CHRONIC PROGRESSIVE.	4			5
INFLAMMATION, SUBACUTE/CHRONIC.	1			
URINARY BLADDER	(10)			(10)
NO ABNORMALITY DETECTED	10			10
RESPIRATORY SYSTEM				
LUNGS	(10)			(10)
NO ABNORMALITY DETECTED	5			6
INFLAMMATION, SUBACUTE/CHRONIC.	5			4
TRACHEA	(10)			(10)
NO ABNORMALITY DETECTED	10			10
PHARYNX/LARYNX	(10)			(10)
NO ABNORMALITY DETECTED	10			10
NOSE	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	2		
INFLAMMATION, SUBACUTE/CHRONIC.			5	6
HYPERPLASIA/HYPERTROPHY, TRANSITIONAL CELL, EPITHELIUM.				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 37 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
RESPIRATORY SYSTEM					
NOSE		(10)	(10)	(10)	(10)
DEGENERATION/NECROSIS, OLFACTORY, EPITHELIUM.			8	10	10
CARDIOVASCULAR SYSTEM					
HEART		(10)			(10)
NO ABNORMALITY DETECTED		5			6
CARDIOMYOPATHY.		5			4
AORTA		(10)			(10)
NO ABNORMALITY DETECTED		10			10
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN		(10)			(10)
NO ABNORMALITY DETECTED		10			10
THYMUS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MANDIBULAR LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MESENTERIC LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 37 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM				
BONE MARROW	(10)			(10)
NO ABNORMALITY DETECTED	10			10
ENDOCRINE SYSTEM				
PITUITARY GLAND	(10)			(10)
NO ABNORMALITY DETECTED	10			9
CYST.				1
THYROID GLAND	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	2	2		
HYPERTROPHY, FOLLICULAR.			5	10
ALTERATION, COLLOID.	8	8	10	10
PARATHYROID GLANDS	(6)			(7)
NO ABNORMALITY DETECTED	6			7
ADRENAL GLANDS	(10)			(10)
NO ABNORMALITY DETECTED	10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 37 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
NERVOUS SYSTEM					
BRAIN		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SPINAL CORD		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SCIATIC NERVE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MUSCULAR AND SKELETAL SYSTEM					
SKELETAL MUSCLE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
FEMUR/KNEE JOINT		(10)			(10)
NO ABNORMALITY DETECTED		10			10
STERNUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 37 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
REPRODUCTIVE SYSTEM					
TESTES		(10)			(10)
NO ABNORMALITY DETECTED		10			9
DILATATION, SEMINIFEROUS TUBULES, UNILATERAL.					1
EPIDIDYMIDES		(10)			(10)
NO ABNORMALITY DETECTED		10			10
PROSTATE		(10)			(10)
NO ABNORMALITY DETECTED		9			9
INFLAMMATION, SUBACUTE/CHRONIC.		1			1
SEMINAL VESICLES		(10)			(10)
NO ABNORMALITY DETECTED		10			10
CUTANEOUS SYSTEM					
SKIN		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE		(10)			(10)
NO ABNORMALITY DETECTED		9			10
OPTIC NERVE NOT PRESENT.		1			
FOLD/ROSETTE, RETINAL.		1			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 37 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
LIVER		(10)			(10)
NO ABNORMALITY DETECTED		1			
NECROSIS, FOCAL.					3
INFLAMMATION, SUBACUTE/CHRONIC.		9			10
HYPERTROPHY, HEPATOCELLULAR.					10
FATTY CHANGE, MEDIAN CLEFT.		1			
RESPIRATORY SYSTEM					
NOSE		(10)			(10)
NO ABNORMALITY DETECTED		10			7
DEGENERATION/NECROSIS, OLFACTORY, EPITHELIUM.					3
ENDOCRINE SYSTEM					
THYROID GLAND		(10)			(10)
NO ABNORMALITY DETECTED		4			
HYPERTROPHY, FOLLICULAR.					8
ALTERATION, COLLOID.		6			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 37 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
LIVER		(5)	(5)	(4)	(5)
NECROSIS, FOCAL.			1		2
INFLAMMATION, SUBACUTE/CHRONIC.		5	5	3	4
HYPERTROPHY, HEPATOCELLULAR.				3	4
HYPERPLASIA, BILE DUCT.			1		
FATTY CHANGE, PERIPORTAL.		1	1		1
FATTY CHANGE, MEDIAN CLEFT.		1	2		
FATTY CHANGE, CENTRILOBULAR.					1
RESPIRATORY SYSTEM					
NOSE		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		5	5	4	4
INFLAMMATION, SUBACUTE/CHRONIC.					1
ENDOCRINE SYSTEM					
THYROID GLAND		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED			1		
ALTERATION, COLLOID.		5	4	4	5

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
DIGESTIVE SYSTEM				
LIVER	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	1			
NECROSIS, FOCAL.			1	
INFLAMMATION, SUBACUTE/CHRONIC.	9	10	10	10
FATTY CHANGE, MEDIAN CLEFT.	1	1	1	2
PANCREAS	(10)			(10)
NO ABNORMALITY DETECTED	6			10
ATROPHY.	4			
ESOPHAGUS	(10)			(10)
NO ABNORMALITY DETECTED	9			10
FIBROSIS.	1			
STOMACH	(10)			(10)
NO ABNORMALITY DETECTED	9			10
CYST, KERATIN.	1			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
DIGESTIVE SYSTEM					
DUODENUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
JEJUNUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
ILEUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
CECUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
COLON		(10)			(10)
NO ABNORMALITY DETECTED		10			10
RECTUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
DIGESTIVE SYSTEM				
SALIVARY GLANDS	(10)			(10)
NO ABNORMALITY DETECTED	10			10
URINARY SYSTEM				
KIDNEYS	(10)			(10)
NO ABNORMALITY DETECTED	8			9
NEPHROPATHY, CHRONIC PROGRESSIVE.	1			
INFLAMMATION, SUBACUTE/CHRONIC.				1
HYDRONEPHROSIS, UNILATERAL.	1			
URINARY BLADDER	(10)			(10)
NO ABNORMALITY DETECTED	10			10
RESPIRATORY SYSTEM				
LUNGS	(10)			(10)
NO ABNORMALITY DETECTED	10			9
INFLAMMATION, SUBACUTE/CHRONIC.				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
RESPIRATORY SYSTEM					
TRACHEA		(10)			(10)
NO ABNORMALITY DETECTED		10			10
PHARYNX/LARYNX		(10)			(10)
NO ABNORMALITY DETECTED		10			10
NOSE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	8	6	2
INFLAMMATION, SUBACUTE/CHRONIC.				1	1
HYPERPLASIA/HYPERTROPHY, TRANSITIONAL CELL, EPITHELIUM.				1	
DEGENERATION/NECROSIS, OLFACTORY, EPITHELIUM.			2	4	8
CARDIOVASCULAR SYSTEM					
HEART		(10)			(10)
NO ABNORMALITY DETECTED		8			9
CARDIOMYOPATHY.		2			1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
CARDIOVASCULAR SYSTEM					
AORTA		(10)			(10)
NO ABNORMALITY DETECTED		10			10
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN		(10)			(10)
NO ABNORMALITY DETECTED		9			10
PIGMENT INCREASED.		1			
THYMUS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MANDIBULAR LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MESENTERIC LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM				
BONE MARROW	(10)			(10)
NO ABNORMALITY DETECTED	10			10
ENDOCRINE SYSTEM				
PITUITARY GLAND	(9)			(10)
NO ABNORMALITY DETECTED	9			10
THYROID GLAND	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	7	5	4	
HYPERTROPHY, FOLLICULAR.			2	7
ALTERATION, COLLOID.	3	5	6	10
PARATHYROID GLANDS	(8)			(2)
NO ABNORMALITY DETECTED	8			2
ADRENAL GLANDS	(10)			(10)
NO ABNORMALITY DETECTED	10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
NERVOUS SYSTEM					
BRAIN		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SPINAL CORD		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SCIATIC NERVE		(10)			(9)
NO ABNORMALITY DETECTED		10			9
MUSCULAR AND SKELETAL SYSTEM					
SKELETAL MUSCLE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
FEMUR/KNEE JOINT		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
MUSCULAR AND SKELETAL SYSTEM				
STERNUM	(10)			(10)
NO ABNORMALITY DETECTED	10			10
REPRODUCTIVE SYSTEM				
OVARIES	(10)			(10)
NO ABNORMALITY DETECTED	10			10
UTERUS	(10)			(10)
NO ABNORMALITY DETECTED	10			7
DILATATION, LUMEN.				3
MAMMARY GLAND (FEMALE)	(10)			(10)
NO ABNORMALITY DETECTED	10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
CUTANEOUS SYSTEM					
SKIN		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE		(10)			(10)
NO ABNORMALITY DETECTED		9			10
OPTIC NERVE NOT PRESENT.		1			1
FOLD/ROSETTE, RETINAL.		1			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
DIGESTIVE SYSTEM				
LIVER	(10)			(10)
NO ABNORMALITY DETECTED				1
NECROSIS, FOCAL.				1
INFLAMMATION, SUBACUTE/CHRONIC.	10			9
FATTY CHANGE, MEDIAN CLEFT.	3			1
PANCREAS				(1)
NO ABNORMALITY DETECTED				1
ESOPHAGUS				(1)
NO ABNORMALITY DETECTED				1
STOMACH				(1)
NO ABNORMALITY DETECTED				1
DUODENUM				(1)
NO ABNORMALITY DETECTED				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
DIGESTIVE SYSTEM				
JEJUNUM				(1)
NO ABNORMALITY DETECTED				1
ILEUM				(1)
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.				1
CECUM				(1)
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.				1
COLON				(1)
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.				1
RECTUM				(1)
NO ABNORMALITY DETECTED				1
SALIVARY GLANDS				(1)
NO ABNORMALITY DETECTED				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
URINARY SYSTEM				
KIDNEYS				(1)
NO ABNORMALITY DETECTED				1
URINARY BLADDER				(1)
NO ABNORMALITY DETECTED				1
RESPIRATORY SYSTEM				
LUNGS				(1)
NO ABNORMALITY DETECTED				1
TRACHEA				(1)
NO ABNORMALITY DETECTED				1
PHARYNX/LARYNX				(1)
NO ABNORMALITY DETECTED				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
RESPIRATORY SYSTEM				
NOSE	(10)			(10)
NO ABNORMALITY DETECTED	10			10
CARDIOVASCULAR SYSTEM				
HEART				(1)
NO ABNORMALITY DETECTED				1
AORTA				(1)
NO ABNORMALITY DETECTED				1
LYMPHATIC AND HEMATOPOIETIC SYSTEM				
SPLEEN				(1)
NO ABNORMALITY DETECTED				1
THYMUS				(1)
NO ABNORMALITY DETECTED				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM				
MANDIBULAR LYMPH NODE				(1)
NO ABNORMALITY DETECTED				1
MESENTERIC LYMPH NODE				(1)
NO ABNORMALITY DETECTED				1
BONE MARROW				(1)
NO ABNORMALITY DETECTED				1
ENDOCRINE SYSTEM				
PITUITARY GLAND				(1)
NO ABNORMALITY DETECTED				1
THYROID GLAND	(10)			(10)
NO ABNORMALITY DETECTED	4			2
HYPERTROPHY, FOLLICULAR.				5
ALTERATION, COLLOID.	6			7

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
ENDOCRINE SYSTEM				
THYROID GLAND	(10)			(10)
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.				1
PARATHYROID GLANDS				(1)
NO ABNORMALITY DETECTED				1
ADRENAL GLANDS				(1)
NO ABNORMALITY DETECTED				1
NERVOUS SYSTEM				
BRAIN				(1)
MIXED GLIOMA [M].				1
SPINAL CORD				(1)
NO ABNORMALITY DETECTED				1

[M] Malignant tumor
Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
NERVOUS SYSTEM					
SCIATIC NERVE					(1)
NO ABNORMALITY DETECTED					1
MUSCULAR AND SKELETAL SYSTEM					
SKELETAL MUSCLE					(1)
NO ABNORMALITY DETECTED					1
FEMUR/KNEE JOINT					(1)
NO ABNORMALITY DETECTED					1
STERNUM					(1)
NO ABNORMALITY DETECTED					1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
REPRODUCTIVE SYSTEM				
OVARIES				(1)
NO ABNORMALITY DETECTED				1
UTERUS				(1)
NO ABNORMALITY DETECTED				1
SPECIAL SENSES SYSTEM				
EYE(S) WITH OPTIC NERVE				(1)
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 38 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(3-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
DIGESTIVE SYSTEM				
LIVER	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	2	1	2	
INFLAMMATION, SUBACUTE/CHRONIC.	3	4	3	5
FATTY CHANGE, MEDIAN CLEFT.		1		2
FATTY CHANGE, FOCAL.			1	
RESPIRATORY SYSTEM				
NOSE	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	2	4	5	5
INFLAMMATION, SUBACUTE/CHRONIC.	2	1		
ATROPHY, UNILATERAL, NASAL GLANDS.	1			
ENDOCRINE SYSTEM				
THYROID GLAND	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	2		1	2
HYPERTROPHY, FOLLICULAR.				1
ALTERATION, COLLOID.	3	5	4	3

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
LIVER		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		1			
NECROSIS, FOCAL.					
minimal		2	2		1
Total observations per lesion		2	2		1
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal		9	10	10	10
Total observations per lesion		9	10	10	10
HYPERTROPHY, HEPATOCELLULAR.					
minimal			1	2	
mild				8	10
Total observations per lesion			1	10	10
HYPERPLASIA, BILE DUCT.					
minimal		1	1		
Total observations per lesion		1	1		
FATTY CHANGE, PERIPORTAL.					
minimal			3		
Total observations per lesion			3		
FATTY CHANGE, MEDIAN CLEFT.					
minimal			1		1
mild				1	
Total observations per lesion			1	1	1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
LIVER		(10)	(10)	(10)	(10)
FATTY CHANGE, CENTRILOBULAR.					
minimal				1	
Total observations per lesion				1	
PANCREAS		(10)			(10)
NO ABNORMALITY DETECTED		6			8
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal		4			
Total observations per lesion		4			
ATROPHY.					
minimal		1			2
Total observations per lesion		1			2
ESOPHAGUS		(10)			(10)
NO ABNORMALITY DETECTED		9			9
FIBROSIS.					
minimal		1			1
Total observations per lesion		1			1
STOMACH		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
DUODENUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
JEJUNUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
ILEUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
CECUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
COLON		(10)			(10)
NO ABNORMALITY DETECTED		10			10
RECTUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SALIVARY GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		10			9
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal					1
Total observations per lesion					1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
URINARY SYSTEM					
KIDNEYS		(10)			(10)
NO ABNORMALITY DETECTED		5			5
NEPHROPATHY, CHRONIC PROGRESSIVE.					
minimal		4			5
Total observations per lesion		4			5
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal		1			
Total observations per lesion		1			
URINARY BLADDER		(10)			(10)
NO ABNORMALITY DETECTED		10			10
RESPIRATORY SYSTEM					
LUNGS		(10)			(10)
NO ABNORMALITY DETECTED		5			6
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal		5			4
Total observations per lesion		5			4
TRACHEA		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
RESPIRATORY SYSTEM					
PHARYNX/LARYNX		(10)			(10)
NO ABNORMALITY DETECTED		10			10
NOSE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	2		
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal				5	6
Total observations per lesion				5	6
HYPERPLASIA/HYPERTROPHY, TRANSITIONAL CELL, EPITHELIUM.					
minimal					1
Total observations per lesion					1
DEGENERATION/NECROSIS, OLFACTORY, EPITHELIUM.					
minimal			7	3	1
mild			1	7	7
moderate					2
Total observations per lesion			8	10	10
CARDIOVASCULAR SYSTEM					
HEART		(10)			(10)
NO ABNORMALITY DETECTED		5			6
CARDIOMYOPATHY.					
minimal		5			4
Total observations per lesion		5			4

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
CARDIOVASCULAR SYSTEM					
AORTA		(10)			(10)
NO ABNORMALITY DETECTED		10			10
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN		(10)			(10)
NO ABNORMALITY DETECTED		10			10
THYMUS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MANDIBULAR LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MESENTERIC LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
BONE MARROW		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
ENDOCRINE SYSTEM					
PITUITARY GLAND		(10)			(10)
NO ABNORMALITY DETECTED		10			9
CYST.					
minimal					1
Total observations per lesion					1
THYROID GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		2	2		
HYPERTROPHY, FOLLICULAR.					
minimal				5	2
mild					8
Total observations per lesion				5	10
ALTERATION, COLLOID.					
minimal		8	5	6	1
mild			3	4	3
moderate					3
severe					3
Total observations per lesion		8	8	10	10
PARATHYROID GLANDS		(6)			(7)
NO ABNORMALITY DETECTED		6			7

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
ENDOCRINE SYSTEM					
ADRENAL GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
NERVOUS SYSTEM					
BRAIN		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SPINAL CORD		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SCIATIC NERVE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MUSCULAR AND SKELETAL SYSTEM					
SKELETAL MUSCLE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
FEMUR/KNEE JOINT		(10)			(10)
NO ABNORMALITY DETECTED		10			10
STERNUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
REPRODUCTIVE SYSTEM					
TESTES		(10)			(10)
NO ABNORMALITY DETECTED		10			9
DILATATION, SEMINIFEROUS TUBULES, UNILATERAL.					
mild					1
Total observations per lesion					1
EPIDIDYMIDES		(10)			(10)
NO ABNORMALITY DETECTED		10			10
PROSTATE		(10)			(10)
NO ABNORMALITY DETECTED		9			9
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal		1			1
Total observations per lesion		1			1
SEMINAL VESICLES		(10)			(10)
NO ABNORMALITY DETECTED		10			10
CUTANEOUS SYSTEM					
SKIN		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE		(10)			(10)
NO ABNORMALITY DETECTED		9			10
OPTIC NERVE NOT PRESENT.		1			
FOLD/ROSETTE, RETINAL.					
minimal		1			
Total observations per lesion		1			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
LIVER		(10)			(10)
NO ABNORMALITY DETECTED		1			
NECROSIS, FOCAL.					
minimal					3
Total observations per lesion					3
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal		9			10
Total observations per lesion		9			10
HYPERTROPHY, HEPATOCELLULAR.					
minimal					10
Total observations per lesion					10
FATTY CHANGE, MEDIAN CLEFT.					
minimal		1			
Total observations per lesion		1			
RESPIRATORY SYSTEM					
NOSE		(10)			(10)
NO ABNORMALITY DETECTED		10			7
DEGENERATION/NECROSIS, OLFACTORY, EPITHELIUM.					
minimal					3
Total observations per lesion					3

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
ENDOCRINE SYSTEM				
THYROID GLAND	(10)			(10)
NO ABNORMALITY DETECTED	4			
HYPERTROPHY, FOLLICULAR.				
minimal				5
mild				3
Total observations per lesion				8
ALTERATION, COLLOID.				
minimal	5			2
mild	1			1
moderate				3
severe				4
Total observations per lesion	6			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
LIVER		(5)	(5)	(4)	(5)
NECROSIS, FOCAL.					2
mild			1		
moderate			1		2
Total observations per lesion					
INFLAMMATION, SUBACUTE/CHRONIC.		5	5	3	4
minimal		5	5	3	4
Total observations per lesion					
HYPERTROPHY, HEPATOCELLULAR.				3	4
minimal				3	4
Total observations per lesion					
HYPERPLASIA, BILE DUCT.			1		
minimal			1		
Total observations per lesion					
FATTY CHANGE, PERIPORTAL.		1	1		
minimal					1
mild		1	1		1
Total observations per lesion					
FATTY CHANGE, MEDIAN CLEFT.			2		
minimal		1			
mild		1	2		
Total observations per lesion					

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 39 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS-
NON-NEOPLASTIC LESIONS
(3-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
DIGESTIVE SYSTEM				
LIVER	(5)	(5)	(4)	(5)
FATTY CHANGE, CENTRILOBULAR.				
mild				1
Total observations per lesion				1
RESPIRATORY SYSTEM				
NOSE	(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED	5	5	4	4
INFLAMMATION, SUBACUTE/CHRONIC.				
minimal				1
Total observations per lesion				1
ENDOCRINE SYSTEM				
THYROID GLAND	(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		1		
ALTERATION, COLLOID.				
minimal	4	2	1	1
mild	1	2	1	1
moderate			2	2
severe				1
Total observations per lesion	5	4	4	5

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
DIGESTIVE SYSTEM				
LIVER	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	1			
NECROSIS, FOCAL.				
minimal			1	
Total observations per lesion			1	
INFLAMMATION, SUBACUTE/CHRONIC.				
minimal	9	10	10	10
Total observations per lesion	9	10	10	10
FATTY CHANGE, MEDIAN CLEFT.				
minimal	1	1	1	2
Total observations per lesion	1	1	1	2
PANCREAS	(10)			(10)
NO ABNORMALITY DETECTED	6			10
ATROPHY.				
minimal	4			
Total observations per lesion	4			
ESOPHAGUS	(10)			(10)
NO ABNORMALITY DETECTED	9			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
DIGESTIVE SYSTEM				
ESOPHAGUS	(10)			(10)
FIBROSIS.				
minimal	1			
Total observations per lesion	1			
STOMACH	(10)			(10)
NO ABNORMALITY DETECTED	9			10
CYST, KERATIN.				
minimal	1			
Total observations per lesion	1			
DUODENUM	(10)			(10)
NO ABNORMALITY DETECTED	10			10
JEJUNUM	(10)			(10)
NO ABNORMALITY DETECTED	10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
DIGESTIVE SYSTEM					
ILEUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
CECUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
COLON		(10)			(10)
NO ABNORMALITY DETECTED		10			10
RECTUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SALIVARY GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
URINARY SYSTEM					
KIDNEYS		(10)			(10)
NO ABNORMALITY DETECTED		8			9
NEPHROPATHY, CHRONIC PROGRESSIVE.					
minimal		1			
Total observations per lesion		1			
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal					1
Total observations per lesion					1
HYDRONEPHROSIS, UNILATERAL.					
minimal		1			
Total observations per lesion		1			
URINARY BLADDER		(10)			(10)
NO ABNORMALITY DETECTED		10			10
RESPIRATORY SYSTEM					
LUNGS		(10)			(10)
NO ABNORMALITY DETECTED		10			9

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
RESPIRATORY SYSTEM					
LUNGS		(10)			(10)
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal					1
Total observations per lesion					1
TRACHEA		(10)			(10)
NO ABNORMALITY DETECTED		10			10
PHARYNX/LARYNX		(10)			(10)
NO ABNORMALITY DETECTED		10			10
NOSE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	8	6	2
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal					1
mild				1	
Total observations per lesion				1	1
HYPERPLASIA/HYPERTROPHY, TRANSITIONAL CELL, EPITHELIUM.					
minimal				1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
RESPIRATORY SYSTEM					
NOSE		(10)	(10)	(10)	(10)
HYPERPLASIA/HYPERTROPHY, TRANSITIONAL CELL, EPITHELIUM.					
Total observations per lesion				1	
DEGENERATION/NECROSIS, OLFACTORY, EPITHELIUM.					
minimal			2	3	6
mild				1	2
Total observations per lesion			2	4	8
CARDIOVASCULAR SYSTEM					
HEART		(10)			(10)
NO ABNORMALITY DETECTED		8			9
CARDIOMYOPATHY.					
minimal		2			1
Total observations per lesion		2			1
AORTA		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN		(10)			(10)
NO ABNORMALITY DETECTED		9			10
PIGMENT INCREASED.					
mild		1			
Total observations per lesion		1			
THYMUS		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MANDIBULAR LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
MESENTERIC LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
BONE MARROW		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
ENDOCRINE SYSTEM					
PITUITARY GLAND		(9)			(10)
NO ABNORMALITY DETECTED		9			10
THYROID GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		7	5	4	
HYPERTROPHY, FOLLICULAR.					
minimal				2	4
mild					3
Total observations per lesion				2	7
ALTERATION, COLLOID.					
minimal		3	5	6	9
mild					1
Total observations per lesion		3	5	6	10
PARATHYROID GLANDS		(8)			(2)
NO ABNORMALITY DETECTED		8			2
ADRENAL GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
NERVOUS SYSTEM					
BRAIN		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SPINAL CORD		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SCIATIC NERVE		(10)			(9)
NO ABNORMALITY DETECTED		10			9
MUSCULAR AND SKELETAL SYSTEM					
SKELETAL MUSCLE		(10)			(10)
NO ABNORMALITY DETECTED		10			10
FEMUR/KNEE JOINT		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
MUSCULAR AND SKELETAL SYSTEM				
STERNUM	(10)			(10)
NO ABNORMALITY DETECTED	10			10
REPRODUCTIVE SYSTEM				
OVARIES	(10)			(10)
NO ABNORMALITY DETECTED	10			10
UTERUS	(10)			(10)
NO ABNORMALITY DETECTED	10			7
DILATATION, LUMEN.				
minimal				2
mild				1
Total observations per lesion				3
MAMMARY GLAND (FEMALE)	(10)			(10)
NO ABNORMALITY DETECTED	10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
CUTANEOUS SYSTEM					
SKIN		(10)			(10)
NO ABNORMALITY DETECTED		10			10
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE		(10)			(10)
NO ABNORMALITY DETECTED		9			10
OPTIC NERVE NOT PRESENT.		1			1
FOLD/ROSETTE, RETINAL.					
minimal		1			
Total observations per lesion		1			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
DIGESTIVE SYSTEM					
LIVER		(10)			(10)
NO ABNORMALITY DETECTED					1
NECROSIS, FOCAL.					
minimal					1
Total observations per lesion					1
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal		10			9
Total observations per lesion		10			9
FATTY CHANGE, MEDIAN CLEFT.					
minimal		2			1
mild		1			
Total observations per lesion		3			1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
DIGESTIVE SYSTEM				
PANCREAS				(1)
NO ABNORMALITY DETECTED				1
ESOPHAGUS				(1)
NO ABNORMALITY DETECTED				1
STOMACH				(1)
NO ABNORMALITY DETECTED				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
DIGESTIVE SYSTEM				
DUODENUM				(1)
NO ABNORMALITY DETECTED				1
JEJUNUM				(1)
NO ABNORMALITY DETECTED				1
ILEUM				(1)
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
DIGESTIVE SYSTEM				
CECUM				(1)
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.				1
COLON				(1)
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.				1
RECTUM				(1)
NO ABNORMALITY DETECTED				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
DIGESTIVE SYSTEM					
SALIVARY GLANDS					(1)
NO ABNORMALITY DETECTED					1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
URINARY SYSTEM					
KIDNEYS					(1)
NO ABNORMALITY DETECTED					1
URINARY BLADDER					(1)
NO ABNORMALITY DETECTED					1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
RESPIRATORY SYSTEM				
LUNGS				(1)
NO ABNORMALITY DETECTED				1
TRACHEA				(1)
NO ABNORMALITY DETECTED				1
PHARYNX/LARYNX				(1)
NO ABNORMALITY DETECTED				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
RESPIRATORY SYSTEM					
NOSE		(10)			(10)
NO ABNORMALITY DETECTED		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
CARDIOVASCULAR SYSTEM				
HEART				(1)
NO ABNORMALITY DETECTED				1
AORTA				(1)
NO ABNORMALITY DETECTED				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM				
SPLEEN				(1)
NO ABNORMALITY DETECTED				1
THYMUS				(1)
NO ABNORMALITY DETECTED				1
MANDIBULAR LYMPH NODE				(1)
NO ABNORMALITY DETECTED				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM				
MESENTERIC LYMPH NODE				(1)
NO ABNORMALITY DETECTED				1
BONE MARROW				(1)
NO ABNORMALITY DETECTED				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
ENDOCRINE SYSTEM					
PITUITARY GLAND					(1)
NO ABNORMALITY DETECTED					1
THYROID GLAND		(10)			(10)
NO ABNORMALITY DETECTED		4			2
HYPERTROPHY, FOLLICULAR.					
minimal					4
mild					1
Total observations per lesion					5
ALTERATION, COLLOID.					
minimal		6			5
mild					1
moderate					1
Total observations per lesion		6			7
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
ENDOCRINE SYSTEM					
PARATHYROID GLANDS					(1)
NO ABNORMALITY DETECTED					1
ADRENAL GLANDS					(1)
NO ABNORMALITY DETECTED					1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
NERVOUS SYSTEM				
SPINAL CORD				(1)
NO ABNORMALITY DETECTED				1
SCIATIC NERVE				(1)
NO ABNORMALITY DETECTED				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	II	IV	VI	VIII
MUSCULAR AND SKELETAL SYSTEM				
SKELETAL MUSCLE				(1)
NO ABNORMALITY DETECTED				1
FEMUR/KNEE JOINT				(1)
NO ABNORMALITY DETECTED				1
STERNUM				(1)
NO ABNORMALITY DETECTED				1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
REPRODUCTIVE SYSTEM					
OVARIES					(1)
NO ABNORMALITY DETECTED					1
UTERUS					(1)
NO ABNORMALITY DETECTED					1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE					(1)
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
DIGESTIVE SYSTEM					
LIVER		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		2	1	2	
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal		3	4	3	5
Total observations per lesion		3	4	3	5
FATTY CHANGE, MEDIAN CLEFT.					
minimal			1		1
mild					1
Total observations per lesion			1		2
FATTY CHANGE, FOCAL.					
mild				1	
Total observations per lesion				1	
RESPIRATORY SYSTEM					
NOSE		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		2	4	5	5
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal		2	1		
Total observations per lesion		2	1		

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 40 (CONTINUED)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS-
NON-NEOPLASTIC LESIONS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		II	IV	VI	VIII
RESPIRATORY SYSTEM					
NOSE		(5)	(5)	(5)	(5)
ATROPHY, UNILATERAL, NASAL GLANDS.					
severe		1			
Total observations per lesion		1			
ENDOCRINE SYSTEM					
THYROID GLAND		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		2		1	2
HYPERTROPHY, FOLLICULAR.					
minimal					1
Total observations per lesion					1
ALTERATION, COLLOID.					
minimal		3	5	4	2
mild					1
Total observations per lesion		3	5	4	3

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
LIVER		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		641094			
NECROSIS, FOCAL.		641149	641081		641157
		641172	641198		
INFLAMMATION, SUBACUTE/CHRONIC.		641069	641055	641061	641067
		641070	641056	641089	641077
		641147	641073	641102	641086
		641149	641081	641134	641095
		641155	641144	641137	641097
		641172	641146	641162	641132
		641206	641178	641190	641157
		641214	641198	641197	641166
		641222	641218	641200	641201
			641224	641202	641223
HYPERTROPHY, HEPATOCELLULAR.			641081	641061	641067
				641089	641077
				641102	641086
				641134	641095
				641137	641097
				641162	641132
				641190	641157
				641197	641166
				641200	641201

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
LIVER		(10)	(10)	(10)	(10)
HYPERTROPHY, HEPATOCELLULAR.				641202	641223
HYPERPLASIA, BILE DUCT.		641172	641081		
FATTY CHANGE, PERIPORTAL.			641144		
			641198		
			641224		
FATTY CHANGE, MEDIAN CLEFT.			641218	641200	641201
FATTY CHANGE, CENTRILOBULAR.				641200	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
PANCREAS		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641094			641077
		641147			641095
		641155			641132
		641172			641157
		641222			641166
					641201
					641223
INFLAMMATION, SUBACUTE/CHRONIC.		641070			
		641149			
		641206			
		641214			
ATROPHY.		641214			641086
					641097

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
ESOPHAGUS		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641206			641157
		641214			641201
		641222			641223
FIBROSIS.		641172			641166

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
STOMACH		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
DUODENUM		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
JEJUNUM		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
ILEUM		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
CECUM		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
DIGESTIVE SYSTEM				
COLON	(10)			(10)
NO ABNORMALITY DETECTED	641069			641067
	641070			641077
	641094			641086
	641147			641095
	641149			641097
	641155			641132
	641172			641157
	641206			641166
	641214			641201
	641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
RECTUM		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
SALIVARY GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641157
		641172			641166
		641206			641201
		641214			641223
		641222			
INFLAMMATION, SUBACUTE/CHRONIC.					641132

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
URINARY SYSTEM					
KIDNEYS		(10)			(10)
NO ABNORMALITY DETECTED		641069			641086
		641155			641132
		641172			641166
		641214			641201
		641222			641223
NEPHROPATHY, CHRONIC PROGRESSIVE.		641070			641067
		641147			641077
		641149			641095
		641206			641097
					641157
INFLAMMATION, SUBACUTE/CHRONIC.		641094			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
URINARY SYSTEM					
URINARY BLADDER		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
RESPIRATORY SYSTEM					
LUNGS		(10)			(10)
NO ABNORMALITY DETECTED		641094			641077
		641147			641086
		641149			641132
		641214			641157
		641222			641166
					641223
INFLAMMATION, SUBACUTE/CHRONIC.		641069			641067
		641070			641095
		641155			641097
		641172			641201
		641206			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
RESPIRATORY SYSTEM					
TRACHEA		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
RESPIRATORY SYSTEM					
PHARYNX/LARYNX		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
RESPIRATORY SYSTEM					
NOSE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		641069	641178		
		641070	641198		
		641094			
		641147			
		641149			
		641155			
		641172			
		641206			
		641214			
		641222			
INFLAMMATION, SUBACUTE/CHRONIC.				641089	641067
				641102	641086
				641162	641095
				641190	641132
				641202	641157
					641201
					641201
HYPERPLASIA/HYPERTROPHY, TRANSITIONAL CELL, EPITHELIUM.			641055	641061	641067
DEGENERATION/NECROSIS, OLFACTORY, EPITHELIUM.			641056	641089	641077
			641073	641102	641086
			641081	641134	641095
			641144	641137	641097

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
RESPIRATORY SYSTEM				
NOSE	(10)	(10)	(10)	(10)
DEGENERATION/NECROSIS, OLFACTORY, EPITHELIUM.		641146	641162	641132
		641218	641190	641157
		641224	641197	641166
			641200	641201
			641202	641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
CARDIOVASCULAR SYSTEM					
HEART		(10)			(10)
NO ABNORMALITY DETECTED		641070			641086
		641094			641097
		641155			641157
		641172			641166
		641222			641201
					641223
CARDIOMYOPATHY.		641069			641067
		641147			641077
		641149			641095
		641206			641132
		641214			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
CARDIOVASCULAR SYSTEM					
AORTA		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM				
SPLEEN	(10)			(10)
NO ABNORMALITY DETECTED	641069			641067
	641070			641077
	641094			641086
	641147			641095
	641149			641097
	641155			641132
	641172			641157
	641206			641166
	641214			641201
	641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
THYMUS		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
MANDIBULAR LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
MESENTERIC LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
BONE MARROW		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
ENDOCRINE SYSTEM					
PITUITARY GLAND		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641095
		641147			641097
		641149			641132
		641155			641157
		641172			641166
		641206			641201
		641214			641223
		641222			
CYST.					641086

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
ENDOCRINE SYSTEM					
THYROID GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		641069	641218		
		641070	641224		
HYPERTROPHY, FOLLICULAR.				641102	641067
				641137	641077
				641162	641086
				641197	641095
				641202	641097
					641132
					641157
					641166
					641201
					641223
ALTERATION, COLLOID.		641094	641055	641061	641067
		641147	641056	641089	641077
		641149	641073	641102	641086
		641155	641081	641134	641095
		641172	641144	641137	641097
		641206	641146	641162	641132
		641214	641178	641190	641157
		641222	641198	641197	641166
				641200	641201
				641202	641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
ENDOCRINE SYSTEM					
PARATHYROID GLANDS		(6)			(7)
NO ABNORMALITY DETECTED		641070			641067
		641147			641077
		641172			641095
		641206			641132
		641214			641157
		641222			641166
					641201

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
ENDOCRINE SYSTEM					
ADRENAL GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
NERVOUS SYSTEM					
BRAIN		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
NERVOUS SYSTEM					
SPINAL CORD		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
NERVOUS SYSTEM					
SCIATIC NERVE		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
MUSCULAR AND SKELETAL SYSTEM					
SKELETAL MUSCLE		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
MUSCULAR AND SKELETAL SYSTEM					
FEMUR/KNEE JOINT		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
MUSCULAR AND SKELETAL SYSTEM					
STERNUM		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
REPRODUCTIVE SYSTEM					
TESTES		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			
DILATATION, SEMINIFEROUS TUBULES, UNILATERAL.					641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
REPRODUCTIVE SYSTEM					
EPIDIDYMIDES		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
REPRODUCTIVE SYSTEM					
PROSTATE		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641094			641077
		641147			641086
		641149			641095
		641155			641097
		641172			641132
		641206			641166
		641214			641201
		641222			641223
INFLAMMATION, SUBACUTE/CHRONIC.		641070			641157

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
REPRODUCTIVE SYSTEM					
SEMINAL VESICLES		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
CUTANEOUS SYSTEM					
SKIN		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641172			641157
		641206			641166
		641214			641201
		641222			641223

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE		(10)			(10)
NO ABNORMALITY DETECTED		641069			641067
		641070			641077
		641094			641086
		641147			641095
		641149			641097
		641155			641132
		641206			641157
		641214			641166
		641222			641201
					641223
OPTIC NERVE NOT PRESENT.		641069			
FOLD/ROSETTE, RETINAL.		641172			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
DIGESTIVE SYSTEM				
LIVER	(10)			(10)
NO ABNORMALITY DETECTED	641083			
NECROSIS, FOCAL.				641189
				641203
				641213
INFLAMMATION, SUBACUTE/CHRONIC.	641084			641064
	641085			641092
	641101			641143
	641105			641153
	641123			641167
	641154			641185
	641159			641189
	641165			641203
	641215			641213
				641216
HYPERTROPHY, HEPATOCELLULAR.				641064
				641092
				641143
				641153
				641167
				641185
				641189
				641203

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
DIGESTIVE SYSTEM					
LIVER		(10)			(10)
HYPERTROPHY, HEPATOCELLULAR.					641213
					641216
FATTY CHANGE, MEDIAN CLEFT.		641159			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
RESPIRATORY SYSTEM					
NOSE		(10)			(10)
NO ABNORMALITY DETECTED		641083			641092
		641084			641153
		641085			641185
		641101			641189
		641105			641203
		641123			641213
		641154			641216
		641159			
		641165			
		641215			
DEGENERATION/NECROSIS, OLFACTORY, EPITHELIUM.					641064
					641143
					641167

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
ENDOCRINE SYSTEM				
THYROID GLAND	(10)			(10)
NO ABNORMALITY DETECTED	641083			
	641084			
	641165			
	641215			
HYPERTROPHY, FOLLICULAR.				641064
				641092
				641153
				641167
				641185
				641189
				641203
				641216
ALTERATION, COLLOID.	641085			641064
	641101			641092
	641105			641143
	641123			641153
	641154			641167
	641159			641185
				641189
				641203
				641213
				641216

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(3-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
DIGESTIVE SYSTEM				
LIVER	(5)	(5)	(4)	(5)
NECROSIS, FOCAL.		641113		641169
				641196
INFLAMMATION, SUBACUTE/CHRONIC.	641066	641059	641141	641057
	641098	641113	641148	641130
	641104	641160	641187	641169
	641115	641194		641196
	641220	641225		
HYPERTROPHY, HEPATOCELLULAR.			641076	641130
			641141	641169
			641148	641196
				641205
HYPERPLASIA, BILE DUCT.		641113		
FATTY CHANGE, PERIPORTAL.	641115	641113		641205
FATTY CHANGE, MEDIAN CLEFT.	641098	641059		
		641113		
FATTY CHANGE, CENTRILOBULAR.				641205

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(3-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC) 0	50	250	1000
		I	III	V	VII
RESPIRATORY SYSTEM					
NOSE		(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		641066	641059	641076	641057
		641098	641113	641141	641130
		641104	641160	641148	641169
		641115	641194	641187	641196
		641220	641225		
INFLAMMATION, SUBACUTE/CHRONIC.					641205

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 41 (CONTINUED)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED-
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(3-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)			
TREATMENT (mg/kg/day)	0	50	250	1000
	I	III	V	VII
ENDOCRINE SYSTEM				
THYROID GLAND	(5)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		641194		
ALTERATION, COLLOID.	641066	641059	641076	641057
	641098	641113	641141	641130
	641104	641160	641148	641169
	641115	641225	641187	641196
	641220			641205

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified