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TRADE SECRET

Study Title

H-24516: Subchronic Toxicity
90-Day Gavage Study in Rats
with One-Generation Reproduction Evaluations

Revision No. 1

Volume 1 of 5

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

AUTHOR: Gregory S. Ladics, Ph.D., D.A.B.T.

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PERFORMING LABORATORY: E.I. du Pont de Nemours and Company
Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road, P.O. Box 50
Newark, Delaware 19714-0050

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Company Sanitized. Does not contain TSCA CBI

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. The item listed does not impact the validity of the study.

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.

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

Study Director: Gregory S. Ladics 3-Dec-2001
Gregory S. Ladics, Ph.D., D.A.B.T. Date
Senior Research Scientist

Applicant / Sponsor: _____

DuPont Representative Date

QUALITY ASSURANCE STATEMENT

Haskell Sample Number(s):

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Dates of Inspections:

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Conduct: January 15,30, 2001; February 13,14,28, 2001;
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Study Director: January 15, 2001; March 1,14, 2001; July 5,6,13,9, 2001;
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Management: February 6, 2001; March 5,14, 2001; July 5,6,13, 2001;
August 29, 2001; September 27, 2001; October 17,23, 2001;
November 18, 2001

Reported by:

Kimberly B. Brebner

Kimberly B. Brebner
Quality Assurance Auditor

3-DEC-2001
Date

CERTIFICATION

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

Analytical Evaluations Reported by:	<u>Janet C. Maslanka</u> Janet C. Maslanka, B.S. Staff Scientist	<u>3-Dec-2001</u> Date
Neurobehavioral Evaluations Reported by:	<u>Linda A. Malley</u> Linda A. Malley, Ph.D., D.A.B.T. Senior Research Scientist	<u>3-Dec-2001</u> Date
Clinical Pathology Evaluations Reported by:	<u>Steven R. Frame for</u> Nancy E. Everds, D.V.M. Diplomate A.C.V.P. Principal Research Scientist	<u>3-Dec-2001</u> Date
Biochemical Evaluations Reported by:	<u>John C. O'Connor</u> John C. O'Connor, M.S. Research Scientist	<u>3-Dec-2001</u> Date
Reproductive Evaluations Reported by:	<u>Eve Michreest</u> Eve Michreest, Ph.D. Research Scientist	<u>3-Dec-2001</u> Date
Pathological Evaluations Reported by:	<u>G. Tracy Makovec</u> G. Tracy Makovec, D.V.M. Diplomate A.C.V.P. Senior Research Scientist	<u>3-Dec-2001</u> Date
Pathological Evaluations Peer Review Reported by:	<u>Steven R. Frame</u> Steven R. Frame, D.V.M., Ph.D. Diplomate A.C.V.P. Director, Anatomic Pathology	<u>3-Dec-2001</u> Date
Approved by:	<u>Judith C. Stadler</u> Judith C. Stadler, Ph.D., D.A.B.T. Director, General Toxicology	<u>3-DEC-2001</u> Date
Issued by Study Director:	<u>Gregory S. Ladics</u> Gregory S. Ladics, Ph.D., D.A.B.T. Senior Research Scientist	<u>3-Dec-2001</u> Date

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Substance Tested: [REDACTED]

Synonyms/Codes:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- H-24516

Haskell Number: 24516

Composition:

Purity: [REDACTED]

Known Impurities: [REDACTED]

Physical Characteristics: [REDACTED]

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

Study Initiated/Completed: December 12, 2000/ (see report cover page)

In-Life Initiated/Completed: December 12, 2000 / June 11, 2001

STUDY PERSONNEL

Study Director: Gregory S. Ladics, Ph.D.

Management: Judith C. Stadler, Ph.D.

Nancy C. Chromey, Ph.D.

Janice L. Connell, M.S., B.A., C.I.H.

Primary Technician: Janine A. Britton, B.S.

Analytical Chemist: Janet C. Maslanka, B.S.

Management: S. Mark Kennedy, Ph.D.

Reproductive Toxicologist: Eve Mylchreest, Ph.D.

Management: Robert M. Parker, Ph.D.

Clinical Pathologist: Nancy E. Everds, D.V.M.

Management: Steven R. Frame, D.V.M., Ph.D.

Pathologist: G. Tracy Makovec, D.V.M.

Management: Steven R. Frame, D.V.M., Ph.D.

Peer Review Pathologist: Steven R. Frame, D.V.M., Ph.D.

Neurotoxicologist: Linda A. Malley, Ph.D.

Management: Robert M. Parker, Ph.D.

Biochemical Evaluation: John C. O'Connor, M.S.

Management: Matthew S. Bogdanffy, Ph.D.

Toxicology Report Preparation: Cecilia R. Kee, B.S.

Mary K. LaRoe

Ophthalmologist: Nancy M. Bromberg, V.M.D., M.S.

6119 Massachusetts Avenue

Bethesda, Maryland 20816

Laboratory Veterinarians: William Singleton, D.V.M., A.C.L.A.M.

Wanda L. West, D.V.M., A.C.L.A.M.

SUMMARY

Four groups of young adult male and female Crl:CD[®](SD)IGS BR rats were administered H-24516 by gavage at dosages of 0, 25, 100, and 250 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 on weeks 7, 13, and near the end of the one-month recovery period. 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 animals after 10 and approximately 90 days of dosing and following one- and three-month recovery periods. After approximately 90 days of dosing, 10 rats/sex/dose were sacrificed and given a gross and microscopic pathological examination. Approximately one month after the 90-day dosing period, 10 animals/sex in the control and high dose group were examined for recovery of toxic effects. An additional five animals/sex/dose were evaluated for recovery approximately 3 months following the end of the dosing period.

The range of mean daily dose volumes of H-24516 administered to male rats was 2.5 to 4.6 ml. The range administered to female rats was 1.9 to 2.8 ml.

In-Life Toxicology Parameters: No test substance-related mortality occurred in the study. A test substance-related, toxicologically significant increase in the incidence of broken (males) and absent teeth (males and females) was observed in the 250 mg/kg/day dose group. Test substance-related, toxicologically significant decrements in body weight, body weight gain, and food efficiency occurred in males dosed with 100 and 250 mg/kg/day H-24516. Statistically significant decrements in mean body weight parameters and food consumption occurred for the female groups dosed with 100 or 250 mg/kg/day. The mean body weight and body weight gain decrements observed for the 100 and 250 mg/kg/day female groups, however, were of small magnitude. They were associated with decreased food consumption, but not with any alterations in food efficiency, and, therefore, were not considered to be toxicologically significant. Furthermore, the decrements in body weight parameters observed for both males and females appear to be related in part to test substance-induced toxicity to the teeth and subsequent decreased ability of the animals to eat the pelleted chow.

Neurotoxicology Parameters: No adverse changes in neurobehavioral parameters were observed in male or female rats in any dose group.

Biochemical Toxicology: The rate of hepatic β -oxidation, a measure of peroxisome proliferation, was increased in a dose-dependent manner with statistical significance occurring in males and females administered 100 or 250 mg/kg/day H-24516. Following a one- or three-month recovery period, the rate of hepatic β -oxidation was still significantly increased in males and females administered 250 mg/kg/day.

Clinical Pathology: Samples were collected at mid-study, at the end of treatment, and after one month of recovery for hematology, clinical chemistry, urinalysis, coagulation (end of study only), and plasma and urine fluoride (end of study and end of one- and three-month recovery).

Males and females dosed with 250 mg/kg/day had decreased red cell mass parameters, along with correlative changes in other hematology parameters and in red cell morphology. After one month of recovery, mean red cell mass of female rats was similar to the control group, although some changes were still present in other hematologic parameters. Male rats still had decreased red cell mass effects, and associated alterations in other hematologic parameters.

Other changes in clinical pathology parameters, during treatment or after a one- or three-month recovery, were considered treatment-related but non-adverse because the magnitude of change was small, transient, and/or in a direction not associated with toxicity. The serum parameters thus affected included serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, cholesterol, triglycerides, total protein and albumin, calcium, phosphorus, sodium, chloride, and potassium. Affected plasma parameters were activated partial thromboplastin time and plasma fluoride. Affected urinalysis parameters were urine volume, osmolality, specific gravity, and fluoride.

Anatomical Pathology (Subchronic Toxicity): Test substance related, toxicologically significant degeneration/disorganization of enamel organ ameloblast cells occurred in male and female rats administered 100 or 250 mg/kg/day H-24516. Test substance related, potentially adverse increases in thyroid hypertrophy were observed in the 100 and 250 mg/kg/day male and 250 mg/kg/day female dose groups. In addition, alterations in thyroid colloid were observed in male and female rats at all dose levels, but were not considered to be toxicologically significant.

Test-substance related and statistically significant increases in liver weight parameters were present in males and females administered 25, 100, or 250 mg/kg/day for approximately 90 days. The increased liver weights correlated with microscopic centrilobular hepatocellular hypertrophy in the 100 and 250 mg/kg/day male and 250 mg/kg/day female groups. Test-substance related and statistically significant increases in kidney weight parameters also occurred in males and females administered 25, 100, or 250 mg/kg/day. The increased kidney weights correlated with microscopic renal tubular hypertrophy in the 100 (1 of 10 rats) and 250 mg/kg/day male groups only. The liver and kidney alterations, however, were considered to be a pharmacologically adaptive response by these organs to the test-substance and therefore, not considered toxicologically significant.

After one month of recovery, rats dosed with 250 mg/kg/day showed reversibility of some effects. The ameloblastic degeneration/disorganization persisted with decreased incidence and severity in the 250 mg/kg/day male and female groups. Thyroid hypertrophy was no longer observed. Alterations in thyroid colloid persisted in both male and female rats. Increased liver weight parameters persisted in the 250 mg/kg/day male and female groups, although their magnitude was decreased relative to that observed at the end of the 90 day exposure period. Hepatocellular hypertrophy was no longer observed in female rats but persisted with decreased severity in male rats. Renal tubular hypertrophy persisted with decreased incidence and severity in males, while some kidney weight parameters remained increased in both male and female rats.

After the three-month recovery period, ameloblastic degeneration/disorganization was still present in the 100 mg/kg/day male and 250 mg/kg/day male and female dose groups but at a lower incidence and severity relative to the one-month-recovery animals. Alterations in thyroid colloid persisted in both males and females. Liver weight parameters remained increased in both the 250 mg/kg/day male and female groups, although their magnitude was decreased relative to that observed after the 90-day period. Hepatocellular hypertrophy was observed only in the 250 mg/kg/day male group (1 of 5 rats). Alterations in kidney weight parameters or renal tubular hypertrophy were not observed at any dose level.

Reproduction: Twenty male and female rats from each dose group were designated for reproductive evaluations. Parental rats (P₁ generation) were dosed daily for 74 days prior to cohabitation, during the cohabitation period (mating), during gestation, and during lactation, until the weaning of the F₁ offspring. The following parameters were conducted on P₁ rats: body weights, food consumption, clinical signs, gross pathology, sperm parameters, estrous cyclicity and reproductive performance. 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 rats (F₁ generation) were retained at weaning, and the following parameters evaluated for 6 weeks: body weights, food consumption, clinical signs, and age at onset of vaginal opening and preputial separation. After 6 weeks, the F₁ generation rats were given a gross pathological examination, selected reproductive organs and target organs of toxicity were weighed.

There were no toxicologically significant pathology findings in the P₁ or F₁ generation rats. No test substance-related mortality occurred in the study. There was a statistically significant reduction in body weight in P₁ male rats during and after the cohabitation period. Although this finding was test substance-related, it was not considered toxicologically significant.

There was a statistically significant increase in testicular spermatid numbers in P₁ male rats administered 100 or 250 mg/kg/day. This finding was not considered test substance-related.

Implantation efficiency was significantly reduced at 100 and 250 mg/kg/day and reflects a reduction in the number of pups born.

There were statistically significant reductions in the number of pups born, the number of pups born alive and the number of pups alive on day 4 of lactation in the 250 mg/kg/day group. Reductions of similar magnitude as in the 250 mg/kg/day group were also observed for the number of pups born and born alive in the 100 mg/kg/day group. Although not statistically significant, these changes were considered test substance-related and toxicologically significant, as was the significant reduction in the number of pups alive on day 4 of lactation in the 100 mg/kg/day group. There were statistically significant reductions in pup weights on lactation days 4, 7, 14 and 21 in the 250 mg/kg/day group.

On the day of weaning, mean body weights were significantly lower than control in both F₁ males and females in the 250 mg/kg/day group. However, mean body weights in these groups progressively returned to control values during the post-weaning period. These findings were not considered toxicologically significant.

NOEL for Subchronic Toxicity: The no-observed-effect level (NOEL)^a for males was 25 mg/kg/day H-24516 based on adverse decrements in body weight parameters and food efficiency, increased hepatic peroxisomal β -oxidation, and the degeneration and/or disorganization of enamel organ ameloblast cells in males administered 100 mg/kg/day. The NOEL for females was 25 mg/kg/day H-24516 based on increased hepatic peroxisomal β -oxidation and the degeneration and/or disorganization of enamel organ ameloblast cells in females administered 100 mg/kg/day.

NOEL for Reproductive Evaluations: The NOEL for the reproductive toxicity parameters evaluated under the conditions of this study was 25 mg/kg/day based on decreases in the number of pups born, born alive, and the number of pups alive on day 4 of lactation at the 100 mg/kg/day dose level.

^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-24516, is an [REDACTED]. The 25, 100, and 250 mg/kg/day dose levels for this study were selected based on the toxicity and pharmacokinetic analysis of plasma fluorine concentrations from a range-finding study with H-24516. In rats exposed to 200 mg/kg/day H-24516 for 35 days, toxicity (i.e., body weight effects or clinical observations) was not observed. Plasma fluorine levels approached levels previously found when animals were exposed to dosages that induced lethality. The high-dose level of 250 mg/kg/day for this 90-day study was expected to produce toxicity without excessive mortality. The low dose of 25 mg/kg/day was expected to be the no-observed-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-24516 when administered by gavage to male and female rats. Recovery evaluations were 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.

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 the H-24516 were supplied near the beginning and end of the study for stability analysis and analyzed by the DuPont Regional Analytical Services (RAS), Jackson Laboratories, Deepwater, NJ. Methods and results for the stability analysis of the test substance are documented in study records.

C. Test Species

On November 16, 2000, 176 male and 176 female Crl:CD[®](SD)IGS BR rats, with an assigned birth date of October 25, 2000, were received from Charles River Laboratories, Inc., Raleigh, North Carolina for use on this study.

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 accepted ranges were minor and did not affect the study.

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

Cage racks were relocated within the animal room each week and cages were repositioned on the racks every 2 weeks

- for animals designated for the 90-day exposure period and one- and three-month recovery periods.
- during the 74-day pre-mating period for animals designated for reproductive assessment, and
- the 40-day post-weaning period for F₁ generation rats.

2. Feed and Water

Tap water was provided *ad libitum*. All rats were fed PMI Nutrition International, Inc. Certified Rodent LabDiet[®] 5002 *ad libitum*. Initially, all rats were fed pelleted chow, however, beginning on test day 57, animals exhibiting effects to the teeth were placed on ground chow. On test day 74, all rats in the 250 mg/kg/day dose group that were designated for reproductive toxicity evaluations were placed on ground chow. On test day 77, all other rats in the 250 mg/kg/day dose group were placed on ground chow.

3. Identification

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

included the unique 6-digit Haskell animal number and the individual identification number assigned to each rat.

4. Health Monitoring Program

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

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

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

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

E. Quarantine and Pretest Period

Upon arrival at Haskell Laboratory, the rats were quarantined for 11 days of the 26-day pretest period. The rats were observed daily for any clinically apparent signs of disease or injury, weighed 4 times, and examined by a veterinary ophthalmologist to identify animals with preexisting ocular lesions.

Prior to grouping, one male rat (animal no. 643168) was accidentally killed and discarded without necropsy. One male rat (animal no. 643186) and 2 female rats (animal nos. 643355 and 643469) were found dead and necropsied to check for the presence of disease. No disease was found.

On the basis of acceptable body weight gains and clinical observations, all surviving rats were released from quarantine on test day -15 by the laboratory animal veterinarian designee.

F. Study Design

Groups		No./ Group		Dietary 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	250

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	250

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

The first ten rats in each group were designated for the 90-day exposure evaluation. The next five rats in each group were initially designated as a satellite subset for serial blood collection in the event findings warranted analytical evaluations. Due to findings after the one-month recovery period, these rats were designated for evaluation of selected tissues following a three-month recovery period; 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 65 days after study start for the biochemical evaluations (hepatic β -oxidation) following a 10-day exposure.

Male and female rats designated for the 90-day exposure evaluation were dosed for 90 and 92 days, and necropsied on test days 91 and 93, respectively. Male and female rats designated for the one- and three-month recovery evaluations were dosed for 90 days and necropsied 36 days and 92 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). Biochemical evaluations (hepatic β -oxidation) were performed on animals after 10 and approximately 90 days of dosing and following one- and three-month recovery periods. Clinical pathology evaluations were conducted on animals designated for the 90-day exposure evaluation on weeks 7 and 13 and on animals designated for the one-month recovery evaluation immediately prior to necropsy. Reproductive evaluations began on test day 74 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. 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-24516 began on test day 0. The rats were approximately 49 days of age on test day 0. Prior to the start of the test substance administration, rats with body weights that were not within $\pm 20\%$ 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.

On test day 0, two male rats had clinical signs of hair loss (animal numbers 643232 (control) and 643315 (250 mg/kg/day)). Inclusion of these animals on the study does not impact the outcome of the study.

2. Rats Designated for 10-Day Biochemical Analysis

The rats designated for the 10-day biochemical analysis arrived separately, 65 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 is compared among themselves. Oral administration of H-24768 began on test day 76.

H. Dose Suspension Preparation

Dose suspensions of 0, 2.5, 10, or 25 mg test substance/mL were prepared with 0.5% methylcellulose. Methylcellulose was selected as the vehicle because it is the vehicle of choice for reproductive studies. Dose suspensions were prepared daily prior to dosing from test day 0 through test day 37 with a dose volume of 10 mL/kg. However, in order to administer a dose volume under 5 mL to comply with laboratory procedure, the dosing volume for male and female rats was decreased from 10 mL/kg to 7.5 mL/kg on test day 38, and the suspension concentrations were increased to 0, 3.33, 13.33, and 33.33 mg/mL. Starting on test day 42 until the end of the dosing period, these dose suspensions were prepared twice a week.

The test material was melted down to approximately 90°C, mixed for approximately 30 minutes, aliquoted, then mixed with methylcellulose for one minute to make the dose suspensions. When the dose suspension was prepared twice a week, the suspension was refrigerated until used. Each day the suspensions were then homogenized for one minute and then stirred for 30 minutes.

before the day's aliquots were removed. Remaining dose suspensions were returned to the refrigerator. The dose suspensions were stirred prior to and during dosing.

I. Test Substance Administration and Sampling

Animals designated for the 90-day exposure period and one- and three-month recovery periods were dosed for up to 92 days. Animals designated for reproductive evaluations, were dosed for the 74-day premating period and during the mating period. P₁ male rats continued to be dosed until sacrifice. Pregnant female rats were dosed during the gestation period. Lactating females and females with no evidence of copulation were dosed until pups were weaned on day 21.

The test substance was administered daily to the study animals by oral gavage to achieve dosage levels of 25, 100, or 250 mg active ingredient/kg body weight/day, based on the most recently recorded body weight. All male and female control animals were treated with 0.5% aqueous methylcellulose at the same dose volume as that used for the high dose group. On test day 3, five male rats in the 25 mg/kg/day group were dosed with vehicle only. On test day 18, all male rats and the first 11 female rats in the 25 mg/kg/day groups received 37-39 mg/kg/day. 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 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.

At the initiation of the study (test day 0), samples of the dosing suspensions containing H-24516 at the concentrations of 0, 2.5, 10, and, 25 mg/mL were collected. On test day 6, to verify that the 10.0 mg/mL level was mixed homogeneously, samples of the dosing suspensions containing H-24516 at the concentrations of 0 and 10 mg/mL were collected. These samples were analyzed to verify homogeneity/concentration of the test substance in the vehicle and 5-hour room temperature stability to verify the test substance stability while the animals were being dosed.

Prior to the initiation of a change in frequency of dosing preparation, a long term refrigerated stability (4 days) analysis was required. Also, a need to change dose volume (10 mL/kg to 7.5 mL/kg) was identified and a subsequent change in the concentrations of the suspensions was necessary. Therefore, an additional mixing and stability study was performed. The samples collected during this additional study were not administered to the animals but addressed the mixing, range of concentrations and the stability parameters that would be needed after the frequency of mixing and dose volume changes were made in the study. In this separate study, samples of dosing suspensions containing H-24516 at the concentrations of 0, 5, 20, and, 50 mg/mL (based on a 5 mL/kg dose volume) were collected. These samples were analyzed to verify homogeneity, concentration and 5-hour room temperature stability. On subsequent days 2, 3, and 4 after this preparation, samples from the same preparation were collected and analyzed to verify concentration after re-dispersion of the test substance and refrigerated stability (4 days) along with 5-hour room temperature stability (day 4 samples, only). Later in the 90-day gavage study, to satisfy the dose volume change of 5 mL/kg to 7.5 mL/kg, samples of the dosing

suspensions containing H-24516 at the concentrations of 0 and 3.33 mg/mL were collected and analyzed to verify homogeneity, concentration and 5-hour room temperature stability. Four days later, samples from the same preparation were collected and analyzed to verify concentration after re-dispersion of the test substance and refrigerated stability (4 days) along with 5-hour room temperature stability.

On test day 38, after the mixing and stability was established for the storage conditions and the concentration range, the mixing frequency and dose volume change (10 mL/kg to 7.5 mL/kg) was initiated in the study. Therefore on test day 49, samples of the dosing suspensions containing H-24516 at the concentrations of 0, 3.33, 13.33, and 33.33 mg/mL were collected and analyzed to verify homogeneity and concentration. On test day 91, samples of the dosing suspensions containing H-24516 at the same concentrations were collected. The 3.33 mg/mL samples were analyzed to verify homogeneity and concentration while the remaining levels were analyzed for concentration verification.

All dosing suspension samples were collected on the same day the suspensions were prepared or at the prescribed protocol time for analysis. They were analyzed when received or were frozen until analyzed.

J. Analytical Methods

1. Dosing Suspension Treatment

Each dosing sample was diluted to 100 mL with methanol and sonicated to dissolve the H-24516 in the suspension. The dosing samples were further diluted with the 0 mg/mL sample (initial dilution) to an expected concentration of approximately 0.05, 0.06, 0.075 or 0.09 mg/mL (a.i.) prior to analysis. An internal standard (refer to Calibration and Quantitation Section) at an equivalent amount was added to each sample before the final analysis dilution.

Samples submitted for analysis were analyzed the day the suspensions were received or stored frozen until analyzed by the testing group.

2. Chromatographic Conditions

Instrument:	Hewlett-Packard Model 6890 GC
Column:	J & W, DB-1701, 30 m, 0.32 mm ID, 1 um film thickness
Injector:	Split, 250°C
Detector:	FID; 250°C
Carrier Gas:	Helium (2.1 mL/min)
Split vent:	22.3 mL/min
Injection Volume:	2 microliter
Oven Program:	Gradient
Initial Temperature:	100°C
Initial Time	1.00 min.
Level 1 Rate:	20.0°C/min.
Level 1 Temperature:	260°C
Level 1 Time:	0.00 min.
Total run time:	9.00 min.

3. Calibration and Quantitation

A separate sample of H-24516 (-3) was obtained to use as the analytical reference standard [REDACTED]. A stock solution was prepared in methanol. This stock solution was sonicated to assure that all material was in solution. Before analysis, appropriate aliquots of the stock were diluted with methanol to make calibration standards, which bracketed the target concentration of the diluted dosing samples. A stock solution of the internal standard [REDACTED] was prepared in methanol and added to each calibration standard and test sample to give an equivalent final concentration in all dilutions. The ratio of the peak heights for internal standard and H-24516 at three retention times (3.5, 4.17, and 4.77 minutes) from replicate GC analysis of these suspensions were used to construct calibration curves by least squares regression (see Appendix A, Figure 1a, 1b, and 1c for a representative curves). Measured concentrations for the dosing samples were determined by applying the peak height ratios from replicate injections of each sample to the respective calibration curve.

Test substance homogeneity in the dosing suspensions was evaluated by calculating the coefficient of variation (C.V. = standard deviation/mean x 100) of the measured concentrations in samples obtained from the top, middle, and bottom (T, M, and B) of the dosing preparation or the mean of duplicate samples for each concentration. A coefficient of variation of less than 10% is the standard criterion at Haskell Laboratory for acceptable distribution of the test substance throughout the dosing suspension. The mean result of the top, middle, and bottom homogeneity samples or duplicate concentration verification 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 top, middle, and bottom homogeneity samples or duplicate concentration verification samples (0-day room temperature) as the baseline for comparing the corresponding room temperature and 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 substudy, male rats were weighed on a weekly schedule and female rats were weighed during gestation on days 0, 7, 14, 18, and 21, and 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 (test day 36).

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. The only exception is that food consumption was not determined for animals designated for three-month recovery during the urine and feces collection period on test days 83-89.

During the reproductive assessment, food consumption was determined for rats designated for reproductive assessment as follows:

- Premating Dosing period – individual food consumption was determined weekly, ending test day 74.
- Cohabitation period, beginning test day 74 – food consumption was not determined.
- Following the end of cohabitation period – food consumption was not determined for males.
- 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 inadvertently not collected or spillage not recorded during the postweaning period for many animals. As a result, available food consumption data are not presented in the report but are included in the study records.

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 throughout the study. 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

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

On test day -11, the initial examination was performed on all rats received for the study, prior to selection and grouping. On test day 80, all surviving rats designated for the 90-day exposure and one-month recovery were examined again. On test day 122, all surviving rats designated for the one-month recovery evaluation were given a final examination.

O. Neurotoxicity Evaluations

1. Sensory Function Evaluation

Prior to test substance administration (test days -6 and -7), during week 13 (test days 86 and 87) of test substance administration, and following an approximately one-month recovery period (test day 120), 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 the one-month 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. Due to the technical difficulty of evaluating pupil size in albino rats under ambient light conditions, pupil size was evaluated by assessment of pupillary 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 during week 13, 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 were also recorded following each motor activity session.

3. Test Facility Positive Control Data

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

P. Clinical Pathology

A clinical pathology evaluation was conducted on the first 10 male and 10 female rats per group on test days 44 and 91 (males) or test days 45 and 93 (females). The rats were fasted overnight (approximately 16 hours) and urine was collected during this interval. Blood samples for hematology and clinical chemistry measurements were collected from the orbital sinus of each fasted rat while the rat was under light carbon dioxide anesthesia. Blood samples for coagulation parameters and plasma fluoride were collected from the abdominal *vena cava* while the rat was under carbon dioxide anesthesia, immediately prior to sacrifice (days 91 and 93 in males and females, respectively). All blood samples were examined visually and observations recorded. A clinical pathology evaluation (hematology, clinical chemistry, and urinalysis only) was also conducted on all one-month recovery rats from blood and urine collected on the day of necropsy (test day 125). In addition, urine samples were collected from three-month recovery rats for urine fluoride analysis only.

1. Hematology/Coagulation

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

The following hematology and coagulation parameters were determined:

Erythrocyte count (RBC)	Red cell distribution width (RDW)
Hemoglobin concentration (HGB)	Absolute reticulocyte counts (ARET)
Hematocrit (HCT)	Total leukocyte count (WBC)
Mean corpuscular volume (MCV)	Differential leukocyte count
Mean corpuscular hemoglobin (MCH)	Platelet count (PLT)
Mean corpuscular hemoglobin concentration (MCHC)	Microscopic blood smear examination

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

2. Clinical Chemistry

Clinical chemistry parameters were measured or calculated on a Roche Diagnostics (BMC)/Hitachi® 917 clinical chemistry analyzer. Plasma fluoride concentration was determined using a phi/12pH meter with a fluoride-selective electrode. Plasma fluorides were determined at the end of treatment and at the end of a one-month recovery period.

The following serum 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 (OSMO)	Urobilinogen (URO)
Specific gravity (SG)	Urine fluoride (UFLU)
pH	Protein (UMTP)
Glucose (UGLU)	Microscopic urine examination
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 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. Sediments from all urine specimens were evaluated microscopically. Urine fluoride was determined by multiplication of measured urine volume by urine fluoride concentration (measured using a phi/12pH meter and a fluoride selective electrode). Urine fluorides were determined at the end of treatment and at the end of the one- and three-month recovery periods.

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

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. On the day of blood collection (except test day -4), blood was collected from the animals 2 hours ($\pm$ 30 minutes) after 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 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 analysis at 3, 7, 12, 19, 26, 36, 50, 71, and 92 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 collected blood, urine, and feces may be evaluated in the future for the test substance and/or possible metabolites. Resulting data will be reported separately.

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

After approximately 90 days of exposure to the test substance (test days 91 and 93 for males and females, respectively), groups of 10 male and 10 female rats from the 0, 25, 100, and 250 mg/kg/day groups were sacrificed and necropsied. Additional groups of 10 male and 10 female rats from 0 and 250 mg/kg/day groups were sacrificed and necropsied approximately one month after the last exposure (test day 125). In addition, groups of 5 male and 5 female rats from all groups designated for the three-month recovery period were sacrificed and necropsied on test day 181. In the discussion of pathology findings, groups sacrificed after approximately 90 days are referred to as the 90-day exposure groups, and groups sacrificed on test days 125 and 181 are referred to as one-month and three-month recovery groups, respectively.

Rats scheduled for sacrifice were fasted overnight on the afternoon before their scheduled sacrifice. The order of sacrifice for scheduled deaths were random among all treatment groups. Rats were euthanatized by carbon dioxide anesthesia and exsanguination. Gross examinations were performed on all male and female rats.

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

<u>Digestive System</u>	<u>Cardiovascular System</u>	<u>Musculoskeletal System</u>
liver	heart	skeletal muscle
esophagus	aorta	femur/knee joint ^a
stomach		sternum
duodenum	<u>Hematopoietic System</u>	mandible ^b
jejunum	spleen	
ileum	thymus	<u>Reproductive System</u>
cecum	mandibular lymph node	<u>Male</u>
colon	mesenteric lymph node	testes
rectum	bone marrow ^c	epididymides
salivary glands		prostate
pancreas	<u>Endocrine System</u>	seminal vesicles
	pituitary gland	<u>Female</u>
<u>Urinary System</u>	thyroid gland	ovaries
kidneys	parathyroid glands	uterus
urinary bladder	adrenal glands	mammary gland
<u>Respiratory System</u>	<u>Nervous System</u>	<u>Miscellaneous</u>
lungs	brain (including cerebrum,	skin
trachea	cerebellum, medulla/pons)	eyes (including optic nerve)
nose	spinal cord (3 levels: cervical,	gross observations
larynx	mid-thoracic, lumbar)	
pharynx	sciatic nerve	

- Both femur/knee joints were taken from 90-day exposure rats . One femur/knee joint was frozen and the other processed as described below.
- The mandible was taken from 90-day exposure and one-month recovery animals. One-half of the mandible was frozen and the other half processed as described below.
- Bone marrow was collected with the femur and sternum.

The following tissues were collected from three-month recovery group rats sacrificed by design: liver, kidneys, thyroid gland, nose, testes, and fat (approximately 1 gram). The testes, fat and portions of the liver and kidney were placed in plastic freezer bags and stored frozen ; these tissues may be evaluated in the future for total fluorine levels to study the distribution of the test substance. Resulting data will be reported separately.

The following tissues were weighed from rats sacrificed by design in the 90-day exposure group and the one-month recovery groups: liver, kidneys, adrenal glands, brain, spleen, thymus, heart, ovaries, uterus, epididymides, and testes. Organ weight/final body weight and organ weight/brain weight ratios were calculated. The thyroid gland (after fixation) was also weighed in the P₁ adults. Liver, kidneys, thyroid gland (after fixation), and testes from rats sacrificed by design after three months recovery were weighed and organ weight/final body weight ratios were calculated. Organ weight/brain weight ratios were not determined for three-month sacrifice rats.

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 exposure group rats sacrificed on test days 91/93 from control and 250 mg/kg/day rats, and all found dead or accidentally killed rats were processed and received a full histopathological examination. Liver, kidneys, thyroid gland, nose, and mandible were processed from 25 and 100 mg/kg/day 90-day exposure group rats and from one-month recovery rats. Liver, kidneys, thyroid gland, and nose from males and thyroid gland and nose from females sacrificed after the three-month recovery period were processed from all groups. Tissues were microscopically examined in descending order of dose until a no-effect level was reached.

S. Reproductive Assessment

1. Breeding

After approximately 10 weeks of exposure to the test substance, on test day 74, each female was continually housed on a 1:1 basis with a randomly selected male of the same dose concentration level in the male's cage. On the day copulation was confirmed, the female was transferred back to individual cage housing. Mating pairs were cohoused until evidence of copulation was observed (designated as day 0 of gestation), or until 2 weeks elapsed. The presence of an intravaginal or extruded copulation plug was considered evidence of copulation.

2. Estrous Cycle Evaluation

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

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

3. Gestation Procedures

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

4. Lactation Procedures

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

a. Day 0 Postpartum

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

b. Day 4 Postpartum

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

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

5. Post Weaning and Developmental Landmarks

Developmental landmarks in the F₁ generation male and female rats (one/sex/litter) were monitored on a daily basis until criterion was achieved. Once developmental landmark criterion was achieved, the animals were weighed. Body weight and food consumption were also determined weekly until postnatal day 56 (test day 36).

a. Vaginal Patency

Female rats were examined beginning on postpartum day 21.

b. Preputial Separation

Male rats were examined beginning on postpartum day 35.

T. Anatomical Pathology - Rats Designated for Reproductive Evaluations

1. P₁ Adults

All rats found dead, accidentally killed, or sacrificed *in extremis* prior to the cohabitation period underwent a gross and microscopic evaluation. The tissues collected are the same as those for rats designated for the 90-day exposure period.

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

Sperm parameters for the first 10 out of 20 P₁ male animals in each treatment group were evaluated. The right cauda epididymis was weighed. Sperm was collected from the right cauda epididymis and percent motility and morphology was determined. The left epididymis and testis were frozen in liquid nitrogen and stored between -65 and -85° C for sperm and spermatid counts, respectively. The right testis and epididymis from these 10 rats were saved and placed in fixative.

The following table lists tissues that were collected:

Tissues Collected from P ₁ Adults		
<u>Male</u>	<u>Female</u>	<u>Both Sexes</u>
Testes/Testis ^a	Ovaries	Thyroid Gland ^b
Epididymides/Epididymis ^a	Uterus (with oviducts)	Gross Observations ^c
Prostate	Vagina	Pituitary Gland
Seminal Vesicles		
Coagulating Gland		

a Testes/Testis and epididymides/epididymis collected from male rats were placed in Bouin's solution. All other tissues (reproductive and non-reproductive) collected from male and female rats were placed in formalin.

b Thyroid glands were weighed after fixation.

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

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. Gross lesions were preserved.

4. F₁ Adults

All F₁ generation rats were sacrificed by carbon dioxide asphyxiation and exsanguination, and subjected to a gross pathological examination. Selected tissues and gross lesions were preserved.

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

Tissues Collected from F ₁ Adults		
<u>Male</u>	<u>Female</u>	<u>Both Sexes</u>
Testes	Ovaries	Thyroid Gland
Epididymides	Uterus (with oviducts)	Gross Observations
Prostate	Vagina	Pituitary
Seminal Vesicles		Liver
Coagulating Gland		Kidney
		Nose

Tissues Weighed from F ₁ Adults		
<u>Male</u>	<u>Female</u>	<u>Both Sexes</u>
Testes	Uterus (with oviducts and cervix)	Thyroid Gland (after fixation)
Epididymides		Liver
Seminal Vesicles (with coagulating glands)		Brain
Prostate		Kidney

Processed tissues for histopathological examination were embedded in paraffin, cut at a nominal thickness of 5 micrometers, and stained with hematoxylin and eosin (H&E). Histopathological examination of reproductive organs was conducted only for P₁ males and females with impaired reproductive performance. Selected gross lesions were evaluated microscopically. Gross lesions observed at necropsy for which histopathology was not appropriate or would not be additive were generally not collected.

U. Biochemical Measurements

Following 10 or approximately 90 days of test substance administration, after 36 days on recovery, or after 92 days on recovery (control and high-dose only), five rats from each group designated for biochemical evaluation were weighed and then sacrificed by CO₂ anesthesia and exsanguination. Rats were fasted overnight on the afternoon before their sacrifice. The livers were removed, weighed, and then homogenized (1 gram tissue/4 mL buffer). 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 mg/mL. Peroxisomal β -oxidation activity was

determined using [¹⁴C]palmitoyl CoA as the substrate.⁽⁵⁾ The protein content of the peroxisomes was determined before and after analysis by the Biorad method.⁽⁶⁾

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	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⁾	Kruskall-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⁾	Kruskall-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⁾	Kruskall-Wallis test ⁽¹⁵⁾ followed with Dunn's test ⁽⁸⁾
Survival Incidence of Clinical 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	

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

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

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

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

e If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test⁽¹⁹⁾ with a Bonferroni correction was used.

The following table lists 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	Test for lack of trend ⁽⁹⁾	Sequential application ⁽¹⁰⁾ of the Jonckheere-Terpstra trend test ⁽¹¹⁾	Preliminary tests for pairwise comparison
Percent Born Alive Precoital Interval Estrous Cycle Length Sperm Parameters Vaginal Patency Preputial Separation	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⁾	Kruskall-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 are tied and the standard large sample version of Jonckheere's test is 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 will be stored at Regional Analytical Services (RAS), Jackson Laboratories, Deepwater, New Jersey.

RESULTS AND DISCUSSION

ANALYTICAL EVALUATIONS

A. Test Substance Stability

Analyses of bulk samples of H-24516 near the beginning and end of the study for stability indicated that the test substance was stable for the duration of the study. The average percent of H-24516 in the sample submitted near the beginning of the study (test day 7) and analyzed (test day 23) was [REDACTED]. The average percent of H-24516 in the sample submitted at the end of the study (test day 90) and analyzed (test day 105) was [REDACTED]. This work can be found in [REDACTED] H-24516 [REDACTED]. The purity was reported by the sponsor to be [REDACTED]. The differences in values between the sponsor reported purity and the experimental data represent analytical variability and not instability of the test substance.

B. Chromatography

H-24516 eluted from the GC column as resolved peaks with retention times from 2.9 minutes to approximately 6.0 minutes. For the purpose of quantitation, resolved peaks at the retention times of approximately 3.5, 4.17, and 4.77 minutes were used. The internal standard [REDACTED] eluted as a resolved peak at approximately 3.99 minutes. Representative GC chromatograms are shown in Appendix A, Figures 2(a - c). Test substance was not detected in the 0 mg/mL control.

C. Homogeneity, Concentration Verification and Stability Samples for Initial Mixing Procedures and Concentrations Based on Dose Volume of 10 mL/kg (Test Day 0 to Test Day 41)

Analytical results from dosing suspensions collected on test day 0 and test day 6 and analyzed for homogeneity/concentration verification and 5-hour room temperature stability are shown in Table 1 and Appendix A, Table I.

The following table summarizes the results for homogeneity, concentration verification and stability analyses.

Preparation Date	Nominal mg/mL	Measured T,M,B ^a mg/mL	Mean (T,M,B) % Nominal	C.V. (%)	Stability ^b % Nominal
Test Day 0	0	ND ^c	---	---	---
	2.5	2.30, 2.47, 2.40	95.6	3	82.4
	10	8.97, 10.2, 14.0	111.0	24	88.9
	25	26.8, 24.8, 23.5	100.0	7	96.4
Test Day 6	0	ND ^c	---	---	---
	10	9.26, 9.58, 9.23	93.6	2	90.3

a Mean results for the analysis of the top (T), middle (M) and bottom (B) samples.

b Samples held 5 hours at room temperature.

c Denotes none detected.

The data for samples collected on test day 0 indicates that the test substance was homogeneously mixed in the vehicle except for the 10 mg/mL level (C.V. = 24). The test substance was at the targeted concentration in the samples ($\pm 11\%$ of nominal) and was stable in the vehicle when held 5 hours at room temperature. The 10 mg/mL level samples were collected again on test day 6 to show that the mixing and the room temperature stability was acceptable. The data indicated that the test substance was homogeneously mixed in the vehicle (C.V. = 2%), at the targeted concentration in the samples ($\pm 6.4\%$ of nominal) and stable in the vehicle when held 5 hours at room temperature.

The lower than expected result for the 2.5 mg/mL (82.4% of nominal) for the 5-hour sample was within the targeted range of the study ($\pm 20\%$ of nominal) and is due to sampling and analytical variability of the method and not stability of the test material in the vehicle. This was concluded based on the data from the remainder of the levels in this study, which were stable for the 5-hour room temperature period.

Test substance was not found in the 0 mg/mL samples.

D. Mixing and Stability Study for Change in Frequency of Dosing Preparation (2 times/week) and Dose Volume Change (5 mL/Kg to 7.5 mL/Kg)

This work was done prior to initiating any mixing or storage condition changes in the study.

Analytical results from dosing suspensions collected for the special mixing study and analyzed to verify homogeneity and/or concentration with stability are shown in Table 1 and Appendix A, Table II.

The following table summarizes the results for homogeneity/concentration verification and stability analyses.

Dose Volume Sample Type	Nominal mg/mL	Measured mg/mL	Mean % Nominal	C.V. (%)	Stability ^a % Nominal
<u>5.0 mL/kg</u>					
Homogeneity ^b	0	ND ^c	---	---	---
	5.0	4.53, 4.25, 4.39	87.8	3	92.0
	20	19.9, 17.7, 18.6	93.5	6	86.0
	50	53.4, 52.6, 54.0	106.6	1	96.6
Stability					
2-Day Refrigerated ^d	5.0	4.77, 4.76	95.4	0.2	---
3-Day Refrigerated ^d	5.0	4.74, 4.48	92.2	4	---
4-Day Refrigerated ^f	5.0	4.81	96.1	---	97.1
2-Day Refrigerated ^d	20	18.7, 18.0	91.5	3	---
3-Day Refrigerated ^d	20	39.3, 19.6 ^e	147.0	47	---
4-Day Refrigerated ^f	20	19.6	97.8	---	88.2
2-Day Refrigerated ^d	50	47.3, 48.4	95.8	2	---
3-Day Refrigerated ^d	50	46.5, 46.9	93.4	1	---
4-Day Refrigerated ^f	50	48.9	97.8	---	95.7
<u>7.5 mL/kg</u>					
Homogeneity ^b	0	ND ^c	---	---	---
	3.33	2.88, 2.54, 2.67	81.1	6	79.9
Stability					
4-Day Refrigerated ^g	3.33	2.94, 2.88	87.4	1	82.3

a Samples held 5 hours at room temperature.

b Mean results for the analysis of the top (T), middle (M) and bottom (B) samples.

c Denotes none detected.

d Mean results of duplicate concentration verification samples.

e Original analysis not reported because of apparent aliquot error. Mean result of duplicate re-analysis (n=2) of the original sample reported.

f Mean result of single sample for concentration verification and a single sample for 5-hour room temperature stability.

g Mean result of duplicate samples for concentration verification and a single sample for 5-hour room temperature stability.

The data for samples collected initially (5.0 mL/kg dose volume change) indicate that the test substance was homogeneously mixed in the vehicle, at the targeted concentration ($\pm 12.2\%$ of nominal) and was stable in the vehicle when held 4 days refrigerated followed by 5 hours at room temperature. The higher than expected result for the 3-Day refrigerated samples at the 20 mg/mL level (147.0% of nominal, C.V. = 47%) indicates that the test substance was not properly re-dispersed in the vehicle after refrigeration and before sampling. This was concluded because duplicate samples were collected and analyzed with one of the samples having a higher than expected result (39.3 mg/mL) in the analysis. The sample was reanalyzed and the results supported the duplicate reported analysis. This data along with the results from the last sampling time at this level (4-day refrigerated/97.8% of nominal) supported this conclusion.

Company Sanitized. Does not contain TSCA CBI

The data for samples collected for the 7.5 mL/kg dose volume change indicate that the test substance was homogeneously mixed in the vehicle for the 3.33 mg/mL level (C.V. = 6) and stable in the vehicle when held 5 hours at room temperature. The concentration was lower than expected (81.1% of nominal) but was probably due to initial sampling of the mixture before adequate mixing. The results from the 4-day refrigerated samples from the same preparation indicated the material was at the targeted level ($\pm 12.6\%$ of nominal) and stable when held 4 days refrigerated followed by 5 hours at room temperature.

The results from this mixing and stability study indicated that the mixing time for preparation of the suspensions before use with the animals would have to be monitored for both the initial preparation and the re-dispersion of the suspensions after refrigeration. The test substance was shown to be stable in the vehicle over the concentration range needed for the dose volume change and under the storage conditions for the change in frequency of preparation (3 or 4 days/ twice a week) of the dosing suspensions.

E. Homogeneity and Concentration Verification Samples for Final Mixing Procedures and Concentration Change Based on Dose Volume of 7.5 mg/kg (Test Day 42)

Analytical results from dosing suspensions collected on test day 49 and test day 91 and analyzed for homogeneity and/or concentration verification are shown in Table 1 and Appendix A, Table III.

The following table summarizes the results for homogeneity and concentration verification analyses.

Preparation Date	Nominal mg/mL	Measured T,M,B ^a mg/mL	Mean (T,M,B) % Nominal	C.V. (%)
Test Day 49	0	ND ^b	---	---
	3.33	2.71, 2.99, 3.42	91.3	12
	13.33	10.8, 12.7, 12.8	90.8	9
	33.33	31.0, 32.4, 33.4	96.8	4
Test Day 91	0	ND ^b	---	---
	3.33	3.05, 3.00, 3.01	90.7	1
	13.33 ^c	12.8, 12.2	93.8	3
	33.33 ^c	32.7, 32.3	97.5	1

a Mean results for the analysis of the top (T), middle (M) and bottom (B) samples.

b Denotes none detected.

c Duplicate samples submitted. C.V. for the duplicate samples used to confirm uniformity of mixture.

The data for samples collected on test day 49 indicates that the test substance was homogeneously mixed in the vehicle except for the 3.33 mg/mL level (C.V. = 12). The test substance was at the targeted concentration in the samples ($\pm 9.2\%$ of nominal).

The data for samples collected on test day 91 show that the 3.33 mg/mL level was homogeneously mixed, indicated that the test substance was properly mixed in the vehicle

(C.V. = 1%) and at the targeted concentration in the samples ($\pm 9.3\%$ of nominal). The data for the duplicate concentration verification samples for the remaining levels indicated that the test substance was at the targeted level ($\pm 6.2\%$ of nominal) and mixed properly (C.V.'s = 3 and 1%, respectively).

Test substance was not found in the 0 mg/mL samples.

F. Analytical Conclusions

Data from the analysis of the samples at the initiation of the study indicate that the test substance in the vehicle was mixed homogeneously, was at the targeted levels and was stable for 5 hours at room temperature.

Data for the analysis of the samples after the mixing and dose volume changes indicated that the test substance in the vehicle was mixed homogeneously and at the targeted levels. All stability conditions were addressed in the additional stability/mixing study and the test substance in the vehicle had been shown to be stable after 4 days of refrigeration followed by 5 hours at room temperature over the concentration range. The data also indicated that controlled mixing was necessary for the initial mixing and redispersion of the test substance in the vehicle after refrigeration.

Test substance was not found in the 0 mg/mL samples.

Analysis of the test substance near the beginning and the end of the study indicates that the H-24516 was stable during the study.

SUBCHRONIC TOXICITY EVALUATIONS

IN-LIFE TOXICOLOGY

A. Dosage Data

(Tables 2-3, Appendix B)

Rats were dosed with suspensions of H-24516 in 0.5% aqueous methylcellulose, prepared at concentrations of 0, 2.5, 10, and 25 mg/ml, designed to deliver the targeted dose of test substance at a dosing volume of 10 ml/kg body weight. However, in order to administer a dose volume under 5 mL to comply with animal welfare guidelines, the dosing volume for male and female rats was decreased from 10mL/kg to 7.5 mL/kg and the suspension concentrations were increased to 3.33, 13.33, and 33.33 mg/mL on test day 38. The quantity of H-24516 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 2.5-4.6 mL for the control group, 2.5-4.6 mL for the 25 mg/kg/day group, 2.5-4.6 mL for the 100 mg/kg/day group, and 2.5-4.6 mL for the 250 mg/kg/day group. The range of mean daily dose volumes administered to female rats was 1.9-2.8 mL for the control group, 1.9-2.8 mL for the 25 mg/kg/day group, 1.9-2.6 mL for the 100 mg/kg/day group, and 1.9-2.8 mL for the 250 mg/kg/day group.

B. Mean Body Weights and Body Weight Gains

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

Statistically significant decrements in body weight compared to control were observed in males in the 100 mg/kg/day dose group after day 77 (7-8%) and in the 250 mg/kg/day group after test day 56 (6-14%). Statistically significant decrements in body weight in females compared to control were observed in the 100 mg/kg/day dose group after day 77 (6-7%) and in the 250 mg/kg/day group after test day 56 (6-12%). These weight gain differences appear to be directly related to test-substance induced adverse effects to the teeth (see Section C and Anatomic Pathology Report) and subsequent decreases in food consumption in the 100 mg/kg/day female and 250 mg/kg/day male and female groups (see Section C).

The 250 mg/kg/day male group had significantly lower mean body weight gains compared to control over the course of the study. Significantly lower mean body weight gains were observed for the 100 mg/kg/day male group during the 35-42 and 49-56 day intervals. A significantly lower mean body weight gain also occurred for the 25 mg/kg/day male group during the 35-42 day interval. The mean body weight gain of the 250 mg/kg/day male group was significantly higher than the mean weight gain of male controls during the first week of the study and during the 77-84 and 84-90 day intervals. The increased mean body weight gains observed after test day 77 appear to be associated with an increase in food consumption and food efficiency after both the male and female rats in the 250 mg/kg/day dosage group were placed on ground chow because of adverse effects to the teeth. Overall (0-90 day interval), significantly lower mean

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body weight gains of 13% and 16% compared to control occurred in the 100 and 250 mg/kg/day male groups. This reduction in body weight gain was considered test substance-related and toxicologically significant.

The 250 mg/kg/day female group had significantly lower mean body weight gains compared to the control group over the course of the study. Significantly lower mean body weight gains also occurred for the 100 mg/kg/day female group during the 28-35 day interval and for both the 25 and 100 mg/kg/day groups during the 42-49 day interval. The mean body weight gain of the 250 mg/kg/day group was significantly higher than control during the second week of the study and during the 77-84 day interval. As with males, the increased body weight gain occurring after test day 77 appears to be associated with an increase in food consumption and food efficiency (see Section B) after the animals were placed on ground chow. Overall (0-91 day interval), significantly lower mean body weight gains of 12% occurred in both the 100 and 250 mg/kg/day female groups. The mean body weight and body weight gain decrements observed for the 100 mg/kg/day and 250 mg/kg/day female groups, however, were of small magnitude and were associated with decreased food consumption but not with any alterations in food efficiency (see Section B). Therefore, the statistically significant mean body weight and body weight gain decrements for the 100 mg/kg/day and 250 mg/kg/day females were considered to be test substance-related but not toxicologically significant. Furthermore, the decrements in body weight parameters observed for both males and females appear to be related to test substance-induced adverse effects to the teeth (see Section D and Pathology Section) and subsequent decreased ability of the animals to eat the pelleted chow.

Following a one-month recovery period, the mean body weight and body weight gain of both male and female rats that received 250 mg/kg/day approached control. For the overall one-month recovery period (90-119 day interval), a statistically significant decrement in mean body weight gain occurred for the 100 mg/kg/day group. The lower mean body weight gain did not occur in a dose-dependent manner and appeared to be due to test substance-induced adverse effects to the teeth and a subsequent large decrease in food consumption for one male in the 100 mg/kg/day group. Therefore, this effect was not considered toxicologically significant. Following the three-month recovery period, the mean body weight (females only) and body weight gain of both males and females exceeded control levels.

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

Male rats in the 250 mg/kg/day group had statistically significant and lower food consumption compared to control over the course of the study. Overall (0-90 day interval), a significantly lower food consumption of 7% compared to control occurred in the 250 mg/kg/day male group. Females in the 100 and 250 mg/kg/day had statistically significant and lower food consumption compared to control over the course of the study. Overall (0-91 day interval), significantly lower food consumption of 9% and 8% occurred in the 100 and 250 mg/kg/day female groups. However, after the rats received ground chow as a result of tooth toxicity, their food consumption immediately increased and began to approach or exceed (female 77-84 day interval) control

levels. Test-substance related and statistically significant effects on food consumption were observed in the 100 mg/kg/day female and 250 mg/kg/day male and female groups.

Male rats in the 250 mg/kg/day group had significantly lower mean food efficiency compared to control over the course of the study except during the first and third week of the study and test days 77-84 and 84-91 in which significantly higher food efficiencies were observed. The 100 mg/kg/day male group had significantly lower mean food efficiency during test days 35-42 and 49-56. For the entire study interval, significantly lower food efficiencies of 8% and 9%, respectively, were observed for the 100 and 250 mg/kg/day male groups.

With the exception of the first two weeks of the study and test days 77-84 in which a significantly higher mean food efficiency occurred, female rats in the 250 mg/kg/day group had significantly lower mean food efficiency compared to control over the course of the study. A significantly lower mean food efficiency was also observed for the 100 mg/kg/day female group during test days 28-35, 42-49, and 49-56, while a significant increase occurred during test days 35-42. During test days 42-49, the 25 mg/kg/day female group had significantly lower mean food efficiency. These differences were not considered to be of toxicological significance as overall mean food efficiencies for test-substance treated female groups were similar to control. The decreased mean food efficiency in the 250 mg/kg/day male group appears to be directly related to test substance-induced toxicity of the teeth. Following the replacement of pelleted chow with ground chow on test day 77 for the 250 mg/kg/day male and female groups, a significantly higher mean food efficiency was observed for the 77-84 and 84-90 (males only) day intervals. Nevertheless, based on the parallel reduction in body weight parameters observed in the 100 and 250 mg/kg/day male groups, this reduction in food efficiency is considered to be toxicologically significant.

After a one-month recovery period, mean food consumption in the 250 mg/kg/day male group was still significantly lower, while mean food efficiency was the same as that observed in control rats. For females, lower food consumption was also observed following the one-month recovery period. For the overall one-month recovery period (90-119 day interval), a statistically significant decrement in mean food efficiency occurred for the 100 mg/kg/day male and female groups. The lower mean food efficiency did not occur in a dose-dependant manner and therefore was not considered to be toxicologically significant. Following three months of recovery, mean food consumption for males and females was similar to control levels, while mean food efficiency for the 250 mg/kg/day males exceeded control levels.

D. Clinical Observations, Ophthalmology Evaluations, and Survival (Tables 12-17, Appendix F)

A test substance-related, toxicologically significant increase in the incidence of broken (males) and absent teeth (males and females) was observed in the 250 mg/kg/day dose group. In addition, there was an increase in tooth clipping required for both males and females in the 250 g/kg/day dose group. There was also a statistically significant increase compared to control in the incidence of stained red perineum and clear discharge from the mouth in the 250 g/kg/day male dose group. The increased incidence of stained red perineum and clear discharge from the mouth was considered to be test substance-related.

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No test substance-related ophthalmological signs of toxicity or effects on survival were observed.

E. In-Life Toxicology Conclusions

Under the conditions of this study, the no-observed-effect-level (NOEL) for in-life toxicology parameters (body weight, body weight gain, food consumption, food efficiency, and clinical signs of toxicity) was 25 mg/kg/day for males and 100 mg/kg/day for females.

NEUROBEHAVIORAL TOXICOLOGY

A. Sensory Function Evaluations

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

There were no test substance-related effects or statistically significant differences on forelimb grip strength in males or females administered any dosage of H-24516. Females administered 100 or 250 mg/kg/day had slightly lower (12% and 14% lower than the control value, respectively) forelimb grip strength at week 13, however, a linear dose response-relationship was not present, and the values were within the range of normal variation for this measurement. In addition, the forelimb grip strength in the control group during the recovery evaluation was similar to the values of the 100 and 250 mg/kg/day female groups during the week 13 evaluation demonstrating the degree of variability in this type of measurement. Therefore, the slightly lower forelimb grip strength in 100 and 250 mg/kg/day females was not considered to be test substance-related.

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

There were no test substance-related effects or statistically significant differences in hindlimb grip strength for either males or females administered any dosage of H-24516.

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

There were no test substance-related changes in neurobehavioral parameters in males or females administered any dosage of H-24516.

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 tested. Males assigned to the 100 and 250 mg/kg/day group had significantly lower mean duration of movement during the third 10-minute interval for the baseline evaluation. In addition, mean duration of movements was significantly lower for 25,

100, and 250 mg/kg/day males compared to control during the fourth 10-minute interval of the baseline evaluation. However, test substance administration had not been initiated, and therefore, these statistical differences were not considered to be test substance related.

Females in the 250 mg/kg/day group had significantly lower total duration of movement and number of movements during the recovery evaluation. The total duration of movements for both the control females and 250 mg/kg/day females was lower relative to the baseline and week 13 evaluations. However, the number of movements for both control and the 250 mg/kg/day females were within the range of baseline values for females in this study. Since there was no increase or decrease from the range of baseline values with respect to number of movements, and since there were no changes in motor activity observed at week 13 or in any other neurobehavioral parameter, the statistically significant differences compared to control were not considered to be test substance related.

C. Neurobehavioral Toxicity Conclusions

Under the conditions of the study, the no-observable-effect level (NOEL) for neurobehavioral parameters was 250 mg/kg/day in males and females, the highest concentration tested.

CLINICAL PATHOLOGY

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

Rats dosed with 250 mg/kg/day had minimally decreased RBC mass parameters (RBC, hemoglobin, hematocrit; variable statistical significance) (Clinical Pathology Text Table 1). These decrements were associated with minimally increased RDW in both sexes, anisocytosis, microcytes, and increased reticulocytes in males, and poikilocytosis in females. Following the approximately one-month recovery period, male rats previously dosed with 250 mg/kg/day still had minimally to mildly decreased red cell mass parameters, and decreased reticulocytes compared to control group rats. Female rats previously dosed with 250 mg/kg/day had red cell mass parameters similar to controls by day 125, although MCV, MCH, RDW and reticulocytes were decreased. The minimal red cell effects discussed above are not expected to affect red cell function or the health of the animal. Nevertheless, based on the progressive nature of the effects during treatment and the persistence of many effects into the recovery period, the red cell changes noted at 250 mg/kg/day were considered toxicologically adverse.

Clinical Pathology Text Table 1:
Red cell mass parameters as a percent of control group mean*

Parameter	Interval	Males				Females		
		25	100	250		25	100	250
RBC	Day 44/45	101%	97%	98%		95%	99%	94%
	Day 91/93	97%	93%	90%		96%	97%	93%
	Day 125			89%				101%
HGB	Day 44/45	101%	100%	98%		96%	98%	94%
	Day 91/93	99%	98%	93%		98%	97%	92%
	Day 125			92%				98%
HCT	Day 44/45	101%	100%	98%		96%	97%	94%
	Day 91/93	97%	97%	93%		96%	97%	92%
	Day 125			91%				97%

* Statistical significance indicated by bold italicized type

Females dosed with 250 mg/kg/day had shortened APTTs at day 93. This change was not considered to be treatment related because there was no clear dose-related response. Similar APTTs were present in all treated groups. Additionally, shortened coagulation times are not considered adverse; prolonged, rather than shortened, coagulation times are toxicologically significant. Because there were no treatment-related alterations in coagulation parameters at the end of dosing, coagulation parameters were not measured at the end of the one-month recovery (Day 125).

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

- Decreased hemoglobin and hematocrit in females dosed with 25 mg/kg/day at Day 45
- Increased MCH in males dosed with 100 mg/kg/day, and increased MCHC in males dosed with 25 mg/kg/day at Day 91
- Increased eosinophils in males dosed with 25 mg/kg/day at Day 44, and decreased eosinophils in females dosed with 25 mg/kg/day at day 45.

The following minimal but statistically significant changes in hematology parameters were considered to be unrelated to treatment because they only occurred after one month of recovery:

- Increased neutrophils in females dosed with 100 (day 93) or 250 mg/kg/day (day 125; recovery)
- Increased eosinophils in females dosed with 250 mg/kg/day (day 125 recovery)

Decreased APTT in males dosed with 25 or 100 mg/kg/day at day 91 was not considered adverse because decreases in coagulation times are not associated with toxicity.

Red cell counts were statistically decreased at test day 91 in males dosed with 100 mg/kg/day. This change was small, was not associated with changes in other red cell mass parameters, and did not appear to follow a dose response; and thus was considered unrelated to treatment.

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

There were no toxicologically significant changes in clinical chemistry parameters in rats dosed with 25, 100 or 250 mg/kg/day. All statistically significant changes in clinical chemistry parameters were considered non-adverse (not toxicologically significant) or unrelated to treatment. These changes are detailed below.

Alkaline phosphatase was minimally increased in male rats dosed with 100 (day 91 only) or 250 mg/kg/day (days 44 and 91). Toxicologically important increased ALKP activity generally occurs as a result of cholestasis, but may also be due to direct enzyme induction by a xenobiotic⁽²³⁾. In this study, there was no evidence of cholestasis (bilirubinemia, bilirubinuria, or histologic evidence of cholestasis). There was histologic evidence of enzyme induction (see Anatomic Pathology report). Therefore, the ALKP changes were most likely due to direct enzyme induction and therefore were considered non-adverse. After one month of recovery, alkaline phosphatase activity in 250 mg/kg/day males was similar to control values.

Clinical Pathology Text Table 2:
Alkaline phosphatase as a percent of control group mean

Males			
	25	100	250
Day 44	107%	116%	<i>138%</i>
Day 91	98%	<i>143%</i>	<i>192%</i>
Day 125			95%

* Statistical significance indicated by bold italicized type

Cholesterol and triglycerides were mildly decreased in males dosed with 100 or 250 mg/kg/day at days 44 and 91 (variable statistical significance). In females dosed with 100 or 250 mg/kg/day, triglycerides only were decreased at days 45 and 93 (variable statistical significance). After one month of recovery, both cholesterol and triglycerides were still statistically decreased in 250 mg/kg/day males. For females, triglycerides in most rats were still minimally decreased after one month of recovery, although there was much variability among individual rats, and values from some previously treated rats were higher than any control rat. Therefore, the relevance of the effect in recovery females is equivocal. The changes in cholesterol and triglycerides were treatment-related and indicate altered lipid metabolism, but were not considered adverse because mild decreases in cholesterol and triglycerides do not have any known adverse effects.

Males and females dosed with 100 or 250 mg/kg/day had alterations in serum proteins. The primary change was mildly increased total protein in rats dosed with 100 (females only) or 250 mg/kg/day (variable statistical significance). The increased total protein was generally due to increased albumin; increased albumin also occurred in males dosed with 100 mg/kg/day (day 91), but this change did not affect total protein concentration. Globulin changes were minimal and variable between sexes; at day 91, 250 mg/kg/day males had decreased globulins, while 250 mg/kg/day females had increased globulins. After one month of recovery, protein concentrations in rats previously dosed with 250 mg/kg/day were similar to control values. The increases in serum protein noted above were primarily due to increased serum albumin. Mildly increased serum albumin is not known to have any adverse consequences, so these protein changes were considered non-adverse.

Increased serum albumin in females dosed with 100 or 250 mg/kg/day caused secondary hypercalcemia. 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. Thus, increased calcium in association with increased albumin is considered physiologically appropriate and thus non-adverse. After one month of recovery, calcium concentrations in 250 mg/kg/day females were similar to control values.

Inorganic phosphorus was minimally and statistically increased in females dosed with 100 or 250 mg/kg/day at day 93 only. After one month of recovery, inorganic phosphorus values in 250 mg/kg/day females were similar to control values. Increased inorganic phosphorus was not associated with other changes that would indicate toxicity (such as increased urea nitrogen or

creatinine, or histologic changes indicative of renal damage). In addition, rats with the highest inorganic phosphorus concentration were those dosed with 100 rather than 250 mg/kg/day. Therefore, this minimal change, although possibly related to treatment, was not considered adverse.

Sodium and chloride were minimally decreased in males dosed with 250 mg/kg/day at day 91. The magnitude of change in these parameters was very small, and in individual rats there was no consistent relationship between sodium and chloride concentrations. Therefore, these changes, although possibly related to treatment, were considered non-adverse.

Potassium was minimally increased in females dosed with 250 mg/kg/day at days 45 and 93. The magnitude of change was small compared to the normal variability of the parameter, and was not associated with changes that might indicate toxicity. Therefore, this change was considered non-adverse. At day 125 (one-month recovery), potassium in 250 mg/kg/day females was similar to control group values.

The following minimal but statistically significant changes in clinical chemistry parameters were considered to be unrelated to treatment because they did not occur in a dose-related manner.

- Transiently increased phosphorus in males dosed with 100 mg/kg/day at Day 44
- Decreased creatinine in females dosed with 25 or 100 mg/kg/day at Day 45 (in addition, decreases in creatinine are not toxicologically significant)
- Increased glucose in females dosed with 25 mg/kg/day at Day 45
- Decreased sodium in males dosed with 250 mg/kg/day

The following minimal but statistically significant changes in clinical chemistry parameters were considered to be unrelated to treatment because they only occurred after one month of recovery

- Decreased SDH in males dosed with 250 mg/kg/day (in addition, decreases in SDH are not toxicologically significant)
- Increased urea nitrogen in males dosed with 250 mg/kg/day
- Decreased calcium in males dosed with 250 mg/kg/day
- Decreased sodium in females dosed with 250 mg/kg/day

Decreased AST and ALT in females dosed with 250 mg/kg/day at day 45 were considered to be non-adverse because decreases in transaminase activity are not considered toxicologically adverse.

C. Urinalysis (Tables 32-33, Appendix K)

Urine volume was increased in males and females dosed with 250 mg/kg/day at days 44 (males equivocal) and 91 (variable statistical significance). Urine osmolality and specific gravity were correspondingly decreased at these same time-points with statistical significance occurring only for males at 91 days. In addition, in males dosed with 250 mg/kg/day, urine total protein was decreased at day 91. Increased urine volume and decreased urine concentration can occur due to

decreased renal function or secondary to increased water consumption. Effects on urine volume and concentration in the 250 mg/kg/day groups were not associated with changes in other clinical pathology parameters (creatinine, BUN, phosphorus) indicative of primary renal toxicity. Furthermore, although renal tubular hypertrophy and increased renal weights were present in male rats, there was no evidence of cytotoxic effects in the kidney. Therefore, these urinalysis changes were considered non-adverse.

At day 125 (one-month recovery), urine volume of males previously dosed with 250 mg/kg/day was decreased, compared to control and end-of-study results. Urine concentration (measured by osmolality and specific gravity) was correspondingly increased at this time-point. These changes were not considered adverse because production of low levels of concentrated urine is considered normal for rats. The urine volume and concentration of female rats after recovery were similar to controls.

D. Plasma and Urine Fluoride Measurements (Tables 30-33, Appendix K)

Plasma fluoride was mildly increased in males and females dosed with 100 or 250 mg/kg/day at day 91/93. At day 125 (one-month recovery), plasma fluoride in 250 mg/kg/day rats was similar to control group values.

At the end of the exposure phase of the study, urine fluoride (as determined by total fluoride excreted over the collection period) was increased in a dose-related manner in males and females dosed with 25, 100, or 250 mg/kg/day (Clinical Pathology Text Table 3).

At day 125 (one-month recovery), daily urine fluoride excretion was increased in males and females previously treated with 250 mg/kg/day, although levels were markedly reduced relative to those present at the end of exposure. Thus increased urine fluoride showed evidence of reversibility, albeit incomplete, following the one-month recovery period.

Additional urine was collected from males and females designated for three months of recovery, to determine whether or not further recovery had occurred. For rats previously dosed with 250 mg/kg/day, urine samples collected at day 181 still contained significant amounts of fluoride, although the total fluoride was less than at day 125. In addition, urine fluoride at Day 181 was still increased over control group values for males and females previously dosed with 100 mg/kg/day (males statistically significant). Urine fluoride was also probably increased in males and possibly females dosed with 25 mg/kg/day; but the change in females was equivocal due to the low numbers of values and the variability of the data. Increases in plasma and urine fluoride were considered to be secondary to the administration of a mixture containing fluorinated compounds and/or free fluoride. The presence of fluoride in urine three months after exposure suggests that fluoride containing compounds are slowly being released from tissue sites.

Clinical Pathology Text Table 3: Daily urine fluoride (µg)*

Dose (mg/kg/day)	0	25	100	250		25	100	250
Males								
Day 91	20.2	213.0	662.7	1473.6		1054%	3281%	7295%
Day 125	14.2	ND	ND	87.4		ND	ND	615%
Day 181**	12.1	22.8	39.1	69.1		188%	323%	571%
Females								
Day 93	16.7	99.2	460.3	914.7		594%	2756%	5477%
Day 125	8.6	ND	ND	43.8		ND	ND	509%
Day 181**	8.8	15.9	20.0	29.3		181%	227%	333%

ND Group not sampled at this time point.

* Data presented as absolute values (left) and as percent of control group mean (right).

Bold italicized font indicates that the change was statistically significant

** Data collected from rats designated for biochemical analysis

E. Clinical Pathology Conclusions

Under the conditions of this study, the NOEL for males and females was 100 mg/kg/day. These were based on the findings of minimal decreased red cell mass parameters in males and females dosed with 250 mg/kg/day. After one month of recovery, red cell mass parameters were still decreased in males previously dosed with 250 mg/kg/day, and some hematologic parameters were still altered in females previously dosed with 250 mg/kg/day. There were no adverse findings for coagulation, clinical chemistry, or urinalysis parameters at any dose.

ANATOMICAL PATHOLOGY

A. Subchronic Toxicity and Recovery

1. Organ Weight Data (Tables 36-37, Appendix L)

Test substance-related and/or statistically significant increases, compared to controls, in liver weight parameters were present in 25, 100, and 250 mg/kg/day males and females sacrificed at the end of the approximately 90-day exposure period. At the 250 mg/kg/day dose level, liver weight parameters remained increased in the one- and three-month recovery group males and females, although the magnitude of these effects was decreased relative to that observed in the 250 mg/kg/day exposure group. No statistically significant liver weight effects were present in the three-month recovery groups previously dosed with 25 or 100 mg/kg/day (organ weights were not evaluated in these groups at one-month recovery). In 100 and 250 mg/kg/day exposure group male rats and 250 mg/kg/day one- and three-month recovery male rats and in 250 mg/kg/day exposure group females, increased liver weights correlated with microscopic hepatocellular hypertrophy (see discussion under Microscopic Findings).

Test substance-related and/or statistically significant increases, compared to controls, in one or more kidney weight parameters occurred in male and female rats at all exposure concentrations. Some kidney weight parameters remained increased in males and females in the 250 mg/kg/day one-month recovery groups. However, there were no statistically significant kidney weight changes in any dosed group following three months of recovery. In male rats, increased kidney weights correlated with microscopic tubular hypertrophy in the 100 and 250 mg/kg/day groups sacrificed at the end of the exposure period and in the 250 mg/kg/day group sacrificed following a one-month recovery period (see discussion under Microscopic Findings). There were no microscopic correlates to kidney weight changes in females.

There were no other test substance-related organ weight effects. All other statistically significant organ weight changes in exposure and recovery groups were secondary to decreases in body weight. In 100 and 250 mg/kg/day male rats sacrificed at the end of the exposure period, organ weight changes included: decreases in absolute organ weight and/or organ weight relative to brain weight for heart and epididymides and increased brain weights relative to body weight. There were no weight changes in heart and epididymides when adjusted to final body weight. In 250 mg/kg/day males sacrificed at the end of the exposure period, testes weight relative to body weight was increased, however, absolute testes weight was not statistically different from control testes weight. In addition, no test substance-related microscopic changes were present. In female one-month recovery rats brain and adrenal gland weights relative to body weight were increased at 250 mg/kg/day. There were no correlative effects in other weight parameters or microscopic changes in these organs. Weights for these latter organs are generally maintained despite body weight loss, and thus this pattern of organ weight change is also consistent with effects occurring secondary to decrements in body weight.

2. Gross Observations
(Tables 38-39, Appendix M)

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

3. Microscopic Findings
(Tables 40-45, Appendix M)

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

**Incidences and Average Lesion Grades of Test Substance-Related Microscopic Findings
In Male and Female Rats**

Dose: mg/kg/day	0	25	100	250
Males: Exposure				
Teeth:				
Degeneration, ameloblasts (nose)	0/10 ^a (0.0) ^b	0/10 (0.0)	5/10 (0.5)	11/11 (2.0)
Degeneration, ameloblasts (mandible)	0/10 (0.0)	0/10 (0.0)	1/9 (0.1)	10/10 (1.8)
Thyroid gland:				
Hypertrophy, follicular	0/10 (0.0)	0/10 (0.0)	2/10 (0.2)	10/11 (1.5)
Alteration, colloid	9/10 (0.9)	9/10 (1.4)	9/10 (2.3)	11/11 (2.8)
Liver:				
Hypertrophy, hepatocyte, centrilobular	0/10 (0.0)	0/10 (0.0)	9/10 (0.9)	11/11 (1.9)
Kidneys:				
Hypertrophy, tubular	0/10 (0.0)	0/10 (0.0)	1/10 (0.1)	11/11 (1.7)
Males: One-Month Recovery				
Teeth:				
Degeneration, ameloblasts (nose)	0/10 (0.0)	NA	NA	9/10 (1.3)
Thyroid gland:				
Alteration, colloid	10/10 (1.2)	NA	NA	10/10 (2.7)
Liver:				
Hypertrophy, hepatocyte, centrilobular	0/10 (0.0)	NA	NA	10/10 (1.6)
Kidneys:				
Hypertrophy, tubular	0/10 (0.0)	NA	NA	2/10 (0.2)
Males: Three-Month Recovery				
Teeth:				
Degeneration, ameloblasts (nose)	0/5 (0.0)	0/5 (0.0)	1/5 (0.2)	2/5 (0.6)
Thyroid gland:				
Alteration, colloid	5/5 (1.6)	5/5 (2.6)	5/5 (4.0)	5/5 (3.2)
Liver:				
Hypertrophy, hepatocyte, centrilobular	0/5 (0.0)	NE	0/5 (0.0)	1/5 (0.2)

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Dose: mg/kg/day	0	25	100	250
Females: Exposure				
Teeth:				
Degeneration, ameloblasts (nose)	0/10 (0.0)	0/10 (0.0)	6/10 (0.6)	11/11 (2.0)
Degeneration, ameloblasts (mandible)	0/10 (0.0)	0/9 (0.0)	0/10 (0.0)	7/8 (1.4)
Thyroid gland:				
Hypertrophy, follicular	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	6/11 (0.5)
Alteration, colloid	0/10 (0.0)	6/10 (0.6)	4/10 (0.7)	7/11 (0.8)
Liver:				
Hypertrophy, hepatocyte, centrilobular	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	9/11 (1.3)
Females: One-Month Recovery				
Teeth:				
Degeneration, ameloblasts (nose)	0/10 (0.0)	NA	NA	7/10 (1.1)
Thyroid gland:				
Alteration, colloid	5/10 (0.5)	NA	NA	9/10 (1.1)
Females: Three-Month Recovery				
Teeth:				
Degeneration, ameloblasts (nose)	0/5 (0.0)	NE	0/5 (0.0)	2/5 (0.4)
Thyroid gland:				
Alteration, colloid	5/5 (1.2)	4/4 (1.5)	4/5 (1.0)	5/5 (2.2)

^a Numerator indicates incidence of rats with microscopic lesion. Denominator indicates number of rats in group.

^b Number in parentheses indicates group average severity of lesion.

NA Tissue not available.

NE Tissue not examined.

Test substance-related tooth lesions in male and female rats administered 100 or 250 mg/kg/day consisted of degeneration and/or disorganization of enamel organ ameloblast cells. This lesion was most evident in the upper incisors of the level 1 (anterior) nose section. A similar lesion was present in cross sections of mandibular teeth, however, the frequency of occurrence and severity were generally less than the ameloblastic degeneration/disorganization observed in the nose sections. Following a one-month recovery, ameloblastic degeneration/disorganization was still present in male and female rats previously dosed with 250 mg/kg/day; following three months of recovery this lesion was present in males previously dosed with 100 and 250 mg/kg/day and in females previously dosed with 250 mg/kg/day. This tooth lesion is consistent with fluoride toxicosis and is considered adverse.⁽²⁴⁾

Thyroid follicular hypertrophy was present in males administered 100 and 250 mg/kg/day and females administered 250 mg/kg/day. Follicular hypertrophy was characterized by low columnar follicular epithelium with a finely granular or vacuolated cytoplasm. Hypertrophy was reversible in both male and female rats, as this change was not present in dosed rats following the one- and three-month recovery periods. Thyroid hypertrophy was minimal and unassociated with proliferative thyroid lesions. However, this hypertrophy indicates possible disruption of thyroid homeostasis and thus was considered potentially adverse.

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In the thyroid gland, the relative degree (and in females, the incidence) of altered colloid was increased in males and females in all dosed groups at the end of the exposure period. Following the one- and/or three-month recovery periods, severity grades for colloid clumping were increased in males at all dose levels and in females at the 250 mg/kg/day level only. The diagnosis of "alteration, colloid" was used for colloid changes characterized by stippled, granular, clumped, and/or diffusely basophilic colloid. A 4-level grading scheme was applied based on an estimate of the percentage of follicles that contained altered colloid. A grade of 1 was applied when 1 follicle to about 25% of the follicles were involved, with grades 2, 3, and 4 applied for each 25% increase in follicular involvement. The size, density, or staining intensity of stipples, granules, clumps, or diffuse basophilia within individual follicles did not impact the grading. There was no consistent association between the presence or absence of altered colloid and the presence of hypertrophy of thyroid follicular cells.

Altered colloid described as clumped or granular has been reported to occur spontaneously in Sprague-Dawley rats with increasing incidence correlating to increasing age.⁽²⁵⁾ Because altered colloid occurs spontaneously in healthy Sprague-Dawley rats, and since increases in its grading score did not consistently correlate with other morphologic alterations in the thyroid gland, altered colloid was interpreted as not biologically meaningful and not adverse.

Hypertrophy of centrilobular hepatocytes was present in 100 and 250 mg/kg/day males and 250 mg/kg/day females sacrificed at the end of the exposure period. In male rats previously dosed with 250 mg/kg/day, hepatocellular hypertrophy was present, but was less severe, after a one-month recovery period and was present in only one of 5 rats sacrificed after a three-month recovery period. Microscopic hepatocellular hypertrophy was not observed in male rats in the 100 mg/kg/day three-month recovery group or in any female rat recovery group. Taken together, these findings suggest that microscopic hepatocellular hypertrophy was mostly reversible in males following three-months recovery and in females within one month of 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, and hepatic enzyme levels were not elevated (see clinical pathology section). Thus, hepatocellular hypertrophy (and the associated increase in liver weights) was considered a test substance-related physiologic response to metabolism of a xenobiotic and not toxicologically adverse.^(26,27,28)

Renal tubular hypertrophy was present in 250 mg/kg/day male rats sacrificed at the end of the exposure period. In addition, hypertrophy was seen in one of ten rats in the 100 mg/kg/day male exposure group. Following the one-month recovery period, minimal hypertrophy was present in 2 of 10 male rats, but this change was not observed in rats sacrificed after the three-month recovery period. Thus, hypertrophy decreased in incidence and severity after one-month recovery and appeared to be reversible by three-months recovery. Microscopically, tubular hypertrophy was characterized by increased eosinophilic staining of cortical tubule epithelium and a slight increase in cell height. Cortical tubule epithelial cells appeared to contain more granular cytoplasmic material than cortical tubules of control rats. Tubular lumina of hypertrophied tubules were slightly smaller than those in control rat kidneys. There was no histomorphologic evidence of renal damage, and renal clinical pathology parameters were not indicative of adverse effects (see clinical pathology section). Thus, the renal tubular hypertrophy

(and the associated increase in kidney weights) was considered a test substance-related physiologic response to a xenobiotic and not toxicologically adverse.⁽²⁹⁾ Renal tubular hypertrophy was not observed in female rats at any dose level.

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

4. Cause of Death

There were no test substance-related deaths. One 25 mg/kg/day female rat (Animal No. 643411) was accidentally killed during blood collection. One male rat in the 100 mg/kg/day group (Animal No. 643175) and one male rat and one female rat in the 250 mg/kg/day groups (Animal Nos. 643309 and 643368, respectively) died from dosing injuries. Two female rats in the control (Animal No. 643336) and 25 mg/kg/day (Animal No. 643321) groups died from urogenital inflammation/obstruction/calculi complications. A cause of death was not determined for a 250 mg/kg/day female subchronic toxicity rat (Animal No. 643340) that was found dead on test day 69.

5. Anatomical Pathology Conclusions for Subchronic Toxicity Evaluation

Exposure to 100 or 250 mg/kg/day of the test substance for approximately 90 days produced degeneration/disorganization of enamel organ ameloblast cells in male and female rats. Ameloblastic degeneration/disorganization was not reversible after three-months recovery in 100 mg/kg/day males and in 250 mg/kg/day males and females. Thyroid gland hypertrophy observed in 100 and 250 mg/kg/day males and in 250 mg/kg/day females was reversible at one month and was considered to be potentially adverse. The severity of altered colloid in thyroid glands increased beyond control level as the dose increased, however, it was not consistently associated with any other morphologic alteration and was not considered biologically adverse. Increased liver weights were present in males and females at 25, 100, and 250 mg/kg/day. The increased liver weights correlated with microscopic centrilobular hepatocellular hypertrophy in males at 100 and 250 mg/kg/day and in females at 250 mg/kg/day groups. Hepatocellular hypertrophy was mostly reversible in males following three-months recovery and in females within one month of recovery. Increased kidney weights were present in 25, 100 and 250 mg/kg/day males and females. In males, these kidney weight changes correlated with microscopic renal tubular hypertrophy. The increased kidney weights and male renal tubular hypertrophy appeared to be reversible by three months of recovery. These liver and kidney changes were considered to represent physiologic responses to administration of a xenobiotic and thus were not considered to be toxicologically significant. Under the conditions of this study, the NOEL for pathology for male and female rats was 25 mg/kg/day based on tooth lesions at the 100 and 250 mg/kg/day dose levels.

REPRODUCTIVE TOXICOLOGY EVALUATIONS

REPRODUCTIVE FUNCTION

A. P₁ Generation

1. Mean Body Weights and Body Weight Gains (Table 44-46, Appendices O-T)

There was a statistically significant reduction (89-91% of control mean) in body weight in P₁ male rats at 250 mg/kg/day during and after the cohabitation period. Although this finding was test substance-related, it was not considered toxicologically significant since there was no concomitant reduction in body weight gain in P₁ males during that period. There were no test substance-related effects on body weight or body weight gain in P₁ female rats during gestation or lactation.

2. Food Consumption and Food Efficiency During Gestation (Table 47, Appendix U)

There were no test substance-related effects on food consumption and food efficiency in P₁ female rats during gestation.

3. Clinical Observations (Tables 48, Appendices V-X)

There were no toxicologically significant clinical observations in male and female rats at any dose level. There was an increase in tooth clipping required in male rats administered 250 mg/kg/day. Two females in the 250 mg/kg/day dose group also required teeth clipping (Animal No. 643429 on Day 0G and 643417 on Lactation Day 7). One P₁ female rat (Animal No. 643429) in the 250 mg/kg/day group and her 16 pups were found dead on Lactation Day 0. Prior to death this animal exhibited weakness, diarrhea, wet underbody, facial staining on Gestation Day 21; this animal also had teeth clipped on Gestation Day 0. The cause of death was determined to be dystocia and was not considered test substance-related due to the single occurrence of this finding and the occasional occurrence of this condition in control animals of the strain of rat used in this study. One P₁ female rat (Animal No. 643454) in the 100 mg/kg/day group died on gestation day 22. The cause of death was undetermined but was not considered test substance-related due to the absence of signs of toxicity or gross lesions in this animal.

4. Reproductive Indices (Tables 49-51, Appendices Y-EE)

There were no test substance-related effects on estrous cycle parameters, sperm morphology, motility, or epididymal sperm counts in the P₁ generation. At 100 and 250 mg/kg/day, there was a statistically significant increase in testicular spermatid numbers (123% and 113% of control, respectively) in P₁ male rats. This finding was not considered test substance-related since the

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means for these groups were within the historical control range for previous studies and the increase appeared to be due to a slightly lower than usual mean in the control group.

There were no test substance-related effects on mating or fertility indices, gestation length or number of implantation sites. Implantation efficiency (number of pups born ÷ uterine implantation sites × 100) was significantly reduced at 100 and 250 mg/kg/day (83.4% and 84.5%, respectively, compared to 96.6% in the control group), and reflects the reduction in the number of pups born (see section B.1.).

B. Offspring Data

1. Litter Size, and Pup Weights, Clinical Observations, and Survival (Table 52-54; Appendix FF-HH)

At 250 mg/kg/day, there were statistically significant reductions in the number of pups born, the number of pups born alive and the number of pups alive on day 4 of lactation (85%, 83% and 81% of control mean, respectively). At 100 mg/kg/day, reductions of similar magnitude as in the 250 mg/kg/day group were observed for the number of pups born and born alive (84% and 77% of control, respectively). Although not statistically significant these changes were considered test substance-related, as was the significant reduction in the number of pups alive on Day 4 of lactation (68% of control) at 100 mg/kg/day.

There were no significant reductions in gestation index, mean % born alive, 0-4 day viability, lactation index or litter survival.

At 250 mg/kg/day, there were statistically significant reductions in pup weights on lactation days 4, 7, 14, and 21 (89%, 85%, 78%, and 75% of control mean, respectively).

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

C. F₁ Generation

Mean Body Weights and Body Weight Gains (Table 55-56, Appendices II-JJ)

On the day of weaning (Lactation Day 21 = test day 1) mean body weights were significantly lower than control (74%-78% of control mean) in both F₁ males and females at 250 mg/kg/day. Subsequently, weekly mean body weights in F₁ males were significantly lower than control throughout the post-weaning period (81%-93% of control) in this group. For F₁ females weekly mean body weights were significantly lower than control for test days 8 and 15 (85%-92% of control) and were similar to control thereafter. Thus mean body weights in these groups progressively returned to control values during the post-weaning period. Because the lower body weights in the F₁ generation at 250 mg/kg/day appeared to be due to a test substance-related effect on pup weight during the lactation period (see section B.1.) and there was no concomitant reduction in body weight gain in F₁ males or females during the post-weaning period these findings were not considered toxicologically significant.

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1. Clinical Observations
(Tables 57, Appendices LL)

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

2. Developmental Landmarks
(Tables 58, Appendices LL)

The age at onset of vaginal opening in F₁ female rats was similar across groups. The age at onset of preputial separation in F₁ male rats was similar across groups.

D. Reproductive Function Conclusions

For the reproductive toxicity parameters evaluated under the condition of this study, the NOEL was 25 mg/kg/day.

REPRODUCTIVE TOXICOLOGY EVALUATIONS

ANATOMICAL PATHOLOGY

A. Organ Weight Data

Parental P₁ Adults and F₁ Adults
(Tables 59-62; Appendix MM)

There was a statistically significant increase in thyroid gland weight relative to body weight in P₁ males at 250 mg/kg/day, however, thyroid absolute weight was not significantly different from thyroid control weights. The increased thyroid weight was secondary to decreased final body weight in the 250 mg/kg/day P₁ males.

In F₁ males at 250 mg/kg/day there were statistically significant decreases in liver and testes absolute weights and in epididymide absolute and relative to brain weights. There were no weight changes in these organs when adjusted to final body weight. These statistically significant organ weight changes were secondary to decreased final body weight in the 250 mg/kg/day F₁ males.

In F₁ females there were statistically significant increases in liver weight relative to final body weight and relative to brain weight at 250 mg/kg/day and in kidney weight relative to brain weight at 100 and 250 mg/kg/day dose levels. Neither liver nor kidney absolute weights were statistically different from control weights. The kidney to brain weight changes were not dose dependent.

None of the organ weight changes were considered to be toxicologically or biologically adverse.

B. Gross Observations

Parental P₁ Adults (Tables 63-64, Appendix NN)
F₁ Adults and Weanlings (Tables 65-71, Appendix OO-QQ)

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

C. Microscopic Observations

Parental P₁ Adults (Tables 72-73, Appendix NN)

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

D. Mortality

Parental P₁ Adults and F₁ Adults (Appendices NN and QQ)

There were no test substance-related effects on mortality. Two P₁ female rats were found dead. Cause of death appeared to be dystocia for rat Animal No. 643429 (250 mg/kg/day) and was undetermined for rat Animal No. 643454 (100 mg/kg/day). One 250 mg/kg/day P₁ female rat (Animal No. 643346) was sacrificed *in extremis* after sustaining an injury in its cage; the fate of this animal is reported as accidentally killed.

E. Anatomical Pathology Conclusions for Reproductive Toxicity

For pathology, the NOEL was 250 mg/kg/day (the highest dose level) for both male and female rats.

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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-24516 in rats following 10 or 90 (males) and 92 (females) days of test substance administration or following a one- or three-month recovery period.

Dose-dependent increases in the rate of hepatic β -oxidation were observed at the 10-day time point with statistical significance occurring for rats administered 100 or 250 mg/kg/day (223 and 349% of control, respectively, in the males and 170 and 260% of control, respectively, in the females). Dose-dependent increases in the rate of hepatic β -oxidation were also observed at the 90-day time point with statistical significance occurring for rats administered 100 or 250 mg/kg/day (398 and 856% of control, respectively, in the males and 345 and 381% of control, respectively, in the females). At both time points, the increases in hepatic β -oxidation activity were accompanied by increases in liver weights.

Following a one-month recovery period, statistically significant increases in the rate of hepatic β -oxidation persisted in rats administered 250 mg/kg/day (353 and 207% of control, respectively, in males and females). Statistically significant increases in the rate of hepatic β -oxidation also persisted after the three-month recovery period for the 250 mg/kg/day dose group (302 and 172% of control, respectively, in males and females). At the one-month recovery time point, the increase in hepatic β -oxidation activity was accompanied by increased liver weights in the males, but not the females.

B. Biochemical Measurements Conclusions

Under the conditions of this study, H-24516 is an inducer of hepatic peroxisomal β -oxidation. At dosages of 100 mg/kg/day and greater, changes in the rate of hepatic peroxisome proliferation were considered to be biologically significant effects. After three months of recovery, the rate of hepatic peroxisome proliferation was still increased in rats administered 250 mg/kg/day.

CONCLUSIONS

No test substance-related mortality or alterations in neurobehavioral parameters were observed in male or female rats. Test substance-related and toxicologically significant decrements in mean body weight, body weight gain, and food efficiency were observed in male rats administered 100 and 250 mg/kg/day compared to controls. Food consumption was also significantly lower in male rats administered 250 mg/kg/day. After a one- and/or three-month recovery period, these parameters were similar to or exceeded control. Test substance-related, toxicologically significant increases in the incidence of broken (males) and absent teeth (males and females) occurred in the 250 mg/kg/day dose group. Statistically significant decrements in mean body weight parameters and food consumption occurred for females administered 100 or 250 mg/kg/day. The decrements in female body weight parameters were not considered to be toxicologically significant. Furthermore, the decrements in body weight parameters appear to be related to test substance-induced adverse effects to the teeth and decreased ability of the animals to eat pelleted chow.

Toxicologically adverse findings of minimally decreased red cell mass parameters (RBC, hemoglobin, and hematocrit), along with correlative changes in other hematology parameters and in red cell morphology were observed after the 90-day exposure period in males and females administered 250 mg/kg/day H-24516. After a one-month recovery period, the 250 mg/kg/day male dose group still had minimally to mild decreased red cell mass parameters as well as decreased reticulocytes compared to control. Red cell mass parameters for the 250 mg/kg/day female group returned to control levels, however, some hematological parameters (MCV, MCH, RDW, and reticulocytes) were still decreased.

A statistically significant rate of hepatic β -oxidation occurred in males and females administered 100 or 250 mg/kg/day H-24516. The increased rate persisted in the 250 mg/kg/day groups after one and three months.

Test substance related, toxicologically significant degeneration/disorganization of enamel organ ameloblasts cells occurred in male and female rats dosed with 100 or 250 mg/kg/day H-24516. This tooth lesion is consistent with fluoride toxicosis.⁽²⁴⁾ After three months, the degeneration/disorganization of ameloblasts persisted, at a lower incidence and severity.

Test substance related, potentially adverse increases in thyroid hypertrophy were observed in the 100 and 250 mg/kg/day male and 250 mg/kg/day female dose groups after the 90-day exposure period. After the one-month recovery period, thyroid hypertrophy was not observed in any dose group.

Increased liver weights and/or hepatocellular hypertrophy were observed in male and female rats at all dose levels. Similarly, increased kidney weights and/or renal tubular hypertrophy were observed in male and female rats at all dose levels. These latter changes were considered to be a pharmacologically adaptive, non-adverse response. After the three-month recovery period, liver weights remained increased in the 250 mg/kg/day male and female groups, while hepatocellular

hypertrophy was observed only in the 250 mg/kg/day male group (1 of 5 rats). Alterations in kidneys were not observed at any dose level after the three-month recovery period.

There were no toxicologically significant pathology findings in the P₁ and F₁ generation rats. A statistically significant increase in testicular spermatid numbers in P₁ male rats was not considered test substance-related.

Implantation efficiency was significantly reduced at 100 and 250 mg/kg/day and reflects the reduction in the number of pups born.

There were statistically significant reductions in the number of pups born, the number of pups born alive and the number of pups alive on day 4 of lactation in the 250 mg/kg/day group. Reductions of similar magnitude were also observed for the number of pups born and born alive in the 100 mg/kg/day group. Although not statistically significant, these changes were considered test substance-related and toxicologically significant, as was the significant reduction in the number of pups alive on day 4 of lactation in the 100 mg/kg/day group. There were statistically significant reductions in pup weights on lactation days 4, 7, 14 and 21 in the 250 mg/kg/day groups.

On the day of weaning mean body weights were significantly lower than control in both F₁ males and females in the 250 mg/kg/day group. F₁ generation body weights at 250 mg/kg/day progressively returned to control values during the post-weaning period indicating that the test substance-related effect on pup weight during the lactation period was reversed following cessation of exposure and therefore, were not considered toxicologically significant.

The no-observed-effect level (NOEL)^a for H-24516 for the 90-day exposure period was 25 mg/kg/day based on adverse decrements in body weight parameters and food efficiency, increased hepatic peroxisomal β -oxidation, and the degeneration and/or disorganization of enamel organ ameloblast cells in males administered 100 mg/kg/day. The NOEL for females was 25 mg/kg/day H-24516 based on increased hepatic peroxisomal β -oxidation and the degeneration and/or disorganization of enamel organ ameloblast cells in females administered 100 mg/kg/day. The NOEL for reproductive evaluations was 25 mg/kg/day based on decreases in the number of pups born, born alive, and the number of pups alive on day 4 of lactation at the 100 mg/kg/day dose level.

^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⁽³⁰⁾ and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union⁽³¹⁾.

REFERENCES

1. DuPont (1995). Neurotoxicity Evaluation of Trimethyltin in Rats (Positive Control Study).
[REDACTED]
2. DuPont (1997). Neurotoxicity Evaluation of Amphetamine in Rats (Positive Control Study).
[REDACTED]
3. DuPont (1997). Neurotoxicity Evaluation of Carbaryl in Rats (Positive Control Study).
[REDACTED]
4. DuPont (1996). Neurotoxicity Evaluation of Acrylamide in Rats (Positive Control Study).
[REDACTED]
5. Lazarow, P.B. (1981). Assay of Peroxisomal Beta-Oxidation of Fatty Acids. *Methods in Enzymology* 72, 315-319.
6. Bradford, M.M. (1976). A Rapid and Sensitive Method for the Quantitation of Microgram Quantities of Protein Utilizing the Principle of Protein-Dye Binding. *Anal. Biochem.* 72, 248-254.
7. Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Amer. Statist. Assoc.* 50, 1096-1121.
8. Dunn, O.J. (1964). Multiple contrasts using rank sums. *Technometrics* 6, 241-252.
9. Draper, N.R. and Smith, H. (1981). *Applied Regression Analysis*, 2nd edition, pp 266-273. Wiley, New York.
10. Selwyn, M.R. (1995). The use of trend tests to determine a no-observable-effect level in animal safety studies. *Journal of the American College of Toxicology* 14(2), 158-168.
11. Jonckheere, A.R. (1954). A distribution-free K-sample test against ordered alternatives. *Biometrika* 41, 133-145.
12. Levene, H. (1960). Robust test for equality of variances. *Contributions to Probability and Statistics* (J. Olkin, ed.), pp 278-292. Stanford University Press, Palo Alto.
13. Shapiro, S.S. and Wilk., M.B. (1965). An analysis of variance test for normality (complete samples). *Biometrika* 52, 591-611.
14. Snedecor, G.W. and Cochran, W.G. (1967). *Statistical Methods*, 6th edition, pp 246-248 and 349-352. The Iowa State University Press, Ames.
15. Kruskal, W.H. and Wallis, W.A. (1952). Use of ranks in one-criterion analysis of variance. *J. Amer. Statist. Assoc.* 47, 583-621.

16. Milliken, G.A. and Johnson, D.A. (1984). *Analysis of Messy Data, Volume 1.: Designed Experiments*. Lifetime Learning Publications, Belmont.
17. Hocking, R.A. (1985). *The Analysis of Linear Models*. Brooks/Cole, Monterey.
18. Bartlett, M.S. (1937). Some examples of statistical methods of research in agriculture and applied biology. *J. Royal. Statis. Soc. Suppl.* **4**, 137-170.
19. Fisher, R.A. (1985). *Statistical Methods for Research Workers*, 13th edition. Haffner, New York.
20. Dempster, A.P., Selwyn, M.R., Patel, C.M., and Roth, A.J. (1984). Statistical and computational aspects of mixed model analysis. *The Journal of the Royal Statistical Society, Series C (Applied Statistics)* **33(2)**, 203-214.
21. Haseman, J.K. and Hogan, M.D. (1975). Selection of the experimental unit in teratology studies. *Teratology*, **12**, 165-171.
22. Patefield, W. (1982). Exact tests for trends in ordered contingency tables. *Applied Statistics* **31**, 32-43.
23. Hoffman, W.E. and Solter, P.F. (1999). Clinical Enzymology. The Clinical Chemistry of Laboratory Animals (W.F. Loeb and F.W. Quimby, eds.), Taylor and Francis, Philadelphia, PA. pp399-454.
24. Reddy, C.S., and Hayes, A.W. (1989). Food Borne Toxicants. In Principles and Methods of Toxicology (A. W. Hayes, Ed.), Raven Press, New York, pp67-110.
25. Rao-Rupanagudi, S., Heywood, R., and Gopinah, C. (1991). "Age-related Changes in Thyroid Structures and Function in Sprague-Dawley Rats," *Vet. Pathol.*, Vol. 29, No. 4, pp. 278-287.
26. Sipes, G. I., and Gandolfi, A. J. (1991). In Biotransformation of Toxicants. In Casarett and Doull's Toxicology: The Basic Science of Poisons (Amdur, M. O., Doull, J., and Klaassen, C. D., Ed.), Pergamon Press, New York, pp 88-126.
27. Paynter, O.E., Harris, J.E., Burin, G.J., and Jaeger, R.B. (1985). Guidance for Analysis of Evaluation of Subchronic Exposure Studies. United States Environmental Protection Agency, EPA-540/9-85-020.
28. Greaves, P. (1990). Digestive System 2. In Histopathology of Preclinical Toxicity Studies: Interpretation and Relevance in Drug Safety Evaluation (P. Greaves, Ed.), Elsevier, Amsterdam, pp 393-496.
29. Greaves, P. (1990). Urinary Tract. In Histopathology of Preclinical Toxicity Studies: Interpretation and Relevance in Drug Safety Evaluation (P. Greaves, Ed.), Elsevier, Amsterdam, pp 497-583.

30. Hazard Evaluation Division, Standard Evaluation Procedure, Toxicity Potential: Guidance for Analysis and Evaluation of Subchronic and Chronic Exposure Studies Paynter, O. E. et al., United States Environmental Protection Agency, Office of Pesticide Programs, Washington, D.C., 20406. EPA-540/9-85-020. (June 1985).
31. Risk Assessment of Notified New Substances. Technical Guidance Document (XI/283/94-EN), Chapter I, Sections 2.24 and 2.25. 1994.

TABLES

TABLES

EXPLANATORY NOTES

Critical Dates

- Day 74 Male and female rats designated for reproduction evaluations were co-housed. 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.
- Days 83-89 Rats designated for the 3-month recovery period were temporarily housed in metabolism cages for urine and feces collection. Food consumption data was not collected for these animals during this period.
- Day 89 Last day of test substance administration for male and female rats designated for one-month and 3-month recovery periods.
- Day 90
- Last day of test substance administration for male rats designated for the 90-day exposure period.
 - Last day of non-fasted body weight and food consumption data collection for male rats designated for the 90-day exposure period.
- Day 91
- Last day of non-fasted body weight and food consumption data collection for female rats designated for the 90-day exposure period.
 - Male rats designated for the 90-day exposure period were sacrificed.
- Day 92 Last day of test substance administration for female rats designated for the 90-day exposure period.
- Day 93 Female rats designated for 90-day exposure period were sacrificed.
- Day 119 Last day of non-fasted body weight and food consumption data collection for rats designated for the one-month recovery period.
- Day 125 Male and female rats designated for the one-month recovery were sacrificed.
- Day 175 Last day of non-fasted body weight and food consumption data collection for rats designated for the 3-month recovery period.
- Day 181 Male and female rats designated for the 3-month recovery period were sacrificed.

Note

On test day 18, all male rats and the first 11 female rats in the 25 mg/kg/day group received 38 mg/kg/day.

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

Summary of Hematology Values

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

Summary of Coagulation Values

PT	-	prothrombin time
APTT	-	activated partial thromboplastin time

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TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

Summary of Serum and Plasma Chemistry Values

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

Summary of Urinalysis Values

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

Notes for Clinical Pathology data:

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

Company Sanitized. Does not contain TSCA CBI

TABLE 1
SUMMARY OF DOSING ANALYSES

Nominal:	Dosing Concentration of H-24516 (mg/mL)		
	2.5	10.0	25.0
Homogeneity Samples			
Test Day 0			
Top	2.30 (92.0) ^a	8.97 (89.7)	26.8 (107.2)
Middle	2.47 (98.8)	10.2 (102.0)	24.8 (99.2)
Bottom	2.40 (96.0)	14.0 (140.0)	23.5 (94.0)
Average Measured Conc. ^b	2.39	11.1	25.0
Average Percent Nominal	(95.6)	(111.0)	(100.0)
Standard Deviation ^b	± 0.08	± 2.6	± 1.6
Coefficient of Variation ^b	3%	24%	7%
Stability Samples			
5 Hour Room Temperature	2.06 (82.4)	8.89 (88.9)	24.1 (96.4)
Homogeneity Samples			
Test Day 6			
Top	--- ^c	9.26 (92.6)	--- ^c
Middle	--- ^c	9.58 (95.8)	--- ^c
Bottom	--- ^c	9.23 (92.3)	--- ^c
Average Measured Conc. ^b	---	9.36	---
Average Percent Nominal	---	(93.6)	---
Standard Deviation ^b	---	± 0.19	---
Coefficient of Variation ^b	---	2%	---
Stability Samples			
5 Hour Room Temperature	--- ^c	9.03 (90.3)	--- ^c

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

^b Statistics based on the average measured concentration (ppm) of the top, middle and bottom of each dosing level.

^c Samples not required for study.

Company Sanitized. Does not contain TSCA CBI

TABLE 1 (CONTINUED)

SUMMARY OF DOSING ANALYSES

		Dosing Concentration of H-24516 (mg/mL)		
Nominal:		3.33	13.33	33.33
Homogeneity Samples				
Test Day 49				
Top		2.71 (81.4) ^a	10.8 (81.0)	31.0 (92.9)
Middle		2.99 (89.8)	12.7 (95.3)	32.4 (97.1)
Bottom		3.42 (102.8)	12.8 (96.3)	33.4 (100.3)
Average Measured Conc. ^b		3.04	12.1	32.3
Average Percent Nominal		(91.3)	(90.8)	(96.8)
Standard Deviation ^b		± 0.4	± 1.1	± 1.2
Coefficient of Variation ^b		12%	9%	4%
Test Day 91				
Top		3.05 (91.6)	12.8 (96.0)	32.7 (98.1)
Middle		3.00 (90.1)	12.2 (91.5)	32.3 (96.6)
Bottom		3.01 (90.4)	--- ^c	--- ^c
Average Measured Conc. ^b		3.02	12.5	32.5
Average Percent Nominal		(90.7)	(90.8)	(97.5)
Standard Deviation ^b		± 0.03	± 0.4	± 0.3
Coefficient of Variation ^b		1%	3%	1%

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

^b Statistics based on the average measured concentration (ppm) of the top, middle and bottom of each dosing level for homogeneity samples or the average of duplicate sample for concentration verification samples (13.33 mg/mL and 33.33 mg/mL submitted test day 91).

^c Samples not required for study.

TABLE 1 (CONTINUED)

SUMMARY OF DOSING ANALYSES

		Dosing Concentration of H-24516 (mg/mL)			
<u>Stability Study</u>					
Nominal:		3.33 ^a	5.0 ^b	20.0 ^b	50.0 ^b
Homogeneity Samples					
Top		2.88 (86.5) ^c	4.53 (90.6)	19.9 (99.5)	53.4 (106.8)
Middle		2.54 (76.3)	4.25 (85.0)	17.7 (88.5)	52.6 (105.2)
Bottom		2.67 (80.2)	4.39 (87.8)	18.6 (93.0)	54.0 (108.0)
Average Measured Conc. ^d		2.70	4.39	18.7	53.3
Average Percent Nominal		(81.1)	(87.8)	(93.5)	(106.6)
Standard Deviation ^d		± 0.2	± 0.14	± 1.1	± 0.7
Coefficient of Variation ^d		6%	3%	6%	1%
Stability Samples					
0-Day Room Temperature ^e		2.70 (81.1)	4.39 (87.8)	18.7 (93.5)	53.4 (106.8)
5 Hour Room Temperature		2.66 (79.9)	4.60 (92.0)	17.2 (86.0)	48.3 (96.6)
2-Day Refrigerated		--- ^f	4.77 (95.4)	18.3 (91.5)	47.9 (95.8)
3-Day Refrigerated		--- ^f	4.61 (92.2)	29.4 (147.0)	46.7 (93.4)
4-Day Refrigerated		2.91 (87.4)	4.81 (96.1)	19.6 (97.8)	48.9 (97.8)
4-Day Refrigerated/5 hr.		2.74 (82.3)	4.85 (97.1)	17.6 (88.2)	47.9 (95.7)

^a Samples prepared based on 7.5 mL/Kg dose volume.

^b Samples prepared based on 5.0 mL/Kg dose volume.

^c Numbers in parentheses are the respective percent of nominal values.

^d Statistics based on the average measured concentration (ppm) of the top middle and bottom of each dosing level.

^e The mean measured values from analysis of homogeneity samples (considered fresh/0-day room temperature samples) were used as baselines for comparison with the respective stability samples.

^f Samples not required for study.

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 250 mg/kg/day
DAY 0 -DAY 6	2.5 0.2 (45)	2.5 0.2 (35)	2.5 0.2 (35)	2.5 0.2 (45)
DAY 7 -DAY 13	3.1 0.2 (45)	3.0 0.2 (35)	3.1 0.2 (35)	3.1 0.2 (45)
DAY 14 -DAY 20	3.6 0.3 (45)	3.6 0.3 (35)	3.6 0.3 (35)	3.6 0.3 (45)
DAY 21 -DAY 27	4.0 0.3 (45)	3.9 0.3 (35)	4.0 0.3 (35)	4.0 0.3 (45)
DAY 28 -DAY 34	4.3 0.4 (45)	4.3 0.4 (35)	4.3 0.3 (35)	4.3 0.4 (45)
DAY 35 -DAY 41	4.6 0.4 (45)	4.6 0.4 (35)	4.6 0.3 (35)	4.6 0.4 (45)
DAY 42 -DAY 48	3.6 0.3 (45)	3.6 0.3 (35)	3.6 0.3 (35)	3.6 0.3 (45)
DAY 49 -DAY 55	3.8 0.3 (45)	3.7 0.3 (35)	3.7 0.3 (35)	3.6 0.3 (45)
DAY 56 -DAY 62	3.9 0.4 (45)	3.8 0.4 (35)	3.8 0.3 (35)	3.6 0.3 (45)
DAY 63 -DAY 69	4.0 0.4 (45)	3.9 0.4 (35)	4.0 0.3 (35)	3.7 0.4 (45)
DAY 70 -DAY 76	4.1 0.4 (45)	4.0 0.4 (35)	4.0 0.3 (35)	3.6 0.4 (45)
DAY 77 -DAY 83	4.2 0.5 (25)	4.1 0.4 (15)	3.9 0.3 (14)	3.6 0.4 (26)
DAY 84 -DAY 89	4.3 0.5 (25)	4.2 0.4 (15)	3.9 0.3 (14)	3.8 0.4 (25)
DAY 90	4.5 0.4 (10)	4.3 0.5 (10)	4.0 0.2 (9)	4.0 0.3 (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 250 mg/kg/day
DAY 0 - DAY 6	1.9 0.2 (45)	1.9 0.2 (35)	1.9 0.1 (35)	1.9 0.2 (45)
DAY 7 - DAY 13	2.1 0.2 (45)	2.2 0.2 (34)	2.1 0.2 (35)	2.2 0.2 (45)
DAY 14 - DAY 20	2.3 0.2 (45)	2.3 0.2 (34)	2.3 0.2 (35)	2.4 0.2 (45)
DAY 21 - DAY 27	2.5 0.2 (45)	2.6 0.2 (34)	2.5 0.2 (35)	2.5 0.2 (45)
DAY 28 - DAY 34	2.6 0.2 (45)	2.7 0.2 (34)	2.6 0.2 (35)	2.6 0.2 (45)
DAY 35 - DAY 41	2.8 0.3 (45)	2.8 0.2 (33)	2.7 0.2 (35)	2.8 0.2 (45)
DAY 42 - DAY 48	2.1 0.2 (45)	2.2 0.2 (33)	2.1 0.2 (35)	2.1 0.2 (45)
DAY 49 - DAY 55	2.2 0.2 (45)	2.2 0.2 (33)	2.1 0.2 (35)	2.1 0.2 (45)
DAY 56 - DAY 62	2.3 0.2 (45)	2.3 0.2 (33)	2.2 0.2 (35)	2.1 0.2 (44)
DAY 63 - DAY 69	2.3 0.2 (45)	2.3 0.2 (33)	2.2 0.2 (35)	2.1 0.2 (44)
DAY 70 - DAY 76	2.3 0.2 (45)	2.4 0.2 (33)	2.2 0.2 (35)	2.1 0.2 (43)
DAY 77 - DAY 83	2.3 0.3 (25)	2.3 0.2 (13)	2.2 0.2 (15)	2.1 0.2 (24)
DAY 84 - DAY 90	2.4 0.3 (25)	2.3 0.2 (13)	2.2 0.2 (15)	2.2 0.2 (24)
DAY 90 - DAY 92	2.3 0.3 (10)	2.4 0.2 (9)	2.2 0.2 (10)	2.2 0.2 (9)

Data summarized as: Mean
Standard Deviation (n)

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0	250.1 18.5(45)	247.7 20.0(35)	250.4 18.0(35)	251.6 17.2(45)
DAY 7	305.6 23.2(45)	304.3 24.2(35)	307.8 21.8(35)	312.9 22.2(45)
DAY 14	356.2 29.2(45)	356.6 28.5(35)	357.1 26.3(35)	360.0 26.1(45)
DAY 21	398.3 33.7(45)	392.8 32.2(35)	398.8 28.3(35)	404.4 30.9(45)
DAY 28	431.2 38.7(45)	428.1 35.0(35)	431.1 30.9(35)	434.0 37.6(45)
DAY 35	457.5 41.8(45)	458.6 39.4(35)	455.1 34.3(35)	459.3 39.5(45)
DAY 42	483.1 44.2(45)	477.1 40.6(35)	476.2 36.0(35)	475.7 40.9(45)
DAY 49	501.5 45.8(45)	490.8 43.2(35)	493.1 37.5(35)	483.4 43.7(45)
DAY 56	519.4 50.4(45)	507.0 50.1(35)	508.1 39.8(35)	486.6# 46.1(45)
DAY 63	535.4 53.5(45)	523.6 51.9(35)	525.3 40.5(35)	487.7# 48.6(45)
DAY 70	551.1 56.7(45)	538.6 52.9(35)	537.0 44.8(35)	473.8# 58.2(45)
DAY 74 ^a	558.1 60.8(20)	548.3 53.8(20)	558.5 39.7(20)	479.6# 49.1(19)

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 77	555.5 60.4(25)	543.7 55.9(15)	513.7# 50.7(15)	479.2# 57.9(25)
DAY 84	567.5 59.6(25)	555.7 59.2(15)	523.2# 38.3(14)	508.8# 52.2(25)
DAY 90	573.5 60.0(25)	560.7 62.1(15)	531.1# 37.4(14)	522.1# 51.4(25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 98	578.2 63.6(15)	539.6 49.3(5)	527.9 39.1(5)	526.2# 58.9(15)
DAY 105	586.2 73.8(15)	549.8 52.7(5)	513.5# 66.0(5)	534.3# 62.7(15)
DAY 112	598.5 70.7(15)	556.8 53.7(5)	525.4# 66.4(5)	540.6# 67.8(15)
DAY 119	597.4 73.5(15)	552.5 60.6(5)	531.7 58.9(5)	548.6 68.4(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 250 mg/kg/day
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 126	567.3 34.4(5)	545.3 47.9(5)	531.1 62.9(5)	530.0 109.7(5)
DAY 133	582.3 36.1(5)	561.1 45.3(5)	545.1 54.0(5)	546.1 113.3(5)
DAY 140	592.6 39.9(5)	569.8 54.3(5)	560.5 58.2(5)	556.6 107.9(5)
DAY 147	598.3 48.2(5)	581.9 56.7(5)	575.0 60.7(5)	573.6 110.3(5)
DAY 154	606.9 45.6(5)	586.5 59.7(5)	587.1 63.4(5)	582.4 108.6(5)
DAY 161	614.4 48.0(5)	592.1 61.1(5)	594.6 67.9(5)	593.9 106.0(5)
DAY 168	619.1 48.8(5)	602.1 61.1(5)	608.0 77.7(5)	607.7 113.4(5)
DAY 175	635.5 53.8(5)	609.7 64.1(5)	618.6 81.8(5)	610.6 112.8(5)

Data summarized as: Mean
Standard Deviation (n)

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

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 74; subsequent data are reported as part of the reproduction evaluation.

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0	191.1 15.5(45)	192.4 15.2(35)	187.6 14.4(35)	190.3 14.9(45)
DAY 7	214.4 19.2(45)	215.4 19.5(34)	211.9 15.4(35)	215.5 18.6(45)
DAY 14	232.5 20.5(45)	233.9 19.0(34)	231.6 18.6(35)	237.5 20.3(45)
DAY 21	249.2 21.8(45)	254.8 22.1(34)	247.8 19.1(35)	251.9 22.6(45)
DAY 28	262.6 24.9(45)	267.6 23.4(34)	260.0 22.9(35)	264.1 23.1(45)
DAY 35	276.0 26.3(45)	280.5 24.7(33)	268.7 23.7(35)	274.9 24.4(45)
DAY 42	283.0 27.8(45)	290.7 26.7(33)	279.0 24.1(35)	283.6 24.0(45)
DAY 49	293.0 28.9(45)	297.7 28.3(33)	286.0 22.0(35)	287.0 28.6(45)
DAY 56	300.5 29.0(45)	301.9 29.5(33)	288.6 20.7(35)	283.7# 32.3(44)
DAY 63	304.3 29.8(45)	307.8 27.9(33)	292.7 21.2(35)	281.5# 29.2(44)
DAY 70	310.4 30.3(45)	313.8 27.9(33)	298.2 19.8(35)	280.0# 32.6(43)
DAY 74 ^a	309.2 30.2(20)	318.2 31.5(20)	302.8 16.2(20)	282.2# 37.3(19)

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 77	311.8 31.9(25)	305.7 25.4(13)	292.1# 21.8(15)	274.5# 24.7(24)
DAY 84	317.1 33.9(25)	309.4 25.5(13)	293.6# 21.6(15)	296.5# 25.7(24)
DAY 91	318.1 40.0(25)	310.4 24.5(13)	295.8# 22.3(15)	299.4# 28.9(24)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 98	332.1 42.4(15)	305.6 18.5(4)	286.6 21.8(5)	304.8 29.4(15)
DAY 105	337.1 45.0(15)	307.7 20.8(4)	291.6 18.3(5)	310.4 33.2(15)
DAY 112	347.8 48.3(14)	317.1 21.1(4)	288.4 39.2(5)	318.6 34.8(15)
DAY 119	348.3 50.5(14)	320.7 22.2(4)	282.2 46.9(5)	322.5 38.5(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 250 mg/kg/day
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 126	292.6 17.7(5)	317.7 23.2(4)	293.2 34.8(5)	325.0 51.9(5)
DAY 133	308.4 17.7(5)	327.4 25.0(4)	301.4 27.9(5)	333.9 52.4(5)
DAY 140	307.8 16.8(5)	333.5 29.6(4)	303.1 29.2(5)	338.0 53.5(5)
DAY 147	315.3 15.8(5)	338.7 29.3(4)	310.9 33.2(5)	349.4 54.0(5)
DAY 154	316.3 22.5(5)	344.3 23.7(4)	316.1 30.8(5)	356.7 54.4(5)
DAY 161	322.9 19.3(5)	344.3 29.9(4)	319.8 31.5(5)	362.1 56.2(5)
DAY 168	329.6 21.1(5)	348.6 31.4(4)	322.0 32.2(5)	359.2 57.2(5)
DAY 175	328.1 20.1(5)	351.0 29.1(4)	326.5 35.6(5)	361.7 58.4(5)

Data summarized as: Mean
Standard Deviation (n)

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

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 74; subsequent data are reported as part of the reproduction evaluation.

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0 - DAY 7	55.5 7.8(45)	56.6 7.0(35)	57.4 8.7(35)	61.3# 7.1(45)
DAY 7 - DAY 14	50.5 8.6(45)	52.3 7.3(35)	49.2 8.0(35)	47.1# 6.5(45)
DAY 14 - DAY 21	42.1 7.5(45)	36.2 6.6(35)	41.7 6.2(35)	44.5# 6.8(45)
DAY 21 - DAY 28	33.0 7.7(45)	35.3 6.7(35)	32.3 7.4(35)	29.6# 12.1(45)
DAY 28 - DAY 35	26.3 6.9(45)	30.5 8.0(35)	24.0 6.4(35)	25.3 6.0(45)
DAY 35 - DAY 42	25.6 5.9(45)	18.5# 5.8(35)	21.1# 5.8(35)	16.4# 13.9(45)
DAY 42 - DAY 49	18.4 8.4(45)	13.7 8.0(35)	16.9 13.3(35)	7.8# 11.8(45)
DAY 49 - DAY 56	17.9 10.3(45)	16.3 11.5(35)	15.0# 7.2(35)	3.1# 22.9(45)
DAY 56 - DAY 63	16.0 7.8(45)	16.5 9.2(35)	17.2 7.5(35)	1.2# 20.0(45)
DAY 63 - DAY 70	15.7 6.0(45)	15.1 5.6(35)	11.7 16.3(35)	-13.9# 39.3(45)
DAY 70 - DAY 74 ^a	3.6 6.7(20)	6.8 7.6(20)	2.3 5.0(20)	4.9 36.7(19)
DAY 0 - DAY 74 ^a	308.8 46.8(20)	300.5 41.5(20)	307.9 32.9(20)	228.6# 39.3(19)

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 70 - DAY 77	7.1 11.5(25)	8.8 7.4(15)	2.4 17.3(15)	6.6 43.9(25)
DAY 77 - DAY 84	12.0 7.3(25)	12.0 8.3(15)	1.2 20.6(14)	29.6# 20.0(25)
DAY 84 - DAY 90	6.0 6.7(25)	5.1 10.2(15)	7.9 14.2(14)	13.3# 10.1(25)
DAY 0 - DAY 90	322.7 49.9(25)	313.0 51.9(15)	281.8# 28.1(14)	271.4# 41.2(25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 90 - DAY 98	19.2 10.0(15)	14.2 4.5(5)	4.9# 11.4(5)	12.7# 8.9(15)
DAY 98 - DAY 105	8.0 14.1(15)	10.2 5.0(5)	-14.4 58.3(5)	8.0 8.7(15)
DAY 105 - DAY 112	12.3 7.5(15)	7.0 14.7(5)	11.9 17.6(5)	6.3 11.2(15)
DAY 112 - DAY 119	-1.1 14.2(15)	-4.3 12.6(5)	6.3 27.4(5)	8.0 7.4(15)
DAY 90 - DAY 119	38.4 16.7(15)	27.2 25.2(5)	8.7* 19.5(5)	35.1 17.9(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 250 mg/kg/day
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 119 - DAY 126	0.6 14.2(5)	-7.2 17.7(5)	-0.6 26.4(5)	7.9 7.0(5)
DAY 126 - DAY 133	15.0 6.0(5)	15.8 15.2(5)	14.0 18.7(5)	16.1 6.2(5)
DAY 133 - DAY 140	10.2 10.7(5)	8.8 10.8(5)	15.4 9.3(5)	10.5 5.8(5)
DAY 140 - DAY 147	5.7 18.4(5)	12.1 3.6(5)	14.4 3.5(5)	17.0 7.3(5)
DAY 147 - DAY 154	8.6 2.9(5)	4.6 7.0(5)	12.1 7.3(5)	8.7 5.6(5)
DAY 154 - DAY 161	7.5 7.0(5)	5.6 1.9(5)	7.5 7.1(5)	11.5 6.7(5)
DAY 161 - DAY 168	4.7 8.3(5)	10.0 3.6(5)	13.4 10.7(5)	13.9 9.0(5)
DAY 168 - DAY 175	16.4 6.1(5)	7.6 6.9(5)	10.7 6.2(5)	2.9# 7.1(5)
DAY 119- DAY 175	68.7 37.4(5)	57.2 13.3(5)	86.9 29.1(5)	88.6# 14.9(5)

Data summarized as: Mean
Standard Deviation (n)

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

* Statistically significant difference at $p < 0.05$ by Dunnett's test.

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 74; subsequent data are reported as part of the reproduction evaluation.

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0 - DAY 7	23.3 8.6(45)	22.5 7.5(34)	24.3 6.1(35)	25.3 6.5(45)
DAY 7 - DAY 14	18.0 7.1(45)	18.4 8.1(34)	19.7 6.9(35)	22.0# 5.8(45)
DAY 14 - DAY 21	16.8 6.9(45)	21.0 6.0(34)	16.2 6.4(35)	14.4# 6.7(45)
DAY 21 - DAY 28	13.4 7.3(45)	12.7 7.6(34)	12.2 10.9(35)	12.2 6.7(45)
DAY 28 - DAY 35	13.4 7.2(45)	12.0 6.2(33)	8.7# 9.2(35)	10.8# 6.1(45)
DAY 35 - DAY 42	7.1 6.3(45)	10.2 6.6(33)	10.3 8.3(35)	8.7 5.7(45)
DAY 42 - DAY 49	10.0 5.6(45)	7.0# 7.8(33)	7.0# 10.8(35)	3.4# 14.1(45)
DAY 49 - DAY 56	7.4 7.8(45)	4.1 11.6(33)	2.7# 5.6(35)	-4.5# 14.5(44)
DAY 56 - DAY 63	3.8 7.2(45)	6.0 9.7(33)	4.0 6.5(35)	-2.2# 22.2(44)
DAY 63 - DAY 70	6.1 6.1(45)	5.9 6.4(33)	5.5 7.3(35)	-1.7# 22.4(43)
DAY 70 - DAY 74 ^a	-1.0 4.2(20)	-1.7 11.2(20)	-1.7 10.0(20)	4.4 31.9(19)
DAY 0- DAY 74 ^a	115.5 20.1(20)	120.3 21.5(20)	111.5 15.2(20)	85.9# 32.1(19)

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 70 - DAY 77	1.3 4.5(25)	1.4 6.2(13)	2.2 5.1(15)	-7.2# 16.3(24)
DAY 77 - DAY 84	5.3 5.6(25)	3.6 3.9(13)	1.4 6.0(15)	22.0# 12.9(24)
DAY 84 - DAY 91	1.0 13.6(25)	1.0 5.3(13)	2.2 4.7(15)	2.8 8.7(24)
DAY 0- DAY 91	129.1 32.5(25)	125.1 20.8(13)	113.1# 14.8(15)	114.1# 20.2(24)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 91 - DAY 98	10.8 13.5(15)	7.9 7.1(4)	0.3 9.6(5)	5.4 10.2(15)
DAY 98 - DAY 105	5.0 11.7(15)	2.0 6.2(4)	5.0 4.0(5)	5.6 5.9(15)
DAY 105 - DAY 112	10.0 8.5(14)	9.4 3.8(4)	-3.2 22.0(5)	8.2 6.2(15)
DAY 112 - DAY 119	0.5 7.6(14)	3.6 3.2(4)	-6.2 25.3(5)	3.9 5.8(15)
DAY 91- DAY 119	27.6 23.4(14)	22.9 9.0(4)	-4.1 24.4(5)	23.2 19.1(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 250 mg/kg/day
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 119 - DAY 126	-5.9 7.9(5)	-3.0 2.1(4)	11.0# 18.9(5)	3.2# 5.3(5)
DAY 126 - DAY 133	15.8 3.5(5)	9.7 2.8(4)	8.2 12.1(5)	8.9 8.4(5)
DAY 133 - DAY 140	-0.6 4.9(5)	6.1 7.1(4)	1.7 7.2(5)	4.1 8.8(5)
DAY 140 - DAY 147	7.5 2.8(5)	5.2 7.8(4)	7.8 5.1(5)	11.4 4.2(5)
DAY 147 - DAY 154	1.0 10.0(5)	5.5 7.6(4)	5.2 8.9(5)	7.3 4.7(5)
DAY 154 - DAY 161	6.6 7.6(5)	0.1 7.0(4)	3.7 7.0(5)	5.4 4.6(5)
DAY 161 - DAY 168	6.7 7.6(5)	4.3 2.2(4)	2.2# 0.9(5)	-2.9# 11.4(5)
DAY 168 - DAY 175	-1.5 3.2(5)	2.3 4.7(4)	4.5 5.3(5)	2.5 4.2(5)
DAY 119- DAY 175	29.6 16.5(5)	30.3 8.3(4)	44.2 18.9(5)	39.9 15.1(5)

Data summarized as: Mean
Standard Deviation (n)

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

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 74; subsequent data are reported as part of the reproduction evaluation.

Company Sanitized. Does not contain TSCA CB

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

	Group I 0 mg/kg/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0 - DAY 7	25.8 2.2(45)	25.8 2.5(35)	26.1 2.2(35)	26.5 2.8(45)
DAY 7 - DAY 14	27.4 2.9(45)	27.7 2.8(35)	28.1 2.7(35)	28.5# 2.4(45)
DAY 14 - DAY 21	28.3 2.6(45)	28.1 3.2(35)	28.1 2.3(35)	28.2 2.6(45)
DAY 21 - DAY 28	28.2 2.8(45)	28.2 3.2(35)	28.9 2.6(35)	28.6 3.7(45)
DAY 28 - DAY 35	28.5 2.7(45)	29.2 3.4(35)	30.0 5.6(35)	29.2 2.9(45)
DAY 35 - DAY 42	28.7 2.7(45)	28.8 3.1(35)	29.1 2.6(35)	28.5 3.6(45)
DAY 42 - DAY 49	29.2 2.6(45)	27.6 4.0(35)	28.6 3.6(35)	26.2# 3.3(45)
DAY 49 - DAY 56	29.2 3.0(45)	29.1 4.1(35)	29.4 2.5(35)	26.0# 4.8(45)
DAY 56 - DAY 63	28.9 4.2(45)	28.9 3.4(35)	29.5 2.9(35)	24.5# 4.4(45)
DAY 63 - DAY 70	28.9 3.3(45)	28.8 3.4(35)	28.8 4.5(35)	21.8# 7.9(45)
DAY 70 - DAY 74 ^a	31.1 4.1(20)	30.1 3.4(20)	28.8 3.7(20)	25.2# 7.5(19)
DAY 0 - DAY 74 ^a	28.4 2.9(20)	28.4 3.2(20)	29.5 2.0(20)	27.1 1.9(19)

Company Sanitized. Does not contain TSCA CB

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 70 - DAY 77	28.2 3.5(25)	27.4 3.5(15)	25.7 5.8(15)	24.2# 5.9(25)
DAY 77 - DAY 84	28.0 3.6(25)	27.9 3.1(15)	25.0 3.5(14)	26.8 3.5(25)
DAY 84 - DAY 90	27.0 2.9(25)	26.3 3.5(15)	24.7 2.9(14)	25.3 3.7(25)

DAY 0 - DAY 90	28.2 2.4(25)	27.9 2.6(15)	27.1 2.0(14)	26.2# 2.4(25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 90 - DAY 98	28.4 2.7(15)	26.8 2.4(5)	25.4# 3.6(5)	25.4# 2.9(15)
DAY 98 - DAY 105	28.0 5.0(15)	27.7 2.6(5)	22.4 12.1(5)	25.6# 3.5(15)
DAY 105 - DAY 112	28.7 2.8(15)	27.7 2.2(5)	25.0 5.5(5)	24.7# 3.8(15)
DAY 112 - DAY 119	26.2 5.0(15)	25.9 4.4(5)	25.5 4.4(5)	25.4 3.3(15)

DAY 90 - DAY 119	27.8 3.1(15)	27.0 2.4(5)	24.6 4.1(5)	25.3# 3.1(15)

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 119 - DAY 126	27.3 0.9(5)	26.2 0.9(5)	25.5 6.3(5)	25.1 4.1(5)
DAY 126 - DAY 133	27.5 1.7(5)	26.5 6.2(5)	27.3 1.9(5)	25.8 4.1(5)
DAY 133 - DAY 140	27.9 4.3(5)	28.7 2.7(5)	26.8 7.9(5)	26.9 2.5(5)
DAY 140 - DAY 147	26.0 7.0(5)	29.5 2.3(5)	31.7 3.0(5)	28.8 2.8(5)
DAY 147 - DAY 154	30.4 2.2(5)	30.6 1.8(5)	31.2 3.2(5)	29.5 2.9(5)
DAY 154 - DAY 161	32.4 2.4(5)	28.8 1.8(5)	30.9 3.6(5)	30.7 3.7(5)
DAY 161 - DAY 168	29.5 1.7(5)	29.2 1.9(5)	31.6 5.2(5)	30.9 3.3(5)
DAY 168 - DAY 175	30.8 2.9(5)	29.0 2.0(5)	30.7 4.2(5)	28.9 3.4(5)
DAY 119 - DAY 175	29.0 2.2(5)	28.6 1.7(5)	29.5 2.8(5)	28.3 3.2(5)

Data summarized as: Mean
Standard Deviation (n)

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

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 74; food consumption data were not collected during the cohabitation and postmating periods.

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0 - DAY 7	18.7 1.9(45)	18.9 4.0(34)	17.9 1.6(35)	18.0# 1.8(45)
DAY 7 - DAY 14	20.1 2.2(45)	19.7 4.0(34)	18.5# 1.5(35)	19.4# 1.6(45)
DAY 14 - DAY 21	19.9 2.2(45)	20.9 3.9(34)	19.9 1.6(35)	20.8 2.3(45)
DAY 21 - DAY 28	19.7 2.3(45)	20.6 4.0(34)	19.8 2.9(35)	20.0 2.0(45)
DAY 28 - DAY 35	21.0 2.3(45)	21.3 3.5(33)	19.3 2.4(35)	20.6 2.2(45)
DAY 35 - DAY 42	20.4 2.2(45)	21.5 3.4(33)	18.4# 2.8(35)	19.6# 2.2(45)
DAY 42 - DAY 49	20.8 2.4(45)	21.0 4.3(33)	20.0 2.4(35)	19.1# 3.4(45)
DAY 49 - DAY 56	21.1 2.1(45)	21.3 4.0(33)	20.5 1.7(35)	19.3# 4.4(44)
DAY 56 - DAY 63	21.1 2.0(45)	20.9 1.8(33)	19.5# 2.1(35)	17.9# 4.5(44)
DAY 63 - DAY 70	20.9 2.2(45)	20.3 2.3(33)	19.8# 1.9(35)	16.7# 5.2(43)
DAY 70 - DAY 74 ^a	21.9 2.0(20)	21.3 3.7(20)	20.2 2.9(20)	20.3# 11.4(19)
DAY 0 - DAY 74 ^a	20.5 1.9(20)	21.1 3.5(20)	20.0 1.0(20)	19.8 2.0(19)

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 70 - DAY 77	21.1 2.6(25)	20.9 2.7(13)	19.2# 2.1(15)	16.6# 4.3(24)
DAY 77 - DAY 84	21.4 3.6(25)	20.8 3.1(13)	18.9@ 1.8(15)	22.6 3.0(24)
DAY 84 - DAY 91	19.1 3.4(25)	19.0 2.3(13)	17.3 2.0(15)	18.8 3.1(24)

DAY 0 - DAY 91	20.4 1.7(25)	20.1 1.7(13)	18.6# 1.5(15)	18.8# 1.4(24)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 91 - DAY 98	20.4 3.2(15)	19.0 1.7(4)	17.1 1.7(5)	19.7 3.4(15)
DAY 98 - DAY 105	21.1 4.3(15)	20.0 1.1(4)	18.3 1.8(5)	20.3 3.6(15)
DAY 105 - DAY 112	21.6 2.9(14)	20.7 1.5(4)	17.9 4.8(5)	19.1# 2.6(15)
DAY 112 - DAY 119	21.4 3.3(14)	20.4 1.4(4)	16.9 5.8(5)	19.3 3.1(15)

DAY 91 - DAY 119	21.2 2.9(14)	20.0 1.3(4)	17.5 2.9(5)	19.6 2.8(15)

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 119 - DAY 126	19.4 2.2(5)	20.6 1.8(4)	20.6 2.8(5)	18.5 2.6(5)
DAY 126 - DAY 133	21.2 1.8(5)	20.4 1.8(4)	20.3 2.1(5)	18.4# 2.2(5)
DAY 133 - DAY 140	20.1 2.2(5)	22.0 1.4(4)	22.8 4.7(5)	20.4 3.2(5)
DAY 140 - DAY 147	21.9 1.7(5)	22.3 1.3(4)	24.5 3.4(5)	22.3 2.4(5)
DAY 147 - DAY 154	23.2 3.0(5)	23.1 1.2(4)	21.3 2.1(5)	22.9 2.7(5)
DAY 154 - DAY 161	24.2 2.0(5)	21.3 1.6(4)	22.6 2.9(5)	22.5 2.6(5)
DAY 161 - DAY 168	22.5 3.5(5)	21.7 1.4(4)	21.3 2.4(5)	22.2 1.8(5)
DAY 168 - DAY 175	20.9 1.6(5)	21.1 2.6(4)	21.0 3.1(5)	20.6 2.2(5)

DAY 119 - DAY 175	21.7 2.1(5)	21.6 1.5(4)	21.8 2.0(5)	21.0 1.9(5)

Data summarized as: Mean
Standard Deviation (n)

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

@ Statistically significant difference at $p < 0.05$ by Dunn's test.

- a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 74; data were not collected during the cohabitation and postmating periods.

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0 - DAY 7	0.307 0.026(45)	0.314 0.032(35)	0.314 0.033(35)	0.331# 0.032(45)
DAY 7 - DAY 14	0.262 0.027(45)	0.270 0.028(35)	0.249 0.025(35)	0.235# 0.024(45)
DAY 14 - DAY 21	0.211 0.028(45)	0.184 0.025(35)	0.213 0.028(35)	0.225# 0.022(45)
DAY 21 - DAY 28	0.166 0.028(45)	0.178 0.028(35)	0.159 0.032(35)	0.135# 0.129(45)
DAY 28 - DAY 35	0.131 0.029(45)	0.148 0.031(35)	0.115 0.029(35)	0.124 0.026(45)
DAY 35 - DAY 42	0.127 0.025(45)	0.091# 0.026(35)	0.103# 0.026(35)	0.072# 0.126(45)
DAY 42 - DAY 49	0.089 0.038(45)	0.068 0.036(35)	0.076 0.095(35)	0.038# 0.067(45)
DAY 49 - DAY 56	0.086 0.050(45)	0.072 0.081(35)	0.072# 0.035(35)	-0.019# 0.246(45)
DAY 56 - DAY 63	0.075 0.048(45)	0.081 0.050(35)	0.083 0.035(35)	-0.010# 0.136(45)
DAY 63 - DAY 70	0.076 0.026(45)	0.074 0.027(35)	0.031 0.217(35)	-0.368# 0.919(45)
DAY 70 - DAY 74 ^a	0.028 0.049(20)	0.053 0.061(20)	0.017 0.042(20)	-0.073 0.476(19)
DAY 0 - DAY 74 ^a	0.146 0.011(20)	0.143 0.011(20)	0.141 0.009(20)	0.114# 0.015(19)

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 70 - DAY 77	0.029 0.079(25)	0.045 0.035(15)	-0.048 0.320(15)	-0.027 0.333(25)
DAY 77 - DAY 84	0.063 0.046(25)	0.059 0.039(15)	-0.008 0.159(14)	0.158# 0.110(25)
DAY 84 - DAY 90	0.035 0.045(25)	0.028 0.074(15)	0.050 0.089(14)	0.082# 0.064(25)
DAY 0 - DAY 90	0.126 0.012(25)	0.124 0.012(15)	0.116# 0.009(14)	0.115# 0.011(25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 90 - DAY 98	0.084 0.042(15)	0.066 0.020(5)	0.019# 0.053(5)	0.062# 0.043(15)
DAY 98 - DAY 105	0.024 0.113(15)	0.051 0.023(5)	-2.355 5.392(5)	0.041 0.045(15)
DAY 105 - DAY 112	0.061 0.037(15)	0.034 0.074(5)	0.075 0.124(5)	0.031 0.071(15)
DAY 112 - DAY 119	-0.021 0.112(15)	-0.033 0.080(5)	0.024 0.145(5)	0.044# 0.043(15)
DAY 90 - DAY 119	0.047 0.017(15)	0.034 0.030(5)	0.009* 0.027(5)	0.047 0.022(15)

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 250 mg/kg/day
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 119 - DAY 126	0.002 0.072(5)	-0.039 0.096(5)	-0.041 0.205(5)	0.046 0.038(5)
DAY 126 - DAY 133	0.078 0.031(5)	0.070 0.088(5)	0.071 0.094(5)	0.089 0.031(5)
DAY 133 - DAY 140	0.049 0.048(5)	0.040 0.051(5)	0.092 0.071(5)	0.058 0.034(5)
DAY 140 - DAY 147	-0.000 0.156(5)	0.058 0.014(5)	0.064 0.011(5)	0.083 0.031(5)
DAY 147 - DAY 154	0.041 0.014(5)	0.021 0.032(5)	0.054 0.031(5)	0.043 0.027(5)
DAY 154 - DAY 161	0.031 0.029(5)	0.028 0.008(5)	0.033 0.029(5)	0.055 0.031(5)
DAY 161 - DAY 168	0.021 0.040(5)	0.049 0.018(5)	0.056 0.034(5)	0.062 0.036(5)
DAY 168 - DAY 175	0.075 0.021(5)	0.037 0.033(5)	0.048 0.023(5)	0.015# 0.035(5)
DAY 119 - DAY 175	0.041 0.020(5)	0.036 0.007(5)	0.052 0.014(5)	0.056# 0.009(5)

Data summarized as: Mean
Standard Deviation (n)

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

* Statistically significant difference at $p < 0.05$ by Dunnett's test.

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 74; data were not collected during the cohabitation and postmating periods.

Company Sanitized. Does not contain TSCA CB

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY 0 - DAY 7	0.176 0.060(45)	0.170 0.048(34)	0.193 0.043(35)	0.199# 0.037(45)
DAY 7 - DAY 14	0.128 0.048(45)	0.134 0.057(34)	0.150 0.047(35)	0.162# 0.042(45)
DAY 14 - DAY 21	0.120 0.045(45)	0.146 0.039(34)	0.117 0.044(35)	0.098# 0.044(45)
DAY 21 - DAY 28	0.095 0.048(45)	0.088 0.050(34)	0.070 0.156(35)	0.087 0.045(45)
DAY 28 - DAY 35	0.089 0.043(45)	0.081 0.036(33)	0.061# 0.069(35)	0.074# 0.038(45)
DAY 35 - DAY 42	0.048 0.042(45)	0.067 0.045(33)	0.072@ 0.076(35)	0.063 0.040(45)
DAY 42 - DAY 49	0.067 0.034(45)	0.040# 0.087(33)	0.046# 0.080(35)	-0.000# 0.191(45)
DAY 49 - DAY 56	0.048 0.053(45)	0.020 0.096(33)	0.018# 0.039(35)	-0.120# 0.532(44)
DAY 56 - DAY 63	0.023 0.049(45)	0.042 0.073(33)	0.028 0.048(35)	-0.064# 0.257(44)
DAY 63 - DAY 70	0.041 0.038(45)	0.041 0.043(33)	0.038 0.050(35)	-0.220# 0.929(43)
DAY 70 - DAY 74 ^a	-0.014 0.050(20)	-0.062 0.289(20)	-0.048 0.234(20)	-0.188 0.733(19)
DAY 0 - DAY 74 ^a	0.076 0.007(20)	0.078 0.013(20)	0.076 0.010(20)	0.058# 0.020(19)

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY 70 - DAY 77	0.001 0.002(5)	-0.002 0.001(4)	0.001 0.004(5)	-0.011# 0.009(5)
DAY 77 - DAY 84	0.034 0.036(25)	0.023 0.026(13)	0.009 0.045(15)	0.136# 0.079(24)
DAY 84 - DAY 91	-0.020 0.208(25)	0.008 0.042(13)	0.017 0.039(15)	0.015 0.067(24)
DAY 0 - DAY 91	0.069 0.013(25)	0.068 0.007(13)	0.067 0.005(15)	0.066 0.008(24)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 91 - DAY 98	0.077 0.111(15)	0.057 0.047(4)	0.001 0.077(5)	0.034 0.074(15)
DAY 98 - DAY 105	0.018 0.105(15)	0.014 0.046(4)	0.040 0.033(5)	0.037 0.039(15)
DAY 105 - DAY 112	0.064 0.051(14)	0.064 0.023(4)	-0.083 0.279(5)	0.059 0.042(15)
DAY 112 - DAY 119	-0.000 0.060(14)	0.024 0.021(4)	-0.159 0.452(5)	0.026 0.039(15)
DAY 91 - DAY 119	0.044 0.040(14)	0.040 0.014(4)	-0.015* 0.055(5)	0.039 0.029(15)

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 250 mg/kg/day
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY 119 - DAY 126	-0.048 0.068(5)	-0.022 0.017(4)	0.069# 0.115(5)	0.023# 0.042(5)
DAY 126 - DAY 133	0.107 0.028(5)	0.068 0.018(4)	0.060 0.084(5)	0.067 0.063(5)
DAY 133 - DAY 140	-0.007 0.034(5)	0.038 0.047(4)	0.010 0.048(5)	0.023 0.058(5)
DAY 140 - DAY 147	0.050 0.019(5)	0.032 0.049(4)	0.046 0.028(5)	0.074 0.027(5)
DAY 147 - DAY 154	0.001 0.061(5)	0.035 0.046(4)	0.034 0.058(5)	0.045 0.032(5)
DAY 154 - DAY 161	0.041 0.047(5)	-0.001 0.046(4)	0.019 0.043(5)	0.033 0.027(5)
DAY 161 - DAY 168	0.040 0.043(5)	0.028 0.012(4)	0.015# 0.005(5)	-0.019# 0.073(5)
DAY 168 - DAY 175	-0.009 0.021(5)	0.014 0.034(4)	0.028 0.029(5)	0.016 0.030(5)
DAY 119 - DAY 175	0.024 0.012(5)	0.025 0.005(4)	0.036 0.014(5)	0.034 0.012(5)

Data summarized as: Mean
Standard Deviation (n)

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

* Statistically significant difference at $p < 0.05$ by Dunnett's test.

@ Statistically significant difference at $p < 0.05$ by Dunn's test.

a. Rats designated for reproduction evaluation (20 rats/group) were cohoused on test day 74; data were not collected during the cohabitation and postmating periods.

Company Sanitized. Does not contain TSCA CBI

TABLE 12

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	250 mg/kg/day
Number Animals at Study Start	45	35	35	45
Mass Thoracic				
Lateral				
Mass #1				
Ulcerated				
Incidence	0	0	1	0
Mean onset (Days)	-	-	84	-
Lateral				
Mass #1				
Not Ulcerated				
Incidence	0	0	1	0
Mean onset (Days)	-	0	58	-
Eye Observations				
Corneal Opacity				
Incidence	2	1	3	1
Mean onset (Days)	77	77	89	28
Exophthalmus				
Incidence	2	2	3	1
Mean onset (Days)	31	88	84	28
Enophthalmus				
Incidence	2	0	1	2
Mean onset (Days)	46	-	77	56

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 250 mg/kg/day 45
Dose				
Number Animals at Study Start				
Partially Closed				
Incidence	2	0	2	1
Mean onset (Days)	102	-	126	119
Closed Left				
Incidence	1	0	0	0
Mean onset (Days)	181	-	-	-
Abnormal Gait Hindlimb Left				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	63
Muscle Tone Decreased				
Incidence	0	0	1	0
Mean onset (Days)	-	-	73	-
Pale				
Incidence	0	0	1	0
Mean onset (Days)	-	-	73	-

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	250 mg/kg/day
Number Animals at Study Start	45	35	35	45
General Teeth Observations				
Clipped				
Incidence	1	2	1	32
Mean onset (Days)	58	89	77	75
Maloccluded				
Incidence	0	0	1	1
Mean onset (Days)	-	-	119	58
Broken				
Incidence	0	0	0	10 #
Mean onset (Days)	-	-	-	72
Absent				
Incidence	0	1	1	5 #
Mean onset (Days)	-	56	84	68
Loose				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	67
Diarrhea				
Brown				
Incidence	0	0	0	2
Mean onset (Days)	-	-	-	70

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day 45
Dose				
Number Animals at Study Start				
Breathing Observations				
Noise				
Incidence	0	1	0	1
Mean onset (Days)	-	147	-	69
Labored				
Incidence	0	0	1	1
Mean onset (Days)	-	-	77	70
Fast				
Incidence	0	0	1	0
Mean onset (Days)	-	-	77	-
Discharge				
Eye				
Incidence	4	4	4	3
Mean onset (Days)	60	116	76	65
Nose				
Incidence	2	2	1	6
Mean onset (Days)	21	77	63	77
Mouth				
Clear				
Incidence	0	0	0	3 #
Mean onset (Days)	-	-	-	31

Company Sanitized. Does not contain TSCA CBI

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	250 mg/kg/day
Number Animals at Study Start	45	35	35	45
Mouth Red				
Incidence	0	0	1	1
Mean onset (Days)	-	-	66	69
Ear left Black				
Incidence	0	2	0	0
Mean onset (Days)	-	126	-	-
Hair Loss				
Incidence	5	6	4	5
Mean onset (Days)	49	98	77	31
Wound Superficial (nose, mouth, face, tail, shoulders)				
Incidence	2	2	0	2
Mean onset (Days)	21	30	-	18
Hyperreactive				
Incidence	2	0	3	3
Mean onset (Days)	116	-	68	81
Aggressive Behavior				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	119

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day 45
Dose				
Number Animals at Study Start				
Excessive Toe Nail Bleed				
Incidence	0	0	1	0
Mean onset (Days)	-	-	76	-
Stain Fur/Skin				
Periocular				
Right				
Brown				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	74
Periocular				
Bilateral				
Black				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	74
Face				
Red				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	70

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 250 mg/kg/day 45
Dose				
Number Animals at Study Start				
Incidence	0	1	0	0
Mean onset (Days)	-	119	-	-
Face				
Black				
Chin				
Red				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	70
Tail				
Brown				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	119
Perineum				
Yellow				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	70
Perineum				
Red				
Incidence	0	0	0	3 #
Mean onset (Days)	-	-	-	70

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day 45
Dose				
Number Animals at Study Start				
Perineum Brown				
Incidence	0	0	1	0
Mean onset (Days)	-	-	73	-
Inguen Brown				
Incidence	0	0	1	0
Mean onset (Days)	-	-	77	-
Forepaw Left Red				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	70
Forepaw Bilateral Red				
Incidence	0	0	0	2
Mean onset (Days)	-	-	-	70

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	250 mg/kg/day
Number Animals at Study Start	45	35	35	45
Misshapen Observations Tail				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	7
Swollen Observations Nose				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	84
Face				
Incidence	0	0	1	0
Mean onset (Days)	-	-	56	-
Hindlimb Left				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	63

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.

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

TABLE 13

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II	IV	VI	VIII
Dose	0 mg/kg/day	25 mg/kg/day	100 mg/kg/day	250 mg/kg/day
Number Animals at Study Start	45	35	35	45
Mass Side				
Left				
Mass #1				
Not Ulcerated				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	64
Mass Perineum				
Mass #1				
Ulcerated				
Incidence	1	0	0	0
Mean onset (Days)	105	-	-	-
Mass Abdomen				
Mass #2				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	119
Eye Observations				
Corneal Opacity				
Incidence	2	0	3	3
Mean onset (Days)	44	-	56	93

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 250 mg/kg/day 45
Dose				
Number Animals at Study Start				
Exophthalmus				
Incidence	3	0	3	3
Mean onset (Days)	70	-	64	109
Enophthalmus				
Incidence	1	0	1	3
Mean onset (Days)	77	-	49	84
Partially Closed Left				
Incidence	1	0	1	1
Mean onset (Days)	112	-	112	112
Closed Left				
Incidence	1	0	0	0
Mean onset (Days)	175	-	-	-
Wet Fur Perineum				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	47
Prostrate				
Incidence	0	1	0	0
Mean onset (Days)	-	29	-	-

Company Sanitized. Does not contain TSCA CBI

TABLE 13 (CONTINUED)
SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II	IV	VI	VIII
Dose	0 mg/kg/day	25 mg/kg/day	100 mg/kg/day	250 mg/kg/day
Number Animals at Study Start	45	35	35	45
General Teeth Observations				
Clipped				
Incidence	0	1	2	31 #
Mean onset (Days)	-	58	144	79
Maloccluded				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	119
Broken				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	71
Absent				
Incidence	0	0	0	3 #
Mean onset (Days)	-	-	-	66
Loose				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	71
Diarrhea (Brown, Black)				
Incidence	0	1	0	1
Mean onset (Days)	-	29	-	70

TABLE 13 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II	IV	VI	VIII
Dose	0 mg/kg/day	25 mg/kg/day	100 mg/kg/day	250 mg/kg/day
Number Animals at Study Start	45	35	35	45
Breathing Observations				
Noise				
Incidence	2	0	0	1
Mean onset (Days)	140	-	-	140
Fast				
Incidence	0	1	0	0
Mean onset (Days)	-	29	-	-
Discharge				
Eye				
Incidence	3	2	3	4
Mean onset (Days)	115	103	54	108
Nose				
Incidence	2	0	1	1
Mean onset (Days)	102	-	119	70
Mouth				
Clear				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	63
Mouth				
Tan				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	47

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 250 mg/kg/day 45
Dose				
Number Animals at Study Start				
Vulva Red				
Incidence	1	0	0	0
Mean onset (Days)	105	-	-	-
Hair Loss				
Incidence	4	3	2	5
Mean onset (Days)	78	47	39	43
Wound				
Superficial (Nose, Mouth)				
Incidence	0	1	1	0
Mean onset (Days)	-	14	63	-
Hyperreactive				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	70
Hyperactive				
Incidence	0	1	0	1
Mean onset (Days)	-	56	-	70
Convulsions				
Clonic				
Incidence	0	1	0	0
Mean onset (Days)	-	29	-	-

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day 45
Dose				
Number Animals at Study Start				
Vocalization				
Abnormal				
Incidence	0	1	0	0
Mean onset (Days)	-	29	-	-
Growth on left eye				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	181
Dehydrated				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	47
Stain Fur/Skin				
Face				
Brown				
Incidence	0	0	0	2
Mean onset (Days)	-	-	-	67
Shoulder				
Right				
Brown				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	21

TABLE 13 (CONTINUED)
SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II	IV	VI	VIII
Dose	0 mg/kg/day	25 mg/kg/day	100 mg/kg/day	250 mg/kg/day
Number Animals at Study Start	45	35	35	45
Perineum Yellow				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	47
Inguen Yellow				
Incidence	0	0	0	1
Mean onset (Days)	-	-	-	70

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.

Statistically significant difference at $p < 0.05$ by Cochran-Armitage trend 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 250 mg/kg/day
-------------------------	------------------	---------------------	--------------------	----------------------

Examination Day : Test Day 80

Number of Rats Examined

20

10

9

20

There were no ophthalmological abnormalities detected.

Examination Day : Test Day 122

Number of Rats Examined

10

0

0

10

There were no ophthalmological abnormalities detected.

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 250 mg/kg/day
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Examination day: Test day 80

Number of Rats Examined	20	10	10	20
-------------------------	----	----	----	----

Retina
Retinal Degeneration Diffuse
Left

Incidence	0 (0%)	0 (0%)	1 (10%)	0 (0%)
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Examination day: Test day 122

Number of Rats Examined	9	0	0	10
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There were no ophthalmological abnormalities detected.

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

Statistical Methods: Trend test (Cochran-Armitage).

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

TABLE 16

PERCENT SURVIVAL OF MALE RATS

Treatment Group	I	III	V	VII
Dose (mg/kg/day)	0	25	100	250
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	100	100	100	100
77 ^a	100	100	100	100 ^b
84	100	100	100 ^b	100
91 ^{c,d}	100	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	0	0	1	1
Removed from study ^a	20	20	20	19
Sacrificed by design ^d	10	10	9	10
Alive on test day 119	15	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 - accidentally killed.

- a. Rats designated for reproduction evaluation were removed from study (cohoused) on test day 74.
- b. One rat was accidentally killed during the previous week.
- c. Recovery period began on test day 90.
- d. Rats designated for the 90-day exposure period were sacrificed on test day 91.

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

Company Sanitized. Does not contain TSCA CB

TABLE 17

PERCENT SURVIVAL OF FEMALE RATS

Treatment Group	II	IV	VI	VIII
Dose (mg/kg/day)	0	25	100	250
Number Animals at Study Start	45	35	35	45
DAYS ON TEST				
0	100	100 ^a	100	100
7	100	100	100	100
14	100	100	100	100
21	100	100	100	100
28	100	100	100	100
35	100	97 ^c	100	100
42	100	97	100	100
49	100	97	100	100
56	100	97	100	100 ^b
63	100	97	100	100
70	100	97	100	98 ^d
77 ^e	100	93	100	96
84	100	93	100	96
91 ^{f,g}	100	93	100	96
98	100	80	100	96
105	100	80	100	96
112	93 ^c	80	100	96
119	93	80	100	96
Number at study start	45	35	35	45
Accidentally killed	0	1	0	1
Found dead	0	0	0	1
Sacrificed <i>in extremis</i>	1	1	0	0
Removed from study ^e	20	20	20	19
Sacrificed by design ^g	10	9	10	9
Alive on test day 119	14	4	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 - accidentally killed.

a. One rat was accidentally killed on test day 0 and replaced day 0.

b. One rat was accidentally killed during the previous week.

c. One rat was sacrificed *in extremis* during the previous week.

d. One rat was found dead during the previous week.

e. Rats designated for reproduction evaluation were removed from study (cohoused) on test day 74.

f. Recovery period began on test day 90.

g. Rats designated for the 90-day exposure period were sacrificed on test day 93.

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

Company Sanitized. Does not contain TSCA CB

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	0.51 (0.08)	0.40 (0.06)
	III	25	0.52 (0.10)	0.38 (0.07)
	V	100	0.54 (0.08)	0.36 (0.03)
	VII	250	0.54 (0.09)	0.40 (0.06)
<u>Week 13</u>				
	I	0	1.38 (0.34)	0.84 (0.15)
	III	25	1.35 (0.29)	0.80 (0.07)
	V	100	1.38 (0.32)	0.80 (0.13)
	VII	250	1.31 (0.23)	0.73 (0.11)
<u>Recovery</u>				
	I	0	1.27 (0.31)	0.74 (0.14)
	VII	250	1.03 (0.32)	0.75 (0.09)

Data arranged as : Mean (Standard Deviation)

Statistical Methods: Bartlett's test for homogeneity followed by analysis of variance and Dunnett's test.

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

TABLE 19

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	0.58 (0.08)	0.37 (0.04)
	IV	25	0.54 (0.12)	0.39 (0.06)
	VI	100	0.54 (0.12)	0.36 (0.05)
	VIII	250	0.59 (0.14)	0.36 (0.04)
<u>Week 13</u>				
	II	0	1.18 (0.25)	0.73 (0.10)
	IV	25	1.22 (0.21)	0.72 (0.12)
	VI	100	1.04 (0.21)	0.65 (0.10)
	VIII	250	1.01 (0.22)	0.64 (0.14)
<u>Recovery</u>				
	II	0	1.07 (0.27)	0.69 (0.09)
	VIII	250	1.13 (0.35)	0.66 (0.11)

Data arranged as : Mean (Standard Deviation)

Statistical Methods: Bartlett's test for homogeneity followed by analysis of variance and Dunnett's test.

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

TABLE 20
SUMMARY OF FUNCTIONAL OBSERVATION 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	250	0	25	100	250	0	250
Number Examined:	10	10	10	10	10	10	9	10	10	10
APPROACH & TOUCH:										
no reaction	0	0	0	0	0	0	1	0	0	0
normal	10	10	10	10	9	10	8	10	10	10
increased reaction (jumps away or attacks)	0	0	0	0	1	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	9	10	10	10
exaggerated reaction (rat jumps, flips)	0	0	0	0	0	0	0	0	0	0
TAIL PINCH:										
no response	0	1	0	0	0	0	0	0	0	0
normal (turns toward site)	9	9	9	10	10	9	9	10	9	10
exaggerated response	1	0	1	0	0	1	0	0	1	0
<u>IN MOTOR ACTIVITY MONITOR:</u>										
DEFECATION										
present	7	9	8	8	3	6	5	7	8	6
absent	3	1	2	2	7	4	4	3	2	4
diarrhea	0	0	0	0	0	0	0	0	0	0
URINATION:										
present	7	8	7	4	4	7	3	7	7	5
absent	3	2	3	6	6	3	6	3	3	5
PUPILLARY RESPONSE										
present	10	10	10	10	10	10	9	10	10	10
absent	0	0	0	0	0	0	0	0	0	0

TABLE 20 (CONTINUED)

SUMMARY OF FUNCTIONAL OBSERVATION 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	250	0	25	100	250	0	250
Number Examined:	10	10	10	10	10	10	9	10	10	10

ADDITIONAL OBSERVATIONS NOTED

Sore, right axilla										
Present	0	0	0	0	0	0	1	0	0	0
Absent	10	10	10	10	10	10	8	10	10	10
Ptosis										
present	0	0	0	0	0	0	0	0	0	1
absent	10	10	10	10	10	10	9	10	10	9

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

TABLE 21
SUMMARY OF FUNCTIONAL OBSERVATION 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	250	0	25	100	250	0	250
Number Examined:	10	10	10	10	10	9	10	10	9	10
APPROACH & TOUCH:										
no reaction	0	0	0	0	0	0	0	0	0	0
normal	10	10	10	10	10	9	10	10	9	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	1	0	0	0
normal reaction (rat flinches or flicks ear)	10	10	10	10	10	9	9	10	9	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	9	10	9	9	10
exaggerated response	0	0	1	0	0	0	0	1	0	0
<u>IN MOTOR ACTIVITY MONITOR:</u>										
DEFECATION										
present	2	4	2	6	3	0	4	5	3	1
absent	8	6	8	4	7	9	6	5	6	9
diarrhea	0	0	0	0	0	0	0	0	0	0
URINATION:										
present	7	6	5	9	2	2	3	4	6	3
absent	3	4	5	1	8	7	7	6	3	7
PUPILLARY RESPONSE										
present	10	10	10	10	10	9	10	10	9	10
absent	0	0	0	0	0	0	0	0	0	0

TABLE 21 (CONTINUED)

SUMMARY OF FUNCTIONAL OBSERVATION 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	250	0	25	100	250	0	250
Number Examined:	10	10	10	10	10	9	10	10	9	10

ADDITIONAL OBSERVATIONS NOTED

Ptois										
present	0	0	0	0	0	0	0	1	0	1
absent	10	10	10	10	10	9	10	9	9	9
Scratch, right corner of eye										
present	0	0	0	0	0	0	0	0	0	2
absent	10	10	10	10	10	9	10	10	9	8
Chromodacryorrhea										
present	0	0	0	0	0	0	0	0	0	1
absent	10	10	10	10	10	9	10	10	9	9

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

TABLE 22

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

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS					
			<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
<u>BASELINE</u>								
	I	0	430(67)	313(106)	275(89)	187(127)	70(81)	34(53)
	III	25	419(45)	329(80)	257(138)	87(88) *	11(14)	5(6)
	V	100	403(52)	322(59)	196(110)*	96(119)*	42(78)	54(91)
	VII	250	392(53)	287(61)	178(114)*	73(88) *	47(80)	46(78)
								<u>TOTAL</u>
								1321(375)
								1117(341)
								1123(395)
								1033(343)
<u>WEEK 13</u>								
	I	0	407(40)	301(45)	233(49)	174(63)	116(71)	102(108)
	III	25	392(56)	297(66)	218(71)	172(109)	99(81)	72(46)
	V	100	368(39)	273(58)	233(99)	180(103)	171(92)	135(87)
	VII	250	368(71)	265(98)	210(117)	147(93)	145(84)	93(95)
								<u>TOTAL</u>
								1332(231)
								1250(298)
								1360(387)
								1228(477)
<u>RECOVERY</u>								
	I	0	324(58)	202(45)	140(44)	145(51)	121(44)	140(58)
	VII	250	295(52)	184(42)	147(48)	131(50)	120(47)	116(61)
								<u>TOTAL</u>
								1072(247)
								995(213)

Data arranged as: Mean (Standard Deviation).

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

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

TABLE 23

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

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
			<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>TOTAL</u>
<u>BASELINE</u>	II	0	371(45)	304(84)	163(109)	166(102)	130(90)	31(58)	1176(236)
	IV	25	400(27)	286(60)	249(66)	153(110)	109(113)	32(42)	1239(215)
	VI	100	409(50)	327(73)	169(135)	152(157)	92(128)	79(143)	1240(588)
	VIII	250	364(48)	261(80)	222(97)	164(147)	104(141)	74(121)	1190(478)
<u>WEEK 13</u>	II	0	372(56)	263(59)	223(89)	148(86)	108(66)	116(118)	1230(310)
	IV	25	432(58)	323(94)	239(87)	166(103)	101(111)	153(84)	1413(366)
	VI	100	386(76)	266(85)	202(129)	144(132)	134(111)	111(76)	1242(430)
	VIII	250	371(69)	268(65)	148(96)	139(80)	111(73)	91(93)	1128(268)
<u>RECOVERY</u>	II	0	330(55)	223(57)	173(29)	157(69)	106(41)	103(64)	1091(191)
	VIII	250	297(56)	153(73)	105(83)	86(73)	41(35)	92(62)	775(290)*

Data arranged as: Mean (Standard Deviation).

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

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

TABLE 24

MOTOR ACTIVITY ASSESSMENT:
NUMBER OF MOVEMENTS FOR MALE RATS

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS					
			1	2	3	4	5	6
<u>BASELINE</u>								<u>TOTAL</u>
I		0	120(31)	115(22)	124(22)	88(42)	49(45)	20(26)
III		25	117(24)	121(25)	107(33)	50(42)	9(10)	6(4)
V		100	123(17)	133(21)	111(33)	55(38)	30(40)	29(38)
VII		250	138(12)	140(17)	102(54)	54(55)	32(50)	34(49)
								510(175)
<u>WEEK 13</u>								<u>TOTAL</u>
I		0	128(31)	125(27)	109(29)	95(32)	69(38)	55(54)
III		25	129(20)	115(17)	106(20)	72(37)	52(38)	44(26)
V		100	151(25)	136(18)	119(38)	96(50)	108(44)	84(52)
VII		250	135(18)	122(27)	98(41)	80(40)	86(40)	56(43)
								575(151)
<u>RECOVERY</u>								<u>TOTAL</u>
I		0	133(19)	106(26)	80(25)	81(18)	77(20)	80(24)
VII		250	131(19)	96(20)	81(26)	80(33)	72(25)	76(35)
								537(124)

Data arranged as: Mean (Standard Deviation).

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

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

TABLE 25

**MOTOR ACTIVITY ASSESSMENT:
NUMBER OF MOVEMENTS FOR FEMALE RATS**

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS					
			<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
<u>BASELINE</u>								
	II	0	134(15)	137(16)	94(49)	95(49)	93(61)	28(37)
	IV	25	130(16)	137(19)	135(19)	100(62)	64(61)	28(34)
	VI	100	123(28)	127(26)	80(42)	66(51)	45(33)	34(46)
	VIII	250	136(13)	132(35)	127(33)	90(63)	59(63)	47(63)
								<u>TOTAL</u>
								590(117)
								605(156)
								486(125)
								591(201)
<u>WEEK 13</u>								
	II	0	143(16)	132(16)	120(31)	88(45)	71(41)	74(67)
	IV	25	123(31)	121(27)	106(51)	93(50)	59(52)	81(46)
	VI	100	132(30)	118(26)	91(42)	67(50)	77(58)	73(43)
	VIII	250	131(24)	125(12)	91(42)	92(41)	70(40)	55(42)
								<u>TOTAL</u>
								628(164)
								583(198)
								557(158)
								565(94)
<u>RECOVERY</u>								
	II	0	138(11)	130(15)	111(16)	110(27)	80(20)	83(50)
	VIII	250	140(12)	101(41)	74(37)	62(40)	41(30)	75(35)
								<u>TOTAL</u>
								652(55)
								493(137)*

Data arranged as: Mean (Standard Deviation).

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

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

TABLE 26

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 250 mg/kg
RBC (x10 ⁶ /μL)				
DAY 44	8.22 0.41(10)	8.34 0.23(10)	7.96 0.36(10)	8.06 0.32(10)
DAY 91	8.88 0.56(9)	8.57 0.38(9)	8.27* 0.35(9)	7.99* 0.43(10)
DAY 125	8.93 0.38(10)	^a	^a	7.97* 0.31(10)
HGB (g/dL)				
DAY 44	15.1 0.5(10)	15.3 0.4(10)	15.1 0.6(10)	14.8 0.4(10)
DAY 91	15.3 0.7(9)	15.1 0.8(9)	15.0 0.5(9)	14.3* 0.8(10)
DAY 125	15.6 0.5(10)	^a	^a	14.3* 0.8(10)
HCT (%)				
DAY 44	46.0 1.7(10)	46.6 1.5(10)	45.8 2.1(10)	45.2 1.4(10)
DAY 91	48.9 2.7(9)	47.4 2.9(9)	47.2 2.1(9)	45.4* 2.5(10)
DAY 125	48.3 1.8(10)	^a	^a	43.9* 2.7(10)
MCV (fl)				
DAY 44	56.0 1.8(10)	55.9 1.5(10)	57.6 1.4(10)	56.1 1.3(10)
DAY 91	55.2 2.5(9)	55.3 1.7(9)	57.0 1.2(9)	56.8 2.1(10)
DAY 125	54.2 1.8(10)	^a	^a	55.0 2.1(10)
MCH (pg)				
DAY 44	18.4 0.6(10)	18.4 0.4(10)	19.0 0.5(10)	18.3 0.5(10)
DAY 91	17.3 0.6(9)	17.7 0.4(9)	18.1* 0.4(9)	17.8 0.5(10)
DAY 125	17.5 0.6(10)	^a	^a	17.9 0.7(10)

Company Sanitized. Does not contain TSCA CBI

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 250 mg/kg
MCHC (g/dL)				
DAY 44	32.9 0.5(10)	32.9 0.7(10)	32.9 0.5(10)	32.6 0.5(10)
DAY 91	31.3 0.6(9)	31.9* 0.4(9)	31.7 0.6(9)	31.4 0.4(10)
DAY 125	32.2 0.5(10)	a	a	32.6 0.4(10)
RDW (%)				
DAY 44	12.2 0.5(10)	12.1 0.5(10)	11.9 0.6(10)	12.6 0.4(10)
DAY 91	13.2 0.7(9)	12.9 0.3(9)	13.5 0.5(9)	15.1@ 1.3(10)
DAY 125	13.6 0.8(10)	a	a	12.7 1.3(10)
ARET (x10 ³ /μL)				
DAY 44	200 40(10)	185 32(10)	179 21(10)	177 25(10)
DAY 91	181 49(9)	179 23(9)	196 36(9)	218 46(10)
DAY 125	188 31(10)	a	a	150* 22(10)
WBC (x10 ³ /μL)				
DAY 44	17.36 2.17(10)	16.34 4.10(10)	17.97 3.83(10)	19.29 3.11(10)
DAY 91	14.37 2.08(9)	12.15 3.14(9)	14.04 3.05(9)	15.25 3.14(10)
DAY 125	13.11 3.83(10)	a	a	13.23 3.45(10)
ANEU (x10 ³ /μL)				
DAY 44	2.32 1.01(10)	2.31 0.76(10)	2.50 0.75(10)	2.48 0.97(10)
DAY 91	2.14 0.47(9)	1.92 0.47(9)	1.75 0.75(9)	2.34 0.66(10)
DAY 125	1.79 0.97(10)	a	a	1.94 0.74(10)

Company Sanitized. Does not contain TSCA CBI

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 250 mg/kg
ALYM (x10 ³ /μL)				
DAY 44	14.19 1.91(10)	13.03 4.07(10)	14.65 3.82(10)	15.86 2.55(10)
DAY 91	11.54 1.59(9)	9.57 3.16(9)	11.56 3.23(9)	12.12 2.80(10)
DAY 125	10.60 3.36(10)	^a	^a	10.62 2.98(10)
AMON (x10 ³ /μL)				
DAY 44	0.34 0.10(10)	0.40 0.10(10)	0.39 0.17(10)	0.44 0.13(10)
DAY 91	0.45 0.20(9)	0.38 0.21(9)	0.37 0.21(9)	0.40 0.16(10)
DAY 125	0.34 0.19(10)	^a	^a	0.28 0.11(10)
AEOS (x10 ³ /μL)				
DAY 44	0.16 0.04(10)	0.23* 0.05(10)	0.15 0.05(10)	0.15 0.07(10)
DAY 91	0.15 0.07(9)	0.20 0.15(9)	0.17 0.10(9)	0.21 0.13(10)
DAY 125	0.14 0.08(10)	^a	^a	0.13 0.13(10)
ABAS (x10 ³ /μL)				
DAY 44	0.11 0.03(10)	0.10 0.04(10)	0.11 0.07(10)	0.10 0.05(10)
DAY 91	0.03 0.04(9)	0.03 0.03(9)	0.04 0.04(9)	0.04 0.04(10)
DAY 125	0.07 0.03(10)	^a	^a	0.08 0.05(10)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 250 mg/kg
ALUC (x10 ³ /μL)				
DAY 44	0.24 0.06(10)	0.27 0.19(10)	0.18 0.10(10)	0.26 0.14(10)
DAY 91	0.07 0.09(9)	0.07 0.07(9)	0.15 0.17(9)	0.13 0.13(10)
DAY 125	0.17 0.12(10)	a	a	0.18 0.06(10)
PLT (x10 ³ /μL)				
DAY 44	1141 103(9)	1077 92(9)	1069 225(8)	1008 102(8)
DAY 91	1178 153(7)	1055 122(9)	1092 155(8)	1111 90(7)
DAY 125	1059 126(7)	a	a	1081 78(9)

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

a Group not sampled at this timepoint.

* 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	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 250 mg/kg
RBC (x10 ⁶ /μL)				
DAY 45	8.26 0.17(10)	7.85 0.30(9)	8.14 0.45(10)	7.75* 0.45(10)
DAY 93	8.41 0.27(10)	8.08 0.28(9) a	8.17 0.62(10) a	7.82* 0.32(9)
DAY 125	7.95 0.38(9)			8.00 0.50(9)
HGB (g/dL)				
DAY 45	15.4 0.5(10)	14.8* 0.3(9)	15.1 0.4(10)	14.5* 0.7(10)
DAY 93	15.5 0.5(10)	15.2 0.6(9) a	15.1 0.5(10) a	14.2* 0.5(9)
DAY 125	15.1 0.7(9)			14.8 0.8(9)
HCT (%)				
DAY 45	46.9 1.1(10)	44.9* 1.8(9)	45.6 1.7(10)	44.3* 2.1(10)
DAY 93	47.6 1.9(10)	45.7 2.0(9) a	46.2 2.4(10) a	44.0* 1.5(9)
DAY 125	45.7 2.0(9)			44.3 2.3(9)
MCV (fl)				
DAY 45	56.8 1.2(10)	57.2 1.7(9)	56.0 1.6(10)	57.1 1.2(10)
DAY 93	56.6 1.5(10)	56.6 1.9(9) a	56.8 3.9(10) a	56.3 1.1(9)
DAY 125	57.5 1.5(9)			55.5* 2.1(9)
MCH (pg)				
DAY 45	18.7 0.5(10)	18.9 0.6(9)	18.5 0.6(10)	18.7 0.7(10)
DAY 93	18.5 0.4(10)	18.8 0.7(9) a	18.5 0.8(10) a	18.2 0.5(9)
DAY 125	19.1 0.3(9)			18.5* 0.7(9)

Company Sanitized. Does not contain TSCA CBI

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 250 mg/kg
MCHC (g/dL)				
DAY 45	32.9 0.8(10)	33.0 0.9(9)	33.1 0.5(10)	32.7 0.8(10)
DAY 93	32.7 0.5(10)	33.2 1.4(9) ^a	32.6 1.2(10) ^a	32.3 0.4(9)
DAY 125	33.2 0.8(9)			33.4 0.5(9)
RDW (%)				
DAY 45	11.7 0.5(10)	11.9 0.5(9)	11.7 0.7(10)	12.2 0.4(10)
DAY 93	11.3 0.5(10)	11.3 0.4(9) ^a	12.3 2.5(10) ^a	12.3@ 1.0(9)
DAY 125	12.4 0.7(9)			11.7@ 0.3(9)
ARET (x10 ³ /μL)				
DAY 45	208 25(10)	216 35(9)	201 37(10)	210 39(10)
DAY 93	151 35(10)	157 0.036(9) ^a	219 181(10) ^a	172 28(9)
DAY 125	171 24(9)			145@ 39(9)
WBC (x10 ³ /μL)				
DAY 45	13.67 3.13(10)	12.83 2.99(9)	13.42 3.12(10)	13.59 1.93(10)
DAY 93	9.96 1.66(10)	9.86 1.76(9) ^a	10.36 2.27(10) ^a	10.50 1.98(9)
DAY 125	7.98 1.76(9)			8.12 1.47(9)
ANEU (x10 ³ /μL)				
DAY 45	1.77 0.70(10)	1.62 0.48(9)	1.69 0.54(10)	1.81 0.67(10)
DAY 93	1.15 0.32(10)	1.46 0.49(9) ^a	2.31@ 0.94(10) ^a	1.65 0.78(9)
DAY 125	1.13 0.27(9)			1.58* 0.54(9)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 250 mg/kg
ALYM ($\times 10^3/\mu\text{L}$)				
DAY 45	11.10 2.43(10)	10.52 2.87(9)	10.91 2.57(10)	10.99 1.67(10)
DAY 93	8.22 1.50(10)	7.83 1.70(9)	7.39 2.29(10)	8.19 1.66(9)
DAY 125	6.41 1.77(9)	^a	^a	5.94 1.51(9)
AMON ($\times 10^3/\mu\text{L}$)				
DAY 45	0.30 0.09(10)	0.25 0.08(9)	0.31 0.08(10)	0.29 0.10(10)
DAY 93	0.21 0.07(10)	0.24 0.10(9)	0.26 0.08(10)	0.29 0.17(9)
DAY 125	0.21 0.07(9)	^a	^a	0.29 0.14(9)
AEOS ($\times 10^3/\mu\text{L}$)				
DAY 45	0.19 0.07(10)	0.10* 0.05(9)	0.18 0.09(10)	0.18 0.04(10)
DAY 93	0.18 0.09(10)	0.14 0.06(9)	0.22 0.09(10)	0.18 0.06(9)
DAY 125	0.10 0.04(9)	^a	^a	0.15* 0.03(9)
ABAS ($\times 10^3/\mu\text{L}$)				
DAY 45	0.10 0.07(10)	0.09 0.05(9)	0.11 0.05(10)	0.10 0.03(10)
DAY 93	0.08 0.02(10)	0.07 0.04(9)	0.07 0.03(10)	0.05 0.03(9)
DAY 125	0.04 0.03(9)	^a	^a	0.04 0.02(9)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 250 mg/kg
ALUC ($\times 10^3/\mu\text{L}$)				
DAY 45	0.21 0.08(10)	0.24 0.18(9)	0.22 0.09(10)	0.22 0.06(10)
DAY 93	0.12 0.05(10)	0.12 0.08(9) ^a	0.12 0.06(10) ^a	0.14 0.07(9)
DAY 125	0.09 0.03(9)			0.11 0.04(9)
PLT ($\times 10^3/\mu\text{L}$)				
DAY 45	1186 110(6)	1081 202(9)	1084 108(8)	1068 106(9)
DAY 93	1025 144(10)	1004 102(8) ^a	1118 105(6) ^a	1029 143(6)
DAY 125	1043 217(9)			1172 159(5)

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

^a Group not sampled at this timepoint.

* 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	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 250 mg/kg
PT (seconds)				
DAY 91	15.2 0.8(10)	14.7 0.4(10)	15.2 0.9(9)	15.5 0.7(10)
APTT (seconds)				
DAY 91	18.7 2.5(10)	16.3* 2.2(10)	15.8* 2.1(9)	16.8 0.8(10)

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

* 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	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 250 mg/kg
PT (seconds)				
DAY 93	14.5 0.8(9)	14.4 0.3(9)	14.5 0.5(10)	14.1 0.5(9)
APTT (seconds)				
DAY 93	17.1 1.4(9)	15.8 1.4(9)	15.4 1.7(10)	15.1* 1.5(9)

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

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

TABLE 30

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 250 mg/kg
AST (U/L)				
DAY 44	78 10(10)	84 13(10)	76 7(8)	82 14(9)
DAY 91	99 29(10)	87 18(10) ^a	80 15(9) ^a	96 30(10)
DAY 125	78 7(10)			79 10(10)
ALT (U/L)				
DAY 44	30 4(10)	33 5(10)	28 6(8)	33 8(9)
DAY 91	36 8(10)	36 8(10) ^a	33 5(9) ^a	43 22(10)
DAY 125	33 7(10)			36 14(10)
SDH (U/L)				
DAY 44	18.8 4.2(10)	17.9 4.6(10)	18.2 2.6(10)	17.4 6.3(10)
DAY 91	28.6 8.1(10)	23.3 6.2(10) ^a	23.4 5.8(9) ^a	25.8 9.1(10)
DAY 125	21.5 6.5(10)			14.0* 3.4(10)
ALKP (U/L)				
DAY 44	134 31(10)	144 35(10)	156 21(8)	185* 30(9)
DAY 91	97 22(10)	95 20(10) ^a	139* 20(9) ^a	186* 32(10)
DAY 125	81 18(10)			77 14(10)
BILI (mg/dL)				
DAY 44	0.09 0.03(10)	0.09 0.04(10)	0.08 0.04(8)	0.06 0.02(9)
DAY 91	0.07 0.03(10)	0.06 0.02(10) ^a	0.05 0.00(9) ^a	0.05 0.00(10)
DAY 125	0.06 0.02(10)			0.05 0.00(10)

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 250 mg/kg
BUN (mg/dL)				
DAY 44	14 2(10)	14 2(10)	15 2(10)	14 2(10)
DAY 91	15 2(10)	15 2(10)	16 2(9)	15 1(10)
DAY 125	15 1(10)	^a	^a	18* 2(10)
CREA (mg/dL)				
DAY 44	0.34 0.05(10)	0.31 0.05(10)	0.30 0.04(10)	0.34 0.07(10)
DAY 91	0.42 0.07(10)	0.40 0.09(10)	0.39 0.05(9)	0.45 0.06(10)
DAY 125	0.40 0.06(10)	^a	^a	0.40 0.06(10)
CHOL (mg/dL)				
DAY 44	84 22(10)	65 11(10)	56* 16(10)	54* 18(10)
DAY 91	78 27(10)	65 13(10)	48@ 16(9)	47@ 15(10)
DAY 125	75 13(10)	^a	^a	56* 10(10)
TRIG (mg/dL)				
DAY 44	97 58(10)	90 30(10)	75 38(8)	53 39(9)
DAY 91	127 51(10)	98 39(10)	49* 24(9)	39* 27(10)
DAY 125	95 37(10)	^a	^a	55@ 37(10)
GLUC (mg/dL)				
DAY 44	110 17(10)	104 12(10)	108 11(10)	112 16(10)
DAY 91	125 38(10)	102 14(10)	112 27(9)	116 30(10)
DAY 125	127 37(10)	^a	^a	106 16(10)

Company Sanitized. Does not contain TSCA CBI

TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 250 mg/kg
TP (g/dL)				
DAY 44	6.6 0.3(10)	6.6 0.3(10)	6.7 0.3(8)	7.3* 0.4(9)
DAY 91	6.9 0.4(10)	6.8 0.3(10) a	7.1 0.4(9) a	7.7* 0.4(10)
DAY 125	7.0 0.3(10)			6.7 0.3(10)
ALB (g/dL)				
DAY 44	4.1 0.2(10)	4.2 0.2(10)	4.3 0.5(8)	5.0@ 0.3(9)
DAY 91	4.3 0.2(10)	4.4 0.2(10) a	4.7* 0.2(9) a	5.4* 0.3(10)
DAY 125	4.4 0.2(10)			4.3 0.3(10)
GLOB (g/dL)				
DAY 44	2.4 0.2(10)	2.4 0.2(10)	2.5 0.4(8)	2.3 0.2(9)
DAY 91	2.6 0.2(10)	2.4 0.2(10) a	2.4 0.3(9) a	2.3* 0.1(10)
DAY 125	2.6 0.3(10)			2.4 0.2(10)
CALC (mg/dL)				
DAY 44	10.8 0.4(10)	10.9 0.4(10)	10.8 0.5(10)	11.2 0.3(10)
DAY 91	11.0 0.7(10)	10.6 0.4(10) a	10.5 0.5(9) a	10.9 0.5(10)
DAY 125	10.6 0.3(10)			10.2* 0.3(10)
IPHS (mg/dL)				
DAY 44	8.6 0.7(10)	9.1 0.5(10)	9.5* 0.8(8)	9.4 0.9(9)
DAY 91	9.2 2.2(10)	8.7 1.5(10) a	8.9 1.0(9) a	9.1 1.4(10)
DAY 125	8.1 1.5(10)			7.8 0.8(10)

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TABLE 30 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 250 mg/kg
NA (mmol/L)				
DAY 44	144.5 1.9(10)	143.5 1.0(10)	144.4 0.9(10)	143.9 1.2(10)
DAY 91	147.2 2.2(10)	145.9 1.4(10)	146.1 1.5(9)	145.2* 2.0(10)
DAY 125	146.4 0.8(10)	^a	^a	146.6 1.5(10)
K (mmol/L)				
DAY 44	6.02 0.40(10)	6.05 0.23(10)	6.24 0.40(8)	5.98 0.47(9)
DAY 91	6.33 0.60(10)	6.07 0.42(10)	6.24 0.39(9)	6.25 0.56(10)
DAY 125	6.41 0.63(10)	^a	^a	6.05 0.41(10)
CL (mmol/L)				
DAY 44	100.5 1.8(10)	99.4 2.1(10)	99.5 2.3(10)	99.3 1.6(10)
DAY 91	100.7 1.7(10)	100.1 1.8(10)	100.5 1.3(9)	98.9* 1.3(10)
DAY 125	103.4 0.9(10)	^a	^a	103.4 1.6(10)
PFLU (µg/mL)				
DAY 44	^a	^a	^a	^a
DAY 91	0.1 0.0(10)	0.2 0.0(10)	0.4@ 0.1(9)	0.7@ 0.1(10)
DAY 125	0.1 0.0(10)	^a	^a	0.1 0.1(9)

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

^a Group not sampled at this timepoint.

* 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).

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TABLE 31

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 250 mg/kg
AST (U/L)				
DAY 45	87 14(10)	76 15(9)	77 17(10)	69* 8(10)
DAY 93	90 27(10)	79 16(9) a	89 10(10) a	87 19(9)
DAY 125	124 61(9)			152 198(10)
ALT (U/L)				
DAY 45	37 6(10)	31 7(9)	31 5(10)	29* 8(10)
DAY 93	33 8(10)	33 7(9) a	33 4(10) a	38 16(9)
DAY 125	65 40(9)			62 72(10)
SDH (U/L)				
DAY 45	18.2 5.4(10)	18.3 4.6(9)	16.3 3.8(10)	15.8 4.6(10)
DAY 93	18.9 7.5(10)	16.4 3.8(9) a	18.3 4.2(10) a	17.2 5.0(9)
DAY 125	25.8 12.0(9)			25.0 27.6(10)
ALKP (U/L)				
DAY 45	66 18(10)	71 22(9)	83 18(10)	81 18(10)
DAY 93	42 10(10)	44 17(9) a	55 15(10) a	52 18(9)
DAY 125	33 13(9)			38 14(10)
BILI (mg/dL)				
DAY 45	0.13 0.04(10)	0.11 0.05(9)	0.11 0.04(10)	0.09 0.04(10)
DAY 93	0.13 0.06(10)	0.10 0.04(9) a	0.10 0.05(10) a	0.11 0.04(9)
DAY 125	0.10 0.04(9)			0.09 0.06(10)

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TABLE 31 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 250 mg/kg
BUN (mg/dL)				
DAY 45	16 2(10)	15 2(9)	16 2(10)	16 2(10)
DAY 93	17 2(10)	16 2(9)	16 3(10)	16 1(9)
DAY 125	16 3(9)	^a	^a	16 2(10)
CREA (mg/dL)				
DAY 45	0.40 0.04(10)	0.35* 0.03(9)	0.35* 0.05(10)	0.37 0.07(10)
DAY 93	0.47 0.05(10)	0.44 0.04(9)	0.51 0.08(10)	0.50 0.06(9)
DAY 125	0.48 0.06(9)	^a	^a	0.48 0.04(10)
CHOL (mg/dL)				
DAY 45	83 12(10)	89 19(9)	82 13(10)	92 15(10)
DAY 93	79 14(10)	90 19(9)	76 13(10)	95 20(9)
DAY 125	106 36(9)	^a	^a	98 51(10)
TRIG (mg/dL)				
DAY 45	63 26(10)	78 41(9)	44 18(10)	42 13(10)
DAY 93	160 136(10)	87 45(9)	53@ 24(10)	54@ 22(9)
DAY 125	136 72(9)	^a	^a	102 96(10)
GLUC (mg/dL)				
DAY 45	97 9(10)	109* 13(9)	98 5(10)	101 7(10)
DAY 93	92 8(10)	97 5(9)	100 17(10)	94 5(9)
DAY 125	107 20(9)	^a	^a	104 14(10)

Company Sanitized. Does not contain TSCA CBI

TABLE 31 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 250 mg/kg
TP (g/dL)				
DAY 45	7.3 0.5(10)	7.4 0.4(9)	7.7 0.3(10)	8.2* 0.4(10)
DAY 93	7.5 0.5(10)	7.8 0.4(9) a	8.3* 0.4(10) a	8.6* 0.4(9)
DAY 125	8.2 0.5(9)			8.2 0.5(10)
ALB (g/dL)				
DAY 45	5.0 0.5(10)	5.0 0.4(9)	5.4 0.2(10)	5.7* 0.3(10)
DAY 93	5.2 0.5(10)	5.4 0.4(9) a	6.0* 0.3(10) a	6.0* 0.3(9)
DAY 125	5.7 0.3(9)			5.5 0.3(10)
GLOB (g/dL)				
DAY 45	2.3 0.2(10)	2.4 0.2(9)	2.3 0.2(10)	2.4 0.2(10)
DAY 93	2.3 0.2(10)	2.4 0.1(9) a	2.4 0.2(10) a	2.6* 0.2(9)
DAY 125	2.5 0.3(9)			2.7 0.3(10)
CALC (mg/dL)				
DAY 45	11.0 0.4(10)	11.2 0.4(9)	11.2 0.3(10)	11.7* 0.4(10)
DAY 93	10.8 0.3(10)	11.0 0.5(9) a	11.3* 0.4(10) a	11.5* 0.3(9)
DAY 125	11.1 0.5(9)			10.9 0.3(10)
IPHS (mg/dL)				
DAY 45	7.5 0.7(10)	7.6 1.2(9)	7.9 0.6(10)	7.8 0.5(10)
DAY 93	5.6 0.7(10)	6.0 0.5(9) a	6.7* 1.3(10) a	6.6* 0.7(9)
DAY 125	5.7 0.9(9)			6.4 0.9(10)

Company Sanitized. Does not contain TSCA CBI

TABLE 31 (Continued)

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 250 mg/kg
NA (mmol/L)				
DAY 45	143.5 2.4(10)	143.5 2.7(9)	142.5 1.6(10)	143.3 1.3(10)
DAY 93	143.7 1.6(10)	142.8 1.6(9)	144.1 2.2(10)	143.2 1.3(9)
DAY 125	145.5 1.3(9)	a	a	143.9* 1.8(10)
K (mmol/L)				
DAY 45	5.66 0.21(10)	5.73 0.40(9)	5.88 0.28(10)	6.32* 0.32(10)
DAY 93	5.29 0.36(10)	5.29 0.26(9)	5.62 0.40(10)	6.05* 0.40(9)
DAY 125	5.31 0.44(9)	a	a	5.45 0.48(10)
CL (mmol/L)				
DAY 45	100.8 0.9(10)	99.9 1.6(9)	99.7 1.2(10)	99.5 1.0(10)
DAY 93	99.2 2.2(10)	98.9 2.3(9)	99.3 2.1(10)	97.9 1.4(9)
DAY 125	102.6 1.4(9)	a	a	103.2 1.8(10)
PFLU (µg/mL)				
DAY 45	a	a	a	a
DAY 93	0.1 0.1(10)	0.2 0.1(9)	0.4@ 0.1(10)	0.8@ 0.2(9)
DAY 125	0.1 0.0(9)	a	a	0.1 0.0(10)

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

a Group not sampled at this timepoint.

* 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	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 250 mg/kg
VOL (mL)				
DAY 44	8.6 5.6(10)	10.0 5.3(10)	8.0 5.6(10)	17.1 16.7(10)
DAY 91	7.1 5.6(10)	10.0 6.8(9) ^a	10.0 9.0(9) ^a	15.4@ 7.0(10)
DAY 125	12.0 5.4(10)			7.2@ 6.1(10)
UOSM (mOsm)				
DAY 44	1183 346(10)	1019 474(10)	1333 592(9)	938 685(10)
DAY 91	1330 474(7)	1158 473(10) ^a	1315 556(9) ^a	793 297(10)
DAY 125	952 364(10)			1759* 932(10)
SG				
DAY 44	1.037 0.011(10)	1.032 0.014(10)	1.045 0.019(10)	1.029 0.019(10)
DAY 91	1.048 0.017(9)	1.036 0.013(10) ^a	1.040 0.016(9) ^a	1.027* 0.009(10)
DAY 125	1.031 0.011(10)			1.051* 0.023(10)
pH				
DAY 44	7.2 0.6(10)	7.3 0.8(10)	7.0 0.6(10)	7.5 0.7(10)
DAY 91	6.7 0.4(10)	6.9 0.7(10) ^a	7.1 0.8(9) ^a	6.6 0.5(10)
DAY 125	6.8 0.5(10)			6.6 0.5(10)
URO (EU/dL)				
DAY 44	0.2 0.0(10)	0.3 0.3(10)	0.2 0.0(10)	0.2 0.0(10)
DAY 91	0.2 0.0(10)	0.3 0.3(10) ^a	0.2 0.0(9) ^a	0.2 0.0(10)
DAY 125	0.2 0.0(10)			0.2 0.0(10)

Company Sanitized. Does not contain TSCA CBI

TABLE 32 (Continued)

SUMMARY OF URINALYSIS VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg	Group III 25 mg/kg	Group V 100 mg/kg	Group VII 250 mg/kg
UFLU (µg)				
DAY 44	a	a	a	a
DAY 91	20.2 5.3(7)	213.0 36.8(9)	662.7@ 188.5(9)	1473.6@ 313.0(10)
DAY 125	14.2 2.9(10)	a	a	87.4* 22.8(10)
DAY 181	12.1 4.8(5)	22.8 3.2(5)	39.1* 11.5(5)	69.1* 6.6(5)
UMTP (mg/dL)				
DAY 44	77 37(10)	63 47(10)	103 53(10)	66 60(10)
DAY 91	119 71(10)	78 64(10)	91 50(9)	40* 20(10)
DAY 125	66 49(10)	a	a	121 73(10)

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

a Group not sampled at this timepoint.

* 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).

Company Sanitized. Does not contain TSCA CE

TABLE 33
SUMMARY OF URINALYSIS VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 250 mg/kg
VOL (mL)				
DAY 45	5.8 4.2(9)	6.9 3.6(9)	8.2 3.6(10)	12.6* 4.6(10)
DAY 93	3.1 3.1(7)	4.9 2.6(8) a	4.0 3.0(10) a	10.7@ 7.8(9)
DAY 125	5.2 4.7(9)			6.2 3.1(7)
UOSM (mOsm)				
DAY 45	1271 960(8)	1117 711(9)	786 249(10)	589 197(10)
DAY 93	1178 464(3)	1204 372(7) a	1541 622(9) a	764 269(9)
DAY 125	976 380(7)			983 512(7)
SG				
DAY 45	1.035 0.021(8)	1.033 0.017(9)	1.024 0.007(10)	1.018 0.006(10)
DAY 93	1.044 0.021(4)	1.042 0.019(8) a	1.048 0.017(10) a	1.024 0.008(9)
DAY 125	1.040 0.021(9)			1.031 0.014(7)
pH				
DAY 45	7.1 0.8(9)	6.9 0.3(9)	7.2 0.6(10)	7.7 0.4(10)
DAY 93	6.5 0.9(7)	6.4 0.7(8) a	6.2 0.4(10) a	6.2 0.8(9)
DAY 125	5.7 0.4(9)			5.8 0.5(7)
URO (EU/dL)				
DAY 45	0.2 0.0(9)	0.2 0.0(9)	0.2 0.0(10)	0.2 0.0(10)
DAY 93	0.2 0.0(7)	0.2 0.0(8) a	0.2 0.0(10) a	0.2 0.0(9)
DAY 125	0.2 0.0(9)			0.2 0.0(7)

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TABLE 33 (Continued)

SUMMARY OF URINALYSIS VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg	Group IV 25 mg/kg	Group VI 100 mg/kg	Group VIII 250 mg/kg
UFLU (µg)				
DAY 45	a	a	a	a
DAY 93	16.7 3.8(2)	99.2 32.1(6)	460.3 127.0(4)	914.7@ 618.1(9)
DAY 125	8.6 5.1(7)	a	a	43.8@ 14.9(7)
DAY 181	8.8 3.8(5)	15.9 6.9(3)	20.0 5.6(5)	29.3* 13.1(4)
UMTP (mg/dL)				
DAY 45	41 34(9)	24 22(9)	18 5(10)	21 11(10)
DAY 93	84 56(6)	49 43(8)	57 31(10)	54 26(9)
DAY 125	109 130(9)	a	a	69 76(7)

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

a Group not sampled at this timepoint.

* 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 ^a	Dosage (mg/kg/day)	Hepatic Peroxisomal Beta-Oxidation Activity (nmol/min/mg protein)			
		10-Day Time Point	90-Day Time Point	36-Day Recovery	92-Day Recovery
I	0	4.7 ± 1.7 ^b	5.1 ± 1.4	8.5 ± 2.8	8.3 ± 1.3
III ^c	25	8.9 ± 1.8	13.0 ± 4.8	-----	-----
V ^c	100	10.5 ± 2.6*	20.7 ± 1.5*	-----	-----
VII	250	16.4 ± 4.2*	44.5 ± 9.9*	30.0 ± 4.1*	25.1 ± 6.0#

a. Group designations for animals evaluated at the 10-day time point are I-A, III-A, V-A, and VII-A.

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

c. Samples were not prepared for analysis from groups III and V at the 30- and 90-day recovery time points.

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

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

TABLE 35

SUMMARY OF PEROXISOMAL BETA-OXIDATION ACTIVITY IN FEMALE RATS

Group ^a	Dosage (mg/kg/day)	Hepatic Peroxisomal Beta-Oxidation Activity (nmol/min/mg protein)		
		10-Day Timepoint	90-Day Timepoint	36-Day Recovery 92-Day Recovery
II	0	8.1 ± 2.2 ^b	7.8 ± 1.9	9.6 ± 1.4 18.4 ± 1.8
IV ^c	25	7.7 ± 2.3	12.3 ± 4.2	-----
VI ^c	100	13.8 ± 2.3*	26.9 ± 3.7*	-----
VIII	250	21.1 ± 2.8*	29.7 ± 7.1*	19.9 ± 3.6* 31.7 ± 3.4*

a. Group designations for animals evaluated at the 10-day time point are II-A, IV-A, VI-A, and VIII-A.

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

c. Samples were not prepared for analysis from groups IV and VI at the 30- and 90-day recovery timepoints.

* 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 250 mg/kg/day
LIVER	15.61430 2.40914 (10)	16.87710 2.21000 (10)	21.08367# 2.16729 (9)	25.53740# 2.01802 (10)
KIDNEYS	3.87130 0.32057 (10)	4.16070 0.40193 (10)	4.18767# 0.26834 (9)	4.62600# 0.44545 (10)
HEART	1.71400 0.15515 (10)	1.71110 0.16522 (10)	1.53744# 0.13457 (9)	1.51080# 0.12204 (10)
SPLEEN	0.82560 0.10868 (10)	0.73400 0.17504 (10)	0.79833 0.08688 (9)	0.71340 0.07769 (10)
BRAIN	2.11810 0.06517 (10)	2.16130 0.11475 (10)	2.07144 0.09339 (9)	2.09800 0.08814 (10)
THYMUS	0.44800 0.13463 (10)	0.37290 0.09756 (10)	0.37211 0.09829 (9)	0.35967 0.07953 (9)
ADRENAL GLANDS	0.05540 0.00947 (10)	0.06010 0.00881 (10)	0.05167 0.00811 (9)	0.05450 0.00798 (10)
TESTES	3.62880 0.32307 (10)	3.39690 0.38948 (10)	3.55367 0.14742 (9)	3.54910 0.30220 (10)
EPIDIDYMIDES	1.60570 0.15978 (10)	1.50770 0.13254 (10)	1.43100# 0.09600 (9)	1.46750# 0.10973 (10)
FINAL BODY WEIGHT	569.92000 46.42274 (10)	556.23001 62.22883 (10)	514.55556# 31.85973 (9)	508.24000# 35.48981 (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 250 mg/kg/day
LIVER/ FINAL BODY * 100	2.72792 0.24256(10)	3.02910# 0.10928(10)	4.09189# 0.26331(9)	5.02981# 0.30664(10)
KIDNEYS/ FINAL BODY * 100	0.68187 0.06254(10)	0.75073# 0.05504(10)	0.81464# 0.04174(9)	0.91000# 0.05964(10)
HEART/ FINAL BODY * 100	0.30111 0.01945(10)	0.30962 0.03418(10)	0.29877 0.01816(9)	0.29751 0.01679(10)
SPLEEN/ FINAL BODY * 100	0.14549 0.02010(10)	0.13149 0.02476(10)	0.15512 0.01376(9)	0.14058 0.01383(10)
BRAIN/ FINAL BODY * 100	0.37366 0.02959(10)	0.39140 0.03280(10)	0.40363# 0.02587(9)	0.41417# 0.02660(10)
THYMUS/ FINAL BODY * 100	0.07853 0.02208(10)	0.06735 0.01762(10)	0.07197 0.01718(9)	0.07151 0.01422(9)
ADRENAL GLANDS/ FINAL BODY * 100	0.00978 0.00182(10)	0.01087 0.00169(10)	0.01001 0.00120(9)	0.01073 0.00155(10)
TESTES/ FINAL BODY * 100	0.64020 0.07536(10)	0.61616 0.09099(10)	0.69236 0.04100(9)	0.69863# 0.04115(10)
EPIDIDYMIDES/ FINAL BODY * 100	0.28214 0.02174(10)	0.27346 0.03430(10)	0.27948 0.02996(9)	0.28923 0.01927(10)

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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/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 250 mg/kg/day
LIVER/ BRAIN * 100	735.74333 99.37257(10)	780.17520 85.08778(10)	1019.5284# 115.06490(9)	1218.7006# 103.65133(10)
KIDNEYS/ BRAIN * 100	182.68506 12.66199(10)	192.36680 13.14320(10)	202.51532# 15.84059(9)	220.59585# 20.88300(10)
HEART/ BRAIN * 100	80.91023 6.82263(10)	79.30874 8.23777(10)	74.35749 7.41525(9)	72.04801# 5.53580(10)
SPLEEN/ BRAIN * 100	38.93490 4.57844(10)	33.91403 7.51428(10)	38.56439 4.15459(9)	34.01722 3.46850(10)
THYMUS/ BRAIN * 100	21.03669 5.97190(10)	17.30890 4.63114(10)	18.00484 4.76335(9)	17.12540 3.81584(9)
ADRENAL GLANDS/ BRAIN * 100	2.62137 0.47467(10)	2.78484 0.40829(10)	2.49488 0.38735(9)	2.59483 0.34618(10)
TESTES/ BRAIN * 100	171.16403 11.88715(10)	156.96718 13.69597(10)	171.72378 7.58365(9)	169.09911 11.50305(10)
EPIDIDYMIDES/ BRAIN * 100	75.74999 6.44128(10)	69.76881 4.95178(10)	69.16509 4.92678(9)	70.02996 5.78874(10)

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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 250 mg/kg/day
LIVER	15.30650 2.06770(10)	18.99580# 2.41188(10)
KIDNEYS	3.92180 0.43359(10)	4.52600# 0.45123(10)
HEART	1.78690 0.22877(10)	1.70310 0.09352(10)
SPLEEN	0.79060 0.15057(10)	0.82750 0.12262(10)
BRAIN	2.15100 0.10458(10)	2.14830 0.06237(10)
THYMUS	0.30370 0.10010(10)	0.29500 0.08028(10)
ADRENAL GLANDS	0.05500 0.00939(10)	0.05390 0.00769(10)
TESTES	3.40390 0.45855(10)	3.35360 0.56712(10)
EPIDIDYMIDES	1.51050 0.21531(10)	1.89860 1.25596(10)
FINAL BODY WEIGHT	590.65000 82.53324(10)	537.98000 37.55428(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/day	Group VII 250 mg/kg/day
LIVER/ FINAL BODY * 100	2.59628 0.14348(10)	3.52278# 0.28354(10)
KIDNEYS/ FINAL BODY * 100	0.67037 0.07651(10)	0.84084# 0.05450(10)
HEART/ FINAL BODY * 100	0.30689 0.05285(10)	0.31726 0.01716(10)
SPLEEN/ FINAL BODY * 100	0.13384 0.01870(10)	0.15447 0.02480(10)
BRAIN/ FINAL BODY * 100	0.37046 0.05358(10)	0.40104# 0.02998(10)
THYMUS/ FINAL BODY * 100	0.05128 0.01463(10)	0.05494 0.01501(10)
ADRENAL GLANDS/ FINAL BODY * 100	0.00943 0.00187(10)	0.01005 0.00145(10)
TESTES/ FINAL BODY * 100	0.58528 0.10321(10)	0.62490 0.11357(10)
EPIDIDYMIDES/ FINAL BODY * 100	0.25949 0.04537(10)	0.35028 0.22128(10)

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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/day	Group VII 250 mg/kg/day
LIVER/ BRAIN * 100	711.34075 88.59504(10)	884.91171# 116.18812(10)
KIDNEYS/ BRAIN * 100	182.34225 18.44671(10)	210.72828# 20.63654(10)
HEART/ BRAIN * 100	83.23074 11.73675(10)	79.38841 5.76903(10)
SPLEEN/ BRAIN * 100	36.81368 7.14802(10)	38.56659 5.91619(10)
THYMUS/ BRAIN * 100	14.01786 4.23746(10)	13.72581 3.74259(10)
ADRENAL GLANDS/ BRAIN * 100	2.54745 0.35256(10)	2.51164 0.37062(10)
TESTES/ BRAIN * 100	158.19880 19.42657(10)	155.98933 25.95332(10)
EPIDIDYMIDES/ BRAIN * 100	70.20005 9.34995(10)	88.28783 58.20703(10)

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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/day	Group III 25 mg/kg/day	Group V 100 mg/kg/day	Group VII 250 mg/kg/day
LIVER	16.86360 1.23511 (5)	14.89120 1.29310 (5)	17.20660 1.65902 (5)	18.53760 3.89685 (5)
KIDNEYS	4.22420 0.38656 (5)	4.12580 0.60763 (5)	4.20240 0.18598 (5)	4.49080 0.75755 (5)
THYROID GLAND	0.02460 0.00288 (5)	0.02120 0.00455 (5)	0.02480 0.00421 (5)	0.02360 0.00336 (5)
TESTES	3.73740 0.41919 (5)	3.71440 0.46067 (5)	3.76060 0.66540 (5)	3.70660 0.38273 (5)
FINAL BODY WEIGHT	609.24000 49.85251 (5)	584.40000 60.48766 (5)	597.36000 78.98329 (5)	589.00000 118.00491 (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 250 mg/kg/day
LIVER/ FINAL BODY * 100	2.77049 0.08130 (5)	2.55621 0.17311 (5)	2.89634 0.24254 (5)	3.14311# 0.14527 (5)
KIDNEYS/ FINAL BODY * 100	0.69433 0.05264 (5)	0.70486 0.06776 (5)	0.71061 0.07278 (5)	0.76965 0.07781 (5)
THYROID GLAND/ FINAL BODY * 100	0.00407 0.00064 (5)	0.00360 0.00048 (5)	0.00427 0.00114 (5)	0.00410 0.00082 (5)
TESTES/ FINAL BODY * 100	0.61346 0.04906 (5)	0.64182 0.11379 (5)	0.62851 0.06407 (5)	0.64002 0.07619 (5)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).

Statistically significant difference at $p = 0.05$.

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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/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 250 mg/kg/day
LIVER	8.42890 0.89310 (10)	9.28989 1.29807 (9)	10.29410# 0.93782 (10)	12.58311# 1.50915 (9)
KIDNEYS	2.06880 0.21132 (10)	2.34367# 0.28624 (9)	2.32900# 0.22209 (10)	2.60533# 0.26021 (9)
HEART	1.00350 0.11037 (10)	1.13856 0.23821 (9)	1.01180 0.06157 (10)	1.02956 0.10404 (9)
SPLEEN	0.50600 0.10310 (10)	0.50611 0.05648 (9)	0.50710 0.10450 (10)	0.52567 0.07700 (9)
BRAIN	1.88390 0.07620 (10)	1.98522 0.10422 (9)	1.91420 0.08526 (10)	1.94378 0.09538 (9)
THYMUS	0.29780 0.10562 (10)	0.31222 0.08160 (9)	0.28500 0.06451 (10)	0.28444 0.09108 (9)
ADRENAL GLANDS	0.06490 0.01047 (10)	0.06567 0.00907 (9)	0.06550 0.00956 (10)	0.06589 0.00819 (9)
OVARIES	0.11550 0.02923 (10)	0.12211 0.01825 (9)	0.12870 0.01818 (10)	0.11122 0.01719 (9)
UTERUS	0.57820 0.06982 (10)	0.66122 0.23047 (9)	0.58070 0.10303 (10)	0.66444 0.19643 (9)
FINAL BODY WEIGHT	297.45000 35.81503 (10)	303.66667 24.73525 (9)	286.41000 22.00290 (10)	283.48889 31.74474 (9)

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 250 mg/kg/day
LIVER/ FINAL BODY * 100	2.84076 0.15250(10)	3.06088 0.33230(9)	3.59318# 0.15126(10)	4.44566# 0.32538(9)
KIDNEYS/ FINAL BODY * 100	0.69736 0.03459(10)	0.77374# 0.08951(9)	0.81333# 0.04616(10)	0.92685# 0.12559(9)
HEART/ FINAL BODY * 100	0.33821 0.02157(10)	0.37345 0.05777(9)	0.35399 0.01733(10)	0.36475 0.03120(9)
SPLEEN/ FINAL BODY * 100	0.16960 0.02557(10)	0.16691 0.01532(9)	0.17675 0.03224(10)	0.18588 0.02188(9)
BRAIN/ FINAL BODY * 100	0.64099 0.07665(10)	0.65779 0.06489(9)	0.67035 0.03525(10)	0.69254 0.07652(9)
THYMUS/ FINAL BODY * 100	0.09848 0.02656(10)	0.10282 0.02489(9)	0.09959 0.02191(10)	0.09983 0.02528(9)
ADRENAL GLANDS/ FINAL BODY * 100	0.02185 0.00259(10)	0.02170 0.00299(9)	0.02301 0.00405(10)	0.02353 0.00419(9)
OVARIES/ FINAL BODY * 100	0.03897 0.00965(10)	0.04042 0.00646(9)	0.04513 0.00682(10)	0.03964 0.00742(9)
UTERUS/ FINAL BODY * 100	0.19700 0.03626(10)	0.21987 0.08249(9)	0.20335 0.03753(10)	0.23844 0.08261(9)

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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/day	Group IV 25 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 250 mg/kg/day
LIVER/ BRAIN * 100	447.97404 49.75332(10)	468.70612 66.48212(9)	537.69731# 41.01697(10)	647.32738# 71.76231(9)
KIDNEYS/ BRAIN * 100	109.90153 11.16263(10)	117.94290 12.14897(9)	121.67541# 10.15327(10)	133.95247# 10.39944(9)
HEART/ BRAIN * 100	53.25450 5.29987(10)	57.72897 14.36366(9)	52.87944 2.70601(10)	52.91567 4.05247(9)
SPLEEN/ BRAIN * 100	26.83701 5.20406(10)	25.51771 2.75891(9)	26.45901 5.11411(10)	27.02573 3.60259(9)
ADRENAL GLANDS/ BRAIN * 100	3.43808 0.47647(10)	3.31554 0.48277(9)	3.42792 0.52547(10)	3.38577 0.34751(9)
THYMUS/ BRAIN * 100	15.78037 5.45880(10)	15.77146 4.41570(9)	14.89897 3.36605(10)	14.67010 4.68613(9)
OVARIES/ BRAIN * 100	6.12137 1.49504(10)	6.14360 0.78541(9)	6.72625 0.90372(10)	5.72555 0.84613(9)
UTERUS/ BRAIN * 100	30.74888 4.02620(10)	33.16601 10.88714(9)	30.38154 5.49538(10)	34.36785 10.75106(9)

Company Sanitized. Does not contain TSCA CBI

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 250 mg/kg/day
LIVER	10.09844 1.67206 (9)	9.99330 1.38877 (10)
KIDNEYS	2.43678 0.24189 (9)	2.50730 0.40643 (10)
HEART	1.17433 0.10505 (9)	1.08270 0.08698 (10)
SPLEEN	0.56733 0.08403 (9)	0.53740 0.13757 (10)
BRAIN	1.92800 0.07213 (9)	1.91180 0.09510 (10)
THYMUS	0.26833 0.07819 (9)	0.22790 0.04946 (10)
ADRENAL GLANDS	0.06656 0.01321 (9)	0.07440 0.01056 (10)
OVARIES	0.11544 0.02939 (9)	0.11770 0.01938 (10)
UTERUS	0.69278 0.15294 (9)	0.68910 0.20245 (10)
FINAL BODY WEIGHT	353.11111 37.83244 (9)	308.58000# 32.73340 (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 250 mg/kg/day
LIVER/ FINAL BODY * 100	2.85512 0.29184 (9)	3.24730 0.39525 (10)
KIDNEYS/ FINAL BODY * 100	0.69394 0.06941 (9)	0.81594# 0.12449 (10)
HEART/ FINAL BODY * 100	0.33509 0.04017 (9)	0.35335 0.03687 (10)
SPLEEN/ FINAL BODY * 100	0.16188 0.02643 (9)	0.17524 0.04700 (10)
BRAIN/ FINAL BODY * 100	0.55117 0.05678 (9)	0.62527# 0.06535 (10)
THYMUS/ FINAL BODY * 100	0.07543 0.01729 (9)	0.07430 0.01715 (10)
ADRENAL GLANDS/ FINAL BODY * 100	0.01885 0.00301 (9)	0.02445# 0.00468 (10)
UTERUS/ FINAL BODY * 100	0.19783 0.04722 (9)	0.22259 0.05160 (10)
OVARIES/ FINAL BODY * 100	0.03278 0.00845 (9)	0.03839 0.00689 (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 250 mg/kg/day
LIVER/ BRAIN * 100	524.83765 90.51244 (9)	521.86193 59.78217 (10)
KIDNEYS/ BRAIN * 100	126.46850 12.50757 (9)	130.75642 16.47766 (10)
HEART/ BRAIN * 100	61.06879 6.79149 (9)	56.66965 4.22303 (10)
SPLEEN/ BRAIN * 100	29.51530 4.82384 (9)	28.05377 6.80548 (10)
THYMUS/ BRAIN * 100	13.96338 4.15109 (9)	11.88806 2.39151 (10)
ADRENAL GLANDS/ BRAIN * 100	3.44923 0.65823 (9)	3.89537 0.55037 (10)
OVARIES/ BRAIN * 100	5.95250 1.37403 (9)	6.15911 0.98456 (10)
UTERUS/ BRAIN * 100	35.89360 7.44208 (9)	36.14787 10.89853 (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 250 mg/kg/day
LIVER	9.09860 1.06866 (5)	9.22750 0.75842 (4)	9.61700 1.19121 (5)	11.08840# 1.39013 (5)
KIDNEYS	2.32080 0.18101 (5)	2.43700 0.15436 (4)	2.46780 0.29636 (5)	2.70440 0.54874 (5)
THYROID GLAND	0.01660 0.00114 (5)	0.01825 0.00419 (4)	0.01920 0.00349 (5)	0.01940 0.00351 (5)
FINAL BODY WEIGHT	312.62000 20.92813 (5)	334.42501 28.71253 (4)	315.18001 32.76441 (5)	347.56000 55.42101 (5)

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 250 mg/kg/day
LIVER/ FINAL BODY * 100	2.90754 0.24314 (5)	2.76175 0.12111 (4)	3.05101 0.17390 (5)	3.20511# 0.17235 (5)
KIDNEYS/ FINAL BODY * 100	0.74382 0.06063 (5)	0.73438 0.09856 (4)	0.78637 0.08983 (5)	0.77523 0.06208 (5)
THYROID GLAND/ FINAL BODY * 100	0.00532 0.00041 (5)	0.00556 0.00176 (4)	0.00620 0.00161 (5)	0.00574 0.00163 (5)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).

Statistically significant difference at $p = 0.05$.

Company Sanitized. Does not contain TSCA CBI

TABLE 38

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	250	
		I	III	V	VII	
LIVER		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	9	10	
DISCOLORATION, MOTTLED, TAN.					1	
DISCOLORATION, TAN, LEFT.				1		
KIDNEYS		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
LUNGS		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
HEART		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
SKELETAL MUSCLE		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
SPLEEN		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
AORTA		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	

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 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	250	
		I	III	V	VII	
BRAIN		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
SPINAL CORD		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
STOMACH		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
SMALL INTESTINE DISTENDED WITH GAS.					(1)	1
DUODENUM		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
JEJUNUM		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
ILEUM		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
PANCREAS		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	

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 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	250			
		I	III	V	VII			
CECUM		(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED		10	10	10	11			
COLON		(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED		10	10	10	11			
RECTUM		(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED		10	10	10	11			
MESENTERIC LYMPH NODE		(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED		10	10	10	11			
SALIVARY GLANDS		(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED		10	10	10	11			
EDEMA.		(10)	(10)	(10)	(11)			
		10	10	10	10			
					1			
MANDIBULAR LYMPH NODE		(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED		10	10	10	11			
THYMUS		(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED		10	10	10	11			
ADRENAL GLANDS		(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED		10	10	10	11			

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 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	250	
		I	III	V	VII	
SACRAT NERVE NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11	
PITUITARY GLAND NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11	
THYROID GLAND NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11	
PARATHYROID GLANDS NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11	
TRACHEA NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11	
ESOPHAGUS NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11	
PHARYNX/LARYNX NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11	
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11	

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

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		I	III	V	VII	
Males						
SKIN		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	10	
STAIN, RED, FACE.					1	
PROSTATE		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
SEMINAL VESICLES		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
URINARY BLADDER		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
TESTES		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
EPIDIDYIMIDES		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
FEMUR/KNEE JOINT		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
STERNUM		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	

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 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	250	
		I	III	V	VII	
NOSE		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
PLEURAL CAVITY FLUID, CLEAR.					(1)	
MANDIBLE					1	
NO ABNORMALITY DETECTED		(10)	(10)	(9)	(10)	
		10	10	9	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 MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESION	LESION INCIDENCE	
	Males	
	TREATMENT (mg/kg/day)	0 250 I VII
LIVER		(10) (10) 10 10
NO ABNORMALITY DETECTED		
KIDNEYS		(10) (10) 10 10
NO ABNORMALITY DETECTED		
LUNGS		(10) (10) 10 10
NO ABNORMALITY DETECTED		
HEART		(10) (10) 10 10
NO ABNORMALITY DETECTED		
SKELETAL MUSCLE		(10) (10) 10 10
NO ABNORMALITY DETECTED		
SPLEEN		(10) (10) 9 10 1
NO ABNORMALITY DETECTED		
DEFORMITY.		
AORTA		(10) (10) 10 10
NO ABNORMALITY DETECTED		
BRAIN		(10) (10) 10 10
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 39 (CONTINUED)

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

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

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

TABLE 39 (CONTINUED)

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

LESION INCIDENCE	Males	
	TREATMENT (mg/kg/day)	0 250 I VII
RECTUM NO ABNORMALITY DETECTED	(10) 10	(10) 10
MESENTERIC LYMPH NODE NO ABNORMALITY DETECTED	(10) 10	(10) 10
SALIVARY GLANDS NO ABNORMALITY DETECTED	(10) 10	(10) 10
MANDIBULAR LYMPH NODE NO ABNORMALITY DETECTED DISCOLORATION, RED.	(10) 9 1	(10) 10
THYMUS NO ABNORMALITY DETECTED SMALL.	(10) 9 1	(10) 9 1
ADRENAL GLANDS NO ABNORMALITY DETECTED	(10) 10	(10) 10
SCIATIC 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 39 (CONTINUED)

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

LESION	INCIDENCE	
	TREATMENT (mg/kg/day)	Males
	0	250
	I	VII
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 MALE RATS
(ONE-MONTH RECOVERY EVALUATION)

LESION	LESION INCIDENCE	
	Males	
LESION	TREATMENT (mg/kg/day)	
	0	250
LESION	I	VII
PROSTATE	(10) 10	(10) 10
NO ABNORMALITY DETECTED		
SEMINAL VESICLES	(10) 10	(10) 9
NO ABNORMALITY DETECTED		1
SMALL, LEFT.		
URINARY BLADDER	(10) 10	(10) 10
NO ABNORMALITY DETECTED		
TESTES	(10) 8	(10) 9
NO ABNORMALITY DETECTED		1
SOFT, BILATERAL.	1	
DEFORMITY, RIGHT.	1	
SMALL, LEFT.		
EPIDIDYIMIDES	(10) 8	(10) 9
NO ABNORMALITY DETECTED		1
DEFORMITY, LEFT.	1	
SMALL, LEFT.	1	
SMALL, RIGHT.		
FEMUR/KNEE JOINT	(10) 10	(10) 10
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 39 (CONTINUED)

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

LESION	TREATMENT		LESION INCIDENCE	
	(mg/kg/day)		Males	
	0	250	I	VII
STERNUM			(10)	(10)
NO ABNORMALITY DETECTED			10	10
NOSE			(10)	(10)
NO ABNORMALITY DETECTED			10	10
MANDIBLE			(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 MALE RATS
(THREE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)					
		Males					
		0	50	100	250		
		I	III	V	VII		
LIVER		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
KIDNEYS		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
LUNGS		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
HEART		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
SKELETAL MUSCLE		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
SPLEEN		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
AORTA		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
BRAIN		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		

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

TABLE 39 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)				
		0	50	100	250	Males
		I	III	V	VII	
SPINAL CORD		(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	
STOMACH		(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	
DUODENUM		(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	
JEJUNUM		(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	
ILEUM		(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	
PANCREAS		(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	
CECUM		(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	
COLON		(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	

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 MALE RATS
(THREE-MONTH RECOVERY EVALUATION)

LESION	LESION INCIDENCE (Numeric)						
	Males						
	TREATMENT (mg/kg/day)	0	50	100	250		
		I	III	V	VII		
RECTUM		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
MESENTERIC LYMPH NODE		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
SALIVARY GLANDS		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
MANDIBULAR LYMPH NODE		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
THYMUS		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
ADRENAL GLANDS		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
SCIATIC NERVE		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		
PITUITARY GLAND		(5)	(5)	(5)	(5)		
NO ABNORMALITY DETECTED		5	5	5	5		

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

TABLE 39 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)						
		0	50	100	250	Males		
		I	III	V	VII			
THYROID GLAND NO ABNORMALITY DETECTED		(5) 5	(5) 5	(5) 5	(5) 5			
PARATHYROID GLANDS NO ABNORMALITY DETECTED		(5) 5	(5) 5	(5) 5	(5) 5			
TRACHEA NO ABNORMALITY DETECTED		(5) 5	(5) 5	(5) 5	(5) 5			
ESOPHAGUS NO ABNORMALITY DETECTED		(5) 5	(5) 5	(5) 5	(5) 5			
PHARYNX/LARYNX NO ABNORMALITY DETECTED		(5) 5	(5) 5	(5) 5	(5) 5			
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED		(5) 5	(5) 5	(5) 5	(5) 5			
SKIN NO ABNORMALITY DETECTED		(5) 5	(5) 5	(5) 5	(5) 5			
PROSTATE NO ABNORMALITY DETECTED		(5) 5	(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 39 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)				
		Males				
		0	50	100	250	
		I	III	V	VII	
SEMINAL VESICLES NO ABNORMALITY DETECTED		(5) 5	(5) 5	(5) 5	(5) 5	
URINARY BLADDER NO ABNORMALITY DETECTED		(5) 5	(5) 5	(5) 5	(5) 5	
TESTES NO ABNORMALITY DETECTED SMALL, SOFT, RIGHT.		(5) 5	(5) 4 1	(5) 5	(5) 5	
EPIDIDYIMIDES NO ABNORMALITY DETECTED		(5) 5	(5) 5	(5) 5	(5) 5	
FEMUR/KNEE JOINT NO ABNORMALITY DETECTED		(5) 5	(5) 5	(5) 5	(5) 5	
STERNUM NO ABNORMALITY DETECTED		(5) 5	(5) 5	(5) 5	(5) 5	
NOSE NO ABNORMALITY DETECTED		(5) 5	(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 39

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

LESION	LESION INCIDENCE (Numeric)				
	Females				
TREATMENT (mg/kg/day)	0	25	100	250	
	II	IV	VI	VIII	
LIVER	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED	10	10	10	11	
KIDNEYS	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED	10	9	10	11	
DISCOLORATION, TAN, BILATERAL.		1			
DILATATION, BILATERAL, PELVIS.		1			
LUNGS	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED	10	10	9	11	
DISCOLORATION, DARK.			1		
HEART	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED	10	10	10	11	
SKELETAL MUSCLE	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED	10	10	10	11	
SPLEEN	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED	10	10	10	11	
AORTA	(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED	10	10	10	11	

N=11 in Group VIII reflects one reproduction designated animal that died on test day 53. 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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)				
		Females				
		0	25	100	250	
		II	IV	VI	VIII	
BRAIN		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
SPINAL CORD		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
STOMACH		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
DUODENUM		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
JEJUNUM		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
ILEUM		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
PANCREAS		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	
CECUM		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	10	10	11	

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)					
		Females					
		0	25	100	250		
		II	IV	VI	VIII		
COLON		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		10	10	10	11		
RECTUM		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		10	10	10	11		
MESENTERIC LYMPH NODE		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		10	10	10	11		
SALIVARY GLANDS		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		10	10	10	11		
MANDIBULAR LYMPH NODE		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		10	10	10	11		
THYMUS		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		10	10	10	11		
ADRENAL GLANDS		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		10	10	10	10		
LARGE, BILATERAL.					1		
SCIATIC NERVE		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		10	10	10	11		

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (Numeric)				
	Females				
TREATMENT (mg/kg/day)	0	25	100	250	
	II	IV	VI	VIII	
PITUITARY GLAND NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(11) 11	
THYROID GLAND NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(11) 11	
PARATHYROID GLANDS NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(11) 11	
TRACHEA NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(11) 11	
ESOPHAGUS NO ABNORMALITY DETECTED PUNCTURE, GAVAGE ERROR.	(10) 10	(10) 10	(10) 10	(11) 10	1
PHARYNX/LARYNX NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(11) 11	
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(11) 11	
SKIN NO ABNORMALITY DETECTED	(10) 10	(10) 10	(10) 10	(11) 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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)			
		Females			
		0	25	100	250
		II	IV	VI	VIII
SKIN STAIN. RED, PERINEUM.		(10)	(10)	(10)	(11) 1 1
MAMMARY GLAND (FEMALE) NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11
OVARIES NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11
UTERUS NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11
URINARY BLADDER NO ABNORMALITY DETECTED		(10) 10	(10) 9	(10) 10	(11) 11
CALCULUS\CALCULI. DILATATION.			1 1		
FEMUR/KNEE JOINT NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11
STERNUM NO ABNORMALITY DETECTED		(10) 10	(10) 10	(10) 10	(11) 11

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)			
		Females			
		0	25	100	250
		II	IV	VI	VIII
NOSE		(10)	(10)	(10)	(11)
NO ABNORMALITY DETECTED		10	10	10	11
MANDIBLE		(10)	(9)	(9)	(8)
NO ABNORMALITY DETECTED		10	9	9	8

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)

LESION	INCIDENCE	
	Female	
TREATMENT (mg/kg/day)	0	250
	II	VIII
LIVER	(10)	(10)
NO ABNORMALITY DETECTED	10	10
KIDNEYS	(10)	(10)
NO ABNORMALITY DETECTED	9	10
CALCULUS\CALCULI, BILATERAL.	1	
LUNGS	(10)	(10)
NO ABNORMALITY DETECTED	10	10
HEART	(10)	(10)
NO ABNORMALITY DETECTED	10	10
SKELETAL MUSCLE	(10)	(10)
NO ABNORMALITY DETECTED	10	10
SPLEEN	(10)	(10)
NO ABNORMALITY DETECTED	10	10
AORTA	(10)	(10)
NO ABNORMALITY DETECTED	10	10
BRAIN	(10)	(10)
NO ABNORMALITY DETECTED	10	10

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

TABLE 39 (CONTINUED)

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

LESION INCIDENCE	Female		
	TREATMENT (mg/kg/day)	0	250
LESION INCIDENCE	TREATMENT (mg/kg/day)	II	VIII
SPINAL CORD NO ABNORMALITY DETECTED		(10) 10	(10) 10
STOMACH NO ABNORMALITY DETECTED		(10) 10	(10) 10
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
COLON 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)

LESION	TREATMENT		LESION INCIDE	
	(mg/kg/day)		Female	
	0	250		
	II	VIII		
RECTUM	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
MESENTERIC LYMPH NODE	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
SALIVARY GLANDS	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
MANDIBULAR LYMPH NODE	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
THYMUS	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
ADRENAL GLANDS	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
SCIATIC NERVE	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
PITUITARY GLAND	(10)	(10)		
NO ABNORMALITY DETECTED	8	10		
LARGE.	2			

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)

LESION	TREATMENT (mg/kg/day)		INCIDENCE	
	0	250	Female	
			II	VIII
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		
MAMMARY GLAND (FEMALE) 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)

LESION	LESION INCIDE	
	Female	
	TREATMENT (mg/kg/day)	
	0	250
	II	VIII
OVARIES	(10)	(10)
NO ABNORMALITY DETECTED	10	10
UTERUS	(10)	(10)
NO ABNORMALITY DETECTED	10	10
URINARY BLADDER	(10)	(10)
NO ABNORMALITY DETECTED	9	10
CALCULUS\CALCULI.	1	
FEMUR/KNEE JOINT	(10)	(10)
NO ABNORMALITY DETECTED	10	10
STERNUM	(10)	(10)
NO ABNORMALITY DETECTED	10	10
NOSE	(10)	(10)
NO ABNORMALITY DETECTED	10	10
MANDIBLE	(9)	(10)
NO ABNORMALITY DETECTED	9	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)				
		0	25	100	250	Females
		II	IV	VI	VIII	
LIVER		(5) 5	(4) 4	(5) 5	(5) 5	
NO ABNORMALITY DETECTED						
KIDNEYS		(5) 5	(4) 4	(5) 5	(5) 5	
NO ABNORMALITY DETECTED						
LUNGS		(5) 5	(4) 4	(5) 5	(5) 5	
NO ABNORMALITY DETECTED						
HEART		(5) 5	(4) 4	(5) 5	(5) 5	
NO ABNORMALITY DETECTED						
SKELETAL MUSCLE		(5) 5	(4) 4	(5) 5	(5) 5	
NO ABNORMALITY DETECTED						
SPLEEN		(5) 5	(4) 4	(5) 5	(5) 5	
NO ABNORMALITY DETECTED						
AORTA		(5) 5	(4) 4	(5) 5	(5) 5	
NO ABNORMALITY DETECTED						
BRAIN		(5) 5	(4) 4	(5) 5	(5) 5	
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 39 (CONTINUED)

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

LESION	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)				
		0	25	100	250	
		II	IV	VI	VIII	
Females						
SPINAL CORD		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
STOMACH		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
DUODENUM		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
JEJUNUM		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
ILEUM		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
PANCREAS		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
CECUM		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
COLON		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	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 (CONTINUED)

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

LESION	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)				
		0	25	100	250	Females
		II	IV	VI	VIII	
RECTUM		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
MESENTERIC LYMPH NODE		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
SALIVARY GLANDS		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
MANDIBULAR LYMPH NODE		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
THYMUS		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
ADRENAL GLANDS		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
SCIATIC NERVE		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	4	5	5	
PITUITARY GLAND		(5)	(4)	(5)	(5)	
NO ABNORMALITY DETECTED		5	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 (CONTINUED)

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

LESION	TREATMENT (mg/kg/day)					LESION INCIDENCE (Numeric)				
						Females				
	0	25	100	250		II	IV	VI	VIII	
THYROID GLAND NO ABNORMALITY DETECTED	(5) 5	(4) 4	(5) 5	(5) 5						
PARATHYROID GLANDS NO ABNORMALITY DETECTED	(5) 5	(4) 4	(5) 5	(5) 5						
TRACHEA NO ABNORMALITY DETECTED	(5) 5	(4) 4	(5) 5	(5) 5						
ESOPHAGUS NO ABNORMALITY DETECTED	(5) 5	(4) 4	(5) 5	(5) 5						
PHARYNX/LARYNX NO ABNORMALITY DETECTED	(5) 5	(4) 4	(5) 5	(5) 5						
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED	(5) 5	(4) 4	(5) 5	(5) 5						
SKIN NO ABNORMALITY DETECTED	(5) 5	(4) 4	(5) 5	(5) 5						
MAMMARY GLAND (FEMALE) NO ABNORMALITY DETECTED	(5) 5	(4) 4	(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 39 (CONTINUED)

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

LESION	TREATMENT (mg/kg/day)	LESION INCIDENCE (Numeric)					
		0	25	100	250	Females	
		II	IV	VI	VIII		
OVARIES		(5)	(4)	(5)	(5)		
NO ABNORMALITY DETECTED		5	4	5	5		
UTERUS		(5)	(4)	(5)	(5)		
NO ABNORMALITY DETECTED		5	4	5	5		
URINARY BLADDER		(5)	(4)	(5)	(5)		
NO ABNORMALITY DETECTED		5	4	5	5		
FEMUR/KNEE JOINT		(5)	(4)	(5)	(5)		
NO ABNORMALITY DETECTED		5	4	5	5		
STERNUM		(5)	(4)	(5)	(5)		
NO ABNORMALITY DETECTED		5	4	5	5		
NOSE		(5)	(4)	(5)	(5)		
NO ABNORMALITY DETECTED		5	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 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 (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		I	III	V	VII	
DIGESTIVE SYSTEM						
LIVER		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED			1			
NECROSIS, FOCAL.				1	3	
INFLAMMATION, SUBACUTE/CHRONIC.		10	9	9	10	
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR.				9	11	
FATTY CHANGE, MEDIAN CLEFT.		2	2	2		
FATTY CHANGE, CENTRILOBULAR.		1	2	6	3	
PANCREAS		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		7		1	9	
INFLAMMATION, SUBACUTE/CHRONIC.		2			1	
ATROPHY.		2			1	

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

TABLE 40 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
DIGESTIVE SYSTEM							
ESOPHAGUS		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10			9		
INFLAMMATION, SUBACUTE/CHRONIC.				1	2		
EDEMA.					1		
STOMACH		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		
DUODENUM		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		
JEJUNUM		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		
ILEUM		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		

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 (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
DIGESTIVE SYSTEM							
CECUM		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		
COLON		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		
RECTUM		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		
SALIVARY GLANDS		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		

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	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC)				
		0	25	100	250	
		I	III	V	VII	
URINARY SYSTEM						
KIDNEYS		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		6	7	5		
NEPHROPATHY, CHRONIC PROGRESSIVE.		4	3	4	6	
HYPERTROPHY, TUBULAR.				1	11	
HYDRONEPHROSIS, UNILATERAL.					1	
HYDRONEPHROSIS, BILATERAL.					1	
URINARY BLADDER		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	

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 (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
RESPIRATORY SYSTEM							
LUNGS		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		8			8		
INFLAMMATION, SUBACUTE/CHRONIC.		2		1	2		
INFLAMMATION, GRANULOMATOUS.					1		
TRACHEA		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		
PHARYNX/LARYNX		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	10		
HEMORRHAGE.					1		
NOSE		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		10	10	4			
INFLAMMATION, SUBACUTE/CHRONIC.				1	2		
HYPERPLASIA/HYPERTROPHY, TRANSITIONAL CELL, EPITHELIUM.					2		
DEGENERATION/NECROSIS, RESPIRATORY, EPITHELIUM.				1			
DEGENERATION, AMELOBLASTS.				5	11		

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 (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
CARDIOVASCULAR SYSTEM							
HEART		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		5			8		
CARDIOMYOPATHY.		5		1	3		
INFLAMMATION, SUBACUTE/CHRONIC.							
AORTA		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		

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 (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
SPLEEN		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	
THYMUS		(10)			(11)	
NO ABNORMALITY DETECTED		10			10	
ATROPHY.					1	
MANDIBULAR LYMPH NODE		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	
MESENTERIC LYMPH NODE		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	
BONE MARROW		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	10	
HYPERPLASIA, GRANULOCYTIC.				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 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 (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
ENDOCRINE SYSTEM							
PITUITARY GLAND		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		
THYROID GLAND		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		1	1	1			
INFLAMMATION, SUBACUTE/CHRONIC.		1		2	10		
HYPERTROPHY, FOLLICULAR.				9	11		
ALTERATION, COLLOID.		9	9				
PARATHYROID GLANDS		(8)			(10)		
NO ABNORMALITY DETECTED		8			10		
ADRENAL GLANDS		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		

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 (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		I	III	V	VII	
NERVOUS SYSTEM						
BRAIN						
NO ABNORMALITY DETECTED	(10) 10	(1) 1			(11) 11	
SPINAL CORD						
NO ABNORMALITY DETECTED	(10) 10	(1) 1			(11) 11	
SCIATIC NERVE						
NO ABNORMALITY DETECTED	(10) 10				(11) 11	

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	TREATMENT (mg/kg/day)	LESION INCIDENCE (NUMERIC)				
		0	25	100	250	
		I	III	V	VII	
MUSCULAR AND SKELETAL SYSTEM						
SKELETAL MUSCLE		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	
FEMUR/KNEE JOINT		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	
STERNUM		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	
MANDIBLE		(10)	(10)	(9)	(10)	
NO ABNORMALITY DETECTED		10	10	8	10	
DEGENERATION, AMELOBLASTS.				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 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 (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		I	III	V	VII
REPRODUCTIVE SYSTEM					
TESTES					
NO ABNORMALITY DETECTED	(10)			(1)	(11)
SPERMATID RETENTION, SEMINIFEROUS TUBULES.	10			1	11
EPIDIDYMIDES					
NO ABNORMALITY DETECTED	(10)			(1)	(11)
	10			1	11
PROSTATE					
NO ABNORMALITY DETECTED	(10)			(1)	(11)
INFLAMMATION, SUBACUTE/CHRONIC.	9				10
	1			1	1
SEMINAL VESICLES					
NO ABNORMALITY DETECTED	(10)			(1)	(11)
	10			1	11

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 (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		I	III	V	VII
CUTANEOUS SYSTEM					
SKIN		(10)		(1)	(11)
NO ABNORMALITY DETECTED		10		1	11

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 (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		I	III	V	VII	
SPECIAL SENSES SYSTEM						
EYE(S) WITH OPTIC NERVE.	(10)			(1)	(11)	
NO ABNORMALITY DETECTED	9			1	9	
OPTIC NERVE NOT PRESENT.					2	
FOLD/ROSETTE, RETINAL.	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 40 (CONTINUED)

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

LESIONS	TREATMENT		Males		LESION INCIDENCE
	(mg/kg/day)		0	250	
			I	VII	
DIGESTIVE SYSTEM					
LIVER			(10)	(10)	
NECROSIS, FOCAL.				1	
INFLAMMATION, SUBACUTE/CHRONIC.			10	9	
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR.				10	
FOCUS OF CELLULAR ALTERATION, BASOPHILIC.				1	
FATTY CHANGE, MEDIAN CLEFT.			1	1	
FATTY CHANGE, CENTRILOBULAR.			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 40 (CONTINUED)

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

LESION	LESION INCIDENCE	
	Males	
LESION	TREATMENT (mg/kg/day)	
	0	250
URINARY SYSTEM	I	VII
	(10)	(10)
KIDNEYS	5	5
NO ABNORMALITY DETECTED	5	4
NEPHROPATHY, CHRONIC PROGRESSIVE.		2
HYPERTROPHY, TUBULAR.		1
HYDRONEPHROSIS, UNILATERAL.		

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)

LESION	INCIDENCE	
	Males	
LESION	TREATMENT (mg/kg/day)	INCIDENCE
	0	250
RESPIRATORY SYSTEM	I	VII
NOSE	(10)	(10)
NO ABNORMALITY DETECTED	9	1
ODONTODYSPLASIA.	1	9
DEGENERATION, AMELOBLASTS.		

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		
	Males		
	TREATMENT (mg/kg/day)	0	250
		I	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM			
SPLEEN		(1)	(1)
NO ABNORMALITY DETECTED		1	1
THYMUS		(1)	(1)
NO ABNORMALITY DETECTED		1	1
MANDIBULAR LYMPH NODE		(1)	(1)
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS.		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 40 (CONTINUED)

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

LESION INCIDE	Males	
	TREATMENT (mg/kg/day)	0 250 I VII
LESION		
ENDOCRINE SYSTEM		
THYROID GLAND ALTERATION, COLLOID.		(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 40 (CONTINUED)

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

LESION	LESION INCIDENCE	
	Males	
TREATMENT (mg/kg/day)	0	250
	I	VII
MUSCULAR AND SKELETAL SYSTEM		
MANDIBLE	(10)	(10)
NO ABNORMALITY DETECTED	10	10

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

TABLE 40 (CONTINUED)

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

LESION INCIDENCE	Males	
	TREATMENT (mg/kg/day)	0 250 I VII
REPRODUCTIVE SYSTEM		
TESTES		
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, UNILATERAL.	(2) 2	(1) 1
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, BILATERAL.		
EPIDIDYMIDES		
NO ABNORMALITY DETECTED	(2) 1	(1) 1
OLIGOSPERMIA/GERM CELL DEBRIS, UNILATERAL.	1	1
SEMINAL VESICLES		
NO ABNORMALITY DETECTED		(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 40 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		I	III	V	VII
DIGESTIVE SYSTEM					
LIVER		(5)		(5)	(5)
NECROSIS, FOCAL.		1		2	1
INFLAMMATION, SUBACUTE/CHRONIC.		5		5	5
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR.					1
FATTY CHANGE, MEDIAN CLEFT.					1
FATTY CHANGE, CENTRILOBULAR.		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
(THREE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		I	III	V	VII
URINARY SYSTEM					
KIDNEYS		(5)			(5)
NO ABNORMALITY DETECTED		2			1
CALCULUS\CALCULI.		3			4
NEPHROPATHY, CHRONIC PROGRESSIVE.					1
INFLAMMATION, SUBACUTE/CHRONIC.					1
HYPERPLASIA, TRANSITIONAL CELL.					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
(THREE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)					LESION INCIDENCE (NUMERIC)				
						0	25	100	250	
						I	III	V	VII	
RESPIRATORY SYSTEM										
NOSE										
NO ABNORMALITY DETECTED						(5) 3	(5) 1	(5) 3	(5)	
INFLAMMATION, SUBACUTE/CHRONIC, NASOLACRIMAL DUCT.							1	1		
INFLAMMATION, SUBACUTE/CHRONIC.						2	3	2	4	
HYPERPLASIA/SQUAMOUS METAPLASIA, RESPIRATORY, EPITHELIUM.						2	1	2	1	
HYPERPLASIA/HYPERTROPHY, TRANSITIONAL CELL, EPITHELIUM.							3		2	
FRACTURE/CALLUS, TOOTH.								1		
DEGENERATION/NECROSIS, RESPIRATORY, EPITHELIUM.									1	
DEGENERATION, AMELOBLASTS.								1		
SCHWANNOMA [B].									2	

[B] Benign tumour

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 (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		I	III	V	VII
ENDOCRINE SYSTEM					
THYROID GLAND ALTERATION, COLLOID.		(5) 5	(5) 5	(5) 5	(5) 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 41

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

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
DIGESTIVE SYSTEM					
LIVER		(10)	(10)	(10)	(11)
NO ABNORMALITY DETECTED		1	1	1	2
NECROSIS, FOCAL.		1		1	
INFLAMMATION, SUBACUTE/CHRONIC.		9	9	9	7
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR.					9
FATTY CHANGE, MEDIAN CLEFT.		2	1		
PANCREAS		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		9
ATROPHY.					2
ESOPHAGUS		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		10
INFLAMMATION, SUBACUTE/CHRONIC.					1
STOMACH		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
DIGESTIVE SYSTEM					
DUODENUM		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
JEJUNUM		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					2
ILEUM		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
CECUM		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
COLON		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
DIGESTIVE SYSTEM					
RECTUM		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
SALIVARY GLANDS		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
URINARY SYSTEM					
KIDNEYS		(10)	(10)	(10)	(11)
NO ABNORMALITY DETECTED		6	7	7	7
NEPHROPATHY, CHRONIC PROGRESSIVE.		3	2	3	4
NECROSIS, TUBULAR.			1		
INFLAMMATION, ACUTE.			1		
INFARCT.					1
HYPERPLASIA, TRANSITIONAL CELL.			1		
HYDRONEPHROSIS, BILATERAL.			1		
CYST.		1			
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					1
URINARY BLADDER					
NO ABNORMALITY DETECTED		(10)	(1)		(10)
HYPERPLASIA, SIMPLE, TRANSITIONAL CELL.		10			10
			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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		II	IV	VI	VIII	
RESPIRATORY SYSTEM						
LUNGS		(10)	(1)	(1)	(11)	
NO ABNORMALITY DETECTED		9	1	1	11	
THROMBUS.		1				
TRACHEA		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		11	
PHARYNX/LARYNX		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		11	
NOSE		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED		10	9	4		
INFLAMMATION, SUBACUTE/CHRONIC.			1		1	
FRACTURE/CALLUS, TOOTH.			1			
DEGENERATION, AMELOBLASTS.				6	11	

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
CARDIOVASCULAR SYSTEM					
HEART		(10)	(1)		(11)
NO ABNORMALITY DETECTED		7			11
CARDIOMYOPATHY.		3	1		
AORTA		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN		(10)	(1)		(10)
NO ABNORMALITY DETECTED		10			8
DEPLETION, LYMPHOID.			1		2
THYMUS		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10			9
ATROPHY.			1		2
MANDIBULAR LYMPH NODE		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
MESENTERIC LYMPH NODE		(9)	(1)		(9)
NO ABNORMALITY DETECTED		9	1		9
BONE MARROW		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10			10
HYPERPLASIA, GRANULOCYTIC.					1
ATROPHY.			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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)							
	TREATMENT (mg/kg/day)	0	25	100	250			
		II	IV	VI	VIII			
ENDOCRINE SYSTEM								
PITUITARY GLAND		(10)	(1)					(11)
NO ABNORMALITY DETECTED		10	1					11
THYROID GLAND		(10)	(10)	(10)	(11)			
NO ABNORMALITY DETECTED		10	4	6	3			6
HYPERTROPHY, FOLLICULAR ALTERATION, COLLOID.			6	4	7			
PARATHYROID GLANDS		(6)	(1)		(7)			
NO ABNORMALITY DETECTED		6	1		7			
ADRENAL GLANDS		(10)	(1)		(11)			
NO ABNORMALITY DETECTED		10	1		11			

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		II	IV	VI	VIII	
NERVOUS SYSTEM						
BRAIN		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		11	
SPINAL CORD		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		11	
SCIATIC NERVE		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		11	

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		II	IV	VI	VIII	
MUSCULAR AND SKELETAL SYSTEM						
SKELETAL MUSCLE		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		11	
FEMUR/KNEE JOINT		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		11	
STERNUM		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		11	
MANDIBLE		(10)	(9)	(10)	(8)	
NO ABNORMALITY DETECTED		10	9	10	1	
DEGENERATION, AMELOBLASTS.					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 41 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
REPRODUCTIVE SYSTEM					
OVARIES		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
UTERUS		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		8
DILATATION, LUMEN.					3
MAMMARY GLAND (FEMALE)		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
CUTANEOUS SYSTEM					
SKIN		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
OPTIC NERVE NOT PRESENT.		2			3
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					1

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

TABLE 41 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)		LESION INCIDENCE	
			Female	
			0	250
			II	VIII
DIGESTIVE SYSTEM				
LIVER			(10)	(10)
NO ABNORMALITY DETECTED			1	1
NECROSIS, FOCAL.			1	1
INFLAMMATION, SUBACUTE/CHRONIC.			8	9
FATTY CHANGE, MEDIAN CLEFT.			1	1
PANCREAS			(1)	
NO ABNORMALITY DETECTED			1	
ESOPHAGUS			(1)	
NO ABNORMALITY DETECTED			1	
STOMACH			(1)	
NO ABNORMALITY DETECTED			1	
DUODENUM			(1)	
NO ABNORMALITY DETECTED			1	

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

TABLE 41 (CONTINUED)

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

LESIONS	LESION INCIDENCE		
	Female		
	TREATMENT (mg/kg/day)	0	250
		II	VIII
DIGESTIVE SYSTEM			
JEJUNUM		(1)	
NO ABNORMALITY DETECTED		1	
ILEUM		(1)	
NO ABNORMALITY DETECTED		1	
CECUM		(1)	
NO ABNORMALITY DETECTED		1	
COLON		(1)	
NO ABNORMALITY DETECTED		1	
RECTUM		(1)	
NO ABNORMALITY DETECTED		1	
DIGESTIVE SYSTEM			
SALIVARY GLANDS		(1)	
NO ABNORMALITY DETECTED		1	

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

TABLE 41 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)		LESION INCIDENCE	
	0	250	Female	
	II	VIII		
URINARY SYSTEM				
KIDNEYS			(10)	(10)
NO ABNORMALITY DETECTED			3	4
NEPHROPATHY, CHRONIC PROGRESSIVE.			5	6
NECROSIS, TUBULAR.			1	
MINERALIZATION.			1	
INFLAMMATION, ACUTE.			1	
HYPERPLASIA, TRANSITIONAL CELL.			1	
HYDRONEPHROSIS, BILATERAL.			1	
CYST.			1	
URINARY BLADDER			(1)	
INFLAMMATION, SUBACUTE/CHRONIC.			1	
HYPERPLASIA, SIMPLE, TRANSITIONAL CELL.			1	
HEMORRHAGE.			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	TREATMENT (mg/kg/day)		LESION INCIDENCE	
			Female	
	0	250		
	II	VIII		
RESPIRATORY SYSTEM				
LUNGS			(1)	
NO ABNORMALITY DETECTED			1	
TRACHEA			(1)	
NO ABNORMALITY DETECTED			1	
PHARYNX/LARYNX			(1)	
NO ABNORMALITY DETECTED			1	
NOSE			(10)	(10)
NO ABNORMALITY DETECTED			9	3
SQUAMOUS HYPERPLASIA, NASOLACRIMAL DUCT.			1	1
INFLAMMATION, SUBACUTE/CHRONIC, NASOLACRIMAL DUCT.				7
DEGENERATION, AMELOBLASTS.				

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	
	Female	
	TREATMENT (mg/kg/day)	
	0	250
	II	VIII
CARDIOVASCULAR SYSTEM		
HEART		(1)
NO ABNORMALITY DETECTED		1
AORTA		(1)
NO ABNORMALITY DETECTED		1

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

TABLE 41 (CONTINUED)

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

LESION	LESION INCIDENCE	
	TREATMENT (mg/kg/day)	Female
	0	250
	II	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM		
SPLEEN		(1)
NO ABNORMALITY DETECTED		1
THYMUS		(1)
ATROPHY.		1
MANDIBULAR LYMPH NODE		(1)
NO ABNORMALITY DETECTED		1
MESENTERIC LYMPH NODE		(1)
NO ABNORMALITY DETECTED		1
BONE MARROW		(1)
HYPERPLASIA, GRANULOCYTIC.		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)

LESION	INCIDENCE	
	Female	
	TREATMENT (mg/kg/day)	
	0	250
	II	VIII
ENDOCRINE SYSTEM		
PITUITARY GLAND	(2)	
NO ABNORMALITY DETECTED	1	
HYPERPLASIA, DIFFUSE.	1	
THYROID GLAND	(10)	(10)
NO ABNORMALITY DETECTED	5	1
ALTERATION, COLLOID.	5	9
PARATHYROID GLANDS	(1)	
NO ABNORMALITY DETECTED	1	
ADRENAL GLANDS	(1)	
NO ABNORMALITY DETECTED	1	

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

TABLE 41 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)		LESION INCIDENCE	
			Female	
			0	250
			II	VIII
NERVOUS SYSTEM				
BRAIN				
NO ABNORMALITY DETECTED			(1) 1	
SPINAL CORD				
NO ABNORMALITY DETECTED			(1) 1	
SCIATIC NERVE				
NO ABNORMALITY DETECTED			(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 41 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)		LESION INCIDENCE	
			Female	
	0	250		
	II	VIII		
MUSCULAR AND SKELETAL SYSTEM				
SKELETAL MUSCLE	(1)			
NO ABNORMALITY DETECTED	1			
FEMUR/KNEE JOINT	(1)			
NO ABNORMALITY DETECTED	1			
STERNUM	(1)			
NO ABNORMALITY DETECTED	1			
MANDIBLE	(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
(ONE-MONTH RECOVERY EVALUATION)

LESION	INCIDENCE	
	TREATMENT (mg/kg/day)	Female
	0	250
	II	VIII
REPRODUCTIVE SYSTEM		
OVARIES		(1)
NO ABNORMALITY DETECTED		1
UTERUS		(1)
NO ABNORMALITY DETECTED		1
MAMMARY GLAND (FEMALE)		(1)
NO ABNORMALITY DETECTED		1

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

TABLE 41 (CONTINUED)

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

LESIONS	TREATMENT		LESION INCIDENCE	
	(mg/kg/day)		Female	
	0	250		
	II	VIII		
CUTANEOUS SYSTEM				
SKIN				
NO ABNORMALITY DETECTED			(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 41 (CONTINUED)

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

LESION INCIDENCE	Female	
	TREATMENT (mg/kg/day)	0 250 II VIII
LESIONS		
SPECIAL SENSES SYSTEM		
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED		(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 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	250
		II	IV	VI	VIII
RESPIRATORY SYSTEM					
NOSE		(5)		(5)	(5)
NO ABNORMALITY DETECTED		2		3	1
INFLAMMATION, SUBACUTE/CHRONIC.		3		2	2
HYPERPLASIA/SQUAMOUS METAPLASIA, TRANSITIONAL CELL.		3		2	3
DEGENERATION, AMELOBLASTS.					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 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	250
		II	IV	VI	VIII
ENDOCRINE SYSTEM					
THYROID GLAND		(5)	(4)	(5)	(5)
NO ABNORMALITY DETECTED		5	4	1	5
ALTERATION, COLLOID.				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 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 (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		I	III	V	VII	
DIGESTIVE SYSTEM						
LIVER		(10)	(10)	(10)	(11)	
NO ABNORMALITY DETECTED			1			
NECROSIS, FOCAL.						
minimal						2
mild				1	1	1
total observations per lesion				1	3	
INFLAMMATION, SUBACUTE/CHRONIC.						
minimal						
total observations per lesion	10	9	9	9	10	10
HYPERTROPHY, HEPATOCYTE, CENTRIOLOBULAR.						
minimal	10	9				10
mild				9	2	2
moderate					8	
total observations per lesion				9	1	11
FATTY CHANGE, MEDIAN CLEFT.						
minimal	2	2	2	1		
mild				1		
total observations per lesion	2	2	2	2		
FATTY CHANGE, CENTRIOLOBULAR.						
minimal	1	2	2	6	3	3
total observations per lesion	1	2	2	6	3	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 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 (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
DIGESTIVE SYSTEM							
PANCREAS		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		7		1	9		
INFLAMMATION, SUBACUTE/CHRONIC.							
minimal		2			1		
total observations per lesion		2			1		
ATROPHY.							
minimal		2			1		
total observations per lesion		2			1		
ESOPHAGUS		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10			9		
INFLAMMATION, SUBACUTE/CHRONIC.							
minimal					1		
mild					1		
moderate				1			
total observations per lesion				1	2		
EDEMA.							
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	LESION INCIDENCE (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
DIGESTIVE SYSTEM							
STOMACH NO ABNORMALITY DETECTED	(10) 10	(1) 1		(1) 1	(11) 11		
DUODENUM NO ABNORMALITY DETECTED	(10) 10	(1) 1		(1) 1	(11) 11		
JEJUNUM NO ABNORMALITY DETECTED	(10) 10	(1) 1		(1) 1	(11) 11		
ILEUM NO ABNORMALITY DETECTED	(10) 10	(1) 1		(1) 1	(11) 11		
CECUM NO ABNORMALITY DETECTED	(10) 10	(1) 1		(1) 1	(11) 11		

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 (NUMERIC)				
		0	25	100	250	
		I	III	V	VII	
DIGESTIVE SYSTEM						
COLON		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	
RECTUM		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	
SALIVARY GLANDS		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	

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 (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
URINARY SYSTEM							
KIDNEYS		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		6	7	5			
NEPHROPATHY, CHRONIC PROGRESSIVE.							
minimal		4	3	4	5		
mild					1		
total observations per lesion		4	3	4	6		
HYPERTROPHY, TUBULAR.							
minimal				1	3		
mild							
total observations per lesion				1	8		
HYDRONEPHROSIS, UNILATERAL.				1	11		
minimal							
total observations per lesion					1		
HYDRONEPHROSIS, BILATERAL.							
minimal							
total observations per lesion					1		
URINARY BLADDER							
NO ABNORMALITY DETECTED		(10)		(1)	(11)		
		10		1	11		

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 (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		I	III	V	VII	
RESPIRATORY SYSTEM						
LUNGS		(10) 8		(1)	(11) 8	
NO ABNORMALITY DETECTED						
INFLAMMATION, SUBACUTE/CHRONIC.						
minimal		2			2	
total observations per lesion		2			2	
INFLAMMATION, GRANULOMATOUS.						
minimal					1	
severe				1		
total observations per lesion				1	1	
TRACHEA						
NO ABNORMALITY DETECTED		(10) 10		(1) 1	(11) 11	
PHARYNX/LARYNX						
NO ABNORMALITY DETECTED		(10) 10		(1) 1	(11) 10	
HEMORRHAGE.						
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	LESION INCIDENCE (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
RESPIRATORY SYSTEM							
NOSE		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		10	10	4			
INFLAMMATION, SUBACUTE/CHRONIC.							
minimal						1	
mild				1		1	
total observations per lesion				1		2	
HYPERPLASIA/HYPERTROPHY, TRANSITIONAL CELL, EPITHELIUM.							
minimal						1	
mild						1	
total observations per lesion						2	
DEGENERATION/NECROSIS, RESPIRATORY, EPITHELIUM.							
minimal				1			
total observations per lesion				1			
DEGENERATION, AMELOBLASTS.							
minimal				5			
mild						11	
total observations per lesion				5		11	

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 (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
CARDIOVASCULAR SYSTEM							
HEART		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		5			8		
CARDIOMYOPATHY.							
minimal		5			3		
total observations per lesion		5			3		
INFLAMMATION, SUBACUTE/CHRONIC.							
moderate				1			
total observations per lesion				1			
AORTA		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		

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 (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
SPLEEN		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	
THYMUS		(10)			(11)	
NO ABNORMALITY DETECTED		10			10	
ATROPHY.						
mild					1	
total observations per lesion					1	
MANDIBULAR LYMPH NODE		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	
MESENTERIC LYMPH NODE		(10)		(1)	(11)	
NO ABNORMALITY DETECTED		10		1	11	

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 (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
BONE MARROW		(10) 10		(1)	(11) 10
NO ABNORMALITY DETECTED					1
HYPERPLASIA, GRANULOCYTIC.					1
mild					
moderate				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
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
ENDOCRINE SYSTEM							
PITUITARY GLAND		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		
THYROID GLAND		(10)	(10)	(10)	(11)		
NO ABNORMALITY DETECTED		1	1	1			
INFLAMMATION, SUBACUTE/CHRONIC.							
minimal		1					
total observations per lesion		1					
HYPERTROPHY, FOLLICULAR.							
minimal							
mild				2	3		
total observations per lesion				2	7		
ALTERATION, COLLOID.					10		
minimal		9	6	3			
mild			2	2	4		
moderate					5		
severe			1	4	2		
total observations per lesion		9	9	9	11		

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 (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
ENDOCRINE SYSTEM							
PARATHYROID GLANDS NO ABNORMALITY DETECTED		(8) 8			(10) 10		
ADRENAL GLANDS NO ABNORMALITY DETECTED		(10) 10		(1) 1	(11) 11		

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 (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
NERVOUS SYSTEM							
BRAIN							
NO ABNORMALITY DETECTED		(10) 10		(1) 1	(11) 11		
SPINAL CORD							
NO ABNORMALITY DETECTED		(10) 10		(1) 1	(11) 11		
SCIATIC NERVE							
NO ABNORMALITY DETECTED		(10) 10			(11) 11		

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 (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
MUSCULAR AND SKELETAL SYSTEM							
SKELETAL MUSCLE		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		
FEMUR/KNEE JOINT		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		
STERNUM		(10)		(1)	(11)		
NO ABNORMALITY DETECTED		10		1	11		
MANDIBLE		(10)		(9)	(10)		
NO ABNORMALITY DETECTED		10	10	8			
DEGENERATION, AMELOBLASTS.							
minimal							2
mild							8
total observations per lesion							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
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		I	III	V	VII
REPRODUCTIVE SYSTEM					
TESTES					
NO ABNORMALITY DETECTED		(10)		(1)	(11)
SPERMATID RETENTION, SEMINIFEROUS TUBULES.		10			11
minimal				1	
total observations per lesion				1	
EPIDIDYIMIDES					
NO ABNORMALITY DETECTED		(10)		(1)	(11)
		10		1	11
PROSTATE					
NO ABNORMALITY DETECTED		(10)		(1)	(11)
INFLAMMATION, SUBACUTE/CHRONIC.		9			10
minimal		1		1	
moderate					1
total observations per lesion		1		1	1
SEMINAL VESICLES					
NO ABNORMALITY DETECTED		(10)		(1)	(11)
		10		1	11

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 (NUMERIC)						
	TREATMENT (mg/kg/day)	0	25	100	250		
		I	III	V	VII		
CUTANEOUS SYSTEM							
SKIN		(10) 10		(1) 1	(11) 11		
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 (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		I	III	V	VII
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED OPTIC NERVE NOT PRESENT. FOLD/ROSETTE, RETINAL.		(10) 9		(1) 1	(11) 9 2
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
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT		LESION INCIDENCE	
	(mg/kg/day)		Males	
	0	250		
	I	VII		
DIGESTIVE SYSTEM				
LIVER	(10)	(10)		
NECROSIS, FOCAL.				
minimal				1
total observations per lesion				1
INFLAMMATION, SUBACUTE/CHRONIC.				
minimal				9
total observations per lesion				9
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR.				
minimal				4
mild				6
total observations per lesion				10
FOCUS OF CELLULAR ALTERATION, BASOPHILIC.				
minimal				1
total observations per lesion				1
FATTY CHANGE, MEDIAN CLEFT.				
minimal				1
total observations per lesion				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
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE	
		Males	
	0	250	
	I	VII	
URINARY SYSTEM			
KIDNEYS			
NO ABNORMALITY DETECTED	(10)	(10)	
NEPHROPATHY, CHRONIC PROGRESSIVE.	5	5	
minimal	5	4	
total observations per lesion	5	4	
HYPERTROPHY, TUBULAR.			
minimal		2	
total observations per lesion		2	
HYDRONEPHROSIS, UNILATERAL.			
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	TREATMENT (mg/kg/day)		LESION INCIDENCE	
			Males	
	0	250	I	VII
RESPIRATORY SYSTEM				
NOSE			(10)	(10)
NO ABNORMALITY DETECTED			9	1
ODONTODYSPLASIA.				
moderate			1	
total observations per lesion			1	
DEGENERATION, AMELOBLASTS.				
minimal				5
mild				4
total observations per lesion				9

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

TABLE 42 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)		LESION INCIDENCE	
			Males	
	0	250		
	I	VII		
LYMPHATIC AND HEMATOPOIETIC SYSTEM				
SPLEEN			(1)	
NO ABNORMALITY DETECTED			1	
THYMUS			(1)	(1)
NO ABNORMALITY DETECTED			1	1
MANDIBULAR LYMPH NODE			(1)	
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS.				
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
(ONE-MONTH RECOVERY EVALUATION)

LESION INCIDE	Males	
	TREATMENT (mg/kg/day)	0 250 I VII
LESION		
ENDOCRINE SYSTEM		
THYROID GLAND		(10) (10)
ALTERATION, COLLOID.		
minimal	8	1
mild	2	3
moderate		4
severe		2
total observations per lesion	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 42 (CONTINUED)

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

LESIONS	TREATMENT		LESION INCIDENCE	
	(mg/kg/day)		Males	
	0	250		
	I	VII		
MUSCULAR AND SKELETAL SYSTEM				
MANDIBLE	(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 42 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE	
		Males	
	0	250	
	I	VII	
REPRODUCTIVE SYSTEM			
TESTES			
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, UNILATERAL.	(2)	(1)	
mild	1		
severe	1		
total observations per lesion	2		
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, BILATERAL.			
moderate		1	
total observations per lesion		1	
EPIDIDYIMIDES			
NO ABNORMALITY DETECTED	(2)	(1)	
OLIGOSPERMIA/GERM CELL DEBRIS, UNILATERAL.	1		
moderate		1	
severe	1		
total observations per lesion	1	1	
SEMINAL VESICLES			
NO ABNORMALITY DETECTED		(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	LESION INCIDENCE (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		I	III	V	VII	
DIGESTIVE SYSTEM						
LIVER		(5)		(5)	(5)	
NECROSIS, FOCAL. minimal		1		2	1	
mild		1		2	1	
total observations per lesion						
INFLAMMATION, SUBACUTE/CHRONIC. minimal		5		5	5	
total observations per lesion		5		5	5	
HYPERTROPHY, HEPATOCYTE, CENTRIOLOBULAR. minimal						
total observations per lesion						
FATTY CHANGE, MEDIAN CLEFT. mild						
total observations per lesion						
FATTY CHANGE, CENTRIOLOBULAR. mild		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	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
URINARY SYSTEM		I	III	V	VII
KIDNEYS		(5)			(5)
NO ABNORMALITY DETECTED		2			1
CALCULUS\CALCULI.					1
minimal					3
total observations per lesion					1
NEPHROPATHY, CHRONIC PROGRESSIVE.		3			1
minimal					4
moderate					1
total observations per lesion		3			4
INFLAMMATION, SUBACUTE/CHRONIC.					1
minimal					1
total observations per lesion					1
HYPERPLASIA, TRANSITIONAL CELL.					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

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

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 (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		I	III	V	VII
RESPIRATORY SYSTEM					
NOSE		(5)	(5)	(5)	(5)
DEGENERATION, AMELOBLASTS.					
mild					1
total observations per lesion				1	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	LESION INCIDENCE (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		I	III	V	VII	
ENDOCRINE SYSTEM						
THYROID GLAND ALTERATION, COLLOID.		(5)	(5)	(5)	(5)	
minimal		3	1		1	
mild		1	2		1	
moderate		1			3	
severe			2	5	5	
total observations per lesion		5	5	5	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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
DIGESTIVE SYSTEM					
LIVER		(10)	(10)	(10)	(11)
NO ABNORMALITY DETECTED		1	1	1	2
NECROSIS, FOCAL, minimal		1		1	
total observations per lesion		1		1	
INFLAMMATION, SUBACUTE/CHRONIC, minimal		9	9	9	7
total observations per lesion		9	9	9	7
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, minimal					4
mild					5
total observations per lesion					9
FATTY CHANGE, MEDIAN CLEFT, minimal			1		
mild		2			
total observations per lesion		2	1		

N=11 in Group VII reflects one reproduction designated animal that died on test day 53.
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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		II	IV	VI	VIII	
DIGESTIVE SYSTEM						
PANCREAS		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		9	
ATROPHY.					2	
minimal					2	
total observations per lesion						
ESOPHAGUS		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		10	
INFLAMMATION, SUBACUTE/CHRONIC.						
severe					1	
total observations per lesion					1	
STOMACH		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		11	
DUODENUM		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		11	

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
DIGESTIVE SYSTEM					
JEJUNUM		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					
moderate					2
total observations per lesion					2
ILEUM		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
CECUM		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
COLON		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
RECTUM		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
SALIVARY GLANDS		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
URINARY SYSTEM					
KIDNEYS		(10) 6	(10) 7	(10) 7	(11) 7
NO ABNORMALITY DETECTED					
NEPHROPATHY, CHRONIC PROGRESSIVE.					
minimal		3	2	3	3
moderate					1
total observations per lesion		3	2	3	4
NECROSIS, TUBULAR.					
moderate			1		
total observations per lesion			1		
INFLAMMATION, ACUTE.					
moderate			1		
total observations per lesion			1		
INFARCT.					
minimal					1
total observations per lesion					1
HYPERPLASIA, TRANSITIONAL CELL.					
mild			1		
total observations per lesion			1		
HYDRONEPHROSIS, BILATERAL.					
mild			1		
total observations per lesion			1		
CYST.					
minimal		1			

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

TABLE 43 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
URINARY SYSTEM					
KIDNEYS		(10)	(10)	(10)	(11)
CYST.		1			
total observations per lesion					1
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					1
mild					
total observations per lesion					1
URINARY BLADDER		(10)	(1)		(10)
NO ABNORMALITY DETECTED		10			10
HYPERPLASIA, SIMPLE, TRANSITIONAL CELL.					
moderate			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
(90-DAY EXPOSURE EVALUATION INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
RESPIRATORY SYSTEM					
LUNGS		(10)	(1)	(1)	(11)
NO ABNORMALITY DETECTED		9	1	1	11
THROMBUS.					
minimal		1			
total observations per lesion		1			
TRACHEA		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
PHARYNX/LARYNX		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
NOSE		(10)	(10)	(10)	(11)
NO ABNORMALITY DETECTED		10	9	4	
INFLAMMATION, SUBACUTE/CHRONIC.					1
minimal					
mild			1		
total observations per lesion			1		1
FRACTURE/CALLUS, TOOTH.			1		
DEGENERATION, AMELOBLASTS.					
minimal				6	
mild					11
total observations per lesion				6	11

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		II	IV	VI	VIII	
CARDIOVASCULAR SYSTEM						
HEART		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		7			11	
CARDIOMYOPATHY.		3	1			
minimal		3	1			
total observations per lesion						
AORTA		(10)	(1)		(11)	
NO ABNORMALITY DETECTED		10	1		11	

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN		(10) 10	(1)		(10) 8
NO ABNORMALITY DETECTED					
DEPLETION, LYMPHOID.					
mild					2
moderate			1		
total observations per lesion			1		2
THYMUS		(10) 10	(1)		(11) 9
NO ABNORMALITY DETECTED					
ATROPHY.					
moderate			1		2
severe					
total observations per lesion			1		2
MANDIBULAR LYMPH NODE		(10) 10	(1)		(11) 11
NO ABNORMALITY DETECTED					
MESENTERIC LYMPH NODE		(9) 9	(1)		(9) 9
NO ABNORMALITY DETECTED			1		

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

TABLE 43 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
BONE MARROW		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10			10
HYPERPLASIA, GRANULOCYTIC. severe					1
total observations per lesion					1
ATROPHY.					
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 43 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT (mg/kg/day)	0	25	100	250	
		II	IV	VI	VIII	
ENDOCRINE SYSTEM						
PITUITARY GLAND		(10) 10	(1) 1			(11) 11
NO ABNORMALITY DETECTED						
THYROID GLAND		(10) 10	(10) 4	(10) 6		(11) 3
NO ABNORMALITY DETECTED						
HYPERTROPHY, FOLLICULAR. minimal						6
total observations per lesion						6
ALTERATION, COLLOID. minimal			6	3		5
mild						2
moderate				1		
total observations per lesion			6	4		7
PARATHYROID GLANDS		(6) 6	(1) 1			(7) 7
NO ABNORMALITY DETECTED						
ADRENAL GLANDS		(10) 10	(1) 1			(11) 11
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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
NERVOUS SYSTEM					
BRAIN					
NO ABNORMALITY DETECTED		(10) 10	(1) 1		(11) 11
SPINAL CORD					
NO ABNORMALITY DETECTED		(10) 10	(1) 1		(11) 11
SCIATIC NERVE					
NO ABNORMALITY DETECTED		(10) 10	(1) 1		(11) 11

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
MUSCULAR AND SKELETAL SYSTEM					
SKELETAL MUSCLE		(10) 10	(1) 1		(11) 11
NO ABNORMALITY DETECTED					
FEMUR/KNEE JOINT		(10) 10	(1) 1		(11) 11
NO ABNORMALITY DETECTED					
STERNUM		(10) 10	(1) 1		(11) 11
NO ABNORMALITY DETECTED					
MANDIBLE		(10) 10	(9) 9	(10) 10	(8) 1
NO ABNORMALITY DETECTED					
DEGENERATION, AMELOBLASTS.					
minimal					3
mild					4
total observations per lesion					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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
REPRODUCTIVE SYSTEM					
OVARIES					
NO ABNORMALITY DETECTED	(10) 10	(1) 1			(11) 11
UTERUS					
NO ABNORMALITY DETECTED	(10) 10	(1) 1			(11) 8
DILATATION, LUMEN.					
minimal					2
mild					1
total observations per lesion					3
MAMMARY GLAND (FEMALE)					
NO ABNORMALITY DETECTED	(10) 10	(1) 1			(11) 11

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
CUTANEOUS SYSTEM					
SKIN		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11

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 INCLUDING EARLY DEATHS FROM THE REPRODUCTION EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE		(10)	(1)		(11)
NO ABNORMALITY DETECTED		10	1		11
OPTIC NERVE NOT PRESENT		2			3
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					
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 43 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)		LESION INCIDENCE	
	0	250	Female	
	II	VIII		
DIGESTIVE SYSTEM				
LIVER			(10)	(10)
NO ABNORMALITY DETECTED	1	1	1	1
NECROSIS, FOCAL, minimal	1	1	1	1
total observations per lesion	1	1	1	1
INFLAMMATION, SUBACUTE/CHRONIC, minimal	8	9	8	9
total observations per lesion	8	9	8	9
FATTY CHANGE, MEDIAN CLEFT, minimal	1	1	1	1
total observations per lesion	1	1	1	1
PANCREAS			(1)	
NO ABNORMALITY DETECTED	1		1	
ESOPHAGUS			(1)	
NO ABNORMALITY DETECTED	1		1	
STOMACH			(1)	
NO ABNORMALITY DETECTED	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	TREATMENT (mg/kg/day)	LESION INCIDENCE	
		0	Female
		II	VIII
DIGESTIVE SYSTEM			
DUODENUM			(1)
NO ABNORMALITY DETECTED			1
JEJUNUM			(1)
NO ABNORMALITY DETECTED			1
ILEUM			(1)
NO ABNORMALITY DETECTED			1
CECUM			(1)
NO ABNORMALITY DETECTED			1
COLON			(1)
NO ABNORMALITY DETECTED			1
RECTUM			(1)
NO ABNORMALITY DETECTED			1
SALIVARY GLANDS			(1)
NO ABNORMALITY DETECTED			1

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

TABLE 43 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE	
		Female	
	0	250	
	II	VIII	
URINARY SYSTEM			
KIDNEYS			
NO ABNORMALITY DETECTED		(10)	(10)
NEPHROPATHY, CHRONIC PROGRESSIVE.		3	4
minimal		5	6
total observations per lesion		5	6
NECROSIS, TUBULAR.			
mild		1	
total observations per lesion		1	
MINERALIZATION.			
mild		1	
total observations per lesion		1	
INFLAMMATION, ACUTE.			
mild		1	
total observations per lesion		1	
HYPERPLASIA, TRANSITIONAL CELL.			
moderate		1	
total observations per lesion		1	
HYDRONEPHROSIS, BILATERAL.			
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	TREATMENT (mg/kg/day)		LESION INCIDENCE	
	0	250	Female	
URINARY SYSTEM				
KIDNEY				
CYST.				
minimal				
total observations per lesion			1	
URINARY BLADDER			1	
INFLAMMATION, SUBACUTE/CHRONIC.			(1)	
mild			1	
total observations per lesion			1	
HYPERPLASIA, SIMPLE, TRANSITIONAL CELL.				
moderate			1	
total observations per lesion			1	
HEMORRHAGE.				
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 43 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)	LESION INCIDENCE	
		0	Female
		II	VIII
RESPIRATORY SYSTEM			
LUNGS		(1)	
NO ABNORMALITY DETECTED		1	
TRACHEA		(1)	
NO ABNORMALITY DETECTED		1	
PHARYNX/LARYNX		(1)	
NO ABNORMALITY DETECTED		1	
NOSE		(10)	(10)
NO ABNORMALITY DETECTED		9	3
SQUAMOUS HYPERPLASIA, NASOLACRIMAL DUCT. mild		1	
total observations per lesion		1	
INFLAMMATION, SUBACUTE/CHRONIC, NASOLACRIMAL DUCT. mild			1
total observations per lesion			1
DEGENERATION, AMELOBLASTS. minimal			3
mild			4
total observations per lesion			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
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE	
	TREATMENT (mg/kg/day)	Female
	0	250
	II	VIII
CARDIOVASCULAR SYSTEM		
HEART		(1)
NO ABNORMALITY DETECTED		1
AORTA		(1)
NO ABNORMALITY DETECTED		1

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

TABLE 43 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)		Female		LESION INCIDENCE
	0	250	II	VIII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN					(1)
NO ABNORMALITY DETECTED					1
THYMUS					(1)
ATROPHY.					1
mild					1
total observations per lesion					
MANDIBULAR LYMPH NODE					(1)
NO ABNORMALITY DETECTED					1
MESENTERIC LYMPH NODE					(1)
NO ABNORMALITY DETECTED					1
BONE MARROW					(1)
HYPERPLASIA, GRANULOCYTIC.					1
mild					1
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 43 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)		LESION INCIDENCE	
	0	250	Female	
	II	VIII		
ENDOCRINE SYSTEM				
PITUITARY GLAND			(2)	
NO ABNORMALITY DETECTED			1	
HYPERPLASIA, DIFFUSE.			1	
mild			1	
total observations per lesion			1	
THYROID GLAND			(10)	(10)
NO ABNORMALITY DETECTED			5	1
ALTERATION, COLLOID.				
minimal			5	8
moderate				1
total observations per lesion			5	9
PARATHYROID GLANDS			(1)	
NO ABNORMALITY DETECTED			1	
ADRENAL GLANDS			(1)	
NO ABNORMALITY DETECTED			1	

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

TABLE 43 (CONTINUED)

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

LESION INCIDENCE	Female	
	TREATMENT (mg/kg/day)	0 250 II VIII
LESIONS		
NERVOUS SYSTEM		
BRAIN		(1) 1
NO ABNORMALITY DETECTED		
SPINAL CORD		(1) 1
NO ABNORMALITY DETECTED		
SCIATIC NERVE		(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 43 (CONTINUED)

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

LESIONS	TREATMENT (mg/kg/day)		LESION INCIDENCE	
			Female	
			0	250
			II	VIII
MUSCULAR AND SKELETAL SYSTEM				
SKELETAL MUSCLE				
NO ABNORMALITY DETECTED			(1)	1
FEMUR/KNEE JOINT				
NO ABNORMALITY DETECTED			(1)	1
STERNUM				
NO ABNORMALITY DETECTED			(1)	1
MANDIBLE				
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
(ONE-MONTH RECOVERY EVALUATION)

LESIONS	TREATMENT		LESION INCIDENCE	
	(mg/kg/day)		Female	
	0	250		
	II	VIII		
REPRODUCTIVE SYSTEM				
OVARIES			(1)	
NO ABNORMALITY DETECTED			1	
UTERUS			(1)	
NO ABNORMALITY DETECTED			1	
MAMMARY GLAND (FEMALE)			(1)	
NO ABNORMALITY DETECTED			1	

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

TABLE 43 (CONTINUED)

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

LESION	LESION INCIDENCE	
	Female	
LESIONS	TREATMENT (mg/kg/day)	250
		VIII
CUTANEOUS SYSTEM	0	II
SKIN		
NO ABNORMALITY DETECTED	(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	TREATMENT		LESION INCIDENCE	
	(mg/kg/day)		Female	
SPECIAL SENSES SYSTEM	0		250	
	II		VIII	
EYE(S) WITH OPTIC NERVE NO ABNORMALITY DETECTED			(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)			
		0	25	100	250
		II	IV	VI	VIII
RESPIRATORY SYSTEM					
NOSE		(5)		(5)	(5)
NO ABNORMALITY DETECTED		2		3	1
INFLAMMATION, SUBACUTE/CHRONIC.					
minimal		2		2	1
mild		1			1
total observations per lesion		3		2	2
HYPERPLASIA/SQUAMOUS METAPLASIA, TRANSITIONAL CELL.					
minimal				1	2
mild		3		1	1
total observations per lesion		3		2	3
DEGENERATION, AMELOBLASTS.					
minimal					2
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
(THREE-MONTH RECOVERY EVALUATION)

LESIONS	LESION INCIDENCE (NUMERIC)				
	TREATMENT (mg/kg/day)	0	25	100	250
		II	IV	VI	VIII
ENDOCRINE SYSTEM					
THYROID GLAND		(5)	(4)	(5)	(5)
NO ABNORMALITY DETECTED				1	
ALTERATION, COLLOID.					
minimal		4	3	3	4
mild		1	1	1	1
moderate					
total observations per lesion		5	4	4	5

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