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TRADE SECRET***Study Title***

H-24768: Subchronic Toxicity
90-Day Gavage Study in Rats
with One-Generation Reproduction Evaluations

Volume 1 of 5

Laboratory Project ID: DuPont-5990

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

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STUDY COMPLETED ON: January 18, 2002

PERFORMING LABORATORY: E.I. du Pont de Nemours and Company
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[REDACTED]
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[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 item documented below. None of the items listed impact the validity of the study.

1. Test substance characterization and stability analyses were performed at Regional Analytical Services (RAS), a non-GLP laboratory. The test substance analyses performed were in compliance with regulatory guidelines. 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. The original necropsy sheets for 23 rats from the reproductive toxicology subset could not be located. Necropsy sheets for these rats were reprinted from the study electronic database. All information that is normally hand-entered that could be recalled or is documented elsewhere was added to these reprinted sheets. The names of the prosector and recorder for each specific rat could not be reconstructed.

Applicant / Sponsor: E.I. du Pont de Nemours and Company
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QUALITY ASSURANCE STATEMENT

Haskell Sample Number(s):

24768

Dates of Inspections:

Protocol: March 1, 2001

Conduct: March 15, 2001; May 10, 2001; June 1, 14, 29, 2001;
July 11, 2001; August 8, 2001; September 14, 2001

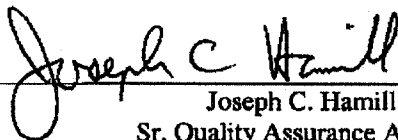
Records, Reports: September 21, 24, 25, 2001;
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Study Director: October 15, 22, 30, 2001; November 5, 9, 2001;
December 14, 18, 2001

Management: October 22, 30, 2001; November 5, 9, 20, 2001;
December 14, 2001; January 11, 2002

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Date

CERTIFICATION

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

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STUDY INFORMATION

9th Collective Nomenclature:

Synonyms/Codes:

- H-24768

Haskell Number: 24768

CAS Registry Number:

Composition

Purity:

Known Impurities:

Physical Characteristics: Tan to light brown paste

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

Study Initiated/Completed: March 14, 2001 / (see report cover page)

In-Life Initiated/Completed: March 15, 2001 / September 14, 2001

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SUMMARY

Four groups of young adult male and female Crl:CD[®](SD)IGS BR rats were administered H-24768 in deionized water by gavage for approximately 90 days, at dosages of 0, 25, 100, or 500 mg/kg/day. Selected animals from each dosage 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 14 of the 90-day dosing period, and near the end of the one-month and three-month recovery periods.

Neurobehavioral assessments were also performed prior to dosing, during week 13, and near the end of the one-month recovery period. Biochemical evaluations (hepatic β -oxidation) were performed on rats after 10 and approximately 90 days of dosing, and following one-month and three-month (males only) recovery periods. After approximately 90 days of dosing, 10 rats/sex/dose were sacrificed and given a gross and microscopic pathological examination. One month after the 90-day dosing period, 10 rats/sex in the control and high dose group were examined for recovery of toxic effects. An additional 5 rats/sex/dose were evaluated for recovery approximately 3 months following the end of the dosing period.

The range of mean daily dose volumes of H-24768 administered to male rats was 1.6 to 4.6 mL. The range administered to female rats was 1.3-2.4 mL. Analytical results demonstrated that the test substance was mixed properly, was at the targeted concentrations, and was stable in deionized water under relevant storage conditions used in this study.

In-Life Toxicology Parameters: No test substance-related deaths occurred in the subchronic toxicity part of the study. Test substance-related clinical signs of toxicity were observed in males and/or females dosed with 100 or 500 mg/kg/day. Compared to control, statistically significant lower body weight, body weight gain, and food efficiency were observed in male and female rats dosed with 500 mg/kg/day and in male rats dosed with 100 mg/kg/day, and were considered to be adverse. Mean body weight on test day 91 was 83% and 94% of control in male 500 and 100 mg/kg/day groups, respectively. Mean body weight on test day 91 was 94% of control in the female 500 mg/kg/day group. The body weight effects were attributed primarily to the reduced food efficiency. Mean food efficiency over test days 0-91 was 77% and 90% of control in male 500 and 100 mg/kg/day groups, respectively, and 88% of control in 500 mg/kg/day females. Adverse test substance-related reductions in food consumption were observed in male rats dosed with 500 mg/kg/day. Reversal of these effects was observed in both males and females by the end of the three-month recovery period. No test substance-related ophthalmologic effects were observed in any dose group.

Neurotoxicology Parameters: No test substance-related neurological effects were observed. Test substance-related reductions in forelimb and hindlimb grip strength were observed in 500 mg/kg/day male rats at the end of the dosing period, but were associated with reduced body weight and were partially reversible.

Biochemical Toxicology: Reversible increases in the rate of hepatic β -oxidation, a measure of peroxisome proliferation, were observed in male rats dosed with 100 or 500 mg/kg/day. No biologically significant effects on hepatic β -oxidation were observed in female rats.

Clinical Pathology: In males, adverse increases in liver enzyme activities (alanine aminotransferase and sorbitol dehydrogenase) were observed during treatment and following a three-month recovery period in rats dosed with 500 mg/kg/day; however, they were not associated with histological evidence of liver cytotoxicity. In females, adverse, but reversible, findings of decreased red cell mass (hemoglobin, hematocrit, and red cell count) were observed in rats dosed with 500 mg/kg/day. Other observed changes in clinical pathology parameters were considered treatment-related but non-adverse. The parameters thus affected were red cell mass and red cell indices in males, red cell shape, urea nitrogen, creatinine, inorganic phosphorus, cholesterol, triglycerides, alkaline phosphatase, bilirubin, albumin, globulin, calcium, sodium, chloride, potassium, urine volume, urine concentration, and urine pH.

Plasma fluoride concentration was increased during the dosing period in rats dosed with 25 (males only), 100, or 500 mg/kg/day, but returned to control levels following the three-month recovery period. Urine fluoride (total fluoride excreted over the collection period) was increased in males and females dosed with 25, 100, or 500 mg/kg/day. Urine fluoride greatly decreased during the recovery period, but remained slightly above control values at the end of the three-month recovery period in 100 and 500 mg/kg/day males and females, thus indicating the continued presence of fluorinated material.

Anatomic Pathology (Subchronic Toxicity): Exposure to the test substance for approximately 90 days produced alterations in the liver, kidney, spleen, and thyroid. Increased liver weights and/or microscopic hepatocellular hypertrophy were present in 25, 100, and 500 mg/kg/day males and females at the end of the dosing period, and in 500 mg/kg/day males and females after the one-month recovery. These liver changes were considered to be a non-adverse, physiologic response to metabolism of a xenobiotic. In 100 and 500 mg/kg/day male rats, the liver changes were associated with the induction of hepatic β -oxidation activity. Increased extramedullary hematopoiesis and increased pigment in the spleen were observed in 100 and 500 mg/kg/day males and females and, in females, were associated with increased relative spleen weight; they were considered to be non-adverse, secondary physiologic responses to changes in red cell mass.

Increased chronic progressive nephropathy, sometimes accompanied by increased kidney weight in females, was present in 500 and/or 100 mg/kg/day males and females, and did not demonstrate recovery in females. These histological findings were considered to be adverse. Non-adverse increases in urine volume, associated with reduced urine osmolality and specific gravity, were observed during the dosing period in 500 mg/kg/day males and females, but were reversed by the end of the one-month recovery period.

Compound-related hypertrophy of follicular epithelium in the thyroid was present in 100 and 500 mg/kg/day males and females at the 90-day sacrifice, in 500 mg/kg/day males and females at the one-month sacrifice, and in the 500 mg/kg/day males at the three-month sacrifice, and was considered potentially adverse. Non-adverse alteration of colloid was present in the thyroids of males and females at all dose levels at all time points.

Reproduction: Twenty male and 20 female rats from each dose group were designated for reproductive evaluations. Parental rats (P₁ generation) were dosed daily for 72 days prior to cohabitation, during the cohabitation period (mating) and during lactation, until the weaning of the F₁ offspring. The following parameters were evaluated in P₁ rats: body weight, food consumption, clinical signs, gross pathology, sperm parameters, estrous cyclicity, and reproductive performance. Reproductive organs of animals with impaired reproductive performance were evaluated microscopically. The F₁ offspring were evaluated during the lactation period for growth and survival and given a gross pathological examination at weaning. A subset of F₁ generation rats were retained at weaning, and the following parameters were evaluated for 6 weeks: body weight, food consumption, clinical signs, and age at onset of vaginal opening or preputial separation. After 6 weeks, the F₁ generation rats were given a gross pathological examination, and selected reproductive organs and target organs of toxicity were weighed.

Test substance-related reductions in body weight gain were observed in 500 mg/kg/day P₁ males during mating and in 500 mg/kg/day P₁ females during gestation. The female body weight gain reduction was associated with reduced food efficiency. Clinical observations in the reproduction subset of animals were similar to those reported for the subchronic toxicity subset.

Female rats exposed to all doses had a reduced fertility index (55%, 58%, and 65% of control in 25, 100, and 500 mg/kg/day groups, respectively) and increased estrus cycle length (109%, 114%, and 112% of control in 25, 100, and 500 mg/kg/day groups, respectively). For both endpoints, the magnitude of effects in the high-dose group was similar to that observed in the low-dose group. The lower fertility index was considered adverse in all groups. The toxicological significance of the increased estrous cycle length is unclear. Females dosed with 500 mg/kg/day also had a reduction in the number of uterine implantation sites (70% of control). No adverse test substance-related effects on sperm parameters or other reproductive indices were observed. Groups of male rats exposed to all doses had non-adverse reductions in epididymal sperm counts (88%, 91%, and 88% of control in 25, 100, and 500 mg/kg/day groups, respectively). There was no associated histopathology in the testis or epididymis. No test substance-related histopathology was observed in the reproductive organs of P₁ rats with impaired reproductive performance.

In the 500 mg/kg/day group, the following parameters were affected (% control): number of pups born (72%), number of pups born alive (66%), number of pups alive on day 4, 7, 14, and 21 of lactation (53, 60, 14, 10% of control respectively). The viability index (day 0-4 viability) was 83% compared to 98% in the control group. Live pup weight at birth was 90% of control and mean pup weights were 54%-71% of the control mean during lactation (days 4-21). The lactation index (survival to day 21) was 11.4% compared to 100% in the control group. The litter survival was also reduced (25% compared to 100% in the control group). Based on these data, the number of offspring in the 500 mg/kg/day group was already reduced at birth and death of live offspring continued during lactation, mainly after day 14 of lactation. Due to the high pup mortality in the 500 mg/kg/day group, there was an inadequate number to evaluate further endpoints and the remaining pups in this group were euthanized on postnatal day 33-35.

In the 100 mg/kg/day group, there was no apparent effect on number of pups until lactation day 14; the number of live pups was 79% and 76% of control at days 14 and 21, respectively. The lactation index was 76.1% compared to 100% in the control group. Pup weights were slightly reduced during lactation (86-94% of control mean). In the 25 mg/kg/day group, there were no effects on pup viability, survival or pup weights. No test substance-related clinical observations or effects on male or female developmental landmarks were observed in 100 or 25 mg/kg/day F₁ rats.

NOEL for Subchronic Toxicity: Under the conditions of this study, the no-observed-effect level (NOEL)^a for subchronic toxicity endpoints in male and female rats was 25 mg/kg/day. This level was based on clinical signs of toxicity, decrements in body weight parameters and food efficiency (males), thyroid follicular hypertrophy, and chronic progressive nephropathy (females), all observed in the 100 mg/kg/day groups. Other adverse, compound-related effects observed in males and/or females dosed with 500 mg/kg/day include decrements in body weight parameters and food efficiency (females), chronic progressive nephropathy (males), increased liver enzyme activity (males), reduction in red blood cell mass parameters (females), and reductions in forelimb and hindlimb grip strength (males). Most of the effects observed during the dosing period demonstrated full or partial reversal following one or three months of recovery. Reversal of many effects in females was not observed until after the one-month recovery. Thyroid follicular hypertrophy (500 mg/kg/day males) and chronic progressive nephropathy (100 and 500 mg/kg/day females) were still present at the end of the three-month recovery period.

NOEL for Reproductive Evaluations: Under the conditions of this study, there was no NOEL for reproductive evaluations. This was based on reductions in the fertility index in P₁ rats in all dose groups. Estrous cycle length was prolonged in P₁ rats in all dose groups, but the toxicological significance of this change is unclear. Other adverse, compound-related effects observed in P₁ rats dosed with 500 mg/kg/day include decrements in body weight parameters and food efficiency and reduced number of implantation sites. In F₁ generation rats, adverse, compound-related effects were observed in 100 and/or 500 mg/kg/day groups and included reductions in mean litter size, number of pups born and born alive, pup survival during lactation, and pup weight at birth and during lactation.

^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-24768, is a fluorinated organic ethoxylate used as a surfactant. The dose levels for this study were selected based on the toxicity and an analysis of blood fluorine concentrations from a range-finding study in which rats were dosed by oral gavage with 50, 100, 500, or 1000 mg/kg/day for approximately 62 days.

In the range-finding study, rats exposed to 1000 mg/kg/day were sacrificed on test day 18, due to body weight loss and reductions in body weight gain in males. Transient, statistically significant body weight loss or reductions in body weight gain (compared to control) were observed in male and female rats exposed to 500 mg/kg/day during the first week of exposure. In the 500 mg/kg/day male rats, mean body weights remained approximately 10-12% below control throughout the study. Weights of female rats in this group were similar to control throughout most of the study (no statistically significant differences). Reduced body weight over test days 0-4 was also observed in rats exposed to lower doses, but body weight parameters in these groups were comparable to control over the rest of the study. No compound-related clinical signs of toxicity were observed in any group. Blood fluorine levels in this range-finding study appeared to have reached a plateau within approximately 2-3 weeks of dosing.

Therefore, the high-dose level for this 90-day study of 500 mg/kg/day was selected based on the ability of rats to tolerate this dose in the range-finding study. This dose was expected to produce toxicity without excessive mortality. The low dose of 25 mg/kg/day was expected to be the no-observed-adverse-effect level, while the 100 mg/kg/day dose was expected to induce minimal or no toxicity.

OBJECTIVE

The objective of this study was to evaluate the potential subchronic and reproductive toxicity of H-24768 when administered by gavage to male and female rats. A recovery group was included to investigate the reversibility of any observed toxicological effects. The oral route of administration was selected as the most efficient way to deliver an accurate dosage. Blood, urine, feces, and tissues were collected for evaluation of the pharmacokinetic profile of H-24768, but have not been evaluated. Data from analysis of these samples will be reported separately.

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

Samples of H-24768 were supplied near the beginning, middle, and end of the study for stability analysis and analyzed by the DuPont Regional Analytical Services (RAS). The stability analysis of H-24768 was based on the physical characterization of the test substance. Due to insufficient sample volume, the sample submitted near the beginning of the study could not be completely analyzed.

C. Test Species

On March 1, 2001, 176 male and 176 female Crl:CD[®](SD)IGS BR rats, with an assigned birth date of January, 25, 2001 were received from Charles River Laboratories, Inc., Raleigh, North Carolina for use on this study. An additional 44 rats (22 male and 22 females), with an assigned birth date of April 8, 2001, were received in a separate shipment 63 days after study start on May 17, 2001. The additional rats were designated for the 10-day hepatic biochemical analysis.

The rat was selected because it is the species recommended 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, 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 $22 \pm 3^{\circ}\text{C}$ and a relative humidity of $50\% \pm 20\%$. Occasional excursions outside the acceptable 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 entire in-life period for rats evaluated for subchronic toxicity, the 72-day prematuring period for P₁ adults, and the 40-day postweaning period for F₁ 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. Subsequently, 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. F₁ generation rats retained after lactation were tattooed when they were approximately 21 days old.

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 12 days of the 14-day pretest period. The rats were observed daily for any clinically apparent signs of disease or injury, weighed 3 times, and examined by a veterinary ophthalmologist to identify animals with preexisting ocular lesions.

On the basis of acceptable body weight gains and clinical observations, all surviving rats were released from quarantine on test day -2 by the laboratory animal veterinarian designee.

Additional male and female rats designated for the 10-day hepatic biochemical analysis were quarantined for 6 days of the 11- and 12-day pretest period, respectively. The rats were observed daily for any clinically apparent signs of disease or injury and weighed three times, then released from quarantine on test day 70.

F. Study Design

Groups		No./ Group		Dosage ^a (mg/kg/day)
Male	Female	Male	Female	
I	II	45	45	0 (Control)
III	IV	35	35	25
V	VI	35	35	100
VII	VIII	45	45	500
Biochemical Evaluations at the 10-day Time Point				
I-A	II-A	5	5	0 (Control)
III-A	IV-A	5	5	25
V-A	VI-A	5	5	100
VII-A	VIII-A	5	5	500

a Weight of test substance / kg animal body weight.

The first 10 rats in each group were designated for the 90-day exposure evaluation and are referred to in this report as the 90-day exposure animals. The next 5 rats in each group were initially designated for analysis of fluorine in the blood. However, to assess three-month recovery from test substance-related effects, these rats were also evaluated for biochemical (males), clinical, and anatomic pathology endpoints; these rats are reported as the three-month recovery animals. 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 recovery evaluations and are reported as the one-month recovery animals. An additional 5 rats/sex/dose were received as a separate shipment 63 days after study start for evaluation of hepatic biochemical analysis following a 10-day exposure.

Male and female rats designated for the 90-day exposure evaluation were dosed for 95 (male) and 96 (female) days, and necropsied on test days 95 and 96, respectively. One male control rat was dosed for 96 days and necropsied on test day 96. Male and female rats designated for the one- and three-month recovery evaluations were dosed for 91 days and necropsied 33 (males) or 34 (females) days and 93 days postdosing, respectively.

Neurobehavioral evaluations were conducted on male and female animals designated for the 90-day exposure evaluation (predose and week 13) and on control and high-dose animals designated for the one-month recovery (predose, week 13, one-month post-dose). Clinical pathology evaluations were conducted on animals designated for the 90-day exposure evaluation on weeks 7 and 14 and on animals designated for the one-month and three-month recovery evaluations immediately prior to necropsy. Biochemical evaluations were conducted on selected animals designated for the 90-day exposure evaluation, the one-month and three-month recovery

evaluations, and the 10-day exposure evaluation. Rats designated for reproduction evaluations were transferred to the reproduction group on test day 70, and reproductive evaluations began on test day 72, when designated male and female rats were cohoused.

G. Assignment to Groups and Study Start

1. Rats Designated for the 90-Day Exposure, One-Month Recovery, and Three-Month Recovery Evaluations and Reproductive Evaluations.

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 $\pm 20\%$ of the mean within a sex. One male rat with a pretest ophthalmologic observation was included in the high-dose group (rat 646365). However, it was designated for the reproductive subset, which was not evaluated for post-exposure eye effects. Therefore, this did not affect study results. 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-24768 began on test day 0, when the rats were approximately 49 days of age. Prior to the start of test substance administration, 2 male rats with body weights that were not within $\pm 20\%$ 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 $\pm 20\%$ of the mean within a sex. One male rat designated for the reproduction evaluation was replaced based on a clinical observation made at the time of dosing on test day 0.

2. Rats Designated for 10-Day Biochemical Analysis

The rats designated for the 10-day biochemical analysis arrived separately, 63 days after study start. They were handled the same as the other rats during the quarantine and pretest periods, except they did not receive an ophthalmological examination. They were distributed by computerized, stratified randomization into study groups (5/sex/dose), so that there were no statistically significant differences among group body weight means within a sex when this subset of rats was compared among themselves. Oral administration of H-24768 to male and female rats began on test days 74 and 75, respectively. In-life data (body weight, food consumption, clinical observations) were collected from these animals and are in study records. However, these data will not be included in this report.

H. Dose Solution Preparation

Dose solutions of 0, 3.33, 13.33, or 66.67 mg test substance/mL were prepared with deionized water. The test substance, a brown paste, was melted and stirred in a 77°C water bath. The appropriate amount of test substance was weighed out, then dissolved in deionized water. The dosing solutions were mixed for approximately one minute with a polytron homogenizer. Dose solutions were prepared twice a week and refrigerated until used. On the day of use, the dose solutions were removed from the refrigerator and stirred while they were brought to room

temperature. A one-day aliquot was then removed and the remaining dose solutions were returned to the refrigerator. The daily aliquots were stirred prior to and during dosing.

I. Test Substance Administration and Sampling

Animals designated for the 90-day dosing period were dosed through test day 94 (males) or 95 (females). One control male in this subset was dosed through test day 95. Animals designated for the one- and three-month recovery evaluations were dosed through test day 90. Animals designated for reproduction evaluations were dosed through the 72-day premating period and during the mating period. P₁ males continued to be dosed until sacrifice. Pregnant females were dosed during the gestation period. Lactating females and females with no evidence of copulation were dosed until pups were weaned on postnatal day 21. All P₁ animals in the reproduction study, with the exception of pregnant females in the process or showing signs of delivery, were dosed daily until sacrifice.

The test substance was administered daily to the study animals by oral gavage to achieve dosage levels of 25, 100, or 500 mg active ingredient/kg body weight/day, based on the most recently recorded body weight. All male and female control animals were dosed with deionized water at 7.5 mL/kg, the same dose volume used in other groups.

On test day 21, Group III, rat 646458 was inadvertently dosed twice. During the course of the study, there were individual rats across dose groups that were misdosed; these rats are documented in study records and reported in Appendix B. The incidences of misdosing described above are considered not to have affected the outcome of the study.

All dosing solution samples were collected on the same day the solutions were prepared or as indicated by the stability analysis for the study. The solution vehicle was deionized water.

Samples of dosing solutions containing H-24768 in deionized water, at targeted concentrations of 0, 3.33, 13.33, and 66.67 mg/mL were collected at the initiation of the study (test day 0) for verification of uniformity, concentration, and 5-hour room temperature stability. The 5-hour stability sample was analyzed to demonstrate stability of the test substance in dosing solutions over the time the animals were being dosed. Samples of dosing solutions prepared at the same concentrations were collected on test days 32, 42, and 91 for concentration verification. Dosing solutions were prepared twice a week, then refrigerated until used (up to 4 days). Samples at the same concentrations as above, prepared on test day 39, were collected on test day 43, after 4 days of refrigeration, to verify stability under these storage conditions.

All dosing samples, except those for verification of 4-day refrigeration stability, were collected on the same day the solutions were prepared. Samples submitted for analysis were analyzed the day the solutions were received or refrigerated until analyzed. The stability of the test substance under 4-day refrigerated conditions was also supported prior to study start by analytical results from a developmental toxicity study previously conducted with this test substance [REDACTED]

[REDACTED]

J. Analytical Methods

1. Dosing Solution Treatment

Prior to analysis, each dosing sample was diluted with methanol and an equivalent amount of diluted control, to an expected concentration of 1.67 or 3.33 mg/mL (a.i.).

2. Chromatographic Conditions

Instrument:	Hewlett-Packard Model 6890 GC
Column:	HP-1, 30 m x 0.32 mm ID, 0.25 μ m film thickness
Injector:	Split, 250°C
Detector:	FID; 300°C
Carrier Gas:	Helium (2.7 mL/min)
Split vent:	53.2 mL/min
Injection Volume:	1 microliter
Oven Program:	Gradient
Initial Temperature:	50°C
Initial Time	0.0 min.
Level 1 Rate:	40°C/min.
Level 1 Temperature:	300°C
Run Time:	22.25 minutes

3. Calibration and Quantitation

A stock solution of the test substance (a separate sample of H-24768, used as analytical reference) was made in methanol. Appropriate aliquots of the stock were diluted with the methanol and an equivalent amount of the diluted control to match the samples. These solutions were used to make calibration standards that bracketed the target concentration of the diluted dosing samples. Peak heights (4 retention times) from GC analysis of these standards were used to construct calibration curves by least square regression (see Appendix A, Figure 1a - 1d for representative calibration curves). Measured concentrations for dosing solutions were determined by applying the peak heights from replicate injections of the samples to each calibration curve. The mean result from the concentrations at all retention times ($n = 4$) is reported as the concentration for the sample.

Test substance uniformity in the vehicle was evaluated by calculating the coefficient of variation (C.V. = standard deviation/mean x 100) of the measured concentrations in duplicate samples for each dosing level. A coefficient of variation of less than 10% is the standard criterion at Haskell Laboratory for acceptable distribution of the test substance throughout the solution. The mean result of the duplicate samples for each dosing level was used to determine the concentration of the test substance for the respective dosing levels.

Stability was evaluated by using the mean of the duplicate samples for concentration verification as the baseline for comparing the corresponding 5-hour room temperature and 4-day refrigerated results.

K. Body Weights

All rats were weighed once per week during the 90-day exposure 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 assessment, male rats were weighed on a weekly schedule and female rats were weighed during gestation on days 0, 7, 14, 18, and 21, and on lactation days 0, 7, 14, and 21. P₁ female rats with no evidence of copulation, or that did not deliver a litter, continued to be weighed weekly. Weaned F₁ rats were weighed weekly until postnatal day 56 (equivalent to test day 36 for the F₁ generation). Gestation day 18 body weights were collected solely for the purpose of adjusting dose volumes and are not reported.

L. Food Consumption and Food Efficiency

The amount of food consumed by each rat over each weighing interval was determined throughout the study. Each 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 animals designated for one- and three-month recovery evaluations through test day 119, but was not determined for animals designated for the three-month recovery evaluations after test day 119.

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 70.
- Cohabitation period beginning test day 72 and P₁ males after the end of cohabitation – food consumption was not determined.
- Gestation period – individual food consumption was determined on gestation days 0, 7, 14, and 21.
- Lactation period – food consumption was not determined.
- Postweaning F₁ rats – individual food consumption was determined weekly, ending on postnatal day 56 (equivalent to test day 36 for the F₁ generation).

M. 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. 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.

N. Ophthalmological Evaluations

Two 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 -13, the initial examination was performed on all rats received for the study, prior to selection and grouping. On test day 85, all surviving rats designated for the 90-day exposure and one-month recovery were examined again.

O. Neurotoxicity Evaluations

1. Sensory Function Evaluation

Prior to test substance administration, during week 13 (test days 88 and 89) of test substance administration, and following an approximately one-month recovery period (test day 118), 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 13 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 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

Following the evaluation of grip strength and sensory function, assessment of motor activity 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 was 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.

P. Clinical Pathology

Samples for clinical pathology evaluations were collected from the first 10 male and 10 female rats per group in all groups on test days 39 and 95 (males), or 40 and 96 (females). One control group male rat had samples collected on test day 96. After one month of recovery, samples for clinical pathology evaluations (excluding coagulation) were also collected from 10 recovery rats per group (control and 500 mg/kg/day only) on test day 123 or 124 (males or females, respectively). Additionally, after 3 months of recovery, samples for clinical pathology evaluations (excluding coagulation and including selected urinalysis tests) were collected from up to 5 satellite recovery rats per group (all groups) on test day 184.

The rats were fasted overnight (approximately 16 hours). During this interval, urine was collected from each rat into vials containing EDTA. Blood samples for hematology and serum 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) and plasma fluoride 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.

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:

Red blood cell count (RBC)	Red cell distribution width (RDW)
Hemoglobin (HGB)	Absolute reticulocyte count (ARET)
Hematocrit (HCT)	Platelet count (PLT)
Mean corpuscular volume (MCV)	White blood cell count (WBC)
Mean corpuscular hemoglobin (MCH)	Differential leukocyte count
Mean corpuscular hemoglobin concentration (MCHC)	Microscopic blood smear examination
Prothrombin time (PT)	
Activated partial thromboplastin time (APTT)	

2. Clinical Chemistry

All clinical chemistry parameters were measured in serum, with the exception of fluoride, which was measured in EDTA plasma. 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/12pH meter with a fluoride-selective electrode.

The following clinical chemistry parameters were determined:

Aspartate aminotransferase (AST)	Total protein (TP)
Alanine aminotransferase (ALT)	Albumin (ALB)
Sorbitol dehydrogenase (SDH)	Globulin (GLOB)
Alkaline phosphatase (ALKP)	Calcium (CALC)
Total bilirubin (BILI)	Inorganic phosphorus (IPHS)
Urea nitrogen (BUN)	Sodium (NA)
Creatinine (CREA)	Potassium (K)
Cholesterol (CHOL)	Chloride (CL)
Triglyceride (TRIG)	Plasma fluoride (PFLU)
Glucose (GLUC)	

3. Urinalysis

The following urinalysis parameters were determined:

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

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 with a fluoride selective electrode). Sediments from all urine specimens were evaluated microscopically.

Q. Collection of Blood, Urine, Feces, and Tissue (Three-Month Recovery and F₁ Generation)

On test day -4 (pre-bleed) and test days 0, 3, 9, 21, 34, 55, 76, and 89, blood (approximately 0.5 - 1 mL) was collected from the orbital sinus of designated animals (5 rats/sex/dose) while the rat was under light carbon dioxide anesthesia for possible analysis of total fluorine. On the day of blood collection (except test day -4), blood was collected from the animals 2 hours ($\pm$ 30 minutes) after dosing. Inadvertently, on test day 34, some rats were bled within 2 hours ($\pm$ 50 minutes) of dosing. The blood was collected in plastic tubes containing EDTA while on ice. The blood was then separated into plasma and RBCs by centrifugation and 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 and the last week of the three-month recovery 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 for possible analysis at 3, 7, 12, 19, 26, 36, 50, 71, and 93 days postdosing for both male and female animals of each dose group and stored frozen. Animals were sacrificed at the end of the three-month recovery period. The testes, fat (1 gram), and aliquots of liver and kidney were collected and frozen for possible analysis of total fluorine.

On postnatal days 33-35 (F₁ test days 13-15), all surviving F₁ generation rat pups in the 500 mg/kg/day group were euthanized. At the time of necropsy, approximately 1 mL of blood was collected from the orbital sinus of each rat. On the same day as the 500 mg/kg/day group sacrifice and blood collection, 5 F₁ male pups and up to 5 F₁ female pups (that had demonstrated vaginal patency) from the 0, 25, and 100 mg/kg/day groups had approximately 0.7 mL blood collected from the orbital sinus, while the rat was under carbon dioxide anesthesia. This blood was collected from pups in all groups for possible comparison of selected parameters among these groups. These blood samples were stored for possible comparison of these parameters over time.

The collected blood, urine, feces, and tissues may be evaluated in the future for total fluorine. Resulting data will be reported separately.

R. Biochemical Measurements

Following 10 or approximately 90 days of test substance administration, or after approximately one month or three months of recovery, five rats from each group designated for biochemical evaluation were weighed and then euthanized by carbon dioxide anesthesia and exsanguination. At each time point, the livers were removed, weighed, and then a portion was homogenized (1 gram tissue/4 mL buffer) in homogenization buffer (50 mM Tris-HCl, 50 mM Trizma-base, 0.25 M sucrose, and 5.4 mM EDTA, pH 7.4). Hepatic peroxisomes were prepared using differential

centrifugation. The resulting peroxisomal pellets were resuspended in the homogenization buffer, aliquoted, and stored between -65 and -85°C until analyzed for peroxisomal β -oxidation activity. The peroxisomal suspensions were diluted to a protein concentration of approximately 0.25 or 0.5 mg/mL. Peroxisomal β -oxidation activity was determined using [14 C]palmitoyl CoA as the substrate.⁽⁵⁾ The protein content of the peroxisomes was determined before and after analysis by the Biorad method.⁽⁶⁾ Final rate calculations were made using the post-assay protein concentrations.

S. Anatomic Pathology – Rats Designated for 90-Day Exposure and Recovery Evaluations

After approximately 90 days of dosing (95 for males; 96 for females and one control male), groups of 10 male and 10 female rats from the 0, 25, 100, and 500 mg/kg/day groups were sacrificed and necropsied. Following a recovery period of approximately 30 days (one-month recovery), rats from 0 and 500 mg/kg/day groups were sacrificed and necropsied. Male and female animals from a second recovery subset were sacrificed and necropsied following a recovery period of approximately 90 days (three-month recovery), where all exposure groups were represented. Rats were euthanatized by carbon dioxide anesthesia and exsanguination. Gross examinations were performed on all male and female rats. In rats sacrificed after three months of recovery, the gross examination was limited to the abdominal and thoracic cavities.

The following tissues were collected from rats designated for the 90-day exposure and one-month recovery.

<u>Digestive System</u>	<u>Cardiovascular System</u>	<u>Musculoskeletal System</u>
Liver	Heart	Skeletal muscle
Esophagus	Aorta	Femur/knee joint
Stomach		Sternum
Duodenum	<u>Hematopoietic System</u>	
Jejunum	Spleen	<u>Reproductive System</u>
Ileum	Thymus	<u>Male</u>
Cecum	Mandibular lymph node	Testes
Colon	Mesenteric lymph node	Epididymides
Rectum	Bone marrow ^a	Prostate
Salivary glands		Seminal vesicles
Pancreas	<u>Endocrine System</u>	<u>Female</u>
	Pituitary gland	Ovaries
<u>Urinary System</u>	Thyroid gland	Uterus
Kidneys	Parathyroid glands	Mammary glands
Urinary bladder	Adrenal glands	
	<u>Nervous System</u>	<u>Miscellaneous</u>
<u>Respiratory System</u>	Brain (including cerebrum, cerebellum, medulla/pons)	Skin
Lungs	Spinal cord (cervical, mid-thoracic, lumbar)	Eyes (including optic nerve)
Trachea	Sciatic nerve	Gross observations
Nose		
Larynx		
Pharynx		

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. Thyroid glands were weighed after fixation.

The following tissues were weighed from rats sacrificed after three-month recovery: liver, kidney, testes, spleen, thyroid (after fixation), and 1 gram of fat. A sample of liver was taken for biochemical analysis from control and 500 mg/kg/day males. A sample of liver, kidney, spleen, and thyroid was taken from all rats for histopathologic evaluation. A sample of testes, fat, kidney, and liver was saved frozen for possible analysis of total fluorine.

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 the control and high-dose rats sacrificed on test days 95 and 96, and all found dead or accidentally killed rats were processed and received a full histopathological examination. Liver, thyroid gland, spleen, and kidneys were processed and examined microscopically from low- and intermediate-exposure groups of 90-day rats, and from all rats sacrificed at the one-month and three-month recovery time points. The key to the Pathology Evaluation appendix describes the lesion grading system used in this study.

T. Reproductive Assessment

1. Breeding

After approximately 10 weeks of exposure to the test substance, on test day 72, each female was continually housed on a 1:1 basis with a randomly selected male of the same dose 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. Two 500 mg/kg/day males in the reproduction subset died during the premating period. Two surviving males in this group were cohoused with the extra female rats after copulation was confirmed with the original female.

2. Estrous Cycle Evaluation

Vaginal smears were collected from all P₁ female rats in order to determine the stages of the estrous cycle. Vaginal smears were collected daily beginning approximately 3 weeks prior to cohabitation, and continuing until copulation was confirmed, or the cohabitation period ended.

Vaginal smears were also collected from all P₁ parental female rats at the time of sacrifice to determine the stage of estrous cycle. These data are not presented in the report but are included in the study records.

3. Gestation Procedures

After being 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), female rats were observed at least twice daily for signs of delivery and pups.

The day of gestation was presumed to have been miscalculated (due to the missed first copulation plug) for one pregnant female in group VIII-0 (Animal No. 646663) since at delivery pups were much larger than expected for day 16 of gestation and were the size expected for a litter delivered at term (day 22 of gestation). Data from this animal were excluded from group means (gestation body weight and food consumption, gestation length, estrous cycle parameters and precoital interval).

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 were weighed and had 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.

Due to the low number of 500 mg/kg/day F₁ rats still alive after weaning, post-weaning body weight, nutritional, and clinical observations data are not reported on the summary data tables. Individual animal data are included in the appendices.

5. Post Weaning and Developmental Landmarks

On postnatal days 33-35 (F₁ test days 13-15), all surviving F₁ generation rat pups in the 500 mg/kg/day group were euthanized due to high pup mortality in this group. The method of euthanasia and the endpoints evaluated followed procedures for F₁ adults (Materials and Methods, Section U., Anatomical Pathology - Rats Designated for Reproductive Evaluations, 1. F₁ Adults. At the time of 500 mg/kg/day necropsy, blood was collected from each rat in the 500 mg/kg/day group and blood was collected from 5 F₁ male pups and up to 5 F₁ female pups (that had demonstrated vaginal patency) from the 0, 25, and 100 mg/kg/day groups. The methods and process are described in detail in Materials and Methods, Section Q. Collection of Blood, Urine, Feces, and Tissue (Three-Month Recovery and F₁ Generation).

Developmental landmarks in the F₁ 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 56 (F₁ test day 36). Animals were weighed on the day the developmental landmark was achieved.

a. Vaginal Patency

Female rats were examined beginning on postnatal day 21.

b. Preputial Separation

Male rats were examined beginning on postnatal day 35.

U. Anatomical Pathology - Rats Designated for Reproductive Evaluations

Sacrifice Schedule

<u>Animals</u>	<u>Schedule</u>
Adult Males	After siring litters (at discretion of reproductive toxicologist)
Pregnant Females	On day of weaning litters
Nonpregnant Females	With pregnant females
Weanlings	3 of 4 rats/sex/litter will be sacrificed on postnatal day 21.
F ₁ Adults	At postnatal day 60

1. P₁ Adults

All P₁ parental rats were sacrificed by carbon dioxide asphyxiation and exsanguination, and received gross pathological examination, including the females that died and those males and females for which mating did not result in a production of offspring. The uteri of all cohabited females were examined for the presence and number of implantation sites.

Sperm parameters for the first 10 surviving P₁ male animals sacrificed by design in each treatment group were evaluated. The right epididymis was removed, and 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°C and -85°C for sperm and spermatid counts, respectively.

The following table lists tissues that were collected and saved in the appropriate fixative:

Tissues Collected from P₁ Adults

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

a 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 Gross lesions observed at necropsy for which histopathology was not appropriate or would not be additive were generally not collected.

2. Offspring

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

3. F₁ Weanlings

Three F₁ weanlings/sex/litter (randomly selected), litter size permitting, were sacrificed by carbon dioxide asphyxiation and underwent a gross pathological evaluation on postnatal day 21. All surviving F₁ generation rats in the 500 mg/kg/day group were euthanized by carbon dioxide anesthesia and exsanguination on postnatal days 33-35 and received a gross pathological evaluation. Gross lesions were preserved.

4. F₁ Adults

All F₁ generation rats were sacrificed by carbon dioxide asphyxiation and exsanguination, and received 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 F₁ Adults

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

a 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 Gross lesions observed at necropsy for which histopathology was not appropriate or would not be additive were generally not collected.

Tissues Weighed from F₁ Adults

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

5. Processing of Tissues

Processed tissues (testes, epididymides, seminal vesicles, prostate, and uterus, ovaries, and vagina) for histopathological examination were embedded in paraffin, cut at a nominal thickness of 5 micrometers, and stained with hematoxylin and eosin (H&E).

Histopathological examination of tissues was conducted only for P₁ adults with impaired reproductive performance. Reproductive tissues from some male rats with impaired reproductive performance were saved but inadvertently not processed to slides, and thus not microscopically examined. As these same tissues were microscopically examined in test substance-exposed rats from the 90-day subchronic toxicity sacrifice, and found to have no test substance-related alterations, the absence of these tissues for microscopic evaluation in the reproductive portion of the study did not impact the conclusions of the study. Furthermore, no test substance-related alterations were observed in the male rats with impaired reproductive performance that were evaluated microscopically.

Gross lesions were saved but not evaluated microscopically because they would not have been additive to the interpretations of the study. 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.

V. 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.

Parameter	Preliminary Test	Method of Statistical Analysis	
		If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Food Efficiency Organ Weight Biochemical Measurements	Test for lack of trend ⁽⁹⁾	Sequential application ⁽¹⁰⁾ of the Jonckheere-Terpstra trend test ⁽¹¹⁾	Preliminary tests for pairwise comparison
		OR ^a	
	Levene's test for homogeneity ⁽¹²⁾ and Shapiro-Wilk test ⁽¹³⁾ for normality ^b	One-way analysis of variance ⁽¹⁴⁾ followed with Dunnett's test ⁽⁷⁾	Kruskal-Wallis test ⁽¹⁵⁾ followed with Dunn's test ⁽⁸⁾
Motor Activity ^c	Levene's test for homogeneity ⁽¹²⁾ and Shapiro-Wilk test ⁽¹³⁾ for normality ^b	Repeated measures analysis of variance ⁽¹⁶⁾ followed by contrasts ⁽¹⁷⁾	Sequential application ⁽¹⁰⁾ of the Jonckheere-Terpstra trend test ⁽¹¹⁾
Grip Strength	Bartlett's test ⁽¹⁸⁾ for homogeneity of variances	One-way analysis of variance ⁽¹⁴⁾ followed with Dunnett's test ⁽⁷⁾	Kruskal-Wallis test ⁽¹⁵⁾ followed with Dunn's test ⁽⁸⁾
Clinical Pathology ^d	Levene's test for homogeneity ⁽¹²⁾ and Shapiro-Wilk test ⁽¹³⁾ for normality ^b	One-way analysis of variance ⁽¹⁴⁾ followed with Dunnett's test ⁽⁷⁾	Kruskal-Wallis test ⁽¹⁵⁾ followed with Dunn's test ⁽⁸⁾
Survival Incidence of Clinical Observations Incidence of Ophthalmology Observations Incidence of FOB Descriptive Parameters	None	Cochran-Armitage test for trend ^{(14)e}	
Biochemical Measurements	None	One-way analysis of variance ⁽¹⁴⁾ followed with Dunnett's test ⁽⁷⁾ or Dunn's test ⁽⁸⁾	
Incidence of Microscopic Lesions	None	None	

- Pairwise comparisons and associated preliminary tests were only conducted if the test for lack of trend was significant.
- If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used.
- Test day and block (10-minute EPOCH) was used as repeated-measure factors.
- 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.
- If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test⁽¹⁹⁾ with a Bonferroni correction was used.

The following table lists the statistical analyses conducted on the indices of reproductive function that were calculated for the P₁ and F₁ adults.

Parameter	Preliminary Test	Method of Statistical Analysis	
		If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Gestation Length Organ Weight Implantation Site Numbers Implantation Efficiency Mean Number of Pups Per Litter Percent Born Alive Precoital Interval Estrous Cycle Length Sperm Parameters Vaginal Patency Preputial Separation	Test for lack of trend ⁽⁹⁾	Sequential application ⁽¹⁰⁾ of the Jonckheere-Terpstra trend test ⁽¹¹⁾	Preliminary tests for pairwise comparison
		OR ^a	
	Levene's test for homogeneity ⁽¹²⁾ and Shapiro-Wilk test ⁽¹³⁾ for normality ^b	One-way analysis of variance ⁽¹⁴⁾ followed with Dunnett's test ⁽⁷⁾	Kruskal-Wallis test ⁽¹⁵⁾ followed with Dunn's test ⁽⁸⁾
Food Efficiency	None	One-way analysis of variance ⁽¹⁴⁾ followed with Dunnett's test ⁽⁷⁾	
Incidence of Clinical Observations Mating Index Fertility Index Gestation Index Viability Index Lactation Index	None	Cochran-Armitage test for trend ^{(14)c}	
Mean Pup Weights (Covariates: litter size, sex ratio) Sex Ratio	None	Linear contrast of least squares means ⁽²⁰⁾	Dunn's test ⁽⁸⁾

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⁽¹⁹⁾ 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.⁽¹⁰⁾ For litter parameters, the proportion of affected fetuses per litter or the litter mean was used as the experimental unit for statistical evaluation.⁽²¹⁾

Where the data were tied and the standard large sample version of Jonckheere's test was not applicable, exact p values were calculated using permutation methodology.⁽²²⁾

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 (percent purity, composition, and known impurities) will be stored at Regional Analytical Services (RAS), Jackson Laboratories, Deepwater, New Jersey. Characterization data used to support test substance stability will be retained at Haskell Laboratory, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware.

RESULTS AND DISCUSSION

ANALYTICAL EVALUATIONS

A. Test Substance Stability

Analyses of bulk samples of H-24768 near the beginning, middle, and end of the study indicated that the test substance was stable for the duration of the study. Due to insufficient sample volume, complete analysis of the sample submitted near the beginning of the study could not be conducted. However, analyses of surface tension and density, reported on the certificate of analysis, dated 29-Jan-2001, support the stability of the test substance over the duration of the study.

The stability of the H-24768 in the samples was based on the physical characterization of the test substance. The analyses consisted of the density at 65° C, the upper cloud point, the surface tension, the residual ethylene oxide (E.O.), the appearance, and the percent fluoride. This work can be found in [REDACTED] Haskell No. H-24768, [REDACTED]

Analytical Text Table: Analytical Results for Test Substance Stability

Sample Collection Day	Type of Analyses					
	Density @65°	Upper Cloud Point (°C)	Surface Tension (dynes/cm)	Residual Ethylene Oxide	Appearance	% Fluoride
Test Day 3	1.321 ^(a,b)	--- ^(a)	22.0 ^(a,b)	ND ^c	OK	--- ^(a)
Test Day 49	1.3270	91.0	22.0	ND	OK	32.5
Test Day 123	1.3210	91.5	21.0	ND	OK	32.0

a Sample supplied at study start for analysis was insufficient to perform entire battery of tests.

b Values listed are values reported on the sponsor's certificate of analysis dated 29-JAN-2001.

c Not detected

B. Chromatography

H-24768 eluted from the GC column as resolved peaks over retention time range of approximately 5 to 20 minutes. For the purpose of quantitation, the retention times of approximately 7.9, 8.2, 8.5, and 9.0 minutes were determined to be representative of H-24768 in the dosing matrix. Representative GC chromatograms are shown in Appendix A, Figures 2(a - c). Test substance was not detected in the 0 mg/mL control sample.

C. Uniformity of Mixing, Concentration Verification and Stability Samples

Analytical results from dosing solutions prepared test day 0, and test day 39 and analyzed for uniformity of mixing, concentration verification, and stability are shown in Table 1 and Appendix A, Table I.

Analytical Text Table: Analytical Results for Uniformity, Concentration, and Stability

Nominal mg/mL	Measured ^{a,b} mg/mL	Average ^b % Nominal	CV ^b %	5-Hour Stability ^{b,c} % Nominal	4-Day Stability ^{a,d} % Nominal
3.33	3.11, 2.82	89.2	7	88.0	94.3
13.33	12.1, 11.6	89.3	3	87.0	90.0
66.67	60.4, 55.1	86.7	6	87.1	88.3

- a Duplicate samples analyzed.
- b Samples taken from dose solutions prepared on test day 0.
- c Stability samples held for 5 hours at room temperature.
- d Stability samples prepared Test day 39 and held for 4 days refrigerated and sampled. Initial baseline sampling on Test day 39 was not submitted.

The results for samples prepared on test day 0, show that the test substance was uniformly mixed (CV's less than 10), at the targeted levels (target = $\pm 13.3\%$ of nominal) and stable in the vehicle when held 5 hours at room temperature. The samples prepared on test day 39 were sampled after 4 days refrigeration. No analyses were conducted on these samples, on the day of preparation, to establish the baseline. However, the results indicated that the test substance concentrations following this storage time were similar to those observed in other analyses conducted at the time of dose solution preparation (i.e., test days 32, 42, 91). Furthermore, stability under these storage conditions was demonstrated in a previous study (see following paragraph). Test substance was not detected in the 0 mg/mL sample.

The following table summarizes results for stability samples from a developmental toxicity study [redacted] previously conducted with this test substance. These results indicate that the test substance in the vehicle was stable when held 4 days refrigerated followed by 5 hours at room temperature and support the stability of the test substance under the conditions of this study. Thus, dosing solutions could be prepared twice a week and stored refrigerated until use, and would still provide the targeted dose. This was further confirmed by analysis of samples collected on test day 39 of this 90-day study, and held under the same conditions prior to analysis (see above).

Analytical Text Table: Analytical Results for Stability

Nominal mg/mL	Measured ^a mg/mL	Average % Nominal	CV %	Stability ^b % Nominal	Stability ^c % Nominal
5.0	4.72, 4.54	92.6	3	101.2	107.4
10.0	9.36, 8.75	90.5	5	97.0	97.2
40.0	40.2, 38.9	98.9	2	105.2	103.3
70.0	63.2, 61.7	89.1	2	120.3	99.6

- a Duplicate samples analyzed.
- b Stability samples held for 4 days refrigerated.
- c Stability samples held for 4 days refrigerated, then 5 hours at room temperature.

D. Concentration Verification Samples During the Study

Analytical results from dosing solutions prepared test day 32, test day 42 and test day 91 and analyzed for concentration verification are shown in Table 1 and Appendix A, Table II.

The following table summarizes the results for concentration verification analyses for the test day 32, 42, and 91 preparations.

Analytical Text Table: Analytical Results for Concentration

Preparation Day	Nominal mg/mL	Measured ^a mg/mL	Average % Nominal	CV %
Test day 32	3.33	3.05, 3.08	92.2	1
	13.33	11.5, 11.6	87.0	1
	66.67	59.0, 61.7	90.6	3
Test day 42	3.33	3.13, 3.12	93.7	0
	13.33	12.5, 12.5	93.8	0
	66.67	58.8, 57.6	87.3	1
Test day 91	3.33	3.17, 3.18	95.2	0
	13.33	12.4, 12.6	93.8	1
	66.67	58.7, 60.0	88.9	2

a Duplicate samples per level were analyzed. C.V. calculated to verify uniformity of mixture.

The results for samples prepared on test days 32, 42, and 91 indicate that the test substance was adequately mixed (CV's less than 10) and at the targeted levels (target = $\pm 13\%$ of nominal) for all samples. Test substance was not detected in the 0 mg/mL sample.

E. Analytical Conclusions

Results from the analysis of the samples collected at study start and during the study indicate that the test substance was mixed uniformly, was at the targeted levels, and was stable under the conditions of the study. Test substance was not found in the 0 mg/mL samples. Based on analyses of physiochemical properties, the test substance was demonstrated to be stable over the course of the study.

SUBCHRONIC TOXICITY EVALUATIONS

IN-LIFE TOXICOLOGY

Rats designated for evaluation of reproductive toxicity were transferred to the reproduction group on test day 70, and were co-housed for mating beginning on test day 72. All results reported in this section up to test day 70 (including day 0-70 intervals) include data from both the subchronic toxicity and reproductive toxicity subsets. All results after test day 70 (including day 0-91 intervals) are from subchronic toxicity rats alone.

A. Dosage Data

(Tables 2-3, Appendix B)

Rats were dosed with solutions of H-24768 in deionized water, prepared at concentrations of 0, 3.33, 13.33, and 66.67 mg/ml, designed to deliver the targeted dose of test substance at a dosing volume of 7.5 ml/kg body weight. The quantity of H-24768 administered to each rat was calculated, based on the most recent body weight for each rat, and subsequently rounded by a computer program.

The range of mean daily dose volumes administered to male rats was 1.6-4.5 ml for the control group, 1.6-4.6 ml for the 25 mg/kg/day group, 1.6-4.1 ml for the 100 mg/kg/day group, and 1.6-3.6 ml for the 500 mg/kg/day group. The range of mean daily dose volumes administered to female rats was 1.3-2.4 ml for the control group, 1.3-2.3 ml for the 25 mg/kg/day group, 1.3-2.4 ml for the 100 mg/kg/day group, and 1.3-2.3 ml for the 500 mg/kg/day group.

B. Mean Body Weights and Body Weight Gains

(Tables 4-7, Figures 1-2, Appendices C-D)

Mean body weight gain in 500 mg/kg/day male rats was lower than control over the entire dosing phase (test day 0-91). Mean body weight in this group was 83% of control on test days 70 and 91, and mean body weight gain was 73% and 72% of control over test days 0-70 and 0-91, respectively. All differences were statistically significant. In the 500 mg/kg/day group, mean body weight and mean body weight gain were lower than control on all test days and over all weekly intervals of the dosing phase except test days 7-14. Differences in mean body weight were statistically significant on all test days and differences in mean body weight gain were statistically significant over all weekly intervals, except over test days 7-14, 56-63, 77-84, or 84-91. In 100 mg/kg/day males, mean body weight was lower than control over the entire dosing phase, but the differences were mild and were only statistically significant on test days 35-70. Mean body weight in this group was 95% (statistically significant) and 94% (not statistically significant) of control on test days 70 and 91, respectively. Mean body weight gain was 91% (statistically significant) and 88% (not statistically significant) of control over test days 0-70 and 0-91, respectively. Although the body weight effects in the 100 mg/kg/day group were mild, they were considered to be compound related and adverse. No compound-related effects on body weight or body weight gain were observed in male rats dosed with 25 mg/kg/day. In this group,

mean body weight on test day 91 and mean body weight gain over test days 0-91 were 105% and 107% of control, respectively. Neither difference was statistically significant.

Mean body weight in 500 mg/kg/day female rats was lower than control over the entire dosing phase. Mean body weight was 95% and 94% of control (both statistically significant) on test days 70 and 91, respectively. Weekly mean body weight gain in this group was significantly below control over test days 0-7, 28-35, and 63-70 but was significantly higher than control over test days 7-14. Mean body weight gain over other weekly intervals was comparable to control. However, mean body weight gain over test days 0-70 and 0-91 was 87% and 85% of control, respectively (both statistically significant). Therefore, the body weight effects in this group were considered to be mild, but adverse. No compound-related effects on body weight or body weight gain were produced in female rats dosed with 25 or 100 mg/kg/day. Mean body weight on test day 91 was 95% and 99% of control for the 25 and 100 mg/kg/day groups, respectively. Mean body weight gain over test days 0-91 was 92% and 98% of control for the 25 and 100 mg/kg/day groups, respectively. None of these differences in the 25 or 100 mg/kg/day groups was statistically significant. Statistically significant lower body weight gains were observed in the 100 mg/kg/day group over test days 0-7 and 63-70. However, overall body weight gain in this group over the 0-70 and 0-91 test day intervals was 94% and 98% of control, respectively (neither statistically significant) and there were no statistically significant differences in mean body weight on any day during the dosing phase. Therefore, the body weight effects in the 100 mg/kg/day female group were not considered to be adverse.

Body weight effects were reversible in male rats. In the 500 mg/kg/day group mean body weight gain was 51% higher than control over the first month of recovery (test days 91-119), due mainly to significantly higher mean body weight gain over test days 91-98 and 98-105. Mean body weight gain was 81% higher than control over the three months of recovery (test days 91-182). Differences in body weight gain were statistically significant over both intervals. Mean body weight in the 500 mg/kg/day group was still lower than in control on test day 119 (90% of control) but was 8% higher than control at the end of the three-month recovery phase (test day 182; not statistically significant).

During recovery, much of the difference in body weight gain between the control and 500 mg/kg/day male groups reflects a reduction in the control group mean body weight following the 90-day dosing and one-month recovery sacrifices. This reduction is attributed to sampling variability. Although rats were randomly assigned to subsets, and all were treated the same throughout the dosing and recovery periods, the control rats sacrificed at the end of dosing and one-month recovery periods tended to be heavier than those retained for evaluation after three months of recovery.

In the 100 mg/kg/day group mean body weight gain was 19% higher than control over the first month of recovery (test days 91-119) and 18% higher than control over the three-month recovery (test days 91-182; neither statistically significant). Mean body weight gain did not differ significantly from control over any weekly intervals during recovery. Mean body weight in the 100 mg/kg/day group was still lower than in control on test day 119 (96% of control), but was 6% higher than control on test day 182. Neither difference was statistically significant.

In 500 mg/kg/day females, body weight effects did not demonstrate reversibility over the first month of recovery. In fact, mean body weight gain was below control over 3 of the 4 weekly intervals (variable statistical significance) and mean body weight gain over test days 91-119 was 26% of control. Mean body weights remained significantly below control over the entire first month of recovery. No statistically significant differences in mean body weight or weekly body weight gain were observed over any weekly intervals during these two months, nor over the test day 91-182 interval. Some of the loss of statistical significance is attributed to the reduced statistical power due to a reduction in the number of rats per group. However, mean body weight gain over test days 91-182 was 90% of control and mean body weight gain exceeded that of control over many intervals. Therefore, partial recovery was observed over the second and third months of recovery.

Overall, adverse, compound-related reductions (compared to control) in mean body weight and body weight gain were observed in male and female rats dosed with 500 mg/kg/day, and in male rats dosed with 100 mg/kg/day. The effects in 500 mg/kg/day females and in 100 mg/kg/day males were considered to be mild. Weight effects were more readily reversible in males than in females.

C. Food Consumption and Food Efficiency (Tables 8-11, Appendix E)

In 500 mg/kg/day male rats, mean food consumption was lower than control through test day 63. The differences were statistically significant through test day 56. No statistically significant differences in food consumption were observed over the rest of the dosing phase. However, mean food consumption over test days 0-70 and 0-91 was 90% and 93% of control, respectively (both statistically significant). Food consumption in 100 mg/kg/day male rats was generally comparable to control. Mean food consumption in this group was 96% of control over test days 0-70 (statistically significant) and was significantly below control over test days 49-56. These differences in the 100 mg/kg/day group were not considered adverse as the differences were small and the differences in food consumption over most weekly intervals and over test days 0-91 (98% of control) were not statistically significant. No compound-related effects on food consumption were observed in male rats dosed with 25 mg/kg/day.

No adverse effects on food consumption were observed in female rats in any dose group. Statistically significant reductions compared to control were observed in the 500 mg/kg/day group over test days 0-7, 7-14, 21-28, and 35-42, and statistically significant increases in food consumption were observed over test days 77-84 and 84-91. However, food consumption over the 0-70 and 0-91 test day intervals was 95% and 97% of control (neither statistically significant). No compound-related effects on food consumption were observed in female rats dosed with 25 or 100 mg/kg/day. In the 100 mg/kg/day group, mean food consumption was significantly below control over test days 0-7. However, mean food consumption over test days 0-70 and 0-91 was 100% of control, therefore the isolated interval of reduced food consumption was not considered to be adverse or a compound-related effect.

Food consumption effects were reversible in 500 mg/kg/day male rats. Mean food consumption over the first two weeks of recovery was significantly higher than control and overall mean food

consumption over test days 91-119 was 112% of control (not statistically significant). Mean food consumption in 500 mg/kg/day female rats was also significantly higher than control over test days 91-98, but was comparable to control over the rest of the one-month recovery phase.

Mean food efficiency in 500 mg/kg/day male rats was lower than control over the entire dosing phase (test day 0-91). Mean food efficiency in this group was 79% and 77% of control over test days 0-70 and 0-91, respectively (both statistically significant). Mean food efficiency was lower than control over all weekly intervals during the dosing phase. All differences were statistically significant through test day 56 and over test days 63-70. In the 100 mg/kg/day male group, mean food efficiency over test days 0-70 and 0-91 were 95% and 90% of control, respectively (both statistically significant). Differences in weekly mean food efficiency were only statistically significant over test days 0-7, 14-21, 28-35, and 49-56. However, the effects in this group were considered adverse because they were associated with adverse reductions in body weight gain. No compound-related effects on food efficiency were observed in male rats dosed with 25 mg/kg/day.

Compound-related adverse reductions in mean food efficiency were observed in female rats dosed with 500 mg/kg/day. Mean food efficiency was 92% and 88% of control over test days 0-70 and 0-91, respectively. The differences in weekly mean food efficiency were only sporadically statistically significant but the effects on food efficiency were considered adverse based on the magnitude of the overall effect, and because they were associated with reductions in body weight gain. Mean food efficiency in the 100 mg/kg/day female group was significantly lower than control over test days 0-7 and 63-70 and over the 0-70 test day interval (94% of control). However, the effects on food efficiency in this group were not considered to be adverse as they were of small magnitude, were not associated with adverse reductions in body weight gain. Furthermore, mean food efficiency over test days 0-91 was 97% of control (not statistically significant) and weekly mean food efficiency exceeded that of control over numerous weekly intervals (none statistically significant).

The recovery in food efficiency was similar to that observed for body weight gain. In 500 mg/kg/day males, food efficiency over the first month of recovery was 27% higher than in control (statistically significant), mainly due to significantly higher food efficiency over the first 2 weeks of recovery. In 500 mg/kg/day females, food efficiency over the first month of recovery remained significantly below control, although weekly food efficiency was only significantly lower than control over test days 91-98. Food consumption data were not collected after test day 119; therefore, food efficiency was not calculated after that day.

Mild but adverse, compound-related reductions in mean food consumption were observed in male rats dosed with 500 mg/kg/day. Adverse, compound-related reductions in mean food efficiency were observed in male and female rats dosed with 500 mg/kg/day and in male rats dosed with 100 mg/kg/day. Reductions in food efficiency indicate that test substance exposure at these dosages reduced the rats' ability to convert feed into increased body mass, resulting in lower body weight gain in these groups. Although the effects on food consumption in 100 mg/kg/day males and 500 mg/kg/day females were not considered to be adverse, they were likely compound related, and may have contributed to the reduced body weight gain observed in these groups.

D. Clinical Observations and Mortality
(Tables 12,13,16,17, Appendix F)

There was no compound-related effect on mortality in either male or female rats. Compound-related increases in clinical observations were observed in the 500 mg/kg/day male and female groups. In both sexes, there was a statistically significant increase in the incidence of wet fur (chin/perineum), clear discharge from the mouth, hair loss, and stained fur/skin. The hair loss was observed in many sites including side, perineum, abdomen, ventral body, sacral region, and/or hindlimb. The hair loss was due to rats chewing, possibly in response to general toxicity and discomfort. Therefore, the hair loss was considered indicative of an adverse effect.

The stained fur/skin was also observed in many locations, but most notably in the perineum in both males and females. The perineum staining is likely related to staining with urine, since an increase in the volume of urine production was observed in both sexes (see Clinical Pathology section). The increased urination was considered to be a non-adverse, transient pharmacologic effect of test substance administration. Therefore, the stained perineum was considered non-adverse. Statistically significant increases in the incidence of clear discharge from the mouth (males and females) and in hair loss over the dorsal body (females only) were also observed in rats dosed with 100 mg/kg/day, and were considered compound related because they were similar to those observed in the 500 mg/kg/day group. The clear discharge from the mouth was observed most often when rats were handled prior to dosing, and it was considered likely to be a behavioral response to dosing with the test substance.

E. Ophthalmology Evaluations
(Tables 14-15, Appendix F)

No compound-related ophthalmological lesions were observed in male or female rats examined near the end of the dosing phase of the study. Three rats were observed to have unilateral, focal retinal degeneration (one each in the 25 mg/kg/day male, 500 mg/kg/day male, and 500 mg/kg/day female groups) and one rat had phthisis bulbi of the globe (one 500 mg/kg/day male). None of these lesions was attributed to dosing with the test substance.

F. In-Life Toxicology Conclusions

Under the conditions of this study, the no-observed-effect level (NOEL) for in-life parameters was 25 mg/kg/day for males and females. The NOEL was based on clinical signs of toxicity observed in males and females dosed with 100 and 500 mg/kg/day, and reductions in body weight and nutritional parameters observed in males dosed with 100 and 500 mg/kg/day. In females, compound-related reductions in body weight and nutritional parameters were observed in rats dosed with 500 mg/kg/day.

NEUROBEHAVIORAL TOXICOLOGY

A. Sensory Function Evaluations

1. Forelimb Grip Strength (Table 18-19, Figures 3-4, Appendix G)

Males administered 500 mg/kg/day H-24768 had significantly lower forelimb grip strength during the week 13 evaluation (25% lower compared to control). In addition, forelimb grip strength in males administered 500 mg/kg/day was 10% lower than the control value during the recovery evaluation (not statistically significant). The decreased forelimb grip strength observed in 500 mg/kg/day males correlates with decreased hindlimb grip strength, and may be secondary to reduced body weight (17% and 10% lower than control values for week 13 and week 17, respectively). Forelimb grip strength for 500 mg/kg/day females was slightly lower (11%)(not statistically significant) compared to the control value for the recovery (week 17) evaluation, which correlated with a slightly lower (10%) body weight, compared to the control value.

There were no test substance-related effects on forelimb grip strength in males or females administered 100 mg/kg/day or below.

2. Hindlimb Grip Strength (Table 18-19, Figures 5-6, Appendix G)

Males administered 500 mg/kg/day H-24768 had significantly lower hindlimb grip strength during the week 13 evaluation (18% compared to control), and recovery evaluation (15% compared to control). The lower hindlimb grip strength for 500 mg/kg/day males correlated with the lower forelimb grip strength and may be secondary to the lower body weights. Hindlimb grip strength was also slightly lower in 500 mg/kg/day females during the recovery evaluation (13% compared to control), which may be secondary to the slightly lower body weight during recovery (week 17).

There were no test substance-related effects on hindlimb grip strength in males or females administered 100 mg/kg/day or below.

3. Sensory Function Observation (Table 20-21, Appendix H)

There were no test substance-related changes in sensory function parameters in males or females administered any dosage of H-24768. However, male and female rats administered 500 mg/kg/day had higher incidences of stained perineum (4/10 males and 5/10 females compared to 0/10 control males or females) during the week 13 evaluation. The increased incidences of stained perineum in 500 mg/kg/day males and females were considered to be test substance-related.

Male rat 646373 (100 mg/kg/day group) had abnormal gait during the week 13 evaluation. However, since this observation did not occur in any male administered 500 mg/kg/day or in any

females administered 100 or 500 mg/kg/day, it was not considered to be test substance-related. A higher incidence of an exaggerated reaction to tail pinch (3/10) was observed in males administered 25 mg/kg/day. However, the incidences were not increased in the 100 or 500 mg/kg/day groups, and therefore, the incidence in 25 mg/kg/day males was not considered to be test substance-related.

B. Motor Activity

(Tables 22-25, Figures 7-10, 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. Females in the 25, 100, and 500 mg/kg/day groups had significantly higher mean number of movements during the sixth 10-minute interval of the week 13 evaluation. However, a dose-response relationship was not present, and the total number of movements was similar to the control value. Therefore, the increased number of movements in the sixth 10-minute interval for females administered 25, 200, or 500 mg/kg/day was not considered to be test substance-related.

C. Neurobehavioral Toxicity Conclusions

Under the conditions of the study, the no-observed-effect level (NOEL) for neurobehavioral parameters was 100 mg/kg/day in males and females. The NOEL is based on the significantly decreased forelimb and hindlimb grip strength in 500 mg/kg/day males, and the increased incidences of stained perineum in 500 mg/kg/day males and females. The reductions in grip strength were attributed to reduced body weight and were not considered evidence of neurotoxicity. Although the slightly lower forelimb and hindlimb grip strength was also observed in 500 mg/kg/day females, the minor differences were not considered to be biologically significant.

CLINICAL PATHOLOGY

A. Hematology/Coagulation (Tables 26-29, Appendix K)

Males and females dosed with 100 or 500 mg/kg/day had minimal to mild decreases in some or all parameters indicating red cell mass (hemoglobin, hematocrit, and/or red cell count) (Clinical Pathology Text Table 1).

In males dosed with 100 or 500 mg/kg/day, minimal decreases in hemoglobin and hematocrit, but not red cell counts, were associated with small red cells. These changes were indicated by decreases in both MCV and MCH, and increased RDW. Increased incidence of microcytes and anisocytosis were also present in males dosed with 500 mg/kg/day. Male rats dosed with 500 mg/kg/day also had accelerated production of red cells (regeneration), indicated by decreased MCHC, increased reticulocytes, and polychromasia; increased reticulocytes and polychromasia were also observed in a few rats dosed with 100 mg/kg/day. Several minor treatment-related red cell microscopic changes were observed on blood smears of males dosed with 100 or 500 mg/kg/day only. Histologically, males dosed with 500 mg/kg/day had minimally increased splenic extramedullary hematopoiesis (see Anatomic Pathology section). Hematology changes present at the end of dosing were generally of greater magnitude or incidence than those present at mid-study.

For male rats, hematology changes were improving, albeit not completely, after one month of recovery (Day 123/124R), and were completely reversed after 3 months of recovery (Day 183R). After one month of recovery, males previously dosed with 500 mg/kg/day still had minimally decreased hemoglobin and hematocrit, but red cell mass was recovering. However, RDW was increased to a greater magnitude compared to the end of dosing, and was consistent with the microscopic changes of increased anisocytosis, microcytes, and macrocytes. Reticulocytes, polychromatophilic cells, and acanthocytes were increased. After 3 months of recovery, red cell parameters in rats were similar to control values in rats previously dosed with test substance.

Compared to males, females dosed with 100 or 500 mg/kg/day had similar decrements in red cell mass, however, the relative decrease in red cell mass (compared to control values) was greater, and the response of the bone marrow (accelerated production of red cells indicating regeneration) was more marked. Female rats dosed with 100 or 500 mg/kg/day had decreased red cell mass parameters (decreased red cell count, hemoglobin, and hematocrit), and alterations in hematologic parameters indicating accelerated production (increased reticulocytes, RDW, and polychromasia, and decreased MCHC). MCH was decreased (500 mg/kg/day only); in some animals, this decrease correlated with decreased MCV, suggesting the presence of smaller cells with less hemoglobin. Other minor treatment-related red cell microscopic changes were observed in females dosed with 100 and 500 mg/kg/day. Histologically, females dosed with 500 mg/kg/day had minimally increased splenic extramedullary hematopoiesis (see Anatomic Pathology section). Red cell changes that were present at the end of dosing were generally of greater magnitude or incidence than those present at mid-study.

In female rats, hematology changes were improving, albeit not completely, after one month of recovery, and were completely reversed after 3 months of recovery. After one month of recovery, females previously dosed with 500 mg/kg/day still had minimally decreased hematocrit (not statistically significant), but red cell mass was recovering. However, RDW, echinocytes, and acanthocytes were still increased compared to control values. After 3 months of recovery, red cell parameters in rats were similar to control values in rats previously dosed with test substance.

The red cell mass changes, during dosing, in female rats dosed with 500 mg/kg/day were considered adverse due to the magnitude of the change. Similar types of changes occurred in males during dosing, but these changes were not considered adverse because the magnitude of change was not expected to have an adverse impact on function of red cells.

Clinical Pathology Text Table 1: Red cell mass parameters*

		Males			Females		
Dose (mg/kg/day)		25	100	500	25	100	500
Parameter	Day						
RBC	39/40	98%	99%	102%	101%	93%	93%
	95/96	100%	98%	103%	97%	91%	89%
	123/124R	NT	NT	97%	NT	NT	98%
	183R	99%	98%	97%	100%	99%	101%
HGB	39/40	99%	99%	96%	101%	94%	91%
	95/96	99%	95%	92%	97%	90%	85%
	123/124R	NT	NT	95%	NT	NT	97%
	183R	101%	98%	99%	101%	94%	97%
HCT	39/40	99%	99%	96%	102%	95%	94%
	95/96	99%	96%	94%	98%	91%	87%
	123/124R	NT	NT	96%	NT	NT	97%
	183R	100%	99%	100%	104%	96%	100%

R: recovery time-point.

* Results presented as percent of concurrent control group mean. Statistical significance is indicated by bold italicized type

NT: Not taken

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

- Females dosed with 500 mg/kg/day had mildly increased platelets at Day 96. Increased platelets were likely secondary to increased erythropoietin production in response to the red cell changes. Mildly increased platelets are not associated with adverse effects. After one month of recovery, platelet counts were similar to control values in rats previously dosed with 500 mg/kg/day.
- Males dosed with 25, 100, or 500 mg/kg/day had minimally increased monocytes at Day 39. This change is possibly related to treatment. However, because there was a relatively flat dose response, no peripheral need for increased monocytes (no inflammation observed in clinical or anatomic pathology results), and because the change was minimal and transient, this change was not considered adverse.
- Females dosed with 500 mg/kg/day had minimally increased white blood cells and lymphocytes at Day 40 only. This change is possibly related to treatment. However, because this change was minimal and transient, it was not considered adverse.
- At the end of dosing (Day 95/96), males dosed with 100 or 500 mg/kg/day had minimally shortened activated partial thromboplastin time, and females dosed with 500 mg/kg/day had minimally shortened activated partial thromboplastin time and prothrombin time. After one month of recovery, coagulation times were similar to control values in rats previously dosed with 500 mg/kg/day. The coagulation time changes were likely related to treatment, but were not considered adverse, because shortened coagulation times are not associated with adverse effects.

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

- Increased neutrophils in males dosed with 500 mg/kg/day after one month of recovery
- Increased neutrophils and monocytes in females dosed with 25 mg/kg/day at Day 40
- Increased platelets in one female previously dosed with 500 mg/kg/day, after 3 months of recovery. This change was considered to be unrelated to treatment because subjective evaluation of platelet counts on blood smears from 2 other rats in the group did not indicate increased platelet counts. In addition, increased platelets occurred after 3 months but not one month of recovery.

B. Clinical Chemistry
(Tables 30-31, Appendix K)

Liver Tests

Males dosed with 500 mg/kg/day had minimally to mildly increased ALT and SDH activities during the dosing period (Clinical Pathology Text Table 2). Animals with more pronounced changes (Rat Numbers. 646346 and 646475) had similar histologic changes compared to those with less prominent enzyme changes. Changes in ALT and SDH activities were of similar magnitude at both time-points, and persisted during one and three months of recovery.

In contrast, females dosed with 500 mg/kg/day had transiently (Day 40 only) increased ALT activity, without an associated increase in SDH. ALT activities were similar to control values at other time-points. Therefore, this change was considered to be unrelated to treatment.

The minimally to mildly increased ALT and SDH activities in male rats suggest hepatocellular injury. Histologic changes (see Anatomic Pathology section) did not indicate cellular damage, only hypertrophy. In individual animals, the magnitude of enzyme increase did not correlate with degree of hypertrophy. However, due to the consistency and persistence of the enzyme changes, the increases in ALT and SDH in male rats were considered potentially adverse.

Males and females dosed with 500 mg/kg/day had minimally increased ALKP activity and bilirubin concentration during the dosing period. (Clinical Pathology Text Table 2). Compared to control values, the change was similar at both time-points. There was only occasional correlation between ALKP activities and bilirubin concentrations, suggesting that a mechanism other than cholestasis might be involved in ALKP or bilirubin increases. Males and females dosed with 500 mg/kg/day had increased liver weights and liver hypertrophy, changes that normally are associated with enzyme induction (see Anatomic Pathology section). Enzyme induction is consistent with the ALKP changes, but would not be expected to result in increased bilirubin unless cholestasis occurred secondary to hypertrophy. Therefore, the cause for increased bilirubin is unknown.

These minimal changes in ALKP and bilirubin were not present after one or three months of recovery in rats previously dosed with test substance. The changes in ALKP and bilirubin were considered non-adverse because they were minimal and were reversible on cessation of dosing.

Clinical Pathology Text Table 2: Changes in hepatic parameters for males and females

Dose (mg/kg/day)		Males				Females		
		25	100	500		25	100	500
Parameter	Day							
ALT	39/40	92%	106%	164%		114%	125%	164%
	95/96	109%	112%	152%		76%	61%	73%
	123/124R	NT	NT	129%		NT	NT	55%
	183R	156%	147%	194%		83%	94%	109%
SDH	39/40	102%	104%	137%		102%	90%	92%
	95/96	113%	124%	130%		89%	68%	75%
	123/124R	NT	NT	219%		NT	NT	112%
	183R	157%	160%	221%		86%	120%	131%
ALKP	39/40	92%	91%	125%		108%	101%	174%
	95/96	89%	94%	142%		102%	113%	207%
	123/124R	NT	NT	94%		NT	NT	92%
	183R	124%	113%	106%		109%	82%	133%
BILI	39/40	75%	113%	250%		100%	100%	129%
	95/96	92%	125%	200%		88%	94%	124%
	123/124R	NT	NT	100%		NT	NT	84%
	183R	80%	50%	60%		80%	53%	80%

R: recovery time-point.

*Results presented as percent of concurrent control group mean. Statistical significance is indicated by bold italicized type

NT: Not taken

Renal and Electrolyte Changes

Males dosed with 100 or 500 mg/kg/day had either no change or minimal increases in parameters that measure glomerular filtration (urea nitrogen, creatinine, and inorganic phosphorus) during the dosing period (Clinical Pathology Text Table 3). Concentrations were similar at both time-points for urea nitrogen and creatinine. After one month of recovery, creatinine was decreased, whereas urea nitrogen and inorganic phosphorus were increased in males previously dosed with 500 mg/kg/day. Histologically, there was no correlation between individual rats with chronic progressive nephropathy and rats with increased urea nitrogen and inorganic phosphorus. After three months of recovery, a few rats previously dosed with 500 mg/kg/day had increased inorganic phosphorus; again, this change did not correlate with rats that had chronic progressive nephropathy.

Females dosed with 500 mg/kg/day also had minimal increases in urea nitrogen, creatinine, and inorganic phosphorus during the dosing period (Clinical Pathology Text Table 3). In addition, females dosed with 25 or 100 mg/kg/day had minimally increased urea nitrogen, without changes in creatinine or inorganic phosphorus, but only at the end of dosing. In females previously dosed with 500 mg/kg/day, these changes were not present after one month of recovery. After three months of recovery, inorganic phosphorus was increased (not statistically significant) in females

previously dosed with 100 or 500 mg/kg/day; this change was considered to be unrelated to treatment because there was no effect observed after one month of recovery.

The minimal increases in parameters reflecting glomerular filtration (urea nitrogen, creatinine, and inorganic phosphorus) were generally considered treatment-related in males and females dosed with 100 (males only) or 500 mg/kg/day. For these parameters, changes of the magnitude measured in this study would not be, in isolation, considered adverse. Changes of this magnitude can be observed in the absence of renal histologic alterations. However, in this study, histologic evidence of renal injury was observed in males and females dosed with 500 mg/kg/day. Therefore, although the changes in urea nitrogen, creatinine, and phosphorus, by themselves, were not considered adverse, they were supportive of adverse findings in histology.

Some male rats (500 mg/kg/day) and a few female rats (100 or 500 mg/kg/day) had minimally decreased sodium and chloride during the dosing period. The effect was similar at both time-points. Effects on chloride were still possibly present after one month of recovery in male rats; however, the possible change in chloride at this time-point occurred in the absence of changes in other parameters. Increased sodium after three months of recovery was considered unrelated to treatment because this change was not present after one month of recovery.

Decreased sodium and chloride during dosing indicate loss of fluid containing these two electrolytes. Because of the marked increase in urine volume in individual rats, loss through the urinary tract is most likely. This change was not considered adverse due to the minimal degree of change.

Males dosed with 100 or 500 mg/kg/day had minimally increased potassium during the dosing period. A few female rats at the same doses had similar changes. The effects were similar at both time-points. After one or three months of recovery, potassium concentrations were similar to control values in rats previously dosed with test substance. The reason for altered potassium was not determined, but was likely related to treatment due to the consistency of change across time-points, groups, and sexes. The magnitude of increase in potassium was always minimal and was not considered adverse.

Clinical Pathology Text Table 3: Parameters indicating glomerular filtration rate

Dose (mg/kg/day)		Males				Females		
		25	100	500		25	100	500
Parameter	Day							
BUN	39/40	100%	107%	143%		100%	106%	131%
	95/96	106%	119%	125%		119%	119%	125%
	123/124R	NT	NT	125%		NT	NT	106%
	183R	88%	82%	106%		107%	120%	120%
CREA	39/40	106%	113%	125%		95%	95%	113%
	95/96	108%	124%	111%		98%	105%	114%
	123/124R	NT	NT	98%		NT	NT	98%
	183R	93%	88%	109%		92%	104%	98%
IPHS	39/40	100%	106%	101%		103%	105%	122%
	95/96	107%	113%	111%		107%	115%	125%
	123/124R	NT	NT	116%		NT	NT	106%
	183R	100%	109%	129%		104%	136%	136%

R: recovery time-point.

* Results presented as percent of concurrent control group mean. Statistical significance is indicated by bold italicized type

NT: Not taken

Protein

Male and female rats dosed with 25 (males only), 100, or 500 mg/kg/day had dose-dependant, mildly increased albumin, which generally resulted in increased total protein during the dosing period (Clinical Pathology Text Table 4). This effect was slightly more pronounced at the end of dosing compared to mid-study. Changes in albumin were still present after one month of recovery in male rats previously dosed with 500 mg/kg/day. In addition, after one month of treatment, globulin concentration was mildly increased in both males and females. The albumin and globulin increases after one month of recovery could not be definitively attributed to treatment; however, the consistency of the result and the continued presence of compound (as indicated by urine fluoride measurements) makes this change of uncertain relationship to treatment. After three months of recovery, females previously dosed with 100 or 500 mg/kg/day had minimally increased globulins (no dose response); this change may or may not be related to treatment.

Increased albumin causing increased total protein indicates alterations in albumin synthesis, distribution, or metabolism. Minimally increased globulin in the presence of increased albumin is interpreted similarly. Although the changes in albumin and globulin concentrations were considered related to treatment, they were not considered adverse because mild increases in these parameters have no known adverse effects.

Clinical Pathology Text Table 4: Protein parameters

		Males			Females		
Dose (mg/kg/day)		25	100	500	25	100	500
Parameter	Day						
TP	39/40	102%	108%	112%	99%	107%	104%
	95/96	101%	111%	114%	105%	111%	111%
	123/124R	NT	NT	110%	NT	NT	109%
	183R	97%	101%	101%	101%	104%	101%
ALB	39/40	105%	112%	124%	102%	114%	110%
	95/96	107%	119%	128%	106%	115%	113%
	123/124R	NT	NT	115%	NT	NT	105%
	183R	93%	98%	98%	104%	98%	95%
GLOB	39/40	100%	109%	100%	100%	96%	96%
	95/96	93%	100%	93%	104%	108%	104%
	123/124R	NT	NT	107%	NT	NT	115%
	183R	100%	107%	103%	97%	114%	114%

R: recovery time-point.

* Results presented as percent of concurrent control group mean. Statistical significance is indicated by bold italicized type

NT: Not taken

Calcium

Males and females dosed with 100 or 500 mg/kg/day had mildly increased calcium during the dosing period. The effect was similar at both time-points. Calcium was still minimally increased in males previously dosed with 500 mg/kg/day after one month of recovery, but had recovered in females. After three months of recovery, calcium concentrations were similar to control values in rats previously dosed with test substance. The calcium changes paralleled the albumin changes discussed above. Calcium exists in serum in two forms, either bound to albumin or unbound ("ionized" calcium). Ionized calcium is the physiologically active form, and is tightly regulated. Increases in albumin are necessarily associated with physiologically appropriate increased bound calcium, with resultant increased total calcium. However, ionized calcium is unaffected. Changes in calcium are secondary to changes in albumin, and are considered physiologically insignificant, and therefore non-adverse.

Lipids

Males and females dosed with 100 or 500 mg/kg/day had mildly increased cholesterol and moderately decreased triglyceride concentrations during the dosing period. The effects were similar at both time-points. In rats previously dosed with 500 mg/kg/day, cholesterol was still increased (not statistically significant in males) after one month of recovery. After three months of recovery, cholesterol and triglyceride concentrations were similar to control values in rats previously dosed with test substance. Increased cholesterol and decreased triglycerides indicate alterations in lipid metabolism. Changes in lipids were considered non-adverse because the magnitude was small and was not expected to result in toxicity.

The following changes in chemistry parameters were considered to be unrelated to treatment because they occurred after three months, but not one month, of recovery.

- Increased sodium in males previously dosed with 500 mg/kg/day after three months of recovery
- Increased inorganic phosphorus in females previously dosed with 100 or 500 mg/kg/day after three months of recovery

C. Urinalysis

(Tables 32-33, Appendix K)

Males and females dosed with 500 mg/kg/day had mildly to markedly decreased urine specific gravity/osmolality and increased urine volume during the dosing period. This effect was similar at both time-points during dosing, but was not present after one month of recovery. Production of increased volumes of dilute urine can be due to polyuria (increased loss of water through the renal tract) or polydipsia (increased drinking of water). In this study, the cause of dilute urine was not determined. However, some rats dosed with 500 mg/kg/day had small volumes of concentrated urine. In addition, this change was reversible after one month of recovery in rats previously dosed with 500 mg/kg/day. It follows that dilute urine was not caused by renal impairment, but was a transient pharmacologic effect of test substance administration.

Males and females dosed with 500 mg/kg/day had moderately decreased urine pH only at the end of the dosing period. These changes were not present in males or females previously dosed with 500 mg/kg/day after one month of recovery. Decreased urine pH is generally the result of physiological renal compensation for excess acids in blood. This change was considered to be a physiologic rather than a toxicologic response.

Males and females dosed with 500 mg/kg/day had mildly decreased urine protein concentration (males at the end of the study, and females at mid-study). This change was caused by increased urine volume, which diluted the protein present in urine. Decreased urine protein concentration has no toxicologic significance.

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

At the end of one-month recovery, urine protein concentration was increased in female rats previously dosed with 500 mg. This increase was due to the presence of blood in urine (incidental finding), rather than glomerular or tubular injury, and thus was not considered related to treatment.

Plasma and urine fluoride

Males (25, 100, or 500 mg/kg/day) and females (100 or 500 mg/kg/day) had increased plasma fluoride concentrations during the dosing period (Clinical Pathology Text Table 5-6). After one month of recovery, plasma fluoride concentrations were decreased, relative to end of study values, in males and females previously dosed with 500 mg/kg/day. However, in females, plasma fluorides were still minimally increased compared to controls at this time-point. After three months of recovery, plasma fluoride concentrations were similar to control values in all rats previously dosed with test substance.

Males and females dosed with 25, 100, or 500 mg/kg/day had increased urine fluorides (total urine fluoride excreted during urine collection period) (Clinical Pathology Text Table 5-6). Increased urine fluorides were still present after one month of recovery in males and females previously dosed with 500 mg/kg/day, although the magnitude of the effect had decreased substantially. After three months of recovery, urine fluorides were further decreased relative to end-of-study and one-month recovery values in rats previously dosed with 500 mg/kg/day. However, urine fluorides were clearly increased compared to concurrent control values in both males and females previously dosed with 100 or 500 mg/kg/day. Urine fluorides in females previously dosed with 25 mg/kg/day were also slightly increased compared to control values, although this change was not statistically significant.

The presence of increased plasma and urine fluoride indicates exposure to a fluoride-containing compound. The presence of fluoride in urine 3 months after exposure suggests that fluoride-containing compounds are slowly being released from tissue sites.

Clinical Pathology Text Table 5: Fluoride parameters (absolute values)

		Males				Females			
Dose (mg/kg/day)		0	25	100	500	0	25	100	500
Parameter	Day								
PFLU ($\mu\text{g/mL}$)	95/96	0.1	0.2	0.2	0.5	0.1	0.1	0.2	0.5
	123/124R	0.1	NT	NT	0.1	0	NT	NT	0.1
	183R	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
UFLU (μg)	39/40	ND	ND	ND	ND	ND	ND	ND	ND
	95/96	12.1	50.6	140.8	632.6	5.5	23.7	59.4	291.2
	123/124R	8.1	NT	NT	98.3	4.2	NT	NT	30
	183R	10.2	13.5	21.5	46.8	5.9	8.6	9.9	15.7

R: recovery time-point.

* Statistical significance is indicated by bold italicized type

NT: Not taken

ND: Not done

Clinical Pathology Text Table 6: Fluoride parameters (compared to concurrent control values)

		Males				Females			
Dose (mg/kg/day)									
Parameter	Day/	0	25	100	500	0	25	100	500
PFLU	95/96	NA	200%	200%	500%	NA	100%	200%	500%
	123/124R	NA	NT	NT	100%	NA	NT	NT	NA
	183R	NA	100%	100%	100%	NA	100%	100%	100%
UFLU	39/40	NA	ND	ND	ND	NA	ND	ND	ND
	95/96	NA	418%	1164%	5228%	NA	431%	1080%	5295%
	123/124R	NA	NT	NT	1214%	NA	NT	NT	714%
	183R	NA	132%	211%	459%	NA	146%	168%	266%

R: recovery time-point.

* Results presented as percent of concurrent control group mean. Statistical significance is indicated by bold italicized type

NA: Not applicable (either because the calculation would be 100%--dividing a number by itself, or because the denominator was zero)

NT: Not taken

ND: Not done

D. Clinical Pathology Conclusions

Under the conditions of this study and for the parameters measured, the no adverse effect level for males was 100 mg/kg/day, based on the presence of increased ALT and SDH during treatment, which persisted into recovery. The no adverse effect level for female rats was 100 mg/kg/day, based on the presence of mild decrements in red cell mass parameters (hemoglobin, hematocrit, and red cell counts), associated with regeneration. There were no adverse findings for coagulation or urinalysis parameters for either sex.

BIOCHEMICAL MEASUREMENTS

A. Biochemical Measurements (Table 34-35, Appendix L)

The rate of hepatic β -oxidation, a measure of peroxisome proliferation, was determined in a subchronic oral toxicity study with H-24768 in male and female rats after 10 days or 95 days (males) or 96 days (females) of test substance administration or following a one-month or three-month (male only) recovery period.

At the 10-day time point in male rats, the rate of hepatic β -oxidation was increased in a dose-dependent manner and was statistically significantly increased in rats dosed with 100 and 500 mg/kg/day (171 and 286% of control, respectively). At the 90-day time point, the rate of hepatic β -oxidation was statistically significantly increased in rats dosed with 500 mg/kg/day (181% of control). At the one-month recovery time point, the rate of hepatic β -oxidation was statistically significantly increased in rats dosed with 500 mg/kg/day (195% of control). At the three-month recovery time point, the rate of hepatic β -oxidation had returned to control levels. At the 10-day, 90-day, and one-month recovery time points, the increases in hepatic β -oxidation activity were accompanied by increases in liver weights.

In female rats, the rate of hepatic β -oxidation was reduced at the 90-day time point in rats dosed with 25 mg/kg/day. This decrease was not considered a compound-related effect due to a lack of a dose-response and lack of concordant changes in any of the other dose groups at any of the sampling time points. At the one-month recovery time point, the rate of hepatic β -oxidation was increased in rats dosed with 500 mg/kg/day (131% of control). Due to the small magnitude of the increase (131% of control), the increase at the one-month recovery time point was not considered to be biologically significant. Hepatic β -oxidation was not evaluated at the three-month recovery time point in female rats.

In-life data (body weight, nutritional and clinical observation parameters) collected for the rats evaluated for 10-day biochemical evaluations will not be included in this report but are in study records.

B. Biochemical Measurements Conclusions

Under the conditions of this study, H-24768 was a mild inducer of hepatic peroxisomal β -oxidation in male rats. At dosages of 100 mg/kg/day and greater, changes in the rate of hepatic peroxisome proliferation were considered to be biologically significant effects. At the one-month recovery time point, the rate of hepatic peroxisome proliferation was increased in male rats dosed with 500 mg/kg/day, but had returned to control levels by the three-month recovery time point.

ANATOMICAL PATHOLOGY

SUBCHRONIC TOXICITY AND RECOVERY

A. Cause of Death

(Tables 46-47, Appendix N)

No unscheduled deaths occurred in any female rats in the 90-day exposure or one-month recovery groups. One male rat dosed with 100 mg/kg/day died of trauma secondary to the bleeding procedure. One control male and 2 males dosed with 500 mg/kg/day died of kidney inflammation and/or obstruction. None of these deaths was considered test substance related. One control female in the three-month recovery group died of trauma secondary to the bleeding process. There were no compound-related deaths at any dose level.

B. Organ Weight Data

(Tables 36-37, Appendix M)

Liver:

Mean liver weights (absolute and relative to body and to brain) were significantly higher in all dose groups at the 90-day sacrifice in males and females, and correlated with microscopic hepatocellular hypertrophy (see discussion under Microscopic Findings). Liver weights at the one-month recovery sacrifice were significantly higher in the 500 mg/kg/day males and females than in controls. There were no intermediate groups evaluated at the one-month recovery sacrifice. Mean absolute and relative (to body) liver weights were higher, compared to controls, in the 500 mg/kg/day males and in the 100 and 500 mg/kg/day females at the three-month recovery. Higher liver weights were considered compound-related and correlated with microscopic hepatocellular hypertrophy diagnosed in animals from the 90-day and one-month recovery sacrifices.

Kidney:

At the 90-day sacrifice, mean kidney weights (absolute and relative to body and to brain) were significantly higher than controls in 500 and 100 mg/kg/day females. The mean relative (to body) kidney weight was significantly higher in 500 mg/kg/day females at the one-month recovery and three-month recovery sacrifices. Higher mean kidney weights in females were considered compound-related and possibly associated with increased chronic progressive nephropathy detected microscopically.

Mean relative (to body) kidney weights were significantly higher than in controls in 500 and 100 mg/kg/day males at the 90-day sacrifice and in 500 mg/kg/day males at the one-month recovery sacrifice. The increase in relative (to body) kidney weight in these groups primarily reflects the reduced body weight in these animals, but, in the 500 mg/kg/day group, was also possibly associated with increased chronic progressive nephropathy detected microscopically.

Spleen:

Relative (to body and/or to brain) spleen weights were increased compared to controls in 100 and 500 mg/kg/day females at the 90-day sacrifice (relative to body at 500 mg/kg/day and relative to brain at 100 and 500 mg/kg/day). Mean spleen weights were not significantly different from controls at the one-month recovery sacrifice but relative (to body) spleen weights in the 500 mg/kg/day females were higher than controls at the three-month recovery sacrifice. The higher spleen weights were considered compound-related and correlated with increased extramedullary hematopoiesis detected microscopically.

There were no other compound-related organ weight effects. All other statistically significant organ weight changes in the subchronic and recovery groups were secondary to decreases in body weight or were spurious.

C. Gross Observations
(Tables 38-39, Appendix N)

Large livers were observed at the 90-day sacrifice in 500 and 100 mg/kg/day males and in 500 mg/kg/day females. This observation correlated with hepatocellular hypertrophy diagnosed microscopically and was considered to be compound-related. There were no compound-related gross observations in one-month or three-month recovery animals.

Other gross observations noted at any time point were sporadic across groups and were not considered to be compound-related.

D. Microscopic Findings
(Tables 40-47, Appendix N)

Liver:

There was minimal to mild diffuse hepatocellular hypertrophy in 90-day males (all dose groups) and females (100 and 500 mg/kg/day), and in 500 mg/kg/day males and females at the one-month recovery time point. There was no hepatocellular hypertrophy in males or females at the three-month recovery. 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 rats than in 90-day rats and was absent in three-month recovery rats. Thus, complete reversibility of the microscopic hepatocellular hypertrophy was established, although liver weights remained elevated through the three-month recovery period. The hepatocellular hypertrophy and the associated increase in liver weights were considered a compound-related physiologic response to a xenobiotic and not toxicologically adverse.^(23,24,25)

Microscopic Compound-Related Lesions in Liver								
	Males				Females			
Dose (mg/kg/day)	0	25	100	500	0	25	100	500
Hypertrophy 90-Day	1/11	5/10# ^a	10/11#	12/12#	0/10	0/10	9/10#	10/10#
Hypertrophy 1-Month Recovery	0/10	NA ^b	NA	7/10	0/10	NA	NA	1/10
Hypertrophy 3-Month Recovery	0/4	0/5	0/4	0/5	0/4	0/5	0/5	0/5

a A pound sign (#) indicates an effect level.

b NA indicated tissues were not available.

Kidney:

The incidence of chronic progressive nephropathy, a spontaneously occurring lesion in rats, was increased (compared with controls) in 500 mg/kg/day males and in 100 and 500 mg/kg/day females at the 90-day sacrifice. The incidence of this lesion was also increased in males and females at the one-month recovery (500 mg/kg/day) and in 100 and 500 mg/kg/day females at the three-month recovery. This lesion was considered compound related and adverse.

Microscopic Compound-Related Lesions in Kidney								
	Males				Females			
Dose (mg/kg/day)	0	25	100	500	0	25	100	500
Nephropathy 90-Day	5/11	2/10	5/11	7/12# ^a	2/10	2/10	5/10#	5/10#
Nephropathy 1-Month Recovery	3/10	NA ^b	NA	8/10#	1/10	NA	NA	8/10#
Nephropathy 3-Month Recovery	4/4	4/5	3/4	2/5	2/4	2/5	4/5#	4/5#

a A pound sign (#) indicates an effect level.

b NA indicated tissues were not available.

Spleen:

An increased incidence of extramedullary hematopoiesis was observed in 25, 100, and 500 mg/kg/day males and females at the 90-day sacrifice, in 500 mg/kg/day males and females at the one-month recovery, and was not observed in any exposure group at the three-month recovery. Thus, reversibility of increased extramedullary hematopoiesis was established. The occurrence of a single incidence in some groups of extramedullary hematopoiesis (25 mg/kg/day males and females at the 90-day sacrifice and 25 and 100 mg/kg/day males at the three-month

recovery sacrifice) was not considered a compound-related effect, as this can occur spontaneously in an occasional animal. Increased extramedullary hematopoiesis was considered a secondary physiologic response to changes in red cell mass and not a primary adverse effect. Hematological findings and interpretations are discussed within the clinical pathology portion of this report.

Increased pigment in the spleen was observed in 100 and 500 mg/kg/day males and 500 mg/kg/day females at the 90-day sacrifice, in 500 mg/kg/day males at the one-month recovery and in 100 and 500 mg/kg/day females at the three-month recovery. The pigment observed was consistent with hemosiderin and could be an indication of increased red cell turnover. As with extramedullary hematopoiesis, the presence of increased pigment was not considered a primary adverse finding.

Microscopic Compound-Related Lesions in Spleen								
	Males				Females			
Dose (mg/kg/day)	0	25	100	500	0	25	100	500
Hematopoiesis 90-Day	0/11	1/10	8/11# ^a	10/12#	0/10	1/10	6/10#	7/10#
Hematopoiesis 1-Month Recovery	0/10	NA ^b	NA	8/10#	0/10	NA	NA	1/10
Hematopoiesis 3-Month Recovery	0/4	1/5	1/4	0/5	0/4	0/5	0/5	0/5
Pigment 90-Day	0/11	0/10	4/11#	6/12#	1/10	0/10	0/10	10/10#
Pigment 1-Month Recovery	0/10	NA	NA	7/10#	0/10	NA	NA	0/10
Pigment 3-Month Recovery	0/4	0/5	0/4	0/5	0/4	0/5	2/5#	2/5#

a A pound sign (#) indicates an effect level.

b NA indicated tissues were not available.

Thyroid:

Follicular hypertrophy was present in thyroid glands in all male dosage groups and in 100 and 500 mg/kg/day female groups at the 90-day sacrifice and in 500 mg/kg/day males and females at the one-month recovery. Follicular hypertrophy was present in 500 mg/kg/day males at the three-month recovery, but not in females. Follicular hypertrophy was characterized by tall columnar follicular epithelium with a finely granular or vacuolated cytoplasm. The occurrence of a single incidence of follicular hypertrophy in a 25 mg/kg/day male at the 90-day sacrifice was not considered compound related because this lesion can occasionally occur spontaneously. Hypertrophy of thyroid follicular epithelium is, as is hypertrophy of other endocrine organs, often an indication of a physiologic response and not necessarily adverse. However, in the absence of

hormonal data to demonstrate maintenance of normal hormonal levels, the thyroid hypertrophy was considered potentially adverse.

Follicles containing altered colloid were found in thyroids from controls as well as in treated 90-day, one-month recovery and three-month recovery rats. An increase in incidence and/or in severity grade of this lesion was present in all exposure groups at all time points and was considered compound-related. The diagnosis "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 up 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. Although follicular hypertrophy was usually accompanied by altered colloid, the reverse was not necessarily the case, as altered colloid was observed in the absence of follicular hypertrophy.

Altered colloid described as clumped or granular has been reported to occur spontaneously in Sprague-Dawley rats with increasing incidence correlating to increasing age.⁽²⁶⁾ Because altered colloid occurs spontaneously in healthy Sprague-Dawley rats, and since increases in its grading score occurred in some groups without morphologic alterations in the thyroid, altered colloid was interpreted in the present study as not biologically adverse.

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.

Microscopic Compound-Related Lesions in Thyroid								
	Males				Females			
Dose (mg/kg/day)	0	25	100	500	0	25	100	500
Hypertrophy 90-Day	0/11	1/10	9/11# ^a	11/12#	0/10	0/10	2/10#	9/10#
Hypertrophy 1-Month Recovery	0/10	NA ^b	NA	8/10#	0/10	NA	NA	6/10#
Hypertrophy 3-Month Recovery	0/4	0/5	0/4	4/5#	0/4	0/5	0/4	0/4
Alteration, Colloid 90-Day	6/11	10/10#	10/11#	11/12#	3/10	6/10#	10/10#	10/10#
Alteration, Colloid 1-Month Recovery	6/10	NA	NA	10/10#	1/10	NA	NA	10/10#
Alteration, Colloid 3-Month Recovery	1/4	5/5#	4/4#	5/5#	1/4	3/5#	4/4#	3/4#

a A pound sign (#) indicates an effect level.

b NA indicated tissues were not available.

E. Anatomical Pathology Conclusions for Subchronic Toxicity Evaluation

Exposure to the test substance for approximately 90 days produced alterations in the liver, kidney, spleen, and thyroid. Increased liver weights and/or microscopic hepatocellular hypertrophy were present in 25, 100, and 500 mg/kg/day males and in 100 and 500 mg/kg/day females at 90-days, and in 500 mg/kg/day males and females at the one-month recovery. These liver changes were considered to represent a physiologic response to metabolism of a xenobiotic and thus were not considered to be adverse.

Increased chronic progressive nephropathy, sometimes accompanied by increased kidney weight in females, was present in 500 mg/kg/day males and 100 and 500 mg/kg/day females at the 90-day sacrifice, in 500 mg/kg/day males and females at the one-month recovery, and in 100 and 500 mg/kg/day females at the three-month sacrifice. This finding was considered to be adverse.

Alteration of colloid was present in the thyroids of males and females at all exposure levels at all time points. The severity of altered colloid in thyroid glands increased beyond control levels as the dose increased, however it was not associated with any adverse cellular morphologic alterations and was not considered biologically adverse.

Compound-related hypertrophy of follicular epithelium in the thyroid was present in 100 and 500 mg/kg/day males and females at the 90-day sacrifice, in 500 mg/kg/day males and females at the one-month recovery sacrifice, and in the 500 mg/kg/day males at the three-month recovery sacrifice. Thyroid gland follicular hypertrophy, in the absence of hormonal data, was considered potentially adverse.

The no-observed-effect level (NOEL) for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Under the conditions of this study, the NOEL for pathology was 25 mg/kg/day in male and female rats. These NOELs were based on microscopic chronic progressive nephropathy in males and females dosed with 500 mg/kg/day and in females dosed with 100 mg/kg/day, and on follicular hypertrophy of the thyroid in 100 and 500 mg/kg/day males and females.

REPRODUCTIVE TOXICOLOGY EVALUATIONS

REPRODUCTIVE FUNCTION

A. P₁ Generation

1. Mean Body Weights and Body Weight Gains (Table 48-50, Appendices O-T)

Mean body weights and body weight gains in the P₁ generation rats were lower than control at 500 mg/kg/day.

Mean body weight gain was significantly lower than control (68% of control) in P₁ male rats during and after the cohabitation period (test days 77-98) at 500 mg/kg/day. Weekly mean body weights were also significantly lower than control (83%-84% of control) in this group. Weekly mean body weights were statistically significantly lower than control on test days 77-98 in P₁ male rats at 100 mg/kg/day. This change was not considered toxicologically significant because it was small (93%-94% of control) and was not associated with lower body weight gain in this group.

Mean body weight gain was significantly lower than control (72% of control) in P₁ females rats during gestation (days 0-21G) at 500 mg/kg/day. Weekly mean body weights were also significantly lower than control (85%-92% of control) in this group. Reductions in mean body weights and body weight gains occurred during gestation in P₁ female rats at 25 and 100 mg/kg/day. These changes were not considered toxicologically significant because they were small (90%-95% of control), sporadic, and were not associated with any significant reduction in overall body weight gain in these groups.

Statistically significant differences (both higher and lower than control) in mean body weight gain were observed in P₁ female rats during lactation at all dose levels. These changes were not considered test substance-related due to their sporadic and inconsistent nature, and lack of effect on overall body weight gain at any dose level. Weekly mean body weights were statistically significantly lower than control in P₁ female rats during lactation at 100 and 500 mg/kg/day. These changes were not considered toxicologically significant because they were small (87%-97% of control) and were not associated with lower body weight gain in these groups.

2. Food Consumption and Food Efficiency During Gestation (Table 51, Appendix U)

Food consumption was not affected in P₁ female rats during gestation at any dose level. Food efficiency was lower than control (73% of control) in P₁ female rats during gestation (days 0-21G) at 500 mg/kg/day. This change is consistent with the lower mean body weight gain observed during gestation in this group.

3. Clinical Observations
(Tables 52, Appendices V-X)

There was no test substance-related mortality. Salivation at the time of daily dosing was observed in male rats at all dose levels and in female rats during gestation at ≥ 100 mg/kg/day. Staining of the perineal or inguinal area was observed in a few animals at 500 mg/kg/day. The toxicological significance of salivation in P₁ males at 25 mg/kg/day is uncertain due to its low incidence and sporadic occurrence.

4. Reproductive Indices
(Tables 53-55, Appendices Y-EE)

There were no test substance-related effects on percent days in estrus, diestrus, or proestrus. Individual animals displayed persistent or prolonged estrus or diestrus during the evaluation period. These abnormal cycling patterns were not considered test substance-related since they occurred to a similar degree in the control and treated groups. Mean cycle length was similar at 25, 100, and 500 mg/kg/day (4.7, 4.9, and 4.8 days, respectively) but was significantly greater than the control group (4.3 days), however, mean values were within the historical control range for Haskell Laboratory.^a The toxicological significance of these changes is unclear.

There were no test substance-related effects on sperm motility, morphology or testicular spermatid counts. The mean number of epididymal sperm per cauda was similar at 25, 100, and 500 mg/kg/day (278.8, 291.1, and 279.4 million sperm, respectively) but was significantly lower than the control group (318.4 million sperm). Although not statistically significant, a change of similar magnitude was observed in the mean number of epididymal sperm per gram cauda at 25, 100, and 500 mg/kg/day (979.2, 969.0, and 1062.1 million sperm, respectively) compared to the control group (1180.2 million sperm). These changes were not considered toxicologically significant because they were small (82%-91% of control), mean values were within the historical control range for Haskell Laboratory,^a and were not associated with any histopathological changes in the testis or epididymis. The mean number of testicular spermatids per testis was statistically significantly higher than control at 500 mg/kg/day (126.5 vs. 137.0 million spermatids). This change was not considered test substance-related since the mean number of spermatids per gram testis at 500 mg/kg/day was similar to the control group.

There was no test substance-related effect on the length of the precoital interval or on the mating index (number of females with evidence of copulation / number of females cohabited x 100) or gestation length. The fertility index (number of females delivering a litter/number of females with evidence of copulation x 100) was similar at 25, 100, and 500 mg/kg/day (55%, 58%, and 65% at 25, 100, and 500 mg/kg/day, respectively) but was lower than the control group (85%). This change was considered test substance-related. The number of uterine implantation sites was significantly reduced at 500 mg/kg/day (10.7 vs. 15.3 for the control group). There was no effect on implantation efficiency (number of pups born/number of implantation sites x 100) at any dose level, indicating no post-implantation loss (no resorptions).

^a For seven studies conducted at Haskell Laboratory between 1999 and 2001 the mean estrous cycle length among the control groups ranged from 4.2-4.9 days; the mean epididymal sperm number among the control groups ranged from 274.3-345.5 million sperm.

B. Offspring Data

1. Litter Size, and Pup Weights, Clinical Observations, and Survival (Table 56-58; Appendices FF-HH)

Mean litter size was lower than control at 500 mg/kg/day. Sex ratio and gestation index (percent litters having at least one live pup) were unaffected in F₁ litters at any dose level. The numbers of pups born and born alive were significantly lower than control at 500 mg/kg/day (72% and 66% of control, respectively). As a result, the mean percent pups born alive was significantly lower than control at 500 mg/kg/day (86.5% compared to 100% in the control group).

Pup survival during lactation was lower than control at 100 and 500 mg/kg/day. The mean number of pups per litter on day 4 preculling, day 7, 14, and 21 of lactation were significantly lower than control at 500 mg/kg/day (53%, 60%, 14%, 10% of control respectively). The mean number of pups per litter was similar to control on day 4 and 7 of lactation at 100 mg/kg/day. The mean number of pups alive at day 14 and 21 was significantly lower than control at 100 mg/kg/day (79% and 76% of control, respectively). As a result, the lactation index (survival from day 4 postculling to day 21) was significantly lower than control at 100 and 500 mg/kg/day (76.1% and 11.4% compared to 100% in the control group). The litter survival index (percent litters born with at least one live pup on day 21) was significantly lower than control at 500 mg/kg/day (25% compared to 100% in the control group).

Pup weights at birth and during lactation were lower than control at 100 and 500 mg/kg/day. Mean pup weight at birth was significantly lower than control at 500 mg/kg/day (90% of control). Mean pup weights during lactation were lower than control at 100 and 500 mg/kg/day. Mean pup weights were significantly lower than control at 500 mg/kg/day on days 4, 7, 14, and 21 of lactation (71%, 54%, 56%, 57% of control, respectively). Mean pup weights were significantly lower than control at 100 mg/kg/day on days 4, 7, 14, and 21 (94%, 86%, 94%, 94% of control, respectively).

There were no test substance-related clinical signs in pups during lactation at any dose level.

C. F₁ Generation

Due to poor survival in 500 mg/kg/day F₁ generation rats, there are insufficient data available to evaluate post-weaning in-life parameters. Therefore, results from this group will not be discussed.

1. Mean Body Weights and Body Weight Gains (Table 59-60, Appendices II-JJ)

There were no test substance-related effects on body weight and body weight gain in F₁ male and female rats during the post-weaning period at 25 or 100 mg/kg/day.

2. Food Consumption and Food Efficiency
(Tables 61-62, Appendix KK)

There were no test substance-related effects on food consumption and food efficiency in F₁ male and female rats during the post-weaning period at 25 or 100 mg/kg/day.

3. Clinical Observations
(Tables 63, Appendix LL)

The few pups in the 500 mg/kg/day group that survived to weaning on postnatal day 21 either died soon after weaning or were sacrificed on postnatal day 33-35. There were no test substance-related clinical signs in F₁ male and female rats during the post-weaning period at 25 and 100 mg/kg/day.

4. Developmental Landmarks
(Tables 64, Appendix LL)

There were no test substance-related effects on the age at onset of vaginal opening in F₁ female rats or of preputial separation in F₁ male rats at 25 and 100 mg/kg/day.

D. Reproductive Function Conclusions

There was no NOEL for the reproductive toxicity parameters evaluated under the conditions of this study; this was based on effects at all dose levels on the fertility index in the P₁ generation.

ANATOMICAL PATHOLOGY

REPRODUCTIVE TOXICOLOGY EVALUATIONS

A. Mortality

F₁ Adults
(Appendix NN)

Due to excessive toxicity, the 500 mg/kg/day F₁ animals retained after weaning were sacrificed on postnatal day 33-35. There were no compound-related effects on post-weaning mortality for the other groups.

B. Organ Weight Data

F₁ Adults
(Tables 65-66; Appendix MM)

Organ weight data was not collected on the 500 mg/kg F₁ animals retained after weaning because they were sacrificed early.

There were no compound-related effects on the organ weights of F₁ adult males or females dosed with 25 or 100 mg/kg/day. A significant decrease in mean liver weights (absolute and relative to body and to brain), and an increase in mean brain weight (relative to body) in 100 mg/kg males were considered to be secondary to lower body weight in that group.

C. Gross Observations

Parental P₁ Adults (Tables 67-68, Appendix NN)
F₁ Adults and Weanlings (Tables 69-75, Appendices OO-QQ)

There were no compound-related gross observations in parental or weanling rats. Observations in parental or weanling rats occurred in low incidences and were randomly distributed across control and treatment groups.

Observations in pups of lungs not expanded, and no milk spot in the stomach, are nonspecific lesions that are commonly seen in all pups that are born dead, and thus are not considered to be compound-related. Pup viability and mortality are discussed elsewhere in this report.

D. Microscopic Observations

Parental P₁ Adults (Tables 76-77, Appendix NN)

There were no compound-related microscopic findings in any of the P₁ males or females that received microscopic evaluation. 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.

E. Anatomical Pathology Conclusions for Reproductive Toxicity

The no-observed-effect level (NOEL) for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Under the conditions of this study, the NOEL for pathology was 100 mg/kg/day for males and females, the highest F₁ adult dosage group evaluated for reproductive anatomic pathology.

CONCLUSIONS

Under the conditions of this study, the no-observed-effect level (NOEL)^a for H-24768 for the 90-day exposure in male and female rats was 25 mg/kg/day. This level was based on clinical signs of toxicity, decrements in body weight parameters and food efficiency (males), thyroid follicular hypertrophy, and chronic progressive nephropathy (females), all observed in the 100 mg/kg/day groups. Other adverse, compound-related effects observed in males and/or females dosed with 500 mg/kg/day include decrements in body weight parameters and food efficiency (females), chronic progressive nephropathy (males), increased liver enzyme activities (males), reduction in red blood cell mass parameters (females), and reductions in forelimb and hindlimb grip strength (males). The reductions in grip strength were considered secondary to body weight effects and were not considered evidence of neurotoxicity.

Other compound-related effects were observed that were not considered adverse, but were either physiologic responses to exposure to the test substance or markers of exposure. Increased liver weight and hepatocellular hypertrophy were observed in all dosed male groups and in 100 and 500 mg/kg/day female groups. These effects were considered non-adverse physiologic responses. In 100 and 500 mg/kg/day males, the liver effects were associated with reversible induction of hepatic β -oxidation. Microscopic changes in the spleen, including extramedullary hematopoiesis and pigment, sometimes associated with increased spleen weight (in females) were considered non-adverse and secondary to effects on red cell mass. Clinical observations attributed to increased urination were observed in male and female 100 and/or 500 mg/kg/day groups, and were associated with changes in clinical chemistry and urinalysis that were attributed to a physiological effect on kidney function. An increase in altered colloid was observed in the thyroids of all dosed male and female groups. This lesion was also observed in some control rats and was not considered adverse.

Most of the effects observed during the dosing period demonstrated full or partial reversal following one or three months of recovery. Reversal of many effects in females was not observed until after the one-month recovery. Thyroid follicular hypertrophy in 500 mg/kg/day males and chronic progressive nephropathy in 100 and 500 mg/kg/day females were still present at the end of the three-month recovery period.

Under the conditions of this study, there was no NOEL for reproductive parameters. This was based on reductions in the fertility index in all dose groups. Prolongation of estrous cycle length was also observed in P₁ rats in all dose groups but the toxicological significance of this effect is unclear. Other adverse, compound-related effects observed in P₁ rats dosed with 500 mg/kg/day include decrements in body weight parameters and food efficiency and reduced number of implantation sites. A reduction in epididymal sperm counts was observed in all male groups dosed with test substance, but this effect was not considered adverse.

^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⁽²⁷⁾ and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union⁽²⁸⁾.

Adverse, compound-related effects observed in 100 and/or 500 mg/kg/day group F₁ rats included reductions in mean litter size, number of pups born and born alive, pup survival during lactation, and pup weight at birth and during lactation. In the 500 mg/kg/day F₁ group high mortality, during lactation and post-weaning, resulting in early sacrifice of this group, precluded evaluation of post-weaning parameters (body weight and nutritional parameters, clinical observations, developmental landmarks). No compound-related effects on any post-weaning parameters were observed in the 100 or 25 mg/kg/day F₁ groups.

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TABLES

TABLES

EXPLANATORY NOTES

Critical Dates

- Day 70 Last day data from the male and female rats designated for reproduction evaluations were reported with the subchronic toxicity animals. Body weights and clinical observations collected 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 and female rats designated for one-month and three-month recovery periods.
- Day 91 Last day of body weight and food consumption data collection for male and female rats designated for the 91-day exposure period.
- Day 94 Last day of test substance administration for male rats designated for the 91-day exposure period.
- Day 95 • Male rats designated for the 91-day exposure period were sacrificed.
• Last day of test substance administration for female rats designated for the 91-day exposure period.
- Day 96 Female rats designated for 91-day exposure period were sacrificed.
- Day 119 • Last day of body weight and food consumption data collection for rats designated for the one-month recovery period.
• Last day of food consumption data collection for rats designated for the three-month recovery period.
- Day 123 Male rats designated for the one-month recovery were sacrificed.
- Day 124 Female rats designated for the one-month recovery were sacrificed.
- Day 182 Last day of non-fasted body weight data collection for rats designated for the three-month recovery period.
- Day 183 Male and female rats designated for the three-month recovery period were sacrificed.

Note: Group I, Male Rat No. was dosed through test day 95, and bled for clinical pathology and necropsied on test day 96. This rat's clinical and anatomical pathology data are reported with the other males from test day 95.

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
PLT	-	platelet 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
AHSN	-	absolute hypersegmented neutrophil
ABAN	-	absolute neutrophil band
AMET	-	absolute neutrophil metamyelocyte
AMYE	-	absolute neutrophil myelocyte
APRO	-	absolute neutrophil promyelocyte
AMYB	-	absolute neutrophil myeloblast
ARL	-	absolute reactive lymphocyte
AAL	-	absolute atypical lymphocyte
AIL	-	absolute immature lymphocyte
ACL	-	absolute clefted lymphocyte
ABLB	-	absolute lymphoblast
AIE	-	absolute immature eosinophil
AIM	-	absolute immature monocyte
APLA	-	absolute plasma cell count
NC	-	not calculated or not calculable

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
SOSM	-	serum osmolality

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.

When an individual observation was recorded as being greater than a certain value, calculations were performed on the recorded value. For example, if specific gravity was reported as >1.083, 1.083 was used for any calculations performed with that specific gravity data.

TABLE 1
SUMMARY OF DOSING SOLUTION ANALYSES

Sample Type	Dosing Concentrations and Stability of H-24768 (mg/mL)			
Test Day 0	Nominal:	3.33	13.33	66.67
<u>Concentration Verification</u>		3.11	12.1	60.4 ^b
		(93.4) ^a	(90.8)	(90.6)
		2.82	11.6 ^b	55.1 ^b
		(84.7)	(87.0)	(82.6)
Average Measured Conc. ^c		2.98	11.9	57.8
Average Percent Nominal ^c		(89.2)	(89.3)	(86.7)
Standard Deviation ^c		± 0.21	± 0.35	± 3.7
Coefficient of Variation ^c		7%	3%	6%
<u>Stability</u>		2.93 ^d	11.6 ^d	58.1 ^d
		(88.0)	(87.0)	(87.1)
		3.14 ^e	12.0 ^e	58.9 ^e
		(94.3)	(90.0)	(88.3)
<u>Concentration Verification</u> ^f				
Test Day 32		3.07	11.6	60.4
		(92.2)	(87.0)	(90.6)
Test Day 42		3.12	12.5	58.2
		(93.7)	(93.8)	(87.3)
Test Day 91		3.17	12.5	59.3
		(95.2)	(93.8)	(88.9)
<u>Concentration Verification</u> ^g		4.72	9.36	40.2
		(94.4) ^a	(93.6)	(100.5)
		4.54	8.75	38.9
		(90.8)	(87.5)	(97.3)
Average Measured Conc. ^c		4.63	9.05	39.6
Average Percent Nominal ^c		(92.6)	(90.5)	(98.9)
Standard Deviation ^c		± 0.1	± 0.4	± 0.9
Coefficient of Variation ^c		3%	5%	2%
<u>Stability</u>		5.06 ^e	9.70 ^e	42.1 ^e
		(101.2)	(97.0)	(105.2)
		5.37 ^h	9.72 ^h	41.3 ^h
		(107.4)	(97.2)	(103.3)

a Numbers in parentheses are the respective percent of nominal values.

b Mean result of all analyses.

c Mean, S.D. and C.V. for duplicate samples calculated to verify uniformity of mixture.

d Samples (Test Day 0) held at room temperature for 5 hours.

e Samples (Test Day 39) held refrigerated for 4 days and sampled.

f Duplicate samples submitted. Mean result reported.

g Samples from previous study for [REDACTED]

h Samples held refrigerated for 4 days followed by 5 hours at room temperature.

TABLE 2

MEAN DAILY DOSE VOLUMES (mL) FOR MALE RATS

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
DAY 0 - DAY 6	1.6 0.1 (45)	1.6 0.1 (35)	1.6 0.1 (35)	1.6 0.1 (45)
DAY 7 - DAY 13	2.0 0.2 (45)	2.0 0.1 (35)	2.0 0.1 (35)	1.8 0.1 (45)
DAY 14 - DAY 20	2.4 0.3 (45)	2.4 0.2 (35)	2.4 0.2 (35)	2.2 0.2 (45)
DAY 21 - DAY 27	2.8 0.3 (45)	2.9 0.5 (35)	2.7 0.2 (35)	2.5 0.2 (45)
DAY 28 - DAY 34	3.1 0.3 (45)	3.1 0.3 (35)	2.9 0.2 (35)	2.7 0.3 (45)
DAY 35 - DAY 41	3.3 0.4 (45)	3.4 0.3 (35)	3.2 0.2 (35)	2.8 0.3 (43)
DAY 42 - DAY 48	3.5 0.4 (45)	3.6 0.3 (35)	3.3 0.2 (35)	3.0 0.3 (43)
DAY 49 - DAY 55	3.7 0.4 (45)	3.8 0.4 (35)	3.5 0.3 (35)	3.1 0.3 (43)
DAY 56 - DAY 62	3.8 0.5 (45)	3.9 0.4 (35)	3.6 0.3 (34)	3.2 0.3 (43)
DAY 63 - DAY 69	4.0 0.5 (44)	4.1 0.4 (35)	3.7 0.3 (34)	3.3 0.3 (43)
DAY 70	4.1 0.5 (44)	4.2 0.4 (35)	3.9 0.3 (34)	3.4 0.4 (43)
DAY 71 - DAY 76	4.0 0.5 (24)	4.2 0.4 (15)	3.8 0.3 (14)	3.3 0.3 (25)
DAY 77 - DAY 83	4.1 0.6 (24)	4.3 0.4 (15)	3.9 0.4 (14)	3.4 0.3 (25)
DAY 84 - DAY 90	4.2 0.6 (24)	4.4 0.4 (15)	4.0 0.4 (14)	3.5 0.3 (25)
DAY 91 - DAY 94	4.5 0.4 (10)	4.6 0.4 (10)	4.1 0.4 (10)	3.6 0.4 (10)

Data summarized as: Mean
Standard Deviation (n)

TABLE 3

MEAN DAILY DOSE VOLUMES (mL) FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
DAY 0 - DAY 6	1.3 0.1 (45)	1.3 0.1 (35)	1.3 0.1 (35)	1.3 0.1 (45)
DAY 7 - DAY 13	1.5 0.1 (45)	1.5 0.1 (35)	1.5 0.1 (35)	1.4 0.1 (45)
DAY 14 - DAY 20	1.6 0.1 (45)	1.6 0.1 (35)	1.6 0.1 (35)	1.6 0.1 (45)
DAY 21 - DAY 27	1.8 0.2 (45)	1.8 0.2 (35)	1.8 0.1 (35)	1.7 0.1 (45)
DAY 28 - DAY 34	1.9 0.2 (45)	1.9 0.2 (35)	1.9 0.1 (35)	1.8 0.2 (45)
DAY 35 - DAY 41	2.0 0.2 (45)	2.0 0.2 (35)	1.9 0.1 (35)	1.9 0.2 (45)
DAY 42 - DAY 48	2.1 0.2 (45)	2.0 0.2 (35)	2.0 0.2 (35)	2.0 0.2 (45)
DAY 49 - DAY 55	2.2 0.2 (45)	2.1 0.2 (35)	2.1 0.2 (35)	2.1 0.2 (45)
DAY 56 - DAY 62	2.2 0.2 (45)	2.2 0.2 (35)	2.2 0.2 (35)	2.1 0.2 (45)
DAY 63 - DAY 69	2.2 0.2 (45)	2.2 0.2 (35)	2.2 0.2 (35)	2.1 0.2 (45)
DAY 70	2.3 0.2 (45)	2.2 0.2 (35)	2.2 0.2 (35)	2.2 0.2 (45)
DAY 71 - DAY 76	2.3 0.2 (25)	2.2 0.3 (15)	2.3 0.2 (15)	2.2 0.2 (25)
DAY 77 - DAY 83	2.3 0.2 (25)	2.2 0.3 (15)	2.3 0.2 (15)	2.2 0.2 (25)
DAY 84 - DAY 91	2.4 0.2 (25)	2.3 0.3 (15)	2.4 0.2 (15)	2.2 0.2 (25)
DAY 91 - DAY 95	2.4 0.3 (10)	2.3 0.3 (10)	2.4 0.2 (10)	2.3 0.2 (10)

Data summarized as: Mean
Standard Deviation (n)

TABLE 4
MEAN BODY WEIGHTS (g) OF MALE RATS

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0	215.7 14.3 (45)	216.5 13.0 (35)	218.3 13.1 (35)	215.2 12.2 (45)
DAY 7	271.8 21.1 (45)	273.7 18.6 (35)	267.0 17.9 (35)	237.8# 16.6 (45)
DAY 14	321.2 34.6 (45)	328.3 25.2 (35)	314.9 19.6 (35)	287.7# 22.7 (45)
DAY 21	370.5 38.2 (45)	376.7 30.5 (35)	357.7 25.0 (35)	328.7# 28.9 (45)
DAY 28	409.7 42.4 (45)	419.0 35.9 (35)	393.7 30.2 (35)	359.7# 32.9 (45)
DAY 35	441.3 48.6 (45)	451.0 42.4 (35)	420.9# 32.4 (35)	376.4# 36.4 (43)
DAY 42	465.0 52.1 (45)	476.4 44.5 (35)	443.6# 32.4 (35)	392.7# 40.1 (43)
DAY 49	489.9 55.4 (45)	501.2 46.4 (35)	466.3# 33.7 (35)	410.7# 42.5 (43)
DAY 56	511.1 60.3 (45)	523.4 50.4 (35)	482.8# 33.9 (34)	427.9# 43.2 (43)
DAY 63	526.7 63.6 (44)	540.2 52.5 (35)	499.2# 35.0 (34)	442.5# 44.9 (43)
DAY 70 ^a	541.6 65.6 (44)	559.9 54.2 (35)	515.5# 37.2 (34)	452.1# 45.5 (43)

TABLE 4 (Continued)

MEAN BODY WEIGHTS (g) OF MALE RATS

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 77	547.8 75.4(24)	573.0 55.1(15)	520.0 51.8(14)	452.6# 42.0(25)
DAY 84	558.7 77.8(24)	583.5 59.6(15)	531.5 52.5(14)	461.8# 44.0(25)
DAY 91	568.0 77.2(24)	594.8 61.1(15)	532.1 53.0(14)	470.4# 44.9(25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 98	551.3 83.9(14)	562.9 49.1(5)	523.7 54.2(4)	491.4# 42.8(15)
DAY 105	562.0 86.3(14)	570.7 46.0(5)	543.0 57.0(4)	513.6# 40.6(15)
DAY 112	572.0 86.8(14)	580.5 46.2(5)	555.8 64.8(4)	518.8# 48.6(15)
DAY 119	577.3 86.5(14)	582.2 42.1(5)	556.8 67.4(4)	522.0# 56.1(15)

TABLE 4 (Continued)

MEAN BODY WEIGHTS (g) OF MALE RATS

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 126	539.3 94.8 (4)	593.7 42.9 (5)	567.1 71.1 (4)	533.2 30.7 (5)
DAY 133	550.2 99.1 (4)	607.0 44.1 (5)	572.0 67.4 (4)	555.5 32.6 (5)
DAY 140	560.3 101.9 (4)	616.3 47.2 (5)	585.9 74.2 (4)	569.8 32.8 (5)
DAY 154	558.2 97.4 (4)	625.6 45.6 (5)	595.2 65.3 (4)	593.6 38.9 (5)
DAY 147	553.4 97.1 (4)	622.9 48.6 (5)	585.9 67.3 (4)	578.6 37.2 (5)
DAY 161	573.2 101.1 (4)	634.1 45.8 (5)	599.9 59.4 (4)	608.7 44.9 (5)
DAY 168	581.6 105.2 (4)	643.0 52.4 (5)	611.0 63.4 (4)	614.8 49.0 (5)
DAY 175	578.0 102.7 (4)	647.2 47.5 (5)	615.2 68.3 (4)	622.3 39.6 (5)
DAY 182	588.0 104.5 (4)	655.1 53.3 (5)	621.3 72.4 (4)	634.3 44.0 (5)

Data summarized as: Mean
Standard Deviation (n)

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 70; subsequent data are reported as part of the reproduction evaluation.

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 5

MEAN BODY WEIGHTS (g) OF FEMALE RATS

	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0	175.6 11.5 (45)	177.1 12.6 (35)	177.3 10.8 (35)	176.6 12.4 (45)
DAY 7	197.0 13.5 (45)	196.4 14.8 (35)	193.9 11.4 (35)	185.0# 15.0 (45)
DAY 14	216.9 17.5 (45)	215.1 17.6 (35)	214.2 14.2 (35)	209.9 16.1 (45)
DAY 21	236.5 20.8 (45)	234.1 20.2 (35)	234.6 15.5 (35)	229.5 17.6 (45)
DAY 28	252.5 22.0 (45)	252.4 22.8 (35)	250.0 17.5 (35)	246.8 19.1 (45)
DAY 35	265.3 25.8 (45)	265.3 23.9 (35)	258.9 18.0 (35)	255.3# 20.2 (45)
DAY 42	276.9 25.4 (45)	273.4 25.4 (35)	270.8 20.1 (35)	265.5# 20.2 (45)
DAY 49	287.3 28.5 (45)	284.4 27.2 (35)	283.4 22.0 (35)	275.1# 22.9 (45)
DAY 56	292.7 28.4 (45)	291.0 28.0 (35)	288.2 23.5 (35)	280.7# 22.7 (45)
DAY 63	297.1 27.9 (45)	293.9 30.5 (35)	294.2 25.3 (35)	285.2 22.9 (45)
DAY 70 ^a	305.3 28.3 (45)	300.2 30.0 (35)	299.8 24.2 (35)	289.2# 23.6 (45)

TABLE 5 (Continued)

MEAN BODY WEIGHTS (g) OF FEMALE RATS

	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 77	312.0 30.1(25)	296.3 38.3(15)	307.5 30.9(15)	295.1 22.8(25)
DAY 84	316.3 30.5(25)	301.4 38.6(15)	316.0 32.1(15)	299.9 21.8(25)
DAY 91	320.0 31.2(24)	305.5 39.2(15)	317.3 32.0(15)	300.0# 19.8(25)

One-Month Recovery Period for Subchronic Toxicity Evaluation

DAY 98	326.5 27.3(14)	308.9 46.2(5)	316.4 47.0(5)	299.1# 18.7(15)
DAY 105	328.8 27.6(14)	309.6 61.2(5)	323.9 47.8(5)	298.7# 21.0(15)
DAY 112	340.9 31.4(14)	321.0 51.2(5)	332.2 42.9(5)	312.0# 22.4(15)
DAY 119	341.2 33.0(14)	326.4 54.5(5)	327.2 47.6(5)	304.6# 29.1(15)

TABLE 5 (Continued)

MEAN BODY WEIGHTS (g) OF FEMALE RATS

	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 126	339.3 38.8(4)	330.8 55.6(5)	335.8 44.3(5)	310.4 28.4(5)
DAY 133	339.1 39.2(4)	331.3 55.9(5)	337.8 46.7(5)	314.3 34.0(5)
DAY 140	339.7 43.0(4)	335.4 58.9(5)	344.4 50.1(5)	320.8 39.0(5)
DAY 147	346.3 33.6(4)	334.5 62.1(5)	345.1 46.4(5)	321.9 32.6(5)
DAY 154	345.6 39.9(4)	335.7 60.7(5)	342.1 46.0(5)	323.0 36.0(5)
DAY 161	352.6 38.4(4)	341.3 61.7(5)	345.7 49.1(5)	330.0 39.1(5)
DAY 168	351.5 42.8(4)	345.8 63.0(5)	346.2 51.4(5)	329.1 40.9(5)
DAY 175	357.7 39.5(4)	346.1 62.4(5)	345.7 55.0(5)	328.1 42.0(5)
DAY 182	356.0 46.2(4)	349.9 64.2(5)	355.3 54.8(5)	335.6 45.9(5)

Data summarized as: Mean
Standard Deviation (n)

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 70; subsequent data are reported as part of the reproduction evaluation.

Statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 6

MEAN BODY WEIGHT GAINS (g) OF MALE RATS

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0 - DAY 7	56.1 9.2(45)	57.3 7.3(35)	48.7# 8.8(35)	22.5# 9.2(45)
DAY 7 - DAY 14	49.4 20.0(45)	54.5 8.9(35)	47.9 10.0(35)	50.0 10.6(45)
DAY 14 - DAY 21	49.3 12.2(45)	48.4 8.7(35)	42.8# 8.4(35)	40.9# 9.7(45)
DAY 21 - DAY 28	39.2 8.2(45)	42.3 9.5(35)	36.0 9.8(35)	31.0# 7.6(45)
DAY 28 - DAY 35	31.6 9.2(45)	32.0 8.8(35)	27.2# 6.7(35)	18.0# 6.5(43)
DAY 35 - DAY 42	23.7 8.5(45)	25.5 8.1(35)	22.7 10.2(35)	16.2# 10.4(43)
DAY 42 - DAY 49	24.8 6.2(45)	24.7 7.1(35)	22.7 5.6(35)	18.1# 8.6(43)
DAY 49 - DAY 56	21.2 8.7(45)	22.3 6.8(35)	16.3# 5.4(34)	17.2# 7.4(43)
DAY 56 - DAY 63	16.8 6.4(44)	16.8 9.5(35)	16.5 5.7(34)	14.6 8.2(43)
DAY 63 - DAY 70	14.8 6.1(44)	19.7 6.2(35)	16.3 5.6(34)	9.7# 6.4(43)
DAY 0 - DAY 70 ^a	326.2 56.6(44)	343.4 47.4(35)	296.9# 32.6(34)	237.0# 40.7(43)

TABLE 6 (Continued)

MEAN BODY WEIGHT GAINS (g) OF MALE RATS

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 70 - DAY 77	12.5 6.9(24)	12.7 4.4(15)	9.8 9.2(14)	8.2# 10.5(25)
DAY 77 - DAY 84	10.8 6.0(24)	10.6 9.7(15)	11.4 4.9(14)	9.2 8.5(25)
DAY 84 - DAY 91	9.3 7.7(24)	11.3 9.9(15)	0.6 6.3(14)	8.6 8.3(25)
DAY 0 - DAY 91	354.0 67.8(24)	377.9 54.8(15)	312.6 48.1(14)	255.6# 41.2(25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 91 - DAY 98	11.5 6.7(14)	8.4 2.0(5)	11.5 8.0(4)	26.0# 8.7(15)
DAY 98 - DAY 105	10.7 7.1(14)	7.8 6.7(5)	19.3 3.2(4)	22.2# 12.3(15)
DAY 105 - DAY 112	10.0 3.5(14)	9.8 4.6(5)	12.8 8.5(4)	5.2 26.2(15)
DAY 112 - DAY 119	5.3 5.6(14)	1.7 5.5(5)	1.1 3.9(4)	3.3 11.1(15)
DAY 91 - DAY 119	37.5 9.7(14)	27.7 7.5(5)	44.7 9.9(4)	56.6# 41.0(15)

TABLE 6 (Continued)

MEAN BODY WEIGHT GAINS (g) OF MALE RATS

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 119 - DAY 126	14.0 7.2(4)	11.5 6.5(5)	10.3 6.2(4)	21.8 27.4(5)
DAY 126 - DAY 133	11.0 4.9(4)	13.3 8.0(5)	4.8 4.1(4)	22.3 7.3(5)
DAY 133 - DAY 140	10.1 3.0(4)	9.2 6.2(5)	14.0 8.4(4)	14.2 5.9(5)
DAY 140 - DAY 147	-7.0 17.7(4)	6.7 4.9(5)	-0.1 10.0(4)	8.9 12.1(5)
DAY 147 - DAY 154	4.8 7.0(4)	2.6 6.9(5)	9.3 3.2(4)	15.0# 9.9(5)
DAY 154 - DAY 161	15.0 4.2(4)	8.6 1.5(5)	4.7 6.5(4)	15.1 9.7(5)
DAY 161 - DAY 168	8.4 8.7(4)	8.8 8.0(5)	11.0 4.6(4)	6.1 11.4(5)
DAY 168 - DAY 175	-3.7 5.6(4)	4.2 6.7(5)	4.3 5.5(4)	7.5 12.4(5)
DAY 175 - DAY 182	10.0 4.4(4)	8.0 7.8(5)	6.1 6.2(4)	12.0 6.0(5)
DAY 91 - DAY 182	92.3 42.0(4)	100.6 19.1(5)	109.2 14.1(4)	167.1# 44.4(5)

Data summarized as: Mean
Standard Deviation (n)

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 70; subsequent data are reported as part of the reproduction evaluation.

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 7
MEAN BODY WEIGHT GAINS (g) OF FEMALE RATS

	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0 - DAY 7	21.4 6.7(45)	19.3 6.2(35)	16.5# 5.3(35)	8.3# 10.9(45)
DAY 7 - DAY 14	19.9 7.9(45)	18.7 6.5(35)	20.3 5.2(35)	24.9# 6.9(45)
DAY 14 - DAY 21	19.6 8.8(45)	19.0 6.6(35)	20.4 5.1(35)	19.6 5.6(45)
DAY 21 - DAY 28	15.9 8.5(45)	18.4 6.7(35)	15.3 7.1(35)	17.3 6.7(45)
DAY 28 - DAY 35	12.9 7.8(45)	12.8 5.4(35)	8.9 8.6(35)	8.6# 6.1(45)
DAY 35 - DAY 42	11.6 7.1(45)	8.1 6.0(35)	11.9 8.7(35)	10.2 5.9(45)
DAY 42 - DAY 49	10.4 6.8(45)	11.0 6.7(35)	12.6 7.6(35)	9.5 7.0(45)
DAY 49 - DAY 56	5.5 6.4(45)	6.6 6.0(35)	4.8 5.4(35)	5.7 6.2(45)
DAY 56 - DAY 63	4.4 5.6(45)	2.9 4.4(35)	6.1 6.0(35)	4.5 5.0(45)
DAY 63 - DAY 70	8.2 5.9(45)	6.4 6.3(35)	5.5# 6.4(35)	4.0# 6.2(45)
DAY 0 - DAY 70 ^a	129.7 20.9(45)	123.1 21.7(35)	122.4 19.7(35)	112.6# 18.4(45)

TABLE 7 (Continued)

MEAN BODY WEIGHT GAINS (g) OF FEMALE RATS

	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 70 - DAY 77	4.1 6.9(25)	4.4 6.6(15)	2.3 6.8(15)	4.2 5.5(25)
DAY 77 - DAY 84	4.3 6.6(25)	5.2 4.8(15)	8.4 4.0(15)	4.8 5.2(25)
DAY 84 - DAY 91	2.2 5.8(24)	4.1 6.1(15)	1.4 4.5(15)	0.0 6.5(25)
DAY 0 - DAY 91	142.9 25.0(24)	132.1 30.4(15)	140.2 26.6(15)	121.7# 13.8(25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 91 - DAY 98	7.2 8.9(14)	2.6 3.6(5)	3.4 6.6(5)	0.4# 8.1(15)
DAY 98 - DAY 105	2.2 8.5(14)	0.8 18.9(5)	7.5 4.3(5)	-0.5 15.1(15)
DAY 105 - DAY 112	12.2 7.4(14)	11.4 11.2(5)	8.4 10.7(5)	13.3 12.4(15)
DAY 112 - DAY 119	0.3 6.3(14)	5.4 5.5(5)	-5.0 6.1(5)	-7.4# 17.2(15)
DAY 91 - DAY 119	21.9 10.7(14)	20.1 11.1(5)	14.2 17.4(5)	5.8# 23.8(15)

TABLE 7 (Continued)

MEAN BODY WEIGHT GAINS (g) OF FEMALE RATS

	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 119 - DAY 126	4.3 6.5(4)	4.3 3.8(5)	8.6 7.1(5)	19.3 31.6(5)
DAY 126 - DAY 133	-0.1 8.5(4)	0.6 4.9(5)	2.0 4.3(5)	3.9 7.3(5)
DAY 133 - DAY 140	0.5 12.7(4)	4.0 7.1(5)	6.6 10.7(5)	6.5 7.0(5)
DAY 140 - DAY 147	6.6 12.8(4)	-0.9 7.4(5)	0.7 8.1(5)	1.1 7.9(5)
DAY 154 - DAY 161	7.0 3.9(4)	5.6 9.0(5)	3.5 4.9(5)	7.0 5.6(5)
DAY 161 - DAY 168	-1.1 10.2(4)	4.5 4.3(5)	0.5 7.1(5)	-0.8 6.9(5)
DAY 147 - DAY 154	-0.7 9.1(4)	1.3 6.1(5)	-2.9 5.9(5)	1.1 6.8(5)
DAY 168 - DAY 175	6.2 5.5(4)	0.3 1.4(5)	-0.5 6.3(5)	-1.1 4.8(5)
DAY 175 - DAY 182	-1.7 11.4(4)	3.9 2.6(5)	9.6 6.8(5)	7.6 10.5(5)
DAY 91 - DAY 182	44.0 24.2(4)	43.6 20.5(5)	42.2 31.1(5)	39.8 28.4(5)

Data summarized as: Mean
Standard Deviation (n)

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 70; subsequent data are reported as part of the reproduction evaluation.

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 8
MEAN DAILY FOOD CONSUMPTION (g) BY MALE RATS

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0 - DAY 7	26.2 3.3(45)	26.4 3.8(35)	25.2 2.4(35)	18.6# 2.2(45)
DAY 7 - DAY 14	28.0 3.2(44)	28.3 2.9(35)	26.7 2.5(35)	24.1# 2.8(45)
DAY 14 - DAY 21	29.3 3.7(45)	30.0 3.2(35)	28.1 2.6(35)	27.0# 3.2(45)
DAY 21 - DAY 28	30.8 3.7(45)	31.9 3.6(35)	29.5 3.6(35)	28.0# 3.4(45)
DAY 28 - DAY 35	30.6 3.9(45)	31.8 3.6(35)	29.8 2.6(35)	27.5# 3.4(43)
DAY 35 - DAY 42	31.1 3.8(45)	31.7 3.6(35)	29.8 2.8(35)	27.7# 3.8(43)
DAY 42 - DAY 49	31.4 3.7(45)	31.7 3.6(35)	30.4 2.7(35)	28.7# 3.8(43)
DAY 49 - DAY 56	31.8 4.3(45)	32.1 3.6(35)	29.3# 2.4(34)	29.6# 3.5(43)
DAY 56 - DAY 63	31.1 4.3(44)	30.9 4.4(35)	29.9 2.3(34)	30.3 4.2(43)
DAY 63 - DAY 70	29.7 3.8(44)	31.4 3.9(35)	29.8 2.2(34)	29.8 3.9(43)
DAY 0 - DAY 70 ^a	30.0 3.5(43)	30.6 3.2(35)	28.8# 2.1(34)	27.1# 3.0(43)

TABLE 8 (Continued)

MEAN DAILY FOOD CONSUMPTION (g) BY MALE RATS

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
Day 70 - Day 77	28.6 4.2(24)	29.1 4.4(15)	28.7 2.3(14)	28.8 3.4(25)
Day 77 - Day 84	28.8 4.1(24)	30.5 3.8(15)	28.8 2.5(14)	29.2 3.1(25)
Day 84 - Day 91	28.8 4.3(24)	30.1 4.2(15)	27.3 2.8(14)	29.6 3.2(25)
DAY 0 - DAY 91	29.2 3.9(24)	30.4 3.3(15)	28.6 2.3(14)	27.1# 3.4(25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
Day 91 - Day 98	28.4 4.6(14)	28.5 3.4(5)	29.7 2.3(4)	33.4# 4.1(15)
Day 98 - Day 105	28.1 5.1(14)	27.7 2.6(5)	31.6 1.3(4)	33.3# 3.1(15)
Day 105 - Day 112	27.3 4.2(14)	27.3 1.6(5)	30.2 2.2(4)	29.2 5.6(15)
Day 112 - Day 119	27.7 4.2(14)	26.6 1.7(5)	28.7 2.0(4)	28.8 6.3(15)
DAY 91 - DAY 119	27.9 4.4(14)	27.5 2.2(5)	30.0 1.4(4)	31.2 3.6(15)

Data summarized as: Mean
Standard Deviation (n)

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 70; food consumption data were not collected during the cohabitation and postmating periods.

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 9
 MEAN DAILY FOOD CONSUMPTION (g) BY FEMALE RATS

	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
Day 0 - Day 7	19.0 1.9(45)	18.8 1.9(35)	17.5# 1.5(35)	12.5# 3.0(45)
Day 7 - Day 14	19.7 1.9(45)	20.0 2.0(35)	19.7 1.5(35)	17.4# 2.1(45)
Day 14 - Day 21	19.7 2.1(45)	20.7 2.4(35)	20.3 1.6(35)	19.0 2.0(45)
Day 21 - Day 28	20.7 2.2(45)	20.8 2.1(35)	20.5 1.7(35)	19.7# 2.4(45)
Day 28 - Day 35	21.8 3.0(45)	21.6 2.4(35)	21.3 2.1(35)	21.7 2.4(45)
Day 35 - Day 42	21.7 2.4(45)	21.5 2.5(35)	20.9 2.2(35)	20.8# 2.5(45)
Day 42 - Day 49	22.2 2.8(45)	22.3 2.9(35)	22.7 2.2(35)	21.9 2.8(45)
Day 49 - Day 56	22.1 2.7(45)	21.8 2.5(35)	22.1 2.5(35)	22.1 2.7(45)
Day 56 - Day 63	21.4 2.8(45)	20.9 2.6(35)	22.3 2.7(35)	22.3 2.6(45)
Day 63 - Day 70	21.2 2.8(45)	20.6 2.5(35)	21.6 2.2(35)	21.9 2.5(45)
DAY 0 - DAY 70 ^a	21.0 2.0(45)	20.9 2.1(35)	20.9 1.7(35)	19.9 2.1(45)

TABLE 9 (Continued)

MEAN DAILY FOOD CONSUMPTION (g) BY FEMALE RATS

	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
Day 70 - Day 77	21.9 2.6(25)	20.9 3.2(15)	22.1 2.9(15)	22.7 2.4(25)
Day 77 - Day 84	21.0 2.2(25)	20.9 2.9(15)	22.1 3.2(15)	22.0# 3.0(25)
Day 84 - Day 91	19.9 2.5(24)	20.2 3.2(15)	21.3 3.0(15)	22.1# 2.1(25)
DAY 0 - DAY 91	21.1 2.0(24)	20.6 2.5(15)	21.2 2.2(15)	20.5 1.9(25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
Day 91 - Day 98	22.1 2.1(14)	22.1 3.6(5)	23.9 3.4(5)	24.3# 2.2(15)
Day 98 - Day 105	21.6 2.0(14)	21.2 5.6(5)	22.9 2.4(5)	22.2 3.3(15)
Day 105 - Day 112	22.5 3.2(14)	22.5 3.6(5)	23.9 2.5(5)	24.1 2.4(15)
Day 112 - Day 119	21.4 2.7(14)	21.5 3.4(5)	22.2 2.4(5)	21.2 4.9(15)
DAY 91 - DAY 119	21.9 2.2(14)	21.8 3.9(5)	23.2 2.4(5)	22.9 2.7(15)

Data summarized as: Mean
Standard Deviation (n)

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 70; data were not collected during the cohabitation period. Food consumption data collected during gestation are reported as part of the reproduction evaluation.

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 10

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

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0 - DAY 7	0.306 0.035 (45)	0.313 0.043 (35)	0.275# 0.037 (35)	0.168# 0.056 (45)
DAY 7 - DAY 14	0.264 0.029 (44)	0.274 0.027 (35)	0.256 0.048 (35)	0.294# 0.042 (45)
DAY 14 - DAY 21	0.240 0.053 (45)	0.230 0.029 (35)	0.217# 0.034 (35)	0.215# 0.037 (45)
DAY 21 - DAY 28	0.181 0.029 (45)	0.188 0.031 (35)	0.173 0.042 (35)	0.157# 0.029 (45)
DAY 28 - DAY 35	0.146 0.031 (45)	0.142 0.029 (35)	0.130# 0.030 (35)	0.092# 0.029 (43)
DAY 35 - DAY 42	0.107 0.031 (45)	0.114 0.030 (35)	0.107 0.045 (35)	0.081# 0.051 (43)
DAY 42 - DAY 49	0.112 0.021 (45)	0.111 0.027 (35)	0.106 0.024 (35)	0.089# 0.040 (43)
DAY 49 - DAY 56	0.093 0.033 (45)	0.098 0.025 (35)	0.079# 0.025 (34)	0.083# 0.037 (43)
DAY 56 - DAY 63	0.076 0.024 (44)	0.074 0.050 (35)	0.079 0.027 (34)	0.068 0.036 (43)
DAY 63 - DAY 70	0.070 0.027 (44)	0.090 0.027 (35)	0.077 0.025 (34)	0.046# 0.030 (43)
DAY 0 - DAY 70 ^a	0.154 0.012 (43)	0.159 0.010 (35)	0.146# 0.011 (34)	0.122# 0.012 (43)

TABLE 10 (Continued)

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

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 70 - DAY 77	0.061 0.032 (24)	0.065 0.030 (15)	0.047 0.043 (14)	0.038 0.063 (25)
DAY 77 - DAY 84	0.052 0.027 (24)	0.048 0.043 (15)	0.057 0.024 (14)	0.044 0.046 (25)
DAY 84 - DAY 91	0.046 0.041 (24)	0.053 0.047 (15)	0.002 0.034 (14)	0.040 0.040 (25)
DAY 0 - DAY 91	0.132 0.011 (24)	0.136 0.008 (15)	0.119# 0.012 (14)	0.102# 0.012 (25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 91 - DAY 98	0.055 0.027 (14)	0.042 0.009 (5)	0.053 0.035 (4)	0.111# 0.034 (15)
DAY 98 - DAY 105	0.053 0.037 (14)	0.039 0.033 (5)	0.087 0.013 (4)	0.094# 0.054 (15)
DAY 105 - DAY 112	0.053 0.019 (14)	0.052 0.024 (5)	0.059 0.036 (4)	-0.008 0.215 (15)
DAY 112 - DAY 119	0.028 0.030 (14)	0.010 0.032 (5)	0.005 0.021 (4)	0.005 0.067 (15)
DAY 91 - DAY 119	0.048 0.009 (14)	0.036 0.012 (5)	0.053 0.010 (4)	0.061# 0.048 (15)

Data summarized as: Mean
Standard Deviation (n)

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 70; data were not collected during the cohabitation and postmating periods.

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 11

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

	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0 - DAY 7	0.160 0.048(45)	0.145 0.039(35)	0.134# 0.039(35)	0.119# 0.258(45)
DAY 7 - DAY 14	0.142 0.049(45)	0.132 0.040(35)	0.146 0.033(35)	0.205# 0.054(45)
DAY 14 - DAY 21	0.141 0.058(45)	0.130 0.041(35)	0.144 0.033(35)	0.148 0.041(45)
DAY 21 - DAY 28	0.109 0.053(45)	0.125 0.043(35)	0.105 0.044(35)	0.125 0.047(45)
DAY 28 - DAY 35	0.081 0.045(45)	0.085 0.036(35)	0.056 0.065(35)	0.056# 0.039(45)
DAY 35 - DAY 42	0.076 0.045(45)	0.052 0.039(35)	0.079 0.056(35)	0.071 0.038(45)
DAY 42 - DAY 49	0.065 0.040(45)	0.069 0.039(35)	0.078 0.044(35)	0.060 0.039(45)
DAY 49 - DAY 56	0.035 0.041(45)	0.043 0.039(35)	0.029 0.035(35)	0.036 0.039(45)
DAY 56 - DAY 63	0.028 0.036(45)	0.018 0.029(35)	0.038 0.036(35)	0.029 0.033(45)
DAY 63 - DAY 70	0.055 0.039(45)	0.045 0.046(35)	0.037# 0.044(35)	0.026# 0.040(45)
DAY 0 - DAY 70 ^a	0.088 0.009(45)	0.084 0.010(35)	0.083# 0.009(35)	0.081# 0.010(45)

TABLE 11 (Continued)

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

	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 70 - DAY 77	0.026 0.043 (25)	0.027 0.042 (15)	0.013 0.045 (15)	0.026 0.035 (25)
DAY 77 - DAY 84	0.029 0.043 (25)	0.037 0.037 (15)	0.054 0.025 (15)	0.032 0.037 (25)
DAY 84 - DAY 91	0.013 0.043 (24)	0.028 0.045 (15)	0.009 0.031 (15)	0.001 0.043 (25)
DAY 0 - DAY 91	0.074 0.009 (24)	0.070 0.011 (15)	0.072 0.008 (15)	0.065# 0.005 (25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 91 - DAY 98	0.046 0.057 (14)	0.017 0.023 (5)	0.019 0.038 (5)	0.001# 0.047 (15)
DAY 98 - DAY 105	0.012 0.058 (14)	-0.033 0.194 (5)	0.046 0.023 (5)	-0.021 0.154 (15)
DAY 105 - DAY 112	0.073 0.040 (14)	0.083 0.097 (5)	0.050 0.063 (5)	0.077 0.071 (15)
DAY 112 - DAY 119	0.000 0.044 (14)	0.034 0.030 (5)	-0.036 0.044 (5)	-0.108 0.318 (15)
DAY 91 - DAY 119	0.035 0.016 (14)	0.032 0.013 (5)	0.021 0.027 (5)	0.006# 0.043 (15)
Data summarized as: Mean Standard Deviation (n)				

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 70; data were not collected during the cohabitation periods. Food efficiency data from the gestation period are reported as part of the reproduction evaluation.

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 12

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group Dose Animal Count	I 0 mg/kg/day 45	III 25 mg/kg/day 35	V 100 mg/kg/day 35	VII 500 mg/kg/day 45
Mass Inguen				
Incidence Mean onset (Days)	0 -	0 -	0 -	1 172
Eye Observations Dark				
Incidence Mean onset (Days)	0 -	3 110	0 -	0 -
Corneal Opacity/Opaque ^a				
Incidence Mean onset (Days)	0 -	2 154	2 130	0 -
Exophthalmus				
Incidence Mean onset (Days)	0 -	0 -	1 14	1 42
Enophthalmus				
Incidence Mean onset (Days)	0 -	1 154	0 -	1 84
Closed/Partially Closed				
Incidence Mean onset (Days)	0 -	1 126	0 -	1 63
Wet Fur (Chin, Perineum)				
Incidence Mean onset (Days)	0 -	0 -	0 -	3 # 46
Ruffled Fur				
Incidence Mean onset (Days)	1 14	0 -	0 -	0 -

TABLE 12 (Continued)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group	I 0 mg/kg/day 45	III 25 mg/kg/day 35	V 100 mg/kg/day 35	VII 500 mg/kg/day 45
Dose				
Animal Count				
Carriage				
Low				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	112
Head Tilt				
Incidence	1	0	0	0
Mean onset (Days)	105	-	-	-
Abnormal Gait				
Hindlimb				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	74
Scab				
Inguen				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	183
General Teeth Observations				
Clipped				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	118
Maloccluded				
Incidence	0	0	2	0
Mean onset (Days)	-	-	11	-
Absent				
Incidence	0	0	1	0
Mean onset (Days)	-	-	14	-

TABLE 12 (Continued)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group	I 0 mg/kg/day 45	III 25 mg/kg/day 35	V 100 mg/kg/day 35	VII 500 mg/kg/day 45
Dose				
Animal Count				
Breathing Observations				
Labored				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	63
Discharge				
Eye				
Incidence	2	2	3	4
Mean onset (Days)	56	95	56	74
Nose				
Incidence	0	1	1	1
Mean onset (Days)	-	42	147	168
Mouth				
Clear				
Incidence	0	1	4 #	14 #
Mean onset (Days)	-	70	58	39
Mouth				
Red				
Incidence	0	0	1	1
Mean onset (Days)	-	-	13	22
Penis				
Red				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	49
Hair Loss				
Neck				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	77

TABLE 12 (Continued)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group	I 0 mg/kg/day 45	III 25 mg/kg/day 35	V 100 mg/kg/day 35	VII 500 mg/kg/day 45
Dose				
Animal Count				
Face				
Incidence	0	0	1	1
Mean onset (Days)	-	-	28	56
Ventral body				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	7
Thoracic				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	49
Side				
Incidence	0	0	0	3 #
Mean onset (Days)	-	-	-	49
Shoulder				
Incidence	1	0	0	1
Mean onset (Days)	49	-	-	35
Perineum				
Incidence	0	0	0	4 #
Mean onset (Days)	-	-	-	19
Lumbar				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	35
Hindpaw				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	49

TABLE 12 (Continued)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group Dose Animal Count	I 0 mg/kg/day 45	III 25 mg/kg/day 35	V 100 mg/kg/day 35	VII 500 mg/kg/day 45
Hindlimb				
Incidence	0	0	1	2
Mean onset (Days)	-	-	49	56
Forepaw				
Incidence	14	5	5	9
Mean onset (Days)	56	22	57	66
Forelimb				
Incidence	6	1	4	7
Mean onset (Days)	57	49	47	78
Base of tail				
Incidence	1	0	1	1
Mean onset (Days)	77	-	133	42
Abdomen				
Incidence	0	0	0	7
Mean onset (Days)	-	-	-	34
Wound				
Superficial (mouth, face, shoulders, perineum, forelimb, forepaw, hindpaws)				
Incidence	1	2	2	5
Mean onset (Days)	11	27	81	64
Lethargic				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	22

TABLE 12 (Continued)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group	I	III	V	VII
Dose	0 mg/kg/day	25 mg/kg/day	100 mg/kg/day	500 mg/kg/day
Animal Count	45	35	35	45
Hyperreactive				
Incidence	2	0	0	0
Mean onset (Days)	53	-	-	-
Missshapen Observations				
Ear				
Incidence	0	0	0	2
Mean onset (Days)	-	-	-	18
Stain Fur/Skin				
Incidence	2	2	3	27 #
Mean onset (Days)	46	35	81	55
Swollen Observations				
Abdomen				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	28

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.

a. The observation "corneal opacity/opaque" includes "Eye observations, corneal opacity, left" and "Eye observations, corneal opacity, right" and "Eye observations, opaque, left."

Statistically significant difference at $p < 0.05$ by Cochran-Armitage trend test.

TABLE 13

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II 0 mg/kg/day 45	IV 25 mg/kg/day 35	VI 100 mg/kg/day 35	VIII 500 mg/kg/day 45
Dose				
Animal Count	45	35	35	45
Mass Perineum				
Incidence	0	0	1	0
Mean onset (Days)	-	-	63	-
Eye Observations				
Corneal Opacity / Opaque ^a				
Incidence	2	2	0	1
Mean onset (Days)	124	119	-	105
Exophthalmus				
Incidence	1	1	0	1
Mean onset (Days)	102	91	-	105
Enophthalmus				
Incidence	2	2	0	1
Mean onset (Days)	144	105	-	147
Wet Fur (perineum, inguen)				
Incidence	0	0	1	3 #
Mean onset (Days)	-	-	56	73
Abnormal Gait				
Hindlimb				
Incidence	0	1	0	0
Mean onset (Days)	-	35	-	-
Discharge				
Eye				
Incidence	1	2	2	0
Mean onset (Days)	147	72	172	-

TABLE 13 (Continued)

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II 0 mg/kg/day 45	IV 25 mg/kg/day 35	VI 100 mg/kg/day 35	VIII 500 mg/kg/day 45
Dose				
Animal Count				
Nose				
Incidence	1	0	0	0
Mean onset (Days)	14	-	-	-
Mouth				
Clear				
Incidence	0	0	3 #	6 #
Mean onset (Days)	-	-	21	33
Hair Loss				
Neck				
Incidence	1	0	0	0
Mean onset (Days)	21	-	-	-
Head				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	140
Ventral body				
Incidence	0	0	0	6 #
Mean onset (Days)	-	-	-	46
Thoracic				
Incidence	0	0	0	2
Mean onset (Days)	-	-	-	35
Side				
Incidence	0	0	0	14 #
Mean onset (Days)	-	-	-	30
Sacral				
Incidence	0	0	0	9 #
Mean onset (Days)	-	-	-	52

TABLE 13 (Continued)

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II 0 mg/kg/day 45	IV 25 mg/kg/day 35	VI 100 mg/kg/day 35	VIII 500 mg/kg/day 45
Dose				
Animal Count				
Perineum				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	21
Lumbar				
Incidence	0	0	0	2
Mean onset (Days)	-	-	-	94
Hindlimb				
Incidence	0	0	1	10 #
Mean onset (Days)	-	-	70	41
Forepaw				
Incidence	8	8	3	10
Mean onset (Days)	49	39	95	60
Forelimb				
Incidence	3	6	7	9
Mean onset (Days)	51	38	51	57
Dorsal Body				
Incidence	1	2	9 *	1
Mean onset (Days)	49	49	49	49
Base of tail				
Incidence	1	0	1	3
Mean onset (Days)	49	-	147	35
Abdomen				
Incidence	1	0	2	9 #
Mean onset (Days)	56	-	35	20

TABLE 13 (Continued)

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II 0 mg/kg/day 45	IV 25 mg/kg/day 35	VI 100 mg/kg/day 35	VIII 500 mg/kg/day 45
Dose				
Animal Count				
Wound				
Superficial (Lumbar, Hindlimb, Forepaws)				
Incidence	1	1	0	3
Mean onset (Days)	21	21	-	69
Hyperreactive				
Incidence	0	0	1	1
Mean onset (Days)		-	14	91
Hyperactive				
Incidence	0	1	0	2
Mean onset (Days)	-	56	-	98
Missshapen Observations Tail				
Incidence	0	1	0	0
Mean onset (Days)	-	84	-	-
Stain Fur/Skin				
Incidence	2	2	3	31 #
Mean onset (Days)	49	72	50	52
Swollen Observations (toe, forepaw)				
Incidence	0	0	0	2
Mean onset (Days)	-	-	-	56

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.

a. The observation "corneal opacity/opaque" includes "Eye observations, corneal opacity, left," "Eye observations, corneal opacity, right," "Eye observations, corneal opacity, bilateral," and "Eye observations, opaque, left."

Statistically significant difference at $p < 0.05$ by Cochran-Armitage trend test.

• Statistically significant difference at $p < 0.05$ by Fisher's Exact test.

TABLE 14

SUMMARY OF OPHTHALMOLOGICAL OBSERVATIONS FOR MALE RATS

Treatment Group Dose	I 0 mg/kg/day	III 25 mg/kg/day	V 100 mg/kg/day	VII 500 mg/kg/day
Examination Day : Test Day 85				
Number of Rats Examined	20	10	10	20
Retina				
Retinal Degeneration Focal Right	0	1 (10%)	0	1 (5%)
Globe				
Phthisis Bulbi Left	0	0	0	1 (5%)

Incidence - The number of animals (percent of animals examined) for which an observation was recorded.
There were no statistically significant differences at $p < 0.05$ by Cochran-Armitage trend test.

TABLE 15
 SUMMARY OF OPHTHALMOLOGICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group Dose	II 0 mg/kg/day	IV 25 mg/kg/day	VI 100 mg/kg/day	VIII 500 mg/kg/day
Examination Day : Test Day 85				
Number of Rats Examined	20	10	10	20
Retina				
Retinal Degeneration Focal Left	0	0	0	1 (5%)

Incidence - The number of animals (percent of animals examined) for which an observation was recorded.
 There were no statistically significant differences at $p < 0.05$ by Cochran-Armitage trend test.

TABLE 16

PERCENT SURVIVAL OF MALE RATS

Treatment Group	I	III	V	VII
Dose (mg/kg/day)	0	25	100	500
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	96 ^{a,b}
42	100	100	100	96
49	100	100	100	96
56	100	100	97 ^b	96
63	98 ^a	100	97	96
70 ^c	98	100	97	96
77	96	100	93	93
84	96	100	93	93
91 ^{d,e}	96	100	93	93
98	93	100	80	88
105	93	100	80	88
112	93	100	80	88
119	93	100	80	88
Number at study start	45	35	35	45
Sacrificed in extremis	1	0	0	1
Found Dead	0	0	1	1
Removed from study ^c	20	20	20	18
Sacrificed by design ^d	10	10	10	10
Alive on test day 119	14	5	4	15

Percent Survival = (Number of rats alive/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. Rat sacrificed in extremis during the previous week.
- b. Rat found dead during the previous week.
- c. Rats designated for reproduction evaluation were removed from study (cohoused) on test day 70.
- d. Recovery period began on test day 91.
- e. Rats designated for the 91-day exposure period were sacrificed on test days 95.

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

Note: Rats added for evaluation of 10-day hepatic biochemical evaluations not included on this table.

TABLE 17

PERCENT SURVIVAL OF FEMALE RATS

Treatment Group	II	IV	VI	VIII
Dose (mg/kg/day)	0	25	100	500
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	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,c}	100 ^d	100	100	100
98	100	100	100	100
105	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 ^b	20	20	20	20
Sacrificed by design ^c	10	10	10	10
Alive on test day 119	14	5	5	15

Percent Survival = (Number of rats alive/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 - number accidentally killed.

a. Rats designated for reproduction evaluation were removed from study (cohoused) on test day 70.

b. Recovery period began on test day 91.

c. Rats designated for the 91-day exposure period were sacrificed on test day 96.

d. Rat accidentally killed during the previous week.

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

Note: Rats added for evaluation of 10-day hepatic biochemical evaluations not included on this table.

TABLE 18

MEAN FORELIMB AND HINDLIMB GRIP STRENGTH FOR MALE RATS
(MEAN OF THREE TRIALS)

Assessment Period	Group	Dosage (mg/kg/day)	Forelimb Grip Strength (kg)	Hindlimb Grip Strength (kg)
<u>Baseline</u>				
	I	0	0.53 (0.09)	0.33 (0.06)
	III	25	0.55 (0.07)	0.33 (0.05)
	V	100	0.52 (0.10)	0.30 (0.06)
	VII	500	0.54 (0.09)	0.31 (0.04)
<u>Week 13</u>				
	I	0	1.53 (0.30)	0.85 (0.10)
	III	25	1.37 (0.24)	0.74 (0.11)
	V	100	1.33 (0.29)	0.74 (0.15)
	VII	500	1.15 (0.32)*	0.70 (0.13)*
<u>Recovery</u>				
	I	0	1.42 (0.33)	0.82 (0.13)
	VII	500	1.28 (0.38)	0.70 (0.10)*

Data arranged as: Mean (Standard Deviation)

- Statistically significant differences from control by One-way analysis of variance followed by Dunnett's test; $p < 0.05$.

TABLE 19

MEAN FORELIMB AND HINDLIMB GRIP STRENGTH FOR FEMALE RATS
(MEAN OF THREE TRIALS)

Assessment Period	Group	Dosage (mg/kg/day)	Forelimb Grip Strength (kg)	Hindlimb Grip Strength (kg)
<u>Baseline</u>				
	II	0	0.52 (0.11)	0.33 (0.06)
	IV	25	0.54 (0.11)	0.33 (0.07)
	VI	100	0.56 (0.08)	0.32 (0.06)
	VIII	500	0.53 (0.06)	0.33 (0.05)
<u>Week 13</u>				
	II	0	0.98 (0.17)	0.68 (0.14)
	IV	25	0.97 (0.16)	0.62 (0.07)
	VI	100	1.16 (0.24)	0.62 (0.13)
	VIII	500	0.97 (0.23)	0.61 (0.10)
<u>Recovery</u>				
	II	0	1.04 (0.33)	0.71 (0.09)
	VIII	500	0.93 (0.21) ^a	0.62 (0.11)

Data arranged as: Mean (Standard Deviation)

^a Rat 646540 was uncooperative during forelimb grip strength. Data were omitted from summary tables and statistics.

There were no statistically significant differences from control by one-way analysis of variance followed by Dunnett's test; $p < 0.05$.

TABLE 20

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR MALE RATS

	Baseline				Week 13				Recovery	
Group:	I	III	V	VII	I	III	V	VII	I	VII
Dosage (mg/kg/day):	0	25	100	500	0	25	100	500	0	500
Number Examined:	10	10 ^a	10	10	10	10	10	10	10	10
APPROACH & TOUCH:										
no reaction	0	0	0	0	0	0	0	0	0	0
normal	10	10	10	10	10	10	10	10	10	10
increased reaction (jumps away or attacks)	0	0	0	0	0	0	0	0	0	0
AUDITORY STIMULUS:										
no reaction	0	0	0	0	0	1	0	1	0	0
normal reaction (rat flinches or flicks ear)	10	10	10	10	10	9	10	9	10	10
exaggerated reaction (rat jumps, flips)	0	0	0	0	0	0	0	0	0	0
TAIL PINCH:										
no response	0	0	0	0	0	0	0	0	0	0
normal (turns toward site)	10	10	9	10	10	7	9	9	10	10
exaggerated response	0	0	1	0	0	3	1	1	0	0
IN MOTOR ACTIVITY MONITOR:										
DEFECATION:										
present	5	5	3	5	8	5	6	8	4	5
absent	5	4	7	5	2	5	4	2	6	5
diarrhea	0	0	0	0	0	0	0	0	0	0
URINATION:										
present	5	8	8	10	9	9	9	10	10	10
absent	5	1	2	0	1	1	1	0	0	0
PUPILLARY RESPONSE:										
present	10	10	10	10	10	10	10	10	10	10
absent	0	0	0	0	0	0	0	0	0	0

TABLE 20 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR MALE RATS

	Baseline				Week 13				Recovery	
Group:	I	III	V	VII	I	III	V	VII	I	VII
Dosage (mg/kg/day):	0	25	100	500	0	25	100	500	0	500
Number Examined:	10	10 ^a	10	10	10	10	10	10	10	10

ADDITIONAL OBSERVATIONS NOTED

Sore left forelimb:	0	0	0	0	0	0	0	0	1	0	0
Sore forelimb toes	0	0	0	0	0	0	0	2	1	0	0
Stained perineum	0	0	0	0	0	0	0	0	4 *	0	0
Abnormal gait	0	0	0	0	0	0	0	1	0	0	0

* Statistically significant differences by Cochran-Armitage test for trend; $p < 0.05$.

^a For the baseline evaluation, urination and defecation were not recorded for one animal in Group III.

TABLE 21

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR FEMALE RATS

	Baseline				Week 13				Recovery	
Group:	II	IV	VI	VIII	II	IV	VI	VIII	II	VIII
Dosage (mg/kg/day):	0	25	100	500	0	25	100	500	0	500
Number Examined:	10	10	10	10	10	10	10	10	10	10
APPROACH & TOUCH:										
no reaction	0	0	0	0	0	0	0	0	0	0
normal	10	10	10	10	10	10	10	10	10	10
increased reaction (jumps away or attacks)	0	0	0	0	0	0	0	0	0	0
AUDITORY STIMULUS:										
no reaction	0	0	0	0	0	0	0	0	0	0
normal reaction (rat flinches or flicks ear)	10	10	10	10	10	10	10	10	10	10
exaggerated reaction (rat jumps, flips)	0	0	0	0	0	0	0	0	0	0
TAIL PINCH:										
no response	0	0	0	0	0	0	0	0	0	0
normal (turns toward site)	10	10	10	9	10	10	10	10	10	10
exaggerated response	0	0	0	1	0	0	0	0	0	0
IN MOTOR ACTIVITY MONITOR:										
DEFECATION:										
present	3	5	2	3	3	6	7	7	4	5
absent	7	5	8	7	7	4	3	3	6	5
diarrhea	0	0	0	0	0	0	0	0	0	0
URINATION:										
present	9	7	8	7	8	10	9	10	10	10
absent	1	3	2	3	2	0	1	0	0	0
PUPILLARY RESPONSE:										
present	10	10	10	10	10	10	10	10	10	10
absent	0	0	0	0	0	0	0	0	0	0
ADDITIONAL OBSERVATIONS NOTED										
Stained perineum	0	0	0	0	0	0	0	5 *	0	0

* Statistically significant difference by Cochran-Armitage test for trend; $p < 0.05$.

TABLE 22

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

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
			1	2	3	4	5	6	TOTAL
<u>BASELINE</u>	I	0	366(25)	270(64)	211(72)	108(105)	42(81)	28(69)	1025(307)
	III	25	366(52)	282(47)	182(67)	85(85)	57(77)	19(21)	992(270)
	V	100	354(63)	257(87)	164(106)	80(98)	45(54)	7(8)	907(310)
	VII	500	373(38)	269(68)	173(124)	86(73)	48(65)	12(14)	959(309)
<u>WEEK 13</u>	I	0	405(52)	310(100)	253(96)	260(78)	221(102)	165(97)	1613(461)
	III	25	385(47)	299(64)	293(57)	215(76)	235(64)	193(93)	1619(304)
	V	100	410(52)	322(72)	272(77)	222(97)	220(90)	188(63)	1633(356)
	VII	500	407(55)	335(39)	270(51)	241(101)	275(66)	241(75)	1767(330)
<u>RECOVERY</u>	I	0	386(34)	294(65)	249(60)	230(60)	171(81)	149(106)	1478(283)
	VII	500	389(61)	308(46)	257(46)	234(60)	213(58)	136(122)	1536(293)

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 or Jonckheere's trend test were 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; $p < 0.05$.

TABLE 23

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

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS					
			1	2	3	4	5	6
<u>BASELINE</u>								<u>TOTAL</u>
	II	0	363(57)	272(49)	214(73)	196(138)	131(136)	67(79)
	IV	25	374(42)	254(93)	192(98)	165(124)	130(132)	41(75)
	VI	100	353(51)	257(66)	203(83)	191(134)	130(104)	58(69)
	VIII	500	354(59)	261(59)	185(93)	102(86)	72(80)	47(53)
								1242(367)
								1155(413)
								1191(399)
								1020(302)
<u>WEEK 13</u>								<u>TOTAL</u>
	II	0	416(33)	288(49)	251(72)	215(95)	213(95)	154(142)
	IV	25	399(47)	281(45)	194(55)	254(44)	196(79)	203(69)
	VI	100	390(58)	315(77)	236(103)	241(76)	229(73)	220(57)
	VIII	500	406(57)	305(43)	254(57)	223(75)	241(109)	207(69)
								1536(292)
								1527(200)
								1630(367)
								1636(305)
<u>RECOVERY</u>								<u>TOTAL</u>
	II	0	413(48)	323(73)	269(70)	225(84)	167(95)	186(94)
	VIII	500	404(53)	301(85)	258(52)	223(88)	214(63)	180(73)
								1582(358)
								1579(266)

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; $p < 0.05$.

TABLE 24

MOTOR ACTIVITY ASSESSMENT:
MEAN NUMBER OF MOVEMENTS FOR MALE RATS

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS					
			1	2	3	4	5	6
<u>BASELINE</u>	I	0	135(12)	130(15)	119(20)	64(55)	27(40)	19(43)
	III	25	145(12)	145(11)	110(35)	67(56)	40(50)	16(14)
	V	100	127(18)	125(17)	94(53)	51(50)	40(46)	8(4)
	VII	500	127(22)	124(24)	85(50)	51(46)	28(37)	8(5)
								<u>TOTAL</u>
<u>WEEK 13</u>	I	0	131(12)	128(25)	118(41)	117(24)	107(38)	89(44)
	III	25	137(12)	140(15)	136(17)	118(31)	126(16)	110(37)
	V	100	132(16)	134(10)	122(21)	111(40)	112(44)	104(25)
	VII	500	125(30)	127(23)	117(28)	105(41)	111(20)	112(32)
								<u>TOTAL</u>
<u>RECOVERY</u>	I	0	137(14)	134(22)	129(19)	126(21)	103(39)	87(56)
	VII	500	127(14)	129(20)	116(25)	115(24)	109(22)	70(56)
								<u>TOTAL</u>

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 or Jonckheere's trend test were 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; $p < 0.05$.

TABLE 25

MOTOR ACTIVITY ASSESSMENT:
MEAN NUMBER OF MOVEMENTS FOR FEMALE RATS

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS					
			1	2	3	4	5	6
<u>BASELINE</u>	II	0	128(28)	122(31)	110(40)	91(48)	65(49)	37(46)
	IV	25	126(12)	121(27)	94(36)	85(51)	67(61)	32(47)
	VI	100	127(14)	120(17)	114(32)	91(46)	80(51)	43(41)
	VIII	500	135(14)	130(16)	105(33)	70(41)	55(54)	44(46)
								<u>TOTAL</u>
<u>WEEK 13</u>	II	0	123(18)	121(29)	119(31)	112(41)	111(43)	72(53)
	IV	25	128(14)	129(17)	114(24)	126(19)	113(33)	118(29)*
	VI	100	133(27)	124(33)	117(31)	119(33)	120(35)	124(25)*
	VIII	500	131(12)	132(12)	130(14)	116(23)	118(31)	121(24)*
								<u>TOTAL</u>
<u>RECOVERY</u>	II	0	121(22)	128(25)	128(29)	116(33)	97(46)	104(39)
	VIII	500	130(11)	139(10)	126(26)	119(25)	125(27)	119(27)
								<u>TOTAL</u>

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; $p < 0.05$.

TABLE 26

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
RBC (x10 ⁶ /μL)				
DAY 39	8.11 0.35(10)	7.94 0.32(10)	8.04 0.21(10)	8.25 0.33(10)
DAY 95	8.63 0.43(10)	8.60 0.40(10)	8.50 0.49(10)	8.85 0.38(10)
DAY 123	8.62 0.42(9)	^a	^a	8.33 0.40(10)
DAY 183	8.79 0.62(3)	8.71 0.21(5)	8.59 0.43(4)	8.50 0.53(4)
HGB (g/dL)				
DAY 39	14.9 0.5(10)	14.8 0.4(10)	14.7 0.5(10)	14.3* 0.3(10)
DAY 95	15.4 0.6(10)	15.3 0.6(10)	14.7* 0.6(10)	14.2* 0.3(10)
DAY 123	15.3 0.6(9)	^a	^a	14.5* 0.4(10)
DAY 183	15.4 0.4(3)	15.5 0.7(5)	15.1 0.6(4)	15.2 0.7(4)
HCT (%)				
DAY 39	47.9 1.7(10)	47.6 1.2(10)	47.2 1.4(10)	45.9* 1.2(10)
DAY 95	47.4 2.0(10)	46.8 1.7(10)	45.7 2.0(10)	44.4* 1.1(10)
DAY 123	45.9 1.4(9)	^a	^a	44.2* 1.8(10)
DAY 183	46.7 0.4(3)	46.9 1.7(5)	46.4 3.0(4)	46.8 3.1(4)
MCV (fl)				
DAY 39	59.1 1.4(10)	60.1 1.0(10)	58.7 2.1(10)	55.7* 1.6(10)
DAY 95	54.9 1.3(10)	54.5 1.4(10)	53.9 1.8(10)	50.3* 2.1(10)
DAY 123	53.4 2.0(9)	^a	^a	53.1 2.2(10)
DAY 183	53.2 3.4(3)	53.9 2.6(5)	54.0 1.0(4)	55.2 3.7(4)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
MCH (pg)				
DAY 39	18.3 0.5(10)	18.6 0.6(10)	18.4 0.7(10)	17.4* 0.6(10)
DAY 95	17.9 0.4(10)	17.8 0.4(10) a	17.3 0.5(10) a	16.0* 0.7(10)
DAY 123	17.8 0.7(9)			17.5 0.7(10)
DAY 183	17.7 1.7(3)	17.8 1.1(5)	17.6 0.5(4)	17.9 1.3(4)
MCHC (g/dL)				
DAY 39	31.0 0.4(10)	31.0 0.6(10)	31.3 0.4(10)	31.2 0.4(10)
DAY 95	32.5 0.4(10)	32.7 0.3(10) a	32.2 0.4(10) a	31.9* 0.7(10)
DAY 123	33.4 0.4(9)			33.0 0.6(10)
DAY 183	33.1 1.0(3)	33.0 0.9(5)	32.6 1.1(4)	32.5 1.1(4)
RDW (%)				
DAY 39	11.1 0.5(10)	11.5 0.8(10)	11.5 0.3(10)	12.1* 0.7(10)
DAY 95	13.4 0.9(10)	13.7 0.9(10) a	14.3* 0.5(10) a	15.0* 0.8(10)
DAY 123	12.7 0.4(9)			16.5* 1.3(10)
DAY 183	13.7 0.2(3)	13.6 0.6(5)	14.7 0.8(4)	13.6 0.5(4)
ARET (x10 ³ /μL)				
DAY 39	200 29(10)	228 96(10)	212 32(10)	220 53(10)
DAY 95	191 34(10)	184 33(10) a	235 48(10) a	252@ 48(10)
DAY 123	187 38(9)			222* 33(10)
DAY 183	151 8(3)	170 35(5)	181 42(4)	187 29(4)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
PLT ($\times 10^3/\mu\text{L}$)				
DAY 39	1013 146(10)	1084 162(8)	1024 93(8)	1028 133(9)
DAY 95	1121 201(5)	1099 171(8) _a	1163 122(9) _a	1246 158(8)
DAY 123	1097 76(4)			1209 127(7)
DAY 183	1047 194(3)	1084 69(5)	1164 205(2)	1105 110(4)
WBC ($\times 10^3/\mu\text{L}$)				
DAY 39	13.82 2.18(10)	16.15 3.37(10)	15.42 1.74(10)	16.14 2.38(10)
DAY 95	12.76 6.81(10)	12.37 3.15(10) _a	11.66 1.87(10) _a	12.31 1.89(10)
DAY 123	11.46 4.47(9)			11.76 2.48(10)
DAY 183	9.36 1.39(3)	9.11 1.30(5)	10.32 1.90(4)	11.45 3.31(4)
ANEU ($\times 10^3/\mu\text{L}$)				
DAY 39	1.50 0.42(10)	1.88 0.56(10)	1.79 0.50(10)	1.55 0.30(10)
DAY 95	3.33 5.64(10)	1.99 0.40(10) _a	1.79 0.45(10) _a	1.93 0.43(10)
DAY 123	1.99 1.80(9)			2.02@ 0.49(10)
DAY 183	1.90 0.14(3)	1.64 0.63(5)	2.33 0.21(4)	2.01 0.53(4)
ANPR ($\times 10^3/\mu\text{L}$)				
DAY 39	b	b	b	b
DAY 95	b	b	b	b
DAY 123	b	a	a	b

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
ALYM ($\times 10^3/\mu\text{L}$)				
DAY 39	11.61 2.30(10)	13.38 3.12(10)	12.67 1.43(10)	13.60 2.20(10)
DAY 95	8.69 2.45(10)	9.68 2.73(10)	9.18 1.74(10)	9.63 1.77(10)
DAY 123	8.86 3.06(9)	^a	^a	9.14 2.21(10)
DAY 183	6.73 1.29(3)	7.02 1.32(5)	7.49 1.93(4)	8.87 3.30(4)
AMON ($\times 10^3/\mu\text{L}$)				
DAY 39	0.30 0.08(10)	0.43* 0.08(10)	0.50* 0.12(10)	0.52* 0.16(10)
DAY 95	0.30 0.23(10)	0.29 0.11(10)	0.29 0.06(10)	0.28 0.08(10)
DAY 123	0.30 0.15(9)	^a	^a	0.28 0.10(10)
DAY 183	0.32 0.10(3)	0.16 0.04(5)	0.20 0.05(4)	0.30 0.14(4)
AEOS ($\times 10^3/\mu\text{L}$)				
DAY 39	0.12 0.06(10)	0.11 0.04(10)	0.13 0.07(10)	0.15 0.05(10)
DAY 95	0.14 0.05(10)	0.15 0.08(10)	0.16 0.06(10)	0.17 0.06(10)
DAY 123	0.11 0.06(9)	^a	^a	0.12 0.07(10)
DAY 183	0.13 0.04(3)	0.11 0.04(5)	0.11 0.02(4)	0.09 0.06(4)
ABAS ($\times 10^3/\mu\text{L}$)				
DAY 39	0.16 0.04(10)	0.17 0.02(10)	0.16 0.05(10)	0.16 0.05(10)
DAY 95	0.11 0.06(10)	0.10 0.05(10)	0.09 0.03(10)	0.12 0.07(10)
DAY 123	0.10 0.06(9)	^a	^a	0.09 0.05(10)
DAY 183	0.13 0.11(3)	0.08 0.04(5)	0.09 0.02(4)	0.10 0.10(4)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
ALUC (x10 ³ /μL)				
DAY 39	0.14 0.04(10)	0.18 0.05(10)	0.17 0.05(10)	0.17 0.03(10)
DAY 95	0.20 0.14(10)	0.17 0.05(10)	0.16 0.06(10)	0.18 0.05(10)
DAY 123	0.10 0.09(9)	a	a	0.10 0.04(10)
DAY 183	0.15 0.05(3)	0.11 0.02(5)	0.10 0.06(4)	0.09 0.06(4)
ABLT (x10 ³ /μL)				
DAY 39	b	b	b	b
DAY 95	b	b	b	b
DAY 123	b	a	a	b
DAY 183	b	b	b	c
AMSC (x10 ³ /μL)				
DAY 39	b	b	b	b
DAY 95	b	b	b	b
DAY 123	b	a	a	b
AHSN (x10 ³ /μL)				
DAY 183	b	b	b	c
ABAN (x10 ³ /μL)				
DAY 183	b	b	b	c
AMET (x10 ³ /μL)				
DAY 183	b	b	b	c
AMYE (x10 ³ /μL)				
DAY 183	b	b	b	c
APRO (x10 ³ /μL)				
DAY 183	b	b	b	c
AMYB (x10 ³ /μL)				
DAY 183	b	b	b	c

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
ARL ($\times 10^3/\mu\text{L}$) DAY 183	b	b	b	c
AAL ($\times 10^3/\mu\text{L}$) DAY 183	b	b	b	c
AIL ($\times 10^3/\mu\text{L}$) DAY 183	b	b	b	c
ACL ($\times 10^3/\mu\text{L}$) DAY 183	b	b	b	c
ABLB ($\times 10^3/\mu\text{L}$) DAY 183	b	b	b	c
AIE ($\times 10^3/\mu\text{L}$) DAY 183	b	b	b	c
AIM ($\times 10^3/\mu\text{L}$) DAY 183	b	b	b	c
APLA ($\times 10^3/\mu\text{L}$) DAY 183	b	b	b	c

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).

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

TABLE 27

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
RBC (x10 ⁶ /μL)				
DAY 40	7.81 0.53(10)	7.86 0.30(10)	7.30* 0.38(10)	7.26* 0.35(9)
DAY 96	7.91 0.76(10)	7.66 0.37(9) a	7.20@ 0.49(10) a	7.03@ 0.61(10)
DAY 124	8.17 0.45(10)			8.04 0.52(10)
DAY 183	7.99 0.16(3)	7.97 0.43(4)	7.89 0.38(2)	8.06 0.26(3)
HGB (g/dL)				
DAY 40	14.7 0.6(10)	14.8 0.6(10)	13.8* 0.6(10)	13.3* 0.7(9)
DAY 96	15.0 0.9(10)	14.5 0.7(9) a	13.5* 1.0(10) a	12.7* 1.1(10)
DAY 124	15.1 0.7(10)			14.7 0.9(10)
DAY 183	15.3 0.4(3)	15.5 0.6(4)	14.4 0.1(2)	14.9 0.8(3)
HCT (%)				
DAY 40	45.6 2.0(10)	46.3 1.6(10)	43.2* 1.9(10)	42.6* 2.7(9)
DAY 96	44.6 2.7(10)	43.6 1.8(9) a	40.6* 2.7(10) a	38.7* 3.4(10)
DAY 124	46.0 2.8(10)			44.5 2.9(10)
DAY 183	44.7 0.2(3)	46.3 1.7(4)	42.7 0.8(2)	44.7 1.9(3)
MCV (fl)				
DAY 40	58.6 2.6(10)	58.9 1.5(10)	59.2 1.4(10)	58.6 1.9(9)
DAY 96	56.6 3.0(10)	56.9 2.0(9) a	56.4 2.0(10) a	55.1 1.7(10)
DAY 124	56.3 2.3(10)			55.5 1.6(10)
DAY 183	55.9 1.4(3)	58.2 1.6(4)	54.1 1.6(2)	55.5 2.0(3)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
MCH (pg)				
DAY 40	18.9 0.7(10)	18.9 0.6(10)	18.9 0.6(10)	18.3 0.6(9)
DAY 96	19.1 1.0(10)	19.0 0.8(9) a	18.8 0.5(10) a	18.0@ 0.5(10)
DAY 124	18.5 0.4(10)			18.3 0.5(10)
DAY 183	19.1 0.8(3)	19.5 0.4(4)	18.2 0.8(2)	18.5 0.9(3)
MCHC (g/dL)				
DAY 40	32.2 0.5(10)	32.1 0.5(10)	31.9 0.5(10)	31.3* 0.8(9)
DAY 96	33.7 0.3(10)	33.3 0.3(9) a	33.3 0.7(10) a	32.7* 0.4(10)
DAY 124	32.9 0.7(10)			33.0 0.7(10)
DAY 183	34.2 0.6(3)	33.5 0.3(4)	33.7 0.5(2)	33.4 0.5(3)
RDW (%)				
DAY 40	11.3 1.0(10)	11.1 0.4(10)	11.7 0.6(10)	12.6@ 0.7(9)
DAY 96	11.7 1.0(10)	11.8 0.4(9) a	12.9@ 0.9(10) a	14.5@ 1.2(10)
DAY 124	12.0 0.4(10)			13.0* 0.8(10)
DAY 183	12.5 0.8(3)	12.2 0.7(4)	12.1 0.2(2)	12.5 0.5(3)
ARET (x10 ³ /μL)				
DAY 40	199 37(10)	190 35(10)	240 55(10)	252* 37(9)
DAY 96	168 24(10)	168 25(9) a	187 32(10) a	225* 43(10)
DAY 124	164 26(10)			148 28(10)
DAY 183	156 26(3)	155 15(4)	152 22(2)	167 18(3)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
PLT ($\times 10^3/\mu\text{L}$)				
DAY 40	1119 113(9)	1242 154(7)	1175 126(6)	1291 160(5)
DAY 96	904 354(7)	1094 154(7) a	1180 179(8) a	1326@ 165(6)
DAY 124	932 188(5)			1025 183(6)
DAY 183	1084 130(3)	920 24(2)	1308 32(2)	1708* NC(1)
WBC ($\times 10^3/\mu\text{L}$)				
DAY 40	10.78 2.70(10)	13.12 3.36(10)	13.74 2.52(10)	14.52@ 2.16(9)
DAY 96	8.97 1.36(10)	10.13 3.30(9) a	10.02 1.65(10) a	10.54 1.69(10)
DAY 124	8.68 2.41(10)			7.43 1.82(10)
DAY 183	8.14 0.60(3)	7.13 1.05(4)	6.48 2.43(2)	8.83 2.93(3)
ANEU ($\times 10^3/\mu\text{L}$)				
DAY 40	1.12 0.49(10)	1.76@ 0.59(10)	1.51 0.66(10)	1.35 0.26(9)
DAY 96	0.99 0.28(10)	1.40 0.54(9) a	1.17 0.47(10) a	1.22 0.52(10)
DAY 124	1.15 0.35(10)			1.31 0.58(10)
DAY 183	1.58 0.43(3)	1.23 0.39(4)	1.47 0.81(2)	1.95 0.29(3)
ANPR ($\times 10^3/\mu\text{L}$)				
DAY 40	b	b	b	b
DAY 96	c	b	b	b
DAY 124	b	a	a	b

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
ALYM ($\times 10^3/\mu\text{L}$)				
DAY 40	9.02 2.48(10)	10.55 2.84(10)	11.41 2.06(10)	12.35@ 2.11(9)
DAY 96	7.36 1.44(10)	7.98 2.68(9)	8.17 1.58(10)	8.67 1.44(10)
DAY 124	7.07 2.27(10)	^a	^a	5.65 1.42(10)
DAY 183	6.01 0.23(3)	5.41 1.05(4)	4.66 1.46(2)	6.26 3.01(3)
AMON ($\times 10^3/\mu\text{L}$)				
DAY 40	0.26 0.10(10)	0.40* 0.17(10)	0.36 0.09(10)	0.39* 0.07(9)
DAY 96	0.29 0.19(10)	0.37 0.23(9)	0.29 0.08(10)	0.27 0.06(10)
DAY 124	0.21 0.06(10)	^a	^a	0.23 0.13(10)
DAY 183	0.22 0.02(3)	0.18 0.06(4)	0.18 0.01(2)	0.26 0.09(3)
AEOS ($\times 10^3/\mu\text{L}$)				
DAY 40	0.11 0.06(10)	0.13 0.08(10)	0.13 0.06(10)	0.12 0.05(9)
DAY 96	0.10 0.06(10)	0.11 0.05(9)	0.14 0.06(10)	0.13 0.05(10)
DAY 124	0.09 0.04(10)	^a	^a	0.09 0.03(10)
DAY 183	0.16 0.06(3)	0.11 0.04(4)	0.09 0.06(2)	0.14 0.02(3)
ABAS ($\times 10^3/\mu\text{L}$)				
DAY 40	0.10 0.04(10)	0.12 0.04(10)	0.15 0.06(10)	0.12 0.04(9)
DAY 96	0.11 0.04(10)	0.12 0.04(9)	0.08 0.04(10)	0.08 0.03(10)
DAY 124	0.10 0.07(10)	^a	^a	0.07 0.04(10)
DAY 183	0.08 0.06(3)	0.09 0.05(4)	0.03 0.04(2)	0.10 0.08(3)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
ALUC ($\times 10^3/\mu\text{L}$)				
DAY 40	0.17 0.10(10)	0.16 0.05(10)	0.18 0.06(10)	0.19 0.06(9)
DAY 96	0.13 0.05(10)	0.15 0.05(9)	0.18 0.05(10)	0.17 0.06(10)
DAY 124	0.07 0.03(10)	a	a	0.07 0.03(10)
DAY 183	0.09 0.03(3)	0.10 0.03(4)	0.06 0.08(2)	0.11 0.06(3)
ABLT ($\times 10^3/\mu\text{L}$)				
DAY 40	b	b	b	b
DAY 96	c	b	b	b
DAY 124	b	a	a	b
DAY 183	b	b	c	b
AMSC ($\times 10^3/\mu\text{L}$)				
DAY 40	b	b	b	b
DAY 96	c	b	b	b
DAY 124	b	a	a	b
AHSN ($\times 10^3/\mu\text{L}$)				
DAY 183	b	b	c	b
ABAN ($\times 10^3/\mu\text{L}$)				
DAY 183	b	b	c	b
AMET ($\times 10^3/\mu\text{L}$)				
DAY 183	b	b	c	b
AMYE ($\times 10^3/\mu\text{L}$)				
DAY 183	b	b	c	b
APRO ($\times 10^3/\mu\text{L}$)				
DAY 183	b	b	c	b
AMYB ($\times 10^3/\mu\text{L}$)				
DAY 183	b	b	c	b

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
ARL ($\times 10^3/\mu\text{L}$) DAY 183	b	b	c	b
AAL ($\times 10^3/\mu\text{L}$) DAY 183	b	b	c	b
AIL ($\times 10^3/\mu\text{L}$) DAY 183	b	b	c	b
ACL ($\times 10^3/\mu\text{L}$) DAY 183	b	b	c	b
ABLB ($\times 10^3/\mu\text{L}$) DAY 183	b	b	c	b
AIE ($\times 10^3/\mu\text{L}$) DAY 183	b	b	c	b
AIM ($\times 10^3/\mu\text{L}$) DAY 183	b	b	c	b
APLA ($\times 10^3/\mu\text{L}$) DAY 183	b	b	c	b

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).

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

TABLE 28

SUMMARY OF COAGULATION VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
PT (seconds)				
DAY 95	15.7 1.2(9)	15.3 0.5(10) a	14.8 0.8(10) a	15.2 1.2(10)
DAY 123	14.9 0.9(10)			14.8 0.8(10)
APTT (seconds)				
DAY 95	20.1 2.1(9)	18.6 2.2(10) a	16.5* 1.9(10) a	15.6* 1.8(10)
DAY 123	20.1 2.3(10)			19.7 1.7(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).

TABLE 29

SUMMARY OF COAGULATION VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
PT (seconds)				
DAY 96	14.6 0.7(9)	14.5 0.6(10) a	14.2 0.4(10) a	13.7* 0.4(10)
DAY 124	13.9 0.5(9)			13.8 0.3(10)
APTT (seconds)				
DAY 96	18.4 1.6(9)	17.8 1.6(10) a	17.2 1.9(10) a	15.0@ 2.5(10)
DAY 124	17.7 1.8(9)			18.1 2.7(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 30

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
AST (U/L)				
DAY 39	89 22(10)	78 16(10)	71 9(10)	74 9(10)
DAY 95	84 7(10)	90 14(10) a	80 8(10) a	79 13(10)
DAY 123	103 37(10)			108 28(10)
DAY 183	101 18(4)	100 25(5)	94 14(4)	118 43(5)
ALT (U/L)				
DAY 39	36 6(10)	33 3(10)	38 8(10)	59* 14(10)
DAY 95	33 6(10)	36 13(10) a	37 4(10) a	50@ 8(10)
DAY 123	41 14(10)			53* 10(10)
DAY 183	34 6(4)	53 31(5)	50 20(4)	66@ 31(5)
SDH (U/L)				
DAY 39	19.7 5.3(10)	20.1 3.3(10)	20.5 2.4(10)	26.9 11.5(10)
DAY 95	22.3 6.3(10)	25.3 7.1(10) a	27.7 5.7(10) a	29.1@ 4.5(10)
DAY 123	19.4 6.2(10)			42.5* 9.2(10)
DAY 183	11.5 5.2(4)	18.1 4.7(5)	18.4 2.9(4)	25.4* 6.2(5)
ALKP (U/L)				
DAY 39	139 34(10)	128 25(10)	126 17(10)	174 48(10)
DAY 95	90 16(10)	80 13(10) a	85 15(10) a	128 46(10)
DAY 123	80 14(10)			75 12(10)
DAY 183	79 18(4)	98 21(5)	89 18(4)	84 16(5)

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
BILI (mg/dL)				
DAY 39	0.08 0.03(10)	0.06 0.03(10)	0.09 0.04(10)	0.20@ 0.05(10)
DAY 95	0.12 0.03(10)	0.11 0.05(10)	0.15 0.06(10)	0.24* 0.05(10)
DAY 123	0.14 0.03(10)	a	a	0.14 0.02(10)
DAY 183	0.10 0.03(4)	0.08 0.04(5)	0.05 0.00(4)	0.06 0.02(5)
BUN (mg/dL)				
DAY 39	14 1(10)	14 2(10)	15 2(10)	20* 3(10)
DAY 95	16 3(10)	17 2(10)	19@ 3(10)	20@ 2(10)
DAY 123	16 2(10)	a	a	20 5(10)
DAY 183	17 2(4)	15 3(5)	14 1(4)	18 1(5)
CREA (mg/dL)				
DAY 39	0.32 0.04(10)	0.34 0.03(10)	0.36 0.06(10)	0.40* 0.06(10)
DAY 95	0.38 0.06(10)	0.41 0.04(10)	0.47* 0.05(10)	0.42 0.05(10)
DAY 123	0.43 0.04(10)	a	a	0.42 0.04(10)
DAY 183	0.43 0.08(4)	0.40 0.06(5)	0.38 0.06(4)	0.47 0.08(5)
CHOL (mg/dL)				
DAY 39	64 9(10)	66 14(10)	100@ 12(10)	102@ 36(10)
DAY 95	74 12(10)	85 22(10)	112* 29(10)	109* 30(10)
DAY 123	72 10(10)	a	a	87 20(10)
DAY 183	91 37(4)	80 36(5)	83 22(4)	80 25(5)

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
TRIG (mg/dL)				
DAY 39	63 22(10)	71 32(10)	35@ 10(10)	28@ 6(10)
DAY 95	85 39(10)	90 48(10) a	45 17(10) a	26@ 5(10)
DAY 123	72 32(10)			72 35(10)
DAY 183	74 37(4)	115 33(5)	125 56(4)	82 23(5)
GLUC (mg/dL)				
DAY 39	101 8(10)	102 5(10)	96 8(10)	97 7(10)
DAY 95	98 12(10)	98 8(10) a	102 13(10) a	95 5(10)
DAY 123	117 25(10)			112 24(10)
DAY 183	93 7(4)	100 23(5)	105 12(4)	116 21(5)
TP (g/dL)				
DAY 39	6.5 0.3(10)	6.6 0.3(10)	7.0* 0.4(10)	7.3* 0.4(10)
DAY 95	7.2 0.3(10)	7.3 0.3(10) a	8.0* 0.3(10) a	8.2* 0.3(10)
DAY 123	6.9 0.2(10)			7.6* 0.2(10)
DAY 183	7.4 0.4(4)	7.2 0.3(5)	7.5 0.3(4)	7.5 0.3(5)
ALB (g/dL)				
DAY 39	4.1 0.2(10)	4.3 0.1(10)	4.6* 0.2(10)	5.1* 0.2(10)
DAY 95	4.3 0.3(10)	4.6* 0.2(10) a	5.1* 0.2(10) a	5.5* 0.3(10)
DAY 123	4.1 0.2(10)			4.7* 0.2(10)
DAY 183	4.5 0.2(4)	4.2 0.4(5)	4.4 0.2(4)	4.4 0.3(5)

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
GLOB (g/dL)				
DAY 39	2.3 0.2(10)	2.3 0.2(10)	2.5 0.3(10)	2.3 0.2(10)
DAY 95	2.9 0.4(10)	2.7 0.1(10) a	2.9 0.2(10) a	2.7 0.1(10)
DAY 123	2.7 0.1(10)			2.9* 0.1(10)
DAY 183	3.0 0.3(4)	3.0 0.3(5)	3.2 0.2(4)	3.1 0.2(5)
CALC (mg/dL)				
DAY 39	11.1 0.4(10)	11.2 0.4(10)	11.7* 0.5(10)	11.7* 0.4(10)
DAY 95	10.7 0.4(10)	10.9 0.5(10) a	11.3* 0.4(10) a	11.5* 0.4(10)
DAY 123	10.9 0.3(10)			11.3* 0.3(10)
DAY 183	10.1 0.5(4)	10.3 0.2(5)	10.4 0.4(4)	10.6 0.3(5)
IPHS (mg/dL)				
DAY 39	8.9 0.7(10)	8.9 0.3(10)	9.4 0.6(10)	9.0 0.4(10)
DAY 95	7.2 0.5(10)	7.7 0.6(10) a	8.1* 0.8(10) a	8.0* 0.8(10)
DAY 123	8.0 0.6(10)			9.3* 0.9(10)
DAY 183	6.9 0.4(4)	6.9 0.6(5)	7.5 0.9(4)	8.9 2.0(5)
NA (mmol/L)				
DAY 39	146.4 1.1(10)	146.2 1.3(10)	145.6 0.9(10)	143.8@ 1.2(10)
DAY 95	149.1 0.7(10)	148.7 1.1(10) a	148.5 1.3(10) a	146.2* 1.3(10)
DAY 123	146.8 1.6(10)			146.6 1.7(10)
DAY 183	146.7 1.4(4)	148.2 0.9(5)	148.1 2.4(4)	150.1* 2.1(5)

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
K (mmol/L)				
DAY 39	6.01 0.27(10)	6.07 0.35(10)	6.62* 0.51(10)	6.75* 0.33(10)
DAY 95	5.88 0.18(10)	6.06 0.32(10) a	6.66@ 0.48(10) a	6.57@ 0.55(10)
DAY 123	6.37 0.48(10)			6.61 0.68(10)
DAY 183	6.17 0.37(4)	6.03 0.24(5)	6.52 0.46(4)	6.47 0.44(5)
CL (mmol/L)				
DAY 39	97.8 1.2(10)	98.1 1.9(10)	97.0 1.8(10)	95.8* 1.5(10)
DAY 95	99.0 1.7(10)	99.9 2.0(10) a	98.7 2.0(10) a	97.7 1.5(10)
DAY 123	102.8 1.4(10)			101.2* 1.6(10)
DAY 183	99.6 1.6(4)	100.8 1.5(5)	101.8 2.3(4)	103.6 3.8(5)
PFLU (µg/mL)				
DAY 39	a	a	a	a
DAY 95	0.1 0.0(10)	0.2 0.1(10) a	0.2@ 0.0(10) a	0.5@ 0.1(10)
DAY 123	0.1 0.1(10)			0.1 0.0(10)
DAY 183	0.1 0.0(4)	0.1 0.0(5)	0.1 0.0(4)	0.1 0.0(5)

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 SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
AST (U/L)				
DAY 40	84 15(10)	93 17(10)	73 16(10)	75 13(10)
DAY 96	128 85(10)	106 65(10) a	75 20(10) a	79 29(10)
DAY 124	117 56(10)			90 18(10)
DAY 183	110 43(4)	79 22(5)	92 23(5)	118 35(5)
ALT (U/L)				
DAY 40	36 7(10)	41 11(10)	45 11(10)	59@ 13(10)
DAY 96	66 63(10)	50 34(10) a	40 7(10) a	48 9(10)
DAY 124	62 37(10)			34@ 8(10)
DAY 183	47 26(4)	39 8(5)	44 16(5)	51 26(5)
SDH (U/L)				
DAY 40	20.4 2.8(10)	20.8 5.4(10)	18.3 1.9(10)	18.8 2.6(10)
DAY 96	24.7 16.1(10)	21.9 11.4(10) a	16.7 3.5(10) a	18.6 4.8(10)
DAY 124	25.1 6.2(10)			28.1 13.5(10)
DAY 183	13.9 4.6(4)	11.9 2.6(5)	16.7 3.9(5)	18.2 7.5(5)
ALKP (U/L)				
DAY 40	85 18(10)	92 20(10)	86 21(10)	148@ 62(10)
DAY 96	45 12(10)	46 9(10) a	51 18(10) a	93@ 42(10)
DAY 124	39 10(10)			36 12(10)
DAY 183	33 9(4)	36 14(5)	27 6(5)	44 14(5)

TABLE 31 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
BILI (mg/dL)				
DAY 40	0.14 0.04(10)	0.14 0.02(10)	0.14 0.04(10)	0.18 0.03(10)
DAY 96	0.17 0.03(10)	0.15 0.03(10) a	0.16 0.04(10) a	0.21* 0.05(10)
DAY 124	0.19 0.04(10)			0.16 0.03(10)
DAY 183	0.15 0.03(4)	0.12 0.06(5)	0.08 0.03(5)	0.12 0.02(5)
BUN (mg/dL)				
DAY 40	16 2(10)	16 3(10)	17 3(10)	21@ 4(10)
DAY 96	16 2(10)	19* 2(10) a	19* 2(10) a	20* 2(10)
DAY 124	17 3(10)			18 3(10)
DAY 183	15 4(4)	16 2(5)	18 4(5)	18 2(5)
CREA (mg/dL)				
DAY 40	0.39 0.05(10)	0.37 0.04(10)	0.37 0.02(10)	0.44* 0.03(10)
DAY 96	0.44 0.06(10)	0.43 0.05(10) a	0.46 0.05(10) a	0.50* 0.05(10)
DAY 124	0.51 0.05(10)			0.50 0.06(10)
DAY 183	0.51 0.08(4)	0.47 0.05(5)	0.53 0.08(5)	0.50 0.04(5)
CHOL (mg/dL)				
DAY 40	84 19(10)	92 11(10)	123* 22(10)	120* 18(10)
DAY 96	98 23(10)	109 19(10) a	154* 39(10) a	148* 44(10)
DAY 124	97 28(10)			138* 30(10)
DAY 183	103 21(4)	129 29(5)	142 62(5)	133 39(5)

TABLE 31 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
TRIG (mg/dL)				
DAY 40	45 19(10)	42 13(10)	37 13(10)	25@ 4(10)
DAY 96	74 54(10)	46 13(10) a	39 15(10) a	23@ 4(10)
DAY 124	96 36(10)			78 26(10)
DAY 183	69 39(4)	132 38(5)	148 154(5)	108 59(5)
GLUC (mg/dL)				
DAY 40	101 8(10)	100 8(10)	101 7(10)	104 9(10)
DAY 96	103 6(10)	102 6(10) a	99 12(10) a	100 6(10)
DAY 124	106 9(10)			92* 6(10)
DAY 183	98 9(4)	99 10(5)	102 2(5)	106 10(5)
TP (g/dL)				
DAY 40	7.4 0.5(10)	7.3 0.5(10)	7.9 0.6(10)	7.7 0.3(10)
DAY 96	7.9 0.5(10)	8.3 0.7(10) a	8.8* 0.4(10) a	8.8* 0.5(10)
DAY 124	8.2 0.4(10)			8.9* 0.5(10)
DAY 183	8.4 0.3(4)	8.5 0.4(5)	8.7 0.6(5)	8.5 0.5(5)
ALB (g/dL)				
DAY 40	5.0 0.3(10)	5.1 0.4(10)	5.7* 0.5(10)	5.5* 0.3(10)
DAY 96	5.4 0.4(10)	5.7 0.4(10) a	6.2* 0.3(10) a	6.1* 0.4(10)
DAY 124	5.6 0.4(10)			5.9 0.4(10)
DAY 183	5.5 0.3(4)	5.7 0.3(5)	5.4 0.3(5)	5.2 0.5(5)

TABLE 31 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
GLOB (g/dL)				
DAY 40	2.3 0.2(10)	2.3 0.2(10)	2.2 0.2(10)	2.2 0.1(10)
DAY 96	2.5 0.2(10)	2.6 0.3(10)	2.7 0.1(10)	2.6 0.2(10)
DAY 124	2.6 0.2(10)	^a	^a	3.0* 0.2(10)
DAY 183	2.9 0.2(4)	2.8 0.1(5)	3.3* 0.3(5)	3.3* 0.1(5)
CALC (mg/dL)				
DAY 40	11.2 0.4(10)	11.2 0.4(10)	11.8 0.6(10)	11.8@ 0.5(10)
DAY 96	11.3 0.5(10)	11.5 0.4(10)	12.1* 0.3(10)	12.2* 0.3(10)
DAY 124	11.5 0.4(10)	^a	^a	11.6 0.5(10)
DAY 183	10.7 0.2(4)	11.1 0.1(5)	11.3 0.7(5)	11.2 0.7(5)
IPHS (mg/dL)				
DAY 40	7.3 0.6(10)	7.5 0.5(10)	7.7 1.0(10)	8.9* 1.1(10)
DAY 96	5.5 0.5(10)	5.9 0.5(10)	6.3 1.0(10)	6.9* 0.5(10)
DAY 124	6.4 0.8(10)	^a	^a	6.8 0.7(10)
DAY 183	5.3 0.8(4)	5.5 0.5(5)	7.2 2.4(5)	7.2 3.3(5)
NA (mmol/L)				
DAY 40	145.9 1.0(10)	145.4 1.4(10)	144.6 1.4(10)	143.5* 1.4(10)
DAY 96	145.8 1.0(10)	145.6 1.0(10)	145.3 1.3(10)	145.2 1.6(10)
DAY 124	143.8 2.3(10)	^a	^a	144.3 1.1(10)
DAY 183	144.9 2.0(4)	146.4 1.4(5)	147.6 3.7(5)	145.6 2.7(5)

TABLE 31 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
K (mmol/L)				
DAY 40	5.63 0.37(10)	5.85 0.30(10)	5.99 0.38(10)	6.34@ 0.50(10)
DAY 96	5.50 0.38(10)	5.47 0.39(10)	5.53 0.56(10)	5.95 0.50(10)
DAY 124	5.90 0.72(10)	^a	^a	5.84 0.76(10)
DAY 183	5.36 0.30(4)	5.57 0.35(5)	5.87 0.89(5)	6.12 1.20(5)
CL (mmol/L)				
DAY 40	98.9 1.0(10)	99.2 1.2(10)	97.6 2.2(10)	96.3* 1.3(10)
DAY 96	101.0 1.8(10)	99.5 1.6(10)	98.5* 1.8(10)	97.5* 2.5(10)
DAY 124	98.4 2.2(10)	^a	^a	98.2 2.0(10)
DAY 183	101.4 2.4(4)	100.5 0.8(5)	102.1 3.6(5)	102.1 3.4(5)
PFLU (μg/mL)				
DAY 40	^a	^a	^a	^a
DAY 96	0.1 0.0(10)	0.1 0.0(10)	0.2 0.0(10)	0.5@ 0.1(10)
DAY 124	0.0 0.0(10)	^a	^a	0.1@ 0.1(10)
DAY 183	0.1 0.1(4)	0.1 0.0(5)	0.1 0.1(4)	0.1 0.0(4)

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 MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
VOL (mL)				
DAY 39	14.1 6.8(10)	14.8 10.0(10)	13.0 10.8(10)	29.6* 17.1(10)
DAY 95	10.1 6.0(10)	13.5 10.0(10) a	8.6 4.5(10) a	37.2@ 17.1(10)
DAY 123	8.0 5.9(10)			9.8 5.0(10)
DAY 183	11.4 7.4(4)	8.8 4.3(5)	8.9 5.7(4)	12.7 4.6(5)
UOSM (mOsm)				
DAY 39	757 283(10)	843 540(10)	1002 606(10)	655 650(10)
DAY 95	1230 583(10)	1046 394(10) a	1222 415(10) a	506* 195(10)
DAY 123	1465 714(10)			1262 474(10)
DAY 183	1089 422(4)	1452 663(5)	1419 396(4)	955 206(5)
SG				
DAY 39	1.024 0.008(10)	1.026 0.015(10)	1.031 0.018(10)	1.020 0.019(10)
DAY 95	1.038 0.016(10)	1.034 0.011(10) a	1.039 0.012(10) a	1.018* 0.006(10)
DAY 123	1.045 0.020(10)			1.040 0.014(10)
DAY 183	1.031 0.011(4)	1.042 0.019(5)	1.039 0.009(4)	1.027 0.004(5)
pH				
DAY 39	7.2 0.2(10)	7.1 0.3(10)	6.9 0.4(10)	7.1 0.3(10)
DAY 95	6.6 0.8(10)	6.5 0.7(10) a	6.2 0.5(10) a	5.3@ 0.3(10)
DAY 123	6.5 0.3(10) a			6.5 0.4(10)
DAY 183		a		

TABLE 32 (Continued)

SUMMARY OF URINALYSIS VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
URO (EU/dL)				
DAY 39	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)
DAY 95	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)
DAY 123	0.2 0.0(10)	a	a	0.2 0.0(10)
DAY 183	a	a	a	a
UFLU (µg)				
DAY 39	a	a	a	a
DAY 95	12.1 5.4(10)	50.6 11.5(10)	140.8@ 39.2(10)	632.6@ 89.0(10)
DAY 123	8.1 2.5(9)	a	a	98.3@ 30.0(10)
DAY 183	10.2 2.9(4)	13.5 3.0(5)	21.5* 4.3(4)	46.8* 4.5(5)
UMTP (mg/dL)				
DAY 39	60 41(10)	59 55(10)	78 69(10)	37 56(10)
DAY 95	101 64(10)	69 45(10)	91 52(10)	38@ 53(10)
DAY 123	127 73(10)	a	a	125 84(10)
DAY 183	61 50(4)	263 468(5)	123 70(4)	49 27(5)

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

SUMMARY OF URINALYSIS VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
VOL (mL)				
DAY 40	7.5 4.6(9)	7.2 3.8(10)	10.2 4.5(10)	23.0* 13.4(10)
DAY 96	4.7 2.7(10)	9.1 6.2(9) a	7.8 7.4(10) a	16.5@ 5.6(10)
DAY 124	4.1 2.4(10)			2.6 1.8(9)
DAY 183	5.4 1.6(4)	7.5 2.1(5)	7.3 3.0(5)	7.1 3.7(5)
UOSM (mOsm)				
DAY 40	1046 582(9)	1028 493(10)	826 270(10)	487@ 264(10)
DAY 96	1178 437(9)	923 381(9) a	1166 443(10) a	595* 173(10)
DAY 124	1347 480(9)			1834 762(7)
DAY 183	971 102(4)	1018 266(5)	935 296(5)	934 317(5)
SG				
DAY 40	1.030 0.015(9)	1.029 0.013(10)	1.025 0.008(10)	1.016@ 0.008(10)
DAY 96	1.040 0.018(10)	1.028 0.011(9) a	1.038 0.014(10) a	1.021* 0.007(10)
DAY 124	1.040 0.013(9)			1.054 0.020(9)
DAY 183	1.027 0.002(4)	1.027 0.006(5)	1.027 0.010(5)	1.027 0.009(5)
pH				
DAY 40	6.9 0.5(9)	6.7 0.3(10)	6.6 0.2(10)	6.7 0.3(10)
DAY 96	6.0 0.7(10)	5.8 0.9(9) a	5.8 0.5(10) a	5.4@ 1.0(10)
DAY 124	5.7 0.4(10) a			5.5 0.5(10) a
DAY 183		a	a	

TABLE 33 (Continued)

SUMMARY OF URINALYSIS VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
URO (EU/dL)				
DAY 40	0.2 0.0(9)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)
DAY 96	0.2 0.0(10)	0.2 0.0(9)	0.2 0.0(10)	0.3 0.3(10)
DAY 124	0.2 0.0(10)	a	a	0.2 0.0(10)
DAY 183	a	a	a	a
UFLU (μg)				
DAY 40	a	a	a	a
DAY 96	5.5 1.8(9)	23.7 7.8(9)	59.4@ 16.0(10)	291.2@ 95.5(10)
DAY 124	4.2 1.3(7)	a	a	30.0@ 10.6(4)
DAY 183	5.9 1.1(4)	8.6 1.6(5)	9.9 2.0(5)	15.7@ 7.1(5)
UMTP (mg/dL)				
DAY 40	25 19(9)	23 18(10)	22 14(10)	20@ 41(10)
DAY 96	45 42(10)	34 36(9)	278 513(10)	165 422(10)
DAY 124	41 23(9)	a	a	538@ 793(8)
DAY 183	45 50(4)	30 18(5)	333 477(5)	157 165(5)

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 34

SUMMARY OF PEROXISOMAL BETA-OXIDATION ACTIVITY IN MALE RATS

Group	Dosage (mg/kg/day)	Hepatic Peroxisomal Beta-Oxidation Activity (nmol/min/mg protein)		
		10-Day Timepoint	90-Day Timepoint	One-Month Recovery Three-Month Recovery
I	0	3.5 ± 1.2 ^a	9.0 ± 2.0	6.4 ± 0.5 18.5 ± 1.0 ^b
III ^c	25	4.1 ± 0.7	12.5 ± 1.6	----- -----
V ^c	100	6.0 ± 1.7 [#]	11.3 ± 2.5	----- -----
VII	500	10.0 ± 4.5 [#]	16.3 ± 1.4 [#]	12.5 ± 2.1* 18.8 ± 1.5

^a Mean ± standard deviation. The n = 5 for each group.

^b n = 4.

^c Samples were not prepared for analysis from groups III and V at the 30- and 90-day recovery timepoints. Statistically significant difference from control (p < 0.05) by Jonckheere Terpstra Trend test (#) or Dunnett's test (*).

TABLE 35

SUMMARY OF PEROXISOMAL BETA-OXIDATION ACTIVITY IN FEMALE RATS

Group	Dosage (mg/kg/day)	Hepatic Peroxisomal Beta-Oxidation Activity (nmol/min/mg protein)		
		10-Day Timepoint	90-Day Timepoint	One-Month Recovery
II	0	5.5 ± 1.0 ^a	12.9 ± 3.0	9.9 ± 1.2
IV ^b	25	6.9 ± 2.6	8.0 ± 2.1*	-----
VI ^b	100	4.3 ± 0.7	10.8 ± 2.7	-----
VIII	500	5.0 ± 0.9	13.4 ± 2.1	13.0 ± 1.9*

a Mean ± standard deviation. The n = 5 for each group.

b Samples were not prepared for analysis from groups IV and VI at the 30-day recovery time point.

* Statistically significant difference from control (p < 0.05) by Dunnett's test.

TABLE 36

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 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
LIVER	16.63310 2.80943(10)	19.02640# 2.29505(10)	21.76290# 2.91519(10)	28.54900# 4.31269(10)
KIDNEYS	4.27300 0.52569(10)	4.31100 0.25110(10)	4.24910 0.52783(10)	4.00840 0.43887(10)
HEART	1.82560 0.12199(10)	1.92220 0.19537(10)	1.72420 0.15012(10)	1.39460# 0.17029(10)
SPLEEN	0.90380 0.19394(10)	0.87540 0.11469(10)	0.79780 0.13239(10)	0.65110# 0.09723(10)
BRAIN	2.13200 0.09280(10)	2.16340 0.05560(10)	2.07150 0.08678(10)	2.07970# 0.04210(10)
THYMUS	0.43440 0.13861(10)	0.45440 0.14653(10)	0.29630# 0.04005(10)	0.26950# 0.05282(10)
ADRENAL GLANDS	0.05700 0.00869(10)	0.05510 0.00962(10)	0.05060 0.00765(10)	0.04870# 0.00735(10)
THYROID GLAND	0.02160 0.00455(10)	0.02040 0.00295(10)	0.02170 0.00427(10)	0.02370 0.00609(10)
TESTES	3.63400 0.29496(10)	3.64140 0.17140(10)	3.61030 0.29853(10)	3.58520 0.20972(10)
EPIDIDYMIDES	1.55710 0.15334(10)	1.57840 0.15123(10)	1.51140 0.16395(10)	1.34760# 0.09038(10)
FINAL BODY WEIGHT	586.97000 55.79240(10)	594.81000 56.63113(10)	521.24000# 49.44560(10)	455.83001# 46.70487(10)

TABLE 36 (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 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
LIVER/ FINAL BODY * 100	2.82741 0.32735(10)	3.19494# 0.16761(10)	4.16752# 0.25124(10)	6.24277# 0.47380(10)
KIDNEYS/ FINAL BODY * 100	0.72909 0.06930(10)	0.72913 0.06408(10)	0.81433# 0.04611(10)	0.88088# 0.06592(10)
HEART/ FINAL BODY * 100	0.31266 0.02647(10)	0.32478 0.03760(10)	0.33309 0.04214(10)	0.30614 0.02431(10)
SPLEEN/ FINAL BODY * 100	0.15358 0.02706(10)	0.14725 0.01424(10)	0.15273 0.01741(10)	0.14324 0.01740(10)
BRAIN/ FINAL BODY * 100	0.36601 0.03583(10)	0.36647 0.03351(10)	0.40022 0.03778(10)	0.46035# 0.04556(10)
THYMUS/ FINAL BODY * 100	0.07367 0.02055(10)	0.07549 0.01890(10)	0.05703# 0.00789(10)	0.05916# 0.01053(10)
ADRENAL GLANDS/ FINAL BODY * 100	0.00977 0.00171(10)	0.00924 0.00113(10)	0.00982 0.00210(10)	0.01079 0.00203(10)
THYROID GLAND/ FINAL BODY * 100	0.00367 0.00058(10)	0.00346 0.00058(10)	0.00419 0.00089(10)	0.00528# 0.00164(10)
TESTES/ FINAL BODY * 100	0.62453 0.08067(10)	0.61777 0.06985(10)	0.70006 0.10332(10)	0.79569# 0.10956(10)
EPIDIDYMIDES/ FINAL BODY * 100	0.26746 0.03552(10)	0.26775 0.03808(10)	0.29268 0.04468(10)	0.29896 0.04172(10)

TABLE 36 (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	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 500 mg/kg
LIVER/ BRAIN * 100	782.96063 147.78552(10)	879.89000# 107.54323(10)	1050.1984# 125.91532(10)	1371.9135# 200.20379(10)
KIDNEYS/ BRAIN * 100	200.90331 27.68803(10)	199.41177 13.25286(10)	205.06197 22.60785(10)	192.60123 19.36248(10)
HEART/ BRAIN * 100	85.68143 5.40052(10)	88.93735 9.68550(10)	83.36613 7.93969(10)	67.03478# 7.96076(10)
SPLEEN/ BRAIN * 100	42.45121 9.35506(10)	40.45059 5.07376(10)	38.47994 5.74742(10)	31.28986# 4.44000(10)
THYMUS/ BRAIN * 100	20.42288 6.61576(10)	20.96895 6.72670(10)	14.31534# 1.89127(10)	12.95050# 2.49419(10)
ADRENAL GLANDS/ BRAIN * 100	2.67508 0.40284(10)	2.54529 0.42819(10)	2.43944 0.32251(10)	2.33982 0.33248(10)
THYROID GLAND/ BRAIN * 100	1.01563 0.22828(10)	0.94388 0.14130(10)	1.04901 0.21199(10)	1.13830 0.27988(10)
TESTES/ BRAIN * 100	170.63301 14.18460(10)	168.35760 7.63521(10)	174.61595 16.78231(10)	172.35943 8.69911(10)
EPIDIDYMIDES/ BRAIN * 100	73.11609 7.48972(10)	73.09237 8.12540(10)	73.14495 9.15417(10)	64.79942# 4.12918(10)

TABLE 36 (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 500 mg/kg/day
LIVER	15.91980 2.61567(10)	19.28230# 2.99843(10)
KIDNEYS	4.01410 0.63080(10)	4.12190 0.56676(10)
HEART	1.81180 0.26704(10)	1.71790 0.20145(10)
SPLEEN	0.77380 0.12216(10)	0.75260 0.13042(10)
BRAIN	2.17610 0.07422(10)	2.08670# 0.10123(10)
THYMUS	0.32740 0.09491(10)	0.31770 0.06795(10)
ADRENAL GLANDS	0.05270 0.01206(10)	0.04960 0.00928(10)
THYROID GLAND	0.02640 0.00513(10)	0.02610 0.00381(10)
TESTES	3.47080 0.37716(10)	3.64160 0.43347(10)
EPIDIDYMIDES	1.52810 0.16851(10)	1.47190 0.18300(10)
FINAL BODY WEIGHT	576.09000 78.02172(10)	507.33999# 57.96794(10)

TABLE 36 (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	Group VII 500 mg/kg
LIVER/ FINAL BODY * 100	2.75706 0.19397(10)	3.79193# 0.30701(10)
KIDNEYS/ FINAL BODY * 100	0.69591 0.04037(10)	0.81175# 0.05428(10)
HEART/ FINAL BODY * 100	0.31585 0.03450(10)	0.33906 0.02237(10)
SPLEEN/ FINAL BODY * 100	0.13459 0.01570(10)	0.14853 0.02032(10)
BRAIN/ FINAL BODY * 100	0.38227 0.03845(10)	0.41503 0.04063(10)
THYMUS/ FINAL BODY * 100	0.05744 0.01742(10)	0.06286 0.01353(10)
ADRENAL GLANDS/ FINAL BODY *100	0.00918 0.00188(10)	0.00987 0.00204(10)
THYROID GLAND/ FINAL BODY * 100	0.00462 0.00092(10)	0.00518 0.00079(10)
TESTES/ FINAL BODY * 100	0.60590 0.05072(10)	0.72098# 0.07942(10)
EPIDIDYMIDES/ FINAL BODY * 100	0.26667 0.02168(10)	0.29132 0.03122(10)

TABLE 36 (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	Group VII 500 mg/kg
LIVER/ BRAIN * 100	729.29332 100.02746(10)	921.83881# 119.30612(10)
KIDNEYS/ BRAIN * 100	184.00069 24.20313(10)	197.44475 24.55331(10)
HEART/ BRAIN * 100	83.11980 10.42723(10)	82.49189 10.31680(10)
SPLEEN/ BRAIN * 100	35.50892 5.12558(10)	36.07912 6.01540(10)
THYMUS/ BRAIN * 100	15.06621 4.37529(10)	15.29145 3.51776(10)
ADRENAL GLANDS/ BRAIN * 100	2.41725 0.51509(10)	2.37473 0.41350(10)
THYROID GLAND/ BRAIN * 100	1.21012 0.21265(10)	1.25315 0.18912(10)
TESTES/ BRAIN * 100	159.39532 14.80609(10)	174.11728 14.55585(10)
EPIDIDYMIDES/ BRAIN * 100	70.13548 6.27701(10)	70.42842 6.58358(10)

TABLE 36 (Continued)

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

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)				
	Group I 0 mg/kg	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 500 mg/kg
LIVER	15.18825 3.97935 (4)	16.16520 2.16983 (5)	17.47825 3.24147 (4)	18.25980# 0.83323 (5)
KIDNEYS	3.57500 0.76015 (4)	4.05200 0.63025 (5)	4.06925 0.53882 (4)	4.14060 0.29634 (5)
SPLEEN	0.70700 0.03459 (4)	0.85960 0.06672 (5)	0.79600 0.14425 (4)	0.85440 0.16217 (5)
THYROID GLAND	0.02450 0.00624 (4)	0.02520 0.00879 (5)	0.02000 0.00183 (4)	0.02760 0.00573 (5)
TESTES	3.74800 0.21840 (4)	3.82800 0.55129 (5)	3.52850 0.27561 (4)	3.62420 0.35247 (5)
FINAL BODY WEIGHT	563.70001 99.80271 (4)	630.94000 47.83004 (5)	597.95000 71.58256 (4)	609.70000 42.75200 (5)

TABLE 36 (Continued)

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

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 500 mg/kg/day
LIVER/ FINAL BODY*100	2.65937 0.31939 (4)	2.56549 0.31336 (5)	2.90979 0.28681 (4)	3.00285# 0.18073 (5)
KIDNEYS/ FINAL BODY*100	0.63343 0.07565 (4)	0.64510 0.10676 (5)	0.68010 0.01923 (4)	0.68060 0.05044 (5)
SPLEEN/ FINAL BODY*100	0.12809 0.02023 (4)	0.13674 0.01296 (5)	0.13283 0.01340 (4)	0.13959 0.02222 (5)
THYROID GLAND/ FINAL BODY*100	0.00432 0.00046 (4)	0.00397 0.00126 (5)	0.00340 0.00061 (4)	0.00455 0.00103 (5)
TESTES/ FINAL BODY*100	0.68104 0.12348 (4)	0.60760 0.08141 (5)	0.59534 0.07245 (4)	0.59769 0.08245 (5)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).

Statistically significant difference at $p < 0.05$.

TABLE 37

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	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 500 mg/kg
LIVER	8.96410 1.17520(10)	10.49990# 1.34755(10)	14.83930# 2.41882(10)	19.06010# 2.86309(10)
KIDNEYS	2.30570 0.25369(10)	2.47140 0.38278(10)	2.74590# 0.42987(10)	2.72540# 0.54824(10)
HEART	1.14650 0.11569(10)	1.13550 0.09633(10)	1.27860 0.19973(10)	1.11550 0.15138(10)
SPLEEN	0.53040 0.06905(10)	0.56770 0.07731(10)	0.59510 0.06199(10)	0.57850 0.04645(10)
BRAIN	1.95650 0.08639(10)	1.95530 0.11202(10)	1.95200 0.07330(10)	1.91380 0.04798(10)
THYMUS	0.24630 0.05982(10)	0.27320 0.09619(10)	0.26660 0.04664(10)	0.24480 0.02340(10)
ADRENAL GLANDS	0.06770 0.01800(10)	0.07100 0.01641(10)	0.06830 0.01302(10)	0.07140 0.00983(10)
THYROID GLAND	0.01660 0.00386(10)	0.01790 0.00363(10)	0.01840 0.00422(10)	0.01940 0.00430(10)
OVARIES	0.13390 0.01952(10)	0.10840 0.01652(10)	0.11990 0.02643(10)	0.11520 0.02006(10)
UTERUS	0.88300 0.32174(10)	0.71410 0.20197(10)	0.80990 0.35177(10)	1.19680 0.72333(10)
FINAL BODY WEIGHT	307.06000 35.30156(10)	296.01000 36.05821(10)	305.97000 24.82257(10)	289.03000 24.17566(10)

TABLE 37 (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 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
LIVER/ FINAL BODY * 100	2.92243 0.26344 (10)	3.55488# 0.29322 (10)	4.83452# 0.55255 (10)	6.57179# 0.57624 (10)
KIDNEYS/ FINAL BODY * 100	0.75622 0.09220 (10)	0.83753 0.11222 (10)	0.89393# 0.08919 (10)	0.93820# 0.13426 (10)
HEART/ FINAL BODY * 100	0.37587 0.04182 (10)	0.38600 0.03060 (10)	0.41663@ 0.04293 (10)	0.38467 0.02624 (10)
SPLEEN/ FINAL BODY * 100	0.17374 0.02282 (10)	0.19331 0.02996 (10)	0.19489 0.01811 (10)	0.20052# 0.01128 (10)
BRAIN/ FINAL BODY * 100	0.64421 0.07213 (10)	0.66816 0.07908 (10)	0.64198 0.05953 (10)	0.66609 0.05485 (10)
THYMUS/ FINAL BODY * 100	0.08023 0.01653 (10)	0.09119 0.02354 (10)	0.08687 0.01132 (10)	0.08491 0.00724 (10)
ADRENAL GLANDS/ FINAL BODY * 100	0.02235 0.00698 (10)	0.02436 0.00658 (10)	0.02225 0.00324 (10)	0.02473 0.00281 (10)
THYROID GLAND/ FINAL BODY * 100	0.00547 0.00137 (10)	0.00616 0.00161 (10)	0.00609 0.00166 (10)	0.00669 0.00127 (10)
OVARIES/ FINAL BODY * 100	0.04355 0.00328 (10)	0.03720 0.00779 (10)	0.03972 0.01047 (10)	0.04024 0.00862 (10)
UTERUS/ FINAL BODY * 100	0.29584 0.12450 (10)	0.24249 0.07305 (10)	0.26205 0.09841 (10)	0.40830 0.22284 (10)

TABLE 37 (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	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 500 mg/kg
LIVER/BRAIN BRAIN * 100	457.49243 52.94763(10)	537.57050# 66.19395(10)	759.94841# 117.36733(10)	994.74997# 137.46968(10)
KIDNEYS/ BRAIN * 100	117.86404 12.33523(10)	125.99830 15.06599(10)	140.64122# 20.77856(10)	142.10320# 26.06927(10)
HEART/ BRAIN * 100	58.69240 6.46805(10)	58.15049 4.87700(10)	65.47801 9.52060(10)	58.26306 7.55341(10)
SPLEEN/ BRAIN * 100	27.17492 3.90257(10)	29.02747 3.59886(10)	30.54374# 3.55350(10)	30.24692# 2.57608(10)
THYMUS/ BRAIN * 100	12.55555 2.82205(10)	13.94615 4.58716(10)	13.69236 2.58117(10)	12.78967 1.14599(10)
ADRENAL GLANDS/ BRAIN * 100	3.46244 0.92313(10)	3.60811 0.67135(10)	3.49437 0.60893(10)	3.72289 0.42145(10)
THYROID GLAND/ BRAIN * 100	0.85209 0.21053(10)	0.91898 0.19671(10)	0.94297 0.21733(10)	1.01498 0.23116(10)
OVARIES/ BRAIN * 100	6.85126 1.04334(10)	5.54150 0.78099(10)	6.14228 1.36604(10)	6.01898 1.04377(10)
UTERUS/ BRAIN * 100	45.19756 16.25939(10)	36.38737 9.19147(10)	41.32404 16.60914(10)	62.57485 38.01544(10)

TABLE 37 (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 500 mg/kg/day
LIVER	9.67850 1.13424 (10)	11.80670# 1.65066 (10)
KIDNEYS	2.44900 0.27689 (10)	2.62610 0.25291 (10)
HEART	1.22860 0.12853 (10)	1.24080 0.15221 (10)
SPLEEN	0.55070 0.10790 (10)	0.52300 0.05378 (10)
BRAIN	1.95200 0.06240 (10)	1.97160 0.05553 (10)
THYMUS	0.22570 0.02587 (10)	0.22010 0.04800 (10)
ADRENAL GLANDS	0.09560 0.07987 (10)	0.07640 0.00866 (10)
THYROID GLAND	0.02070 0.00226 (10)	0.01940 0.00299 (10)
OVARIES	0.10940 0.01580 (10)	0.11040 0.02732 (10)
UTERUS	0.78170 0.15328 (10)	0.91460 0.38329 (10)
FINAL BODY WEIGHT	330.86000 34.33764 (10)	294.59000# 23.94041 (10)

TABLE 37 (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 500 mg/kg/day
LIVER/ FINAL BODY * 100	2.92561 0.19109 (10)	3.99507# 0.32765 (10)
KIDNEYS/ FINAL BODY * 100	0.74132 0.05681 (10)	0.89161# 0.04728 (10)
HEART/ FINAL BODY * 100	0.37328 0.04081 (10)	0.42063# 0.02988 (10)
SPLEEN/ FINAL BODY * 100	0.16646 0.02663 (10)	0.17781 0.01594 (10)
BRAIN/ FINAL BODY * 100	0.59523 0.05966 (10)	0.67285# 0.05154 (10)
THYMUS/ FINAL BODY * 100	0.06887 0.01061 (10)	0.07466 0.01555 (10)
ADRENAL GLANDS/ FINAL BODY * 100	0.02857 0.02206 (10)	0.02599 0.00275 (10)
THYROID GLAND/ FINAL BODY * 100	0.00628 0.00067 (10)	0.00661 0.00105 (10)
OVARIES/ FINAL BODY * 100	0.03334 0.00565 (10)	0.03765 0.00992 (10)
UTERUS/ FINAL BODY * 100	0.23659 0.04298 (10)	0.31188 0.12397 (10)

TABLE 37 (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 500 mg/kg/day
LIVER/ BRAIN * 100	495.94097 56.84798(10)	598.36638# 79.12881(10)
KIDNEYS/ BRAIN * 100	125.38765 12.86108(10)	133.25610 13.06903(10)
HEART/ BRAIN * 100	62.96376 6.57084(10)	62.94811 7.59489(10)
SPLEEN/ BRAIN * 100	28.20259 5.34710(10)	26.52191 2.59702(10)
THYMUS/ BRAIN * 100	11.55511 1.18346(10)	11.14676 2.35367(10)
ADRENAL GLANDS/ BRAIN * 100	4.87004 3.99993(10)	3.87639 0.44163(10)
THYROID GLAND/ BRAIN * 100	1.06030 0.10863(10)	0.98505 0.15984(10)
OVARIES/ BRAIN * 100	5.62234 0.92706(10)	5.58292 1.30758(10)
UTERUS/ BRAIN * 100	40.05367 7.89402(10)	46.70156 20.49091(10)

TABLE 37 (Continued)

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

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHT (grams)

	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
LIVER	8.80150 1.11307(4)	9.37260 1.28006(5)	11.40800# 2.38708(4)	10.77225# 1.16901(4)
KIDNEYS	2.32675 0.33914(4)	2.35700 0.36101(5)	2.83800 0.73122(4)	2.60075 0.23556(4)
SPLEEN	0.50950 0.07548(4)	0.47540 0.04057(5)	0.54400 0.04695(4)	0.60150 0.10743(4)
THYROID GLAND	0.01875 0.00250(4)	0.02050 0.00129(4)	0.01775 0.00171(4)	0.01825 0.00386(4)
FINAL BODY WEIGHT	340.87500 39.19289(4)	336.88000 57.73913(5)	346.57500 55.62664(4)	309.60000 42.33793(4)

TABLE 37 (Continued)

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

	MEAN RELATIVE ORGAN WEIGHTS (% of body weight)			
	Group II 0 mg/kg/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 500 mg/kg/day
LIVER/ FINAL BODY*100	2.58246 0.13689 (4)	2.80327 0.23912 (5)	3.28638# 0.33956 (4)	3.49940# 0.31044 (4)
KIDNEYS/ FINAL BODY*100	0.68217 0.05267 (4)	0.70360 0.06312 (5)	0.81593 0.12727 (4)	0.84656# 0.08237 (4)
SPLEEN/ FINAL BODY*100	0.15176 0.03460 (4)	0.14321 0.01739 (5)	0.15898 0.01976 (4)	0.19457# 0.02305 (4)
THYROID GLAND/ FINAL BODY*100	0.00550 0.00044 (4)	0.00622 0.00120 (4)	0.00518 0.00060 (4)	0.00589 0.00102 (4)

Data summarized as: Mean
 Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).

Statistically significant difference at $p < 0.05$.

TABLE 38

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)				
		Males				
		0	25	100	500	
		I	III	V	VII	
LIVER		(11)	(10)	(11)	(12)	
NO ABNORMALITY DETECTED		11	10	10	7	
LARGE.				1	5	
KIDNEYS		(11)	(10)	(11)	(12)	
NO ABNORMALITY DETECTED		11	9	9	10	
DISCOLORATION, TAN, LEFT.					1	
DILATATION, LEFT.					1	
DILATATION, RIGHT, PELVIS.			1	1		
DILATATION, RIGHT.				1		
SPLEEN		(11)	(10)	(11)	(12)	
NO ABNORMALITY DETECTED		11	10	11	12	
THYROID GLAND		(11)	(10)	(11)	(12)	
NO ABNORMALITY DETECTED		11	10	11	12	
TESTES		(11)	(10)	(11)	(12)	
NO ABNORMALITY DETECTED		11	10	11	12	
ADRENAL GLANDS		(11)	(10)	(11)	(12)	
NO ABNORMALITY DETECTED		11	10	11	12	

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 38 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)				
		Males				
		0	25	100	500	
		I	III	V	VII	
AORTA		(11) 11	(10) 10	(11) 11	(12) 12	
NO ABNORMALITY DETECTED						
BRAIN		(11) 11	(10) 10	(11) 11	(12) 12	
NO ABNORMALITY DETECTED						
CECUM		(11) 11	(10) 10	(11) 11	(12) 12	
NO ABNORMALITY DETECTED						
COAGULATING GLANDS LARGE, LEFT.		(1) 1				
COLON		(11) 11	(10) 10	(11) 11	(12) 12	
NO ABNORMALITY DETECTED						
DUODENUM		(11) 11	(10) 10	(11) 11	(12) 12	
NO ABNORMALITY DETECTED						
EPIDIDYMIDES		(11) 11	(10) 10	(11) 11	(12) 12	
NO ABNORMALITY DETECTED						
ESOPHAGUS		(11) 11	(10) 10	(11) 11	(12) 12	
NO ABNORMALITY DETECTED						

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 38 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)						
		Males						
		0	25	100	500			
		I	III	V	VII			
FEMUR/KNEE JOINT		(11)	(10)	(11)	(12)			
NO ABNORMALITY DETECTED		11	10	11	12			
HEART		(11)	(10)	(11)	(12)			
NO ABNORMALITY DETECTED		11	10	11	12			
ILEUM		(11)	(10)	(11)	(12)			
NO ABNORMALITY DETECTED		11	10	11	12			
JEJUNUM		(11)	(10)	(11)	(12)			
NO ABNORMALITY DETECTED		11	10	11	12			
LUNGS		(11)	(10)	(11)	(12)			
NO ABNORMALITY DETECTED		11	10	11	12			
MANDIBULAR LYMPH NODE		(11)	(10)	(11)	(12)			
NO ABNORMALITY DETECTED		11	10	11	12			
MESENTERIC LYMPH NODE		(11)	(10)	(11)	(12)			
NO ABNORMALITY DETECTED		11	10	11	12			
NOSE		(11)	(10)	(11)	(12)			
NO ABNORMALITY DETECTED		11	10	11	12			

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 38 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)				
		Males				
		0	25	100	500	
		I	III	V	VII	
PANCREAS NO ABNORMALITY DETECTED	(11) 11	(10) 10	(11) 11	(12) 12		
PARATHYROID GLANDS NO ABNORMALITY DETECTED	(11) 11	(10) 10	(11) 11	(12) 12		
PHARYNX/LARYNX NO ABNORMALITY DETECTED	(11) 11	(10) 10	(11) 11	(12) 12		
PITUITARY GLAND NO ABNORMALITY DETECTED	(11) 11	(10) 10	(11) 11	(12) 12		
PROSTATE NO ABNORMALITY DETECTED	(11) 11	(10) 10	(11) 11	(12) 12		
RECTUM NO ABNORMALITY DETECTED	(11) 11	(10) 10	(11) 11	(12) 12		
SALIVARY GLANDS NO ABNORMALITY DETECTED	(11) 11	(10) 10	(11) 11	(12) 12		
SCIATIC NERVE NO ABNORMALITY DETECTED	(11) 11	(10) 10	(11) 11	(12) 12		

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 38 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)				
		Males				
		0	25	100	500	
		I	III	V	VII	
SEMINAL VESICLES NO ABNORMALITY DETECTED		(11) 11	(10) 10	(11) 11	(12) 12	
SKELETAL MUSCLE NO ABNORMALITY DETECTED		(11) 11	(10) 10	(11) 11	(12) 12	
SKIN NO ABNORMALITY DETECTED ALOPECIA, PERINEUM. STAIN, RED, VENTRAL BODY.		(11) 10 1	(10) 10 1	(11) 11	(12) 11 1	
SPINAL CORD NO ABNORMALITY DETECTED		(11) 11	(10) 10	(11) 11	(12) 12	
STERNUM NO ABNORMALITY DETECTED		(11) 11	(10) 10	(11) 11	(12) 12	
STOMACH NO ABNORMALITY DETECTED ULCER/EROSION, GLANDULAR, FEW.		(11) 11	(10) 10	(11) 11	(12) 10 2	
THYMUS NO ABNORMALITY DETECTED DISCOLORATION, BILATERAL.		(11) 11	(10) 9 1	(11) 11	(12) 11 12	

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 38 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)				
	TREATMENT (mg/kg/day)	Males			
		0	25	100	500
		I	III	V	VII
TRACHEA		(11) 11	(10) 10	(11) 11	(12) 12
NO ABNORMALITY DETECTED					
URINARY BLADDER		(11) 9	(10) 9	(11) 11	(12) 11
NO ABNORMALITY DETECTED		1	1		
CALCULUS\CALCULI.		1			1
DILATATION, RED.					
WHOLE BODY				(1) 1	
SITUS INVERSUS.					
EYE(S) WITH OPTIC NERVE		(11) 11	(10) 10	(11) 10	(12) 12
NO ABNORMALITY DETECTED				1	
HEMORRHAGE, RIGHT.					

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 38 (Continued)

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

LESIONS	LESION INCIDENCE (Numeric)	
	Males	
	TREATMENT (mg/kg/day)	
	0	500
	I	VII
LIVER	(10)	(10)
NO ABNORMALITY DETECTED	10	10
KIDNEYS	(10)	(10)
NO ABNORMALITY DETECTED	10	10
SPLEEN	(10)	(10)
NO ABNORMALITY DETECTED	10	10
THYROID GLAND	(10)	(10)
NO ABNORMALITY DETECTED	10	10
TESTES	(10)	(10)
NO ABNORMALITY DETECTED	10	10
ADRENAL GLANDS	(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 38 (Continued)

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

LESIONS	LESION INCIDENCE (Numeric)	
	Males	
	TREATMENT (mg/kg/day)	
	0	500
	I	VII
CECUM NO ABNORMALITY DETECTED	(10) 10	(10) 10
COLON NO ABNORMALITY DETECTED	(10) 10	(10) 10
DUODENUM NO ABNORMALITY DETECTED	(10) 10	(10) 10
EPIDIDYMIDES NO ABNORMALITY DETECTED	(10) 10	(10) 10
ESOPHAGUS NO ABNORMALITY DETECTED	(10) 10	(10) 10
FEMUR/KNEE JOINT NO ABNORMALITY DETECTED	(10) 10	(10) 10
HEART NO ABNORMALITY DETECTED	(10) 10	(10) 10
ILEUM 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 38 (Continued)

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

LESION INCIDENCE (Numeric)	Males	
	TREATMENT (mg/kg/day)	
	0	500
	I	VII
JEJUNUM NO ABNORMALITY DETECTED	(10) 10	(10) 10
LUNGS NO ABNORMALITY DETECTED	(10) 10	(10) 10
MANDIBULAR LYMPH NODE NO ABNORMALITY DETECTED	(10) 10	(10) 10
MESENTERIC LYMPH NODE NO ABNORMALITY DETECTED	(10) 10	(10) 10
NOSE NO ABNORMALITY DETECTED	(10) 10	(10) 10
PANCREAS NO ABNORMALITY DETECTED	(10) 10	(10) 10
PARATHYROID GLANDS NO ABNORMALITY DETECTED	(10) 10	(10) 10
PHARYNX/LARYNX 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 38 (Continued)

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

LESIONS	LESION INCIDENCE (Numeric)	
	Males	
	TREATMENT (mg/kg/day)	
	0	500
	I	VII
PITUITARY GLAND NO ABNORMALITY DETECTED	(10) 10	(10) 10
PROSTATE NO ABNORMALITY DETECTED	(10) 10	(10) 10
RECTUM NO ABNORMALITY DETECTED	(10) 10	(10) 10
SALIVARY GLANDS NO ABNORMALITY DETECTED	(10) 10	(10) 10
SCIATIC NERVE NO ABNORMALITY DETECTED	(10) 10	(10) 10
SEMINAL VESICLES NO ABNORMALITY DETECTED	(10) 10	(10) 10
SKELETAL MUSCLE NO ABNORMALITY DETECTED	(10) 10	(10) 10
SKIN 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 38 (Continued)

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

LESIONS	LESION INCIDENCE (Numeric)	
	Males	
	TREATMENT (mg/kg/day)	
	0	500
	I	VII
SPINAL CORD NO ABNORMALITY DETECTED	(10) 10	(10) 10
STERNUM NO ABNORMALITY DETECTED	(10) 10	(10) 10
STOMACH NO ABNORMALITY DETECTED	(10) 10	(10) 10
THYMUS NO ABNORMALITY DETECTED	(10) 10	(10) 10
TRACHEA NO ABNORMALITY DETECTED	(10) 10	(10) 10
URINARY BLADDER NO ABNORMALITY DETECTED	(10) 10	(10) 10
EYE(S) WITH OPTIC NERVE 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 38 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)				
		0	25	100	500	
		I	III	V	VII	
Males						
LIVER						
NO ABNORMALITY DETECTED		(4) 4	(5) 5	(4) 4	(5) 5	
KIDNEYS						
NO ABNORMALITY DETECTED		(4) 4	(5) 5	(4) 4	(5) 5	
SPLEEN						
NO ABNORMALITY DETECTED		(4) 4	(5) 5	(4) 4	(5) 5	
THYROID GLAND						
NO ABNORMALITY DETECTED		(4) 4	(5) 5	(4) 4	(5) 5	
TESTES						
NO ABNORMALITY DETECTED		(4) 4	(5) 5	(4) 4	(5) 5	
PARATHYROID GLANDS						
NO ABNORMALITY DETECTED		(4) 4	(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 39

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

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT (mg/kg/day)	Females				
		0	25	100	500	
		II	IV	VI	VIII	
LIVER		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	8
LARGE.						2
KIDNEYS		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10
LUNGS		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10
HEART		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10
SKELETAL MUSCLE		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10
SPLEEN		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10
AORTA		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10
BRAIN		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	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 39 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)					
		Females					
		0	25	100	500		
		II	IV	VI	VIII		
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 39 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (Numeric)				
						Females				
	0	25	100	500		0	25	100	500	
	II	IV	VI	VIII						
RECTUM										
NO ABNORMALITY DETECTED	(10)	(10)	(10)	(10)		10	10	10	10	
MESENTERIC LYMPH NODE										
NO ABNORMALITY DETECTED	(10)	(10)	(10)	(10)		10	10	10	10	
SALIVARY GLANDS										
NO ABNORMALITY DETECTED	(10)	(10)	(10)	(10)		10	10	10	10	
MANDIBULAR LYMPH NODE										
NO ABNORMALITY DETECTED	(10)	(10)	(10)	(10)		10	10	10	10	
DISCOLORATION, BILATERAL.	(10)	(10)	(10)	(10)		10	10	10	9	1
THYMUS										
NO ABNORMALITY DETECTED	(10)	(10)	(10)	(10)		10	10	10	10	
ADRENAL GLANDS										
NO ABNORMALITY DETECTED	(10)	(10)	(10)	(10)		10	10	10	10	
SCIATIC NERVE										
NO ABNORMALITY DETECTED	(10)	(10)	(10)	(10)		10	10	10	10	
PITUITARY GLAND										
NO ABNORMALITY DETECTED	(10)	(10)	(10)	(10)		10	9	8	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 39 (Continued)

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

LESIONS	LESION INCIDENCE (Numeric)				
	Females				
	TREATMENT (mg/kg/day)	0	25	100	500
		II	IV	VI	VIII
PITUITARY GLAND LARGE.		(10)	(10) 1	(10) 2	(10) 1
THYROID GLAND NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10
PARATHYROID GLANDS NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10
TRACHEA NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10
ESOPHAGUS NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10
PHARYNX/LARYNX NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10
SKIN NO ABNORMALITY DETECTED ALOPECIA, BILATERAL, HINDLIMB.		(10) 10	(10) 10	(10) 10	(10) 9 1

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

LESIONS	LESION INCIDENCE (Numeric)						
	TREATMENT (mg/kg/day)	0	25	100	500	Females	
		II	IV	VI	VIII		
MAMMARY GLAND (FEMALE) NO ABNORMALITY DETECTED LARGE, VENTRAL.		(10) 10	(10) 10	(10) 9	(10) 10		
OVARIES NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10		
UTERUS NO ABNORMALITY DETECTED LARGE.		(10) 10	(10) 10	(10) 9	(10) 10		
URINARY BLADDER NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10		
FEMUR/KNEE JOINT NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10		
STERNUM NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(10) 10		
NOSE NO ABNORMALITY DETECTED		(10) 10	(10) 10	(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 39 (Continued)

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

LESIONS	LESION INCIDENCE (Numeric)	
	Females	
	TREATMENT (mg/kg/day)	
	0	500
	II	VIII
LIVER		
NO ABNORMALITY DETECTED	(10)	(10)
	10	10
KIDNEYS		
NO ABNORMALITY DETECTED	(10)	(10)
DILATATION, RIGHT, PELVIS.	8	10
CYST, CLEAR, LEFT.	1	
CYST, RIGHT.	1	
	1	
LUNGS		
NO ABNORMALITY DETECTED	(10)	(10)
	10	10
HEART		
NO ABNORMALITY DETECTED	(10)	(10)
	10	10
SKELETAL MUSCLE		
NO ABNORMALITY DETECTED	(10)	(10)
	10	10
SPLEEN		
NO ABNORMALITY DETECTED	(10)	(10)
	10	10
AORTA		
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 39 (Continued)

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

LESIONS	LESION INCIDENCE (Numeric)	
	Females	
	TREATMENT (mg/kg/day)	
	0	500
	II	VIII
BRAIN NO ABNORMALITY DETECTED	(10) 10	(10) 10
SPINAL CORD NO ABNORMALITY DETECTED	(10) 10	(10) 10
STOMACH NO ABNORMALITY DETECTED ULCER/EROSION, GLANDULAR.	(10) 10	(10) 9 1
DUODENUM NO ABNORMALITY DETECTED	(10) 10	(10) 10
JEJUNUM NO ABNORMALITY DETECTED	(10) 10	(10) 10
ILEUM NO ABNORMALITY DETECTED	(10) 10	(10) 10
PANCREAS NO ABNORMALITY DETECTED	(10) 10	(10) 10
CECUM 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 39 (Continued)

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

LESIONS	LESION INCIDENCE (Numeric)			
	Females			
	TREATMENT (mg/kg/day)	0	500	
		II	VIII	
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	
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	

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 39 (Continued)

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

LESIONS	LESION INCIDENCE (Numeric)	
	Females	
	TREATMENT (mg/kg/day)	
	0	500
	II	VIII
PITUITARY GLAND NO ABNORMALITY DETECTED	(10) 10	(10) 10
THYROID GLAND NO ABNORMALITY DETECTED	(10) 10	(10) 10
PARATHYROID GLANDS NO ABNORMALITY DETECTED	(10) 10	(10) 10
TRACHEA NO ABNORMALITY DETECTED	(10) 10	(10) 10
ESOPHAGUS NO ABNORMALITY DETECTED	(10) 10	(10) 10
PHARYNX/LARYNX NO ABNORMALITY DETECTED	(10) 10	(10) 10
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED	(10) 10	(10) 10
SKIN 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 39 (Continued)

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

LESIONS	LESION INCIDENCE (Numeric)	
	Females	
	TREATMENT (mg/kg/day)	
	0	500
	II	VIII
MAMMARY GLAND (FEMALE) NO ABNORMALITY DETECTED	(10) 10	(10) 10
OVARIES NO ABNORMALITY DETECTED	(10) 10	(10) 10
UTERUS NO ABNORMALITY DETECTED	(10) 10	(10) 10
URINARY BLADDER NO ABNORMALITY DETECTED	(10) 10	(10) 10
FEMUR/KNEE JOINT NO ABNORMALITY DETECTED	(10) 10	(10) 10
STERNUM NO ABNORMALITY DETECTED	(10) 10	(10) 10
NOSE 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 39 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)					
		Females					
		0	25	100	500		
		II	IV	VI	VIII		
LIVER							
NO ABNORMALITY DETECTED		(4) 4	(5) 5	(5) 5	(5) 5		
KIDNEYS							
NO ABNORMALITY DETECTED		(4) 4	(5) 5	(5) 4	(5) 5		
SMALL, RIGHT, IRREGULAR				1			
SPLEEN							
NO ABNORMALITY DETECTED		(4) 4	(5) 5	(5) 5	(5) 5		
THYROID GLAND							
NO ABNORMALITY DETECTED		(4) 4	(5) 5	(5) 5	(5) 5		
PARATHYROID GLANDS							
NO ABNORMALITY DETECTED		(4) 4	(5) 5	(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 40

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)					
	Males					
	TREATMENT (mg/kg/day)	0	25	100	500	
		I	III	V	VII	
DIGESTIVE SYSTEM						
LIVER		(11)	(10)	(11)	(12)	
NO ABNORMALITY DETECTED		6	4	1	1	
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.		4	1	1	1	
HYPERTROPHY, CENTRILOBULAR.		1	5	10	12	
FATTY CHANGE, PERIportal.		1				
FATTY CHANGE, MEDIAN CLEFT.		2	2	1		
PANCREAS		(11)		(1)	(12)	
NO ABNORMALITY DETECTED		8		1	12	
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.		3				
ESOPHAGUS		(11)		(1)	(12)	
NO ABNORMALITY DETECTED		11		1	12	

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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION INCIDENCE (Animal #)	Males				
	TREATMENT (mg/kg/day)	0	25	100	500
LESIONS		I	III	V	VII
DIGESTIVE SYSTEM					
STOMACH NO ABNORMALITY DETECTED	(11) 11	(1) 1	(1) 1	(1) 1	(12) 12
DUODENUM NO ABNORMALITY DETECTED	(11) 11	(1) 1	(1) 1	(1) 1	(12) 12
JEJUNUM NO ABNORMALITY DETECTED	(11) 11	(1) 1	(1) 1	(1) 1	(12) 12
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					
ILEUM NO ABNORMALITY DETECTED	(11) 11	(1) 1	(1) 1	(1) 1	(12) 12
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					

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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
DIGESTIVE SYSTEM					
CECUM		(11)		(1)	(12)
NO ABNORMALITY DETECTED		11		1	12
COLON		(11)		(1)	(12)
NO ABNORMALITY DETECTED		11		1	12
RECTUM		(11)		(1)	(12)
NO ABNORMALITY DETECTED		11		1	12
SALIVARY GLANDS		(11)		(1)	(12)
NO ABNORMALITY DETECTED		11		1	12

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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
URINARY SYSTEM					
KIDNEYS		(11)	(10)	(11)	(12)
NO ABNORMALITY DETECTED		5	7	4	4
PYELONEPHRITIS, BILATERAL.		1		1	1
NEPHROPATHY, CHRONIC PROGRESSIVE.		5	2	5	7
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.					1
HYDRONEPHROSIS, UNILATERAL.			1	2	1
HYDRONEPHROSIS, BILATERAL.			1		1
NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING.				1	
URINARY BLADDER		(11)	(1)	(1)	(12)
NO ABNORMALITY DETECTED		9		1	11
INFLAMMATION, SUBACUTE/CHRONIC.		2	1		1
HYPERPLASIA, TRANSITIONAL CELL.		1	1		
HEMORRHAGE.		1			1
CALCULUS/CALCULI.		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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
RESPIRATORY SYSTEM					
LUNGS		(11) 11		(1) 1	(12) 12
NO ABNORMALITY DETECTED					
TRACHEA		(10) 10		(1) 1	(12) 12
NO ABNORMALITY DETECTED					
PHARYNX/LARYNX		(11) 11		(1) 1	(11) 11
NO ABNORMALITY DETECTED					
NOSE I & II		(11) 11		(1) 1	(12) 12
NO ABNORMALITY DETECTED					
NOSE III & IV		(11) 11		(1) 1	(12) 12
NO ABNORMALITY DETECTED					

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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
CARDIOVASCULAR SYSTEM					
HEART					
NO ABNORMALITY DETECTED	(11) 10		(1) 1	(12) 12	
CARDIOMYOPATHY.	1				
AORTA					
NO ABNORMALITY DETECTED	(11) 11		(1) 1	(12) 12	

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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN		(11) 10	(10) 9	(11) 3 4	(12) 1 6
NO ABNORMALITY DETECTED					
PIGMENT INCREASED.					
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.		1	1	8	10
HEMATOPOIESIS, INCREASED.					1
ATROPHY, LYMPHOID.					
THYMUS		(11) 11	(1) 1	(1) 1	(12) 12
NO ABNORMALITY DETECTED					
NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING.					
MANDIBULAR LYMPH NODE		(11) 11		(1) 1	(12) 11 1
NO ABNORMALITY DETECTED					
CONGESTION.					

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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)					
	Males					
	TREATMENT (mg/kg/day)	0	25	100	500	
		I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
MESENTERIC LYMPH NODE		(11) 11		(1) 1	(12) 12	
NO ABNORMALITY DETECTED						
BONE MARROW		(11) 11		(1) 1	(12) 12	
NO ABNORMALITY DETECTED						

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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	TREATMENT (mg/kg/day)	Males			
		0	25	100	500
		I	III	V	VII
ENDOCRINE SYSTEM					
PITUITARY GLAND		(11) 11		(1) 1	(12) 12
NO ABNORMALITY DETECTED					
THYROID GLAND		(11) 5	(10) 1	(11) 9	(12) 11
NO ABNORMALITY DETECTED					
HYPERTROPHY, FOLLICULAR.		6	10	10	11
ALTERATION, COLLOID.				1	
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					
PARATHYROID GLANDS		(9) 9		(1) 1	(12) 12
NO ABNORMALITY DETECTED					
ADRENAL GLANDS		(11) 11		(1) 1	(12) 12
NO ABNORMALITY DETECTED					

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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
Males					
NERVOUS SYSTEM					
BRAIN		(11)		(1)	(12)
NO ABNORMALITY DETECTED		11		1	12
SPINAL CORD		(11)		(1)	(12)
NO ABNORMALITY DETECTED		11		1	12
SCIATIC NERVE		(11)		(1)	(12)
NO ABNORMALITY DETECTED		11		1	12

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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
MUSCULAR AND SKELETAL SYSTEM					
SKELETAL MUSCLE	(11)		(1)	(12)	
NO ABNORMALITY DETECTED	11		1	12	
FEMUR/KNEE JOINT	(11)		(1)	(12)	
NO ABNORMALITY DETECTED	11		1	12	
STERNUM	(11)		(1)	(12)	
NO ABNORMALITY DETECTED	11		1	12	

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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	TREATMENT (mg/kg/day)	LESION INCIDENCE (Animal #)				
		Males				
		0	25	100	500	
		I	III	V	VII	
REPRODUCTIVE SYSTEM						
TESTES		(11) 11		(1) 1	(12) 12	
NO ABNORMALITY DETECTED						
EPIDIDYMIDES		(11) 11		(1) 1	(12) 12	
NO ABNORMALITY DETECTED						
PROSTATE		(11) 8 3		(1) 1	(11) 10 1	
NO ABNORMALITY DETECTED						
INFLAMMATION, SUBACUTE/CHRONIC.						
SEMINAL VESICLES		(11) 10 1		(1) 1	(12) 12	
NO ABNORMALITY DETECTED						
INFLAMMATION, SUBACUTE/CHRONIC.						

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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)					
	Males					
	TREATMENT (mg/kg/day)	0	25	100	500	
		I	III	V	VII	
CUTANEOUS SYSTEM						
SKIN						
NO ABNORMALITY DETECTED		(11)		(1)	(12)	
ALOPECIA/HYPOTRICHOSIS.		11		1	11	
					1	
SPECIAL SENSES SYSTEM						
EYE(S) WITH OPTIC NERVE						
NO ABNORMALITY DETECTED		(11)		(1)	(12)	
OPTIC NERVE NOT PRESENT.		10			8	
HEMORRHAGE/INFLAMMATION (BLEEDING PROCEDURE).		1		1	1	
FOLD/ROSETTE, RETINAL.					2	

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

LESIONS	LESION INCIDENCE (NUMERIC)	
	Males	
	TREATMENT (mg/kg/day)	500 VII
	0 I	
DIGESTIVE SYSTEM		
LIVER		(10)
NO ABNORMALITY DETECTED		6
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.		4
HYPERTROPHY, CENTRILOBULAR.		
FATTY CHANGE, MEDIAN CLEFT.		(10)
		3
		1
		7
		1
URINARY SYSTEM		
KIDNEYS		(10)
NO ABNORMALITY DETECTED		7
NEPHROPATHY, CHRONIC PROGRESSIVE.		3
		(10)
		2
		8

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

LESIONS	LESION INCIDENCE (NUMERIC)	
	TREATMENT (mg/kg/day)	Males
	0	500
	I	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM		
SPLEEN		
NO ABNORMALITY DETECTED	(10)	(10)
PIGMENT INCREASED.	10	2
HEMATOPOIESIS, INCREASED.		7
		8
ENDOCRINE SYSTEM		
THYROID GLAND		
NO ABNORMALITY DETECTED	(10)	(10)
HYPERTROPHY, FOLLICULAR.	4	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 40 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Animal #)				
		Males				
		0	25	100	500	
		I	III	V	VII	
DIGESTIVE SYSTEM						
LIVER		(4)	(5)	(4)	(5)	
NO ABNORMALITY DETECTED		1	3	2	3	
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.		2	1	1		
FATTY CHANGE, PERIPORTAL.		1				
FATTY CHANGE, MEDIAN CLEFT.			1	2	1	
FATTY CHANGE, CENTRILOBULAR.					1	
URINARY SYSTEM						
KIDNEYS		(4)	(5)	(4)	(5)	
NO ABNORMALITY DETECTED			1	1	3	
NEPHROPATHY, CHRONIC PROGRESSIVE.		4	4	3	2	

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 MICROSCOPIC OBSERVATIONS IN MALE RATS -
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
(THREE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)					
	Males					
	TREATMENT (mg/kg/day)	0	25	100	500	
		I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
SPLEEN		(4)	(5)	(4)	(5)	
NO ABNORMALITY DETECTED		4	4	3	5	
HEMATOPOIESIS, INCREASED.			1	1		
ENDOCRINE SYSTEM						
THYROID GLAND		(4)	(5)	(4)	(5)	
NO ABNORMALITY DETECTED		3				
HYPERTROPHY, FOLLICULAR.						
ALTERATION, COLLOID.		1	5	4	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 41

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
DIGESTIVE SYSTEM						
LIVER		(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		5	10	1		
NECROSIS, INDIVIDUAL CELL.					2	
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.		3		9	2	
HYPERTROPHY, CENTRILOBULAR.					10	
FATTY CHANGE, MEDIAN CLEFT.		2				
PANCREAS		(10)			(10)	
NO ABNORMALITY DETECTED		9			10	
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.		1				
ESOPHAGUS		(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 41 (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)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
DIGESTIVE SYSTEM						
STOMACH						
NO ABNORMALITY DETECTED		(10)				(10)
EROSION/ULCER, ACUTE.		10				9
						1
DUODENUM						
NO ABNORMALITY DETECTED		(10)				(10)
		10				10
JEJUNUM						
NO ABNORMALITY DETECTED		(10)				(10)
		10				10
ILEUM						
NO ABNORMALITY DETECTED		(10)				(10)
		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 41 (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)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
DIGESTIVE SYSTEM						
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 41 (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)			
		Females			
		0	25	100	500
		II	IV	VI	VIII
URINARY SYSTEM					
KIDNEYS					
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)
NEPHROPATHY, CHRONIC PROGRESSIVE.		8	7	5	5
INFLAMMATION, LYMPHOID, CORTICAL.		2	2	5	5
URINARY BLADDER					
NO ABNORMALITY DETECTED		(10)			(10)
		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 41 (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)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
RESPIRATORY SYSTEM						
LUNGS						
NO ABNORMALITY DETECTED		(10) 10				(10) 10
TRACHEA						
NO ABNORMALITY DETECTED		(10) 10				(10) 10
PHARYNX/LARYNX						
NO ABNORMALITY DETECTED		(10) 10				(10) 10
NOSE I & II						
NO ABNORMALITY DETECTED		(10) 10				(10) 10
NOSE III & IV						
NO ABNORMALITY DETECTED		(10) 10				(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 41 (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	25	100	500
		II	IV	VI	VIII
CARDIOVASCULAR SYSTEM					
HEART					
NO ABNORMALITY DETECTED		(10) 10			(10) 10
AORTA					
NO ABNORMALITY DETECTED		(10) 10			(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 41 (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)	Females			
	0	25	100	500	
	II	IV	VI	VIII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	9	9	4		
PIGMENT INCREASED.	1			10	
HEMATOPOIESIS, INCREASED.		1	6	7	
THYMUS	(10)			(10)	
NO ABNORMALITY DETECTED	10			10	
MANDIBULAR LYMPH NODE	(10)			(10)	
NO ABNORMALITY DETECTED	10			9	
CONGESTION.				1	
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 41 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC)			
		Females			
		0	25	100	500
		II	IV	VI	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
BONE MARROW					
NO ABNORMALITY DETECTED		(10) 10			(10) 10
ENDOCRINE SYSTEM					
PITUITARY GLAND					
NO ABNORMALITY DETECTED		(10) 10	(1) 1 1		(10) 10
NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING.					
THYROID GLAND					
NO ABNORMALITY DETECTED		(10) 7	(10) 4	(10) 2	(10) 9
HYPERTROPHY, FOLLICULAR. ALTERATION, COLLOID.		3	6	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 41 (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)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
ENDOCRINE SYSTEM						
PARATHYROID GLANDS		(8)			(9)	
NO ABNORMALITY DETECTED		8			9	
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 41 (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	25	100	500
		II	IV	VI	VIII
Females					
NERVOUS SYSTEM					
BRAIN					
NO ABNORMALITY DETECTED		(10) 10			(10) 10
SPINAL CORD					
NO ABNORMALITY DETECTED		(10) 10			(10) 10
SCIATIC NERVE					
NO ABNORMALITY DETECTED		(10) 10			(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 41 (Continued)

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

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	500
		II	IV	VI	VIII
MUSCULAR AND SKELETAL SYSTEM					
SKELETAL MUSCLE		(10) 10			(10) 10
NO ABNORMALITY DETECTED					
FEMUR/KNEE JOINT		(10) 10			(10) 10
NO ABNORMALITY DETECTED					
STERNUM		(10) 10			(10) 10
NO ABNORMALITY DETECTED					

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)

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

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	Females			
		0	25	100	500
		II	IV	VI	VIII
REPRODUCTIVE SYSTEM					
OVARIES					
NO ABNORMALITY DETECTED		(10) 10			(10) 10
UTERUS					
NO ABNORMALITY DETECTED		(10) 9	(1) 1	(1) 1	(10) 7 3
DILATATION, LUMEN.					
MAMMARY GLAND (FEMALE)					
NO ABNORMALITY DETECTED		(10) 10		(1) 1	(10) 10
HYPERPLASIA, LOBULAR.					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 41 (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)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
CUTANEOUS SYSTEM						
SKIN						
NO ABNORMALITY DETECTED		(10)				(10)
ALOPECIA/HYPOTRICHOSIS.		10				9
						1
SPECIAL SENSES SYSTEM						
EYE(S) WITH OPTIC NERVE						
NO ABNORMALITY DETECTED		(10)				(10)
HEMORRHAGE/INFLAMMATION (BLEEDING PROCEDURE).		10				9
						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 41 (Continued)

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

LESIONS	LESION INCIDENCE (NUMERIC)	
	Females	
	TREATMENT (mg/kg/day)	0 500 II VIII
DIGESTIVE SYSTEM		
LIVER		
NO ABNORMALITY DETECTED	(10)	(10)
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.	9	9
HYPERTROPHY, CENTRILOBULAR.	1	1
STOMACH		
EROSION/ULCER, ACUTE.	(1)	(1)
URINARY SYSTEM		
KIDNEYS		
NO ABNORMALITY DETECTED	(10)	(10)
NEPHROPATHY, CHRONIC PROGRESSIVE.	8	2
HYDRONEPHROSIS, UNILATERAL.	1	8
	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 41 (Continued)

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

LESIONS	LESION INCIDENCE (NUMERIC)		
	Females		
	TREATMENT (mg/kg/day)	0	500
		II	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM			
SPLEEN			
NO ABNORMALITY DETECTED		(10)	(10)
HEMATOPOIESIS, INCREASED.		10	9
			1
ENDOCRINE SYSTEM			
THYROID GLAND			
NO ABNORMALITY DETECTED		(10)	(10)
HYPERTROPHY, FOLLICULAR.		9	6
ALTERATION, COLLOID.		1	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 41 (Continued)

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

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	500
		II	IV	VI	VIII
		Females			
DIGESTIVE SYSTEM					
LIVER		(4) 2	(5) 5	(5) 5	(5) 3 1
NO ABNORMALITY DETECTED		1			1
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.		1			
HYPERPLASIA, BILIARY.					
FATTY CHANGE, MEDIAN CLEFT.					
URINARY SYSTEM					
KIDNEYS		(4) 2	(5) 3	(5) 1	(5) 1
NO ABNORMALITY DETECTED		1	2	4	4
PYELONEPHRITIS, UNILATERAL.					
NEPHROPATHY, CHRONIC PROGRESSIVE.					

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)

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

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
TREATMENT (mg/kg/day)	0	25	100	500	
	II	IV	VI	VIII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN	(4) 4	(5) 5	(5) 3 2	(5) 3 2	
NO ABNORMALITY DETECTED PIGMENT INCREASED.					
ENDOCRINE SYSTEM					
THYROID GLAND	(4) 3 1	(5) 2 3	(4) 4	(4) 1 3	
NO ABNORMALITY DETECTED ALTERATION, COLLOID.					

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 42

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
Males					
DIGESTIVE SYSTEM					
LIVER		(11) 6	(10) 4	(11) 1	(12)
NO ABNORMALITY DETECTED					
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.					
minimal		4	1	1	
total observations per lesion		4	1	1	
HYPERTROPHY, CENTRILOBULAR.					
minimal		1	5	8	2
mild					
total observations per lesion		1	5	2	10
FATTY CHANGE, PERIPORTAL.					
minimal		1		10	12
total observations per lesion		1			
FATTY CHANGE, MEDIAN CLEFT.					
minimal		2	2	1	
total observations per lesion		2	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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
DIGESTIVE SYSTEM					
PANCREAS		(11)		(1)	(12)
NO ABNORMALITY DETECTED		8		1	12
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.		3			
minimal		3			
total observations per lesion					
ESOPHAGUS		(11)		(1)	(12)
NO ABNORMALITY DETECTED		11		1	12
STOMACH		(11)		(1)	(12)
NO ABNORMALITY DETECTED		11		1	12
DUODENUM		(11)		(1)	(12)
NO ABNORMALITY DETECTED		11		1	12

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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
DIGESTIVE SYSTEM					
JEJUNUM		(11) 11		(1) 1	(12) 12
NO ABNORMALITY DETECTED				1	
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					
ILEUM		(11) 11		(1) 1	(12) 12
NO ABNORMALITY DETECTED				1	
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					
CECUM		(11) 11		(1) 1	(12) 12
NO ABNORMALITY DETECTED				1	
COLON		(11) 11		(1) 1	(12) 12
NO ABNORMALITY DETECTED					

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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (Animal #)	
						Males	
	0	25	100	500			
	I	III	V	VII			
DIGESTIVE SYSTEM							
RECTUM	(11) 11		(1) 1	(12) 12			
NO ABNORMALITY DETECTED							
SALIVARY GLANDS	(11) 11		(1) 1	(12) 12			
NO ABNORMALITY DETECTED							

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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (Animal #)				
						Males				
		0	25	100	500					
		I	III	V	VII					
URINARY SYSTEM										
KIDNEYS		(11)	(10)	(11)	(12)					
NO ABNORMALITY DETECTED		5	7	4	4					
PYELONEPHRITIS, BILATERAL.				1						
minimal		1								
mild										
moderate										
total observations per lesion		1		1						
NEPHROPATHY, CHRONIC PROGRESSIVE.										
minimal		4	2	5	6					
mild		1			1					
total observations per lesion		5	2	5	7					
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.										
minimal										
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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
URINARY SYSTEM					
KIDNEYS (continued)					
HYDRONEPHROSIS, UNILATERAL.					
minimal			1	1	1
mild					
severe					1
total observations per lesion			1	2	1
HYDRONEPHROSIS, BILATERAL.					
mild			1		1
total observations per lesion			1		1
NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING.				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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (Animal #)				
						Males				
	0	25	100	500		I	III	V	VII	
URINARY SYSTEM										
URINARY BLADDER										
NO ABNORMALITY DETECTED	(11)	(1)	(1)	(12)		9	1	1	11	
INFLAMMATION, SUBACUTE/CHRONIC.										
minimal	2	1								
mild										
moderate										1
total observations per lesion	2	1		1						1
HYPERPLASIA, TRANSITIONAL CELL.										
minimal	1	1								
moderate										
total observations per lesion	1	1								
HEMORRHAGE.										
moderate	1									1
total observations per lesion	1									1
CALCULUS/CALCULI.	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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (Animal #)				
						Males				
	0	25	100	500						
	I	III	V	VII						
RESPIRATORY SYSTEM										
LUNGS	(11)		(1)	(12)						
NO ABNORMALITY DETECTED	11		1	12						
TRACHEA	(10)		(1)	(12)						
NO ABNORMALITY DETECTED	10		1	12						
PHARYNX/LARYNX	(11)		(1)	(11)						
NO ABNORMALITY DETECTED	11		1	11						
NOSE I & II	(11)		(1)	(12)						
NO ABNORMALITY DETECTED	11		1	12						
NOSE III & IV	(11)		(1)	(12)						
NO ABNORMALITY DETECTED	11		1	12						

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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (Animal #)	
						Males	
	0	25	100	500			
	I	III	V	VII			
CARDIOVASCULAR SYSTEM							
HEART	(11)		(1)	(12)			
NO ABNORMALITY DETECTED	10		1	12			
CARDIOMYOPATHY.	1						
minimal	1						
total observations per lesion							
AORTA	(11)		(1)	(12)			
NO ABNORMALITY DETECTED	11		1	12			

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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Animal #)				
		Males				
		0	25	100	500	
		I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
SPLEEN		(11) 10	(10) 9	(11) 3	(12) 1	
NO ABNORMALITY DETECTED						
PIGMENT INCREASED.						
minimal				4	6	
total observations per lesion				4	6	
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.						
minimal		1				
total observations per lesion		1				
HEMATOPOIESIS, INCREASED.						
minimal						
mild			1	8	9	
total observations per lesion			1	8	10	
ATROPHY, LYMPHOID.						
mild						
total observations per lesion					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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)					
	Males					
	TREATMENT (mg/kg/day)	0	25	100	500	
		I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
THYMUS						
NO ABNORMALITY DETECTED		(11)	(1)	(1)	(12)	
NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING.		11	1	1	12	
MANDIBULAR LYMPH NODE						
NO ABNORMALITY DETECTED		(11)		(1)	(12)	
CONGESTION.		11		1	11	
minimal					1	
total observations per lesion					1	
MESENTERIC LYMPH NODE						
NO ABNORMALITY DETECTED		(11)		(1)	(12)	
		11		1	12	
BONE MARROW						
NO ABNORMALITY DETECTED		(11)		(1)	(12)	
		11		1	12	

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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (Animal #)				
						Males				
	0	25	100	500		I	III	V	VII	
ENDOCRINE SYSTEM										
PITUITARY GLAND										
NO ABNORMALITY DETECTED	(11) 11		(1) 1	(12) 12						
THYROID GLAND										
NO ABNORMALITY DETECTED	(11) 5	(10)	(11) 1	(12) 1						
HYPERTROPHY, FOLLICULAR.										
minimal		1	9	3						
mild				8						
total observations per lesion		1	9	11						
ALTERATION, COLLOID.										
minimal	4	3	1	1						
mild	2	2	3	1						
moderate		1	2	3						
severe		4	4	6						
total observations per lesion	6	10	10	11						
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.										

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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (Animal #)	
						Males	
	0	25	100	500			
	I	III	V	VII			
ENDOCRINE SYSTEM							
PARATHYROID GLANDS							
NO ABNORMALITY DETECTED	(9)		(1)	(12)			
	9		1	12			
ADRENAL GLANDS							
NO ABNORMALITY DETECTED	(11)		(1)	(12)			
	11		1	12			

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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (Animal #)				
						Males				
						0	25	100	500	
						I	III	V	VII	
NERVOUS SYSTEM										
BRAIN						(11) 11		(1) 1	(12) 12	
NO ABNORMALITY DETECTED										
SPINAL CORD						(11) 11		(1) 1	(12) 12	
NO ABNORMALITY DETECTED										
SCIATIC NERVE						(11) 11		(1) 1	(12) 12	
NO ABNORMALITY DETECTED										

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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (Animal #)				
						Males				
	0	25	100	500						
	I	III	V	VII						
MUSCULAR AND SKELETAL SYSTEM										
SKELETAL MUSCLE	(11) 11		(1) 1							
NO ABNORMALITY DETECTED										
FEMUR/KNEE JOINT	(11) 11		(1) 1							
NO ABNORMALITY DETECTED										
STERNUM	(11) 11		(1) 1							
NO ABNORMALITY DETECTED										

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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
 NON-NEOPLASTIC LESIONS

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
REPRODUCTIVE SYSTEM					
TESTES		(11)		(1)	(12)
NO ABNORMALITY DETECTED		11		1	12
EPIDIDYMIDES		(11)		(1)	(12)
NO ABNORMALITY DETECTED		11		1	12
PROSTATE		(11)		(1)	(11)
NO ABNORMALITY DETECTED		8			10
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal		1		1	1
mild		1			
moderate		1			
total observations per lesion		3		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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
REPRODUCTIVE SYSTEM					
SEMINAL VESICLES		(11)		(1)	(12)
NO ABNORMALITY DETECTED		10		1	12
INFLAMMATION, SUBACUTE/CHRONIC.					
mild		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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Animal #)				
		Males				
		0	25	100	500	
		I	III	V	VII	
CUTANEOUS SYSTEM						
SKIN		(11) 11		(1) 1	(12) 11	
NO ABNORMALITY DETECTED						1
ALOPECIA/HYPOTRICHOSIS.						1
minimal						
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 42 (Continued)

INCIDENCES OF LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS -
NON-NEOPLASTIC LESIONS
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
Males					
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE		(11)		(1)	(12)
NO ABNORMALITY DETECTED		10			8
OPTIC NERVE NOT PRESENT.					1
HEMORRHAGE/INFLAMMATION (BLEEDING PROCEDURE).		1			2
minimal					
severe				1	
total observations per lesion		1		1	2
FOLD/ROSETTE, RETINAL.					
minimal					
total observations per lesion					2
					2

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 42 (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)	Males
	0	500
	I	VII
DIGESTIVE SYSTEM		
LIVER	(10)	(10)
NO ABNORMALITY DETECTED	6	3
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.		
minimal	4	1
total observations per lesion	4	1
HYPERTROPHY, CENTRIOLOBULAR.		
minimal		7
total observations per lesion		7
FATTY CHANGE, MEDIAN CLEFT.		
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 42 (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)	Males
	0	500
	I	VII
URINARY SYSTEM		
KIDNEYS		
NO ABNORMALITY DETECTED	(10)	(10)
NEPHROPATHY, CHRONIC PROGRESSIVE.	7	2
minimal	3	8
total observations per lesion	3	8

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 42 (Continued)

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

LESIONS	LESION INCIDENCE (NUMERIC)	
	Males	
	TREATMENT (mg/kg/day)	
	0	500
	I	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM		
SPLEEN		
NO ABNORMALITY DETECTED	(10)	(10)
PIGMENT INCREASED.	10	2
minimal		7
total observations per lesion		7
HEMATOPOIESIS, INCREASED.		
minimal		8
total observations per lesion		8

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 42 (Continued)

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

LESIONS	LESION INCIDENCE (NUMERIC)	
	Males	
	TREATMENT (mg/kg/day)	0 500 I VII
ENDOCRINE SYSTEM		
THYROID GLAND		(10) (10)
NO ABNORMALITY DETECTED		4
HYPERTROPHY, FOLLICULAR		
minimal		8
total observations per lesion		8
ALTERATION, COLLOID.		
minimal	6	2
mild		2
moderate		3
severe		3
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 42 (Continued)

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

LESIONS	LESION INCIDENCE (Animal #)				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
DIGESTIVE SYSTEM					
LIVER		(4)	(5)	(4)	(5)
NO ABNORMALITY DETECTED		1	3	2	3
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.					
minimal		2	1	1	
total observations per lesion		2	1	1	
FATTY CHANGE, PERIportal.					
minimal		1			
total observations per lesion		1			
FATTY CHANGE, MEDIAN CLEFT.					
minimal			1	2	1
total observations per lesion			1	2	1
FATTY CHANGE, CENTRILobular.					
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 42 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Animal #)				
		Males				
		0	25	100	500	
		I	III	V	VII	
URINARY SYSTEM						
KIDNEYS		(4)	(5)	(4)	(5)	
NO ABNORMALITY DETECTED			1	1	3	
NEPHROPATHY, CHRONIC PROGRESSIVE.						
minimal		4	3	3	2	
mild			1			
total observations per lesion		4	4	3	2	

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 42 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Animal #)				
		Males				
		0	25	100	500	
		I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
SPLEEN		(4) 4	(5) 4	(4) 3	(5) 5	
NO ABNORMALITY DETECTED						
HEMATOPOIESIS, INCREASED.						
minimal			1	1		
total observations per lesion			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 42 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)	Males					LESION INCIDENCE (Animal #)
		0	25	100	500		
		I	III	V	VII		
ENDOCRINE SYSTEM							
THYROID GLAND		(4)	(5)	(4)	(5)		
NO ABNORMALITY DETECTED		3					
HYPERTROPHY, FOLLICULAR.							
minimal							4
total observations per lesion							4
ALTERATION, COLLOID.							
minimal		1					
mild							
moderate			2	1			2
severe			3				1
total observations per lesion		1	5	4			2
							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 43

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)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
DIGESTIVE SYSTEM						
LIVER		(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		5	10	1		
NECROSIS, INDIVIDUAL CELL.						
minimal						1
mild						1
total observations per lesion						2
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.						
minimal		3				2
total observations per lesion		3				2
HYPERTROPHY, CENTRILOBULAR.						
minimal						1
mild				9		8
moderate						1
total observations per lesion				9		10
FATTY CHANGE, MEDIAN CLEFT.						
minimal						1
mild		1				
total observations per lesion		2				

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 43 (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)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
DIGESTIVE SYSTEM						
PANCREAS						
NO ABNORMALITY DETECTED		(10)				(10)
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal		9				10
total observations per lesion		1				
		1				
ESOPHAGUS						
NO ABNORMALITY DETECTED		(10)				(10)
		10				10
STOMACH						
NO ABNORMALITY DETECTED		(10)				(10)
EROSION/ULCER, ACUTE, minimal		10				9
total observations per lesion						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 43 (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)	Females			
	0	25	100	500	
	II	IV	VI	VIII	
DIGESTIVE SYSTEM					
DUODENUM					
NO ABNORMALITY DETECTED	(10) 10				(10) 10
JEJUNUM					
NO ABNORMALITY DETECTED	(10) 10				(10) 10
ILEUM					
NO ABNORMALITY DETECTED	(10) 10				(10) 10
CECUM					
NO ABNORMALITY DETECTED	(10) 10				(10) 10
COLON					
NO ABNORMALITY DETECTED	(10) 10				(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 43 (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)	Females			
	0	25	100	500	
	II	IV	VI	VIII	
DIGESTIVE SYSTEM					
RECTUM					
NO ABNORMALITY DETECTED	(10) 10				(10) 10
SALIVARY GLANDS					
NO ABNORMALITY DETECTED	(10) 10				(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 43 (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)			
		Females			
		0	25	100	500
		II	IV	VI	VIII
URINARY SYSTEM					
KIDNEYS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		8	7	5	5
NEPHROPATHY, CHRONIC PROGRESSIVE.					
minimal		2	2	4	3
mild				1	1
moderate					1
total observations per lesion				5	5
INFLAMMATION, LYMPHOID, CORTICAL.		2	2		
minimal			1		
total observations per lesion			1		
URINARY BLADDER		(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 43 (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	25	100	500
		II	IV	VI	VIII
RESPIRATORY SYSTEM					
LUNGS		(10) 10			(10) 10
NO ABNORMALITY DETECTED					
TRACHEA		(10) 10			(10) 10
NO ABNORMALITY DETECTED					
PHARYNX/LARYNX		(10) 10			(10) 10
NO ABNORMALITY DETECTED					
NOSE I & II		(10) 10			(10) 10
NO ABNORMALITY DETECTED					
NOSE III & IV		(10) 10			(10) 10
NO ABNORMALITY DETECTED					

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 43 (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)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
CARDIOVASCULAR SYSTEM						
HEART		(10)			(10)	
NO ABNORMALITY DETECTED		10			10	
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 43 (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)				
						Females				
	0	25	100	500						
	II	IV	VI	VIII						
LYMPHATIC AND HEMATOPOIETIC SYSTEM										
SPLEEN	(10)	(10)	(10)	(10)						
NO ABNORMALITY DETECTED	9	9	4							
PIGMENT INCREASED.										
minimal	1									10
total observations per lesion	1									10
HEMATOPOIESIS, INCREASED.										
minimal										5
mild		1	6							2
total observations per lesion		1	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 43 (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)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
THYMUS		(10)			(10)	
NO ABNORMALITY DETECTED		10			10	
MANDIBULAR LYMPH NODE		(10)			(10)	
NO ABNORMALITY DETECTED		10			9	
CONGESTION.					1	
mild					1	
total observations per lesion						
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 43 (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)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
ENDOCRINE SYSTEM						
PITUITARY GLAND						
NO ABNORMALITY DETECTED		(10) 10	(1) 1		(10) 10	
NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING.			1			
THYROID GLAND						
NO ABNORMALITY DETECTED		(10) 7	(10) 4	(10)	(10)	
HYPERTROPHY, FOLLICULAR.						
minimal				2	6	
mild					3	
total observations per lesion				2	9	
ALTERATION, COLLOID.						
minimal		3	6	4	2	
mild				5	4	
moderate				1	3	
severe					1	
total observations per lesion		3	6	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 43 (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	25	100	500
		II	IV	VI	VIII
ENDOCRINE SYSTEM					
PARATHYROID GLANDS		(8) 8			(9) 9
NO ABNORMALITY DETECTED					
ADRENAL GLANDS		(10) 10			(10) 10
NO ABNORMALITY DETECTED					

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 43 (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	25	100	500
		II	IV	VI	VIII
NERVOUS SYSTEM					
BRAIN		(10) 10			(10) 10
NO ABNORMALITY DETECTED					
SPINAL CORD		(10) 10			(10) 10
NO ABNORMALITY DETECTED					
SCIATIC NERVE		(10) 10			(10) 10
NO ABNORMALITY DETECTED					

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 43 (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	25	100	500	Females
		II	IV	VI	VIII	
MUSCULAR AND SKELETAL SYSTEM						
SKELETAL MUSCLE		(10) 10			(10) 10	
NO ABNORMALITY DETECTED						
FEMUR/KNEE JOINT		(10) 10			(10) 10	
NO ABNORMALITY DETECTED						
STERNUM		(10) 10			(10) 10	
NO ABNORMALITY DETECTED						

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 43 (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)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
REPRODUCTIVE SYSTEM						
OVARIES						
NO ABNORMALITY DETECTED		(10) 10			(10) 10	
UTERUS						
NO ABNORMALITY DETECTED		(10) 9		(1)	(10) 7	
DILATATION, LUMEN.						
minimal						
mild		1		1	3	
total observations per lesion		1		1	3	
MAMMARY GLAND (FEMALE)						
NO ABNORMALITY DETECTED		(10) 10		(1)	(10) 10	
HYPERPLASIA, LOBULAR.						
mild						
total observations per lesion				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 43 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)					Females					LESION INCIDENCE (NUMERIC)	
	0	25	100	500		II	IV	VI	VIII			
CUTANEOUS SYSTEM												
SKIN												
NO ABNORMALITY DETECTED						(10)					(10)	
ALOPECIA/HYPOTRICHOSIS.						10					9	
mild											1	
total observations per lesion											1	
SPECIAL SENSES SYSTEM												
EYE(S) WITH OPTIC NERVE												
NO ABNORMALITY DETECTED						(10)					(10)	
HEMORRHAGE/INFLAMMATION (BLEEDING PROCEDURE).						10					9	
											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 43 (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)	Females
	0	500
	II	VIII
DIGESTIVE SYSTEM		
LIVER		
NO ABNORMALITY DETECTED	(10)	(10)
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.	9	9
minimal	1	1
total observations per lesion	1	1
HYPERTROPHY, CENTRILOBULAR.		
minimal		1
total observations per lesion		1
STOMACH		
EROSION/ULCER, ACUTE.		(1)
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 43 (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)	Females
	0	500
	II	VIII
URINARY SYSTEM		
KIDNEYS		
NO ABNORMALITY DETECTED	(10)	(10)
NEPHROPATHY, CHRONIC PROGRESSIVE.	8	2
minimal	1	6
mild		1
moderate		1
total observations per lesion	1	8
HYDRONEPHROSIS, UNILATERAL.		
moderate	1	1
total observations per lesion	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 43 (Continued)

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

LESIONS	LESION INCIDENCE (NUMERIC)	
	Females	
	TREATMENT (mg/kg/day)	0 500 II VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM		
SPLEEN		(10) (10)
NO ABNORMALITY DETECTED		10 9
HEMATOPOIESIS, INCREASED.		
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 43 (Continued)

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

LESIONS	LESION INCIDENCE (NUMERIC)	
	Females	
	TREATMENT (mg/kg/day)	
	0	500
	II	VIII
ENDOCRINE SYSTEM		
THYROID GLAND		
NO ABNORMALITY DETECTED	(10)	(10)
HYPERTROPHY, FOLLICULAR.	9	
minimal		5
mild		1
total observations per lesion		6
ALTERATION, COLLOID.		
minimal	1	1
mild		4
moderate		5
total observations per lesion	1	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 43 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
DIGESTIVE SYSTEM						
LIVER						
NO ABNORMALITY DETECTED		(4)	(5)	(5)	(5)	
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.		2	5	5	3	
mild					1	
total observations per lesion					1	
HYPERPLASIA, BILIARY.					1	
minimal		1				
total observations per lesion		1				
FATTY CHANGE, MEDIAN CLEFT.						
minimal		1			1	
total observations per lesion		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 43 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
URINARY SYSTEM						
KIDNEYS						
NO ABNORMALITY DETECTED		(4) 2	(5) 3	(5) 1	(5) 1	
PYELONEPHRITIS, UNILATERAL.		1				
minimal		1				
total observations per lesion		2	2	2	2	
NEPHROPATHY, CHRONIC PROGRESSIVE.						
minimal				1	1	
mild				1	1	
moderate				4	4	
total observations per lesion		2	2	4	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 43 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (NUMERIC)				
						Females				
	0	25	100	500						
	II	IV	VI	VIII						
LYMPHATIC AND HEMATOPOIETIC SYSTEM										
SPLEEN										
NO ABNORMALITY DETECTED	(4)	(5)	(5)	(5)						
PIGMENT INCREASED.	4	5	3	3						
minimal			1	1						
total observations per lesion			2	2						

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 43 (Continued)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC)				
		Females				
		0	25	100	500	
		II	IV	VI	VIII	
ENDOCRINE SYSTEM						
THYROID GLAND						
NO ABNORMALITY DETECTED		(4)	(5)	(4)	(4)	
ALTERATION, COLLOID.		3	2		1	
minimal		1	3	3	2	
mild				1	1	
moderate						
total observations per lesion		1	3	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 44

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)					

	Males					
TREATMENT (mg/kg/day)	0	25	100	500		
	I	III	V	VII		
DIGESTIVE SYSTEM						
LIVER	(11)	(10)	(11)	(12)		
NO ABNORMALITY DETECTED	646360	646421	646477			
	646367	646423				
	646457	646426				
	646482	646454				
	646489					
	646492					
	646374	646443	646385			
	646379					
	646420					
	646485					
	646379	646370	646349	646343		
		646399	646373	646346		
		646443	646385	646347		
		646458	646435	646380		
		646471	646455	646388		
			646456	646407		
			646463	646413		
			646469	646422		
			646472	646433		
			646488	646437		
				646442		
				646475		
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.						
HYPERTROPHY, CENTRILOBULAR.						

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
DIGESTIVE SYSTEM					
LIVER					
FATTY CHANGE, PERIPORTAL.	(11)	(10)	(11)	(12)	
FATTY CHANGE, MEDIAN CLEFT.	646420	646420	646414	646456	
	646427	646458			

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	TREATMENT (mg/kg/day)	Males			
	0	25	100	500	
	I	III	V	VII	
DIGESTIVE SYSTEM					
PANCREAS	(11)		(1)	(12)	
NO ABNORMALITY DETECTED	646360		646477	646343	
	646367			646346	
	646420			646347	
	646427			646380	
	646457			646388	
	646482			646407	
	646485			646413	
	646492			646422	
				646433	
				646437	
				646442	
				646475	
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.	646374				
	646379				
	646489				

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
DIGESTIVE SYSTEM					
ESOPHAGUS	(11) 646360 646367 646374 646379 646420 646427 646457		(1) 646477	(12) 646343 646346 646347 646380 646388 646407 646413 646422 646433 646437 646442 646475	
NO ABNORMALITY DETECTED					

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)						

	Males						
TREATMENT (mg/kg/day)	0	25	100	500			
	I	III	V	VII			
DIGESTIVE SYSTEM							
STOMACH	(11)		(1)	(12)			
NO ABNORMALITY DETECTED	646360	646367	646477	646343			
	646374	646379		646346			
	646420	646427		646347			
	646457			646380			
	646482			646388			
	646485			646407			
	646489			646413			
	646492			646422			
				646433			
				646437			
				646442			
				646475			

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
DIGESTIVE SYSTEM					
DUODENUM	(11)		(1)	(12)	
NO ABNORMALITY DETECTED	646360		646477	646343	
	646367			646346	
	646374			646347	
	646379			646380	
	646420			646388	
	646427			646407	
	646457			646413	
	646482			646422	
	646485			646433	
	646489			646437	
	646492			646442	
				646475	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
DIGESTIVE SYSTEM					
JEJUNUM	(11) 646360		(1) 646477	(12) 646343	
NO ABNORMALITY DETECTED	646367			646346	
	646374			646347	
	646379			646380	
	646420			646388	
	646427			646407	
	646457			646413	
	646482			646422	
	646485			646433	
	646489			646437	
	646492			646442	
			646477	646475	
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)						
	Males						
TREATMENT (mg/kg/day)							
	0	25	100	500			
	I	III	V	VII			
DIGESTIVE SYSTEM							
ILEUM							
NO ABNORMALITY DETECTED	(11) 646360 646367 646374 646379 646420 646427 646457 646482 646485 646489 646492		(1) 646477	(12) 646343 646346 646347 646380 646388 646407 646413 646422 646433 646437 646442 646475			
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.							

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC

(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
DIGESTIVE SYSTEM					
CECUM NO ABNORMALITY DETECTED	(11) 646360	(1) 646477	(12) 646343		
	646367		646346		
	646374		646347		
	646379		646380		
	646420		646388		
	646427		646407		
	646457		646413		
	646482		646422		
	646485		646433		
	646489		646437		
	646492		646442		
			646475		

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
 NEOPLASTIC AND NON-NEOPLASTIC
 (90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
DIGESTIVE SYSTEM					
COLON NO ABNORMALITY DETECTED	(11) 646360	(1) 646477	(12) 646343		
	646367		646346		
	646374		646347		
	646379		646380		
	646420		646388		
	646427		646407		
	646457		646413		
	646482		646422		
	646485		646433		
	646489		646437		
	646492		646442		
			646475		

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
DIGESTIVE SYSTEM					
RECTUM NO ABNORMALITY DETECTED	(11) 646360		(1) 646477	(12) 646343	
	646367			646346	
	646374			646347	
	646379			646380	
	646420			646388	
	646427			646407	
	646457			646413	
	646482			646422	
	646485			646433	
	646489			646437	
	646492			646442	
				646475	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
DIGESTIVE SYSTEM					
SALIVARY GLANDS NO ABNORMALITY DETECTED	(11)		(1)	(12)	
	646360		646477	646343	
	646367			646346	
	646374			646347	
	646379			646380	
	646420			646388	
	646427			646407	
	646457			646413	
	646482			646422	
	646485			646433	
	646489			646437	
	646492			646442	
				646475	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	TREATMENT (mg/kg/day)	Males			
	0	25	100	500	
	I	III	V	VII	
URINARY SYSTEM					
KIDNEYS	(11)	(10)	(11)	(12)	
NO ABNORMALITY DETECTED	646360	646399	646385	646343	
	646367	646414	646455	646413	
	646374	646421	646456	646433	
	646379	646423	646469	646437	
	646489	646454			
		646458			
		646471			
PYELONEPHRITIS, BILATERAL.	646420		646472	646380	
NEPHROPATHY, CHRONIC PROGRESSIVE.	646427	646370	646349	646346	
	646457	646426	646373	646347	
	646482		646435	646388	
	646485		646463	646407	
	646492		646477	646422	
				646442	
				646475	
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.				646442	
HYDRONEPHROSIS, UNILATERAL.				646422	
		646443	646435	646488	
HYDRONEPHROSIS, BILATERAL.					
NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING.		646426	646463	646380	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
URINARY SYSTEM					
URINARY BLADDER NO ABNORMALITY DETECTED	(11)	(1)	(1)	(12)	
	646360		646477	646343	
	646367			646346	
	646374			646347	
	646379			646388	
	646427			646407	
	646482			646413	
	646485			646422	
	646489			646433	
	646492			646437	
				646442	
				646475	
INFLAMMATION, SUBACUTE/CHRONIC. HYPERPLASIA, TRANSITIONAL CELL. HEMORRHAGE. CALCULUS/CALCULI.	646420	646426		646380	
	646457				
	646420	646426			
	646457				646380

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)					
	TREATMENT (mg/kg/day)	0	25	100	500	
		I	III	V	VII	
RESPIRATORY SYSTEM						
LUNGS		(11) 646360 646367 646374 646379 646420 646427 646457 646482 646485 646489 646492		(1) 646477	(12) 646343 646346 646347 646380 646388 646407 646413 646422 646433 646437 646442 646475	
NO ABNORMALITY DETECTED						

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)					
	Males					
	TREATMENT (mg/kg/day)	0	25	100	500	
		I	III	V	VII	
RESPIRATORY SYSTEM						
TRACHEA		(10) 646367 646374 646379 646420 646427 646457 646482 646485 646489 646492		(1) 646477	(12) 646343 646346 646347 646380 646388 646407 646413 646422 646433 646437 646442 646475	
NO ABNORMALITY DETECTED						

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
RESPIRATORY SYSTEM					
PHARYNX/LARYNX	(11) 646360 646367 646374 646379 646420 646427 646457 646482 646485 646489 646492		(1) 646477	(11) 646343 646346 646347 646388 646407 646413 646422 646433 646437 646442 646475	
NO ABNORMALITY DETECTED					

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)						
	Males						
	TREATMENT (mg/kg/day)	0	25	100	500		
	I	III	V	VII			
RESPIRATORY SYSTEM							
NOSE I & II	(11)	(1)	(12)				
NO ABNORMALITY DETECTED	646360	646477	646343				
	646367		646346				
	646374		646347				
	646379		646380				
	646420		646388				
	646427		646407				
	646457		646413				
	646482		646422				
	646485		646433				
	646489		646437				
	646492		646442				
			646475				

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)						
	Males						
	TREATMENT (mg/kg/day)	0	25	100	500		
RESPIRATORY SYSTEM		I	III	V	VII		
NOSE III & IV NO ABNORMALITY DETECTED	(11)			(1)	(12)		
	646360			646477	646343		
	646367				646346		
	646374				646347		
	646379				646380		
	646420				646388		
	646427				646407		
	646457				646413		
	646482				646422		
	646485				646433		
	646489				646437		
	646492				646442		
					646475		

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
CARDIOVASCULAR SYSTEM					
HEART					
NO ABNORMALITY DETECTED		(11) 646367 646374 646379 646420 646427 646457 646482 646485 646489 646492 646360		(1) 646477	(12) 646343 646346 646347 646380 646388 646407 646413 646422 646433 646437 646442 646475
CARDIOMYOPATHY.					

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)						
	Males						
	TREATMENT (mg/kg/day)	0	25	100	500		
		I	III	V	VII		
CARDIOVASCULAR SYSTEM							
AORTA		(11) 646360 646367 646374 646379 646420 646427 646457 646482 646485 646489 646492		(1) 646477	(12) 646343 646346 646347 646380 646388 646407 646413 646422 646433 646437 646442 646475		
NO ABNORMALITY DETECTED							

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN					
NO ABNORMALITY DETECTED					
	(11)	(10)	(11)	(12)	
	646360	646370	646385	646422	
	646367	646399	646469		
	646379	646414	646488		
	646420	646421			
	646427	646423			
	646457	646426			
	646482	646443			
	646485	646454			
	646489	646458			
	646492		646435	646343	
			646455	646388	
			646456	646407	
			646463	646433	
				646442	
				646475	
	646374	646471	646349	646343	
			646373	646346	
			646435	646347	
			646455	646388	
			646456	646407	
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL. HEMATOPOIESIS, INCREASED.					

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN HEMATOPOIESIS, INCREASED.	(11)	(10)	(11)	(12)	
			646463	646413	
			646472	646433	
			646477	646437	
				646442	
				646475	
				646380	
ATROPHY, LYMPHOID.					

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
THYMUS	(11)	(1)	(1)	(1)	(12)
NO ABNORMALITY DETECTED	646360			646477	646343
	646367				646346
	646374				646347
	646379				646380
	646420				646388
	646427				646407
	646457				646413
	646482				646422
	646485				646433
	646489				646437
	646492				646442
			646443		646475
NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING.					

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
MANDIBULAR LYMPH NODE NO ABNORMALITY DETECTED	(11)		(1)	(12)	
	646360		646477	646343	
	646367			646347	
	646374			646380	
	646379			646388	
	646420			646407	
	646427			646413	
	646457			646422	
	646482			646433	
	646485			646437	
CONGESTION.	646489			646442	
	646492			646475	
				646346	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)					
	Males					
	TREATMENT (mg/kg/day)	0	25	100	500	
		I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
MESENTERIC LYMPH NODE NO ABNORMALITY DETECTED	(11)			(1)	(12)	
	646360			646477	646343	
	646367				646346	
	646374				646347	
	646379				646380	
	646420				646388	
	646427				646407	
	646457				646413	
	646482				646422	
	646485				646433	
	646489				646437	
	646492				646442	
				646475		

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
BONE MARROW NO ABNORMALITY DETECTED	(11)		(1)	(12)	
	646360		646477	646343	
	646367			646346	
	646374			646347	
	646379			646380	
	646420			646388	
	646427			646407	
	646457			646413	
	646482			646422	
	646485			646433	
	646489			646437	
	646492			646442	
				646475	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
ENDOCRINE SYSTEM					
PITUITARY GLAND	(11) 646360	(1) 646477	(12) 646343		
NO ABNORMALITY DETECTED	646367		646346		
	646374		646347		
	646379		646380		
	646420		646388		
	646427		646407		
	646457		646413		
	646482		646422		
	646485		646433		
	646489		646437		
	646492		646442		
			646475		

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)						
	Males						
	TREATMENT (mg/kg/day)	0	25	100	500		
		I	III	V	VII		
ENDOCRINE SYSTEM							
THYROID GLAND		(11)	(10)	(11)	(12)		
NO ABNORMALITY DETECTED		646427		646477	646380		
		646457					
		646482					
		646489					
		646492	646423	646349	646343		
				646373	646346		
				646385	646347		
				646435	646388		
				646455	646407		
				646463	646413		
				646469	646422		
				646472	646433		
				646488	646437		
					646442		
					646475		
		646360	646370	646349	646343		
		646367	646399	646373	646346		
		646374	646414	646385	646347		
		646379	646421	646435	646388		
		646420	646423	646455	646407		
		646485	646426	646456	646413		
ALTERATION, COLLOID.							

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
ENDOCRINE SYSTEM					
THYROID GLAND ALTERATION, COLLOID.	(11)	(10)	(11)	(12)	
		646443	646463	646422	
		646454	646469	646433	
		646458	646472	646437	
		646471	646488	646442	
			646477	646475	
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
 NEOPLASTIC AND NON-NEOPLASTIC
 (90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)						

	Males						
TREATMENT (mg/kg/day)	0	25	100	500			
	I	III	V	VII			
ENDOCRINE SYSTEM							
PARATHYROID GLANDS							
NO ABNORMALITY DETECTED							
	(9)	(1)	(12)				
	646360	646477	646343				
	646367		646346				
	646374		646347				
	646420		646380				
	646427		646388				
	646457		646407				
	646485		646413				
	646489		646422				
	646492		646433				
			646437				
			646442				
			646475				

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)					
	Males					
TREATMENT (mg/kg/day)	0	25	100	500		
	I	III	V	VII		
ENDOCRINE SYSTEM						
ADRENAL GLANDS						
NO ABNORMALITY DETECTED	(11) 646360 646367 646374 646379 646420 646427 646457 646482 646485 646489 646492		(1) 646477	(12) 646343 646346 646347 646380 646388 646407 646413 646422 646433 646437 646442 646475		

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
NERVOUS SYSTEM					
BRAIN NO ABNORMALITY DETECTED	(11) 646360		(1) 646477	(12) 646343	
	646367			646346	
	646374			646347	
	646379			646380	
	646420			646388	
	646427			646407	
	646457			646413	
	646482			646422	
	646485			646433	
	646489			646437	
	646492			646442	
				646475	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
NERVOUS SYSTEM					
SPINAL CORD NO ABNORMALITY DETECTED	(11) 646360		(1) 646477	(12) 646343	
	646367			646346	
	646374			646347	
	646379			646380	
	646420			646388	
	646427			646407	
	646457			646413	
	646482			646422	
	646485			646433	
	646489			646437	
	646492			646442	
				646475	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
NERVOUS SYSTEM					
SCIATIC NERVE	(11) 646360		(1) 646477	(12) 646343	
NO ABNORMALITY DETECTED	646367			646346	
	646374			646347	
	646379			646380	
	646420			646388	
	646427			646407	
	646457			646413	
	646482			646422	
	646485			646433	
	646489			646437	
	646492			646442	
				646475	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)						
	Males						
	TREATMENT (mg/kg/day)	0	25	100	500		
		I	III	V	VII		
MUSCULAR AND SKELETAL SYSTEM							
SKELETAL MUSCLE NO ABNORMALITY DETECTED		(11) 646360 646367 646374 646379 646420 646427 646457 646482 646485 646489 646492		(1) 646477	(12) 646343 646346 646347 646380 646388 646407 646413 646422 646433 646437 646442 646475		

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
 NEOPLASTIC AND NON-NEOPLASTIC
 (90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
	TREATMENT (mg/kg/day)	0	25	100	500
		I	III	V	VII
MUSCULAR AND SKELETAL SYSTEM					
FEMUR/KNEE JOINT		(11)		(1)	(12)
NO ABNORMALITY DETECTED		646360		646477	646343
		646367			646346
		646374			646347
		646379			646380
		646420			646388
		646427			646407
		646457			646413
		646482			646422
		646485			646433
		646489			646437
		646492			646442
					646475

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
 NEOPLASTIC AND NON-NEOPLASTIC
 (90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
MUSCULAR AND SKELETAL SYSTEM					
STERNUM	(11) 646360 646367 646374 646379 646420 646427 646457 646482 646485 646489 646492		(1) 646477	(12) 646343 646346 646347 646380 646388 646407 646413 646422 646433 646437 646442 646475	
NO ABNORMALITY DETECTED					

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
 NEOPLASTIC AND NON-NEOPLASTIC
 (90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
REPRODUCTIVE SYSTEM					
TESTES	(11)		(1)	(12)	
NO ABNORMALITY DETECTED	646360		646477	646343	
	646367			646346	
	646374			646347	
	646379			646380	
	646420			646388	
	646427			646407	
	646457			646413	
	646482			646422	
	646485			646433	
	646489			646437	
	646492			646442	
				646475	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
REPRODUCTIVE SYSTEM					
EPIDIDYMIDES	(11)		(1)	(12)	
NO ABNORMALITY DETECTED	646360		646477	646343	
	646367			646346	
	646374			646347	
	646379			646380	
	646420			646388	
	646427			646407	
	646457			646413	
	646482			646422	
	646485			646433	
	646489			646437	
	646492			646442	
				646475	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)					Males			LESION INCIDENCE (Animal #)
	0	25	100	500					
	I	III	V	VII					
REPRODUCTIVE SYSTEM									
PROSTATE	(11)							(11)	
NO ABNORMALITY DETECTED	646360							646343	
	646367							646346	
	646374							646347	
	646379							646388	
	646457							646407	
	646482							646422	
	646489							646433	
	646492							646437	
								646442	
								646475	
	646420						646477	646413	
	646427								
	646485								
INFLAMMATION, SUBACUTE/CHRONIC.									

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
REPRODUCTIVE SYSTEM					
SEMINAL VESICLES	(11) 646360		(1) 646477	(12) 646343	
NO ABNORMALITY DETECTED	646367			646346	
	646374			646347	
	646379			646380	
	646427			646388	
	646457			646407	
	646482			646413	
	646485			646422	
	646489			646433	
	646492			646437	
				646442	
	646420			646475	
INFLAMMATION, SUBACUTE/CHRONIC.					

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
CUTANEOUS SYSTEM					
SKIN NO ABNORMALITY DETECTED	(11) 646360		(1) 646477	(12) 646343	
	646367			646346	
	646374			646347	
	646379			646380	
	646420			646388	
	646427			646407	
ALOPECIA/HYPOTRICHOSIS.	646457			646413	
	646482			646422	
	646485			646433	
	646489			646442	
	646492			646475	
				646437	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED	(11)		(1)	(12)	
	646360			646343	
	646367			646347	
	646374			646380	
	646379			646388	
	646420			646407	
	646427			646422	
	646457			646437	
	646485			646442	
	646489				
OPTIC NERVE NOT PRESENT. HEMORRHAGE/INFLAMMATION (BLEEDING PROCEDURE). FOLD/ROSETTE, RETINAL.	646492		646477	646475	
				646346	
				646475	
				646413	
				646433	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)	
	TREATMENT (mg/kg/day)	Males
	0	500
	I	VII
DIGESTIVE SYSTEM		
LIVER	(10)	(10)
NO ABNORMALITY DETECTED	646371	646369
	646411	646428
	646432	646484
	646460	
	646487	
	646494	
	646398	646384
	646416	
	646446	
	646459	
		646337
		646364
		646372
		646384
		646397
		646448
		646474
		646448
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.		
HYPERTROPHY, CENTRILOBULAR.		
FATTY CHANGE, MEDIAN CLEFT.		

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)	
	Males	
	TREATMENT (mg/kg/day)	
	0	500
	I	VII
URINARY SYSTEM		
KIDNEYS	(10)	(10)
NO ABNORMALITY DETECTED	646371 646364	646371 646364
	646398 646474	646398 646474
	646446	646446
	646459	646459
	646460	646460
	646487	646487
	646494	646494
	646411 646337	646411 646337
	646416 646369	646416 646369
	646432 646372	646432 646372
	646384	646384
	646397	646397
	646428	646428
	646448	646448
	646484	646484
NEPHROPATHY, CHRONIC PROGRESSIVE.		

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(ONE-MONTH RECOVERY EVALUATION)

LESION INCIDENCE (NUMERIC)	Males	
	TREATMENT (mg/kg/day)	
LYMPHATIC AND HEMATOPOIETIC SYSTEM SPLEEN NO ABNORMALITY DETECTED	0	500
	I	VII
	(10)	(10)
	646371	646369
	646398	646372
	646411	
	646416	
	646432	
	646446	
	646459	
PIGMENT INCREASED.	646460	
	646487	
	646494	646364
		646384
		646397
HEMATOPOIESIS, INCREASED.		646428
		646448
		646474
		646484
		646337
		646364
		646384
		646397
		646428
		646448

TABLE 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)		
	TREATMENT (mg/kg/day)	Males	
		0	500
		I	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM			
SPLEEN HEMATOPOIESIS, INCREASED.		(10)	(10)
			646448
			646474
			646484

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(ONE-MONTH RECOVERY EVALUATION)

LESION	LESION INCIDENCE (NUMERIC)	
	Males	
LESION	TREATMENT (mg/kg/day)	500
	I	VII
ENDOCRINE SYSTEM		
THYROID GLAND	(10)	(10)
NO ABNORMALITY DETECTED	646398	
	646411	
	646460	
	646487	
HYPERTROPHY, FOLLICULAR.		646364
		646369
		646372
		646397
		646428
		646448
		646474
		646484
ALTERATION, COLLOID.	646371	646337
	646416	646364
	646432	646369
	646446	646372
	646459	646384
	646494	646397
		646428
		646448
		646474
		646484

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(THREE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (Animal #)	
						Males	
	0	25	100	500			
	I	III	V	VII			
DIGESTIVE SYSTEM							
LIVER							
NO ABNORMALITY DETECTED	(4) 646468	(5) 646368 646436 646438 646453	(4) 646376 646403	(5) 646355 646391 646466			
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.	646396 646495 646325	646453 646335					
FATTY CHANGE, PERIportal.							
FATTY CHANGE, MEDIAN CLEFT.							
FATTY CHANGE, CENTRILobular.		646449	646327 646335	646344 646361			

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(THREE-MONTH RECOVERY EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
URINARY SYSTEM					
KIDNEYS					
NO ABNORMALITY DETECTED	(4)	(5) 646436	(4) 646327	(5) 646344 646361	
NEPHROPATHY, CHRONIC PROGRESSIVE.	646325 646396 646468 646495	646368 646438 646449 646453	646335 646376 646403	646391 646355 646466	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(THREE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN NO ABNORMALITY DETECTED	(4)	(5)	(4)	(5)	
	646325	646436	646327	646344	
	646396	646438	646376	646355	
	646468	646449	646403	646361	
	646495	646453		646391	
HEMATOPOIESIS, INCREASED.		646368	646335	646466	

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 44 (Continued)

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED -
NEOPLASTIC AND NON-NEOPLASTIC
(THREE-MONTH RECOVERY EVALUATION)

LESION	LESION INCIDENCE (Animal #)				
	Males				
TREATMENT (mg/kg/day)	0	25	100	500	
	I	III	V	VII	
ENDOCRINE SYSTEM					
THYROID GLAND					
NO ABNORMALITY DETECTED	(4) 646325 646396 646468	(5)	(4)	(5)	
HYPERTROPHY, FOLLICULAR.					646344 646355 646361 646466
ALTERATION, COLLOID.	646495	646368 646436 646438 646449 646453	646327 646335 646376 646403	646344 646355 646361 646466	

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