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TRADE SECRET

Study Title

H-25425: Subchronic Toxicity
90-Day Gavage Study in Rats with One-Generation Reproduction Evaluations

Volume 1 of 5

Laboratory Project ID: DuPont-11418

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

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STUDY COMPLETED ON: August 1, 2003

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

SERVICE CODE NUMBER: [REDACTED]

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are consistent with the OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM(98)17 and MAFF Japan Good Laboratory Practice Standards (59 NohSan Number 3850) 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
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QUALITY ASSURANCE STATEMENT

Haskell Sample Number(s):

25425

Dates of Inspections:

Protocol: June 28, 2002; July 2, 2002

Conduct: August 6, 29, 2002; September 10, 20, 2002; October 7, 21, 30, 2002;
November 14, 21, 22, 29, 2002

Records, Reports: February 27-28, 2003; March 2-5, 11-14, 17, 2003; April 7-8, 10-
11, 14-15; 2003; May 6-9, 12-16, 19-20, 2003; July 14-17, 2003

Dates Findings Reported to:

Study Director: July 2, 2002; September 23, 2002; October 8, 21, 31, 2002;
November 22, 2002; March 3, 6, 28, 2003; April 11, 15, 2003; May
20, 2003; July 17, 2003

Management: September 23, 2002; October 18, 21, 31, 2003; December 3, 2003;
March 6, 14, 27, 2003; April 30, 2003; July 18, 2003

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CERTIFICATION

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

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STUDY INFORMATION

9th Collective Nomenclature: [REDACTED]

Synonyms/Codes: [REDACTED]

- H-25425

Haskell Number: 25425

CAS Registry Number: [REDACTED]

Purity: [REDACTED]

Known Impurities: [REDACTED]

Physical Characteristics: Amber-yellow-brown solid

Stability: The test substance appeared to be stable under the conditions of the study; no evidence of instability was observed.

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

Study Initiated/Completed: October 3, 2002 / (see report cover page)

In-Life Initiated/Completed: October 15, 2002 / April 15, 2003

STUDY PERSONNEL

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

Four groups of young adult male and female Crl:CD[®](SD)IGS BR rats were administered H-25425 in 0.5% methylcellulose in deionized water by gavage for approximately 90 days (92 days in males and 93 days in females), at dosages of 0, 10, 100, or 1000 mg/kg/day. Selected animals from each dosage group were designated for evaluation of subchronic toxicity, recovery from subchronic toxicity, or reproductive toxicity.

In the subchronic study, body weights, food consumption, and clinical signs were evaluated weekly. Clinical pathology endpoints were evaluated during weeks 6 and 14 of the dosing period, and near the end of the one-month recovery period. Neurobehavioral assessments were performed prior to dosing, during week 13 of dosing, and near the end of the one-month recovery period. Biochemical evaluations (hepatic β -oxidation) were performed on rats after 10 days (male and female), during week 14 of the dosing period, and following a one-month recovery period. At the end of the dosing period, 10 rats/sex/dose were sacrificed and given a gross and microscopic pathological examination. One month after the end of the dosing period, 10 rats/sex in the control and high dose groups were examined for recovery of toxic effects. An additional 5 rats/sex/dose were held without dosing for approximately 3 months following the end of the dosing period. These rats had blood collected periodically throughout the dosing and recovery periods and selected tissues collected at the end of recovery for possible analysis of fluorine levels. These tissues have not been analyzed to date. Blood was also collected from subchronic toxicity and recovery rats at the end of the dosing and recovery periods for evaluation of perfluorooctanoic acid levels. These levels will be reported in a separate report.

The range of mean daily dose volumes administered to male rats was 1.2-3.0 mL for the control group, and 1.2-2.9 mL for the 10, 100, and 1000 mg/kg/day groups. The range of mean daily dose volumes administered to female rats was 0.9-1.6 mL for the control group, and 0.9-1.5 for the 10, 100, and 1000 mg/kg/day groups.

Analytical results demonstrated that the test substance was mixed properly, was at the targeted concentrations, and was stable in the vehicle under relevant storage conditions used in this study.

In-Life Toxicology Parameters: No test substance-related deaths, clinical signs, or ophthalmologic signs occurred in rats in either the subchronic toxicity or recovery periods of the study. No adverse, test substance-related effects on body weight, body weight gain, food consumption, or food efficiency were observed in any male or female dose group.

Neurobehavioral Parameters: No test substance-related effects on forelimb or hindlimb grip strength, sensory motor function, or motor activity were observed in any male or female dose group.

Biochemical Toxicology: Exposure to 1000 mg/kg/day of H-25425 for 10 days (females only) or approximately 90 days (males and females) produced mild elevations in hepatic β -oxidation activity. This elevation was associated with elevated liver weight in males at the 90-day time point. Activity had returned to control levels in females but remained elevated in males after a

one-month recovery period. These effects were considered test substance-related but not adverse.

Clinical Pathology: No adverse effects were observed on hematology, coagulation, clinical chemistry, or urinalysis parameters in any male or female dose group. In male and/or female rats dosed with 1000 mg/kg/day, minimal to mild reductions in red cell mass parameters, bilirubin, triglycerides (all male dose groups), total protein, and albumin were observed but were not considered adverse based on the very slight level of effect. All effects except the minimal red cell mass effects in males were reversed by the end of the one-month recovery period.

No effects on plasma fluoride concentration were observed in any male or female dose group. Urine fluoride (total fluoride excreted over the collection period) was increased at the end of the dosing period in males and females dosed with 1000 mg/kg/day and in a few males and females dosed with 100 mg/kg/day. Urine fluoride greatly decreased during the one-month recovery period, but remained slightly above control values in 1000 mg/kg/day males, thus indicating the continued presence of fluorinated material. The increased urine fluoride was considered a marker of exposure to a fluorinated material, and was not considered adverse.

Anatomic Pathology (Subchronic Toxicity): Mild increases in absolute and relative liver and kidney weights were observed in male rats dosed with 1000 mg/kg/day at the end of the dosing period. The increased liver weights were associated with minimal hepatocellular hypertrophy and elevated β -oxidation activity, but no histological correlate to the increased kidney weight was observed. The increased liver weights and histopathology were reversed after a one-month recovery period. These liver and kidney changes were considered to be non-adverse, pharmacological responses to exposure to a xenobiotic.

Minimal to mild hypertrophy of thyroid follicular epithelium was present in 1000 mg/kg/day males and females at the end of the dosing period. This effect is indicative of altered thyroid gland homeostasis and, although the follicular cell response observed in this study was within the range of normal physiological response, the effect is potentially adverse. The hypertrophy was still present in both males and females at the end of the one-month recovery period but the incidence and severity were reduced in males and were very low at both time points in females. Therefore, this lesion is considered reversible, even though full reversal had not occurred after one month.

Reproduction: Twenty male and 20 female rats from each dose group were designated for reproductive evaluations. Parental rats (P_1 generation) were dosed daily for 74 days prior to cohabitation, during the cohabitation period (mating) and during lactation, until the weaning of the F_1 offspring. The following parameters were evaluated in P_1 rats: body weight, food consumption, clinical signs, gross pathology, sperm parameters, estrous cyclicity, and reproductive performance. Reproductive organs from animals that did not produce litters were evaluated microscopically. The F_1 offspring were evaluated during the lactation period for growth and survival and given a gross pathological examination at weaning. A subset of F_1 generation rats was retained at weaning, and the following parameters were evaluated for 6 weeks: body weight, food consumption, clinical signs, and age at onset of vaginal opening or

preputial separation. After 6 weeks, the F₁ generation rats were given a gross pathological examination, and selected reproductive organs and target organs of toxicity were weighed.

No systemic toxicity was observed in any dose group in the P₁ or F₁ generation in the reproduction subset. No test substance-related, adverse effects on any reproductive, sperm, estrus, or pathology endpoint were observed in any dose group in the P₁ generation. No effects were observed on litter size, sex ratio, pup survival, or developmental landmark acquisition, nor were any signs of systemic toxicity observed in any dose group in the F₁ generation.

NOEL for Subchronic Toxicity: Under the conditions of this study, the no-observed-effect level (NOEL)^a for subchronic toxicity endpoints in male and female rats was 100 mg/kg/day. This level was based on reversible, minimal to mild thyroid follicular hypertrophy observed in the 1000 mg/kg/day male and female groups. Other test substance-related effects observed in males and/or females dosed with 1000 mg/kg/day include mild alterations in clinical pathology parameters, increased liver and kidney weights, increased hepatic β -oxidation activity and minimal hepatocellular hypertrophy; however, these were not considered to be adverse. Most of the effects observed during the dosing period demonstrated full or partial reversal following one month of recovery. Thyroid follicular hypertrophy was still present at the end of the one-month recovery period; however, the incidence and mean severity level in males had decreased by this time and were very low in females at both time points.

NOEL for Reproductive Evaluations: Under the conditions of this study, the NOEL for reproductive evaluations was 1000 mg/kg/day, the highest dose tested. This NOEL was based on a lack of test substance-related effects on any reproductive parameter in P₁ or F₁ generation animals dosed up to 1000 mg/kg/day.

^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-25425 is a [REDACTED] used as a fabric protector. The dose levels for this study were selected based on the toxicity and an analysis of blood fluorine concentrations from a range-finding study in which rats were dosed by oral gavage with 1, 10, 100, or 1000 mg/kg/day for approximately 45 days.⁽¹⁾

No compound-related effects on body weight, clinical signs of toxicity, organ weights, or gross pathology lesions were observed in rats in any dose group. Blood fluorine levels appeared to have reached a plateau within 1-2 weeks of dosing with 1000 mg/kg/day, and levels remained very low throughout the entire exposure period.

Dose levels of 0, 10, 100, and 1000 mg/kg/day were selected for this study, based on the results of the rangefinder study.

OBJECTIVE

The objective of this study was to evaluate the potential subchronic and reproductive toxicity of H-25425 when administered by gavage to male and female rats. A recovery group was included to investigate the reversibility of any observed toxicological effects. The oral route of administration was selected as the most efficient way to deliver an accurate dosage. Blood, urine, feces, and tissues were collected for evaluation of total fluorine and/or perfluorooctanoic acid (PFOA), but have not been evaluated. Data from analysis of these samples will be reported separately.

STUDY DESIGN

Group		Number/Group		Daily Dosage ^a (mg/kg)	Concentration ^b (mg/mL)
Male	Female	Male	Female		
I	II	50	50	0 (Control)	0
III	IV	40	40	10	2
V	VI	40	40	100	20
VII	VIII	50	50	1000	200

a Weight of test substance/kg animal body weight

b Suspensions will be adjusted for purity [REDACTED]

The first 10 rats/sex/dose were designated for evaluation of subchronic toxicity; the next 5 rats/sex/dose were designated for collection of blood for analysis of fluorine; the next 20 rats/sex/dose were designated for reproductive assessment; the remaining 10 rats/sex/dose (control and high-dose groups only) were designated for one-month recovery assessment. An additional subgroup (5 rats/sex/dose) was received as a separate shipment and was added to each dose group approximately 84 days after study start, for evaluation of hepatic beta-oxidation

activity following a 10-day exposure. The rats designated for collection of blood for fluorine analysis are also referred to as the three-month recovery subset.

Study Parameters	Frequency
Body Weight	Day 0 and weekly thereafter
Food Consumption	Weekly
Detailed Clinical Observations	Day 0 and weekly thereafter
Mortality/Moribundity Checks	Twice daily
Clinical Pathology	Week 6, Week 14, and Week 19
Ophthalmoscopic Evaluations	Pretest and Week 13
Neurobehavioral Evaluations	Pretest, Week 13, and Week 18
Biochemical Analysis	
Subchronic	Week 14
Recovery	Week 17
Satellite (day 10)	After 10 days of dosing
Reproductive Assessments	
P ₁ adults	Week 11-18
F ₁ weanlings	Week 13-18
Vaginal Smears (P ₁ Females)	Week 7-9
Developmental Landmarks (F ₁ adults)	Week 19-23
Necropsy	
Subchronic	Week 14
P ₁ adults	Week 12-18
Weanlings	Week 17-18
Recovery	Week 18
F ₁ adults	Week 23-25
Blood fluorine animals	Week 26

MATERIALS AND METHODS

A. Test Guidelines

The study design complies with the following test guideline:

- 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).

B. Test Substance

The test substance, H-25425, was supplied by the sponsor as an amber-yellow-brown solid. The sponsor reported purity of the sample was [REDACTED]. Stability of the test substance was confirmed by analysis near the beginning and end of the study.

C. Test Species

On October 1, 2002, 176 male and 176 female Crl:CD[®](SD)IGS BR rats, with an assigned birth date of August 26, 2002 were received from Charles River Laboratories, Inc., Raleigh, North Carolina. An additional 45 rats (23 male and 22 females), with an assigned birth date of November 24, 2002, were received in a separate shipment 84 days after study start on January 7, 2003. The additional rats were designated for the 10-day hepatic biochemical analysis.

The rat was selected because it is the species recommended in the subchronic toxicity guidelines and is extensively used in reproduction studies. The Crl:CD[®](SD)IGS BR rat was selected based on consistently acceptable health status and on extensive experience with this strain at Haskell Laboratory.

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 $50 \pm 20\%$.

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

During the entire in-life period for rats evaluated for subchronic toxicity, the 74-day premating period for P₁ adults, and the postweaning period for F₁ weanlings, cage racks were relocated within the animal room each week and cages were repositioned on the racks every 2 weeks.

2. Feed and Water

Tap water was provided *ad libitum*. All rats were fed PMI Nutrition International, Inc. Certified Rodent LabDiet[®] 5002 *ad libitum*. One animal in group V (animal number 665150) was inadvertently without food for approximately 24 hours. This fasting was not considered to have impacted the study as the rat lost approximately 3% body weight, but regained this same amount of weight and more by the next weigh day. Furthermore, no clinical signs were noted after the fasting.

3. Identification

Each rat was assigned a unique 6-digit Haskell number, the last 3 digits of which were tattooed on the tail of each rat. The information on the cage labels included the unique 6-digit Haskell animal number and the cage identification number assigned to each rat. F₁ generation rats retained after lactation were identified by a temporary tail number on postnatal day 21 (weaning), and were tattooed after all litters were weaned.

4. Animal Health and Environmental 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 6 days of the 14-day pretest period. The rats were observed daily for any clinically apparent signs of disease or injury, weighed 3 times, and examined by a veterinary ophthalmologist to identify animals with preexisting ocular lesions.

On the bases of acceptable body weight gains and no clinical observations, all rats were released from quarantine on test day -8 by the laboratory animal veterinarian.

Additional male and female rats designated for the 10-day hepatic biochemical analysis were quarantined for 6 days of the 6- and 7-day pretest period, respectively. The rats were observed daily for any clinically apparent signs of disease or injury and weighed three times, then released from quarantine on test day 90 by the laboratory animal veterinarian.

F. Assignment to Groups and Study Start

1. Rats Designated for the Subchronic Toxicity, One-Month Recovery, Total Fluorine Level Analysis, and Reproductive Evaluations

Rats were selected for study use on the bases of adequate body weight gain, freedom from any ophthalmology 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-25425 began on test day 0 when the rats were approximately 51 days of age. Prior to the start of the test substance administration, 3 female rats were replaced to attain desired body weight mean for each group. One female rat with a body weight that was not within $\pm 20\%$ of the mean within a sex was replaced. One female rat was replaced based on a clinical observation observed on test day 0. Replacement rats were selected on the bases of freedom from any clinical signs of disease or injury and a body weight $\pm 20\%$ of the mean within a sex.

2. Rats Designated for 10-Day Biochemical Analysis

The rats designated for the 10-day biochemical analysis arrived separately, 84 days after study start. They were handled the same as the other rats during the quarantine and pretest periods, except they did not receive an ophthalmological examination. They were distributed by computerized, stratified randomization into study groups (5/sex/dose), so that there were no statistically significant differences among group body weight means within a sex when this subset of rats was compared among themselves. Oral administration of H-25425 to male and female rats began on test days 90 and 91, respectively. The rats were approximately 50 (males) and 51 (females) days of age. In-life data (body weight, food consumption, clinical observations) were collected from these animals and are in study records. However, these data will not be included in this report.

G. Dosing Suspension Preparation

Dose suspensions of 0, 2, 20, or 200 mg test substance/mL were prepared in 0.5% methylcellulose (in deionized water). The dosing suspensions were mixed for approximately one minute with a polytron homogenizer. Then the dosing suspensions were placed on a magnetic stirrer and stirred for 30 minutes prior to dosing and during dosing. Dosing suspensions of the test substance were prepared daily and stored at room temperature until used.

H. Test Substance Administration

Animals designated for evaluation of subchronic toxicity, recovery, and analysis of blood for fluorine were dosed daily by gavage for 92 (males) and 93 (females) days. Animals designated for recovery or blood fluorine analysis were dosed for 91 days. Animals designated for 10-day biochemical evaluation were dosed daily by gavage for 10 days, starting 90 days after study start.

Animals designated for reproductive evaluations were dosed daily by gavage for approximately 74 days, and then daily during the 14-day mating period. The P₁ male rats continued to be dosed following the cohabitation period until sacrifice. Pregnant females were dosed during the three-week gestation period. Pregnant females in the process of delivery or showing signs of delivery were not dosed. From gestation day 18 until delivery, dose volumes were based on the gestation day 18 body weights. Lactating females and females with no evidence of copulation were dosed until pups were weaned on postpartum day 21. The volume of H-25425 given to each rat (5 mL/kg) was based on the most recently recorded body weight. Male and female control animals were similarly treated with 0.5% methylcellulose at the same dose volume as used in the other groups.

On test day 22, one animal in group VII (animal number 665118) struggled during dosing and only received a partial dose. On test day 69, one animal in group VI (animal number 665262) was observed with dose suspension on the lips following dosing. Therefore, a full dose was not delivered. These partial doses were not considered to have impacted the study as they were isolated incidents, the rats were not in the same group, and they received most of the intended dose.

On test day 89, one animal in group VII (animal number 665084) received 0.4 mL over his targeted dose volume (2.5 mL). This single incident of a misdose was not considered to have impacted the study as the rat received the targeted dose thereafter and no adverse clinical signs were observed in this rat subsequent to this misdosing.

I. Test Substance Sampling

Dosing suspensions at concentrations of 2, 20, and 200 mg/mL of H-25425 were prepared and collected for homogeneity/concentration verification and stability analysis (5-hour room temperature) on test day 2 (October 17, 2002). Because of an unexpected high coefficient of variation (C.V.) on the low level for test day 2 samples, samples were collected for the low level from test day 8 dose preparation (October 23, 2002) for the homogeneity/concentration verification. On test day 42 (November 26, 2002) and test day 86 (January 9, 2003), dosing suspensions at all levels were collected for uniformity/concentration verification analysis. In addition, 0 mg/mL (control) samples were submitted for analysis with the each set of samples.

All dosing samples were collected and analyzed on the same day the suspensions were prepared. The suspension vehicle was 0.5% methylcellulose.

J. Analytical Methods

1. Recovery Sample Analysis

Concurrent with dosing suspensions analyses, recovery of H-25425 from spiked 0.5 % methylcellulose was tested at the low level (2 mg/mL), at the mid level (20 mg/mL) and at the high level (200 mg/mL) to confirm the analytical method. For the low level, H-25425 was weighed (approximately 12 mg) and diluted with 6 mL of 0.5% methylcellulose. For the mid and

high level, H-25425 was weighed (approximately 60 and 600 mg, respectively) and diluted with 3 mL of 0.5% methylcellulose. All recovery samples were then vortexed for dispersion of the H-25425 in the methylcellulose. The samples were then processed and analyzed in the same manner as the dosing samples at similar concentrations.

2. Dosing Suspension Treatment

Each dosing sample was collected in a 15 mL centrifuge tube (6 mL for 2 mg/mL level and 3 mL for 20 and 200 mg/mL levels). Methanol (3 mL) was added to each tube, followed by vortexing for mixing, centrifuging and removal of the supernatant. After the supernatant was removed, the test substance, remaining as solids, was washed with 3 replicate washes (3 mL) of methanol with vortexing, centrifuging and removal of the supernatant after each wash. The test substance, remaining as solids, was dried under nitrogen. These solids were then reconstituted in tetrahydrofuran (THF) using sonication to assure all material was dissolved. The 2 mg/mL samples were reconstituted to 3 mL with THF, the 20 mg/mL samples were reconstituted to 10 mL with THF and the 200 mg/mL samples were reconstituted to 100 mL with THF. The following target concentrations were then analyzed: 4.0 mg/mL, 6.0 mg/mL and 6.0 mg/mL, respectively.

3. Chromatographic Conditions

Instrument:	Hewlett-Packard Model 1100 HPLC
Column:	Styragel [®] HR 4; 7.8 mm x 300 mm (GPC column)
Mobile Phase	100% tetrahydrofuran (THF)
Flow Rate:	1.0 mL/min
Injection Volume:	50 µl
Column Temperature:	35°C
Detection:	Refractive Index

4. Calibration and Quantitation

A separate sample of H-25425 test substance was designated as the analytical reference standard [REDACTED]. A stock solution of H-25425 in tetrahydrofuran (THF) was used to make calibration solutions that bracketed the test solutions. Peak heights from replicate HPLC/GPC/RI analysis of each calibration solution were used to construct a calibration curve by least-squares regression. Measured concentrations for each test solution were determined by applying respective peak heights to the calibration curve.

Test substance homogeneity/uniformity in the vehicle was evaluated by calculating the coefficient of variation (C.V. = standard deviation/mean x 100) of the measured concentrations in the top, middle, and bottom samples (homogeneity) or duplicate samples (concentration verification) for each dosing level. A coefficient of variation of less than or equal to 10% is the standard criterion at Haskell Laboratory for acceptable distribution of the test substance throughout the solution. However, if the test substance has been shown to be difficult to disperse in the vehicle or the analysis has shown variability, a coefficient greater than 10 may be acceptable.

The mean result of the homogeneity samples ($n = 3$) or concentration verification samples ($n = 2$) 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 result of the homogeneity samples as the baseline for comparing the corresponding stability results.

Because of the procedure used to isolate the test substance in the method for analysis, spiked recovery samples at each level were monitored. A correction based on these recovery samples was applied to the sample results, if the spiked recovery sample analysis was less than 90% of nominal for the level.

K. Body Weights

All rats were weighed once per week during the subchronic toxicity and recovery periods 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.

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. Food consumption for the rats that were sampled for blood fluorine was only collected during the exposure period.

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. On five occasions, due to inclement weather or technician error, cage-site examinations were only done once a day. These missed cage-site examinations did not affect the validity of the study as there were no animals found dead or sacrificed in extremis at the next cage-site examination.

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 subchronic toxicity 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. Ophthalmology Evaluation

Two ophthalmology 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 87, all surviving rats designated for the 90-day exposure and one-month recovery were examined again.

O. Neurobehavioral Evaluations

1. Sensory Motor Function Evaluation

Prior to test substance administration, during week 13 of test substance administration, and near the end of the recovery period, assessments of responses to approach/touch, sharp auditory stimulus, and tail pinch were made while the animal was in a standard arena. For the 0 mg/kg/day and 1000 mg/kg/day groups, the baseline, week 13, and recovery assessments were conducted on the 10 animals per sex per group designated for recovery. For the 10 mg/kg/day and 100 mg/kg/day groups, the baseline and week 13 assessments were conducted on the 10 animals per sex per group designated for subchronic toxicity. Recovery assessments were not conducted on the 10 or 100 mg/kg/day groups.

Fore- and hindlimb grip strength were measured by a strain gauge device (Chatillon® Digital Force gauge). Pupillary constriction was measured immediately prior to removing the rats from the motor activity chambers (Section 2. below) because the darkened room in which the apparatus was located facilitated observing the response. The presence or absence of pupillary constriction was assessed after a beam of light was directed into each eye. For all these assessments, the experimenter was unaware of the group designation of the animal.

2. Motor Activity Evaluation

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

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

P. Clinical Pathology Evaluation

Clinical pathology evaluations were conducted on the rats designated for subchronic toxicity approximately 6 and 14 weeks after initiation of the study, and on rats designated for recovery (control and high dose only) after approximately 5 weeks of recovery. The day before collection of samples for the clinical pathology evaluations, the animals were placed in metabolism cages. These animals were fasted after 3 p.m. (at least 15 hours) and urine was collected from each animal. On the morning after the fast, blood samples for hematology and clinical chemistry measurements were collected from the orbital sinus of each animal while the animal was under carbon dioxide anesthesia. Blood samples for plasma fluoride and coagulation parameters were collected at sacrifice only from the abdominal *vena cava* of each animal while the animal was under carbon dioxide anesthesia. Additional blood collected from the *vena cava* was placed in a serum tube, processed to serum, and frozen at -80°C. Serum collected from the *vena cava* was discarded without analysis because further tests were not required to support experimental findings. Bone marrow smears were prepared at scheduled sacrifice from all animals. Bone marrow smears were stained with Wright's stain, but analysis was not necessary to support experimental findings.

1. Hematology and Coagulation

Blood samples were evaluated for quality by visual examination prior to analysis. Complete blood counts, including reticulocytes, were determined on a Bayer® Advia 120 hematology analyzer or determined from microscopic evaluation of the blood smear. Wright-stained blood smears from all animals were examined microscopically for confirmation of automated results and evaluation of cellular morphology. Blood smears, stained with new methylene blue, were prepared from each animal undergoing a hematology evaluation, but were not needed for examination. Coagulation times were determined on a Sysmex® CA-1000 Coagulation Analyzer.

The following hematology and coagulation parameters were determined:

red blood cell count	platelet count
hemoglobin	white blood cell count
hematocrit	differential white blood cell count
mean corpuscular volume	microscopic blood smear examination
mean corpuscular hemoglobin	
mean corpuscular hemoglobin concentration	
red cell distribution width	prothrombin time
absolute reticulocyte count	activated partial thromboplastin time

2. Clinical Chemistry

Serum clinical chemistry parameters were determined on a Roche Diagnostics (BMC)/Hitachi® 717 clinical chemistry analyzer. Plasma fluoride concentrations were determined using a Beckman® model Φ12 digital pH/ISE meter and a fluoride-selective electrode.

The following clinical chemistry parameters were determined:

aspartate aminotransferase	glucose
alanine aminotransferase	total protein
sorbitol dehydrogenase	albumin
alkaline phosphatase	globulin
total bilirubin	calcium
urea nitrogen	inorganic phosphorus
creatinine	sodium
cholesterol	potassium
triglycerides	chloride
	fluoride (sacrifice only) ^a

3. Urinalysis

Urine volume and appearance (quality, color, and clarity) were measured and evaluated visually, respectively. Urine constituents were semi-quantitatively measured on a Bayer Clinitek® Atlas™ Automated Urine Chemistry analyzer. Urine protein was measured on a Roche Diagnostics (BMC)/Hitachi® 717 clinical chemistry analyzer. Urine osmolality was determined using an Advanced Osmometer 3900. Urine fluoride concentrations were determined using a Beckman® model Φ12 digital pH/ISE meter and a fluoride-selective electrode, and total urine fluorides were calculated (volume x concentration). Sediments from all urine specimens were evaluated microscopically.

The following urinalysis parameters were determined:

quality	ketone
color	bilirubin
clarity	blood
volume	urobilinogen
osmolality	fluoride (sacrifice only) ^b
pH	protein
glucose	microscopic urine sediment examination

a Fluoride determination was analyzed on EDTA plasma.

b Fluoride determination was analyzed from urine with EDTA added.

Q. Total Fluorine and Perfluorooctanoic Acid Level Evaluations

1. Total Fluorine Evaluations

On test day -4 (pre-bleed), and test days 3, 9, 22, 34, 55, 76, and 89, blood (approximately 0.6 mL) was collected from the orbital sinus of designated animals (5 rats/sex/dose), while the animals were under light carbon dioxide anesthesia, for possible total blood fluorine analysis. On the day of blood collection (except test day -4), blood was collected from the animals 2 hours (± 30 minutes) after dosing. Blood was also collected for possible total blood fluorine analysis at 3, 7, 11, 18, 25, 36, 50, 71, and 92 days postdosing (after the last dose) for both male and female animals of each dose group. Animals were sacrificed after the 3-month recovery period (test day 182).

The blood was collected in plastic tubes containing EDTA while on ice and stored frozen. During the last week of the approximately 90-day exposure period animals were placed in metabolism cages for daily collection of feces and urine. Urine and feces were collected at 24-hour intervals from each animal. Urine and feces were frozen and stored. Blood fluorine analysis has not yet been performed but may be analyzed at a later date.

2. Perfluorooctanoic Acid Level Evaluations

Blood was collected in EDTA from the vena cava at necropsy from all rats designated for subchronic toxicity evaluation and from all rats designated for recovery evaluation. Plasma was prepared and stored frozen at -80 to -20°C until analyzed for concentration of perfluorooctanoic acid (PFOA).

Plasma has not yet been analyzed. Plasma will be analyzed from control and high-dose rats, and data will be reported in a supplementary report. The decision to evaluate low- and intermediate-dose groups will be based on results in the high-dose group. Plasma samples will be extracted by organic solvent protein precipitation using a protein precipitation column and then analyzed for PFOA by LC-MS-MS.

R. Biochemical Measurements

Following 10 days (males and females) or 92 days (males) or 93 days (females) of test substance administration or after one-month of recovery (test day 127 for males and females), five rats from each group designated for biochemical evaluation were weighed and then euthanized by CO_2 anesthesia and exsanguination. At each time point, the livers were removed, weighed, and then a portion was homogenized (1 gram tissue/4 mL buffer) in homogenization buffer (50 mM Tris-HCl, 50 mM Trizma-base, 0.25 M sucrose, and 5.4 mM EDTA, pH 7.4). Hepatic peroxisomes were prepared using differential centrifugation. The resulting peroxisomal pellets were resuspended in the homogenization buffer, aliquoted, and stored between -65 and -85°C until analyzed for peroxisomal β -oxidation activity. The peroxisomal suspensions were diluted to a protein concentration of approximately 0.5 mg/mL. Peroxisomal β -oxidation activity was determined using [^{14}C]palmitoyl CoA as the substrate.⁽²⁾ The protein content of the peroxisomes

was determined before and after analysis by the Biorad method.⁽³⁾ Final rate calculations were made using the post-assay protein concentrations.

S. Anatomic Pathology Evaluation for Rats Designated for Subchronic Toxicity and One-Month Recovery Evaluations

After approximately 90 days of exposure to the test substance (test days 92 and 93 for males and females, respectively), groups of 10 male and 10 female rats from the 0, 10, 100, and 1000 mg/kg/day groups were sacrificed and necropsied. Additional groups of 10 male and 10 female rats from the 0 and 1000 mg/kg/day groups were sacrificed and necropsied approximately one month after the last exposure (test day 127). In the discussion of pathology findings, groups sacrificed after approximately 90 days are referred to as the subchronic toxicity groups, and groups sacrificed on test day 127 are referred to as the one-month recovery groups, respectively. Rats designated for possible evaluation of blood fluorine levels did not receive a gross or microscopic pathology evaluation.

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

The following tissues were collected from subchronic toxicity and one-month recovery group rats sacrificed by design, and from one rat that was accidentally killed.

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

a. Bone marrow was collected with the femur and sternum.

b. Gross observations made at necropsy for which histopathology was not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) were generally not collected.

The following tissues were weighed from rats sacrificed by design in the subchronic toxicity group and the one-month recovery groups: liver, kidneys, adrenal glands, thymus, brain, spleen, heart, thyroid (weighed after fixation), ovaries, uterus, epididymides, and testes. Organ weight/final body weight and organ weight/brain weight ratios were calculated.

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 subchronic toxicity group rats sacrificed on test days 92/93 were evaluated microscopically from control and 1000 mg/kg/day rats. Liver and thyroid gland were processed and evaluated microscopically from 10 and 100 mg/kg/day subchronic toxicity group rats and from one-month recovery rats. All collected tissues were processed and received a full histopathological examination from one control male rat in the recovery subset that was accidentally killed.

T. Reproductive Evaluations

1. Observations and Mortality for Parental Rats

Cage-site examinations were conducted twice daily throughout the study. At least once weekly throughout the premating, cohabitation, gestation, and lactation periods, each of the P₁ parental rats were individually handled and carefully examined for abnormal behavior and/or appearance.

2. Body Weights for Parental Rats

a. Cohabitation Period

All P₁ males and females were weighed on the first day of the cohabitation period, and weekly thereafter. Female rats without evidence of copulation were weighed weekly until delivery or until sacrifice.

b. Gestation and Lactation Periods

P₁ female rats were weighed on days 0, 7, 14, and 21 of each period. In addition, body weight on gestation day 18 was collected in order to adjust the dosage during this period of rapid weight gain. However, these weights are not included in the final report.

3. Food Consumption and Food Efficiency for Parental Rats

a. Cohabitation

Food consumption was not determined during cohabitation.

b. Gestation Period

Individual food consumption of pregnant P₁ females was recorded on gestation days 0, 7, 14, and 21. 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 the food consumption and body weight data, the mean daily food efficiency was calculated.

Food consumption was not measured for females without evidence of copulation or for males following the cohabitation period.

c. Lactation Period

Food consumption was not measured during lactation.

4. Estrous Cycle Evaluation

Vaginal smears were collected daily from all P₁ female rats in order to determine the stages of the estrous cycle. Vaginal smears were collected beginning 3 weeks prior to cohabitation, and continuing until copulation was confirmed or until 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. However, these data were not needed for data interpretation, and will not be included in the final report. These data are maintained with the study records.

5. Breeding

a. Start of Cohabitation

Each female was continually housed on a 1:1 basis with a randomly selected, nonsibling male of the same dosage level, in the male's cage. Cohabitation was initiated on test day 74.

b. Duration of Cohabitation Period

Cohabitation continued until evidence of copulation was observed (designated as day 0 of gestation), or 2 weeks had elapsed. On the day copulation was confirmed, the female was transferred back to individual cage housing.

c. Evidence of Copulation

Each female was examined once daily for the presence of an intravaginal copulation plug or sperm in the vaginal lavage sample.

6. Gestation Procedures

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

7. Lactation Procedures

The day when delivery was complete was designated day 0 postpartum. At each examination period, offspring 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 offspring were euthanized by decapitation and discarded without pathological examination. Litters of 8 offspring or fewer were not reduced. Litter counts were determined prior to and after culling. Individual pup weights were determined prior to culling.

c. Days 7 and 14 Postpartum

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

d. Day 21 Postpartum (Weaning)

Pups in each litter were counted by sex and individually weighed. Randomly selected weanlings (one/sex/litter) were placed in individual cages and monitored for attainment of developmental landmarks. Three of 4 pups/sex/litter were then sacrificed and subjected to a gross pathological examination.

8. F₁ Generation Post Weaning

a. Clinical Observations

Cage-site examinations were conducted at least once daily. At least once weekly each rat was individually handled and carefully examined for abnormal behavior and/or appearance.

b. Body Weight Measurements

All rats were weighed weekly until termination (approximately postnatal day 60). Rats were also weighed on the day of preputial separation or vaginal opening.

c. Food Consumption and Food Efficiency

Individual food consumption was determined weekly until termination (approximately postnatal day 60). 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 determinations and body weight data, individual daily food consumption and food efficiency were calculated.

9. F₁ Generation Developmental Landmarks

a. Vaginal Patency

Female rats were examined once daily beginning on postnatal day 21 until achievement, or postnatal day 43, whichever came first. Body weight was recorded on the day of achievement.

b. Preputial Separation

Male rats were examined beginning on postnatal day 35 until achievement, or postnatal day 55, whichever came first. Body weight was recorded on the day of achievement.

10. Sperm Number, Morphology, and Motility

Sperm parameters were evaluated for the first 10 surviving P₁ males in each dosage group. The right epididymis was removed from each designated rat, and the right cauda epididymis was weighed. Sperm was collected from the right cauda epididymis, and the percent motility and morphology were determined. The left epididymis and testis were frozen in liquid nitrogen and stored between -65° and -85° C until sperm and spermatid counts were determined.

U. Anatomic Pathology Evaluation for Rats Designated for Reproductive Evaluations

1. P₁ Adults

All P₁ parental rats received a gross pathological examination, including rats sacrificed by design or found dead. Rats were sacrificed by carbon dioxide anesthesia and exsanguination. The uteri of all cohabited females were examined for the presence and number of implantation sites.

Sperm parameters for the first 10 P₁ males per group were evaluated as described above. Following collection of samples for sperm parameter evaluation, the right testis and epididymis from these 10 rats were saved and placed in fixative for histopathological evaluation.

The following table lists tissues that were collected from all P₁ adults (including those that died anytime prior to the scheduled sacrifice) and preserved in appropriate fixative for possible future histopathological examination:

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
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 anesthesia 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 anesthesia 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 ^a	Ovaries	Thyroid ^b
Epididymides ^a	Uterus (with oviducts)	Gross Observations ^c
Prostate	Vagina	Pituitary
Seminal Vesicles		
Coagulating Gland		

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

b 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.

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

Processed tissues for histopathological examination were embedded in paraffin, cut at a nominal thickness of 5 micrometers, and stained with hematoxylin and eosin (H&E). Histopathological examination of reproductive organs was conducted only for P₁ males and females with impaired reproductive performance (3 pairs of P₁ rats). Gross lesions were not evaluated microscopically.

V. Statistical Analyses

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

Statistical Methods for Subchronic Toxicity Parameters

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 B-Oxidation	Test for lack of trend ⁽⁴⁾	Sequential application ⁽⁵⁾ of the Jonckheere-Terpstra trend test ⁽⁶⁾	Preliminary tests for pairwise comparison
		OR ^a	
	Levene's test for homogeneity ⁽⁷⁾ and Shapiro-Wilk test ⁽⁸⁾ for normality ^b	One-way analysis of variance ⁽⁹⁾ followed with Dunnett's test ^(10,11,12)	Kruskal-Wallis test ⁽¹³⁾ followed with Dunn's test ⁽¹⁴⁾
Survival Incidence of Clinical Observations Incidence of Ophthalmology Observations Incidence of FOB Descriptive Parameters	None	Cochran-Armitage test for trend ^{(9)c}	
Motor Activity ^d	Levene's test for homogeneity ⁽⁷⁾ and Shapiro-Wilk test ⁽⁸⁾ for normality ^b	Repeated measures analysis of variance ⁽¹⁵⁾ followed by contrasts ⁽¹⁶⁾	Sequential application ⁽⁵⁾ of the Jonckheere-Terpstra trend test ⁽⁶⁾
Grip Strength	Bartlett's test ⁽¹⁷⁾ for homogeneity of variances	One-way analysis of variance ⁽⁹⁾ followed with Dunnett's test ⁽¹⁰⁾	Kruskal-Wallis test ⁽¹³⁾ followed with Dunn's test ⁽¹⁴⁾
Clinical Pathology ^e	Levene's test for homogeneity ⁽⁷⁾ and Shapiro-Wilk test ⁽⁸⁾ for normality ^b	One-way analysis of variance ⁽⁹⁾ followed with Dunnett's test ⁽¹⁰⁾	Kruskal-Wallis test ⁽¹³⁾ followed with Dunn's test ⁽¹⁴⁾
Incidence of Microscopic Lesions	None	none	

- Pairwise comparisons and associated preliminary tests were only conducted if the test for lack of trend was significant.
- If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used. If the Shapiro-Wilk test was significant, Kruskal-Wallis test was followed by Dunn's test.
- If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test⁽¹⁸⁾ with a Bonferroni correction was used.
- Test day and block (10-minute intervals) were used as repeated-measure factors.
- When an individual observation was recorded as being less than a certain value, calculations were performed on one-half of the recorded value. For example, if bilirubin was reported as <0.1 , 0.05 was used for any calculations performed with that bilirubin data. When an individual observation was recorded as being greater than a certain value, calculations were performed on the recorded value. For example, if specific gravity was reported as >1.083 , 1.083 was used for any calculations performed with that data.

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

Mating Index (%)	=	$\frac{\text{Number Copulated}^a}{\text{Number Cohabited}}$	x 100
Fertility Index (%)	=	$\frac{\text{Number Pregnant}^b}{\text{Number Copulated}^a}$	x 100
Gestation Index (%)	=	$\frac{\text{Number of Litters with at Least One Live Pup}}{\text{Number of Litters}}$	x 100
Implantation Efficiency (%) ^c	=	$\frac{\text{Number of Pups Born}}{\text{Number of Implantation Sites}}$	x 100
Pups Born Alive (%) ^c	=	$\frac{\text{Number of Pups Born Alive}}{\text{Number of Pups Born}}$	x 100
Viability Index (%) ^{c,d}	=	$\frac{\text{Number of Pups Alive Day 4 Preculling}}{\text{Number of pups born alive}}$	x 100
Lactation Index (%) ^{c,d}	=	$\frac{\text{Number of pups alive at weaning (Day 21 postpartum)}}{\text{Number of pups alive Day 4 Postculling}}$	x 100
Litter Survival (%) ^d	=	$\frac{\text{Number of litters weaned}}{\text{Number of viable litters delivered}}$	x 100

- a Evidence of copulation = intravaginal copulatory plug, sperm in vaginal lavage sample, found dead pregnant, or delivery of a litter.
b Including pregnant animals that were found dead during gestation.
c Determined for each litter. Mean and standard deviation for each dose level were calculated.
d Excluding litters sacrificed due to death of dam during lactation.

Statistical Methods for Reproductive Toxicity Parameters

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Body Weight	Test for lack of trend ⁽⁴⁾	Sequential application ⁽⁵⁾	Preliminary tests for pairwise comparison
Body Weight Gain		of the Jonckheere-Terpstra trend test ⁽⁶⁾	
Food Consumption	OR ^a		
Food Efficiency	Levene's test for homogeneity ⁽⁷⁾ and Shapiro-Wilk test ⁽⁸⁾ for normality ^b	One-way analysis of variance ⁽⁹⁾ and Dunnett's test ⁽¹⁰⁾	Kruskal-Wallis test ⁽¹³⁾ and Dunn's test ⁽¹⁴⁾
Gestation Length			
Organ Weight			
Implantation Site Numbers			
Implantation Efficiency			
Mean Number of Pups Per Litter			
Percent Born Alive			
Sex Ratio			
0-4 Day Viability			
Lactation Index			
Vaginal Patency			
Preputial Separation			
Estrous Cycle Parameters			
Sperm Parameters			
Incidence of Clinical	None	Cochran-Armitage test for trend ^{(9)c}	
Mating Index			
Fertility Index			
Gestation Index			
Litter Survival			
Mean Pup Weights (Covariates: litter size, sex ratio)	None	Linear contrast of least squares means ⁽¹⁹⁾	Dunn's test ⁽¹⁴⁾
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 If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test⁽¹⁸⁾ 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.⁽⁵⁾ For litter parameters, the proportion of affected fetuses per litter or the litter mean were used as the experimental unit for statistical evaluation.⁽²⁰⁾ The level of significance selected was $p < 0.05$.

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

RESULTS AND DISCUSSION

Analytical Evaluation

A. Test Substance Stability Analyses

Samples of the test substance were analyzed near the beginning and end of the study. These analyses indicated that the H-25425 was stable over the course of the study.

The average of the active ingredient was [REDACTED] for samples analyzed October 15, 2002 and February 27, 2003. This work is reported in analytical reports [REDACTED]

[REDACTED] and can be found in Haskell Laboratory Records [REDACTED]. The H-25425 was reported by the sponsor to be [REDACTED]. The difference between the sponsor reported purity and the experimental data represent analytical variability.

B. Chromatography

H-25425 eluted from the HPLC/GPC column as a resolved peak over an average retention time of 8.5 to 9.0 minutes. Representative HPLC/GPC/IR chromatograms are shown in Appendix A, Figures 2 (a - d). Test substance was not detected in the 0 mg/mL control.

C. Recovery Samples

Detailed analytical results of recovery samples are summarized in Appendix A, Table I. The variability of the analytical method was demonstrated by the coefficients of variation of the recovery results at each targeted dosing concentration (approximately 2, 20, 200 mg/mL) over the course of the study. The measured concentrations of H-25425 for the 2 mg/mL level were 68.5% to 78.4% of nominal (mean percent recovery = $74.2\% \pm 4.2$, C.V. = 6%). The measured concentrations of H-25425 for the 20 mg/mL level were 84.1% to 88.1% of nominal (mean percent recovery = $86.0\% \pm 2.0$, C.V. = 2%). The measured concentrations of H-25425 for the 200 mg/mL level were 89.1% to 96.5% of nominal (mean percent recovery = $92.8\% \pm 3.7$, C.V. = 4%). Based on this data, a correction was applied to all sample results when the spiked recovery for the concentration analyzed below 90% of nominal.

D. Homogeneity and Stability Samples

Analytical results from dosing suspensions collected on test day 2 (October 17, 2002) and analyzed for homogeneity/concentration verification and 5-hour room temperature stability and test day 8 (October 23, 2002) and analyzed for homogeneity/concentration verification are shown in Appendix A, Table II and Summary Table 1.

The following table summarizes the results for homogeneity/concentration verification and stability analyses for these sampling days of the H-25425 sample preparation.

Sample Day Sample Type	Nominal mg/mL	Measured T,M,B ^a mg/mL	Mean (T,M,B) % Nominal	C.V. (%)	Stability ^b % Nominal
Test day 2					
Homogeneity	0	ND ^c	---	---	---
	2 ^d	1.36, 1.87, 2.00	87.0	19	91.5
	20 ^d	19.0, 20.8, 21.3	102.0	6	108.5
	200	187, 188, 191	94.5	1	98.0
Test day 8					
Homogeneity	0	ND ^c	---	---	---
	2 ^d	1.87, 1.97, 1.91	96.0	2	---

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.

d Reported results corrected for recovery of the spiked sample at the level (refer to Table I).

The results for H-25425 samples prepared and collected on test day 2 show that the test substance was at the targeted concentrations for all levels ($\pm 13.0\%$ of nominal), adequately mixed except for the 2.0 mg/mL level (CV = 19) and stable in the vehicle when held 5 hours at room temperature for all levels. Test substance was not detected in the 0 mg/mL samples.

The results for H-25425 samples (2.0 mg/mL level) prepared and collected on test day 8 show that the test substance was at the targeted concentration ($\pm 4.0\%$ of nominal), and adequately mixed (CV = 2). Test substance was not detected in the 0 mg/mL samples.

E. Concentration Verification Samples

Analytical results from dosing suspensions collected on test day 42 (November 26, 2002) and test day 86 (January 9, 2003) and analyzed for concentration verification (uniformity) are shown in Appendix A, Table III and Summary Table 1.

The following table summarizes the results for concentration verification analyses for both sampling days of the H-25425 sample preparation.

Preparation Day	Nominal mg/mL	Measured ^a mg/mL	Average % Nominal	CV %
Test day 42	2 ^b	2.35, 2.36	118.0	0.4
	20 ^b	20.5, 20.8	103.5	1
	200	190, 193	96.0	1
Test day 86	2 ^b	2.03, 2.04	102.0	0.5
	20 ^b	19.6, 21.8	103.5	7
	200 ^b	209, 203	103.0	2

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

b Reported results corrected for recovery of the spiked sample at the level (refer to Table I).

The results for samples prepared and collected on test day 42 indicate that the test substance was at the targeted levels ($\pm 4.0\%$ of nominal) except for the 2.0 mg/mL level that was marginally higher than expected ($\pm 18.0\%$ of nominal) and adequately mixed (CV's less than 10) for all H-25425 samples. Test substance was not detected in the 0 mg/mL samples.

The results for samples prepared and collected on test day 86 indicate that the test substance was at the targeted levels (target = $\pm 3.5\%$ of nominal) and adequately mixed (CV's less than 10) for all H-25425 samples. Test substance was not detected in the 0 mg/mL samples.

F. Analytical Conclusion

Results from the analysis of the test substance dosing suspensions during the study indicate that the test substance was mixed properly except for the initial sampling of the 2 mg/mL level, at the targeted levels and stable under the conditions of the study. Test substance was not found in the 0 mg/mL samples.

In-Life Toxicology

Rats designated for evaluation of reproductive toxicity were transferred to the reproduction group on test day 72, and were co-housed for mating beginning on test day 74. All results reported in this section up to test day 72 (including day 0-70 intervals) include data from both the subchronic toxicity and reproductive toxicity subsets. All results after test day 72 (including day 0-91 intervals) are from subchronic toxicity rats alone.

A. Dosage Data (Tables 2-3, Appendix B)

Rats were dosed with solutions of H-25425 in 0.5% methylcellulose, prepared at concentrations of 0, 2, 20, or 200 mg H-25425/mL, designed to deliver the targeted dose of test substance at a dosing volume of 5.0 mL/kg body weight. The quantity of H-25425 administered to each rat was calculated, based on the most recent body weight for each rat, and subsequently rounded by a computer program.

The range of mean daily dose volumes administered to male rats was 1.2-3.0 mL for the control group, and 1.2-2.9 mL for the 10, 100, and 1000 mg/kg/day groups. The range of mean daily dose volumes administered to female rats was 0.9-1.6 mL for the control group, and 0.9-1.5 for the 10, 100, and 1000 mg/kg/day groups.

B. Mean Body Weights and Body Weight Gains (Tables 4-7, Figures 1-2, Appendices C)

No adverse, test substance-related effects on body weight or body weight gain were observed in any male or female dose group.

No statistically significant differences in mean body weight, compared to control, were observed in male rats on any test day. Mean body weight in the 1000 mg/kg/day group was 97% of control on test days 70 and 91, 96% of control at the end of the one-month recovery (test day 126), and 90% of control at the end of the three-month recovery (test day 182; fluorine analysis subgroup). None of the differences was statistically significant. Statistically significant reductions in mean body weight gain were observed in the male 1000 mg/kg/day group over test days 0-7, 7-14, 21-28, 49-56, 70-77, and 105-112. Although these reductions may have been test substance-related, they were not considered adverse effects as mean body weight gain in this group was comparable to control over most weekly intervals; there was no statistically significant difference in overall mean body weight gain over test days 0-70 or 0-91 (94% of control); and mean body weight gain exceeded control (not statistically significant) over numerous weekly intervals. Furthermore, the latter two weekly intervals occurred during the recovery period. Statistically significant reductions in mean body weight gain were also observed over test days 7-14 and 70-77 in the 100 mg/kg/day group and over test days 7-14 in the 10 mg/kg/day group. These differences were not considered test substance-related as they were isolated intervals, rats were not dosed on test days 70-77, and no statistically significant differences in overall mean body weight gain were observed in these groups over the test day 0-70 or 0-91 dosing periods or the one- or three-month recovery periods.

No statistically significant differences in mean body weight or mean body weight gain were observed in any female dose group on any test day or over any weekly interval of the study. Mean body weight in the female 1000 mg/kg/day group was 99% and 96% of control on test days 70 and 91, respectively. Mean body weight gain in this group was 100% and 93% of control over test days 0-70 and 0-91, respectively. Mean body weight gain in this group was comparable to control (95%) over the one-month recovery and exceeded control (131% of control) over the three-month recovery. None of these interval differences was statistically significant. Mean body weight and body weight gain in other female dose groups were also comparable to control throughout the dosing and recovery periods.

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

No adverse, test substance-related effects on food consumption or food efficiency were observed in any male or female dose group.

In male rats, no statistically significant differences in weekly or overall food consumption were observed in any dose group throughout the dosing or recovery periods of the study. Mean food consumption in the male 1000 mg/kg/day group was 99% and 97% of control over the test day 0-

70 and 0-91 intervals, respectively (neither statistically significant). Mean food consumption in this group was 101% of control during recovery (test days 91-126).

In female rats, no adverse effects on food consumption were observed in any dose group throughout the dosing or recovery periods. Statistically significant reductions in mean food consumption were observed in the 1000 mg/kg/day group over test days 21-28, 28-35, 84-91, and 112-119. Statistically significant reductions in mean food consumption were observed in the 100 mg/kg/day group over test days 84-91. These differences were not considered adverse as mean food consumption in these groups was comparable to control over most weekly intervals, there was no statistically significant difference in overall mean food consumption, and rats were not dosed during the test day 112-119 interval. Mean food consumption in the 1000 mg/kg/day female group was 99% and 97% of control over test days 0-70 and 0-91, respectively and 94% of control during recovery (test days 91-126).

In 1000 mg/kg/day male rats, statistically significant reductions in mean food efficiency were observed over test days 0-7, 7-14, 21-28, 49-56, and 70-77, and statistically significant increases in mean food efficiency were observed over test days 28-35 and 119-126. A few statistically significant decreases and increases in mean food efficiency, compared to control, were also observed in the 10 and 100 mg/kg/day groups over one or more intervals. It is questionable whether these effects were test substance related, and they were not considered adverse as the differences included increases and decreases, a dose-response was not always evident, and overall mean food efficiency in all male dose groups did not differ from control during dosing or recovery periods. Mean overall food efficiency in 1000 mg/kg/day males was 96%, 97%, and 95% of control over test days 0-70, 0-91, and 91-126, respectively (none statistically significant).

No statistically significant differences from control in mean food efficiency were observed in any female dose group throughout the study, except for a single weekly interval (test day 91-98), in which mean food efficiency in the 1000 mg/kg/day group was significantly higher than in control. Mean overall food efficiency in 1000 mg/kg/day females was 102%, 97%, and 97% of control over test days 0-70, 0-91, and 91-126, respectively (none statistically significant).

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

There was no test substance-related effect on mortality in either male or female rats. A male control rat was accidentally killed during the bleeding procedure on test day 127. One male rat in the 100 mg/kg/day group was found dead on test day 108. This rat was part of the subset bled for possible fluorine evaluation and did not receive a pathological evaluation. Therefore, the cause of death is unknown. No early deaths occurred in any female dose group.

No increases in any clinical observations occurred that were attributed to test substance exposure.

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

No compound-related ophthalmological lesions were observed in male or female rats examined near the end of the dosing phase of the study. Unilateral focal retinal degeneration was observed in one male and one female rat. This observation was not test substance related as these rats were in the control group.

F. In-Life Toxicology Conclusions

Under the conditions of this study, the no-observed-effect level (NOEL) for in-life parameters was 1000 mg/kg/day for males and females. The NOEL was based on a lack of adverse effects on any in-life parameters in rats dosed up to 1000 mg/kg/day, the highest dose tested.

Neurobehavioral Evaluation

A. Forelimb Grip Strength (Tables 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 the test substance. Mean values for all groups were similar to the control values for both males and females.

B. Hindlimb Grip Strength (Tables 18-19, Figures 5-6, Appendix G)

There were no test substance-related effects or statistically significant differences for hindlimb grip strength in males or females administered any dosage of the test substance. Mean values for all groups were similar to the control values for both males and females.

C. Sensory Motor Function Observations (Tables 20-21, Appendix H)

There were no test substance-related effects or statistically significant differences for the sensory motor function parameters in either males or females administered any dosage of the test substance. One female in the 1000 mg/kg/day group was observed to be circling during the week 13 and recovery evaluations. Although this observation is suggestive of neurotoxicity, since only one animal administered 1000 mg/kg/day was observed with this behavior, and since no other clinical signs or changes in grip strength or motor activity were evident in any dosage group, the circling behavior was not considered to be test substance-related. The incidences for all groups were similar to the values for the control values for both males and females.

D. Motor Activity (Tables 22-25, Figures 7-9, Appendices I-J)

There were no test substance-related effects on duration of movement or number of movements for males or females administered any dosage of the test substance. During the week 13 evaluation, males administered 1000 mg/kg/day had significantly increased duration of movement and number of movements during the 6th 10-minute interval compared to the control value. The statistical differences may be suggestive of a delayed habituation in the males administered 1000 mg/kg/day compared to control. However, the range of individual duration of movement values during the 6th 10-minute interval for the 13-week evaluation were similar for all 3 treatment groups (45-366, 70-370, 41-320 seconds for the 10, 100, and 1000 mg/kg/day males, respectively), and were higher compared to the range of individual control values during the 6th 10-minute interval (10-207 sec). In addition, the range of individual number of movements for the 6th 10-minute interval during the 13-week evaluation was similar for all groups (14-155, 36-151, 59-152, 37-160 for the 0, 10, 100, and 1000 mg/kg/day males, respectively). Therefore, these statistical differences were not considered to be test substance-related for the following reasons: 1) a dose-response relationship is not evident for the range of individual duration of movement values; 2) a dose-response-relationship is not evident for the mean and range of number of movement values; and 3) the mean duration of movement and number of movement values for 1000 mg/kg/day females were similar to control values. Therefore, these statistical differences were not considered to be treatment-related. Mean values for all other groups and time intervals were similar to the values for the control groups for both males and females.

E. Neurobehavioral Conclusions

Under the conditions of the study, the NOEL for grip strength, sensory motor function observations, and motor activity, was 1000 mg/kg/day, the highest dosage tested.

Clinical Pathology Evaluation

A. Hematology (Tables 26-27, Appendix K)

There were no adverse changes in hematologic parameters in male or female rats. The following statistically significant changes in mean hematologic parameters were not adverse or not related to exposure to compound:

- Red cell mass parameters (red cell count, hemoglobin, and hematocrit) were minimally decreased in males dosed with 1000 mg/kg/day at test days 37 and 92, and after one month of recovery (variable statistical significance). At these three time-points, mean values for red cell mass parameters were 95-97% of respective concurrent control group means. There were no correlative changes in other numeric or microscopic red cell parameters.

Red cell mass parameters (hemoglobin and hematocrit) were minimally but statistically decreased in females dosed with 1000 mg/kg/day at test day 93 (97 and 95% of control group means, respectively). There were no correlative changes in other numeric or microscopic red cell parameters. After one month of recovery, red cell mass parameters in females previously dosed with 1000 mg/kg/day were similar to control values.

The above changes in red cell mass parameters in male and female rats dosed with 1000 mg/kg/day were probably due to treatment due to the consistency of change between sexes and across time-points. However, because the changes were so minimal (all within 95% of control group means, whereas control group means can vary by 10 percentage points between studies), they were considered to be non-adverse. Although the changes in males persisted into the recovery period, the very minimal nature of the effects suggested that the changes were non-adverse.

- Platelets were transiently and minimally decreased in males dosed with 1000 mg/kg/day at test day 37 (91% of control group mean). At the end of the study (test day 92) and after one month of recovery (test day 127), platelets were similar to control group counts. The decrease in platelets at test day 37 was possibly due to treatment. However, the range of individual counts in males dosed with 1000 mg/kg/day was similar to that of other groups. In addition, all values were well within the historical reference range for individual animal values for this parameter ($729-1415 \times 10^3/\mu\text{L}$ for males approximately 19 weeks old). Therefore, although this change was possibly due to treatment, it was considered to be non-adverse.

The following statistically significant changes in mean hematology parameters were considered to be unrelated to treatment and non-adverse because they did not occur in a dose-related pattern, or occurred only after one month of recovery:

- Increased red cell distribution width in males dosed with 100 mg/kg/day at test day 37
- Increased neutrophils and monocytes in males dosed with 100 mg/kg/day at test day 37
- Increased neutrophils in females dosed with 10 mg/kg/day at test day 93
- Increased white blood cells, lymphocytes, monocytes, and large unstained cells in males previously dosed with 1000 mg/kg/day after one month of recovery (test day 127)
- Decreased red cell distribution width in females previously dosed with 1000 mg/kg/day after one month of recovery (test day 127)

B. Coagulation

(Tables 28-29, Appendix K)

There were no adverse changes in coagulation parameters in male or female rats. The following statistically significant changes in mean coagulation parameters were considered to be unrelated to treatment and non-adverse because they did not occur in a dose-related pattern:

- Activated partial thromboplastin time was minimally decreased in males dosed with 100 mg/kg/day at test day 92. This change was considered to be unrelated to treatment because there was no dose-relationship in the response; activated partial thromboplastin times were similar in groups dosed with 10, 100, or 1000 mg/kg/day. In addition, minimally decreased activated partial thromboplastin time has no toxicologic significance. Activated partial thromboplastin times were similar to control group times in males previously dosed with 1000 mg/kg/day after one month of recovery.

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

There were no adverse changes in clinical chemistry parameters in male or female rats. The following statistically significant changes in mean clinical chemistry parameters were not adverse or not related to exposure to compound:

- Alanine aminotransferase activity was decreased in female rats dosed with 100 or 1000 mg/kg/day at test day 93 (not statistically significant). At this time point, there were unusually high activities of both aspartate and alanine aminotransferase in one female (#665221) dosed with 0 (vehicle) and in one female (#665332) dosed with 10 mg/kg/day. These two rats had alanine aminotransferase activities of 223 and 165 U/L, respectively (individual age-matched historical control activities range from 25-122 U/L). These changes were considered to be due to spontaneous lesions unrelated to treatment. Therefore, the *apparent* decrease in mean alanine aminotransferase resulted from spontaneous lesions in *control and low dose* females, rather than from treatment-related changes in females dosed with 1000 mg/kg/day. After one month of recovery, alanine aminotransferase activities in females previously dosed with 1000 mg/kg/day were similar to control values.
- Bilirubin was minimally decreased in males and females dosed with 1000 mg/kg/day at test day 92 and 93, respectively (variable statistical significance). In males, there was histologic evidence of enzyme induction (centrilobular hypertrophy), and liver weights were increased. Decreased bilirubin was likely to be secondary to enzyme induction, as a result of a physiologic response to dosing of a xenobiotic. Therefore, these changes were considered to be non-adverse. After one month of recovery (test day 127), bilirubin concentrations in rats previously dosed with 1000 mg/kg/day were similar to control group values.
- Triglyceride was mildly decreased in males dosed with 10, 100, or 1000 mg/kg/day at test day 92 (70, 76, and 58% of control group means; statistically significant at 10 and 1000 mg/kg/day only). These changes were likely related to treatment. However, mildly decreased triglycerides have no adverse effects; therefore, this change was considered to be non-adverse. After one month of recovery (test day 127), triglyceride concentrations in males previously dosed with 1000 mg/kg/day were similar to control group values.
- Total protein was mildly decreased due to decreased globulin in males dosed with 1000 mg/kg/day at test day 92. Means were 96 and 83% of control group means, respectively. These changes were considered to be due to treatment. However, the group means of 7.1 and 2.4 mg/dL for total protein and globulin, respectively, were within the historical range of means for age-matched control animals (6.8-7.5 and 1.9-2.6 mg/dL,

respectively). In addition, individual animal concentrations of 6.8-7.4 mg/dL for total protein and 1.9-2.7 mg/dL for globulin were within their respective historical reference ranges (6.2-8.2 mg/dL for total protein and 1.5-3.3 mg/dL for globulin). Therefore, this change, although treatment-related, was considered to be non-adverse. After one month of recovery (test day 127), total protein and globulin concentrations in males previously dosed with 1000 mg/kg/day were similar to control group values.

- Calcium was minimally increased in females dosed with 1000 mg/kg/day at test day 38 (104% of control group mean). The change in calcium was due to the minimal increase in albumin (not statistically significant). 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, which results in increased total calcium. However, ionized calcium is unaffected. Therefore, this change was considered to be non-adverse. After one month of recovery (test day 127), calcium concentrations in females previously dosed with 1000 mg/kg/day were similar to control group values.
- Inorganic phosphorus was minimally and transiently increased in females dosed with 10, 100, and 1000 mg/kg/day at test day 38 (108, 107, and 114% of control group mean, not statistically significant at 100 mg/kg/day). Individual phosphorus values were similar across all three groups dosed with the test substance despite the 100-fold difference in dose. In addition, there were no changes in correlative clinical chemistry parameters (urea nitrogen, creatinine) or in histopathology that suggest that these phosphorus changes are treatment-related. Therefore, these changes were considered to be unrelated to treatment and non-adverse.
- Chloride was minimally increased in females dosed with 1000 mg/kg/day at test day 93 (102% of control group mean). This change is possibly related to treatment. However, the mean concentration (100.5 mmol/L) and individual animal concentrations (97.9-103.4 mmol/L) were well within the historical range for age-matched historical data (historical range of means is 95-102 mmol/L and historical range of individual animal values is 91-105). Therefore, although this change is possibly related to treatment, it was considered to be non-adverse. After one month of recovery (test day 127), chloride concentrations were similar to control group values in females previously dosed with 1000 mg/kg/day.

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

- Increased alanine aminotransferase in males dosed with 100 mg/kg/day at test day 37
- Decreased alanine aminotransferase in females dosed with 100 mg/kg/day at test day 38
- Increased aspartate aminotransferase, alanine aminotransferase, and albumin in males previously dosed with 1000 mg/kg/day after one month of recovery (test day 127)
- Decreased triglycerides in females dosed with 10 mg/kg/day at test day 93.

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

The following statistically significant changes in mean urinalysis parameters were considered to be unrelated to treatment and non-adverse because they occurred only after one month of recovery:

- Decreased urine protein and osmolality, and increased urine volume in males previously dosed with 1000 mg/kg/day after one month of recovery (test day 127)
- Decreased urine volume and pH, and increased urine protein and urobilinogen in females previously dosed with 1000 mg/kg/day after one month of recovery (test day 127)

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

There were no treatment-related or statistically significant changes in plasma fluoride in males or females dosed with up to 1000 mg/kg/day.

Urine fluoride was increased (statistically significant) in males and females dosed with 1000 mg/kg/day (see text table below). Urine fluoride was also increased in most males and a few females dosed with 100 mg/kg/day at test day 92/93 (statistically significant in males only). After one month of recovery, urine fluoride was statistically increased in males previously dosed with 1000 mg/kg/day; this change was probably related to treatment based on the individual animal data.

Increased urine fluoride indicates exposure to and metabolism of a fluoride-containing compound.

Plasma and Urine Fluoride Measurements*

Dose (mg/kg/day)			0	10	100	1000	10	100	1000
			I/II	III/IV	V/VI	VII/VIII	III/IV	V/VI	VII/VIII
Plasma (ug/mL)	Males	Day 92	0.1	0.1	0.1	0.1	100%	100%	100%
		Day 127	0.1	--	--	0.1			100%
	Females	Day 93	0.1	0.1	0.1	0.1	100%	100%	100%
		Day 127	0.1	--	--	0.1			100%
Urine (ug)	Males	Day 92	9.5	9.2	17.5	53.4	97%	184%	562%
		Day 127	7.7	--	--	10.8			140%
	Females	Day 93	6.5	5.5	9.8	28.6	85%	151%	440%
		Day 127	6.3	--	--	4.8			76%

*Results expressed as actual values or as percent of control group mean. Statistical significance is indicated by **bold italicized font**

F. Clinical Pathology Conclusions

In conclusion, males and females dosed with 1000 mg/kg/day had minimally decreased red cell mass parameters (red cell count, hemoglobin, and hematocrit) and minimally decreased serum

bilirubin. In addition, male rats dosed for 90 days with the test substance had mildly decreased triglycerides (10, 100, and 1000 mg/kg/day), and mildly decreased total protein due to decreased globulin (1000 mg/kg/day males only). Urine fluoride was increased in males and females dosed with 100 or 1000 mg/kg/day. After one month of recovery, red cell mass parameters were still minimally decreased and urine fluoride was still increased in males previously dosed with 1000 mg/kg/day. None of these effects were considered to be adverse.

Therefore, under the conditions of this study and for the clinical pathology parameters measured, the NOEL was 1000 mg/kg/day for males and females, based on the lack of adverse effects at any dose.

Biochemical Evaluation

A. Biochemical Evaluation (Tables 34-35, Appendix L)

In male rats at the 10-day time point, the rate of hepatic β -oxidation was statistically significantly decreased at a dosage of 1000 mg/kg/day (91% of control). This decrease was considered a spurious finding and was not considered to be test substance-related due to a lack of concordance with the effects observed at the 92-day and one-month recovery time points. At the 92-day and one-month recovery time points in male rats, the rate of hepatic β -oxidation was statistically significantly increased at a dosage of 1000 mg/kg/day (159% and 149% of control, respectively). At the 92-day time point, the increase in hepatic β -oxidation activity at a dosage of 1000 mg/kg/day was accompanied by an increase in absolute and relative liver weight in all subchronic toxicity male rats. Liver weights were not affected at the one-month recovery time point in male rats.

At the 10-day and 93-day time points in female rats, the rate of hepatic β -oxidation was statistically significantly increased at a dosage of 1000 mg/kg/day (120 and 125% of control, respectively). At the one-month recovery time point, hepatic β -oxidation activity had returned to control levels in female rats.

B. Biochemical Evaluation Conclusions

Under the conditions of this study, H-25425 is a mild inducer of hepatic peroxisomal β -oxidation in male and female rats. At a concentration of 1000 mg/kg/day, changes in the rate of hepatic peroxisome proliferation are considered to be test substance-related effects. However, the effects were not considered adverse. At the one-month recovery time point, the rate of hepatic peroxisome proliferation was still increased at a dosage of 1000 mg/kg/day in males, but had returned to control levels in female rats.

Anatomic Pathology Evaluation – Rats Designated for Subchronic Toxicity and Recovery Evaluations

A. Mortality (Tables 16-17, Appendix N)

There were no test substance-related deaths. One control male rat (Animal No. 665042) was accidentally killed during blood collection on the last day of the one-month recovery period. The gross and microscopic pathology data for this rat were included in the incidence tables; organ weights were not taken.

B. Organ Weight Data (Tables 36-39, Appendix M)

In the subchronic toxicity groups, the only test substance-related organ weight effects were increases in mean liver and kidney weights in male rats given 1000 mg/kg/day, as compared to controls. Male liver weight parameters remained increased, to a lesser extent, in the high-dose males following the one-month recovery period.

Mean absolute, relative (liver/body weight), and relative (liver/brain weight) liver weights were increased 19%, 23%, and 22%, respectively, in the 1000 mg/kg/day male rats as compared to the controls. All three increases were statistically significant by the trend test. The increase in liver weights correlated with the microscopic observation of minimal hepatocellular hypertrophy in all ten male rats following the subchronic toxicity exposure period (see discussion under Microscopic Observations). In the one-month recovery 1000 mg/kg/day male rats, mean absolute, relative (liver/body weight), and relative (liver/brain weight) liver weights were still increased 10%, 11%, and 11%, respectively, although only the mean relative (liver/body weight) was statistically significant. Microscopic hepatocellular hypertrophy was not evident in these recovery males. In female rats, increases in absolute and relative (to brain) liver weight parameters that were observed in the subchronic toxicity exposure and one-month recovery groups were considered to be biologically insignificant.

Mean absolute, relative (kidney/body weight), and relative (kidney/brain weight) kidney weights were increased 12%, 16%, and 14%, respectively, in the 1000 mg/kg/day male rats as compared to the control rats. All three increases were statistically significant by the trend test. There was no microscopic morphological correlate to the increase in kidney weights in this study (see discussion under Microscopic Observations). In the one-month recovery 1000 mg/kg/day male rats, kidney weight parameters were similar to control rat values. Test substance-related kidney weight effects were not observed in female rats at any dose level in the subchronic toxicity or one-month recovery groups.

All other individual and mean organ weight differences were considered to be spurious and unrelated to test substance administration. Although some female thyroid weight parameters in the subchronic study were increased in all treated groups (variable statistical significance), there

was no dose response. These increases were attributed to a spuriously low control group mean, and not to a test substance related effect.

C. Gross Observations (Tables 40-43, Appendix N)

There were no test substance-related gross observations. All gross observations at necropsy were interpreted to be naturally occurring background lesions that are typical of rats of this age and strain.

D. Microscopic Observations (Tables 44-51, Appendices N and O)

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

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

Dose: mg/kg/day	0	10	100	1000
Males: Subchronic Toxicity				
Liver:				
Hypertrophy, hepatocyte, centrilobular	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	9/10 (0.9)
Thyroid gland:				
Hypertrophy, follicular cell	1/10 (0.2)	1/10 (0.1)	1/10 (0.1)	10/10 (1.6)
Males: One-Month Recovery				
Thyroid gland:				
Hypertrophy, follicular cell	1/10 (0.1)	NA	NA	6/10 (0.9)
Females: Subchronic Toxicity				
Thyroid gland:				
Hypertrophy, follicular cell	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	2/10 (0.2)
Females: One-Month Recovery				
Thyroid gland:				
Hypertrophy, follicular cell	0/10 (0.0)	NA	NA	2/10 (0.2)

^a Numerator indicates number 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.

Hypertrophy of centrilobular hepatocytes was observed in most (9/10) high-dose (1000 mg/kg/day) males and was graded minimal in all cases. Since hepatocellular hypertrophy was not observed in any of the one-month recovery males, this effect was clearly reversible. Hepatocellular hypertrophy was not observed in any female rats following the 93-day exposure

period. Microscopically, hepatocellular hypertrophy was characterized by an increased amount of finely granular eosinophilic cytoplasm within centrilobular 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 pharmacological response to the metabolism of a xenobiotic and not adverse.

An increased incidence of thyroid follicular cell hypertrophy was present in males and females administered 1000 mg/kg/day for approximately 90 days. Follicular cell hypertrophy was characterized by low columnar follicular epithelium with a finely granular or vacuolated cytoplasm. Follicles were decreased in size, irregular in shape, and contained decreased amounts of normal pink colloid. Following the one-month recovery period, both the incidence and severity of follicular hypertrophy was decreased in the male rats. In female rats, the incidence (2/20) and severity (minimal) was the same in both the exposure and recovery groups. Despite the persistence of the effect following the one-month recovery, the overall decrease in the incidence and severity demonstrates the reversibility of follicular cell hypertrophy in this study.

An increase in the incidence and severity of thyroid follicular cell hypertrophy is indicative of altered thyroid gland homeostasis. Although the follicular cell response observed in this study (minimal to mild hypertrophy) was within the range of normal physiological response, the effect is potentially proliferative and adverse, especially in the rat. Since follicular cell hypertrophy is consistent with several different mechanisms of altered thyroid gland homeostasis, the specific cause of the hypertrophic response in this study is not clear. In rats, a common cause of thyroid follicular cell hypertrophy is an increase in the rate of hepatic thyroxine (T₄) glucuronidation and subsequent biliary excretion.⁽²¹⁾ An increased rate of T₄ excretion results in lower T₄ blood levels which triggers an increase in the release of pituitary-derived thyroid stimulating hormone (TSH), resulting in thyroid follicular cell hypertrophy. Many inducers of hepatic cytochrome P450 isoenzymes in the rat are known to secondarily cause thyroid follicular cell hypertrophy by this mechanism. In this study, the presence of test substance-related hepatocellular hypertrophy in the high-dose males demonstrates that hepatocellular enzyme systems have been induced and that T₄ excretion may have been secondarily increased. Due to differences in T₄ half-life, thyroglobulin binding, and the ease of UDP-glucuronyl-transferase induction, rats are much more susceptible than humans to secondary thyroid follicular cell hypertrophy.⁽²¹⁾

Male and female kidneys did not demonstrate any morphological change despite a 14% increase in mean relative (kidney/brain) kidney weights in the 1000 mg/kg/day male rats, as compared to the controls. Although tubular cell hypertrophy was not apparent, it is likely that the increase in kidney weight parameters in the high-dose males is indicative of a non-adverse, slight, pharmacological response by the kidney to xenobiotic exposure. Since an organ weight increase was not present following the one-month recovery period, the effect was reversible.

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

E. Anatomic Pathology Conclusions for the Subchronic Toxicity and Recovery Evaluations

Exposure to 1000 mg/kg/day of the test substance for approximately 90 days produced minimal to mild thyroid follicular cell hypertrophy in male and female rats, minimal centrilobular hepatocellular hypertrophy in male rats, and increased liver and kidney weights in male rats. Following a one-month recovery period, thyroid follicular cell hypertrophy and organ weight effects were decreased and hepatocellular hypertrophy was not present. Liver and kidney effects were indicative of a pharmacological response to a xenobiotic and were not considered to be biologically adverse. The thyroid effect, although mild and reversible, was regarded to be potentially adverse.

Under the conditions of this study, the NOEL for pathology for male and female rats was 100 mg/kg/day based on thyroid effects at the 1000 mg/kg/day dose level.

Reproductive Toxicity Evaluations

A. P₁ Rats - Clinical Observations and Mortality

1. P₁ Males (Table 52, Appendix P)

No test substance-related effects or statistically significant differences in the incidences of clinical observations were observed in males administered any dosage of the test substance. One male rat in the 1000 mg/kg/day group was found dead on test day 89. The death may be due to a gavage error, and was not considered to be test substance-related.

2. P₁ Females During Gestation (Tables 53, Appendices Q)

No test substance-related effects or statistically significant differences in the incidences of clinical observations were observed in females administered any dosage of the test substance during gestation. Mortality did not occur in female rats during gestation.

3. P₁ Females During Lactation (Tables 54, Appendices R)

No test substance-related effects or statistically significant differences in the incidences of clinical observations were observed in females administered any dosage of the test substance during lactation. One female in the 10 mg/kg/day group was found dead on lactation day 10.

B. P₁ Rats - Mean Body Weights and Body Weight Gains

1. P₁ Males
(Tables 55 and 56, Appendices S and T)

No test substance-related effects or statistically significant differences on body weight or weight gain were observed in males administered any dosage of the test substance during the reproductive portion of the study.

2. P₁ Females During Gestation
(Tables 57 and 58, Appendices U and V)

No test substance-related effects or statistically significant differences in body weight or weight gain were observed in females administered any dosage of the test substance during gestation.

3. P₁ Females During Lactation
(Tables 59 and 60, Appendices W and X)

No adverse test substance-related effects on body weight or weight gain were observed in females administered any dosage of the test substance during lactation. Females administered 1000 mg/kg/day had significantly increased weight gain during lactation days 0-7 and 0-21 compared to the control values. Variability in weight gain during lactation is common, and the increased weight gain was not considered to be test substance-related or adverse.

C. P₁ Rats - Food Consumption and Food Efficiency

- P₁ Females During Gestation
(Tables 61 and 62, Appendix Y)

No test substance-related effects or statistically significant differences in food consumption or food efficiency were observed in females administered any dosage of the test substance during gestation.

D. Reproductive Indices (Table 63, Appendices EE and FF)

No test substance-related effects or statistically significant differences in mating index, fertility index, gestation index, or gestation length were observed in P₁ males and females administered any dosage of the test substance.

E. Sperm Count, Morphology, and Motility (Table 64, Appendices Z-BB)

No test substance-related effects or statistically significant differences in sperm motility, morphology, or number were observed in parental males administered any dosage of the test substance.

F. Estrous Cycle (Table 65, Appendices CC and DD)

No test substance-related effects or statistically significant differences were observed on the percent of days in estrus, percent of days in diestrus, percent of days in proestrus, mean cycle length, or the mean number of days in the precoital interval in females administered any dosage of the test substance.

G. F₁ Offspring Data

1. Litter Size, Sex Ratio and Pup Survival (Table 66, Appendix GG)

No test substance-related effects or statistically significant differences were observed on the number of pups born, number of pups born alive, sex ratio, lactation index, or litter survival in offspring from any dosage group.

2. Clinical Observations in F₁ Pups (Table 67, Appendix HH)

No test substance-related effects or statistically significant differences in the incidence of clinical observations were observed in offspring from any dosage group.

3. Pup Weights (Table 68, Appendix II)

No test substance-related effects or statistically significant differences in body weight of pups during the lactation period were observed in offspring from any dosage group.

H. F₁ Rats - Clinical Observations and Mortality (Tables 69 and 70, Appendix JJ)

No test substance-related effects or statistically significant differences in the incidence of clinical observations were observed in F₁ male or female rats from any dosage group. Test substance-related mortality did not occur in F₁ male or female rats from any dosage group.

I. F₁ Rats - Mean Body Weights and Body Weight Gains
(Tables 71-74, Appendices KK and LL)

No test substance-related effects or statistically significant differences in body weights or weight gain were observed in F₁ male or female rats from any dosage group.

J. F₁ Rats - Food Consumption and Food Efficiency
(Tables 75-78, Appendix MM)

No test substance-related effects or statistically significant differences in food consumption or food efficiency were observed in F₁ male or female rats from any dosage group.

K. F₁ Rats - Developmental Landmarks
(Table 79, Appendix JJ)

No test substance-related effects or statistically significant differences in the development of preputial separation or vaginal patency were observed in F₁ male or female rats from any dosage group.

L. Reproductive Toxicity Conclusions

The no-observed-effect-level (NOEL) for reproductive parameters was 1000 mg/kg/day in parental males and females. In addition, no systemic toxicity was observed in parental males, parental females, or offspring from any dosage group.

**Anatomic Pathology Evaluation –
Rats Designated for Reproductive Evaluations**

A. Organ Weight Data

F₁ Adults
(Tables 80 and 81, Appendix NN)

There were no test substance-related effects on organ weights in the F₁ adults. Minimal differences in some weight parameter means in the high-dose (1000 mg/kg/day) male testes (increased relative to brain weight) and female livers (decreased absolute and relative to body weight and to brain weight) were statistically significant by the trend test. These differences were considered to be spurious and not test substance related.

B. Gross Observations

Parental P₁ Adults (Tables 82 and 83, Appendix OO)

F₁ Adults, Weanlings, and Pups (Tables 84 and 85, Appendices PP and QQ)

In P₁ adults, F₁ adults, F₁ weanlings, and F₁ pups, 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

1. Parental P₁ Adults

(Tables 86 and 87, Appendix OO)

In the P₁ adult generation, there were no test substance-related microscopic findings.

Microscopic examination of P₁ adults was limited to the reproductive tissues of the two found dead rats (see Mortality) and the three pairs of rats that did not produce litters (i.e., reproductive failures). The male and female rats that did not produce litters were in the 0 mg/kg/day group (Animal Nos. 665069 and 665289, respectively), 100 mg/kg/day group (Animal Nos. 665114 and 665298, respectively), and the 1000 mg/kg/day group (Animal Nos. 665133 and 665224, respectively).

2. F₁ Adults

In the F₁ adult generation, there was no histopathology conducted since there was no mortality.

D. Mortality

Parental P₁ Adults and F₁ Adults
(Appendices OO and PP)

In the P₁ adult generation, there were no test substance-related effects on mortality. Of 160 adult P₁ rats, one 1000 mg/kg/day male (Animal No. 665050) and one 10 mg/kg/day female (Animal No. 665248) were found dead. The causes of death were undetermined.

In the F₁ adult generation, there were no test substance-related effects on mortality. There were no deaths among the 152 adult F₁ rats.

E. Anatomical Pathology Conclusions for Reproductive Toxicity

For pathology, the NOEL was 1000 mg/kg/day (the highest dose level) for both male and female rats.

CONCLUSIONS

NOEL for Subchronic Toxicity: Under the conditions of this study, the no-observed-effect level (NOEL)^a for subchronic toxicity endpoints in male and female rats was 100 mg/kg/day. This level was based on reversible, minimal to mild thyroid follicular hypertrophy, observed in the 1000 mg/kg/day male and female groups. Other test substance-related effects observed in males and/or females dosed with 1000 mg/kg/day include mild alterations in clinical pathology parameters and in hepatic β -oxidation activity; however, these were not considered to be adverse. Most of the effects observed during the dosing period demonstrated full or partial reversal following one month of recovery. Thyroid follicular hypertrophy was still present at the end of the one-month recovery period; however, the incidence and mean severity level in males had decreased by this time.

NOEL for Reproductive Evaluations: Under the conditions of this study, the NOEL for reproductive evaluations was 1000 mg/kg/day, the highest dose tested. This was based on a lack of test substance-related effects on any reproductive parameter in P₁ or F₁ generation animals dosed up to 1000 mg/kg/day.

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⁽²²⁾ and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union.⁽²³⁾

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EXPLANATORY NOTES

Critical Dates

- Day 72 Last day data from the male and female rats designated for reproduction evaluations were reported with the subchronic toxicity animals. Body weights and clinical observations collected during the cohabitation and post-mating periods are reported in the Reproductive Toxicology section; Dose volumes administered during the cohabitation and post-mating periods are documented in study records.
- Day 90 Last day of test substance administration for male and female rats designated for one-month and three-month recovery periods.
- Day 91 • Last day of body weight and food consumption data collection for male and female rats designated for the subchronic toxicity evaluation.
• Last day of test substance administration for male rats designated for the subchronic toxicity evaluation.
- Day 92 • Male rats designated for the subchronic toxicity evaluation were sacrificed.
• Last day of test substance administration for female rats designated for the subchronic toxicity evaluation.
- Day 93 Female rats designated for the subchronic toxicity evaluation were sacrificed.
- Day 126 • Last day of body weight and food consumption data collection for rats designated for the one-month recovery period.
• Last day of food consumption data collection for rats designated for the three-month recovery period.
- Day 127 Male and female rats designated for the one-month recovery were sacrificed.
- Day 182 Male and female rats designated for blood fluorine level evaluation were sacrificed.

TABLES

EXPLANATORY NOTES

Abbreviations

mg/kg = mg/kg/day

g/anm/day = grams/animal/day

incide = incidence

Summary of Hematology Values

RBC - red blood cell count
HGB - hemoglobin
HCT - hematocrit
MCV - mean corpuscular volume
MCH - mean corpuscular hemoglobin
MCHC - mean corpuscular hemoglobin concentration
RDW - red cell distribution width
ARET - absolute reticulocyte count
PLT - platelet count
WBC - white blood cell count
ANEU - absolute neutrophil (all forms)
ALYM - absolute lymphocyte
AMON - absolute monocyte
AEOS - absolute eosinophil
ABAS - absolute basophil
ALUC - absolute large unstained cell
-- - no data

Summary of Coagulation Values

PT - prothrombin time
APTT - activated partial thromboplastin time
-- - no data

TABLES

EXPLANATORY NOTES

Abbreviations: (Continued)

Summary of Clinical 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
--	-	no data

Summary of Urinalysis Values

VOL	-	volume
UOSM	-	urine osmolality
pH	-	the logarithm of the reciprocal of the hydrogen ion concentration
URO	-	urobilinogen
UFLU	-	urine fluoride
UMTP	-	urine protein
--	-	no data

TABLES

EXPLANATORY NOTES

Notes:

Summary of Hematology Values

Summary of Coagulation Values

Summary of Clinical Chemistry Values

Summary of Urinalysis Values

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.

Reproduction Tables

Test Day 1 for F1 males and females = Postnatal Day 21

TABLE 1

SUMMARY OF DOSING SUSPENSION ANALYSIS

Sample Type	Dosing Concentrations and Stability of H-25425 (mg/mL)			
	Nominal:	2.00	20.0	200
<u>Homogeneity</u>				
Test day 2				
Top		1.36 ^a (68.0) ^b	19.0 ^a (95.0)	187 (93.5)
Middle		1.87 ^a (93.5)	20.8 ^a (104.0)	188 (94.0)
Bottom		2.00 ^a (100.0)	21.3 ^a (106.5)	191 (95.5)
Average Measured Conc. ^c		1.74	20.4	189
Average Percent Nominal ^c		(87.0)	(102.0)	(94.5)
Standard Deviation ^c		± 0.34	± 1.2	± 2.1
Coefficient of Variation ^c		19%	6%	1%
<u>Stability</u>				
5-hour Room Temperature				
		1.83 ^a (91.5)	21.7 ^a (108.5)	196 (98.0)
<u>Homogeneity</u>				
Test day 8				
Top		1.87 ^a (93.5)	--- ^d	--- ^d
Middle		1.97 ^a (98.5)	--- ^d	--- ^d
Bottom		1.91 ^a (95.5)	--- ^d	--- ^d
Average Measured Conc. ^c		1.92		
Average Percent Nominal ^c		(96.0)		
Standard Deviation ^c		± 0.05		
Coefficient of Variation ^c		2%		
<u>Concentration Verification^e</u>				
Test day 42				
		2.36 ^a (118.0)	20.7 ^a (103.5)	192 (96.0)
Test day 86				
		2.04 ^a (102.0)	20.7 ^a (103.5)	206 ^a (103.0)

^a All reported results corrected based on recovery of the spiked sample (refer to Table I).

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

^c The average measured concentration, average percent of nominal (in parentheses), standard deviation, and coefficient of variation of top, middle, and bottom.

^d Denotes samples not submitted (---)

^e Duplicate samples submitted. Mean result reported.

TABLE 2
MEAN DAILY DOSE VOLUMES FOR MALE RATS

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
DAY0-DAY6	1.2 0.1 (45)	1.2 0.1 (35)	1.2 0.1 (35)	1.2 0.1 (45)
DAY7-DAY13	1.5 0.1 (45)	1.5 0.1 (35)	1.5 0.1 (35)	1.4 0.1 (45)
DAY14-DAY20	1.7 0.1 (45)	1.7 0.1 (35)	1.7 0.1 (35)	1.7 0.1 (45)
DAY21-DAY27	1.9 0.1 (45)	1.9 0.2 (35)	1.9 0.2 (35)	1.9 0.1 (45)
DAY28-DAY34	2.1 0.1 (45)	2.0 0.2 (35)	2.1 0.2 (35)	2.0 0.1 (45)
DAY35-DAY41	2.2 0.2 (45)	2.1 0.2 (35)	2.2 0.2 (35)	2.2 0.1 (45)
DAY42-DAY48	2.3 0.2 (45)	2.3 0.2 (35)	2.3 0.2 (35)	2.3 0.2 (45)
DAY49-DAY55	2.5 0.2 (45)	2.4 0.2 (35)	2.4 0.2 (35)	2.4 0.2 (45)
DAY56-DAY62	2.6 0.2 (45)	2.5 0.2 (35)	2.5 0.2 (35)	2.5 0.2 (45)
DAY63-DAY69	2.6 0.2 (45)	2.6 0.2 (35)	2.6 0.2 (35)	2.6 0.2 (45)
DAY70-DAY72	2.7 0.2 (45)	2.6 0.2 (35)	2.6 0.3 (35)	2.6 0.2 (45)

TABLE 2 (CONTINUED)

MEAN DAILY DOSE VOLUMES FOR MALE RATS

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
DAY73 ^a - DAY76	2.8 0.2 (25)	2.7 0.3 (15)	2.8 0.3 (15)	2.6 0.2 (25)
DAY77 - DAY83	2.8 0.3 (25)	2.7 0.3 (15)	2.8 0.3 (15)	2.7 0.2 (25)
DAY84 - DAY88	2.9 0.3 (25)	2.7 0.3 (15)	2.9 0.3 (15)	2.7 0.2 (25)
DAY89	2.9 0.3 (25)	2.7 0.3 (15)	2.9 0.3 (15)	2.8 ^b 0.2 (25)
DAY90	2.9 0.3 (25)	2.7 0.3 (15)	2.9 0.3 (15)	2.7 0.2 (25)
DAY91	3.0 0.3 (10)	2.9 0.2 (10)	2.9 0.3 (10)	2.9 0.2 (10)

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

- a Rats designated for reproduction evaluation (20 rats/group) were transferred for reproductive assessment on test day 72; subsequent data are reported as part of the reproduction evaluation.
- b Includes rat inadvertently given an additional 0.4 mL dose.

TABLE 3
MEAN DAILY DOSE VOLUMES FOR FEMALE RATS

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
DAY0-DAY6	0.9 0.1 (45)	0.9 0.1 (35)	0.9 0.1 (35)	0.9 0.1 (45)
DAY7-DAY13	1.0 0.1 (45)	1.0 0.1 (35)	1.0 0.1 (35)	1.0 0.1 (45)
DAY14-DAY20	1.1 0.1 (45)	1.1 0.1 (35)	1.1 0.1 (35)	1.1 0.1 (45)
DAY21-DAY27	1.2 0.1 (45)	1.2 0.1 (35)	1.2 0.1 (35)	1.2 0.1 (45)
DAY28-DAY34	1.3 0.1 (45)	1.3 0.1 (35)	1.3 0.1 (35)	1.3 0.1 (45)
DAY35-DAY41	1.3 0.1 (45)	1.3 0.1 (35)	1.3 0.1 (35)	1.3 0.1 (45)
DAY42-DAY48	1.4 0.1 (45)	1.4 0.1 (35)	1.3 0.1 (35)	1.3 0.1 (45)
DAY49-DAY55	1.4 0.1 (45)	1.4 0.1 (35)	1.4 0.1 (35)	1.4 0.1 (45)
DAY56-DAY62	1.4 0.1 (45)	1.4 0.1 (35)	1.4 0.1 (35)	1.4 0.1 (45)
DAY63-DAY69	1.5 0.1 (45)	1.5 0.1 (35)	1.5 0.1 (35)	1.4 0.1 (45)
DAY70-DAY72	1.5 0.1 (45)	1.5 0.1 (35)	1.5 0.1 (35)	1.5 0.1 (45)

TABLE 3 (CONTINUED)

MEAN DAILY DOSE VOLUMES FOR FEMALE RATS

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
DAY73 ^a -DAY76	1.5 0.2 (25)	1.5 0.1 (15)	1.5 0.1 (15)	1.4 0.1 (25)
DAY77-DAY83	1.5 0.2 (25)	1.5 0.1 (15)	1.5 0.1 (15)	1.5 0.1 (25)
DAY84-DAY90	1.5 0.2 (25)	1.5 0.1 (15)	1.5 0.1 (15)	1.5 0.1 (25)
DAY91-DAY92	1.6 0.2 (10)	1.5 0.1 (10)	1.5 0.1 (10)	1.5 0.1 (10)

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

^a Rats designated for reproduction evaluation (20 rats/group) were transferred for reproductive assessment on test day 72; subsequent data are reported as part of the reproduction evaluation.

TABLE 4

MEAN BODY WEIGHTS OF MALE RATS (G)

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY0	240.1 14.3 (45)	238.3 12.6 (35)	239.6 13.1 (35)	241.2 13.1 (45)
DAY7	295.2 19.0 (45)	289.7 16.9 (35)	295.6 18.8 (35)	291.2 16.4 (45)
DAY14	342.8 23.0 (45)	330.8 22.9 (35)	335.6 23.6 (35)	334.5 20.6 (45)
DAY21	387.0 27.6 (45)	371.7 27.9 (35)	377.1 29.7 (35)	378.0 23.6 (45)
DAY28	421.0 31.6 (45)	407.5 32.0 (35)	412.2 33.6 (35)	407.1 27.1 (45)
DAY35	448.4 35.0 (45)	430.7 34.7 (35)	442.9 38.4 (35)	435.2 28.8 (45)
DAY42	469.5 36.3 (45)	452.2 35.3 (35)	461.0 39.7 (35)	456.6 30.6 (45)
DAY49	492.1 40.8 (45)	476.8 39.5 (35)	480.9 42.5 (35)	481.7 35.1 (45)
DAY56	511.7 43.4 (45)	491.8 39.5 (35)	498.3 44.6 (35)	495.5 37.2 (45)
DAY63	529.4 46.1 (45)	509.6 42.5 (35)	515.6 48.9 (35)	512.4 40.7 (45)

TABLE 4 (CONTINUED)

MEAN BODY WEIGHTS OF MALE RATS (g)

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
DAY70 ^a	544.5 48.5 (45)	526.1 44.7 (35)	527.1 54.7 (35)	527.4 43.1 (45)
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY77	563.0 52.2 (25)	538.7 57.9 (15)	560.0 58.8 (15)	537.8 42.3 (25)
DAY84	572.5 54.1 (25)	549.2 60.7 (15)	572.5 58.9 (15)	549.7 45.5 (25)
DAY91	578.9 56.7 (25)	553.8 61.8 (15)	578.0 62.1 (15)	559.0 47.3 (25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY98	576.2 47.4 (15)	512.7 63.5 (5)	602.2 73.8 (5)	555.2 52.1 (15)
DAY105	587.9 47.0 (15)	523.6 60.0 (5)	613.1 75.1 (5)	567.1 52.2 (15)
DAY112	594.4 49.0 (15)	530.0 61.6 (5)	617.3 89.8 (4)	568.8 52.3 (15)
DAY119	610.0 48.8 (15)	541.1 66.3 (5)	636.2 96.5 (4)	583.3 53.8 (15)
DAY126	607.8 48.9 (15)	542.9 68.5 (5)	639.6 99.0 (4)	584.3 56.8 (15)

TABLE 4 (CONTINUED)

MEAN BODY WEIGHTS OF MALE RATS (g)

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
Three-Month Recovery Period for Subchronic Toxicity Evaluation				
DAY133	639.4 33.6 (5)	562.8 73.9 (5)	663.2 100.2 (4)	568.0 46.5 (5)
DAY140	643.7 38.0 (5)	568.2 77.3 (5)	672.7 110.2 (4)	578.2 48.9 (5)
DAY147	649.2 37.4 (5)	571.7 78.3 (5)	676.5 111.4 (4)	581.9 52.0 (5)
DAY154	658.2 43.6 (5)	576.1 80.6 (5)	683.7 110.8 (4)	589.8 51.2 (5)
DAY161	670.3 44.6 (5)	585.1 82.9 (5)	696.7 117.2 (4)	602.8 53.2 (5)
DAY168	672.2 49.2 (5)	587.1 86.0 (5)	697.9 114.2 (4)	604.1 57.9 (5)
DAY175	685.0 50.4 (5)	597.1 89.8 (5)	713.6 115.6 (4)	617.2 59.8 (5)
DAY182	691.6 51.0 (5)	605.5 93.0 (5)	723.8 117.7 (4)	621.8 61.1 (5)

Data arranged as: Mean

Standard deviation (Number of animals included in calculation)

a Rats designated for reproduction evaluation (20 rats/group) were transferred for reproductive assessment on test day 72; subsequent data are reported as part of the reproduction evaluation.

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

TABLE 5

MEAN BODY WEIGHTS OF FEMALE RATS (g)

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY0	173.6 10.7 (45)	172.7 14.3 (35)	174.4 12.2 (35)	170.8 11.8 (45)
DAY7	194.3 14.0 (45)	194.9 17.6 (35)	195.6 14.3 (35)	193.4 14.4 (45)
DAY14	214.5 20.0 (45)	213.0 18.2 (35)	213.7 16.0 (35)	209.8 18.4 (45)
DAY21	236.6 19.6 (45)	236.4 21.4 (35)	234.2 18.1 (35)	232.0 20.0 (45)
DAY28	252.5 21.7 (45)	252.4 24.8 (35)	251.0 20.2 (35)	246.4 21.9 (45)
DAY35	260.9 22.7 (45)	260.7 26.1 (35)	259.5 20.7 (35)	256.3 25.0 (45)
DAY42	271.0 23.3 (45)	272.2 25.3 (35)	268.8 24.2 (35)	266.1 25.0 (45)
DAY49	281.7 25.6 (45)	279.9 27.6 (35)	279.1 24.3 (35)	275.9 27.6 (45)
DAY56	286.3 26.2 (45)	286.5 29.3 (35)	285.9 25.3 (35)	281.3 27.6 (45)
DAY63	291.2 26.4 (45)	291.4 28.1 (35)	291.0 26.0 (35)	286.8 28.2 (45)

TABLE 5 (CONTINUED)

MEAN BODY WEIGHTS OF FEMALE RATS (g)

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
DAY70 ^a	295.3 27.6 (45)	294.8 27.2 (35)	294.3 26.5 (35)	292.7 28.9 (45)
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY77	301.2 31.9 (25)	296.6 24.3 (15)	296.9 18.6 (15)	293.8 19.8 (25)
DAY84	306.4 32.5 (25)	303.0 22.0 (15)	303.3 20.0 (15)	297.0 21.5 (25)
DAY91	311.4 33.4 (25)	305.4 22.8 (15)	306.4 19.3 (15)	299.2 23.4 (25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY98	306.3 35.3 (15)	308.1 9.6 (5)	310.1 24.1 (5)	296.8 18.1 (15)
DAY105	317.1 39.8 (15)	317.5 15.4 (5)	322.6 19.6 (5)	307.4 19.4 (15)
DAY112	322.8 39.2 (15)	322.8 15.7 (5)	328.6 23.3 (5)	313.8 21.5 (15)
DAY119	327.9 44.1 (15)	325.2 16.5 (5)	330.2 24.6 (5)	314.1 20.7 (15)
DAY126	330.2 44.1 (15)	329.5 19.5 (5)	330.9 26.5 (5)	315.7 20.9 (15)

TABLE 5 (CONTINUED)

MEAN BODY WEIGHTS OF FEMALE RATS (g)

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
Three-Month Recovery Period for Subchronic Toxicity Evaluation				
DAY133	308.7 54.0 (5)	334.3 20.4 (5)	341.1 24.7 (5)	323.7 8.6 (5)
DAY140	316.0 55.0 (5)	339.9 16.5 (5)	350.8 29.0 (5)	330.0 8.6 (5)
DAY147	316.2 60.7 (5)	337.8 20.4 (5)	348.3 25.2 (5)	333.2 7.0 (5)
DAY154	316.8 61.8 (5)	342.3 19.6 (5)	352.4 25.2 (5)	335.7 5.9 (5)
DAY161	327.0 70.5 (5)	353.7 24.7 (5)	361.3 27.8 (5)	347.7 8.3 (5)
DAY168	323.2 65.5 (5)	350.1 24.9 (5)	357.9 25.4 (5)	349.3 7.6 (5)
DAY175	327.4 69.8 (5)	354.0 22.7 (5)	363.9 32.0 (5)	356.4 9.9 (5)
DAY182	331.4 67.0 (5)	360.1 23.1 (5)	368.1 27.7 (5)	360.7 11.0 (5)

Data arranged as: Mean

Standard deviation (Number of animals included in calculation)

a Rats designated for reproduction evaluation (20 rats/group) were transferred for reproductive assessment on test day 72; subsequent data are reported as part of the reproduction evaluation.

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

TABLE 6

MEAN BODY WEIGHT GAINS OF MALE RATS (g)

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
Dosing Period for Subchronic Toxicity and Reproduction Evaluations				
DAY0-DAY7	55.0 7.8 (45)	51.4 7.2 (35)	56.0 8.0 (35)	50.0# 6.1 (45)
DAY7-DAY14	47.6 7.2 (45)	41.1# 7.7 (35)	39.9# 7.5 (35)	43.3# 6.6 (45)
DAY14-DAY21	44.2 7.5 (45)	40.8 6.6 (35)	41.5 7.7 (35)	43.5 6.9 (45)
DAY21-DAY28	34.0 6.7 (45)	35.8 6.6 (35)	35.1 7.2 (35)	29.1# 6.1 (45)
DAY28-DAY35	27.5 7.0 (45)	23.3 5.5 (35)	30.6 7.6 (35)	28.1 5.5 (45)
DAY35-DAY42	21.0 7.3 (45)	21.5 6.9 (35)	18.1 6.4 (35)	21.4 6.8 (45)
DAY42-DAY49	22.6 6.9 (45)	24.5 6.9 (35)	20.0 6.7 (35)	25.1 7.7 (45)
DAY49-DAY56	19.7 6.7 (45)	15.0 10.2 (35)	17.3 7.5 (35)	13.8# 5.4 (45)
DAY56-DAY63	17.7 7.4 (45)	17.8 9.6 (35)	17.3 7.4 (35)	16.9 6.1 (45)

TABLE 6 (CONTINUED)

MEAN BODY WEIGHT GAINS OF MALE RATS (g)

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
DAY63-DAY70 ^a	15.1 6.6 (45)	16.4 5.4 (35)	11.5 13.1 (35)	15.1 6.1 (45)
DAY0-DAY70	304.4 41.5 (45)	287.8 37.0 (35)	287.5 46.8 (35)	286.2 35.7 (45)
Dosing Period for Subchronic Toxicity Evaluation (continued)				
DAY70-DAY77	12.7 6.5 (25)	8.3 20.5 (15)	6.7# 7.5 (15)	7.8# 5.6 (25)
DAY77-DAY84	9.4 6.0 (25)	10.6 12.3 (15)	12.5 6.3 (15)	11.9 7.4 (25)
DAY84-DAY91	6.4 6.2 (25)	4.5 9.8 (15)	5.5 6.8 (15)	9.3 7.7 (25)
DAY0-DAY91	335.6 48.1 (25)	314.3 52.7 (15)	335.7 52.5 (15)	316.2 39.5 (25)

TABLE 6 (CONTINUED)

MEAN BODY WEIGHT GAINS OF MALE RATS (g)

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY91-DAY98	11.5 5.5 (15)	6.0 5.2 (5)	1.4 11.5 (5)	8.3 7.0 (15)
DAY98-DAY105	11.6 7.2 (15)	10.9 8.9 (5)	10.9 4.1 (5)	12.0 6.5 (15)
DAY105-DAY112	6.6 7.1 (15)	6.5 5.8 (5)	5.7 6.6 (4)	1.6# 3.7 (15)
DAY112-DAY119	15.6 5.6 (15)	11.1 6.3 (5)	18.9 7.2 (4)	14.5 5.0 (15)
DAY119-DAY126	-2.2 4.1 (15)	1.7 6.2 (5)	3.3 2.6 (4)	1.0 5.5 (15)
DAY91-DAY126	43.0 8.4 (15)	36.2 16.8 (5)	43.6 20.4 (4)	37.5 13.9 (15)
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY126-DAY133	14.9 8.1 (5)	20.0 9.0 (5)	23.7 4.0 (4)	18.1 5.0 (5)
DAY133-DAY140	4.4 6.2 (5)	5.3 4.7 (5)	9.4 10.9 (4)	10.2 6.7 (5)

TABLE 6 (CONTINUED)

MEAN BODY WEIGHT GAINS OF MALE RATS (g)

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
Three-Month Recovery Period for Subchronic Toxicity Evaluation				
DAY140-DAY147	5.5 3.0 (5)	3.6 5.3 (5)	3.8 4.3 (4)	3.7 6.1 (5)
DAY147-DAY154	9.0 6.3 (5)	4.3 4.7 (5)	7.3 1.0 (4)	7.9 4.4 (5)
DAY154-DAY161	12.1 5.1 (5)	9.1 6.4 (5)	13.0 9.2 (4)	13.0 4.3 (5)
DAY161-DAY168	1.9 7.1 (5)	1.9 4.6 (5)	1.2 4.9 (4)	1.3 5.2 (5)
DAY168-DAY175	12.8 3.6 (5)	10.1 5.0 (5)	15.8 6.5 (4)	13.1 5.3 (5)
DAY175-DAY182	6.6 3.5 (5)	8.4 5.9 (5)	10.2 2.2 (4)	4.6 3.2 (5)
DAY91-DAY182	106.6 35.2 (5)	98.8 33.7 (5)	127.8 40.2 (4)	98.4 31.1 (5)

Data arranged as: Mean

Standard deviation (Number of animals included in calculation)

a Rats designated for reproduction evaluation (20 rats/group) were transferred for reproductive assessment on test day 72; subsequent data are reported as part of the reproduction evaluation.

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

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

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY0-DAY7	20.6 8.0 (45)	22.2 7.3 (35)	21.2 5.3 (35)	22.6 6.0 (45)
DAY7-DAY14	20.2 10.2 (45)	18.1 6.6 (35)	18.2 7.3 (35)	16.4 7.9 (45)
DAY14-DAY21	22.1 9.4 (45)	23.4 8.2 (35)	20.5 7.1 (35)	22.3 6.8 (45)
DAY21-DAY28	15.9 6.4 (45)	16.0 6.9 (35)	16.8 6.2 (35)	14.4 6.1 (45)
DAY28-DAY35	8.3 7.1 (45)	8.3 6.4 (35)	8.6 5.7 (35)	9.9 6.7 (45)
DAY35-DAY42	10.1 8.4 (45)	11.6 7.4 (35)	9.3 7.7 (35)	9.8 6.9 (45)
DAY42-DAY49	10.7 6.8 (45)	7.6 7.5 (35)	10.3 8.8 (35)	9.8 7.5 (45)
DAY49-DAY56	4.6 5.5 (45)	6.6 5.4 (35)	6.8 6.7 (35)	5.4 7.0 (45)
DAY56-DAY63	4.9 6.6 (45)	4.9 6.5 (35)	5.1 7.0 (35)	5.5 8.0 (45)

TABLE 7 (CONTINUED)

MEAN BODY WEIGHT GAINS OF FEMALE RATS (g)

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
DAY63-DAY70 ^a	4.2 7.4 (45)	3.4 7.5 (35)	3.4 6.5 (35)	5.9 7.8 (45)
DAY0-DAY70	121.7 21.6 (45)	122.1 18.5 (35)	120.0 18.8 (35)	121.9 20.4 (45)
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY70-DAY77	5.0 7.6 (25)	0.4 9.0 (15)	3.2 5.7 (15)	5.6 6.9 (25)
DAY77-DAY84	5.1 6.3 (25)	6.4 8.6 (15)	6.4 5.8 (15)	3.2 5.5 (25)
DAY84-DAY91	5.1 5.9 (25)	2.4 8.0 (15)	3.1 5.8 (15)	2.2 6.0 (25)
DAY0-DAY91	139.4 27.1 (25)	132.8 17.0 (15)	132.2 14.1 (15)	130.2 16.9 (25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY91-DAY98	1.9 7.9 (15)	5.7 5.7 (5)	1.7 4.4 (5)	5.7 6.6 (15)
DAY98-DAY105	10.8 10.0 (15)	9.4 8.0 (5)	12.4 8.8 (5)	10.6 6.5 (15)
DAY105-DAY112	5.7 5.1 (15)	5.4 1.8 (5)	6.0 9.3 (5)	6.3 8.4 (15)

TABLE 7 (CONTINUED)

MEAN BODY WEIGHT GAINS OF FEMALE RATS (g)

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
DAY112-DAY119	5.1 11.0 (15)	2.4 10.0 (5)	1.6 3.5 (5)	0.3 8.7 (15)
DAY119-DAY126	2.3 5.8 (15)	4.3 8.0 (5)	0.7 3.9 (5)	1.6 8.2 (15)
DAY91-DAY126	25.8 14.3 (15)	27.1 15.3 (5)	22.4 8.2 (5)	24.6 6.8 (15)
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY126-DAY133	4.9 5.8 (5)	4.8 4.9 (5)	10.2 5.7 (5)	4.1 8.7 (5)
DAY133-DAY140	7.4 7.8 (5)	5.5 8.0 (5)	9.7 6.9 (5)	6.2 3.2 (5)
DAY140-DAY147	0.2 6.1 (5)	-2.1 6.1 (5)	-2.6 5.3 (5)	3.2 9.9 (5)
DAY147-DAY154	0.6 7.1 (5)	4.5 7.8 (5)	4.1 4.9 (5)	2.5 5.0 (5)
DAY154 -DAY161	10.2 10.5 (5)	11.4 8.3 (5)	8.9 3.6 (5)	12.0 5.0 (5)
DAY161 -DAY168	-3.8 8.9 (5)	-3.6 2.2 (5)	-3.4 5.9 (5)	1.6 4.6 (5)

TABLE 7 (CONTINUED)

MEAN BODY WEIGHT GAINS OF FEMALE RATS (g)

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
DAY168 - DAY175	4.2 6.6 (5)	3.9 2.4 (5)	6.0 8.4 (5)	7.1 5.0 (5)
DAY175 - DAY182	4.0 4.2 (5)	6.1 6.3 (5)	4.2 6.2 (5)	4.3 5.5 (5)
DAY91 - DAY182	50.3 29.9 (5)	57.7 19.6 (5)	59.6 11.1 (5)	66.1 9.8 (5)

Data arranged as: Mean

Standard deviation (Number of animals included in calculation)

a Rats designated for reproduction evaluation (20 rats/group) were transferred for reproductive assessment on test day 72; subsequent data are reported as part of the reproduction evaluation.

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

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

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
Dosing Period for Subchronic Toxicity and Reproduction Evaluations				
DAY0-DAY7	26.9 2.0 (45)	26.8 1.9 (35)	27.0 2.3 (35)	26.1 1.9 (45)
DAY7-DAY14	28.2 2.0 (45)	27.3 2.5 (35)	27.3 2.7 (35)	27.3 2.1 (45)
DAY14-DAY21	29.5 2.3 (45)	28.8 2.4 (35)	28.7 2.8 (35)	28.7 2.4 (45)
DAY21-DAY28	29.5 2.4 (45)	29.6 2.6 (35)	29.2 2.9 (35)	28.7 2.1 (45)
DAY28-DAY35	29.6 2.4 (45)	29.1 2.6 (35)	29.3 3.1 (35)	28.6 2.2 (45)
DAY35-DAY42	28.6 2.5 (45)	28.1 2.2 (35)	28.2 2.7 (35)	28.5 2.3 (45)
DAY42-DAY49	29.5 2.8 (45)	29.5 3.2 (35)	28.5 3.1 (35)	29.8 2.8 (45)
DAY49-DAY56	29.6 2.6 (45)	28.9 3.0 (35)	28.4 3.2 (35)	28.5 2.5 (45)
DAY56-DAY63	29.9 2.7 (45)	29.8 2.7 (35)	28.7 3.0 (35)	29.0 2.7 (45)
DAY63-DAY70 ^a	28.9 2.9 (45)	29.3 2.9 (35)	28.3 4.0 (35)	29.0 2.8 (45)

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

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
DAY0-DAY70	20.5 1.6(45)	20.4 1.7(35)	20.4 1.9(35)	20.2 1.7(45)
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY70-DAY77	29.4 2.9(25)	28.2 5.7(15)	28.4 3.4(14)	27.8 3.0(25)
DAY77-DAY84	28.1 2.9(25)	29.0 3.5(15)	28.5 2.9(15)	27.6 2.9(25)
DAY84-DAY91	27.4 3.1(25)	27.6 4.2(15)	27.0 2.9(15)	27.4 2.8(25)
DAY0-DAY91	29.0 2.1(25)	28.8 3.0(15)	28.7 2.7(14)	28.2 2.1(25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY91 -DAY98	28.0 2.5(10)	. (0)	. (0)	28.6 2.6(10)
DAY98 -DAY105	28.4 3.0(10)	. (0)	. (0)	29.3 1.1(10)
DAY105-DAY112	29.7 3.0(10)	. (0)	. (0)	29.4 2.9(10)
DAY112-DAY119	29.9 2.6(10)	. (0)	. (0)	29.4 2.9(10)

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

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
DAY119-DAY126	29.3 2.9 (10)	: (0)	: (0)	29.9 2.9 (10)
DAY91-DAY126	29.0 2.6 (10)	: (0)	: (0)	29.3 2.4 (10)

Data arranged as: Mean

Standard deviation (Number of animals included in calculation)

a Rats designated for reproduction evaluation (20 rats/group) were transferred for reproductive assessment on test day 72; food consumption data were not collected during the cohabitation and postmating periods.

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

TABLE 9

MEAN DAILY FOOD CONSUMPTION BY FEMALE RATS (g/day)

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY0-DAY7	18.8 1.7(45)	18.5 1.6(35)	19.2 1.6(35)	19.1 1.5(45)
DAY7-DAY14	20.1 1.8(45)	20.3 1.8(35)	20.2 2.1(35)	19.7 1.7(45)
DAY14-DAY21	21.1 2.1(45)	20.4 2.2(35)	20.8 3.2(35)	20.3 2.0(45)
DAY21-DAY28	21.6 2.3(45)	21.4 2.0(35)	20.7 2.1(35)	20.4# 1.9(45)
DAY28-DAY35	21.2 2.0(45)	21.1 2.9(35)	20.7 1.9(35)	20.4# 2.1(45)
DAY35-DAY42	20.5 1.8(45)	20.9 2.0(35)	20.5 2.4(35)	20.4 2.1(45)
DAY42-DAY49	21.2 2.1(45)	20.9 2.3(35)	21.4 2.1(35)	20.7 2.3(45)
DAY49-DAY56	20.2 2.1(45)	20.3 1.9(35)	19.8 2.4(35)	20.0 1.9(45)
DAY56-DAY63	20.7 1.8(45)	20.4 2.2(35)	20.1 2.0(35)	20.2 1.9(45)
DAY63-DAY70 ^a	20.0 1.8(45)	19.8 1.7(35)	20.6 3.6(35)	20.5 2.0(45)

TABLE 9 (CONTINUED)

MEAN DAILY FOOD CONSUMPTION BY FEMALE RATS (g/day)

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
DAY0-DAY70	20.5 1.6 (45)	20.4 1.7 (35)	20.4 1.9 (35)	20.2 1.7 (45)
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY70-DAY77	20.5 2.1 (25)	20.7 1.5 (15)	20.4 1.6 (15)	19.9 1.3 (25)
DAY77-DAY84	19.7 2.0 (25)	20.4 1.5 (15)	20.1 2.0 (15)	20.2 1.7 (25)
DAY84-DAY91	19.7 2.1 (25)	19.4 1.6 (15)	18.1# 1.1 (15)	18.7# 1.6 (25)
DAY0-DAY91	20.5 1.7 (25)	20.2 1.0 (15)	20.2 1.4 (15)	19.9 1.1 (25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY91-DAY98	20.5 1.8 (10)	. (0)	. (0)	19.7 1.5 (10)
DAY98-DAY105	21.9 2.9 (10)	. (0)	. (0)	20.6 1.7 (10)
DAY105-DAY112	21.9 2.6 (10)	. (0)	. (0)	21.2 2.3 (10)
DAY112-DAY119	22.1 3.0 (10)	. (0)	. (0)	19.4# 2.2 (10)

TABLE 9 (CONTINUED)

MEAN DAILY FOOD CONSUMPTION BY FEMALE RATS (g/day)

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
DAY119-DAY126	22.2 2.5 (10)	: (0)	: (0)	20.8 2.2 (10)
DAY91-DAY126	21.7 2.3 (10)	: (0)	: (0)	20.3 1.6 (10)

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

a Rats designated for reproduction evaluation (20 rats/group) were transferred for reproductive assessment on test day 72; data were not collected during the cohabitation period. Food consumption data collected during gestation are reported as part of the reproduction evaluation.

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

TABLE 10

MEAN DAILY FOOD EFFICIENCY OF MALE RATS

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY0-DAY7	0.292 0.028 (45)	0.274 0.031 (35)	0.296 0.030 (35)	0.273# 0.024 (45)
DAY7-DAY14	0.241 0.028 (45)	0.214# 0.029 (35)	0.208# 0.029 (35)	0.226# 0.024 (45)
DAY14-DAY21	0.213 0.026 (45)	0.202 0.025 (35)	0.207 0.028 (35)	0.216 0.027 (45)
DAY21-DAY28	0.164 0.025 (45)	0.173 0.026 (35)	0.171 0.026 (35)	0.144# 0.024 (45)
DAY28-DAY35	0.132 0.029 (45)	0.114 0.023 (35)	0.148# 0.026 (35)	0.140# 0.025 (45)
DAY35-DAY42	0.104 0.032 (45)	0.109 0.032 (35)	0.091 0.029 (35)	0.106 0.029 (45)
DAY42-DAY49	0.108 0.026 (45)	0.118 0.026 (35)	0.099 0.029 (35)	0.119 0.031 (45)
DAY49-DAY56	0.094 0.030 (45)	0.073 0.049 (35)	0.086 0.034 (35)	0.069# 0.025 (45)
DAY56-DAY63	0.084 0.031 (45)	0.084 0.038 (35)	0.084 0.034 (35)	0.082 0.026 (45)
DAY63-DAY70 ^a	0.074 0.032 (45)	0.079 0.023 (35)	0.050 0.100 (35)	0.073 0.029 (45)

TABLE 10 (CONTINUED)
MEAN DAILY FOOD EFFICIENCY OF MALE RATS

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
DAY0-DAY70	0.149 0.012 (45)	0.143 0.010 (35)	0.144 0.014 (35)	0.143 0.011 (45)
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY70-DAY77	0.060 0.029 (25)	0.012 0.201 (15)	0.032# 0.046 (14)	0.039# 0.027 (25)
DAY77-DAY84	0.047 0.029 (25)	0.050 0.057 (15)	0.063 0.031 (15)	0.060 0.036 (25)
DAY84-DAY91	0.032 0.030 (25)	0.020 0.060 (15)	0.028 0.032 (15)	0.046 0.040 (25)
DAY0-DAY91	0.127 0.011 (25)	0.119 0.011 (15)	0.125 0.009 (14)	0.123 0.008 (25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY91-DAY98	0.060 0.026 (10)	· (0)	· (0)	0.057 0.026 (10)
DAY98-DAY105	0.062 0.038 (10)	· (0)	· (0)	0.065 0.025 (10)
DAY105-DAY112	0.029 0.040 (10)	· (0)	· (0)	0.008 0.020 (10)
DAY112-DAY119	0.079 0.019 (10)	· (0)	· (0)	0.071 0.024 (10)

TABLE 10 (CONTINUED)
MEAN DAILY FOOD EFFICIENCY OF MALE RATS

Group: Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
DAY119-DAY126	-0.012 0.016 (10)	. (0)	. (0)	0.007# 0.029 (10)
DAY91-DAY126	0.044 0.004 (10)	. (0)	. (0)	0.042 0.010 (10)

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

a Rats designated for reproduction evaluation (20 rats/group) were transferred for reproductive assessment on test day 72; food consumption data were not collected during the cohabitation and postmating periods.

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

TABLE II
MEAN DAILY FOOD EFFICIENCY OF FEMALE RATS

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
<u>Dosing Period for Subchronic Toxicity and Reproduction Evaluations</u>				
DAY0-DAY7	0.155 0.053 (45)	0.169 0.052 (35)	0.158 0.036 (35)	0.168 0.041 (45)
DAY7-DAY14	0.143 0.075 (45)	0.127 0.044 (35)	0.127 0.045 (35)	0.116 0.053 (45)
DAY14-DAY21	0.150 0.059 (45)	0.162 0.048 (35)	0.140 0.047 (35)	0.156 0.041 (45)
DAY21-DAY28	0.105 0.042 (45)	0.105 0.042 (35)	0.115 0.038 (35)	0.099 0.038 (45)
DAY28-DAY35	0.055 0.046 (45)	0.055 0.042 (35)	0.058 0.037 (35)	0.068 0.043 (45)
DAY35-DAY42	0.069 0.057 (45)	0.078 0.049 (35)	0.061 0.048 (35)	0.068 0.046 (45)
DAY42-DAY49	0.071 0.044 (45)	0.050 0.047 (35)	0.068 0.057 (35)	0.065 0.049 (45)
DAY49-DAY56	0.032 0.036 (45)	0.046 0.038 (35)	0.048 0.046 (35)	0.038 0.049 (45)
DAY56-DAY63	0.032 0.044 (45)	0.035 0.048 (35)	0.034 0.054 (35)	0.038 0.055 (45)
DAY63-DAY70 ^a	0.028 0.051 (45)	0.023 0.053 (35)	0.023 0.047 (35)	0.039 0.052 (45)

TABLE 11 (CONTINUED)

MEAN DAILY FOOD EFFICIENCY OF FEMALE RATS

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
DAY0-DAY70	0.084 0.011 (45)	0.085 0.009 (35)	0.084 0.009 (35)	0.086 0.009 (45)
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>				
DAY70-DAY77	0.034 0.052 (25)	0.002 0.060 (15)	0.023 0.039 (15)	0.039 0.049 (25)
DAY77-DAY84	0.037 0.045 (25)	0.043 0.058 (15)	0.044 0.038 (15)	0.021 0.038 (25)
DAY84-DAY91	0.036 0.041 (25)	0.018 0.061 (15)	0.024 0.047 (15)	0.016 0.047 (25)
DAY0-DAY91	0.074 0.010 (25)	0.072 0.007 (15)	0.072 0.006 (15)	0.072 0.007 (25)
<u>One-Month Recovery Period for Subchronic Toxicity Evaluation</u>				
DAY91-DAY98	0.014 0.057 (10)	· (0)	· (0)	0.064# 0.031 (10)
DAY98-DAY105	0.068 0.054 (10)	· (0)	· (0)	0.059 0.028 (10)
DAY105-DAY112	0.026 0.032 (10)	· (0)	· (0)	0.036 0.057 (10)
DAY112-DAY119	0.046 0.069 (10)	· (0)	· (0)	0.001 0.079 (10)

TABLE 11 (CONTINUED)
MEAN DAILY FOOD EFFICIENCY OF FEMALE RATS

Group: Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
DAY119-DAY126	0.014 0.034 (10)	: (0)	: (0)	-0.000 0.058 (10)
DAY91-DAY126	0.035 0.015 (10)	: (0)	: (0)	0.034 0.009 (10)

Data arranged as: Mean

Standard deviation (Number of animals included in calculation)

a Rats designated for reproduction evaluation (20 rats/group) were transferred for reproductive assessment on test day 72; data were not collected during the cohabitation period. Food consumption data collected during gestation are reported as part of the reproduction evaluation.

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

TABLE 12

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group		I	III	V	VII
Dosage (mg/kg/day)		0	10	100	1000
Animal Count		45	35	35	45
Eye Observations					
Corneal Opacity					
Right					
Incidence		0	1	0	0
Mean onset (Days)			168		
Enophthalmus					
Left					
Incidence		0	1	0	0
Mean onset (Days)			56		
Wet Fur					
Incidence		0	0	1	0
Mean onset (Days)				63	
General Teeth Observations					
Clipped					
Incidence		0	1	0	0
Mean onset (Days)			77		
Diarrhea					
Brown					
Incidence		0	1	0	0
Mean onset (Days)			77		
Discharge					
Eye					
Incidence		1	2	3	0
Mean onset (Days)		140	102	137	
Nose					
Incidence		0	3	0	0
Mean onset (Days)			75		

TABLE 12 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group Dosage (mg/kg/day) Animal Count	I 0 45	III 10 35	V 100 35	VII 1000 45
Mouth Red				
Incidence Mean onset (Days)	0	0	1 63	0
Hair Loss				
Incidence Mean onset (Days)	5 61	11 26	4 24	8 44
Wound Superficial				
Incidence Mean onset (Days)	0	1 42	0	1 28
Hyperreactive				
Incidence Mean onset (Days)	1 77	1 84	0	1 105
Aggressive Behavior				
Incidence Mean onset (Days)	0	0	0	1 105
Missshapen Observations Tail				
Incidence Mean onset (Days)	1 7	0	0	0

TABLE 12 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group Dosage (mg/kg/day) Animal Count	I 0 45	III 10 35	V 100 35	VII 1000 45
Stain Fur/Skin				
Incidence	0	2	2	1
Mean onset (Days)		112	56	105
Swollen Observations Face				
Incidence	0	1	0	0
Mean onset (Days)		8		

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.

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

TABLE 13

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II	IV	VI	VIII
Dosage (mg/kg/day)	0	10	100	1000
Animal Count	45	35	35	45
Mass Side				
Left				
Mass #1				
Not Ulcerated				
Incidence	0	0	0	1
Mean onset (Days)				91
Eye Observations				
Dark				
Right				
Incidence	0	0	0	1
Mean onset (Days)				77
Corneal Opacity				
Right				
Incidence	0	0	1	1
Mean onset (Days)			147	119
Enophthalmus				
Right				
Incidence	0	0	1	1
Mean onset (Days)			147	154
Discharge				
Eye				
Incidence	4	1	1	1
Mean onset (Days)	105	21	126	126
Hair Loss				
Incidence	6	12	9	9
Mean onset (Days)	63	32	44	68

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

Treatment Group Dosage (mg/kg/day) Animal Count	II 0 45	IV 10 35	VI 100 35	VIII 1000 45
Wound				
Superficial				
Incidence	0	0	2	0
Mean onset (Days)			21	
Arches back during handling				
Incidence	4	2	1	2
Mean onset (Days)	70	70	49	56
Ear twitch				
Bilateral				
Incidence	2	3	1	4
Mean onset (Days)	105	49	49	39
Hyperreactive				
Incidence	1	1	0	0
Mean onset (Days)	77	63		
Hyperactive				
Incidence	1	2	0	2
Mean onset (Days)	14	84		49
Stain Fur/Skin				
Incidence	3	3	4	5
Mean onset (Days)	107	102	99	108

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.

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

TABLE 14

SUMMARY OF OPHTHALMOLOGICAL OBSERVATIONS FOR MALE RATS

Treatment Group Dosage (mg/kg/day)	I 0	III 10	V 100	VII 1000
Examination Day : Test Day 87				
Number of Rats Examined	20	10	10	20
Retina				
Retinal Degeneration, Focal Right				
Incidence	1 (5%)	0	0	0

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

TABLE 15

SUMMARY OF OPHTHALMOLOGICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group Dosage (mg/kg/day)	II 0	IV 10	VI 100	VIII 1000
Examination Day : Test Day 87				
Number of Rats Examined	20	10	10	20
Retina				
Retinal Degeneration, Focal Left				
Incidence	1 (5%)	0	0	0

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

TABLE 16

PERCENT SURVIVAL OF MALE RATS

DAYS ON TEST	Group I 0 mg/kg/day	Group III 10 mg/kg/day	Group V 100 mg/kg/day	Group VII 1000 mg/kg/day
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
84	100	100	100	100
91 ^{b,c}	100	100	100	100
98	100	100	100	100
105	100	100	100	100
112	100	100	80 ^d	100
119	100	100	80	100
126	100	100	80	100
Number at study start	45	35	35	45
Found dead	0	0	1	0
Removed from study ^a	20	20	20	20
Sacrificed by design ^c	10	10	10	10
Alive on test day 126	15	5	4	15

Percent Survival = (Number of Rats Alive/Number of Rats at Risk)*100

Number of rats at risk = Number at study start - number removed from study - number sacrificed by design

- a Rats designated for reproduction evaluation (20 rats/group) were transferred for reproductive assessment on test day 72.
- b Recovery period began on test day 91.
- c Rats designated for the subchronic toxicity evaluation were sacrificed on test day 92.
- d Rat found dead during previous week.

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

Note: Rats designated for evaluation of 10-day hepatic biochemical evaluations are not included in this table.

TABLE 17

PERCENT SURVIVAL OF FEMALE RATS

DAYS ON TEST	Group II 0 mg/kg/day	Group IV 10 mg/kg/day	Group VI 100 mg/kg/day	Group VIII 1000 mg/kg/day
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
84	100	100	100	100
91 ^{b,c}	100	100	100	100
98	100	100	100	100
105	100	100	100	100
112	100	100	100	100
119	100	100	100	100
126	100	100	100	100
Number at study start	45	35	35	45
Removed from study ^a	20	20	20	20
Sacrificed by design ^c	10	10	10	10
Alive on test day 126	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 removed from study - number sacrificed by design

a Rats designated for reproduction evaluation (20 rats/group) were transferred for reproductive assessment on test day 72.

b Recovery period began on test day 91.

c Rats designated for the subchronic toxicity evaluation were sacrificed on test day 93.

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

Note: Rats designated for evaluation of 10-day hepatic biochemical evaluations are not included in this table.

TABLE 18

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

Assessment Period	Group	Dosage (mg/kg/day)	Forelimb Grip Strength (kg)	Hindlimb Grip Strength (kg)
<u>Baseline</u>				
	I	0	0.61 (0.07)	0.38 (0.07)
	III	10	0.62 (0.07)	0.38 (0.05)
	V	100	0.64 (0.09)	0.33 (0.07)
	VII	1000	0.56 (0.08)	0.37 (0.06)
<u>Week 13</u>				
	I	0	1.54 (0.33)	0.74 (0.08)
	III	10	1.64 (0.36)	0.81 (0.15)
	V	100	1.54 (0.40)	0.75 (0.17)
	VII	1000	1.49 (0.14)	0.71 (0.09)
<u>Recovery</u>				
	I	0	1.64 (0.35)	0.68 (0.14)
	VII	1000	1.40 (0.40)	0.62 (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	0.46 (0.08)	0.35 (0.03)
	IV	10	0.47 (0.05)	0.34 (0.06)
	VI	100	0.47 (0.15)	0.32 (0.06)
	VIII	1000	0.49 (0.07)	0.34 (0.08)
<u>Week 13</u>				
	II	0	1.18 (0.28)	0.65 (0.08)
	IV	10	0.99 (0.21)	0.65 (0.10)
	VI	100	1.24 (0.31)	0.61 (0.09)
	VIII	1000	1.16 (0.31)	0.63 (0.10)
<u>Recovery</u>				
	II	0	0.97 (0.29)	0.63 (0.09)
	VIII	1000	1.06 (0.37)	0.61 (0.14)

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 $p < 0.05$ by Dunnett's test.

TABLE 20
SUMMARY OF SENSORY MOTOR FUNCTION PARAMETERS
FOR MALE RATS

	BASELINE				13-WEEK				Recovery	
Group:	I	III	V	VII	I	III	V	VII	I	VII
Dosage (mg/kg/day):	0	10	100	1000	0	10	100	1000	0	1000
Number examined:	10	10	10	10	10	10	10	10	10	10
<u>MANIPULATIONS:</u>										
<u>APPROACH & TOUCH:</u>										
no reaction	0	0	0	0	0	0	0	0	0	0
normal	10	10	10	10	10	10	10	10	10	10
increased reaction (jumps away or attacks)	0	0	0	0	0	0	0	0	0	0
<u>AUDITORY STIMULUS:</u>										
no reaction	0	0	0	0	0	0	0	0	0	0
normal reaction (rat flinches or flicks ear)	10	10	10	10	10	10	10	10	10	10
exaggerated reaction (rat jumps, flips)	0	0	0	0	0	0	0	0	0	0
<u>TAIL PINCH:</u>										
no response	0	0	0	0	0	0	0	0	1	2
normal (turns toward site)	10	10	10	10	10	9	10	10	9	8
exaggerated response (vocalizations, rapid turning)	0	0	0	0	0	1	0	0	0	0
<u>IN MOTOR ACTIVITY MONITOR:</u>										
<u>PUPILLARY RESPONSE</u>										
present	10	10	10	10	10	10	10	10	10	10
absent	0	0	0	0	0	0	0	0	0	0
<u>DEFECATION</u>										
absent	5	6	4	2	6	5	3	6	5	4
present	5	4	6	8	4	5	7	4	5	6
diarrhea	0	0	0	0	0	0	0	0	0	0
<u>URINATION:</u>										
absent	4	2	1	5	1	0	1	1	3	2
present	6	8	9	5	9	10	9	9	7	8
<u>ADDITIONAL OBSERVATIONS NOTED</u>										
<u>VOCALIZATION WHEN HANDLED</u>										
absent	10	10	10	10	10	10	10	10	9	10
present	0	0	0	0	0	0	0	0	1	0

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

TABLE 21

SUMMARY OF SENSORY MOTOR FUNCTION PARAMETERS
FOR FEMALE RATS

	BASELINE				13-WEEK				Recovery	
Group:	II	IV	VI	VIII	II	IV	VI	VIII	II	VIII
Dosage (mg/kg/day):	0	10	100	1000	0	10	100	1000	0	1000
Number examined:	10	10	10	10	10	10	10	10	10	10
<u>MANIPULATIONS:</u>										
<u>APPROACH & TOUCH:</u>										
no reaction	0	0	0	0	0	0	0	0	0	0
normal	10	10	10	10	10	10	10	10	10	10
increased reaction (jumps away or attacks)	0	0	0	0	0	0	0	0	0	0
<u>AUDITORY STIMULUS:</u>										
no reaction	0	0	0	0	0	0	0	0	0	0
normal reaction (rat flinches or flicks ear)	10	10	10	10	9	10	9	10	10	9
exaggerated reaction (rat jumps, flips)	0	0	0	0	1	0	1	0	0	1
<u>TAIL PINCH:</u>										
no response	0	0	0	0	0	0	0	0	0	0
normal (turns toward site)	10	10	10	10	10	10	10	10	10	9
exaggerated response (vocalizations, rapid turning)	0	0	0	0	0	0	0	0	0	1
<u>IN MOTOR ACTIVITY MONITOR:</u>										
<u>PUPILLARY RESPONSE</u>										
present	10	10	10	10	10	10	10	10	10	10
absent	0	0	0	0	0	0	0	0	0	0
<u>DEFECATION</u>										
absent	2	5	4	3	5	4	2	2	4	4
present	8	5	6	7	5	6	8	8	6	6
diarrhea	0	0	0	0	0	0	0	0	0	0
<u>URINATION:</u>										
absent	2	4	2	5	1	0	1	1	4	3
present	8	6	8	5	9	10	9	9	6	7
<u>ADDITIONAL OBSERVATIONS NOTED</u>										
<u>CIRCLING - CLOCKWISE</u>										
absent	10	10	10	10	10	10	10	9	10	9
present	0	0	0	0	0	0	0	1	0	1
<u>MASS - SUBCUTANEOUS, LEFT SIDE</u>										
absent	10	10	10	10	10	10	10	10	10	9
present	0	0	0	0	0	0	0	0	0	1

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

TABLE 22

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

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						TOTAL
			1	2	3	4	5	6	
<u>BASELINE</u>	I	0	391(30)	257(48)	137(97)	36(51)	10(14)	5(7)	836(144)
	III	10	426(40)	301(87)	168(114)	109(116)	39(69)	27(71)	1070(363)
	V	100	404(49)	296(91)	197(120)	95(112)	52(112)	8(7)	1053(410)
	VII	1000	420(18)	312(58)	194(114)	100(99)	41(84)	17(40)	1084(283)
<u>13-WEEK</u>	I	0	387(36)	313(54)	235(56)	266(65)	212(72)	114(78)	1526(223)
	III	10	417(45)	346(52)	292(65)	272(72)	186(62)	173(91)	1685(299)
	V	100	387(59)	284(71)	272(68)	249(83)	235(68)	202(104)	1630(362)
	VII	1000	420(41)	359(69)	321(55)	296(43)	245(33)	215(88) *	1854(233)
<u>RECOVERY</u>	I	0	377(73)	262(68)	226(48)	233(66)	170(65)	174(49)	1442(275)
	VII	1000	415(77)	321(68)	259(70)	236(87)	175(124)	139(95)	1545(366)

Data arranged as: Mean (Standard Deviation).

N=10

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 Interval data and Total data.

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

TABLE 23
MOTOR ACTIVITY ASSESSMENT:
MEAN DURATION OF MOVEMENT FOR FEMALE RATS (sec)

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
<u>BASELINE</u>	II	0	1	2	3	4	5	6	TOTAL
			392(30)	283(82)	216(116)	191(146)	133(88)	129(137)	1343(442)
	IV	10	405(37)	239(102)	158(122)	125(106)	130(109)	79(82)	1137(446)
	VI	100	404(37)	279(66)	196(88)	169(125)	102(107)	69(97)	1218(302)
	VIII	1000	380(52)	307(63)	203(85)	232(107)	133(102)	106(101)	1361(336)
<u>13-WEEK</u>	II	0	436(41)	353(51)	265(95)	247(86)	220(98)	211(114)	1733(341)
	IV	10	430(41)	350(53)	237(128)	249(112)	254(80)	234(133)	1755(446)
	VI	100	438(41)	364(42)	283(44)	280(65)	238(88)	234(46)	1836(249)
	VIII	1000	434(43)	372(74)	274(104)	263(112)	264(94)	208(103)	1815(418)
<u>RECOVERY</u>	II	0	346(72)	259(67)	218(72)	228(80)	207(55)	136(91)	1395(377)
	VIII	1000	354(62)	235(77)	213(65)	214(93)	164(72)	156(78)	1337(344)

Data arranged as: Mean (Standard Deviation).

N=10

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 Interval data and Total data. There were no statistically significant differences from control at $p < 0.05$.

MOTOR ACTIVITY ASSESSMENT: MEAN NUMBER OF MOVEMENTS FOR MALE RATS

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS					
			1	2	3	4	5	6 TOTAL
<u>BASELINE</u>	I	0	134(11)	138(14)	89(54)	34(45)	13(17)	4(3) 413(93)
	III	10	127(19)	134(25)	98(54)	71(66)	35(47)	20(42) 485(189)
	V	100	130(15)	134(15)	106(55)	64(60)	30(49)	10(9) 473(140)
	VII	1000	126(10)	139(26)	107(58)	62(54)	26(45)	17(35) 477(162)
<u>13-WEEK</u>	I	0	141(17)	143(16)	126(36)	133(30)	122(32)	79(47) 744(136)
	III	10	130(17)	147(8)	138(21)	135(12)	107(22)	99(35) 756(73)
	V	100	132(20)	134(12)	134(19)	134(20)	126(20)	111(27) 772(48)
	VII	1000	133(13)	144(18)	141(16)	134(18)	125(20)	115(35)* 792(92)
<u>RECOVERY</u>	I	0	134(25)	129(27)	120(28)	122(31)	100(45)	103(26) 709(146)
	VII	1000	130(23)	137(17)	117(18)	110(31)	92(54)	81(46) 667(118)

Data arranged as: Mean (Standard Deviation).

$$N=10$$

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

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

TABLE 25

MOTOR ACTIVITY ASSESSMENT:
MEAN NUMBER OF MOVEMENTS FOR FEMALE RATS

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS					
			1	2	3	4	5	6
<u>BASELINE</u>								
	II	0	135(22)	141(31)	111(50)	100(63)	89(55)	76(64)
	IV	10	128(14)	121(35)	101(67)	91(69)	78(65)	61(53)
	VI	100	133(20)	134(29)	119(51)	98(63)	66(61)	45(48)
	VIII	1000	136(17)	143(13)	122(40)	118(45)	78(53)	69(59)
								<u>TOTAL</u>
								652(210)
								580(231)
								595(195)
								666(144)
<u>13-WEEK</u>								
	II	0	127(18)	140(20)	129(34)	127(35)	128(41)	122(42)
	IV	10	134(19)	151(20)	115(38)	121(46)	129(31)	118(46)
	VI	100	129(23)	146(21)	139(18)	135(26)	123(37)	126(18)
	VIII	1000	130(21)	145(14)	136(21)	130(27)	135(33)	119(37)
								773(152)
								768(140)
								799(109)
								794(77)
<u>RECOVERY</u>								
	II	0	151(18)	141(14)	132(21)	140(25)	131(16)	87(45)
	VIII	1000	146(16)	137(18)	130(27)	125(42)	115(36)	106(40)
								782(73)
								759(108)

Data arranged as: Mean (Standard Deviation).

N=10

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

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

TABLE 26

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
RBC ($\times 10^6/\mu\text{L}$)				
DAY 37	7.82 0.18(10)	7.70 0.40(10)	7.66 0.39(10)	7.51 0.21(10)
DAY 92	8.58 0.31(10)	8.53 0.42(9)	8.51 0.29(10)	8.22 0.32(10)
DAY 127	8.56 0.39(10)	--	--	8.24 0.30(9)
HGB (g/dL)				
DAY 37	15.8 0.3(10)	15.5 0.6(10)	15.3 0.6(10)	15.0* 0.5(10)
DAY 92	15.8 0.5(10)	15.7 0.6(9)	15.5 0.5(10)	15.2 0.8(10)
DAY 127	15.1 0.7(10)	--	--	14.4* 0.5(9)
HCT (%)				
DAY 37	46.3 0.6(10)	45.4 2.4(10)	44.8 2.1(10)	44.6* 1.3(10)
DAY 92	47.6 2.0(10)	47.6 2.5(9)	47.2 1.6(10)	46.0 2.4(10)
DAY 127	48.6 2.4(10)	--	--	46.7 2.0(9)
MCV (fl)				
DAY 37	59.2 1.3(10)	59.0 1.8(10)	58.5 1.6(10)	59.4 1.6(10)
DAY 92	55.4 1.4(10)	55.8 1.8(9)	55.5 1.7(10)	56.0 2.0(10)
DAY 127	56.8 1.7(10)	--	--	56.7 1.7(9)
MCH (pg)				
DAY 37	20.1 0.5(10)	20.1 0.8(10)	20.0 0.7(10)	20.0 0.8(10)
DAY 92	18.5 0.5(10)	18.4 0.8(9)	18.3 0.6(10)	18.5 0.8(10)
DAY 127	17.7 0.5(10)	--	--	17.4 0.6(9)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
MCHC (g/dL)				
DAY 37	34.0 0.4(10)	34.1 0.8(10)	34.2 0.5(10)	33.7 0.4(10)
DAY 92	33.3 0.7(10)	32.9 0.8(9)	32.9 0.8(10)	33.0 0.7(10)
DAY 127	31.1 0.2(10)	--	--	30.8 0.5(9)
RDW (%)				
DAY 37	11.2 0.2(10)	11.3 0.4(10)	11.6* 0.3(10)	11.2 0.2(10)
DAY 92	12.6 0.5(10)	12.8 0.7(9)	12.7 0.5(10)	12.4 0.8(10)
DAY 127	13.0 0.9(10)	--	--	13.6 0.6(9)
ARET (x10 ³ /μL)				
DAY 37	177.4 19.8(10)	162.8 21.3(10)	179.0 22.9(10)	169.9 21.7(10)
DAY 92	155.6 34.2(10)	173.7 29.3(9)	161.7 30.7(10)	177.1 30.0(10)
DAY 127	184.4 26.7(10)	--	--	190.8 32.7(9)
PLT (x10 ³ /μL)				
DAY 37	1207 99(9)	1237 54(8)	1189 116(10)	1101* 84(10)
DAY 92	1063 166(6)	1192 174(3)	1109 127(7)	1137 35(3)
DAY 127	1135 123(6)	--	--	1277 135(5)
WBC (x10 ³ /μL)				
DAY 37	13.87 1.97(10)	16.01 4.18(10)	15.68 3.36(10)	16.08 4.03(10)
DAY 92	12.28 2.34(10)	13.99 3.39(9)	13.18 3.71(10)	13.32 4.96(10)
DAY 127	10.28 1.82(10)	--	--	14.16* 3.64(9)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
ANEU (x10 ³ /μL)				
DAY 37	1.43 0.33(10)	1.93 0.81(10)	2.01@ 0.37(10)	2.08 1.09(10)
DAY 92	1.66 0.35(10)	2.75 2.31(9)	2.03 0.54(10)	1.87 0.73(10)
DAY 127	1.87 0.62(10)	--	--	2.26 0.69(9)
ALYM (x10 ³ /μL)				
DAY 37	11.79 1.76(10)	13.39 3.47(10)	12.79 3.07(10)	13.28 3.16(10)
DAY 92	9.99 1.91(10)	10.60 2.03(9)	10.41 3.31(10)	10.88 4.53(10)
DAY 127	7.91 1.75(10)	--	--	11.21* 3.10(9)
AMON (x10 ³ /μL)				
DAY 37	0.27 0.05(10)	0.28 0.06(10)	0.42* 0.12(10)	0.29 0.10(10)
DAY 92	0.35 0.08(10)	0.31 0.13(9)	0.40 0.19(10)	0.29 0.12(10)
DAY 127	0.26 0.09(10)	--	--	0.37* 0.10(9)
AEOS (x10 ³ /μL)				
DAY 37	0.13 0.05(10)	0.15 0.08(10)	0.12 0.03(10)	0.12 0.04(10)
DAY 92	0.12 0.05(10)	0.14 0.04(9)	0.14 0.05(10)	0.13 0.07(10)
DAY 127	0.12 0.03(10)	--	--	0.16 0.07(9)
ABAS (x10 ³ /μL)				
DAY 37	0.10 0.05(10)	0.10 0.04(10)	0.12 0.05(10)	0.12 0.06(10)
DAY 92	0.07 0.04(10)	0.07 0.05(9)	0.08 0.04(10)	0.05 0.02(10)
DAY 127	0.08 0.05(10)	--	--	0.09 0.03(9)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
ALUC ($\times 10^3/\mu\text{L}$)				
DAY 37	0.15 0.06(10)	0.15 0.05(10)	0.22 0.20(10)	0.19 0.15(10)
DAY 92	0.10 0.04(10)	0.13 0.07(9)	0.13 0.07(10)	0.11 0.07(10)
DAY 127	0.05 0.02(10)	--	--	0.07* 0.03(9)

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

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

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

TABLE 27

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

	Group II 0 mg/kg	Group IV 10 mg/kg	Group VI 100 mg/kg	Group VIII 1000 mg/kg
RBC ($\times 10^6/\mu\text{L}$)				
DAY 38	7.95 0.33(10)	7.94 0.48(10)	7.87 0.29(10)	7.87 0.34(10)
DAY 93	8.21 0.23(10)	8.19 0.38(10)	8.17 0.21(10)	7.96 0.42(10)
DAY 127	8.14 0.22(10)	--	--	8.12 0.36(10)
HGB (g/dL)				
DAY 38	15.9 0.7(10)	15.9 0.8(10)	15.8 0.4(10)	15.7 0.4(10)
DAY 93	15.8 0.6(10)	15.7 0.4(10)	15.8 0.4(10)	15.3@ 0.5(10)
DAY 127	15.3 0.5(10)	--	--	15.1 0.7(10)
HCT (%)				
DAY 38	45.1 1.9(10)	45.4 2.5(10)	44.9 1.0(10)	44.5 1.3(10)
DAY 93	46.5 1.6(10)	46.1 1.5(10)	46.4 1.2(10)	44.4* 1.8(10)
DAY 127	48.3 1.3(10)	--	--	48.5 3.1(10)
MCV (fl)				
DAY 38	56.7 0.9(10)	57.2 1.3(10)	57.1 1.4(10)	56.6 1.9(10)
DAY 93	56.6 1.6(10)	56.3 1.4(10)	56.9 2.0(10)	55.9 2.2(10)
DAY 127	59.4 1.6(10)	--	--	59.7 2.1(10)
MCH (pg)				
DAY 38	20.1 0.5(10)	20.0 0.5(10)	20.1 0.6(10)	20.0 0.6(10)
DAY 93	19.3 0.6(10)	19.2 0.6(10)	19.3 0.7(10)	19.3 0.7(10)
DAY 127	18.7 0.5(10)	--	--	18.7 0.5(10)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

	Group II 0 mg/kg	Group IV 10 mg/kg	Group VI 100 mg/kg	Group VIII 1000 mg/kg
MCHC (g/dL)				
DAY 38	35.4 0.6(10)	35.0 0.5(10)	35.2 0.5(10)	35.3 0.4(10)
DAY 93	34.1 0.5(10)	34.0 0.5(10)	34.0 0.4(10)	34.5 0.5(10)
DAY 127	31.6 0.5(10)	--	--	31.3 0.8(10)
RDW (%)				
DAY 38	10.6 0.3(10)	10.8 0.4(10)	10.6 0.5(10)	10.7 0.4(10)
DAY 93	11.0 0.4(10)	11.3 0.3(10)	11.0 0.4(10)	11.0 0.4(10)
DAY 127	11.7 0.3(10)	--	--	11.5@ 0.5(10)
ARET (x10 ³ /μL)				
DAY 38	134.6 33.3(10)	154.7 28.6(10)	150.0 38.4(10)	168.3 26.7(10)
DAY 93	122.7 31.2(10)	154.2 48.7(10)	146.4 32.1(10)	146.7 44.7(10)
DAY 127	180.9 35.2(10)	--	--	185.1 43.6(10)
PLT (x10 ³ /μL)				
DAY 38	1183 144(9)	1366 157(6)	1178 94(9)	1254 171(9)
DAY 93	1044 174(4)	1165 51(2)	1120 57(4)	991 221(4)
DAY 127	1148 134(5)	--	--	1008 82(3)
WBC (x10 ³ /μL)				
DAY 38	13.75 2.34(10)	12.29 2.20(10)	14.46 3.31(10)	14.36 2.60(10)
DAY 93	9.89 2.22(10)	9.47 1.50(10)	9.36 2.59(10)	8.96 2.63(10)
DAY 127	7.96 2.73(10)	--	--	8.23 1.50(10)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

	Group II 0 mg/kg	Group IV 10 mg/kg	Group VI 100 mg/kg	Group VIII 1000 mg/kg
ANEU (x10 ³ /μL)				
DAY 38	1.16 0.38(10)	1.20 0.55(10)	1.28 0.51(10)	1.56 0.94(10)
DAY 93	1.15 0.58(10)	1.61@ 0.37(10)	1.26 0.55(10)	1.56 1.00(10)
DAY 127	1.17 0.44(10)	--	--	1.33 0.47(10)
ALYM (x10 ³ /μL)				
DAY 38	11.89 1.99(10)	10.42 1.75(10)	12.51 2.80(10)	12.10 2.05(10)
DAY 93	8.14 1.81(10)	7.27 1.55(10)	7.61 2.09(10)	6.96 1.91(10)
DAY 127	6.43 2.34(10)	--	--	6.50 1.37(10)
AMON (x10 ³ /μL)				
DAY 38	0.32 0.13(10)	0.29 0.09(10)	0.29 0.18(10)	0.34 0.15(10)
DAY 93	0.28 0.18(10)	0.27 0.12(10)	0.21 0.09(10)	0.19 0.13(10)
DAY 127	0.16 0.09(10)	--	--	0.19 0.07(10)
AEOS (x10 ³ /μL)				
DAY 38	0.11 0.03(10)	0.13 0.05(10)	0.12 0.04(10)	0.10 0.03(10)
DAY 93	0.11 0.02(10)	0.11 0.05(10)	0.11 0.06(10)	0.10 0.06(10)
DAY 127	0.10 0.03(10)	--	--	0.13 0.08(10)
ABAS (x10 ³ /μL)				
DAY 38	0.12 0.03(10)	0.12 0.05(10)	0.12 0.03(10)	0.11 0.06(10)
DAY 93	0.08 0.03(10)	0.10 0.06(10)	0.08 0.04(10)	0.06 0.04(10)
DAY 127	0.05 0.03(10)	--	--	0.05 0.02(10)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

	Group II 0 mg/kg	Group IV 10 mg/kg	Group VI 100 mg/kg	Group VIII 1000 mg/kg
ALUC ($\times 10^3/\mu\text{L}$)				
DAY 38	0.15 0.02(10)	0.14 0.04(10)	0.16 0.09(10)	0.15 0.06(10)
DAY 93	0.13 0.07(10)	0.11 0.04(10)	0.09 0.04(10)	0.08 0.05(10)
DAY 127	0.05 0.03(10)	--	--	0.04 0.01(10)

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

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

TABLE 28

SUMMARY OF COAGULATION VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
PT (seconds)				
DAY 92	16.0 0.9(10)	15.9 1.0(10)	15.4 0.3(10)	15.7 0.6(10)
DAY 127	16.0 0.9(9)	--	--	15.5 0.5(10)
APTT (seconds)				
DAY 92	20.6 1.4(10)	19.4 1.4(10)	18.9* 2.0(10)	19.0 1.6(10)
DAY 127	20.7 1.6(9)	--	--	21.1 1.8(10)

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

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

TABLE 29

SUMMARY OF COAGULATION VALUES FOR FEMALE RATS

	Group II 0 mg/kg	Group IV 10 mg/kg	Group VI 100 mg/kg	Group VIII 1000 mg/kg
PT (seconds)				
DAY 93	15.0 0.4(9)	15.5 0.5(10)	15.5 0.4(10)	15.1 0.8(9)
DAY 127	14.9 0.7(10)	--	--	15.3 0.6(10)
APTT (seconds)				
DAY 93	18.0 1.6(9)	18.7 0.8(10)	17.6 2.0(10)	19.2 1.8(9)
DAY 127	17.5 1.9(10)	--	--	17.7 2.5(10)

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

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

TABLE 30

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
AST (U/L)				
DAY 37	73 7(10)	74 6(10)	75 9(10)	70 6(10)
DAY 92	80 11(10)	92 27(10)	78 8(10)	76 9(10)
DAY 127	79 13(10)	--	--	93@ 22(10)
ALT (U/L)				
DAY 37	29 2(10)	31 4(10)	34* 4(10)	31 5(10)
DAY 92	33 4(10)	48 30(10)	38 6(10)	35 7(10)
DAY 127	37 9(10)	--	--	45@ 11(10)
SDH (U/L)				
DAY 37	12.6 1.3(10)	11.6 2.0(10)	11.5 1.2(10)	12.5 2.3(10)
DAY 92	19.2 1.9(10)	20.8 10.6(10)	16.3 3.4(10)	17.5 4.7(10)
DAY 127	17.2 5.4(10)	--	--	18.6 9.4(10)
ALKP (U/L)				
DAY 37	156 44(10)	164 45(10)	159 25(10)	150 31(10)
DAY 92	96 26(10)	103 28(10)	97 15(10)	111 17(10)
DAY 127	82 15(10)	--	--	79 9(10)
BILI (mg/dL)				
DAY 37	0.08 0.03(10)	0.07 0.03(10)	0.06 0.03(10)	0.06 0.02(10)
DAY 92	0.11 0.03(10)	0.10 0.03(10)	0.09 0.04(10)	0.07@ 0.03(10)
DAY 127	0.12 0.04(10)	--	--	0.10 0.03(10)

TABLE 30 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
BUN (mg/dL)				
DAY 37	14 1(10)	14 1(10)	14 1(10)	14 1(10)
DAY 92	15 2(10)	15 2(10)	16 2(10)	16 2(10)
DAY 127	14 2(10)	--	--	15 2(10)
CREA (mg/dL)				
DAY 37	0.36 0.05(10)	0.33 0.03(10)	0.33 0.04(10)	0.31 0.05(10)
DAY 92	0.47 0.07(10)	0.45 0.07(10)	0.41 0.05(10)	0.44 0.06(10)
DAY 127	0.35 0.05(10)	--	--	0.34 0.04(10)
CHOL (mg/dL)				
DAY 37	64 11(10)	65 18(10)	55 8(10)	53 11(10)
DAY 92	68 14(10)	69 23(10)	52 8(10)	51 13(10)
DAY 127	70 15(10)	--	--	60 12(10)
TRIG (mg/dL)				
DAY 37	48 22(10)	37 12(10)	59 27(10)	45 27(10)
DAY 92	79 20(10)	55* 23(10)	60 23(10)	46* 19(10)
DAY 127	71 29(10)	--	--	69 32(10)
GLUC (mg/dL)				
DAY 37	99 10(10)	105 7(10)	98 8(10)	99 7(10)
DAY 92	107 25(10)	135 34(10)	128 48(10)	127 41(10)
DAY 127	113 20(10)	--	--	144 45(10)

TABLE 30 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
TP (g/dL)				
DAY 37	6.8 0.3(10)	6.7 0.3(10)	6.7 0.4(10)	6.6 0.4(10)
DAY 92	7.4 0.3(10)	7.3 0.3(10)	7.2 0.3(10)	7.1* 0.2(10)
DAY 127	7.1 0.3(10)	--	--	7.2 0.4(10)
ALB (g/dL)				
DAY 37	4.4 0.2(10)	4.3 0.2(10)	4.3 0.3(10)	4.4 0.2(10)
DAY 92	4.5 0.2(10)	4.4 0.2(10)	4.5 0.2(10)	4.7 0.1(10)
DAY 127	4.5 0.2(10)	--	--	4.7* 0.2(10)
GLOB (g/dL)				
DAY 37	2.5 0.1(10)	2.4 0.3(10)	2.4 0.2(10)	2.2 0.3(10)
DAY 92	2.9 0.2(10)	2.8 0.3(10)	2.7 0.2(10)	2.4@ 0.2(10)
DAY 127	2.7 0.2(10)	--	--	2.5 0.3(10)
CALC (mg/dL)				
DAY 37	10.9 0.3(10)	11.1 0.5(10)	10.9 0.3(10)	11.1 0.3(10)
DAY 92	11.3 0.6(10)	11.7 0.5(10)	11.4 0.7(10)	11.0 0.5(10)
DAY 127	11.1 0.4(10)	--	--	11.4 0.4(10)
IPHS (mg/dL)				
DAY 37	8.4 0.5(10)	8.5 0.7(10)	8.8 0.3(10)	8.9 0.5(10)
DAY 92	9.6 0.9(10)	9.9 1.1(10)	9.8 1.5(10)	10.4 1.6(10)
DAY 127	8.0 0.8(10)	--	--	9.0@ 0.9(10)

TABLE 30 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
NA (mmol/L)				
DAY 37	151.6 3.2(10)	150.8 3.2(10)	151.2 2.6(10)	151.6 2.8(10)
DAY 92	150.5 2.9(10)	151.6 3.0(10)	151.3 3.5(10)	150.9 2.5(10)
DAY 127	149.5 2.0(10)	--	--	149.9 1.8(10)
K (mmol/L)				
DAY 37	6.04 0.28(10)	6.09 0.67(10)	6.02 0.26(10)	6.14 0.39(10)
DAY 92	6.47 0.52(10)	6.69 0.77(10)	6.46 0.63(10)	6.76 1.10(10)
DAY 127	6.35 0.22(10)	--	--	6.39 0.63(10)
CL (mmol/L)				
DAY 37	102.6 3.0(10)	102.9 2.0(10)	102.2 2.8(10)	103.5 2.7(10)
DAY 92	106.9 3.9(10)	107.2 3.5(10)	107.3 2.9(10)	109.0 3.4(10)
DAY 127	103.6 1.8(10)	--	--	104.3 1.3(10)
PFLU (µg/mL)				
DAY 92	0.1 0.0(10)	0.1 0.0(10)	0.1 0.0(10)	0.1 0.0(10)
DAY 127	0.1 0.0(9)	--	--	0.1 0.0(10)

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

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

TABLE 31

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR FEMALE RATS

	Group II 0 mg/kg	Group IV 10 mg/kg	Group VI 100 mg/kg	Group VIII 1000 mg/kg
AST (U/L)				
DAY 38	75 11(10)	75 10(10)	71 10(10)	77 11(10)
DAY 93	102 64(10)	101 40(10)	84 18(10)	84 19(10)
DAY 127	101 16(10)	--	--	105 31(10)
ALT (U/L)				
DAY 38	34 5(10)	32 6(10)	28* 4(10)	33 6(10)
DAY 93	60 58(10)	57 40(10)	41 20(10)	37 10(10)
DAY 127	58 13(10)	--	--	57 35(10)
SDH (U/L)				
DAY 38	14.4 2.6(10)	13.9 3.8(10)	13.8 3.2(10)	14.8 3.2(10)
DAY 93	23.2 13.8(10)	22.3 12.1(10)	19.8 6.5(10)	14.1 3.8(10)
DAY 127	22.0 6.7(10)	--	--	20.9 12.2(10)
ALKP (U/L)				
DAY 38	120 28(10)	111 32(10)	122 24(10)	118 33(10)
DAY 93	58 9(10)	60 18(10)	60 8(10)	67 19(10)
DAY 127	51 25(10)	--	--	49 14(10)
BILI (mg/dL)				
DAY 38	0.10 0.03(10)	0.12 0.01(10)	0.10 0.03(10)	0.10 0.04(10)
DAY 93	0.09 0.04(10)	0.11 0.04(10)	0.09 0.04(10)	0.05 0.00(10)
DAY 127	0.15 0.03(10)	--	--	0.13 0.02(10)

TABLE 31 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR FEMALE RATS

	Group II 0 mg/kg	Group IV 10 mg/kg	Group VI 100 mg/kg	Group VIII 1000 mg/kg
BUN (mg/dL)				
DAY 38	17 3(10)	16 2(10)	16 2(10)	16 2(10)
DAY 93	17 2(10)	16 1(10)	17 2(10)	18 2(10)
DAY 127	16 2(10)	--	--	18 2(10)
CREA (mg/dL)				
DAY 38	0.47 0.06(10)	0.45 0.05(10)	0.45 0.05(10)	0.44 0.04(10)
DAY 93	0.54 0.05(10)	0.49 0.05(10)	0.52 0.03(10)	0.50 0.04(10)
DAY 127	0.49 0.06(10)	--	--	0.46 0.05(10)
CHOL (mg/dL)				
DAY 38	69 13(10)	65 13(10)	67 10(10)	70 14(10)
DAY 93	76 10(10)	73 18(10)	71 15(10)	71 9(10)
DAY 127	80 16(10)	--	--	78 9(10)
TRIG (mg/dL)				
DAY 38	40 11(10)	34 15(10)	39 14(10)	37 22(10)
DAY 93	53 12(10)	34@ 11(10)	42 11(10)	42 19(10)
DAY 127	45 16(10)	--	--	39 11(10)
GLUC (mg/dL)				
DAY 38	100 8(10)	100 9(10)	100 7(10)	100 10(10)
DAY 93	102 26(10)	94 8(10)	95 4(10)	106 20(10)
DAY 127	115 17(10)	--	--	114 25(10)

TABLE 31 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR FEMALE RATS

	Group II 0 mg/kg	Group IV 10 mg/kg	Group VI 100 mg/kg	Group VIII 1000 mg/kg
TP (g/dL)				
DAY 38	7.2 0.4(10)	7.4 0.3(10)	7.4 0.3(10)	7.6 0.2(10)
DAY 93	7.7 0.5(10)	7.8 0.4(10)	7.6 0.4(10)	7.5 0.2(10)
DAY 127	8.3 0.5(10)	--	--	8.3 0.4(10)
ALB (g/dL)				
DAY 38	4.9 0.3(10)	5.0 0.3(10)	5.0 0.3(10)	5.2 0.2(10)
DAY 93	5.2 0.3(10)	5.2 0.4(10)	5.2 0.5(10)	5.2 0.3(10)
DAY 127	5.6 0.3(10)	--	--	5.6 0.5(10)
GLOB (g/dL)				
DAY 38	2.3 0.2(10)	2.4 0.2(10)	2.4 0.3(10)	2.4 0.3(10)
DAY 93	2.4 0.2(10)	2.5 0.2(10)	2.5 0.2(10)	2.3 0.2(10)
DAY 127	2.6 0.4(10)	--	--	2.7 0.2(10)
CALC (mg/dL)				
DAY 38	11.2 0.3(10)	11.5 0.3(10)	11.5 0.3(10)	11.6* 0.4(10)
DAY 93	11.2 0.4(10)	11.1 0.3(10)	11.1 0.4(10)	11.0 0.4(10)
DAY 127	11.7 0.4(10)	--	--	11.7 0.4(10)
IPHS (mg/dL)				
DAY 38	7.3 0.6(10)	7.9* 0.5(10)	7.8 0.3(10)	8.3* 0.6(10)
DAY 93	6.6 1.5(10)	6.5 1.0(10)	6.3 0.9(10)	7.0 1.0(10)
DAY 127	6.2 0.9(10)	--	--	7.4 1.9(10)

TABLE 31 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR FEMALE RATS

	Group II 0 mg/kg	Group IV 10 mg/kg	Group VI 100 mg/kg	Group VIII 1000 mg/kg
NA (mmol/L)				
DAY 38	145.7 2.0(10)	147.2 2.4(10)	146.8 1.7(10)	146.4 1.4(10)
DAY 93	144.9 1.2(10)	145.6 1.5(10)	145.8 2.0(10)	144.5 1.5(10)
DAY 127	151.9 1.4(10)	--	--	152.2 2.0(10)
K (mmol/L)				
DAY 38	5.75 0.36(10)	6.04 0.39(10)	5.89 0.23(10)	5.97 0.34(10)
DAY 93	5.30 0.48(10)	5.54 0.52(10)	5.65 0.38(10)	5.75 0.37(10)
DAY 127	5.74 0.49(10)	--	--	5.95 0.39(10)
CL (mmol/L)				
DAY 38	100.6 1.7(10)	101.8 1.8(10)	101.3 1.3(10)	101.4 1.8(10)
DAY 93	98.5 1.6(10)	99.7 1.9(10)	99.9 1.7(10)	100.5* 1.9(10)
DAY 127	105.6 2.6(10)	--	--	106.9 1.9(10)
PFLU (µg/mL)				
DAY 93	0.1 0.0(9)	0.1 0.0(10)	0.1 0.0(10)	0.1 0.0(10)
DAY 127	0.1 0.0(10)	--	--	0.1 0.1(10)

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

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

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

TABLE 32

SUMMARY OF URINALYSIS VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
VOL (mL)				
DAY 37	8.6 4.1(10)	11.6 12.1(10)	9.5 3.5(10)	10.2 5.7(10)
DAY 92	8.7 6.2(10)	8.5 5.1(10)	6.7 2.5(10)	9.0 3.8(10)
DAY 127	4.8 1.7(10)	--	--	8.9* 3.5(9)
UOSM (mOsm)				
DAY 37	1043 316(10)	896 425(9)	1014 353(10)	1279 537(10)
DAY 92	1194 383(10)	1070 342(10)	1534 655(10)	1155 407(10)
DAY 127	2092 669(10)	--	--	1228@ 464(9)
pH				
DAY 37	6.8 0.3(10)	6.7 0.3(9)	6.9 0.2(10)	6.9 0.3(10)
DAY 92	6.7 0.5(10)	6.6 0.3(10)	6.8 0.4(10)	6.6 0.3(10)
DAY 127	6.4 0.5(10)	--	--	6.7 0.6(9)
URO (EU/dL)				
DAY 37	0.2 0.0(10)	0.2 0.0(9)	0.2 0.0(10)	0.2 0.0(10)
DAY 92	0.2 0.0(10)	0.2 0.0(10)	0.4 0.4(10)	0.3 0.3(10)
DAY 127	0.5 0.4(10)	--	--	0.3 0.3(9)
UFLU (µg)				
DAY 92	9.5 3.9(10)	9.2 2.6(10)	17.5* 3.5(10)	53.4* 9.0(10)
DAY 127	7.7 1.8(10)	--	--	10.8* 1.5(9)

TABLE 32 (Continued)

SUMMARY OF URINALYSIS VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
UMTP (mg/dL)				
DAY 37	76 34(10)	73 49(9)	58 41(10)	51 35(10)
DAY 92	111 50(10)	75 40(10)	92 55(10)	61 41(10)
DAY 127	143 36(10)	--	--	75@ 59(9)

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

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

TABLE 33

SUMMARY OF URINALYSIS VALUES FOR FEMALE RATS

	Group II 0 mg/kg	Group IV 10 mg/kg	Group VI 100 mg/kg	Group VIII 1000 mg/kg
VOL (mL)				
DAY 38	10.4 6.6(10)	7.7 3.6(10)	7.5 3.2(10)	7.1 8.1(10)
DAY 93	6.1 5.6(10)	4.1 2.5(10)	4.5 3.5(10)	5.8 4.7(9)
DAY 127	8.6 4.7(10)	--	--	3.4@ 1.9(10)
UOSM (mOsm)				
DAY 38	839 486(10)	952 497(10)	868 340(10)	1279 659(10)
DAY 93	1120 538(10)	1339 549(10)	1324 552(10)	1744 1341(9)
DAY 127	1035 342(10)	--	--	1388 443(6)
pH				
DAY 38	7.3 0.7(10)	7.1 0.4(10)	6.9 0.4(10)	7.0 0.2(10)
DAY 93	6.0 0.5(10)	6.1 0.6(10)	5.9 0.4(10)	6.0 0.3(9)
DAY 127	6.2 0.3(10)	--	--	5.7@ 0.5(10)
URO (EU/dL)				
DAY 38	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)
DAY 93	0.3 0.3(10)	0.3 0.3(10)	0.2 0.0(10)	0.2 0.0(9)
DAY 127	0.2 0.0(10)	--	--	0.5@ 0.4(10)
UFLU (µg)				
DAY 93	6.5 3.3(10)	5.5 1.8(9)	9.8 3.2(8)	28.6* 9.1(7)
DAY 127	6.3 2.5(10)	--	--	4.8 1.2(9)

TABLE 33 (Continued)

SUMMARY OF URINALYSIS VALUES FOR FEMALE RATS

	Group II 0 mg/kg	Group IV 10 mg/kg	Group VI 100 mg/kg	Group VIII 1000 mg/kg
UMTP (mg/dL)				
DAY 38	22 13(10)	28 21(10)	19 7(10)	32 19(10)
DAY 93	32 21(10)	38 23(10)	32 22(10)	44 43(9)
DAY 127	19 9(10)	--	--	35* 19(10)

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

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

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

TABLE 34

SUMMARY OF PEROXISOMAL BETA-OXIDATION ACTIVITY IN MALE RATS

Group	Dosage (mg/kg/day)	Hepatic Peroxisomal Beta-Oxidation Activity (nmol/min/mg protein)		
		10-Day Time Point	92-Day Time Point	One-Month Recovery Time Point
I	0	17.4 ± 1.3 ^a	18.7 ± 1.0	16.6 ± 1.4
III	10	18.6 ± 1.8	18.1 ± 2.0	----- ^b
V	100	15.0 ± 0.9	20.1 ± 2.0	----- ^b
VII	1000	15.9 ± 2.1 [#] ^c	29.7 ± 2.0 [#]	24.8 ± 5.6*

^a Mean ± standard deviation. The n = 5 for each group unless otherwise noted.^b Samples were not prepared for analysis from groups III and V at the one-month recovery time points.^c The n = 4.[#] Statistically significant difference at p < 0.05 by Jonckheere's Tend test.

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

TABLE 35

SUMMARY OF PEROXISOMAL BETA-OXIDATION ACTIVITY IN FEMALE RATS

Group	Dosage (mg/kg/day)	Hepatic Peroxisomal Beta-Oxidation Activity (nmol/min/mg protein)		
		10-Day Time Point	93-Day Time Point	One-Month Recovery Time Point
II	0	15.9 ± 3.1 ^a	19.2 ± 1.5	21.2 ± 1.8
IV	10	17.0 ± 3.1	19.4 ± 3.0	----- ^b
VI	100	19.2 ± 2.3	21.0 ± 2.2	----- ^b
VIII	1000	19.1 ± 3.1 [#]	24.0 ± 2.7 [#]	23.4 ± 2.5

^a Mean ± standard deviation. The n = 5 for each group.^b Samples were not prepared for analysis from groups IV and VI at the one-month recovery time point.[#] Statistically significant difference at p < 0.05 by Jonckheere's Trend test.

TABLE 36

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

Group: Dosage (mg/kg)	MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)					
	I 0	III 10	V 100	VII 1000		
Test						
LIVER	15.189 1.815(10)	15.092 1.512(10)	14.964 2.027(10)	18.135# 1.646(10)		
KIDNEYS	3.922 0.498(10)	4.045 0.341(10)	3.995 0.437(10)	4.389# 0.273(10)		
HEART	1.705 0.160(10)	1.729 0.195(10)	1.695 0.164(10)	1.780 0.106(10)		
SPLEEN	0.803 0.098(10)	0.887 0.139(10)	0.813 0.154(10)	0.809 0.091(10)		
BRAIN	2.175 0.110(10)	2.170 0.106(10)	2.128 0.081(10)	2.135 0.109(10)		
THYMUS	0.421 0.079(10)	0.458 0.097(10)	0.428 0.094(10)	0.437 0.088(10)		
ADRENAL GLANDS	0.051 0.008(10)	0.060 0.011(10)	0.057 0.012(10)	0.051 0.008(10)		
THYROID GLAND	0.025 0.006(9)	0.021 0.006(10)	0.023 0.005(10)	0.023 0.005(10)		
TESTES	3.513 0.430(10)	3.637 0.276(10)	3.523 0.316(10)	3.702 0.319(10)		
EPIDIDYMIDES	1.469 0.170(10)	1.564 0.100(10)	1.480 0.189(10)	1.500 0.086(10)		
FINAL BODY WEIGHT	570.380 61.904(10)	552.870 50.408(10)	544.040 54.651(10)	551.070 37.294(10)		

TABLE 36 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

Group: Dosage (mg/kg)	MEAN RELATIVE ORGAN WEIGHTS (% of body weight)					
	I 0	III 10	V 100	VII 1000		
Test						
LIVER/ FINAL BODY * 100	2.665 0.185(10)	2.731 0.138(10)	2.744 0.146(10)	3.289# 0.158(10)		
KIDNEYS/ FINAL BODY * 100	0.688 0.061(10)	0.734 0.052(10)	0.735 0.051(10)	0.799# 0.072(10)		
HEART/ FINAL BODY * 100	0.300 0.023(10)	0.313 0.022(10)	0.312 0.022(10)	0.324# 0.019(10)		
SPLEEN/ FINAL BODY * 100	0.141 0.012(10)	0.160 0.021(10)	0.150 0.026(10)	0.147 0.011(10)		
BRAIN/ FINAL BODY * 100	0.384 0.032(10)	0.395 0.029(10)	0.394 0.036(10)	0.389 0.028(10)		
THYMUS/ FINAL BODY * 100	0.074 0.012(10)	0.083 0.018(10)	0.078 0.014(10)	0.079 0.013(10)		
ADRENAL GLANDS/ FINAL BODY * 100	0.009 0.002(10)	0.011 0.002(10)	0.011 0.002(10)	0.009 0.002(10)		
THYROID GLAND/ FINAL BODY * 100	0.004 0.001(9)	0.004 0.001(10)	0.004 0.001(10)	0.004 0.001(10)		
TESTES/ FINAL BODY * 100	0.617 0.051(10)	0.662 0.077(10)	0.650 0.044(10)	0.676 0.090(10)		
EPIDIDYMIDES/ FINAL BODY * 100	0.259 0.029(10)	0.285 0.029(10)	0.273 0.027(10)	0.274 0.029(10)		

TABLE 36 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

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

Group: Dosage (mg/kg)	I 0	III 10	V 100	VII 1000
Test				
LIVER/ BRAIN * 100	697.326 65.322(10)	695.197 60.585(10)	702.743 89.168(10)	850.523# 78.915(10)
KIDNEYS/ BRAIN * 100	180.200 20.354(10)	186.673 17.166(10)	187.660 18.934(10)	206.158# 18.086(10)
HEART/ BRAIN * 100	78.304 4.845(10)	79.635 7.729(10)	79.557 6.428(10)	83.552 6.374(10)
SPLEEN/ BRAIN * 100	36.949 4.390(10)	40.819 5.911(10)	38.084 6.458(10)	37.916 3.933(10)
THYMUS/ BRAIN * 100	19.362 3.587(10)	21.105 4.463(10)	20.062 3.914(10)	20.438 3.898(10)
ADRENAL GLANDS/ BRAIN * 100	2.339 0.390(10)	2.742 0.489(10)	2.690 0.534(10)	2.405 0.420(10)
THYROID GLAND/ BRAIN * 100	1.148 0.267(9)	0.980 0.275(10)	1.070 0.246(10)	1.080 0.219(10)
TESTES/ BRAIN * 100	161.197 15.013(10)	167.743 12.660(10)	165.607 14.772(10)	173.979 19.138(10)
EPIDIDYMIDES/ BRAIN * 100	67.507 6.869(10)	72.206 5.336(10)	69.672 9.604(10)	70.352 4.315(10)

Data summarized as: Mean
Standard Deviation (n)

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

TABLE 37

**MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
DESIGNATED FOR RECOVERY EVALUATION**

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

Group: Dosage (mg/kg)	I 0	VII 1000
Test LIVER	15.754 2.172 (9)	17.296 2.051 (10)
KIDNEYS	4.105 0.200 (9)	4.081 0.420 (10)
HEART	1.792 0.174 (9)	1.753 0.113 (10)
SPLEEN	0.797 0.175 (9)	0.840 0.072 (10)
BRAIN	2.172 0.157 (9)	2.129 0.067 (10)
THYMUS	0.378 0.113 (9)	0.382 0.104 (10)
ADRENAL GLANDS	0.051 0.008 (9)	0.051 0.005 (10)
THYROID GLAND	0.029 0.006 (9)	0.029 0.005 (10)
TESTES	3.668 0.307 (9)	3.575 0.307 (10)
EPIDIDYMIDES	1.583 0.195 (9)	1.545 0.131 (10)
FINAL BODY WEIGHT	589.344 49.966 (9)	583.300 52.368 (10)

TABLE 37 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
DESIGNATED FOR RECOVERY EVALUATION

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

Group: Dosage (mg/kg)	I 0	VII 1000
Test		
LIVER/ FINAL BODY * 100	2.670 0.259(9)	2.962# 0.178(10)
KIDNEYS/ FINAL BODY * 100	0.701 0.066(9)	0.702 0.068(10)
HEART/ FINAL BODY * 100	0.304 0.017(9)	0.302 0.028(10)
SPLEEN/ FINAL BODY * 100	0.135 0.025(9)	0.144 0.011(10)
BRAIN/ FINAL BODY * 100	0.370 0.033(9)	0.368 0.037(10)
THYMUS/ FINAL BODY * 100	0.064 0.018(9)	0.065 0.014(10)
ADRENAL GLANDS/ FINAL BODY * 100	0.009 0.001(9)	0.009 0.001(10)
THYROID GLAND/ FINAL BODY * 100	0.005 0.001(9)	0.005 0.001(10)
TESTES/ FINAL BODY * 100	0.624 0.056(9)	0.617 0.074(10)
EPIDIDYMIDES/ FINAL BODY * 100	0.269 0.026(9)	0.266 0.030(10)

TABLE 37 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
DESIGNATED FOR RECOVERY EVALUATION

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

Group: Dosage (mg/kg)	I 0	VII 1000
Test		
LIVER/ BRAIN * 100	730.212 128.329(9)	813.590 105.495(10)
KIDNEYS/ BRAIN * 100	189.802 15.475(9)	191.896 22.036(10)
HEART/ BRAIN * 100	82.627 7.037(9)	82.463 6.930(10)
SPLEEN/ BRAIN * 100	36.680 7.454(9)	39.454 3.454(10)
THYMUS/ BRAIN * 100	17.499 5.505(9)	17.923 4.866(10)
ADRENAL GLANDS/ BRAIN * 100	2.367 0.489(9)	2.394 0.287(10)
THYROID GLAND/ BRAIN * 100	1.348 0.264(9)	1.344 0.232(10)
TESTES/ BRAIN * 100	170.012 22.044(9)	167.937 14.182(10)
EPIDIDYMIDES/ BRAIN * 100	73.331 11.109(9)	72.653 7.088(10)

Data summarized as: Mean
Standard Deviation (n)

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

TABLE 38

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)				
Group: Dosage(mg/kg)	II 0	IV 10	VI 100	VIII 1000
Test				
LIVER	8.053 1.128(10)	7.992 0.992(10)	7.990 0.746(10)	8.512 0.581(10)
KIDNEYS	2.220 0.248(10)	2.265 0.210(10)	2.208 0.224(10)	2.282 0.217(10)
HEART	1.098 0.110(10)	1.067 0.117(10)	1.079 0.072(10)	1.092 0.119(10)
SPLEEN	0.498 0.066(10)	0.566 0.082(10)	0.531 0.069(10)	0.547 0.095(10)
BRAIN	1.896 0.086(10)	1.908 0.115(10)	1.960 0.084(10)	1.981 0.119(10)
THYMUS	0.276 0.079(10)	0.292 0.058(10)	0.345 0.073(10)	0.314 0.062(10)
ADRENAL GLANDS	0.068 0.011(10)	0.072 0.009(10)	0.070 0.013(10)	0.071 0.009(10)
THYROID GLAND	0.015 0.004(10)	0.018 0.003(10)	0.018 0.003(10)	0.019# 0.004(10)
OVARIES	0.117 0.019(10)	0.140 0.022(10)	0.137 0.022(10)	0.137 0.023(10)
UTERUS	0.735 0.215(10)	0.761 0.275(10)	0.851 0.325(10)	0.838 0.387(10)
FINAL BODY WEIGHT	303.050 29.058(10)	288.340 26.761(10)	290.080 16.350(10)	294.990 23.672(10)

TABLE 38 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

Group: Dosage (mg/kg)	MEAN RELATIVE ORGAN WEIGHTS (% of body weight)			
	II 0	IV 10	VI 100	VIII 1000
Test				
LIVER/ FINAL BODY * 100	2.654 0.235(10)	2.768 0.170(10)	2.756 0.229(10)	2.891# 0.135(10)
KIDNEYS/ FINAL BODY * 100	0.733 0.052(10)	0.787 0.048(10)	0.761 0.058(10)	0.775 0.064(10)
HEART/ FINAL BODY * 100	0.363 0.024(10)	0.370 0.028(10)	0.373 0.032(10)	0.371 0.036(10)
SPLEEN/ FINAL BODY * 100	0.164 0.019(10)	0.196* 0.016(10)	0.183 0.020(10)	0.184 0.022(10)
BRAIN/ FINAL BODY * 100	0.630 0.054(10)	0.665 0.056(10)	0.677 0.037(10)	0.674 0.046(10)
THYMUS/ FINAL BODY * 100	0.092 0.028(10)	0.102 0.021(10)	0.118# 0.020(10)	0.106# 0.018(10)
ADRENAL GLANDS/ FINAL BODY * 100	0.022 0.003(10)	0.025 0.003(10)	0.024 0.004(10)	0.024 0.004(10)
THYROID GLAND/ FINAL BODY * 100	0.005 0.001(10)	0.006# 0.001(10)	0.006# 0.001(10)	0.006# 0.002(10)
OVARIES/ FINAL BODY * 100	0.039 0.006(10)	0.049 0.007(10)	0.047 0.008(10)	0.047 0.009(10)
UTERUS/ FINAL BODY * 100	0.244 0.075(10)	0.261 0.082(10)	0.289 0.092(10)	0.283 0.122(10)

TABLE 38 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

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

Group: Dosage (mg/kg)	II 0	IV 10	VI 100	VIII 1000
Test				
LIVER/ BRAIN * 100	423.933 49.157(10)	419.320 50.890(10)	408.327 41.392(10)	429.945 20.218(10)
KIDNEYS/ BRAIN * 100	117.072 11.741(10)	118.977 11.451(10)	112.671 10.372(10)	115.414 11.117(10)
HEART/ BRAIN * 100	57.901 4.680(10)	55.937 5.197(10)	55.164 4.690(10)	55.095 5.002(10)
SPLEEN/ BRAIN * 100	26.241 3.181(10)	29.656 3.927(10)	27.122 3.392(10)	27.576 4.484(10)
THYMUS/ BRAIN * 100	14.685 4.718(10)	15.466 3.597(10)	17.553 3.264(10)	15.857 3.253(10)
ADRENAL GLANDS/ BRAIN * 100	3.571 0.526(10)	3.775 0.354(10)	3.569 0.625(10)	3.581 0.391(10)
THYROID GLAND/ BRAIN * 100	0.801 0.185(10)	0.944 0.175(10)	0.915 0.154(10)	0.935 0.226(10)
OVARIES/ BRAIN * 100	6.199 1.068(10)	7.336 1.135(10)	6.990 1.077(10)	6.896 1.011(10)
UTERUS/ BRAIN * 100	38.681 10.903(10)	39.692 13.456(10)	43.155 14.879(10)	41.946 18.021(10)

Data summarized as: Mean
Standard Deviation (n)

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

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

TABLE 39

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
DESIGNATED FOR RECOVERY EVALUATION

Group: Test Liver	MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)	
	II 0	VIII 1000
Dosage (mg/kg)		
KIDNEYS	8.705 1.550 (10)	8.722 1.093 (10)
HEART	2.309 0.254 (10)	2.367 0.230 (10)
SPLEEN	1.135 0.067 (10)	1.114 0.138 (10)
BRAIN	0.564 0.073 (10)	0.526 0.106 (10)
THYMUS	1.903 0.069 (10)	1.891 0.046 (10)
ADRENAL GLANDS	0.277 0.075 (10)	0.300 0.071 (10)
THYROID GLAND	0.066 0.008 (10)	0.069 0.010 (10)
OVARIES	0.021 0.002 (10)	0.026# 0.006 (10)
UTERUS	0.119 0.013 (10)	0.122 0.029 (10)
FINAL BODY WEIGHT	0.844 0.242 (10)	0.772 0.334 (10)
	325.260 34.988 (10)	298.620 22.864 (10)

TABLE 39 (CONTINUED)
MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
DESIGNATED FOR RECOVERY EVALUATION

Group: Test Dosage (mg/kg)	MEAN RELATIVE ORGAN WEIGHTS (% of body weight)	
	II 0	VIII 1000
LIVER/ FINAL BODY * 100	2.669 0.273(10)	2.915# 0.204(10)
KIDNEYS/ FINAL BODY * 100	0.711 0.046(10)	0.793# 0.043(10)
HEART/ FINAL BODY * 100	0.351 0.025(10)	0.373 0.033(10)
SPLEEN/ FINAL BODY * 100	0.174 0.016(10)	0.176 0.036(10)
BRAIN/ FINAL BODY * 100	0.590 0.059(10)	0.637 0.051(10)
THYMUS/ FINAL BODY * 100	0.085 0.017(10)	0.101 0.024(10)
ADRENAL GLANDS/ FINAL BODY * 100	0.020 0.003(10)	0.023# 0.003(10)
THYROID GLAND/ FINAL BODY * 100	0.006 0.001(10)	0.009# 0.002(10)
OVARIES/ FINAL BODY * 100	0.037 0.005(10)	0.041 0.010(10)
UTERUS/ FINAL BODY * 100	0.258 0.067(10)	0.260 0.117(10)

TABLE 39 (CONTINUED)
MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
DESIGNATED FOR RECOVERY EVALUATION

MEAN RELATIVE ORGAN WEIGHTS (% organ to brain weight ratio)			
Group:	II	VIII	
Dosage (mg/kg)	0	1000	
Test			
LIVER/ BRAIN * 100	456.513 71.989 (10)	461.664 60.058 (10)	
KIDNEYS/ BRAIN * 100	121.292 12.325 (10)	125.275 12.836 (10)	
HEART/ BRAIN * 100	59.727 4.623 (10)	58.991 7.676 (10)	
SPLEEN/ BRAIN * 100	29.694 4.143 (10)	27.739 5.218 (10)	
THYMUS/ BRAIN * 100	14.546 3.724 (10)	15.900 3.899 (10)	
ADRENAL GLANDS/ BRAIN * 100	3.463 0.455 (10)	3.652 0.556 (10)	
THYROID GLAND/ BRAIN * 100	1.099 0.135 (10)	1.369# 0.300 (10)	
OVARIES/ BRAIN * 100	6.286 0.763 (10)	6.453 1.448 (10)	
UTERUS/ BRAIN * 100	44.402 13.049 (10)	40.999 18.445 (10)	

Data summarized as: Mean
Standard Deviation (n)

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

TABLE 40
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (Numeric)				
	Males				
	TREATMENT	0	10	100	1000
	I	mg/kg	mg/kg	mg/kg	mg/kg
	I	III	V	VII	
LIVER	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10
KIDNEYS	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	9	1
DILATATION, BILATERAL, PELVIS, LEFT MODERATE RIGHT SEVERE.					
LUNGS	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10
HEART	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10
SKELETAL MUSCLE	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10

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 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (Numeric)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg I	mg/kg III	mg/kg V	mg/kg VII
SPLEEN					
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)
AORTA					
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)
BRAIN					
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)
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)

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 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (Numeric)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
	I	III	V	VII	
JEJUNUM	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10
ILEUM	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10
PANCREAS	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10
CECUM	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10
COLON	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10
RECTUM	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10

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

TABLE 40 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (Numeric)				
	Males				
	TREATMENT	0	10	100	1000
	mg/kg	I	mg/kg III	mg/kg V	mg/kg VII
MESENTERIC LYMPH NODE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SALIVARY GLANDS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
MANDIBULAR LYMPH NODE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
THYMUS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
ADRENAL GLANDS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SCIATIC NERVE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

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

TABLE 40 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (Numeric)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
PITUITARY GLAND					
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)
10		10	10	10	10
THYROID GLAND					
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)
10		10	10	10	10
PARATHYROID GLANDS					
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)
10		10	10	10	10
TRACHEA					
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)
10		10	10	10	10
ESOPHAGUS					
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)
10		10	10	10	10
PHARYNX/LARYNX					
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)
10		10	10	10	10

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

TABLE 40 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (Numeric)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg I	mg/kg III	mg/kg V	mg/kg VII
EYE(S) WITH OPTIC NERVE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SKIN		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
PROSTATE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SEMINAL VESICLES		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
URINARY BLADDER		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
TESTES		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	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 40 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (Numeric)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
EPIDIDYMAIDES		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
FEMUR/KNEE JOINT		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
STERNUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
NOSE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

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

TABLE 41
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESION	TREATMENT		LESION INCIDE	
			Males	
	I	VII	I	VII
LIVER	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
KIDNEYS	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
LUNGS	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
HEART	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
SKELETAL MUSCLE	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
SPLEEN	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		

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 41 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	TREATMENT		LESION INCIDENCE	
	Males		Males	
	0 mg/kg I	1000 mg/kg VII		
AORTA	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
BRAIN	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
SPINAL CORD	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
STOMACH	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
DUODENUM	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
JEJUNUM	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		

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

TABLE 41 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	TREATMENT		LESION INCIDENCE	
	Males		Males	
	0 mg/kg I	1000 mg/kg VII		
ILEUM	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
PANCREAS	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
CECUM	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
COLON	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
RECTUM	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
MESENTERIC LYMPH NODE	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		

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

TABLE 41 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	TREATMENT		LESION INCIDE	
			Males	
		0 mg/kg I	1000 mg/kg VII	
SALIVARY GLANDS		(10)	(10)	
NO ABNORMALITY DETECTED		10	10	
MANDIBULAR LYMPH NODE		(10)	(10)	
NO ABNORMALITY DETECTED		10	10	
THYMUS		(10)	(10)	
NO ABNORMALITY DETECTED		10	10	
ADRENAL GLANDS		(10)	(10)	
NO ABNORMALITY DETECTED		10	10	
SCIATIC NERVE		(10)	(10)	
NO ABNORMALITY DETECTED		10	10	
PITUITARY GLAND		(10)	(10)	
NO ABNORMALITY DETECTED		10	10	

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

TABLE 41 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESION INCIDENCE	TREATMENT	
	0	1000
	mg/kg	mg/kg
	I	VII
THYROID GLAND	(10)	(10)
NO ABNORMALITY DETECTED	10	10
PARATHYROID GLANDS	(10)	(10)
NO ABNORMALITY DETECTED	10	10
TRACHEA	(10)	(10)
NO ABNORMALITY DETECTED	10	10
ESOPHAGUS	(10)	(10)
NO ABNORMALITY DETECTED	10	10
PHARYNX/LARYNX	(10)	(10)
NO ABNORMALITY DETECTED	10	10
EYE(S) WITH OPTIC NERVE	(10)	(10)
NO ABNORMALITY DETECTED	10	10

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 41 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESION	INCIDENCE	
	Males	
TREATMENT	0 mg/kg I	1000 mg/kg VII
SKIN	(10)	(10)
NO ABNORMALITY DETECTED	10	10
PROSTATE	(10)	(10)
NO ABNORMALITY DETECTED	10	10
SEMINAL VESICLES	(10)	(10)
NO ABNORMALITY DETECTED	10	10
URINARY BLADDER	(10)	(10)
NO ABNORMALITY DETECTED	10	10
TESTES	(10)	(10)
NO ABNORMALITY DETECTED	10	10
EPIDIDYMIDES	(10)	(10)
NO ABNORMALITY DETECTED	10	10

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 41 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	TREATMENT	LESION INCIDENCE	
		Males	
		0 mg/kg I	1000 mg/kg VII
FEMUR/KNEE JOINT		(10)	(10)
NO ABNORMALITY DETECTED		10	10
STERNUM		(10)	(10)
NO ABNORMALITY DETECTED		10	10
NOSE		(10)	(10)
NO ABNORMALITY DETECTED		10	10

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

TABLE 42

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	Females			
	LESION INCIDENCE (Animal No)			
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI
LIVER		(10)	(10)	(10)
NO ABNORMALITY DETECTED DEFORMITY, RIGHT, LOBE.		10	10	10
KIDNEYS		(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10
LUNGS		(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10
HEART		(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10
SKELETAL MUSCLE		(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10
SPLEEN		(10)	(10)	(10)
NO ABNORMALITY DETECTED		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 42 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

TREATMENT	Females			
	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
LESIONS				
AORTA	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10
BRAIN	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10
SPINAL CORD	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10
STOMACH	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10
DUODENUM	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10
JEJUNUM	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10

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

TABLE 42 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (Animal No				
	Females				
	TREATMENT	0	10	100	1000
	mg/kg	mg/kg	mg/kg	mg/kg	
	II	IV	VI	VIII	
ILEUM	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	
PANCREAS	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	
CECUM	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	
COLON	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	
RECTUM	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	
MESENTERIC LYMPH NODE	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	

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

TABLE 42 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (Animal No)				
	Females				
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
SALIVARY GLANDS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
MANDIBULAR LYMPH NODE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
THYMUS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
ADRENAL GLANDS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SCIATIC NERVE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
PITUITARY GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED LARGE.		9 1	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 42 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (Animal No)				
	Females				
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
THYROID GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
PARATHYROID GLANDS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
TRACHEA		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
ESOPHAGUS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
PHARYNX/LARYNX		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
EYE(S) WITH OPTIC NERVE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

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 42 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	Females				LESION INCIDENCE (Animal No)
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
SKIN		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
MAMMARY GLAND (FEMALE)		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
OVARIES		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
UTERUS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
VAGINA		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
URINARY BLADDER		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

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

TABLE 42 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (Animal No)				
	Females				
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
FEMUR/KNEE JOINT		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
STERNUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
NOSE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

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

TABLE 43

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESION	LESION INCIDE	
	Females	
LESION	TREATMENT	0 1000
	mg/kg II	mg/kg VIII
LIVER	(10)	(10)
NO ABNORMALITY DETECTED	10	10
KIDNEYS	(10)	(10)
NO ABNORMALITY DETECTED	10	10
LUNGS	(10)	(10)
NO ABNORMALITY DETECTED	10	10
HEART	(10)	(10)
NO ABNORMALITY DETECTED	10	10
SKELETAL MUSCLE	(10)	(10)
NO ABNORMALITY DETECTED	10	10
SPLEEN	(10)	(10)
NO ABNORMALITY DETECTED	10	10

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 43 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS		TREATMENT		LESION INCIDE	
				Females	
		0	1000		
		mg/kg	mg/kg		
		II	VIII		
AORTA		(10)	(10)		
NO ABNORMALITY DETECTED		10	10		
BRAIN		(10)	(10)		
NO ABNORMALITY DETECTED		10	10		
SPINAL CORD		(10)	(10)		
NO ABNORMALITY DETECTED		10	10		
STOMACH		(10)	(10)		
NO ABNORMALITY DETECTED		10	10		
DUODENUM		(10)	(10)		
NO ABNORMALITY DETECTED		10	10		
JEJUNUM		(10)	(10)		
NO ABNORMALITY DETECTED		10	10		

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

TABLE 43 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	TREATMENT		LESION INCIDE	
	Females		Females	
	0 mg/kg II	1000 mg/kg VIII		
ILEUM	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
PANCREAS	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
CECUM	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
COLON	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
RECTUM	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
MESENTERIC LYMPH NODE	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		

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

TABLE 43 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESION	TREATMENT		LESION INCIDE	
	Females		Females	
	0 mg/kg II	1000 mg/kg VIII		
SALIVARY GLANDS	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
MANDIBULAR LYMPH NODE	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
THYMUS	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
ADRENAL GLANDS	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
SCIATIC NERVE	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
PITUITARY GLAND	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		

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

TABLE 43 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR RECOVERY EVALUATION

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

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

TABLE 43 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	TREATMENT		LESION INCIDE	
	Females			
	0 mg/kg II	1000 mg/kg VIII		
SKIN	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
MAMMARY GLAND (FEMALE)	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
OVARIES	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
UTERUS	(10)	(10)		
NO ABNORMALITY DETECTED	10	9		
DILATATION, HORNS.		1		
VAGINA	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
URINARY BLADDER	(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 43 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
DESIGNATED FOR RECOVERY EVALUATION

LESION	TREATMENT		LESION INCIDE	
	Females		Females	
	0 mg/kg II	1000 mg/kg VIII		
FEMUR/KNEE JOINT	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
STERNUM	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		
NOSE	(10)	(10)		
NO ABNORMALITY DETECTED	10	10		

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

TABLE 44

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg I	mg/kg III	mg/kg V	mg/kg VII
DIGESTIVE SYSTEM					
LIVER					
NO ABNORMALITY DETECTED	(10)	(10)	(10)	(10)	(10)
NECROSIS, FOCAL.		1			1
INFLAMMATION, SUBACUTE/CHRONIC.	10	9	10	10	10
HYPERTROPHY, HEPATOCELLULAR, CENTRILLOBULAR.	7	1	3	3	9
FATTY CHANGE, PERIportal.	2			5	1
FATTY CHANGE, MEDIAN CLEFT.					1
DEGENERATION, HEPATOCELLULAR, FOCAL.					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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
LESIONS	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
DIGESTIVE SYSTEM					
PANCREAS		(10)			(10)
NO ABNORMALITY DETECTED INFLAMMATION, FOCAL.		9 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 44 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
LESIONS		mg/kg I	mg/kg III	mg/kg V	mg/kg VII
DIGESTIVE SYSTEM					
ESOPHAGUS		(9)			(10)
NO ABNORMALITY DETECTED		9			10

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

TABLE 44 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
DIGESTIVE SYSTEM					
STOMACH		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 44 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMBER)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg I	mg/kg III	mg/kg V	mg/kg VII
DIGESTIVE SYSTEM					
DUODENUM		(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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg I	mg/kg III	mg/kg V	mg/kg VII
DIGESTIVE SYSTEM					
JEJUNUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 44 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
DIGESTIVE SYSTEM					
ILEUM		(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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
DIGESTIVE SYSTEM					
CECUM		(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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
DIGESTIVE SYSTEM					
COLON		(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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
LESIONS	TREATMENT	0	10	100	1000
		mg/kg I	mg/kg III	mg/kg V	mg/kg VII
DIGESTIVE SYSTEM					
RECTUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
DIGESTIVE SYSTEM					
SALIVARY GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
URINARY SYSTEM		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
KIDNEYS					

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

TABLE 44 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
URINARY SYSTEM	mg/kg	I	mg/kg	mg/kg	mg/kg
			III	V	VII
URINARY BLADDER		(10)			(10)
NO ABNORMALITY DETECTED		8			7
AGGREGATES, LYMPHOID.		2			3

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
RESPIRATORY SYSTEM					
LUNGS		(10)			(10)
NO ABNORMALITY DETECTED		4			4
MACROPHAGES, ALVEOLAR, FOCAL.		2			1
INFLAMMATION, SUBACUTE/CHRONIC, PERIVASCULAR.		1			3
HEMORRHAGE, ALVEOLAR.		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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
RESPIRATORY SYSTEM					
TRACHEA		(10)			(10)
NO ABNORMALITY DETECTED INFLAMMATION, FOCAL.		10			9 1

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
RESPIRATORY SYSTEM					
PHARYNX/LARYNX		(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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
RESPIRATORY SYSTEM					
NOSE		(10)			(10)
NO ABNORMALITY DETECTED		7			6
INFLAMMATION, TURBINATES.		1			2
INFLAMMATION, VOMERONASAL ORGAN.		1			1
INFLAMMATION, ORAL MUCCOSA.		1			1
INFLAMMATION, NASOLACRIMAL DUCT.		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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
CARDIOVASCULAR SYSTEM					
HEART		(10)			(10)
NO ABNORMALITY DETECTED INFLAMMATION, SUBACUTE/CHRONIC.		9 1			9 1

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
CARDIOVASCULAR SYSTEM					
AORTA		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN		(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 44 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
THYMUS		(10)			(10)
NO ABNORMALITY DETECTED		4			2
HEMORRHAGE.		6			8

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
MANDIBULAR LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		8			6
NECROSIS, LYMPHOID.		1			1
LEUKOCYTOSIS, PLASMA CELL, MEDULLARY.		1			1
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS.		1			3

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

TABLE 44 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
MESENTERIC LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
BONE MARROW		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
ENDOCRINE SYSTEM		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
PITUITARY GLAND		(10)			(10)
NO ABNORMALITY DETECTED CYST.		9			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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
ENDOCRINE SYSTEM					
THYROID GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		9	9	9	10
HYPERTROPHY, FOLLICULAR CELL.		1	1	1	

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESION	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
ENDOCRINE SYSTEM					
PARATHYROID GLANDS		(9)			(10)
NO ABNORMALITY DETECTED		9			10

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
ENDOCRINE SYSTEM					
ADRENAL GLANDS		(10)			(10)
NO ABNORMALITY DETECTED ADRENAL MEDULLA MISSING.		9 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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
TREATMENT	0	10	100	1000	
	mg/kg I	mg/kg III	mg/kg V	mg/kg VII	
LESIONS					
NERVOUS SYSTEM					
BRAIN	(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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0	10	100	1000	
		mg/kg	mg/kg	mg/kg	mg/kg	
		I	III	V	VII	
NERVOUS SYSTEM						
SPINAL CORD		(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 44 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		ng/kg I	ng/kg III	ng/kg V	ng/kg VII
NERVOUS SYSTEM					
SCIATIC NERVE		(9)			(10)
NO ABNORMALITY DETECTED		9			10

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
LESIONS					
MUSCULAR AND SKELETAL SYSTEM					
SKELETAL MUSCLE		(9)			(10)
NO ABNORMALITY DETECTED		9			10

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

TABLE 44 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
MUSCULAR AND SKELETAL SYSTEM					
FEMUR/KNEE JOINT		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 44 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
MUSCULAR AND SKELETAL SYSTEM					
STERNUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 44 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
LESIONS	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
REPRODUCTIVE SYSTEM					
TESTES		(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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
REPRODUCTIVE SYSTEM					
EPIDIDYMIDES		(10)			(10)
NO ABNORMALITY DETECTED AGGREGATES, LYMPHOID.		6 4			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 44 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

REPRODUCTIVE SYSTEM	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
LESIONS					
PROSTATE		(10)			(10)
NO ABNORMALITY DETECTED AGGREGATES, LYMPHOID.		3 7			4 6

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
REPRODUCTIVE SYSTEM					
SEMINAL VESICLES		(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 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
CUTANEOUS SYSTEM					
SKIN		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 44 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE		(10)			(10)
NO ABNORMALITY DETECTED		5			8
OPTIC NERVE NOT PRESENT, UNILATERAL.		4			1
INFLAMMATION, PERIOCCULAR, UNILATERAL.		4			1
ATROPHY, RETINAL, UNILATERAL.		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 45
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
DIGESTIVE SYSTEM					
LIVER		(10)			(10)
NECROSIS, FOCAL.					2
INFLAMMATION, SUBACUTE/CHRONIC.					10
FATTY CHANGE, PERIportal.					2
FATTY CHANGE, MEDIAN CLEFT.					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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
DIGESTIVE SYSTEM					
PANCREAS		(1)			
FOCUS OF CELLULAR ALTERATION, BASOPHILIC.		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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII	
DIGESTIVE SYSTEM						
ESOPHAGUS		(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 45 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
DIGESTIVE SYSTEM					
STOMACH		(1)			
NO ABNORMALITY DETECTED		1			

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

TABLE 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
LESIONS					
DIGESTIVE SYSTEM					
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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
DIGESTIVE SYSTEM					
JEJUNUM		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
LESIONS		mg/kg I	mg/kg III	mg/kg V	mg/kg VII
DIGESTIVE SYSTEM					
ILEUM		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
DIGESTIVE SYSTEM					
CECUM		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
TREATMENT	0	10	100	1000	
	mg/kg	mg/kg	mg/kg	mg/kg	
	I	III	V	VII	
DIGESTIVE SYSTEM					
COLON					
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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
DIGESTIVE SYSTEM					
RECTUM		(1)			
NO ABNORMALITY DETECTED		1			

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

TABLE 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
LESIONS		mg/kg	mg/kg	mg/kg	mg/kg
	I	III	V	VII	
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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
	I	III	V	VII	
URINARY SYSTEM					
KIDNEYS	(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
LESIONS	TREATMENT	0	10	100	1000
		mg/kg I	mg/kg III	mg/kg V	mg/kg VII
URINARY SYSTEM					
URINARY BLADDER		(1)			
NO ABNORMALITY DETECTED		1			

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

TABLE 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
TREATMENT	0	10	100	1000	
	mg/kg I	mg/kg III	mg/kg V	mg/kg VII	
LESIONS					
RESPIRATORY SYSTEM					
LUNGS	(1)				
MACROPHAGES, ALVEOLAR, FOCAL. HEMORRHAGE, ALVEOLAR.	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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0	10	100	1000	
LESIONS	mg/kg	I	III	V	VII	
RESPIRATORY SYSTEM						
TRACHEA		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0	10	100	1000	
		mg/kg	mg/kg	mg/kg	mg/kg	
		I	III	V	VII	
RESPIRATORY SYSTEM						
PHARYNX/LARYNX		(1)				
NO ABNORMALITY DETECTED		1				

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

TABLE 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
LESIONS	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
RESPIRATORY SYSTEM					
NOSE		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
CARDIOVASCULAR SYSTEM					
HEART		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
CARDIOVASCULAR SYSTEM					
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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
THYMUS		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
MANDIBULAR LYMPH NODE		(1)			
NO ABNORMALITY DETECTED		1			

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

TABLE 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
	I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
MESENTERIC LYMPH NODE	(1)				
NO ABNORMALITY DETECTED	1				

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

TABLE 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0	10	100	1000	
		mg/kg	mg/kg	mg/kg	mg/kg	
		I	III	V	VII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
BONE MARROW		(1)				
NO ABNORMALITY DETECTED		1				

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

TABLE 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
ENDOCRINE SYSTEM					
PITUITARY GLAND		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
ENDOCRINE SYSTEM					
THYROID GLAND		(10)			(10)
NO ABNORMALITY DETECTED HYPERTROPHY, FOLLICULAR CELL.		9			4
		1			6

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

TABLE 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg I	mg/kg III	mg/kg V	mg/kg VII
ENDOCRINE SYSTEM					
ADRENAL GLANDS					
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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
NERVOUS SYSTEM	I	ng/kg	ng/kg	ng/kg	ng/kg
	III				
	V				
	VII				
BRAIN	(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
NERVOUS SYSTEM					
SPINAL CORD		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
TREATMENT	0	10	100	1000	
	mg/kg	mg/kg	mg/kg	mg/kg	
	I	III	V	VII	
NERVOUS SYSTEM					
SCIATIC NERVE	(1)				
NO ABNORMALITY DETECTED	1				

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

TABLE 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0	10	100	1000	
		mg/kg	mg/kg	mg/kg	mg/kg	
		I	III	V	VII	
MUSCULAR AND SKELETAL SYSTEM						
SKELETAL MUSCLE		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
MUSCULAR AND SKELETAL SYSTEM					
FEMUR/KNEE JOINT		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII	
MUSCULAR AND SKELETAL SYSTEM						
STERNUM		(1)				
NO ABNORMALITY DETECTED		1				

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

TABLE 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII	
REPRODUCTIVE SYSTEM						
TESTES		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
REPRODUCTIVE SYSTEM					
EPIDIDYMIDES		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
REPRODUCTIVE SYSTEM					
PROSTATE		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
LESIONS	TREATMENT	0	10	100	1000
		mg/kg I	mg/kg III	mg/kg V	mg/kg VII
REPRODUCTIVE SYSTEM					
SEMINAL VESICLES		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
LESIONS					
CUTANEOUS SYSTEM					
SKIN		(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 45 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Males				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		I	III	V	VII
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE		(1)			
OPTIC NERVE NOT PRESENT, UNILATERAL.		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 46

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)			
	Females			
TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
DIGESTIVE SYSTEM				
LIVER				
NO ABNORMALITY DETECTED	(10)	(10)	(10)	(10)
NECROSIS, FOCAL.	1	2	1	3
INFLAMMATION, SUBACUTE/CHRONIC.	8	8	10	7
FATTY CHANGE, PERIportal.	6			1
FATTY CHANGE, MEDIAN CLEFT.	3	1	1	

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
	mg/kg	mg/kg	mg/kg	mg/kg	
	II	IV	VI	VIII	
DIGESTIVE SYSTEM					
PANCREAS		(10)			(10)
NO ABNORMALITY DETECTED AGGREGATES, LYMPHOID.		10			8 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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)			
	Females			
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI
		1000 mg/kg VIII		
DIGESTIVE SYSTEM				
ESOPHAGUS		(10)		(10)
NO ABNORMALITY DETECTED		10		10

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Females				
LESIONS	TREATMENT				
	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII	
DIGESTIVE SYSTEM					
STOMACH	(10)				(10)
NO ABNORMALITY DETECTED	10				10

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
LESIONS	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
	II	IV	VI	VIII	
DIGESTIVE SYSTEM					
DUODENUM	(10)				(9)
NO ABNORMALITY DETECTED	10				9

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

TABLE 46 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

		LESION INCIDENCE (NUMERIC)			
		Females			
LESIONS	TREATMENT	0	10	100	1000
		mg/kg II	mg/kg IV	mg/kg VI	mg/kg VIII

DIGESTIVE SYSTEM					
JEJUNUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 46 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)			
	Females			
TREATMENT	0	10	100	1000
	mg/kg II	mg/kg IV	mg/kg VI	mg/kg VIII
DIGESTIVE SYSTEM				
ILEUM	(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 46 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	Females				
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
DIGESTIVE SYSTEM					
CECUM		(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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)			
	Females			
DIGESTIVE SYSTEM	TREATMENT	0	10	100
		mg/kg	mg/kg	mg/kg
COLON	II			
	IV			
NO ABNORMALITY DETECTED	VI			
	VIII			
		(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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
DIGESTIVE SYSTEM					
RECTUM		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Females				
LESIONS	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
DIGESTIVE SYSTEM					
SALIVARY GLANDS		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

	Females				
	LESION INCIDENCE (NUMERIC)				
TREATMENT	0	10	100	1000	
	mg/kg II	mg/kg IV	mg/kg VI	mg/kg VIII	
LESIONS					
URINARY SYSTEM					
KIDNEYS	(10)			(10)	
NO ABNORMALITY DETECTED	6			6	
CHRONIC PROGRESSIVE NEPHROPATHY.	3			1	
AGGREGATES, LYMPHOID.	1			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 46 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
URINARY SYSTEM					
URINARY BLADDER		(9)			(10)
NO ABNORMALITY DETECTED		9			10

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
RESPIRATORY SYSTEM	TREATMENT	0	10	100	1000
		mg/kg II	mg/kg IV	mg/kg VI	mg/kg VIII
LUNGS					
NO ABNORMALITY DETECTED		(10)			(10)
INFLAMMATION, SUBACUTE/CHRONIC, PERIVASCULAR.		2			6
HEMORRHAGE, ALVEOLAR.		2			1
		7			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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

	LESION INCIDENCE (NUMERIC)				
	Females				
LESIONS	TREATMENT				
	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII	
RESPIRATORY SYSTEM					
TRACHEA	(10)				(10)
NO ABNORMALITY DETECTED INFLAMMATION, AGGREGATES, LYMPHOID.	9 1				9 1

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
RESPIRATORY SYSTEM					
PHARYNX/LARYNX		(10)			(10)
NO ABNORMALITY DETECTED DEGENERATION, MYOFIBER.		9			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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
TREATMENT	0	10	100	1000	
	mg/kg II	mg/kg IV	mg/kg VI	mg/kg VIII	
RESPIRATORY SYSTEM					
NOSE	(10)			(10)	
NO ABNORMALITY DETECTED INFLAMMATION, TURBINATES. INFLAMMATION, SINUS. INFLAMMATION, ORAL MUCOSA.	9			7 3 1	
	1				

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
CARDIOVASCULAR SYSTEM					
HEART		(10)			(10)
NO ABNORMALITY DETECTED INFLAMMATION, SUBACUTE/CHRONIC.		10			9 1

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	TREATMENT	Females			
		LESION INCIDENCE (NUMERIC)			
		0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
CARDIOVASCULAR SYSTEM					
AORTA		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
SPLEEN		(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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
THYMUS		(10)			(10)
NO ABNORMALITY DETECTED		5			2
HEMORRHAGE.		5			8
CYST, EPITHELIAL.					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 46 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
MANDIBULAR LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		8			9
LEUKOCYTOSIS, PLASMA CELL, MEDULLARY.		1			1
HYPERPLASIA, LYMPHOID.		1			
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS.					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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
MESENTERIC LYMPH NODE		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
TREATMENT	0	10	100	1000	
	mg/kg II	mg/kg IV	mg/kg VI	mg/kg VIII	
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
BONE MARROW	(10)				(10)
NO ABNORMALITY DETECTED	10				10

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
ENDOCRINE SYSTEM					
PITUITARY GLAND		(10)			(10)
NO ABNORMALITY DETECTED		8			10
CYST.		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 46 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
ENDOCRINE SYSTEM					
THYROID GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	8
HYPERTROPHY, FOLLICULAR CELL.					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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
ENDOCRINE SYSTEM					
PARATHYROID GLANDS		(8)			(9)
NO ABNORMALITY DETECTED		8			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 46 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESION	LESION INCIDENCE (NUMERIC)				
	Females				
TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII	
ENDOCRINE SYSTEM					
ADRENAL GLANDS	(10)				(10)
NO ABNORMALITY DETECTED	10				10

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
NERVOUS SYSTEM					
BRAIN		(10)			(10)
NO ABNORMALITY DETECTED		9			10
AGGREGATES, LYMPHOID, CHOROID PLEXUS.		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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
NERVOUS SYSTEM					
SPINAL CORD		(9)			(10)
NO ABNORMALITY DETECTED		9			10

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

TABLE 46 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
NERVOUS SYSTEM					
SCIATIC NERVE		(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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
MUSCULAR AND SKELETAL SYSTEM					
SKELETAL MUSCLE		(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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0	10	100	1000
		mg/kg	mg/kg	mg/kg	mg/kg
		II	IV	VI	VIII
MUSCULAR AND SKELETAL SYSTEM					
FEMUR/KNEE JOINT		(10)			(10)
NO ABNORMALITY DETECTED		10			10

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII	
MUSCULAR AND SKELETAL SYSTEM					
STERNUM					
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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII	
REPRODUCTIVE SYSTEM					
OVARIES	(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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII	
REPRODUCTIVE SYSTEM					
UTERUS					
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 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
TREATMENT	0	10	100	1000	
	mg/kg	mg/kg	mg/kg	mg/kg	
	II	IV	VI	VIII	
REPRODUCTIVE SYSTEM					
VAGINA					
ESTRUS STAGE: METESTRUS.	(10)			(10)	
ESTRUS STAGE: ESTRUS.	4			2	
ESTRUS STAGE: PROESTRUS.	2			3	
	4			5	

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII	
REPRODUCTIVE SYSTEM					
MAMMARY GLAND (FEMALE)	(10)				(10)
NO ABNORMALITY DETECTED	10				10

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
TREATMENT	0	10	100	1000	
	mg/kg II	mg/kg IV	mg/kg VI	mg/kg VIII	
CUTANEOUS SYSTEM					
SKIN					
NO ABNORMALITY DETECTED DERMATITIS, FOCAL.	(10) 9 1			(10) 9 1	

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

TABLE 46 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR SUBCHRONIC TOXICITY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)					
	Females					
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII	
SPECIAL SENSES SYSTEM	EYE(S) WITH OPTIC NERVE					
	NO ABNORMALITY DETECTED OPTIC NERVE NOT PRESENT, UNILATERAL. OPTIC NERVE NOT PRESENT, BILATERAL. INFLAMMATION, PERIOCCULAR, UNILATERAL. FOLD/ROSETTE, RETINAL.					

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

TABLE 47

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
ENDOCRINE SYSTEM					
THYROID GLAND		(10)			(10)
NO ABNORMALITY DETECTED HYPERTROPHY, FOLLICULAR CELL. ECTOPIC THYMUS TISSUE.		10			7 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 47 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
	TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII
REPRODUCTIVE SYSTEM					
UTERUS					(1)
NO ABNORMALITY DETECTED					1

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

TABLE 47 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
DESIGNATED FOR RECOVERY EVALUATION

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
TREATMENT	0 mg/kg II	10 mg/kg IV	100 mg/kg VI	1000 mg/kg VIII	
REPRODUCTIVE SYSTEM					
VAGINA					(1)
ESTRUS STAGE: PROESTRUS.					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

