

AR226-3272

454

TRADE SECRET*Study Title*

[REDACTED] Subchronic Toxicity
90-Day Oral Gavage Study in Rats

Volume 1 of 3

Laboratory Project ID: DuPont-9478

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

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STUDY COMPLETED ON: April 1, 2003

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

SERVICE CODE NUMBER: [REDACTED]

QUALITY ASSURANCE STATEMENT

Haskell Sample Number(s):

24691

Dates of Inspections:

Protocol: February 1,7, 2002
Conduct: February 12, 2002; March 26, 2002; April 1,2,25, 2002; May
14,23, 2002
Records, Reports: October 1-4,7-9,14-15,22-23,25,28, 2002; November 11-13,24-27
2002; December 16-19,22, 2002; January 12-15, 2003

Dates Findings Reported to:

Study Director: October 9,15,28, 2002; November 13,27; January 14,15, 2003
Management: October 9,18, 2002; November 5,27, 2002; December 10, 2002;
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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]

Haskell Number: 24691

CAS Registry Number: [REDACTED]

Composition: [REDACTED]

Purity: [REDACTED]

Known Impurities: [REDACTED]

Physical Characteristics: [REDACTED]

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

Sponsor: Telomer Research Program
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Study Initiated/Completed: February 7, 2002 / (see report cover page)

In-Life Initiated/Completed: February 12, 2002 / August 22, 2002

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SUMMARY

Five groups of young adult male and female Crl:CD®(SD)IGS BR rats were administered [REDACTED] daily by gavage at dosages of 0, 1, 5, 25, and 125 mg/kg/day for approximately 90 days. Body weights, food consumption, and clinical signs were evaluated weekly. Clinical pathology endpoints were evaluated on weeks 7, 13, and near the end of the three-month recovery period. Neurobehavioral assessments were also performed prior to dosing and during week 13. Biochemical evaluations (hepatic β -oxidation) were performed on animals after 10 and approximately 90 days of dosing and following the three-month recovery period. After approximately 90 days of dosing, 10 rats/sex/dose were sacrificed and given a gross and microscopic pathological examination. Approximately three months after the 90-day dosing period, 10 animals/sex in the control and high dose group were examined for recovery of toxic effects. A subgroup of 5 rats/sex/dose were designated as satellite bleed animals. An additional five animals/sex/dose were designated for hepatic biochemical analysis following a 10-day exposure to the test substance.

The range of mean daily dose volumes of [REDACTED] administered to male rats was 1.2 to 3.0 ml. The range administered to female rats was 0.9 to 1.6 ml.

In-Life Toxicology Parameters: No test substance-related mortality occurred in the study. A test substance-related, toxicologically significant increase in the incidence of striated teeth was observed in the 125 mg/kg/day male and female dose groups. On test day 77, all male and female high dose animals were placed on ground chow due to test substance-induced alterations to the teeth. There were no test substance-related, toxicologically significant alterations in body weight, body weight gain, food consumption, or food efficiency observed in any of the male or female dose groups.

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

Biochemical Toxicology: The rate of hepatic β -oxidation, a measure of peroxisome proliferation, was significantly increased in females administered 25 mg/kg/day [REDACTED] and in males and females administered 125 mg/kg/day [REDACTED]. Following a three-month recovery period, the rate of hepatic β -oxidation was lower but still significantly increased in males administered 125 mg/kg/day [REDACTED] and had returned to control levels in female rats.

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

There were no toxicologically significant changes in clinical pathology parameters observed in rats dosed with up to 125 mg/kg/day [REDACTED]. Other changes during treatment or after a three-month recovery were considered treatment-related but non-adverse because the magnitude of change was small, transient, and/or in a direction not associated with toxicity.

Treatment-related changes observed in rats administered ≥ 25 mg/kg/day included decreases in some red cell mass parameters along with reticulocytosis and increased serum cholesterol (females only). Test substance-related changes in clinical pathology of rats dosed with 125 mg/kg/day included transiently increased alkaline phosphatase (males only), increased phosphorus (males only), decreased triglycerides (males only), increased total protein and albumin, increased calcium (females only), increased urine volume (males only), and decreased urine ketone concentrations (males only). Plasma fluoride levels were significantly increased in males and females dosed with 125 mg/kg/day, but returned to control levels following three months of recovery. Urine fluoride excretion was increased in males and females dosed with ≥ 5 mg/kg/day. After three months of recovery, urine fluoride levels in females returned to control levels, while levels in males were significantly reduced compared to those at the end of the exposure period.

Anatomical Pathology: Test substance-related, toxicologically significant degeneration/disorganization of enamel organ ameloblast cells occurred in male rats administered 125 mg/kg/day [REDACTED]

A test substance-related, adverse increase in the incidence and severity of focal hepatic necrosis was observed in males administered 25 and 125 mg/kg/day. An increased incidence and severity of chronic progressive nephropathy occurred in the 125 mg/kg/day female group and was considered adverse.

Test-substance related and statistically significant increases in liver weight parameters were present in males and females administered 25 or 125 mg/kg/day for approximately 90 days. The increased liver weights correlated with microscopic hepatocellular hypertrophy in the 125 mg/kg/day male dose group. Liver weight changes and microscopic hypertrophy were considered to be a physiological adaptive response to metabolism of the test substance and not adverse. Test-substance related and statistically significant increases in kidney weight parameters occurred in males and females administered 25 or 125 mg/kg/day. The increased kidney weights correlated with microscopic renal tubular hypertrophy in the 25 and 125 mg/kg/day male groups only. However, no correlative microscopic or clinical pathological evidence of renal toxicity were present. Therefore, kidney weight changes and microscopic tubular hypertrophy were not considered adverse findings. Altered colloid, a common spontaneous finding in rats, was increased in incidence and/or severity in treated male groups. This change was not associated with other findings in the thyroid gland and was also not considered an adverse finding.

After three months of recovery, rats dosed with 125 mg/kg/day showed reversibility of some effects. The ameloblastic degeneration/disorganization persisted with decreased incidence and severity in the 125 mg/kg/day male group. Alterations in thyroid colloid persisted in male rats. Increased liver weight parameters and hepatocellular hypertrophy (males only) were no longer observed in the 125 mg/kg/day male and female groups. However, the incidence of hepatocellular necrosis in the 125 mg/kg/day male group increased after three months of recovery. Increased kidney weight parameters and renal tubular hypertrophy (males only) were not observed in rats sacrificed after three months of recovery. In contrast, the incidence and

severity of chronic progressive nephropathy were increased in the 125 mg/kg/day female group following three months of recovery.

In conclusion, the no-observed-effect level (NOEL)^a for males was 5 mg/kg/day [REDACTED] based on the increased incidence of hepatic necrosis observed in males administered $\geq$ 25 mg/kg/day. The NOEL for females was 25 mg/kg/day [REDACTED] based on the increased incidence and severity of chronic progressive nephropathy observed in females administered 125 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, [REDACTED] is an [REDACTED]. The 1, 5, 25, and 125 mg/kg/day dose levels for this study were selected based on the toxicity observed in an 84-day range finding study with 5, 25, and 125 mg/kg/day [REDACTED] and subchronic studies with similar [REDACTED] and perfluorooctanoic acid (PFOA). In the [REDACTED] range finder study, significantly lower mean body weights compared to control were observed in male rats administered 125 mg/kg/day. Similarly, significantly lower mean body weights compared to control were also observed in rats administered 100 mg/kg/day or greater of similar fluorotelomer-based alcohols. Significantly increased liver weights occurred in males dosed with 125 mg/kg/day [REDACTED]. Liver weights were also significantly increased compared to control in rats administered dose levels of [REDACTED] as low as 100 mg/kg/day. Furthermore, data suggest that the PFOA metabolite may accumulate in animals dosed with the [REDACTED]. In repeat dose studies, PFOA at doses of 10 mg/kg/day or lower produced the following effects: increased liver weights, increased hepatic cell proliferation and beta oxidation, and altered serum hormone levels.^(1,2,3,4) The high-dose level of 125 mg/kg/day for this study was selected based on the reductions in body weight and increased liver weights observed in males dosed with 125 mg/kg/day [REDACTED] as well as the ability of rats to tolerate a 100 mg/kg/day dose level in subchronic studies with similar [REDACTED]. The 125 mg/kg/day dose was expected to produce toxicity without excessive mortality. The low dose of 1 mg/kg/day was expected to be the no-observed-effect level (NOEL), while the 5 and 25 mg/kg/day dose levels were expected to induce minimal to no toxicity.

OBJECTIVE

The objective of this study is to evaluate the potential subchronic toxicity and reversibility of [REDACTED] when administered by gavage to male and female rats. The oral route of administration was selected as the most efficient way to deliver an accurate dosage.

MATERIALS AND METHODS

A. Test Guidelines

The subchronic toxicity study design complies with the United States Environmental Protection Agency (EPA), Office of Prevention, Pesticides, and Toxic Substances (OPPTS) Health Effects Test Guidelines, OPPTS 870.3100 90-Day Oral Toxicity in Rodents (Aug-1998).

B. Test Substance

The test substance [REDACTED] was supplied by the sponsor as a [REDACTED] with known purity [REDACTED] and composition. A reserve sample of the test substance was collected and retained by Haskell Laboratory.

C. Test Species

On 29-Jan-2002, Crl:CD[®](SD)IGS BR rats with an assigned birth date of 31-Dec-2001 were received from Charles River Laboratories, Inc., Raleigh, North Carolina. One hundred five male and 105 female rats were received for the main study and 28 male and 28 female rats were received for the 10-day biochemical evaluation.

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

D. Animal Husbandry

1. Housing

All rats were housed one per cage, sexes separate, in stainless steel, wire-mesh cages suspended above cage boards. Cage racks were relocated within the animal room and cages were repositioned on the racks every 2 weeks. Animal rooms were maintained on a 12-hour light/dark cycle (fluorescent light) and at a temperature of $22 \pm 3^{\circ}\text{C}$ and a relative humidity of $50\% \pm 20\%$. Occasional excursions outside the acceptable ranges were minor and did not affect the study.

2. Feed and Water

Tap water was provided *ad libitum*. All rats were fed pelleted PMI Nutrition International, Inc. Certified Rodent LabDiet[®] 5002 *ad libitum*. On test day 77, all rats in the male and female 125 mg/kg/day groups were placed on ground chow because of test substance-induced alterations to the teeth.

3. Identification

An individual identification number was tattooed on the tail of each rat. The information on the cage labels included the unique 6-digit Haskell animal number and the individual identification number assigned to each rat.

4. Health Monitoring Program

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

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Feed samples are analyzed for total bacterial, spore and fungal counts.

- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

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

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

E. Quarantine and Pretest Period

Upon arrival at Haskell Laboratory, all rats were quarantined for 7 days, observed daily for any clinically apparent signs of disease or injury, and weighed 4 times.

Rats designated for the subchronic toxicity and three-month recovery evaluations, and satellite bleeds were also examined by a veterinary ophthalmologist to identify animals with preexisting ocular lesions. Rats designated for the subchronic toxicity and three-month recovery evaluations were given a baseline neurobehavioral evaluation.

On the basis of acceptable body weight gains and clinical observations, all surviving main study rats were released from quarantine by the laboratory animal veterinarian designee on test day -11; rats designated for the 10-day biochemical analysis were released on test day -4.

F. Study Design

Group		Number/Group		Dosage ^a
Male	Female	Male	Female	
I	II	30	30	0 mg/kg/day (Control)
III	IV	20	20	1 mg/kg/day
V	VI	20	20	5 mg/kg/day
VII	VIII	20	20	25 mg/kg/day
IX	X	30	30	125 mg/kg/day

^a Weight/weight of test substance (adjusted for sponsor-supplied purity of active ingredient).

Each group of study animals, except those designated for the 10-day biochemical analysis, consisted of three subgroups: the first 10 rats/sex/dose were designated for evaluation of subchronic toxicity; the next 5 rats/sex/dose were designated as satellite bleed animals; and the last 10 rats/sex/dose (control and high-dose groups only) were designated as three-month recovery animals. An additional subgroup of 5 rats/sex/dose were designated for hepatic biochemical analysis following a 10-day exposure to the test substance.

Male and female rats designated for the subchronic toxicity evaluation were dosed through test days 92 (male) and 93 (female), and necropsied on test days 93 and 94, respectively. Male and female rats designated for the satellite bleeds were dosed through test day 90 and necropsied on test day 175 (85 days post dosing). Male and female rats designated for the three-month recovery evaluations were dosed through test day 90 and necropsied on test day 183 (93 days post dosing).

Neurobehavioral evaluations were conducted on male and female animals designated for the subchronic toxicity evaluation and three-month recovery evaluation (predose and week 13).

A clinical pathology evaluation was conducted on rats designated for the subchronic toxicity evaluation during week 7 and week 13 (prior to necropsy). Coagulation parameters and plasma and urine fluoride were not determined on week 7. Plasma and urine fluoride were determined for the three-month recovery animals on week 26.

Biochemical evaluations were conducted on selected animals designated for the subchronic toxicity evaluation, the three-month recovery evaluations, and the 10-day exposure evaluation. In-life data (body weight, food consumption, clinical observations) for rats designated for the 10-day biochemical analysis were collected from these animals and are in study records. However, these data are not included in this report.

G. Assignment to Groups

1. Rats Designated for the Subchronic Toxicity and Three-Month Recovery Evaluations, and Satellite Bleeds

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

On test day 0, prior to the start of test substance administration, 3 male rats and 3 female rats with out-of-range body weights, clinical signs, or neurobehavioral findings during pretest were replaced. Replacement rats were selected on the basis of freedom from any clinical signs of disease or injury and a body weight $\pm 20\%$ of the mean within a sex. Due to technician error, one male control rat with an out-of-range body weight was used on study.

H. Dose Suspension Preparation

[REDACTED] was suspended in 0.5% aqueous methylcellulose. Dosing suspensions of the test substance were prepared twice per week up to day 48, then prepared daily through the remainder of the dosing period.

I. Test Substance Administration

The test substance was administered daily to the study animals by oral gavage to achieve dosage levels of 1, 5, 25, or 125 mg/kg body weight/day, based on the most recently recorded body weight. Dose volumes for all groups were 5 mL/kg. Male and female control rats were similarly treated with 0.5% aqueous methylcellulose at the same dose volume as used in their respective high-dosage group.

Based on the results of analytical analysis of a 4-day dose preparation obtained on test day 45, rats at all dose levels may not have received a full dose of test substance on test days 45, 46, 47, and 48. Subsequent analytical analysis on additional dose preparations (not administered to rats) indicated that the test day 45 results were due to a sampling error.

1. Rats Designated for the Subchronic Toxicity and Three-Month Recovery Evaluations, and Satellite Bleeds

Oral administration of [REDACTED] began on test day 0, when the rats were approximately 50 days of age. Rats designated for the subchronic toxicity evaluation were dosed through test day 92 (males) or 93 (females). Rats designated for the three-month recovery evaluation and satellite bleeds were dosed through test day 90. Rats designated for recovery and satellite bleeds did not receive test substance during the recovery period.

2. Rats Designated for 10-Day Biochemical Analysis

Oral administration of [REDACTED] began 7 days prior to study start when the rats were approximately 42 days of age and ended on test day 2.

J. Test Substance Sampling

Dosing suspensions for this study were prepared at the beginning of the study as a large volume mix to be used either for 3 or 4 days of dosing. Subsequently, on day 49 of the study, the dosing suspension preparation was changed to a small volume mix to be used for 1 day of dosing.

Samples containing [REDACTED] at the concentrations of 0, 0.2, 1.0, 5.0, and 25.0 mg/mL were collected on test day -6 (large volume/3-4 day mix). These samples were analyzed to determine homogeneity/concentration verification and 5-hour room temperature stability. Samples from the same preparation at the 0.2 mg/mL level only, were collected on test day 0, after 7 days of refrigeration. These samples were analyzed to determine re-dispersion/concentration verification and refrigerated stability along with 5-hour room temperature stability. The refrigerated re-dispersion/concentration verification and stability for the other levels had been established during the mixing/stability study for a previous study.⁽⁵⁾

On test days 48, 52, 56, 58, 65, and 91 (small volume/1 day mix), concentration verification samples for all levels were collected. The test day 48 preparation was not dosed to animals. On test days 42, 45, 63, and 73 (3-4 day mix), concentration verification samples for all levels were collected. Test day 63 and 73 preparations were not used for dosing the animals but for evaluation of the large volume mix (3-4 day).

All dosing suspension samples were collected on the day the suspensions were dosed to the animals or at the established stability time for analysis. They were analyzed when received or frozen until analyzed.

K. Analytical Methods

1. Dosing Solution Treatment

Each dosing sample (10 mL for 0.2 mg/mL; 3 mL for other levels) was diluted to 100 mL with methanol and mixed to dissolve the [REDACTED] in the suspension. The dosing samples were analyzed without further dilution or were further diluted with the 0 mg/mL sample (initial dilution) to an expected concentration of approximately 0.03mg/mL (a.i.) prior to analysis. Before all final dilutions, the internal standard diluted solution (refer to Calibration and Quantitation Section) was added to each test sample to give a final concentration of approximately 0.04 mg/mL. Each sample (final dilution) had an equivalent amount matrix (3%) when analyzed, except the 0.2 mg/mL (10%).

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

2. Chromatographic Conditions

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

3. Calibration and Quantitation

A separate sample of [REDACTED] was obtained for use as the analytical reference standard. A stock solution was prepared in methanol. This stock solution was sonicated to assure that all material was in solution. Before analysis, appropriate aliquots of the stock were diluted with the 0 mg/mL sample (initial dilution) to make calibration standards, which bracketed the target concentration of the diluted dosing samples. A stock solution of internal standard [REDACTED] was prepared in methanol and added to each calibration standard and test sample to give a final concentration of approximately 0.04 mg/mL.

The ratio of the internal standard and [REDACTED] peak heights from replicate GC analysis of these solutions was used to construct a calibration curve by least squares regression (see Appendix A, Figure 1 for a representative curve). Measured concentrations for the dosing samples were determined by applying the peak height ratios from replicate injections of each sample 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 or concentration verification duplicate samples for each dosing level was used to determine the concentration of the test substance for the respective dosing levels.

Stability was evaluated by using the mean result of the homogeneity samples or the duplicate samples from the concentration verification as the baseline for comparing the corresponding stability results.

L. Body Weights

1. Rats Designated for the Subchronic Toxicity and Three-Month Recovery Evaluations, and Satellite Bleeds

Rats were weighed once per week during the approximately 90-day exposure phase of the study. In addition, the rats designated for neurobehavioral evaluations (functional observational battery and motor activity assessments) were weighed on the days of those observations.

2. Rats Designated for 10-Day Biochemical Analysis

Rats were weighed on the first, eighth, and tenth day of test substance administration.

M. 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.

N. 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, except on test day 46 only one cage-site examination was conducted. Moribund rats were sacrificed. 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 and three-month recovery periods. Detailed clinical observations were not evaluated on rats designated for satellite bleeds.

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 unusual behavior.

O. Ophthalmological Evaluations

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

On test day -11, prior to selection and grouping, the initial examination was performed on all main study rats received for the study. On test day 87, all surviving rats designated for the subchronic toxicity and three-month recovery evaluations were examined again.

P. Neurotoxicity Evaluations

1. Sensory Motor Function Evaluation

Prior to test substance administration and during week 13 of test substance administration, assessments of responses to approach/touch, sharp auditory stimulus, and tail pinch were made while the animal was in a standard arena. These assessments were conducted on the 10 animals per group designated for recovery from the control and high-dose groups, and on the 10 animals per group designated for subchronic toxicity from the low-dose and mid-dose 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

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 sex were counterbalanced across the monitors and time of day to the fullest extent possible. The infrared monitoring device enables measurement of 2 dependent variables: duration of movement and number of movements. A continuous movement was counted as 1 movement regardless of duration. Each test session was 60 minutes in duration, and the results were expressed for the total session as well as for 6 successive 10-minute blocks.

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

3. Test Facility Positive Control Data

Data on the effects of acrylamide, carbaryl, d-amphetamine, and trimethyltin are described in four separate reports.^(6,7,8,9) These positive control studies are the basis of training certification for the individuals making judgments in the neurobehavioral and neuropathology tests. The data also document that the equipment and procedures are capable of detecting effects that may be seen in neurotoxicity studies of this type.

Q. Clinical Pathology

A clinical pathology evaluation was conducted on all rats designated for subchronic toxicity on test days 48/49 and 93/94 in males and females, respectively. The day before collection of samples for the clinical pathology evaluation the animals were placed in metabolism cages. These animals were fasted overnight (approximately 15-17 hours) and urine was collected from each animal. Blood samples for hematology and clinical chemistry measurements were collected from the orbital sinus of each animal while the animal was under light carbon dioxide anesthesia. Blood samples for coagulation parameters and fluoride analysis were collected at sacrifice 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 was discarded without analysis, however, because further tests were not required to support experimental findings. Bone marrow smears were prepared at the final sacrifice from all surviving animals. Bone marrow smears were stained with Wright's stain and coverslipped, but analysis was not necessary to support experimental findings.

At the end of a 3-month recovery period, samples for hematology, clinical chemistry, urinalysis, and plasma and urine fluoride were collected and analyzed from rats designated for recovery.

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

prothrombin time
activated partial thromboplastin time

2. Clinical Chemistry

Serum clinical chemistry parameters were determined on a Roche Diagnostics (BMC)/Hitachi® 717 clinical chemistry analyzer. Plasma fluorides were determined using a phi12 pH 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 ^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 fluorides were determined using a phi12 pH meter and a fluoride-selective electrode. Sediments from all urine specimens were evaluated microscopically.

^a Fluoride determination was analyzed on EDTA plasma.

The following urinalysis parameters were determined:

quality	ketone
color	bilirubin
clarity	blood
volume	urobilinogen
osmolality	fluoride ^a
pH	protein
glucose	microscopic urine sediment examination

R. Collection of Blood and Tissue (Three-Month Recovery)

Blood was collected from animals (5 animals/sex/group) designated as satellite bleeds during the 90-day dosing period and recovery period and stored for possible analysis of parent compound and metabolites.

Blood collection time points were: prior to dosing (test day -7), and days 0, 4, 10, 21, 35, 56, 77, 90, 94, 98, 105, 119, 133, 154, and 175. Blood (approximately 0.6 mL) was collected from the orbital sinus of designated animals while under light carbon dioxide anesthesia. On the day of blood collection, blood was collected from the animals approximately 2 hours ($\pm$ 30 minutes) after dosing. For each bleeding, blood was collected at approximately the same time of day. The blood was collected in plastic tubes containing EDTA while on ice. The blood from each animal was then separated into plasma and red blood cells. The separated plasma samples were stored frozen at -80°C and red blood cells were discarded. After the final bleeding (day 175), all animals were euthanatized by carbon dioxide asphyxiation and exsanguination and liver and fat were collected, weighed, and stored at -80°C. The pharmacokinetic profile of [REDACTED] may be evaluated in the future and resulting data reported separately.

S. Biochemical Measurements

Following 10, 93 (males) or 94 (females) days of test substance administration or after three-months (test day 183 for males and females) of recovery, five rats from each group designated for biochemical evaluation were weighed and then euthanized by CO₂ 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 [¹⁴C]palmitoyl CoA as the substrate.⁽¹⁰⁾ The protein content of the peroxisomes was determined before and after analysis by the Biorad method.⁽¹¹⁾ Final rate calculations were made using the post-assay protein concentrations.

^a Fluoride determination was analyzed from urine with EDTA added.

T. Anatomic Pathology

After approximately 90 days of exposure to the test substance (test days 93 and 94 for males and females, respectively), groups of 10 male and 10 female rats from the 0, 1, 5, 25, and 125 mg/kg/day groups were sacrificed and necropsied. Additional groups of 10 male and 10 female rats from the 0 and 125 mg/kg/day groups were sacrificed and necropsied approximately three months after the last exposure (test day 183) to evaluate recovery of toxic effects. In addition, groups of 5 male and 5 female rats from all groups designated for hepatic biochemical analysis were sacrificed and necropsied approximately three months after the last exposure (test day 183).

Rats were euthanatized by carbon dioxide anesthesia and exsanguination. Gross examinations were performed on all male and female rats. The following tissues were collected from subchronic exposure and 3-month recovery group rats sacrificed by design, or rats that were 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>	<u>Female</u>
	pituitary gland	ovaries
<u>Urinary System</u>	thyroid gland	uterus
kidneys	parathyroid glands	mammary gland
urinary bladder	adrenal glands	
	<u>Nervous System</u>	<u>Miscellaneous</u>
<u>Respiratory System</u>	brain (including cerebrum,	skin
lungs	cerebellum, medulla/pons)	eyes (including optic
trachea	spinal cord (3 levels: cervical,	nerve)
nose	mid-thoracic, lumbar)	gross observations
larynx	sciatic nerve	
pharynx		

a Bone marrow was collected with the femur and sternum.

The following tissues were weighed from rats sacrificed by design in the subchronic exposure group and the 3-month recovery groups: liver, kidneys, adrenal glands, thyroid (weighed after fixation), brain, spleen, thymus, heart, 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 90-day exposure group control and 125 mg/kg/day rats, and all accidentally killed rats were processed and received a full histopathological examination. Liver and kidneys were processed from 1, 5, and 25 mg/kg/day 90-day exposure group and from all 3-month recovery group male and female rats. In addition, thymus, thyroid gland, and nose from 1, 5, and 25 mg/kg/day subchronic exposure group and all 3-month recovery group male rats were processed and examined microscopically.

U. Statistical Analyses

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

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 B-Oxidation Organ Weight	Test for lack of trend ⁽¹²⁾	Sequential application ⁽¹³⁾ of the Jonckheere-Terpstra trend test ⁽¹⁴⁾	Preliminary tests for pairwise comparison
		OR ^a	
	Levene's test for homogeneity ⁽¹⁵⁾ and Shapiro-Wilk test ⁽¹⁶⁾ for normality ^b	One-way analysis of variance ⁽¹⁷⁾ followed with Dunnett's test ⁽¹⁸⁾	Kruskal-Wallis test ⁽¹⁹⁾ followed with Dunn's test ⁽²⁰⁾
Motor Activity ^c	Levene's test for homogeneity ⁽¹⁵⁾ and Shapiro-Wilk test ⁽¹⁶⁾ for normality ^b	Repeated measures analysis of variance ⁽²¹⁾ followed by contrasts ⁽²²⁾	Sequential application ⁽¹³⁾ of the Jonckheere-Terpstra trend test ⁽¹⁴⁾
Grip Strength Foot Splay	Bartlett's test ⁽²³⁾ for homogeneity of variances	One-way analysis of variance ⁽¹⁷⁾ followed with Dunnett's test ⁽¹⁸⁾	Kruskal-Wallis test ⁽¹⁹⁾ followed with Dunn's test ⁽²⁰⁾
Clinical Pathology ^d	Levene's test for homogeneity ⁽¹⁵⁾ and Shapiro-Wilk test ⁽¹⁶⁾ for normality ^b	One-way analysis of variance ⁽¹⁷⁾ followed with Dunnett's test ⁽¹⁸⁾	Kruskal-Wallis test ⁽¹⁹⁾ followed with Dunn's test ⁽²⁰⁾
Survival Incidence of Clinical Observations Incidence of Ophthalmological Observations Incidence of FOB Descriptive Parameters	None	Cochran-Armitage test for trend ^{(17)e}	
Incidences of Gross and 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 (Dunnett/Tamhane-Dunnett).
- Test day and block (10-minute EPOCH) was used as repeated-measure factors.
- When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1 , 0.05 was used for any calculations performed with that bilirubin data.
- If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test⁽²⁴⁾ with a Bonferroni correction was used.

RESULTS AND DISCUSSION

ANALYTICAL EVALUATIONS

Dosing suspensions for this study were prepared at the beginning of the study as large volume mixes to be used either for 3 or 4 days of dosing. Samples containing [REDACTED] at the concentrations of 0, 0.2, 1.0, 5.0, and 25.0 mg/mL were collected at the initiation of the 90-day study (test day -6 for large volume/3-4 day mix). These samples were analyzed to determine homogeneity/concentration verification and 5-hour room temperature stability. Samples from the same preparation at the 0.2 mg/mL level only were collected on test day 0, after 7 days of refrigeration. These samples were analyzed to determine re-dispersion/concentration verification and refrigerated stability along with 5-hour room temperature stability. The refrigerated re-dispersion/concentration verification and stability for the other levels had been established during the mixing/stability study for a previous study. These data indicated that the test substance was homogeneously mixed, could be re-dispersed after refrigeration to the expected concentration, and was stable in the vehicle for 5 hours after refrigeration.

On test days 42 and 45 (3-4 day mix), concentration verification samples for all levels were collected. Results from analysis of the dosing suspensions collected near the mid-point of the study (test day 42) for concentration verification indicated that test substance was marginally at the targeted concentration ($\pm 20\%$ of nominal). In order to investigate these results, a new large volume preparation of the dosing suspensions was made and sampled on test day 45. The results for these samples were lower than expected (range: -33.4% to -66.0% of nominal) indicating a sampling problem. Investigation of the study records showed that the correct amount of test material was contained in the preparations but that a possible technician error had occurred with the re-dispersing and sampling of the test material to the analytical group. Due to the length of time needed for evaluation of the samples, the preparations had already been dosed to the animals and further sampling could not be done to define the problem with the sampling of this mix. Therefore, due to the unexpected analytical results observed on test day 45, the following study changes were implemented: 1) on test day 49 of the study, the dosing suspension preparation was changed to small volume mix to be used for 1 day of dosing and concentration verification samples for all levels were collected on test days 48 (not dosed to animals), 52, 56, 58, 65, and 91 (small volume/1 day mix); and 2) on test day 63 and 73 large volume mixes (3-4 day) were prepared and samples were collected from all levels for evaluation of the mixing and sampling for the study before test day 45. These preparations were not used for dosing the animals.

A. Test Substance Stability

Samples of test substance were analyzed near the beginning and the end of the study. These analyses indicated that the test substance was stable over the course of the study. The average percent of active ingredient was $99.1\% \pm 0.81$ and $101.8\% \pm 2.9$ for the samples analyzed on February 15, 2002, and May 30, 2002, respectively.⁽²⁵⁾ [REDACTED] was reported by

the sponsor to have 99.2% active ingredient. The differences in values between the sponsor reported purity and the experimental data represent analytical variability.

B. Chromatography

eluted from the GC column as resolved peak with a retention time of approximately 3.5 minutes. The internal standard eluted from the GC column as a resolved peak with a retention time of approximately 3.9 minutes. Representative GC chromatograms are shown in Appendix A, Figures 2(a - c). Test substance was not detected in the 0 mg/mL control.

C. Homogeneity and Stability Samples

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

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

Test Day Sample Type	Nominal mg/mL	Measured T,M,B ^a mg/mL	Mean (T,M,B) % Nominal	C.V. ^b (%)	Stability ^c % Nominal
Test Day -6					
Homogeneity	0	ND ^d	---	---	---
	0.2	0.163, 0.164, 0.161	81.5	1	83.5
	1.0	0.803, 0.857, 0.890	85.0	5	81.8
	5.0	4.55, 4.80, 4.61	93.0	3	82.8
	25	19.9 ^d , 21.9, 22.9	86.4	7	87.2
Test Day 0					
Stability					
7 Day Refrigerated	0	ND ^d	---	---	---
	0.2 ^f	0.161, 0.173	83.5	5	79.0 ^e

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

b. C.V. = Coefficient of Variation

c. Samples held 5 hours at room temperature.

d. Denotes none detected.

e. Duplicate re-analysis of the original sample supports the original result and are not reported.

f. Mean results for the analysis of duplicate concentration verification samples.

The data for samples collected on test day -6 indicates that the test substance was homogeneously mixed in the vehicle at all levels (C.V.'s = 1, 5, 3 and 7, respectively). The test substance was at the targeted concentration in the samples ($\pm 18.5\%$ of nominal) and was stable in the vehicle when held 5 hours at room temperature.

The data for 0.2 mg/mL sample collected on test day 0 after 7 days of refrigeration indicates that the test substance was homogeneously re-suspended in the vehicle (C.V. = 5). The test substance was at the targeted concentration ($\pm 16.5\%$ of nominal) and stable in the vehicle when held refrigerated for 7 days followed by 5 hours at room temperature. The 5-hour sample analyzed at

79.0% of nominal appeared to be lower than expected but this can be attributed to sampling and analytical variability and not stability of the test material in the vehicle.

All other concentrations in the study had been shown to be homogeneously mixed and stable in the vehicle after 7 days of refrigeration followed by 5 hours at room temperature in the mixing/stability study.⁽⁵⁾ The following table from this study is included.

Test 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 4					
Homogeneity	0	ND ^c	---	---	---
	1.0	0.944, 0.884, 0.836 ^d	88.8	6	85.4 ^e
	5.0	4.43, 4.37, 4.72 ^d	90.2	4	95.0
	25	22.2, 22.7, 24.2	92.0	5	96.0
Test Day 11					
Stability					
7 Day Refrigerated ^f	0	ND ^c	---	---	---
	1.0	0.900, 0.864, 0.859	87.4	3	90.4 ^g
	5.0	4.46, 4.44	89.0	0	84.2 ^g
	25	24.2, 23.9	96.4	1	84.8 ^g

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 Mean result of all analyses reported.

e Mean result of all analyses reported except for one duplicate repeat sample which was low due to aliquot error.

f Duplicate concentration verification samples analyzed except for the 1.0 mg/mL level (homogeneity).

g Mean result of duplicate re-sampling from the original diluted sample. Original analysis was lower than expected due to aliquot error and not reported.

D. Concentration Verification Samples

Analytical results from dosing suspensions prepared test days 42, 45, 48, 52, 56, 58, 65, and 91 and analyzed for concentration verification are shown in Appendix A, Table II and Summary Table 1.

The following table summarizes the results for concentration verification analyses of the sample preparations for the above test days 42 and 45 (3/4-day mix), that were dosed to the animals.

Preparation Day	Nominal mg/mL	Measured ^a mg/mL	Average % Nominal	CV %
Test Day 42	0.2 ^b	0.156, 0.169	81.5	6
	1.0 ^b	0.749, 0.776	76.3	3
	5.0	3.87 ^b , 3.91 ^c	77.8	1
	25.0 ^c	19.4, 19.1	77.2	1
Test Day 45	0.2 ^b	0.066, 0.083	37.5	13
	1.0 ^b	0.676, 0.656	66.6	2
	5.0 ^b	2.20, 2.32	45.2	4
	25.0 ^b	8.34, 8.64	34.0	3

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

b Mean result of the original analysis and duplicate reanalysis of the original sample.

c Mean result of duplicate re-sampling from the original diluted sample. Original analysis was lower than expected due to aliquot error and not reported.

Results from analysis of the dosing suspensions collected on test day 42 for concentration verification indicated that test substance was marginally acceptable (-23.7% of nominal). Therefore, to investigate these results, a new large volume preparation (3/4-day mix) of the dosing suspensions was made and sampled on test day 45. The results for these samples were lower than expected (range: -33.4% to -66.0% of nominal) based on previously analyzed samples for the study.

Additional work was then done to investigate whether the results for test day 45 were unique to the sampling for the analytical group. This involved the preparation of two large volume dose suspensions (3-4 day mixes) on test days 63 and 73 to be used only for analysis to verify the mixing and sampling procedures of the large volume dose preparations. These suspensions were not dosed to the animals. On test day 49 the dose suspensions were prepared daily for the remainder of the study.

The following table summarizes the results for concentration verification analyses of the sample preparations for the test days 48 (not dosed to animals), and 52, 56, 58, 65, and 91 (1-day mixes) that were dosed to the animals.

Preparation Day	Nominal mg/mL	Measured ^a mg/mL	Average % Nominal	CV %
Test Day 48 ^b	0.2	0.197, 0.219	104.0	7
	1.0	0.865, 0.948	90.7	6
	5.0	3.93, 3.90	78.3	1
	25.0	21.9, 22.5	88.8	2
Test Day 52	0.2	0.174, 0.184	89.5	4
	1.0	0.845, 0.895	87.0	4
	5.0	4.22, 4.16	83.8	1
	25.0	23.5, 22.3	91.6	4
Test Day 56	0.2	0.167, 0.189	89.0	9
	1.0	0.964, 0.950	95.7	1
	5.0	4.41, 4.31	87.2	2
	25.0	22.8, 21.4	88.4	4
Test Day 58	0.2	0.174, 0.150	81.0	10
	1.0	0.945, 0.937	94.1	1
	5.0	4.48, 4.17	86.5	5
	25.0	22.5, 22.1	89.2	1
Test Day 65	0.2 ^c	0.159, 0.150	77.5	4
	1.0	0.832, 0.898	86.5	5
	5.0	4.32, 4.40	87.2	1
	25.0	20.8, 20.5	82.6	1
Test Day 91	0.2	0.162, 0.165	82.0	1
	1.0	0.760 ^c , 0.863	81.2	9
	5.0 ^c	3.96, 3.90	78.6	1
	25.0 ^c	19.9, 18.7	77.2	4

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

b Suspensions not dosed to animals.

c Mean result of the original analysis and duplicate reanalysis of the original sample.

Because of the results from test day 45, samples were collected from the daily mixes to verify concentration on test day 48 (not dosed to animals), 52, 56, 58, 65, and 91. With the exception of four samples, results from these analyses indicated that the dosing suspensions were at the targeted concentrations ($\pm 20\%$ of nominal). On test day 48, the result for the 5.0 mg/mL level was marginally acceptable at 78.3% of nominal. On test day 65, the result for the 0.20 mg/mL level was marginally acceptable at 77.5% of nominal. On test day 91, the result for the 5.0 mg/mL and the 25.0 mg/mL levels were marginally acceptable at 78.6% and 77.2% of nominal, respectively.

Based on the statistics (mean % of nominal) for all samples analyzed for the daily mixing, it can be concluded that the dosing suspensions contained the targeted amount of [REDACTED] during the period from test day 48 (not dosed to animals) until the end for the study. The following table shows the mean % of nominal for all analyzed samples at each concentration for the daily preparations and the average of the mean % of nominal, with the SD, and the CV based on this average for all the levels analyzed.

Statistics for all Samples Analyzed for Small Volume Mix (1-day)

Nominal mg/mL	Mean % Nominal
0	---
0.20	87.2
1.0	89.2
5.0	83.6
25	86.3
Mean:	86.6
SD	±2.3
CV	3%

On test day 63 and 73, dose preparations (3-4 day/large volume) were prepared but used only for verification of mixing and sampling procedures on the large volume dose preparation. These suspensions were not dosed to the animals.

The following table summarizes the results for concentration verification analysis for these preparations.

Preparation Day	Nominal mg/mL	Measured ^a mg/mL	Average % Nominal	CV %
Test Day 63	0.2	0.190, 0.192	95.5	1
	1.0	0.784, 0.792	78.8	1
	5.0	4.12, 4.08	82.0	1
	25.0	23.0, 21.4	88.8	5
Test Day 73	0.2	0.176, 0.155	82.8	9
	1.0	0.980, 1.03	101.0	4
	5.0	4.57, 4.60	91.8	0.4
	25.0	23.3, 24.4	95.6	3

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

With the exception of one sample, results from these analyses indicated that the dosing suspensions were at the targeted concentrations ($\pm 20\%$ of nominal). On test day 63, the result for the 1.0 mg/mL level was marginally acceptable at 78.8% of nominal. Neither of these preparations were dosed to the animals but the results were used as statistical data along with the results from the previously dosed large volume preparations (test days -6, 42, and 45) to show that the dosing suspensions contained the targeted amount of test substance before test day 45

and that the results for that day were due to technician error while sampling for the Analytical group.

Based on the statistics (mean % of nominal) for all samples analyzed for a 3-4-day preparation (large volume), it can be concluded that the dosing suspensions contained the targeted amount of [REDACTED] during the period from the initial sampling (test day -6) for the study until test day 45. The following table shows the mean % of nominal for all analyzed samples at each concentration and the average of the mean % of nominal, with the SD, and the CV based on this average for all the levels analyzed. Included are the two preparations (test day 63 and 73) that were not dosed to animals but prepared only to evaluate the mixing and sampling process.

The table includes results (a) with test day 45 and (b) excluding test day 45.

Statistics for all Samples Analyzed for Large Volume Mix (3-4-day)

Nominal mg/mL	Mean % Nominal
(a)	
0	---
0.20	75.8
1.0	81.5
5.0	78.0
25	76.4
Mean:	77.9
SD	±2.6
CV	3%
(b)	
0	---
0.20	85.3
1.0	85.3
5.0	86.2
25	87.0
Mean:	85.9
SD	±0.8
CV	1%

The statistics for the large volume dose preparations with the exclusion of the test day 45 indicate that the samples were at the targeted concentrations having a mean % of nominal 85.9% ± 0.8, and a CV of 1%. Although the statistics based on all large volume preparations are marginally acceptable with the inclusion of test day 45 (77.9% of nominal), the test day 45 sample analysis should not be considered as part of the dose verification samples for the study and should be excluded from these statistics because: 1) previous analysis on large volume mixes indicated no problem; 2) the study notebook dose preparation sheet shows that the correct amount of test substance was present at each dosing level for the preparation, and 3) subsequently, that in sampling and analyzing the two large volume preparations after test day 45 (test days 63 and 73), the test material was dispersed properly and at the targeted concentrations.

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

E. Discussion of Results

Based on the statistics (mean % of nominal) for all sample sets analyzed for the study and dosed to the animals, it can be concluded that the dosing suspensions contained marginally the targeted amount ($\pm 20\%$ of nominal) of [REDACTED] with test day 45 included and the targeted amount ($\pm 20\%$ of nominal) of [REDACTED] with test day 45 excluded. The following table shows the mean % of nominal for all analyzed samples at each concentration and the average of the mean % of nominal, with the SD, and the CV based on this average for all the levels analyzed (a) including test day 45 and (b) excluding test day 45.

Statistics for all Samples Analyzed and Dosed to Animals

Nominal mg/mL	Mean % Nominal
(a)	
0	---
0.20	77.4
1.0	84.1
5.0	79.9
25	78.3
Mean:	79.9
SD	± 2.9
CV	4%
(b)	
0	---
0.20	83.1
1.0	86.5
5.0	84.9
25	84.9
Mean:	84.8
SD	± 1.4
CV	2%

F. Analytical Conclusion

Results from the analysis of the [REDACTED] dosing suspensions prior to the study start, at the initiation of the study, for the daily dose preparations after test day 45, and including the additional large volume dose preparation on test days 63 and 73 (not dosed to the animals) indicated that the test substance was homogeneously mixed, at the targeted concentrations and stable in the vehicle under the conditions of the study. Furthermore, the study records indicate that the correct amount of test substance was contained in the test day 45 dosing suspensions. Taken together, these data point to a problem unique to the analytical samples that were collected on test day 45.

IN-LIFE TOXICOLOGY

A. Dosage Data

(Tables 2-3, Appendix B)

Rats were dosed with suspensions of [REDACTED] in 0.5% aqueous methylcellulose, prepared at concentrations of 0, 0.2, 1, 5, and 25 mg/mL, designed to deliver the targeted dose of test substance at a dosing volume of 5 mL/kg body weight. The quantity of [REDACTED] 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 1.2-2.9 mL for the control group, 1.2-2.8 mL for the 1 mg/kg/day group, 1.2-3.0 mL for the 5 mg/kg/day group, 1.2-3.0 mL for the 25 mg/kg/day group, and 1.2-2.8 mL for the 125 mg/kg/day group. The range of mean daily dose volumes administered to female rats was 0.9-1.5 mL for the control group, 0.9-1.5 mL for the 1 mg/kg/day group, 0.9-1.5 mL for the 5 mg/kg/day group, 0.9-1.6 mL for the 25 mg/kg/day group, and 0.9-1.6 mL for the 125 mg/kg/day group.

B. Mean Body Weights and Body Weight Gains

(Tables 4-7, Figures 1-2, Appendix C)

There were no test substance-related, toxicologically significant alterations in mean body weight or body weight gain observed in any of the male or female dose groups. Significant decrements of 40 and 51%, respectively, occurred in the mean body weight gain of the 25 and 125 mg/kg/day male groups during the 63-70 test day interval, while a significant increase occurred for the 125 mg/kg/day male group during the 7-14 day interval. For the 49-56 day interval, significant increases in mean body weight gain were observed for the 5 and 25 mg/kg/day male groups. On test day 77, all animals in the high-dose male and female dose groups were placed on ground chow because of test substance-induced alterations to the teeth. Once placed on ground chow, males in the 125 mg/kg/day group had a significant increase in mean body weight gain for the 84-91 test day interval. The overall (0-91 day interval) mean body weight gain of male rats, however, was similar to control across all dose levels. Over the course of the three-month recovery period, statistically significant increases in mean body weight gain occurred for the 125 mg/kg/day male group. Overall mean body weight gain for the three-month recovery period for the 125 mg/kg/day male group was significantly increased 36% compared to control.

During the 77-84 test day interval, females in the 125 mg/kg/day dose group had a significant increase in mean body weight gain following their placement on ground chow. For the overall interval (0-91 days), the mean body weight gain for females was similar to control across all dose levels. A significant increase in mean body weight gain occurred for the 25 mg/kg/day female group during the 154-161 test day interval. Statistically significant increases and decreases in mean body weight gain also occasionally occurred over the three-month recovery period for the 125 mg/kg/day female group; however, the mean body weight gain for all female dose groups was similar to control for the overall recovery interval.

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

There were no test substance-related, toxicologically significant alterations in food consumption observed in any of the male or female dose groups. For the 98-105 and 105-112 test day intervals, males in the 125 mg/kg/day three month recovery group had statistically significant and lower food consumption of 9 and 10%, respectively. Overall (91-182 day interval), however, food consumption for the 125 mg/kg/day male three-month recovery group was similar to control.

There were no test substance-related, toxicologically significant alterations in mean daily food efficiency observed in any of the male or female dose groups. Male rats in the 125 mg/kg/day group had several incidences of significantly higher mean daily food efficiency compared to control over the course of the study except during the 63-70 day interval in which significantly lower (59% compared to control) mean daily food efficiency was observed. Males in the 25 mg/kg/day dose group also had a significantly lower mean daily food efficiency of 42% during the 63-70 test day interval. Following the replacement of pelleted chow with ground chow on test day 77 for the 125 mg/kg/day male group, a significantly higher mean daily food efficiency was observed for the 84-91 day interval. For the 0-91 day study interval, however, mean daily food efficiency for male rats was similar to control, while for the overall three-month recovery interval, mean daily food efficiency was significantly increased 26% compared to control for the 125 mg/kg/day male group.

Female rats in the 125 mg/kg/day group had significantly lower (60%) mean daily food efficiency during the 63-70 day interval. Following the replacement of pelleted chow with ground chow on test day 77 for the 125 mg/kg/day female group, a significantly higher mean daily food efficiency was observed for the 77-84 day interval. Overall mean daily food efficiencies for test-substance treated female groups, however, were similar to control. During the three-month recovery (test days 154-161), females in the 125 mg/kg/day group had a significant increase in mean daily food efficiency; however, for the overall three month recovery interval, mean daily food efficiency was similar to control.

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

A test substance-related, toxicologically significant increase in the incidence of striated teeth was observed in the 125 mg/kg/day male and female dose groups. In addition, there was an increase in tooth clipping required for both males and females in the 125 mg/kg/day dose group.

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

E. In-Life Toxicology Conclusions

Under the conditions of this study, the NOEL for in-life toxicology parameters (body weight, body weight gain, food consumption, food efficiency, and clinical signs of toxicity) was 25 mg/kg/day for both males and females based on the increased incidence of striated teeth observed in male and female rats administered 125 mg/kg/day.

NEUROBEHAVIORAL TOXICOLOGY

A. Sensory Function Evaluations

1. Forelimb Grip Strength

(Table 18-19, Figures 3-4, Appendix G)

There were no test substance-related effects on forelimb grip strength in males or females administered any dosage of [REDACTED]. During the baseline evaluation, females in the 5 mg/kg/day group had significantly increased forelimb grip strength. However, since administration of the test material had not been initiated, this statistical difference was not test substance related. There were no statistically significant differences for males administered any dosage of the test material.

2. Hindlimb Grip Strength

(Table 18-19, Figures 5-6, Appendix G)

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

3. Sensory Function Observation

(Table 20-21, Appendix H)

There were no test substance-related changes or statistically significant differences in neurobehavioral parameters in males or females administered any dosage of [REDACTED].

B. Motor Activity

(Tables 22-25, Figures 7-10, Appendices I-J)

There were no test substance-related effects on duration of movement or number of movements for males or females for any dosage of [REDACTED]. During the third 10-minute interval for the baseline evaluation, males in the 1 mg/kg/day group had significantly higher duration of movement compared to the control value. During the fourth 10-minute interval of the baseline evaluation, males in the 1, 5, 25, and 125 mg/kg/day groups had significantly higher duration of movement compared to the control value. During the fifth 10-minute interval of the baseline evaluation, males in the 5 mg/kg/day group had significantly higher duration of

movement compared to the control value. However, since administration of the test material had not been initiated, these statistical differences were not test substance related.

During the fifth 10-minute interval for the 13-week evaluation, duration of movement for 25 mg/kg/day males was significantly lower compared to the control value. However, since duration of movement was similar to control for 125 mg/kg/males, the statistically lower value for the 25 mg/kg/day males was not considered to be test substance-related.

During the fourth 10-minute interval for the baseline evaluation, number of movements for 1, 5, and 25 mg/kg/day males was significantly higher than the control value. In addition, during the fifth 10-minute interval for the baseline evaluation, number of movements for 5 mg/kg/day males was significantly higher than the control value. However, since administration of the test material had not been initiated, these statistical differences were not test substance related.

Total number of movements and the number of movements during the fifth 10-minute interval of the 13-week evaluation were significantly lower for 25 mg/kg/day males compared to the control value. However, since number of movements for 125 mg/kg/day males was similar to control, these statistical differences were not considered to be test substance related. Number of movements for 125 mg/kg/day males during the fourth 10-minute interval for the 13-week evaluation was significantly lower compared to the control value. However, since the total number of movements was similar to the control value, the statistically lower value for 125 mg/kg/day males was not considered to be test substance related.

There were no statistically significant differences for females administered any dosage of the test material.

C. Neurobehavioral Toxicity Conclusions

Under the conditions of the study, the NOEL for neurobehavioral parameters was 125 mg/kg/day of [REDACTED] in males and females, the highest concentration tested.

CLINICAL PATHOLOGY

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

There were no adverse changes in hematologic parameters in male or female rats at either time point during treatment. The following statistically significant changes in mean hematologic parameters were considered to be non-adverse.

- Red cell mass (red cell count, hemoglobin, hematocrit) was minimally decreased in males and females dosed with 125 mg/kg/day (at both time points during treatment, variable statistical significance for males) (Clinical Pathology Text Table 1). Decreased red cell mass was associated with regeneration of red cells (increased reticulocytes) in males (statistically significant only at 125 mg/kg/day, test days 48 and 93) and females (statistically significant at

test day 94 only). Increased reticulocytes resulted in increased red cell distribution width and mean cell volume (variable statistical significance). However, histologically, there was no increase in extramedullary hematopoiesis.

Red cell counts (males) and hematocrits (females) were minimally but statistically decreased in rats dosed with 25 mg/kg/day. These changes were sometimes associated with minimal increases in red cell distribution width and mean cell volume (variable statistical significance).

In addition, minimally increased changes in red cell morphology (acanthocytes) were present in males dosed with 25 or 125 mg/kg/day at both time-points during treatment.

The above changes in red cell parameters were considered to be related to treatment, and indicate minimally increased red cell turnover. However, due to the minimal nature of the changes, they were considered to be non-adverse. After approximately 90 days of recovery, red cell mass parameters, reticulocytes, red cell distribution width, and mean cell volume were similar to control group values of rats previously dosed with 125 mg/kg/day.

- Minimally increased mean corpuscular hemoglobin in males dosed with 125 mg/kg/day at test day 93 was considered to be possibly related to treatment, but was considered to be non-adverse because minimal increases in mean corpuscular hemoglobin are not associated with adverse effects. After approximately 90 days of recovery, mean corpuscular hemoglobin concentrations were similar to control group values of rats previously dosed with 125 mg/kg/day.

The following statistically significant changes in mean clinical chemistry parameters were considered to be non-adverse because they were unrelated to dose and/or occurred only at three months post dosing:

- Minimally and transiently decreased reticulocytes in females dosed with 25 mg/kg/day at test day 49.
- Minimally increased basophils in females previously dosed with 125 mg/kg/day after approximately 90 days of recovery.

Clinical Pathology Text Table 1:
Red cell mass parameters and reticulocytes (expressed as a percent of control group mean)*

Dosage (mg/kg/day):	Test Day	Males				Females			
		1	5	25	125	1	5	25	125
RBC	48/49	99%	98%	95%	93%	98%	98%	97%	91%
	93/94	100%	97%	95%	91%	100%	102%	98%	93%
	183	--	--	--	96%	--	--	--	100%
HGB	48/49	101%	100%	98%	96%	99%	99%	96%	91%
	93/94	100%	98%	98%	94%	102%	102%	98%	94%
	183	--	--	--	98%	--	--	--	103%
HCT	48/49	100%	100%	97%	96%	98%	99%	96%	91%
	93/94	101%	99%	98%	95%	101%	102%	97%	94%
	183	--	--	--	97%	--	--	--	103%
ARET	48/49	97%	111%	113%	123%	88%	97%	85%	94%
	93/94	92%	108%	112%	126%	98%	110%	99%	125%
	183	--	--	--	105%	--	--	--	107%

* Statistical significance indicated by bold italicized type

B. 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 toxicologically significant (i.e., not adverse) or not related to exposure to test substance:

- Alkaline phosphatase activity was minimally and transiently increased in males dosed with 125 mg/kg/day at test day 48. At the end of dosing (test day 93), alkaline phosphatase activity was more similar to controls, although it was still minimally increased (not statistically significant). Increased alkaline phosphatase can be due to induction by a xenobiotic compound or can be due to increased biliary pressure. In this study, males dosed with 125 mg/kg/day had both increased liver weights and histologic evidence of hypertrophy, but no evidence of cholestasis. Therefore, in this study, increased alkaline phosphatase activity was probably due to induction by the test substance. Increased alkaline phosphatase activity was considered to be non-adverse because minimally increased alkaline phosphatase is not associated with adverse effects. After approximately 90 days of recovery, alkaline phosphatase activities were similar to control group values in rats previously dosed with 125 mg/kg/day.

- Cholesterol was mildly increased in females dosed with 25 or 125 mg/kg/day (variable statistical significance) at test days 49 and 94 (group means were 136% to 139% of control group means). Although this change was likely due to treatment, mildly increased cholesterol does not result in adverse events. Therefore, this change was considered to be non-adverse. After approximately 90 days of recovery, cholesterol concentrations were similar to control group values in females previously dosed with 125 mg/kg/day.
- Triglycerides were mildly decreased in males dosed with 125 mg/kg/day at test days 48 and 93 (49 and 48% of control group means, respectively). Mildly decreased triglycerides were considered to be related to treatment; however, mildly decreased triglycerides are not associated with adverse effects, and therefore were considered non-adverse. After approximately 90 days of recovery, triglyceride concentrations were similar to control group values in males previously dosed with 125 mg/kg/day.
- Total protein was mildly increased due to increased albumin in males and females dosed with 125 mg/kg/day at days 48/49 and 93/94. Mildly increased total protein and albumin concentrations were likely due to treatment, but were considered to be non-adverse because mild increases in these parameters are not associated with adverse effects. After approximately 90 days of recovery, protein concentrations were similar to control group values in rats previously dosed with 125 mg/kg/day.
- Calcium was increased in females dosed with 125 mg/kg/day at test day 94. The increased calcium was considered to be secondary to increased albumin. Calcium exists in serum in two forms, either bound to albumin or unbound ("ionized" calcium). Ionized calcium is the physiologically active form and is tightly regulated. Increases in albumin are necessarily associated with physiologically appropriate increased bound calcium, with resultant increased total calcium. However, ionized calcium is unaffected. Therefore, this change was considered to be non-adverse. After approximately 90 days of recovery, calcium concentrations were similar to control group values in rats previously dosed with 125 mg/kg/day.
- Phosphorus was minimally increased in males dosed with 125 mg/kg/day at test day 48 and 93, and at the end of recovery (test day 183). Increased phosphorus was possibly due to treatment at test day 48 and 93, but was likely to be unrelated to treatment at test day 183 (after three months of recovery). Increased phosphorus is of toxicologic significance when it is associated with evidence of decreased glomerular filtration rate, but may also be affected by extrarenal factors. In this study, other indicators of glomerular filtration rate (urea nitrogen and creatinine) were unaffected by treatment. Anatomic pathology changes included increased kidney weights associated with renal tubular hypertrophy; these changes were not present after three months of recovery. However, these anatomic pathology changes are not expected to result in decreased glomerular filtration rates. Therefore, the minimally increased phosphorus was considered to be non-adverse.

The following statistically significant changes in mean clinical chemistry parameters were considered to be non-adverse because they were unrelated to dose and/or occurred only at three months post-dosing:

- Decreased bilirubin in males dosed with 1 mg/kg/day at test days 48 and 93
- Decreased cholesterol in males dosed with 25 mg/kg/day at test day 48
- Increased urea nitrogen in males dosed with 25 mg/kg/day at test day 93
- Decreased urea nitrogen and creatinine in males previously dosed with 125 mg/kg/day at recovery test day 183
- Decreased cholesterol in males dosed with 1 mg/kg/day at test day 93

C. Urinalysis

(Tables 32-33, Appendix K)

Microscopic urine evaluation had lower priority than other urine tests. After other tests were completed on day 94, some females had insufficient urine for microscopic observation. Although no treatment-related changes were present in the samples evaluated, there were too few specimens to make unequivocal determinations. For other time-points and for males at test day 93, there were no adverse changes in urinalysis parameters. The following statistically significant changes in mean or individual urinalysis parameters were considered to be non-adverse.

- Urine volume was increased in males dosed with 125 mg/kg/day at test day 93. Increased urine volume can be due to primary increased urine production, or can be secondary to increased water consumption. The cause of increased urine production in this study was not determined. These changes correlated with anatomic pathology findings of increased kidney weights and renal tubular hypertrophy which were considered to be non-adverse (see discussion under Microscopic Findings). Increased urine production in the absence of alterations in other renal parameters (serum urea nitrogen, serum creatinine, or adverse histologic changes in the kidney) is considered to be non-adverse. After approximately 90 days of recovery, urine volumes were similar to control group values in rats previously dosed with 125 mg/kg/day.
- Decreased urine ketone concentrations were present in males dosed with 125 mg/kg/day at test day 93. These decreases were likely secondary to increased urine volumes, and were considered to be non-adverse. After approximately 90 days of recovery, urine ketone concentrations were similar to control group values in rats previously dosed with 125 mg/kg/day.

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

Plasma fluoride was increased in males dosed with 125 mg/kg/day, and in females dosed with 25 or 125 mg/kg/day at test day 93/94 (not statistically significant in females dosed with 25 mg/kg/day). After approximately 90 days of recovery, plasma fluoride concentrations were similar to control concentrations for males and females previously dosed with 125 mg/kg/day.

Urine fluoride was increased in males and females dosed with 5, 25, and 125 mg/kg/day at test day 93/94 (not statistically significant in females dosed with 5 mg/kg/day). After approximately 90 days of recovery, total urine fluoride amounts were approximately 3 times greater than controls in males previously dosed with 125 mg/kg/day, but only minimally greater than controls in females.

Increased plasma and urine fluoride indicates exposure to and metabolism of a fluoride-containing compound. The presence of fluoride after 90 days of recovery indicates continued metabolism of the test substance.

Clinical Pathology Text Table 2:

Plasma fluoride (expressed as mean and as percent of control group mean)*

<u>Parameter</u>	<u>Sex</u>	<u>Test Day</u>	<u>I/II</u>	<u>III/IV</u>	<u>V/VI</u>	<u>VII/VIII</u>	<u>IX/X</u>
			0	1	5	25	125
			<u>mg/kg/day</u>	<u>mg/kg/day</u>	<u>mg/kg/day</u>	<u>mg/kg/day</u>	<u>mg/kg/day</u>
PFLU (ug/mL)	Males	93	0.1	0.1	0.1	0.1	0.4
				100%	100%	100%	400%
		183	0.1	--	--	--	0.1
				--	--	--	100%
PFLU (ug/mL)	Females	94	0.1	0.1	0.1	0.2	0.5
			--	100%	100%	200%	500%
		183	0.1	--	--	--	0.1
			--	--	--	--	100%
UFLU (ug)	Males	93	10.7	13	38.8	202.4	997.2
			--	121%	363%	1892%	9320%
		183	9.9	--	--	--	27.6
			--	--	--	--	279%
UFLU (ug)	Females	94	6	5.7	14.1	88	702.6
			--	95%	235%	1467%	11710%
		183	11.9	--	--	--	15.7
			--	--	--	--	132%

* Statistical significance indicated by bold italicized type.

E. Clinical Pathology Conclusions

In conclusion, there were no adverse effects, measured by clinical pathology parameters, in rats dosed with [REDACTED] at doses up to 125 mg/kg/day. Treatment related changes in rats dosed with ≥ 25 mg/kg/day included decreases in some red cell mass parameters along with

regeneration (increased reticulocytes), increased serum cholesterol (females only) and increased serum phosphorus (males only). Additional treatment-related changes in clinical chemistry observed in rats dosed with 125 mg/kg/day included transiently increased alkaline phosphatase (males only), decreased triglycerides, increased total protein and albumin, and increased calcium (females only). For urinalysis parameters, males dosed with 125 mg/kg/day had increased urine volume and decreased urine ketone concentration.

Treatment-related changes in fluoride measurements included increased plasma fluoride in males dosed with 125 mg/kg/day, and in females dosed with ≥ 25 mg/kg/day (variable statistical significance). Urine fluoride excretion was increased in males and females dosed with ≥ 5 mg/kg/day (variable statistical significance).

None of the above changes are expected to be adverse. Therefore, under the conditions of this study and for the clinical pathology parameters measured, the NOEL was 125 mg/kg/day for males and females, based on the lack of adverse effects at any dose.

BIOCHEMICAL MEASUREMENTS

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

The rate of hepatic β -oxidation, a measure of peroxisome proliferation, was determined in a subchronic oral toxicity study with [REDACTED] in male and female rats after approximately 10 or 90 days of test substance administration or following a three-month recovery period.

At the 10-day, 90-day, and 3-month recovery time points in male rats, the rate of hepatic β -oxidation was statistically significantly increased at 125 mg/kg/day (163, 166 and 133% of control, respectively). At the 10-day and 90-day time points, the increases in hepatic β -oxidation activity at 125 mg/kg/day in male rats were accompanied by increases in relative liver weights (133 and 152% of control, respectively). At the three-month recovery time point, the relative liver weights had returned to control levels.

At the 10-day time point in female rats, the rate of hepatic β -oxidation was statistically significantly increased at 125 mg/kg/day (131% of control). At the 90-day time point, the rate of hepatic β -oxidation was statistically significantly increased at 25 and 125 mg/kg/day (116 and 152% of control, respectively). Hepatic β -oxidation returned to control levels at the three-month recovery time point. At the 10-day time point, the increase in hepatic β -oxidation activity at 125 mg/kg/day was accompanied by an increase in relative liver weight (132% of control). At the 90-day time point, the increases in hepatic β -oxidation activity at 25 and 125 mg/kg/day were accompanied by increases in relative liver weights (112 and 145% of control, respectively). At the three-month recovery time point, the relative liver weights had returned to control levels.

B. Biochemical Measurements Conclusions

Under the conditions of this study, [REDACTED] is a mild inducer of hepatic peroxisomal β -oxidation in male and female rats. At concentrations of 125 mg/kg/day in males and 25 mg/kg/day in females, changes in the rate of hepatic peroxisome proliferation were considered to be test substance-related effects. At the three-month recovery time point, the rate of hepatic peroxisome proliferation was still slightly increased at 125 mg/kg/day in males, but had returned to control levels in female rats.

ANATOMICAL PATHOLOGY

A. Mortality (Appendix N)

There were no test substance-related deaths. One male rat (animal number 654949) and one female rat (animal number 655071) from the control group were accidentally killed on study days 183 and 19, respectively.

B. Organ Weight Data (Tables 36-37, Appendix M)

Test substance-related and/or statistically significant increases, compared to controls, in liver weight parameters were present in 25 and 125 mg/kg/day males and females sacrificed at the end of the exposure period. Liver weight parameters were not significantly increased in males or females in the 125 mg/kg/day three-month recovery group (there were no recovery groups in intermediate dosed groups). In 125 mg/kg/day exposure group male rats, increased liver weight correlated with microscopic hepatocellular hypertrophy (see discussion under Microscopic Findings).

Test substance-related and/or statistically significant increases, compared to controls, in one or more kidney weight parameters were present in 25 and 125 mg/kg/day males and females sacrificed at the end of the exposure period. Kidney weight parameters were not significantly increased in males or females in the 125 mg/kg/day three-month recovery group (there were no recovery groups in intermediate dosed groups). In male rats, increased kidney weights correlated with microscopic tubular hypertrophy in the 25 and 125 mg/kg/day groups sacrificed at the end of the exposure period (see discussion under Microscopic Findings).

There were no other test substance-related organ weight effects. All other statistically significant organ weight changes in exposure and recovery groups were considered spurious and not biologically significant. These changes included decreased adrenal gland weight relative to body weight in 1 mg/kg/day female rats sacrificed at the end of the exposure period and decreased heart weight relative to body weight in the 125 mg/kg/day three-month recovery group females. In 125 mg/kg/day three-month recovery males, absolute, relative to body weight, and relative to brain weight thymus weights were increased; however, no test substance-related microscopic changes were present.

C. Gross Observations

(Tables 38-39, Appendix N)

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

D. Microscopic Findings

(Tables 40-45, Appendix N)

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

Anatomical Pathology Text Table: Incidences and Average Lesion Grades of Test substance-Related Microscopic Findings In Male and Female Rats

Dose (mg/kg/day):	0	1	5	25	125
Males: 90-Day Exposure					
Liver:					
Hypertrophy, hepatocellular	0/10 ^a (0.0) ^b	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	10/10 (1.6)
Necrosis, focal	0/10 (0.0)	0/10 (0.0)	1/10 (1.0)	5/10 (1.0)	3/10 (1.0)
Kidneys:					
Hypertrophy, tubular	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	9/10 (1.0)	10/10 (1.0)
Thyroid gland:					
Alteration, colloid	3/10 (1.0)	8/10 (1.1)	9/10 (1.0)	10/10 (1.0)	8/10 (2.3)
Teeth:					
Degeneration, ameloblasts (nose)	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	0/10 (0.0)	5/10 (1.6)
Males: Three-Month Recovery					
Liver:					
Necrosis, focal	3/10 (1.3)	NA	NA	NA	7/10 (1.1)
Thyroid gland:					
Alteration, colloid	7/10 (1.4)	NA	NA	NA	10/10 (1.6)
Teeth:					
Degeneration, ameloblasts (nose)	0/10 (0.0)	NA	NA	NA	2/10 (1.0)
Females: 90-Day Exposure					
Kidneys:					
Chronic progressive nephropathy	2/11 (1.0)	2/10 (1.0)	3/10 (1.0)	3/10 (1.0)	7/10 (1.0)
Females: Three-Month Recovery					
Kidneys:					
Chronic progressive nephropathy	5/9 (1.0)	NA	NA	NA	8/10 (1.4)

a. Numerator indicates incidence of rats with microscopic lesion. Denominator indicates number of rats in group.
b. Number in parentheses indicates average severity of lesion.

NA Tissue not available because there were no intermediate recovery groups.

Focal hepatocellular necrosis accompanied by a minimal inflammatory response was present in 25 and 125 mg/kg/day male 90-day exposure groups. In addition, the incidence of hepatocellular necrosis in 125 mg/kg/day three-month recovery males was increased when compared to the control group. The single occurrence of hepatocellular necrosis in males at 5 mg/kg/day was most likely not test substance-related since this lesion can occur spontaneously in control animals.⁽²⁶⁾ Focal liver necrosis was considered to be a test substance-related adverse finding in 25 and 125 mg/kg/day male rats.

Hepatocellular hypertrophy was present in 125 mg/kg/day males sacrificed at the end of the exposure period. In three-month recovery male rats previously dosed with 125 mg/kg/day, hepatocellular hypertrophy was not present and appears to be reversible. Microscopically, hepatocellular hypertrophy was characterized by an increased amount of finely granular eosinophilic cytoplasm within hepatocytes. Thus, hepatocellular hypertrophy (and the associated increase in liver weights) was considered a test substance-related physiologic response to metabolism of a xenobiotic and not biologically adverse.^(27,28,29)

Test substance-related tooth lesions in 125 mg/kg/day exposure group male rats consisted of degeneration and/or disorganization of enamel organ ameloblast cells. This lesion was most evident in the upper incisors of the level 1 (anterior) nose section. Following a three-month recovery, ameloblastic degeneration/disorganization was still present in male rats previously dosed with 125 mg/kg/day. This tooth lesion is similar to lesions seen with fluoride toxicosis and is considered adverse.⁽³⁰⁾

In the thyroid gland, the incidence and/or relative degree of altered colloid was increased in males in all dosed groups at the end of the 90-day exposure period. Following the three-month recovery period, severity and incidence of altered colloid were increased in males at 125 mg/kg/day when compared to controls. The diagnosis of "alteration, colloid" was used for colloid changes characterized by stippled, granular, clumped, and/or diffusely basophilic colloid. A 4-level grading scheme was applied based on an estimate of the percentage of follicles that contained altered colloid. A grade of 1 was applied when 1 follicle to about 25% of the follicles were involved, with grades 2, 3, and 4 applied for each 25% increase in follicular involvement. The size, density, or staining intensity of stipples, granules, clumps, or diffuse basophilia within individual follicles did not impact the grading.

Altered colloid described as clumped or granular has been reported to occur spontaneously in Sprague-Dawley rats with increasing incidence correlating to increasing age.⁽³¹⁾ Because altered colloid occurs spontaneously in healthy Sprague-Dawley rats, and since there were no other microscopic alterations in the thyroid gland, altered colloid, although likely test substance-related, was not considered adverse.

The incidence of chronic progressive nephropathy was increased in 125 mg/kg/day 90-day exposure females when compared to controls. Incidence and severity of this lesion were increased in 125 mg/kg/day females at three months recovery when compared to controls. This lesion appears to progress after cessation of test material exposure and is considered adverse.

Renal tubular hypertrophy was present in 25 and 125 mg/kg/day male rats sacrificed at the end of the exposure period. This change was not observed in male rats sacrificed after the three-month recovery period and appears to be reversible. Microscopically, tubular hypertrophy was characterized by increased eosinophilic staining of cortical tubule epithelium and a slight increase in cell height. Cortical tubule epithelial cells appeared to contain more granular cytoplasmic material than cortical tubules of control rats. Tubular lumina of hypertrophied tubules were slightly smaller than those in control rat kidneys. Tubular hypertrophy was not associated with other histomorphologic evidence of renal damage, and renal clinical pathology parameters indicative of renal toxicity were not present (see clinical pathology section). Increased kidney weights occurring absent correlative evidence of renal toxicity commonly occur in toxicology studies and may represent a physiological response to high doses of a test material.⁽³²⁾ Thus, increased kidney weights and the associated renal tubular hypertrophy were likely test substance-related; however, these changes were not considered adverse but most likely represent a test substance-related physiologic response.

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

E. Anatomical Pathology Conclusions

Exposure to 125 mg/kg/day of the test substance for approximately 90 days produced degeneration/disorganization of enamel organ ameloblast cells in male rats. Ameloblastic degeneration/disorganization was not reversible after three months recovery. Increased incidence and severity of chronic progressive nephropathy in 125 mg/kg/day female recovery rats was considered test substance related and biologically adverse. Focal hepatic necrosis was present in 90-day males at 25 and 125 mg/kg/day and in three-month recovery males at 125 mg/kg/day. This lesion was considered test substance related and adverse. The incidence and/or severity of altered colloid in thyroid glands of male rats increased beyond control level as the dose increased; however, since there were no other microscopic alterations present this finding was not considered adverse.

Increased liver weights were present in males and females at 25 and 125 mg/kg/day. The increased liver weights correlated with microscopic hepatocellular hypertrophy in males at 125 mg/kg/day. Hepatocellular hypertrophy was reversible in males following three-months recovery. These liver changes were considered to represent a physiologic response to metabolism of a xenobiotic and thus were not considered to be adverse. Increased kidney weights were present in 25 and 125 mg/kg/day males and females. In males, these kidney weight changes correlated with microscopic renal tubular hypertrophy. The increased kidney weights and renal tubular hypertrophy appeared to be reversible by three-months recovery. Increased kidney weights and microscopic tubular hypertrophy were not associated with correlative morphologic or clinical pathological changes and thus were not considered to be adverse findings.

Under the conditions of this study, the NOEL for pathology for male rats was 5 mg/kg/day based on hepatic necrosis at the 25 and 125 mg/kg/day dose levels and for female rats was 25 mg/kg/day based on an increased incidence and severity of nephropathy at 125 mg/kg/day.

CONCLUSIONS

No test substance-related mortality or alterations in neurobehavioral parameters were observed in male or female rats. No test substance-related decrements in mean body weight, body weight gain, food consumption, or food efficiency were observed in male or female rats administered up to 125 mg/kg/day. Test substance-related, toxicologically significant increases in the incidence of striated teeth occurred in the 125 mg/kg/day male and female dose groups.

There were no toxicologically significant changes observed in clinical pathology parameters in rats dosed with up to 125 mg/kg/day. A statistically significant increase in the rate of hepatic β -oxidation occurred in the 25 mg/kg/day female and 125 mg/kg/day male and female groups. After the recovery period, the increased rate of β -oxidation persisted, albeit at a reduced level compared to the 90-day time point, in the 125 mg/kg/day male group.

Test substance-related, toxicologically significant degeneration/disorganization of enamel organ ameloblasts cells occurred in male rats dosed with 125 mg/kg/day. This tooth lesion, along with the increased incidence of striated teeth, is consistent with fluoride toxicosis.⁽³⁰⁾ After three months, the degeneration/disorganization of ameloblasts persisted, at a lower incidence and severity.

A test substance-related, adverse increase in the incidence and severity of focal hepatic necrosis was observed in males administered 25 and 125 mg/kg/day. An increased incidence and severity of chronic progressive nephropathy occurred in the 125 mg/kg/day female group that was considered adverse. After three months of recovery, both the incidence of hepatocellular necrosis in the 125 mg/kg/day male group and the incidence and severity of chronic progressive nephropathy in the 125 mg/kg/day female group were increased compared to control.

Test-substance related and statistically significant increases in liver weight parameters were present in males and females administered 25 or 125 mg/kg/day for approximately 90 days. The increased liver weights correlated with microscopic hepatocellular hypertrophy in the 125 mg/kg/day male dose group. Liver weight changes and microscopic hypertrophy were considered to be a physiological adaptive response to metabolism of the test substance and not adverse. Test-substance related and statistically significant increases in kidney weight parameters occurred in males and females administered 25 or 125 mg/kg/day. The increased kidney weights correlated with microscopic renal tubular hypertrophy in the 25 and 125 mg/kg/day male groups only. However, no correlative microscopic or clinical pathological evidence of renal toxicity were present. Therefore, kidney weight changes and microscopic tubular hypertrophy were not considered adverse findings. Altered colloid, a common spontaneous finding in rats, was increased in incidence and/or severity in treated male groups. This change was not associated with other findings in the thyroid gland and was also not considered an adverse finding. After the three-month recovery period, increased liver weight parameters and hepatocellular hypertrophy (males only) were no longer observed in the 125 mg/kg/day male and female groups. Similarly, increased kidney weight parameters and renal tubular hypertrophy (males only) were not observed in rats sacrificed after three months of recovery.

The no-observed-effect level (NOEL)^a for [REDACTED] for the 90-day exposure period was 5 mg/kg/day [REDACTED] based on the increased incidence of hepatic necrosis observed in males administered ≥ 25 mg/kg/day. The NOEL for females was 25 mg/kg/day [REDACTED] based on the increased incidence and severity of chronic progressive nephropathy observed in females administered 125 mg/kg/day.

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. Test Substance characterization data will be retained at Haskell Laboratory, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware.

^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⁽³³⁾ and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union.⁽³⁴⁾

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TABLES

TABLES

EXPLANATORY NOTES

Critical Dates

- Day 91 • Last day of test substance administration for rats designated for satellite bleeds and 3-month recovery.
- Last day of non-fasted body weight and food consumption data collection for rats designated for the 90-day exposure period.
 - Last day of food consumption data collection for rats designated for satellite bleeds in the 1, 5, and 25 mg/kg/day dose groups.
- Day 92 Last day of test substance administration for male rats designated for the 90-day exposure period.
- Day 93 • Last day of test substance administration for female rats designated for the 90-day exposure period.
- Male rats designated for the 90-day exposure period were sacrificed.
- Day 94 Female rats designated for 90-day exposure period were sacrificed.
- Day 175 Rats designated for satellite bleeds were sacrificed
- Day 182 Last day of non-fasted body weight and food consumption data collection for rats designated for the 3-month recovery period.
- Day 183 Male and female rats designated for the 3-month recovery period were sacrificed.

Note

mg/kg = mg/kg/day

Notes for Clinical Pathology data:

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

TABLES

EXPLANATORY NOTES (CONTINUED)

ABBREVIATIONS:

Summary of Hematology Values

RBC	-	red blood cell count
HGB	-	hemoglobin
HCT	-	hematocrit
MCV	-	mean corpuscular volume
MCH	-	mean corpuscular hemoglobin
MCHC	-	mean corpuscular hemoglobin concentration
RDW	-	red cell distribution width
ARET	-	absolute reticulocyte count
PLT	-	platelet count
WBC	-	white blood cell count
ANEU	-	absolute neutrophil (all forms)
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 (CONTINUED)

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

TABLE 1
SUMMARY OF DOSING MIXING AND STABILITY ANALYSES

Nominal: Homogeneity Samples Test Day 1/-6	Dosing Concentration of [REDACTED] mg/mL)			
	0.20	1.0	5.0	25.0
Top	0.163 (81.5) ^b	0.803 (80.3)	4.55 (91.0)	19.9 ^a (79.6)
Middle	0.164 (82.0)	0.857 (85.7)	4.80 (96.0)	21.9 (87.6)
Bottom	0.161 (80.5)	0.890 (89.0)	4.61 (92.2)	22.9 (91.6)
Average Measured Conc. ^c	0.163	0.850	4.65	21.6
Average Percent Nominal	(81.5)	(85.0)	(93.0)	(86.4)
Standard Deviation ^c	± 0.002	± 0.04	± 0.13	± 1.5
Coefficient of Variation ^c	1%	5%	3%	7%
Stability Samples				
5 Hour Room Temperature	0.167 (83.5)	0.818 (81.8)	4.14 (82.8)	21.8 (87.2)
Test Day 1/-6 and Test Day 4 ^d (baseline for stability)	0.163 (81.5)	0.888 (88.8)	4.51 (90.2)	23.0 (92.0)
7-Day Refrigerated				
#1	0.161 (80.5)	0.900 (90.0)	4.46 ^e (89.2)	24.2 ^e (96.8)
#2	0.173 (86.5)	0.864 (86.4)	4.44 (88.8)	23.9 (95.6)
#3	---	0.859 (85.9)	---	---
Average Measured Conc.	0.167 ^e	0.874 ^e	4.45 ^e	24.1 ^{ee}
Average Percent Nominal	(83.5)	(87.4)	(89.0)	(96.4)
Standard Deviation	± 0.01 ^e	± 0.02 ^e	± 0.01 ^e	± 0.21 ^e
Coefficient of Variation	5% ^e	3% ^e	0.2% ^e	1% ^e
5 Hour Room Temperature	0.158 ^a (79.0)	0.904 ^f (90.4)	4.21 ^f (84.2)	21.2 ^f (84.8)

^a Result of the original aliquot. Duplicate reanalysis of original sample support original analysis and not reported.

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

^c Statistics based on the average measured concentration of the top, middle and bottom of each dosing level.

^d Samples analyzed in previous study [REDACTED]

^e Statistics based on the average measured concentration of duplicate samples for the dosing level.

^f Mean results of duplicate re-analysis of the original sample. Original results were low due to aliquot error

TABLE 1 (CONTINUED)

SUMMARY OF DOSING MIXING AND STABILITY ANALYSES

Nominal: Concentration Verification Test Day 42	Dosing Concentration of [REDACTED] (mg/mL)			
	0.20	1.0	5.0	25.0
#1	0.156 ^c (78.0) ^b	0.749 ^c (74.9)	3.87 ^c (77.3)	19.4 ^f (77.6)
#2	0.169 ^c (84.5)	0.776 ^c (77.6)	3.91 ^f (78.2)	19.1 ^f (76.2)
Average Measured Conc. ^e	0.163	0.763	3.89	19.3
Average Percent Nominal	(81.5)	(76.3)	(77.8)	(77.2)
Standard Deviation ^e	± 0.01	± 0.02	± 0.03	± 0.21
Coefficient of Variation ^e	6%	3%	1%	1%
Test Day 45				
#1	0.066 ^c (33.0)	0.676 ^c (67.6)	2.20 ^c (44.0)	8.34 ^f (33.4)
#2	0.083 ^c (41.5)	0.656 ^c (65.6)	2.32 ^c (46.4)	8.64 ^f (34.6)
Average Measured Conc. ^e	0.075	0.666	2.26	8.49
Average Percent Nominal	(37.5)	(66.6)	(45.2)	(34.0)
Standard Deviation ^e	± 0.01	± 0.01	± 0.09	± 0.21
Coefficient of Variation ^e	13%	2%	4%	3%
Test Day 48 ^g				
#1	0.197 (98.5)	0.865 (86.5)	3.93 (78.6)	21.9 (87.6)
#2	0.219 (109.5)	0.948 (94.8)	3.90 (78.0)	22.5 (90.0)
Average Measured Conc. ^e	0.208	0.907	3.92	22.2
Average Percent Nominal	(104.0)	(90.7)	(78.3)	(88.8)
Standard Deviation ^e	± 0.02	± 0.06	± 0.02	± 0.42
Coefficient of Variation ^e	7%	6%	1%	3%
Test Day 52				
#1	0.174 (87.0)	0.845 (84.5)	4.22 (84.4)	23.5 (94.0)
#2	0.184 (92.0)	0.895 (89.5)	4.16 (83.2)	22.3 (89.2)
Average Measured Conc. ^e	0.179	0.870	4.19	22.9
Average Percent Nominal	(89.5)	(87.0)	(83.8)	(91.6)
Standard Deviation ^e	± 0.01	± 0.04	± 0.04	± 0.85
Coefficient of Variation ^e	4%	4%	1%	4%

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

^c Mean result of the original analysis and duplicate reanalysis of the original sample reported.

^e Statistics based on the average measured concentration of duplicate samples for the dosing level.

^f Mean results of duplicate re-analysis of the original sample. Original results were low due to aliquot error

^g Suspension not dosed to animals.

TABLE 1 (CONTINUED)

SUMMARY OF DOSING MIXING AND STABILITY ANALYSES

Nominal: Concentration Verification	Dosing Concentration of [REDACTED] mg/mL			
	0.20	1.0	5.0	25.0
Test Day 56				
#1	0.167 (83.5) ^b	0.964 (96.4)	4.41 (88.2)	22.8 (91.2)
#2	0.189 (94.5)	0.950 (95.0)	4.31 (86.2)	21.4 (85.6)
Average Measured Conc. ^c	0.178	0.957	4.36	22.1
Average Percent Nominal	(89.0)	(95.7)	(87.2)	(88.4)
Standard Deviation ^c	± 0.02	± 0.01	± 0.07	± 0.99
Coefficient of Variation ^c	9%	1%	2%	4%
Test Day 58				
#1	0.174 (87.0)	0.945 (94.5)	4.48 (89.6)	22.5 (90.0)
#2	0.150 (75.0)	0.937 (93.7)	4.17 (83.4)	22.1 (88.4)
Average Measured Conc. ^c	0.162	0.941	4.33	22.3
Average Percent Nominal	(81.0)	(94.1)	(86.5)	(89.2)
Standard Deviation ^c	± 0.02	± 0.01	± 0.22	± 0.28
Coefficient of Variation ^c	10%	1%	5%	1%
Test Day 65				
#1	0.159 ^c (79.5)	0.832 (83.2)	4.32 (86.4)	20.8 (83.2)
#2	0.150 ^c (75.0)	0.898 (89.8)	4.40 (88.0)	20.5 (82.0)
Average Measured Conc. ^c	0.155	0.865	4.36	20.7
Average Percent Nominal	(77.5)	(86.5)	(87.2)	(82.6)
Standard Deviation ^c	± 0.01	± 0.05	± 0.06	± 0.21
Coefficient of Variation ^c	4%	5%	1%	1%

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

^c Mean result of the original analysis and duplicate reanalysis of the original sample reported.

^e Statistics based on the average measured concentration of duplicate samples for the dosing level.

TABLE 1 (CONTINUED)

SUMMARY OF DOSING MIXING AND STABILITY ANALYSES

Nominal: Concentration Verification Test Day 91	Dosing Concentration of [REDACTED] (mg/mL)			
	0.20	1.0	5.0	25.0
#1	0.162 (81.0) ^b	0.760 ^c (76.0)	3.96 ^c (79.2)	19.9 ^c (76.4)
#2	0.165 (82.5)	0.863 (86.3)	3.90 ^c (78.0)	18.7 ^c (74.8)
Average Measured Conc. ^e	0.164	0.812	3.93	19.3
Average Percent Nominal	(82.0)	(81.2)	(78.6)	(77.2)
Standard Deviation ^e	± 0.002	± 0.07	± 0.04	± 0.85
Coefficient of Variation ^e	1% ^c	9%	1%	4%
Test Day 63				
#1	0.190 (95.0) ^a	0.784 (78.4)	4.12 (82.4)	23.0 (92.0)
#2	0.192 (96.0)	0.792 (79.2)	4.08 (81.8)	21.4 (85.6)
Average Measured Conc. ^e	0.191	0.788	4.10	22.2
Average Percent Nominal	(95.5)	(78.8)	(82.0)	(88.8)
Standard Deviation ^e	± 0.001	± 0.01	± 0.03	± 1.1
Coefficient of Variation ^e	1%	1%	1%	5%
Test Day 73				
#1	0.176 (88.0)	0.980 (98.0)	4.57 (91.4)	23.3 (93.2)
#2	0.155 (77.5)	1.03 (103.0)	4.60 (92.0)	24.4 (97.6)
Average Measured Conc. ^e	0.166	1.01	4.59	23.9
Average Percent Nominal	(82.8)	(101.0)	(91.8)	(95.6)
Standard Deviation ^e	± 0.01	± 0.04	± 0.02	± 0.78
Coefficient of Variation ^e	9%	4%	0.4%	3%

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

^c Mean result of the original analysis and duplicate reanalysis of the original sample reported.

^e Statistics based on the average measured concentration of duplicate samples for the dosing level.

TABLE 2

MEAN DAILY DOSE VOLUMES FOR MALE RATS (mL)

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
DAY0 -DAY7	1.2 0.2 (25)	1.2 0.1 (15)	1.2 0.1 (15)	1.2 0.1 (15)	1.2 0.1 (25)
DAY7 -DAY14	1.4 0.2 (25)	1.5 0.1 (15)	1.5 0.1 (15)	1.5 0.1 (15)	1.5 0.1 (25)
DAY14 -DAY21	1.7 0.2 (25)	1.8 0.1 (15)	1.7 0.2 (15)	1.7 0.1 (15)	1.7 0.1 (25)
DAY21 -DAY28	1.9 0.2 (25)	2.0 0.1 (15)	2.0 0.2 (15)	2.0 0.1 (15)	1.9 0.2 (25)
DAY28 -DAY35	2.1 0.2 (25)	2.1 0.1 (15)	2.2 0.2 (15)	2.1 0.2 (15)	2.1 0.2 (25)
DAY35 -DAY42	2.2 0.2 (25)	2.3 0.1 (15)	2.3 0.2 (15)	2.3 0.2 (15)	2.2 0.2 (25)
DAY42 -DAY49	2.3 0.3 (25)	2.4 0.2 (15)	2.4 0.3 (15)	2.4 0.2 (15)	2.4 0.2 (25)
DAY49 -DAY56	2.4 0.3 (25)	2.4 0.2 (15)	2.5 0.2 (15)	2.5 0.2 (15)	2.4 0.2 (25)
DAY56 -DAY63	2.5 0.3 (25)	2.5 0.2 (15)	2.6 0.3 (15)	2.6 0.2 (15)	2.5 0.2 (25)
DAY63 -DAY70	2.7 0.3 (25)	2.7 0.2 (15)	2.8 0.3 (15)	2.8 0.2 (15)	2.6 0.2 (25)
DAY70 -DAY77	2.7 0.3 (25)	2.7 0.2 (15)	2.9 0.3 (15)	2.9 0.2 (15)	2.6 0.3 (25)

TABLE 2 (CONTINUED)
MEAN DAILY DOSE VOLUMES FOR MALE RATS (mL)

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
DAY84 -DAY91	2.8 0.3 (25)	2.7 0.2 (15)	2.9 0.3 (15)	2.9 0.2 (15)	2.7 0.3 (25)
DAY91	2.8 0.3 (25)	2.8 0.2 (15)	2.9 0.3 (15)	3.0 0.2 (15)	2.8 0.3 (25)
DAY92	2.9 0.2 (10)	2.8 0.2 (10)	3.0 0.3 (10)	2.9 0.2 (10)	2.8 0.1 (10)

TABLE 3

MEAN DAILY DOSE VOLUMES FOR FEMALE RATS (mL)

Group: Dosage (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
DAY0 -DAY7	0.9 0.1(25)	0.9 0.1(15)	0.9 0.1(15)	0.9 0.1(15)	0.9 0.1(25)
DAY7 -DAY14	1.0 0.1(25)	1.0 0.1(15)	1.0 0.1(15)	1.0 0.1(15)	1.0 0.1(25)
DAY14 -DAY21	1.1 0.1(25)	1.1 0.1(15)	1.1 0.1(15)	1.1 0.1(15)	1.1 0.1(25)
DAY21 -DAY28	1.2 0.1(24)	1.2 0.1(15)	1.2 0.1(15)	1.2 0.1(15)	1.3 0.1(25)
DAY28 -DAY35	1.3 0.1(24)	1.2 0.1(15)	1.3 0.1(15)	1.2 0.1(15)	1.3 0.1(25)
DAY35 -DAY42	1.3 0.1(24)	1.3 0.1(15)	1.3 0.1(15)	1.3 0.1(15)	1.3 0.1(25)
DAY42 -DAY49	1.4 0.1(24)	1.4 0.1(15)	1.4 0.1(15)	1.4 0.1(15)	1.4 0.1(25)
DAY49 -DAY56	1.4 0.2(24)	1.3 0.1(15)	1.4 0.1(15)	1.4 0.1(15)	1.4 0.2(25)
DAY56 -DAY63	1.4 0.2(24)	1.4 0.1(15)	1.4 0.1(15)	1.5 0.1(15)	1.5 0.2(25)
DAY63 -DAY70	1.4 0.2(24)	1.5 0.1(15)	1.5 0.1(15)	1.5 0.1(15)	1.5 0.2(25)
DAY70 -DAY77	1.5 0.2(24)	1.5 0.1(15)	1.5 0.1(15)	1.5 0.1(15)	1.5 0.1(25)

TABLE 3 (CONTINUED)

MEAN DAILY DOSE VOLUMES FOR FEMALE RATS (mL)

Group: Dosage (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
DAY77 -DAY84	1.5 0.2 (24)	1.5 0.1 (15)	1.5 0.1 (15)	1.6 0.1 (15)	1.5 0.2 (25)
DAY84 -DAY91	1.5 0.2 (24)	1.5 0.1 (15)	1.5 0.1 (15)	1.6 0.1 (15)	1.6 0.2 (25)
DAY91	1.5 0.2 (24)	1.5 0.1 (15)	1.5 0.1 (15)	1.6 0.1 (15)	1.6 0.1 (25)
DAY92 -DAY93	1.5 0.1 (10)	1.5 0.1 (10)	1.5 0.1 (10)	1.6 0.1 (10)	1.5 0.1 (10)

TABLE 4

MEAN BODY WEIGHTS OF MALE RATS (g)

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
<u>Dosing Period for Subchronic Toxicity Evaluation</u>					
DAY0	234.5 23.9(25)	245.6 19.7(15)	240.8 21.0(15)	239.4 16.0(15)	235.1 22.1(25)
DAY7	288.7 29.3(25)	299.2 24.9(15)	295.8 26.6(15)	294.9 18.3(15)	289.2 25.7(25)
DAY14	337.2 33.0(25)	352.6 20.2(15)	348.4 31.7(15)	345.6 22.7(15)	343.3 28.4(25)
DAY21	383.6 37.5(25)	394.9 23.2(15)	396.1 36.4(15)	393.1 27.4(15)	387.9 32.3(25)
DAY28	415.5 40.3(25)	426.0 24.9(15)	432.2 42.8(15)	427.1 32.0(15)	422.0 36.4(25)
DAY35	445.1 48.4(25)	455.1 27.2(15)	464.0 47.0(15)	460.8 36.5(15)	448.9 40.7(25)
DAY42	467.2 56.5(25)	475.8 30.0(15)	487.4 50.4(15)	489.2 37.8(15)	473.8 42.2(25)
DAY49	483.2 52.4(25)	485.0 30.8(15)	498.4 48.7(15)	501.1 39.8(15)	486.8 45.5(25)
DAY56	503.8 56.9(25)	508.4 32.1(15)	525.8 53.1(15)	528.5 43.0(15)	507.2 49.1(25)
DAY63	520.5 58.6(25)	523.2 34.3(15)	545.1 56.7(15)	548.0 44.2(15)	516.0 51.9(25)
DAY70	537.8 57.4(25)	539.2 39.7(15)	559.1 56.4(15)	558.4 45.5(15)	524.5 50.8(25)

TABLE 4 (CONTINUED)
MEAN BODY WEIGHTS OF MALE RATS (g)

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY77	547.7 57.5 (25)	544.8 36.4 (15)	571.1 55.9 (15)	571.2 45.9 (15)	518.5 61.7 (25)
DAY84	554.6 58.2 (25)	549.5 39.1 (15)	582.5 58.0 (15)	581.2 45.7 (15)	531.5 53.6 (25)
DAY91	562.0 54.0 (25)	561.0 42.2 (15)	589.1 60.9 (15)	591.2 47.6 (15)	551.9 53.9 (25)
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>					
DAY98	568.1 55.2 (15)	567.9 58.8 (5)	567.0 69.6 (5)	606.8 59.8 (5)	556.0 65.4 (15)
DAY105	573.3 64.3 (15)	582.8 59.0 (5)	575.6 70.3 (5)	614.6 59.8 (5)	567.8 68.6 (15)
DAY112	581.6 63.4 (15)	584.4 60.6 (5)	579.2 72.9 (5)	619.3 67.0 (5)	573.5 67.4 (15)
DAY119	590.9 62.8 (15)	595.0 58.6 (5)	590.6 74.8 (5)	630.7 69.4 (5)	583.3 71.3 (15)
DAY126	605.5 62.7 (15)	604.5 65.8 (5)	600.6 74.0 (5)	646.4 70.5 (5)	599.3 76.1 (15)
DAY133	613.7 61.8 (15)	615.2 62.5 (5)	610.0 75.9 (5)	654.8 74.0 (5)	610.3 80.7 (15)
DAY140	612.0 64.0 (15)	615.8 65.5 (5)	608.0 87.4 (5)	656.8 76.7 (5)	612.9 81.7 (15)

TABLE 4 (CONTINUED)

MEAN BODY WEIGHTS OF MALE RATS (g)

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY147	617.2 65.6 (15)	626.4 68.2 (5)	618.3 86.9 (5)	665.6 79.9 (5)	621.5 83.0 (15)
DAY154	625.0 68.2 (15)	635.2 65.9 (5)	627.1 82.4 (5)	681.5 82.6 (5)	635.7 81.2 (15)
DAY161	623.7 71.9 (15)	637.2 68.2 (5)	629.5 85.5 (5)	678.9 83.7 (5)	636.5 82.0 (15)
DAY168	629.8 71.5 (15)	642.3 65.9 (5)	631.0 88.6 (5)	690.7 85.1 (5)	649.1 85.3 (15)
DAY175	631.4 79.3 (15)	646.3 66.8 (5)	632.5 85.8 (5)	693.8 81.8 (5)	648.1 84.3 (15)
DAY182	647.6 66.5 (10)	.	.	.	634.7 86.3 (10)

Data summarized as: Mean
Standard Deviation (n)

There were no statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 5
MEAN BODY WEIGHTS OF FEMALE RATS (g)

Group: Dosage (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
<u>Dosing Period for Subchronic Toxicity Evaluation</u>					
DAY0	186.6 15.1(25)	183.8 17.0(15)	182.2 17.0(15)	182.6 14.7(15)	188.5 16.5(25)
DAY7	204.8 18.0(25)	205.7 15.0(15)	204.5 15.3(15)	202.8 18.6(15)	209.0 18.1(25)
DAY14	223.5 21.1(25)	224.8 15.4(15)	223.7 17.1(15)	225.7 16.7(15)	230.4 18.6(25)
DAY21	241.1 24.2(24)	238.7 15.9(15)	239.0 20.8(15)	239.9 17.8(15)	247.7 21.8(25)
DAY28	251.8 26.5(24)	250.1 15.9(15)	250.9 20.0(15)	252.7 21.9(15)	259.9 24.1(25)
DAY35	263.5 27.3(24)	264.3 17.3(15)	264.0 24.3(15)	266.3 20.9(15)	270.3 24.5(25)
DAY42	273.0 27.6(24)	274.1 17.2(15)	274.9 24.1(15)	278.5 22.0(15)	278.2 25.4(25)
DAY49	272.8 30.2(24)	267.2 16.9(15)	271.6 22.6(15)	272.0 25.6(15)	280.4 30.1(25)
DAY56	284.4 30.2(24)	286.4 18.9(15)	286.8 26.2(15)	292.1 27.0(15)	292.1 29.8(25)
DAY63	288.7 31.7(24)	291.4 21.0(15)	292.7 27.3(15)	294.4 25.0(15)	297.1 31.1(25)
DAY70	296.1 31.0(24)	298.5 23.2(15)	297.4 26.2(15)	305.1 27.4(15)	300.0 28.6(25)

TABLE 5 (CONTINUED)

MEAN BODY WEIGHTS OF FEMALE RATS (g)

Group: Dosage (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY77	299.7 31.5 (24)	302.1 22.2 (15)	301.7 27.1 (15)	310.5 28.9 (15)	303.0 29.5 (25)
DAY84	302.5 31.9 (24)	305.8 25.0 (15)	300.8 26.8 (15)	311.3 29.7 (15)	311.3 30.8 (25)
DAY91	303.7 31.5 (24)	304.9 25.4 (15)	302.5 26.5 (15)	310.6 29.0 (15)	310.2 29.3 (25)
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>					
DAY98	310.9 38.7 (14)	306.6 26.3 (5)	299.9 30.8 (5)	322.9 26.3 (5)	317.6 36.4 (15)
DAY105	315.8 39.9 (14)	311.0 24.4 (5)	299.8 34.1 (5)	326.9 30.0 (5)	317.8 35.1 (15)
DAY112	318.0 37.7 (14)	312.5 25.8 (5)	305.7 34.2 (5)	329.6 32.7 (5)	319.1 39.8 (15)
DAY119	320.2 36.9 (14)	313.7 26.9 (5)	309.2 32.0 (5)	340.5 32.2 (5)	324.9 40.8 (15)
DAY126	327.9 38.0 (14)	319.1 27.7 (5)	314.5 35.7 (5)	346.2 39.0 (5)	340.1 45.6 (15)
DAY133	328.9 38.6 (14)	324.4 28.7 (5)	319.8 38.7 (5)	351.3 37.4 (5)	343.9 46.4 (15)
DAY140	331.6 36.5 (14)	325.6 29.6 (5)	320.3 34.9 (5)	351.6 39.7 (5)	343.3 48.3 (15)
DAY147	337.0 39.2 (14)	327.6 32.0 (5)	324.5 42.0 (5)	354.8 39.5 (5)	349.5 50.8 (15)

TABLE 5 (CONTINUED)

MEAN BODY WEIGHTS OF FEMALE RATS (g)

Group: Dosage (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY154	339.3 39.8(14)	331.3 32.0(5)	331.3 45.1(5)	359.1 42.6(5)	355.1 52.2(15)
DAY161	333.4 36.8(14)	330.4 28.7(5)	327.9 41.2(5)	361.6 47.5(5)	353.9 54.0(15)
DAY168	340.3 37.0(14)	336.0 28.3(5)	333.9 44.3(5)	368.3 48.0(5)	360.4 58.2(15)
DAY175	342.3 38.6(14)	336.2 29.3(5)	335.9 44.6(5)	366.8 53.8(5)	363.6 60.0(15)
DAY182	354.1 33.0(9)	. (0)	. (0)	. (0)	368.7 67.8(10)

Data summarized as: Mean
Standard Deviation (n)

There were no statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 6

MEAN BODY WEIGHT GAINS OF MALE RATS (g)

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
<u>Dosing Period for Subchronic Toxicity Evaluation</u>					
DAY0 -DAY7	54.3 7.9(25)	53.6 12.0(15)	55.0 9.3(15)	55.5 6.4(15)	54.1 10.0(25)
DAY7 -DAY14	48.5 7.2(25)	53.5 8.7(15)	52.6 8.7(15)	50.7 7.8(15)	54.1# 6.5(25)
DAY14 -DAY21	46.4 7.8(25)	42.3 4.2(15)	47.8 7.8(15)	47.6 9.2(15)	44.6 8.1(25)
DAY21 -DAY28	31.9 8.8(25)	31.1 6.7(15)	36.0 8.2(15)	34.0 8.9(15)	34.1 6.4(25)
DAY28 -DAY35	29.5 19.4(25)	29.0 5.3(15)	31.8 6.0(15)	33.7 7.1(15)	26.9 6.6(25)
DAY35 -DAY42	22.2 12.4(25)	20.8 6.6(15)	23.4 8.8(15)	28.3 4.8(15)	24.9 6.9(25)
DAY42 -DAY49	16.0 13.0(25)	9.2 6.1(15)	11.0 8.8(15)	11.9 8.7(15)	13.0 8.5(25)
DAY49 -DAY56	20.5 9.2(25)	23.5 5.4(15)	27.4* 8.1(15)	27.4* 7.5(15)	20.5 6.9(25)
DAY56 -DAY63	16.8 6.8(25)	14.8 4.5(15)	19.3 7.1(15)	19.5 4.3(15)	8.7 15.5(25)
DAY63 -DAY70	17.2 7.8(25)	16.0 7.9(15)	14.0 6.6(15)	10.4# 5.3(15)	8.5# 16.7(25)
DAY70 -DAY77	9.9 5.7(25)	5.5 11.4(15)	12.0 8.2(15)	12.8 5.5(15)	-6.0 28.0(25)

TABLE 6 (CONTINUED)
MEAN BODY WEIGHT GAINS OF MALE RATS (g)

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY77 -DAY84	6.9 6.6(25)	4.8 13.7(15)	11.5 5.6(15)	10.0 6.8(15)	13.1 22.4(25)
DAY84 -DAY91	7.5 11.0(25)	11.5 8.0(15)	6.6 9.9(15)	10.1 6.4(15)	20.3# 14.2(25)
DAY0 -DAY91	327.6 43.5(25)	315.4 35.9(15)	348.2 50.8(15)	351.9 47.2(15)	316.8 43.9(25)
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>					
DAY91 -DAY98	13.3 6.5(15)	9.1 3.9(5)	12.2 5.1(5)	9.3 3.8(5)	11.9 6.9(15)
DAY98 -DAY105	5.3 19.1(15)	14.9 2.8(5)	8.6 5.1(5)	7.9 2.2(5)	11.9 6.9(15)
DAY105 -DAY112	8.3 7.1(15)	1.5 4.2(5)	3.6 7.5(5)	4.6 8.6(5)	5.6 7.2(15)
DAY112 -DAY119	9.3 6.9(15)	10.7 3.7(5)	11.4 5.9(5)	11.5 7.5(5)	9.8 6.4(15)
DAY119 -DAY126	14.6 6.7(15)	9.4 8.6(5)	10.0 5.1(5)	15.7 5.3(5)	16.0 7.6(15)
DAY126 -DAY133	8.2 5.7(15)	10.7 7.1(5)	9.4 5.4(5)	8.3 4.2(5)	11.0 6.7(15)

TABLE 6 (CONTINUED)

MEAN BODY WEIGHT GAINS OF MALE RATS (g)

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
Three-Month Recovery Period for Subchronic Toxicity Evaluation (continued)					
DAY133 -DAY140	-1.7 6.4(15)	0.6 6.7(5)	-1.9 16.5(5)	2.0 6.0(5)	2.6 7.4(15)
DAY140 -DAY147	5.2 6.3(15)	10.6 3.0(5)	10.3 8.0(5)	8.9 4.9(5)	8.6 4.9(15)
DAY147 -DAY154	7.8 8.6(15)	8.8 2.7(5)	8.8 6.0(5)	15.9 4.5(5)	14.2# 6.7(15)
DAY154 -DAY161	-1.3 11.9(15)	2.0 2.5(5)	2.4 4.5(5)	-2.6 5.6(5)	0.8 5.6(15)
DAY161 -DAY168	6.1 5.4(15)	5.1 2.8(5)	1.6 4.4(5)	11.8 8.8(5)	12.6# 8.5(15)
DAY168 -DAY175	1.5 12.3(15)	4.0 5.7(5)	1.4 6.8(5)	3.1 5.0(5)	-1.0 7.6(15)
DAY175 -DAY182	2.1 5.0(10)	. (0)	. (0)	. (0)	11.4# 4.6(10)
DAY91 -DAY175	76.6 32.2(15)	87.5 26.9(5)	77.7 18.0(5)	96.4 24.1(5)	104.1# 28.8(15)
DAY91 -DAY182	89.2 21.4(10)	. (0)	. (0)	. (0)	108.2 31.3(10)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test.
* Statistically significant difference at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.

TABLE 7

MEAN BODY WEIGHT GAINS OF FEMALE RATS (g)

Group: Dosage (mg/kg)	II 0	IV 1	VI 5	VIII 25	X 125
<u>Dosing Period for Subchronic Toxicity Evaluation</u>					
DAY0 -DAY7	18.2 5.6(25)	21.9 10.0(15)	22.3 9.0(15)	20.2 6.9(15)	20.5 4.8(25)
DAY7 -DAY14	18.7 7.9(25)	19.1 4.1(15)	19.2 4.0(15)	22.9 7.5(15)	21.4 4.2(25)
DAY14 -DAY21	16.4 5.7(24)	13.9 3.3(15)	15.2 7.6(15)	14.1 7.4(15)	17.3 6.5(25)
DAY21 -DAY28	10.7 5.7(24)	11.4 5.4(15)	11.9 4.4(15)	12.8 6.9(15)	12.2 4.9(25)
DAY28 -DAY35	11.8 5.7(24)	14.2 4.2(15)	13.1 6.7(15)	13.6 5.9(15)	10.4 5.9(25)
DAY35 -DAY42	9.5 5.3(24)	9.8 5.6(15)	10.9 8.9(15)	12.3 7.7(15)	7.9 7.2(25)
DAY42 -DAY49	-0.2 6.2(24)	-6.9 7.1(15)	-3.3 7.2(15)	-6.5 9.6(15)	2.2 9.2(25)
DAY49 -DAY56	11.6 6.0(24)	19.3 7.1(15)	15.2 7.7(15)	20.0 8.2(15)	11.7 12.4(25)
DAY56 -DAY63	4.3 5.4(24)	4.9 6.9(15)	5.9 7.4(15)	2.3 6.4(15)	5.0 7.6(25)
DAY63 -DAY70	7.4 5.7(24)	7.2 4.3(15)	4.7 5.8(15)	10.6 6.2(15)	2.9 6.3(25)
DAY70 -DAY77	3.5 4.2(24)	3.6 5.0(15)	4.3 4.5(15)	5.5 4.8(15)	3.0 5.3(25)

TABLE 7 (CONTINUED)

MEAN BODY WEIGHT GAINS OF FEMALE RATS (g)

Group: Dosage (mg/kg)	II 0	IV 1	VI 5	VIII 25	X 125
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY77 -DAY84	2.8 5.4 (24)	3.7 5.2 (15)	-0.8 3.3 (15)	0.7 5.4 (15)	8.3# 6.2 (25)
DAY84 -DAY91	1.3 6.5 (24)	-0.9 5.9 (15)	1.6 6.3 (15)	-0.7 5.8 (15)	-1.1 6.7 (25)
DAY0 -DAY91	116.9 21.6 (24)	121.1 24.6 (15)	120.2 20.5 (15)	128.0 18.2 (15)	121.7 19.9 (25)
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>					
DAY91 -DAY98	4.5 7.4 (14)	8.0 3.4 (5)	8.8 4.4 (5)	9.7 7.5 (5)	5.0 9.3 (15)
DAY98 -DAY105	4.9 6.8 (14)	4.4 5.6 (5)	-0.1 6.3 (5)	3.9 6.3 (5)	0.2 5.3 (15)
DAY105 -DAY112	2.2 5.3 (14)	1.5 4.5 (5)	5.9 1.3 (5)	2.8 4.1 (5)	1.3 11.7 (15)
DAY112 -DAY119	2.2 6.5 (14)	1.1 2.3 (5)	3.5 5.3 (5)	10.9 3.3 (5)	5.8 10.5 (15)
DAY119 -DAY126	7.7 6.0 (14)	5.4 1.4 (5)	5.2 3.7 (5)	5.7 7.2 (5)	15.2# 7.1 (15)
DAY126 -DAY133	1.0 6.3 (14)	5.3 1.6 (5)	5.3 6.3 (5)	5.1 4.8 (5)	3.8 6.4 (15)
DAY133 -DAY140	2.7 6.2 (14)	1.1 6.1 (5)	0.6 5.3 (5)	0.3 5.1 (5)	-0.6# 5.4 (15)

TABLE 7 (CONTINUED)

MEAN BODY WEIGHT GAINS OF FEMALE RATS (g)

Group: Dosage (mg/kg)	II 0	IV 1	VI 5	VIII 25	X 125
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY140 -DAY147	5.4 5.9 (14)	2.0 4.5 (5)	4.2 7.1 (5)	3.2 11.2 (5)	6.1 6.8 (15)
DAY147 -DAY154	2.4 6.2 (14)	3.7 6.2 (5)	6.8 7.5 (5)	4.4 11.0 (5)	5.6 8.6 (15)
DAY154 -DAY161	-6.0 5.2 (14)	-0.9 5.2 (5)	-3.5 5.0 (5)	2.5# 8.3 (5)	-1.2# 4.6 (15)
DAY161 -DAY168	7.0 5.7 (14)	5.6 4.8 (5)	6.1 4.0 (5)	6.7 3.4 (5)	6.5 6.9 (15)
DAY168 -DAY175	2.0 3.9 (14)	0.2 5.3 (5)	2.0 4.2 (5)	-1.5 7.5 (5)	3.2 5.8 (15)
DAY175 -DAY182	2.7 6.2 (9)	. (0)	. (0)	. (0)	2.9 7.6 (10)
DAY91 -DAY175	36.0 13.8 (14)	37.5 10.7 (5)	44.9 20.1 (5)	53.6 24.3 (5)	51.0 33.1 (15)
DAY91 -DAY182	42.1 15.5 (9)	. (0)	. (0)	. (0)	56.3 38.4 (10)

Data summarized as: Mean
Standard Deviation (n)

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

TABLE 8

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

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
<u>Dosing Period for Subchronic Toxicity Evaluation</u>					
DAY0 -DAY7	27.0 3.0(25)	28.7 2.6(15)	27.2 3.3(15)	27.9 2.5(15)	26.6 2.5(25)
DAY7 -DAY14	28.3 4.1(25)	30.1 2.1(15)	29.6 3.6(15)	30.2 2.7(15)	29.0 2.3(25)
DAY14 -DAY21	29.8 3.3(25)	31.2 2.1(15)	30.7 4.0(15)	31.2 3.4(15)	30.0 3.0(25)
DAY21 -DAY28	30.5 3.3(25)	29.8 1.9(15)	31.3 3.9(15)	30.9 4.1(15)	29.1 2.9(25)
DAY28 -DAY35	30.4 5.9(25)	30.4 2.4(15)	31.8 4.1(15)	32.2 4.1(15)	30.4 3.2(25)
DAY35 -DAY42	29.5 5.2(25)	30.0 1.7(15)	30.9 4.2(15)	31.5 3.7(15)	29.8 3.2(25)
DAY42 -DAY49	28.8 3.6(25)	27.1 2.2(15)	28.6 3.3(15)	29.1 3.7(15)	28.6 3.4(25)
DAY49 -DAY56	29.4 3.2(25)	29.2 1.4(15)	30.2 3.4(15)	31.5 3.3(15)	29.1 3.3(25)
DAY56 -DAY63	28.3 3.9(25)	29.1 1.9(15)	30.1 3.8(15)	31.6 3.2(15)	27.2 4.5(25)
DAY63 -DAY70	29.2 3.3(25)	29.6 2.5(15)	30.2 2.8(15)	30.2 3.1(15)	26.6 4.3(25)
DAY70 -DAY77	28.8 3.1(25)	30.0 2.9(15)	30.1 2.8(15)	30.3 2.8(15)	25.3 6.2(25)

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

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY77 -DAY84	28.3 3.0 (25)	28.0 1.5 (15)	29.7 2.6 (15)	29.2 2.2 (15)	26.6 4.6 (25)
DAY84 -DAY91	27.8 3.2 (25)	28.9 1.9 (15)	28.9 3.1 (15)	30.3 3.0 (15)	29.4 3.5 (25)
DAY0 -DAY91	28.9 3.0 (25)	29.4 1.5 (15)	30.0 3.2 (15)	30.5 2.9 (15)	28.3 2.5 (25)
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>					
DAY91 -DAY98	27.2 1.9 (10)	. (0)	. (0)	. (0)	25.5 3.8 (10)
DAY98 -DAY105	28.4 2.3 (10)	. (0)	. (0)	. (0)	25.9# 3.5 (10)
DAY105 -DAY112	28.8 2.0 (10)	. (0)	. (0)	. (0)	26.0# 2.6 (10)
DAY112 -DAY119	27.6 2.9 (10)	. (0)	. (0)	. (0)	26.6 3.3 (10)
DAY119 -DAY126	27.7 2.3 (10)	. (0)	. (0)	. (0)	26.2 4.6 (10)
DAY126 -DAY133	28.1 2.3 (10)	. (0)	. (0)	. (0)	27.1 3.4 (10)
DAY133 -DAY140	28.1 2.8 (10)	. (0)	. (0)	. (0)	28.1 3.3 (10)

TABLE 8 (CONTINUED)

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

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY140 -DAY147	26.8 2.9(10)	: (0)	: (0)	: (0)	26.4 3.9(10)
DAY147 -DAY154	27.5 2.4(10)	: (0)	: (0)	: (0)	26.8 2.4(10)
DAY154 -DAY161	28.3 2.3(10)	: (0)	: (0)	: (0)	26.1 2.9(10)
DAY161 -DAY168	28.5 2.4(10)	: (0)	: (0)	: (0)	27.5 3.0(10)
DAY168 -DAY175	28.2 3.0(10)	: (0)	: (0)	: (0)	26.4 3.1(10)
DAY175 -DAY182	27.9 2.2(10)	: (0)	: (0)	: (0)	27.0 3.7(10)
DAY91 -DAY175	27.9 2.2(10)	: (0)	: (0)	: (0)	26.6 3.1(10)
DAY91 -DAY182	27.9 2.2(10)	: (0)	: (0)	: (0)	26.6 3.1(10)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant difference 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 1	VI 5	VIII 25	X 125
<u>Dosing Period for Subchronic Toxicity Evaluation</u>					
DAY0 -DAY7	19.4 1.9 (25)	19.9 1.9 (15)	19.8 1.8 (15)	19.5 1.9 (15)	19.1 1.8 (25)
DAY7 -DAY14	19.5 2.2 (25)	19.6 1.4 (15)	19.6 2.0 (15)	19.5 1.6 (15)	20.2 1.8 (25)
DAY14 -DAY21	21.1 2.2 (24)	21.0 1.9 (15)	21.2 2.1 (15)	21.8 2.8 (15)	21.5 2.1 (25)
DAY21 -DAY28	20.3 2.1 (24)	20.1 1.8 (15)	21.0 1.7 (15)	20.8 2.1 (15)	21.0 2.0 (25)
DAY28 -DAY35	21.0 2.3 (24)	20.8 1.8 (14)	21.5 2.2 (15)	21.7 2.3 (15)	21.4 2.2 (25)
DAY35 -DAY42	21.3 2.1 (24)	21.2 1.6 (15)	21.2 2.3 (15)	22.0 2.7 (15)	20.7 2.2 (24)
DAY42 -DAY49	19.7 2.6 (24)	18.9 1.4 (15)	20.2 2.0 (15)	20.4 2.7 (15)	20.7 3.4 (25)
DAY49 -DAY56	21.2 2.2 (24)	21.5 2.3 (15)	22.1 2.0 (15)	23.0 1.6 (15)	21.7 2.6 (25)
DAY56 -DAY63	20.9 2.3 (24)	20.9 2.1 (15)	21.6 2.2 (15)	21.8 1.8 (15)	20.7 2.4 (25)
DAY63 -DAY70	20.5 2.0 (24)	20.6 2.8 (15)	20.8 1.6 (15)	22.1 2.2 (15)	20.5 2.2 (25)
DAY70 -DAY77	20.7 2.2 (24)	20.6 2.1 (15)	20.9 2.0 (15)	21.9 2.2 (15)	20.2 2.4 (25)

TABLE 9 (CONTINUED)

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

Group: Dosage (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY77 - DAY84	20.4 2.6(24)	20.2 2.0(15)	20.3 1.5(15)	21.3 1.9(15)	20.4 4.0(25)
DAY84 - DAY91	19.7 2.3(24)	19.7 1.5(15)	20.2 1.2(15)	20.3 1.9(15)	20.1 3.1(25)
DAY0 - DAY91	20.5 2.0(24)	20.4 1.7(14)	20.8 1.6(15)	21.2 1.7(15)	20.6 2.1(24)
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>					
DAY91 - DAY98	19.6 2.5(9)	. (0)	. (0)	. (0)	19.4 2.5(10)
DAY98 - DAY105	21.1 3.2(9)	. (0)	. (0)	. (0)	20.2 2.9(10)
DAY105 - DAY112	21.9 2.2(9)	. (0)	. (0)	. (0)	20.0 3.0(10)
DAY112 - DAY119	20.6 2.0(9)	. (0)	. (0)	. (0)	21.1 3.8(10)
DAY119 - DAY126	22.0 2.4(9)	. (0)	. (0)	. (0)	22.4 4.5(10)
DAY126 - DAY133	21.8 2.4(9)	. (0)	. (0)	. (0)	22.4 4.6(10)
DAY133 - DAY140	22.5 2.0(9)	. (0)	. (0)	. (0)	23.5 3.3(10)

TABLE 9 (CONTINUED)

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

Group: Dosage (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY140 -DAY147	19.9 4.9(9)	. (0)	. (0)	. (0)	21.9 3.9(10)
DAY147 -DAY154	20.8 2.8(9)	. (0)	. (0)	. (0)	22.2 4.4(10)
DAY154 -DAY161	20.6 2.9(9)	. (0)	. (0)	. (0)	21.7 4.2(10)
DAY161 -DAY168	22.2 2.3(9)	. (0)	. (0)	. (0)	24.5 4.8(10)
DAY168 -DAY175	22.4 1.9(9)	. (0)	. (0)	. (0)	21.1 3.8(10)
DAY175 -DAY182	22.4 2.4(9)	. (0)	. (0)	. (0)	20.6 2.7(10)
DAY91 -DAY175	21.3 2.1(9)	. (0)	. (0)	. (0)	21.7 3.5(10)
DAY91 -DAY182	21.4 2.0(9)	. (0)	. (0)	. (0)	21.6 3.4(10)

Data summarized as: Mean
Standard Deviation (n)

There were no statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 10
MEAN DAILY FOOD EFFICIENCY OF MALE RATS
(g body weight gain/g food consumed)

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
<u>Dosing Period for Subchronic Toxicity Evaluation</u>					
DAY0 -DAY7	0.288 0.026(25)	0.265 0.050(15)	0.288 0.027(15)	0.284 0.025(15)	0.290 0.041(25)
DAY7 -DAY14	0.248 0.040(25)	0.256 0.055(15)	0.253 0.028(15)	0.239 0.023(15)	0.266# 0.025(25)
DAY14 -DAY21	0.222 0.027(25)	0.193 0.016(15)	0.223 0.026(15)	0.217 0.024(15)	0.211 0.026(25)
DAY21 -DAY28	0.149 0.036(25)	0.149 0.027(15)	0.163 0.022(15)	0.156 0.027(15)	0.166# 0.022(25)
DAY28 -DAY35	0.104 0.235(25)	0.136 0.023(15)	0.142 0.018(15)	0.149 0.021(15)	0.125# 0.023(25)
DAY35 -DAY42	0.094 0.104(25)	0.099 0.030(15)	0.107 0.034(15)	0.129 0.022(15)	0.119 0.030(25)
DAY42 -DAY49	0.079 0.067(25)	0.047 0.031(15)	0.055 0.042(15)	0.056 0.035(15)	0.063 0.037(25)
DAY49 -DAY56	0.098 0.046(25)	0.114 0.024(15)	0.129 0.032(15)	0.124 0.027(15)	0.099 0.028(25)
DAY56 -DAY63	0.083 0.037(25)	0.072 0.019(15)	0.090 0.027(15)	0.088 0.020(15)	0.039 0.099(25)
DAY63 -DAY70	0.085 0.044(25)	0.075 0.034(15)	0.067 0.034(15)	0.049# 0.024(15)	0.035# 0.107(25)
DAY70 -DAY77	0.048 0.031(25)	0.029 0.048(15)	0.057 0.038(15)	0.061 0.026(15)	-0.106 0.339(25)

TABLE 10 (CONTINUED)

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

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY77 -DAY84	0.034 0.034 (25)	0.023 0.067 (15)	0.054 0.025 (15)	0.049 0.032 (15)	0.059 0.133 (25)
DAY84 -DAY91	0.034 0.073 (25)	0.055 0.037 (15)	0.029 0.046 (15)	0.046 0.029 (15)	0.096# 0.060 (25)
DAY0 -DAY91	0.124 0.012 (25)	0.118 0.010 (15)	0.128 0.010 (15)	0.127 0.010 (15)	0.123 0.010 (25)
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>					
DAY91 -DAY98	0.074 0.029 (10)	· · (0)	· · (0)	· · (0)	0.064 0.033 (10)
DAY98 -DAY105	0.070 0.024 (10)	· · (0)	· · (0)	· · (0)	0.050 0.027 (10)
DAY105 -DAY112	0.030 0.022 (10)	· · (0)	· · (0)	· · (0)	0.026 0.034 (10)
DAY112 -DAY119	0.035 0.019 (10)	· · (0)	· · (0)	· · (0)	0.051 0.028 (10)
DAY119 -DAY126	0.068 0.024 (10)	· · (0)	· · (0)	· · (0)	0.079 0.044 (10)
DAY126 -DAY133	0.038 0.028 (10)	· · (0)	· · (0)	· · (0)	0.055 0.034 (10)
DAY133 -DAY140	-0.008 0.020 (10)	· · (0)	· · (0)	· · (0)	0.009 0.036 (10)

TABLE 10 (CONTINUED)

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

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
Three-Month Recovery Period for Subchronic Toxicity Evaluation (continued)					
DAY140 -DAY147	0.037 0.015(10)	· (0)	· (0)	· (0)	0.044 0.025(10)
DAY147 -DAY154	0.037 0.024(10)	· (0)	· (0)	· (0)	0.078 0.036(10)
DAY154 -DAY161	0.007 0.030(10)	· (0)	· (0)	· (0)	-0.006 0.029(10)
DAY161 -DAY168	0.027 0.026(10)	· (0)	· (0)	· (0)	0.049 0.033(10)
DAY168 -DAY175	0.025 0.027(10)	· (0)	· (0)	· (0)	0.006 0.025(10)
DAY175 -DAY182	0.012 0.026(10)	· (0)	· (0)	· (0)	0.060 0.020(10)
DAY91 -DAY175	0.037 0.007(10)	· (0)	· (0)	· (0)	0.043 0.009(10)
DAY91 -DAY182	0.035 0.007(10)	· (0)	· (0)	· (0)	0.044# 0.009(10)

Data summarized as: Mean
Standard Deviation (n)

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

TABLE 11
MEAN DAILY FOOD EFFICIENCY OF FEMALE RATS
(g body weight gain/g food consumed)

Group: Dosage (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
<u>Dosing Period for Subchronic Toxicity Evaluation</u>					
DAY0 -DAY7	0.133 0.036(25)	0.157 0.071(15)	0.161 0.066(15)	0.146 0.044(15)	0.153 0.033(25)
DAY7 -DAY14	0.134 0.053(25)	0.138 0.025(15)	0.140 0.023(15)	0.168 0.056(15)	0.152 0.028(25)
DAY14 -DAY21	0.109 0.031(24)	0.095 0.023(15)	0.101 0.049(15)	0.092 0.047(15)	0.114 0.039(25)
DAY21 -DAY28	0.074 0.040(24)	0.081 0.038(15)	0.082 0.032(15)	0.086 0.043(15)	0.082 0.030(25)
DAY28 -DAY35	0.080 0.036(24)	0.100 0.022(14)	0.085 0.038(15)	0.089 0.040(15)	0.069 0.036(25)
DAY35 -DAY42	0.064 0.034(24)	0.065 0.034(15)	0.070 0.063(15)	0.078 0.044(15)	0.053 0.047(24)
DAY42 -DAY49	0.004 0.044(24)	-0.054 0.057(15)	-0.023 0.051(15)	-0.052 0.069(15)	0.008 0.062(25)
DAY49 -DAY56	0.078 0.040(24)	0.125 0.040(15)	0.097 0.045(15)	0.124 0.051(15)	0.077 0.074(25)
DAY56 -DAY63	0.028 0.034(24)	0.032 0.045(15)	0.037 0.044(15)	0.015 0.041(15)	0.032 0.045(25)
DAY63 -DAY70	0.052 0.040(24)	0.048 0.029(15)	0.033 0.039(15)	0.068 0.034(15)	0.021# 0.045(25)
DAY70 -DAY77	0.024 0.028(24)	0.025 0.037(15)	0.028 0.029(15)	0.035 0.030(15)	0.020 0.038(25)

TABLE 11 (CONTINUED)

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

Group: Dosage (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
<u>Dosing Period for Subchronic Toxicity Evaluation (continued)</u>					
DAY77 -DAY84	0.019 0.038 (24)	0.024 0.035 (15)	-0.006 0.023 (15)	0.004 0.037 (15)	0.056# 0.041 (25)
DAY84 -DAY91	0.008 0.045 (24)	-0.007 0.044 (15)	0.010 0.043 (15)	-0.006 0.041 (15)	-0.009 0.047 (25)
DAY0 -DAY91	0.062 0.008 (24)	0.066 0.010 (14)	0.063 0.008 (15)	0.066 0.006 (15)	0.065 0.007 (24)
<u>Three-Month Recovery Period for Subchronic Toxicity Evaluation</u>					
DAY91 -DAY98	0.031 0.064 (9)	· (0)	· (0)	· (0)	0.024 0.078 (10)
DAY98 -DAY105	0.026 0.042 (9)	· (0)	· (0)	· (0)	0.008 0.032 (10)
DAY105 -DAY112	0.019 0.041 (9)	· (0)	· (0)	· (0)	-0.011 0.097 (10)
DAY112 -DAY119	0.013 0.047 (9)	· (0)	· (0)	· (0)	0.046 0.081 (10)
DAY119 -DAY126	0.067 0.029 (9)	· (0)	· (0)	· (0)	0.095 0.039 (10)
DAY126 -DAY133	0.008 0.047 (9)	· (0)	· (0)	· (0)	0.032 0.041 (10)
DAY133 -DAY140	0.010 0.048 (9)	· (0)	· (0)	· (0)	-0.013 0.028 (10)

TABLE 11 (CONTINUED)

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

Group: Dosage (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
Three-Month Recovery Period for Subchronic Toxicity Evaluation (continued)					
DAY140 -DAY147	0.041 0.043 (9)	· (0)	· (0)	· (0)	0.054 0.036 (10)
DAY147 -DAY154	0.007 0.063 (9)	· (0)	· (0)	· (0)	0.032 0.029 (10)
DAY154 -DAY161	-0.044 0.027 (9)	· (0)	· (0)	· (0)	-0.011# 0.030 (10)
DAY161 -DAY168	0.053 0.034 (9)	· (0)	· (0)	· (0)	0.037 0.039 (10)
DAY168 -DAY175	0.013 0.023 (9)	· (0)	· (0)	· (0)	0.026 0.035 (10)
DAY175 -DAY182	0.015 0.039 (9)	· (0)	· (0)	· (0)	0.024 0.054 (10)
DAY91 -DAY175	0.022 0.008 (9)	· (0)	· (0)	· (0)	0.028 0.018 (10)
DAY91 -DAY182	0.021 0.007 (9)	· (0)	· (0)	· (0)	0.028 0.016 (10)

Data summarized as: Mean
Standard Deviation (n)

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

TABLE 12

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group Dosage (mg/kg/day) Animal Count	I 0 25	III 1 15	V 5 15	VII 25 15	IX 125 25
Absent Toe					
Forepaw Right					
Incidence Mean onset (Days)	0 (0%)	0 (0%)	0 (0%)	1 (7%) 35	0 (0%)
Eye Observation Corneal Opacity Right					
Incidence Mean onset (Days)	1 (4%) 91	2 (13%) 14	0 (0%)	0 (0%)	1 (4%) 63
Exophthalmus Right					
Incidence Mean onset (Days)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%) 56
Exophthalmus Bilateral					
Incidence Mean onset (Days)	0 (0%)	1 (7%) 21	0 (0%)	0 (0%)	0 (0%)
Enophthalmus Right					
Incidence Mean onset (Days)	2 (8%) 88	2 (13%) 77	1 (7%) 35	0 (0%)	1 (4%) 63

TABLE 12 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group	I	III	V	VII	IX
Dosage (mg/kg/day)	0	1	5	25	125
Animal Count	25	15	15	15	25
Wet Fur					
Ventral body					
Ventral					
Incidence	0 (0%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)
Mean onset (Days)			70		
General Teeth Observations					
Striated					
Incidence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	24 (96%)
Mean onset (Days)					58
Clipped					
Incidence	0 (0%)	0 (0%)	0 (0%)	1 (7%)	16 (64%)
Mean onset (Days)				86	84
Absent					
Incidence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Mean onset (Days)					91

TABLE 12 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group	I	III	V	VII	IX
Dosage (mg/kg/day)	0	1	5	25	125
Animal Count	25	15	15	15	25
Discharge					
Eye right					
Black					
Incidence	4 (16%)	0 (0%)	1 (7%)	0 (0%)	2 (8%)
Mean onset (Days)	98		91		63
Nose					
Incidence	1 (4%)	0 (0%)	1 (7%)	0 (0%)	3 (12%)
Mean onset (Days)	98		42		98
Hair Loss					
Incidence	4 (16%)	5 (33%)	1 (7%)	1 (7%)	4 (16%)
Mean onset (Days)	65	83	25	18	62
Wound					
Superficial					
Incidence	1 (4%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)
Mean onset (Days)	112				42
Hyperreactive					
Incidence	2 (8%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)
Mean onset (Days)	98				116

TABLE 12 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group	I	III	V	VII	IX
Dosage (mg/kg/day)	0	1	5	25	125
Animal Count	25	15	15	15	25
Hyperactive					
Incidence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Mean onset (Days)					42
Aggressive Behavior					
Incidence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)
Mean onset (Days)					77
Vocalization					
No Abnormality Detected					
Incidence	0 (0%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Mean onset (Days)				21	
Protrusion					
Umbilical Hernia					
Incidence	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mean onset (Days)	21				
Stain Fur/Skin					
Incidence	5 (20%)	2 (13%)	2 (13%)	1 (7%)	6 (24%)
Mean onset (Days)	130	131	112	154	150

TABLE 12 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR MALE RATS

Treatment Group	I	III	V	VII	IX
Dosage (mg/kg/day)	0	1	5	25	125
Animal Count	25	15	15	15	25
Swollen Observations					
Face					
Incidence	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mean onset (Days)	91				
Forepaw					
Right					
Incidence	0 (0%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Mean onset (Days)				35	

Incidence - The number of animals for which an observation was recorded.

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

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

TABLE 13

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group Dosage (mg/kg/day) Animal Count	II 0 25	IV 1 15	VI 5 15	VIII 25 15	X 125 25
Eye Observations					
Dark					
Right					
Incidence	1 (4%)	1 (7%)	1 (7%)	1 (7%)	0 (0%)
Mean onset (Days)	49	91	105	91	
Dark					
Left					
Incidence	0 (0%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)
Mean onset (Days)		49			
Corneal Opacity					
Right					
Incidence	1 (4%)	1 (7%)	1 (7%)	0 (0%)	0 (0%)
Mean onset (Days)	7	140	119		
Corneal Opacity					
Bilateral					
Incidence	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mean onset (Days)	35				
Exophthalmus					
Right					
Incidence	1 (4%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)
Mean onset (Days)	7	147			

TABLE 13 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group Dosage (mg/kg/day) Animal Count	II 0 25	IV 1 15	VI 5 15	VIII 25 15	X 125 25
Exophthalmus Left					
Incidence	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mean onset (Days)	28				
Enophthalmus Right					
Incidence	1 (4%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)
Mean onset (Days)	21		112		
Enophthalmus Bilateral					
Incidence	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mean onset (Days)	42				
Closed Bilateral					
Incidence	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mean onset (Days)	119				
Wet Fur					
Incidence	0 (0%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)
Mean onset (Days)		14			

TABLE 13 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group Dosage (mg/kg/day) Animal Count	II 0 25	IV 1 15	VI 5 15	VIII 25 15	X 125 25
Scab					
Face					
Incidence Mean onset (Days)	1 (4%) 21	0 (0%)	0 (0%)	0 (0%)	0 (0%)
General Teeth Observations					
Striated					
Incidence Mean onset (Days)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	24 (96%) 53
Clipped					
Incidence Mean onset (Days)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (36%) 108
Breathing Observations					
Noise					
Incidence Mean onset (Days)	0 (0%)	0 (0%)	0 (0%)	1 (7%) 63	0 (0%)
Discharge					
Eye					
Incidence Mean onset (Days)	2 (8%) 74	1 (7%) 91	1 (7%) 91	0 (0%)	2 (8%) 137

TABLE 13 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group Dosage (mg/kg/day) Animal Count	II 0 25	IV 1 15	VI 5 15	VIII 25 15	X 125 25
Nose Black					
Incidence Mean onset (Days)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%) 112
Mouth Clear					
Incidence Mean onset (Days)	0 (0%)	1 (7%) 14	0 (0%)	0 (0%)	0 (0%)
Hair Loss					
Incidence Mean onset (Days)	5 (20%) 32	3 (20%) 53	1 (7%) 21	4 (27%) 64	2 (8%) 35
Wound Deep Mouth					
Incidence Mean onset (Days)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%) 112
Superficial					
Incidence Mean onset (Days)	2 (8%) 11	0 (0%)	0 (0%)	1 (7%) 42	1 (4%) 119

TABLE 13 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group Dosage (mg/kg/day) Animal Count	II 0 25	IV 1 15	VI 5 15	VIII 25 15	X 125 25
Arches back during handling					
Incidence	2 (8%)	2 (13%)	4 (27%)	3 (20%)	6 (24%)
Mean onset (Days)	35	25	32	49	42
Ear twitch					
Incidence	3 (12%)	2 (13%)	3 (20%)	3 (20%)	4 (16%)
Mean onset (Days)	39	25	33	54	39
Hyperreactive					
Incidence	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Mean onset (Days)	42				63
Hyperactive					
Incidence	1 (4%)	1 (7%)	1 (7%)	3 (20%)	2 (8%)
Mean onset (Days)	77	35	28	49	74
Vocalization No Abnormality Detected					
Incidence	0 (0%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)
Mean onset (Days)		35			
Comments Excessive Salivation					
Incidence	0 (0%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)
Mean onset (Days)			40		

TABLE 13 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS FOR FEMALE RATS

Treatment Group	II	IV	VI	VIII	X
Dosage (mg/kg/day)	0	1	5	25	125
Animal Count	25	15	15	15	25
Comments					
Teeth Stuck in Cage					
Incidence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)
Mean onset (Days)					108
Misshapen Observations					
Ear					
Incidence	0 (0%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)
Mean onset (Days)		21			
Stain Fur/Skin					
Incidence	2 (8%)	0 (0%)	1 (7%)	1 (7%)	2 (8%)
Mean onset (Days)	147		42	154	110
Swollen Observations					
Nose					
Incidence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Mean onset (Days)					105
Face					
Incidence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)
Mean onset (Days)					109

Incidence - The number of animals for which an observation was recorded.

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

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

TABLE 14

SUMMARY OF OPHTHALMOLOGY OBSERVATIONS FOR MALE RATS

(Test Day 87)

Treatment Group Dosage (mg/kg/day) Number Examined	I 0 20	III 1 10	V 5 10	VII 25 10	IX 125 20
Retina					
Retinal Degeneration Focal					
Incidence	1 (5%)	1 (10%)	1 (10%)	0 (0%)	0 (0%)
Globe					
Phthisis bulbi					
Right					
Incidence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)

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

TABLE 15

SUMMARY OF OPHTHALMOLOGY OBSERVATIONS FOR FEMALE RATS

(Test Day 87)

Treatment Group Dosage (mg/kg/day) Number Examined	II 0 20	IV 1 10	VI 5 10	VIII 25 10	X 125 20
Retina Retinal Degeneration Focal Right					
Incidence	1 (5%)	0 (0%)	0 (0%)	0 (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

Treatment Group Dose (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
<u>DAYS ON TEST</u>					
0	100	100	100	100	100
7	100	100	100	100	100
14	100	100	100	100	100
21	100	100	100	100	100
28	100	100	100	100	100
35	100	100	100	100	100
42	100	100	100	100	100
49	100	100	100	100	100
56	100	100	100	100	100
63	100	100	100	100	100
70	100	100	100	100	100
77	100	100	100	100	100
84	100	100	100	100	100
91	100	100	100	100	100
98 ^{a,b}	100	100	100	100	100
105	100	100	100	100	100
112	100	100	100	100	100
119	100	100	100	100	100
126	100	100	100	100	100
133	100	100	100	100	100
140	100	100	100	100	100
147	100	100	100	100	100
154	100	100	100	100	100
161	100	100	100	100	100
168	100	100	100	100	100
175	100	100	100	100	100
182	100	-	-	-	100
Number at study start	25	15	15	15	25
Sacrificed by design ^{b,c}	15	15	15	15	15
Alive on test day 182	10	0	0	0	10

Percent Survival = (Number of rats alive/Number of rats at risk)*100

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

a. Rats designated for the 90-day recovery period and satellite bleeds began recovery on test day 92.

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

c. Rats designated for satellite bleeds were sacrificed on test day 175.

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

TABLE 17

PERCENT SURVIVAL OF FEMALE RATS

Treatment Group Dose (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
<u>DAYS ON TEST</u>					
0	100	100	100	100	100
7	100	100	100	100	100
14	100	100	100	100	100
21	100	100	100	100	100
28	100	100	100	100	100
35	100	100	100	100	100
42	100	100	100	100	100
49	100	100	100	100	100
56	100	100	100	100	100
63	100	100	100	100	100
70	100	100	100	100	100
77	100	100	100	100	100
84	100	100	100	100	100
91	100	100	100	100	100
98 ^{a,b}	100	100	100	100	100
105	100	100	100	100	100
112	100	100	100	100	100
119	100	100	100	100	100
126	100	100	100	100	100
133	100	100	100	100	100
140	100	100	100	100	100
147	100	100	100	100	100
154	100	100	100	100	100
161	100	100	100	100	100
168	100	100	100	100	100
175	100	100	100	100	100
182	100	-	-	-	100

Number at study start	25	15	15	15	25
Accidentally killed ^a	1	0	0	0	0
Sacrificed by design ^{b,c}	15	15	15	15	15
Alive on test day 182	9	0	0	0	10

Percent Survival = (Number of rats alive/Number of rats at risk)*100

Number of rats at risk = Number at study start - number accidentally killed
- number sacrificed by design.

a. Rats designated for the 90-day recovery period and satellite bleeds began recovery on test days 92.

b. Rats designated for the 90-day exposure period were sacrificed on test day 94.

c. Rats designated for satellite bleeds were sacrificed on test day 175.

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

TABLE 18

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

Assessment Period	Group	Dosage (mg/kg/day)	Forelimb Grip Strength (kg)	Hindlimb Grip Strength (kg)
<u>Baseline</u>				
	I	0	0.53 (0.08)	0.30 (0.06)
	III	1	0.58 (0.11)	0.31 (0.06)
	V	5	0.57 (0.11)	0.28 (0.05)
	VII	25	0.60 (0.11)	0.29 (0.06)
	IX	125	0.58 (0.11)	0.27 (0.07)
<u>Week 13</u>				
	I	0	1.13 (0.31)	0.53 (0.15)
	III	1	1.17 (0.17)	0.58 (0.12)
	V	5	1.22 (0.21)	0.53 (0.10)
	VII	25	1.27 (0.18)	0.58 (0.16)
	IX	125	1.14 (0.29)	0.49 (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 $p < 0.05$.

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	0.56 (0.08)	0.37 (0.07)
	IV	1	0.63 (0.09)	0.35 (0.05)
	VI	5	0.65 (0.09) *	0.36 (0.03)
	VIII	25	0.60 (0.09)	0.35 (0.09)
	X	125	0.60 (0.10)	0.33 (0.06)
<u>Week 13</u>				
	II ^a	0	0.88 (0.21)	0.50 (0.10)
	IV	1	1.03 (0.19)	0.40 (0.09)
	VI	5	1.05 (0.15)	0.49 (0.09)
	VIII	25	0.99 (0.19)	0.47 (0.13)
	X	125	0.97 (0.13)	0.46 (0.07)

Data arranged as : Mean (Standard Deviation)

^a n=9 due to unscheduled death.

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

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

TABLE 20
SUMMARY OF FUNCTIONAL OBSERVATION BATTERY FINDINGS
FOR MALE RATS

	BASELINE					13-WEEK				
Group	I	III	V	VII	IX	I	III	V	VII	IX
Dosage (:mg/kg/day)	0	1	5	25	125	0	1	5	25	125
Number examined:	10	10	10	10	10	10	10	10	10	10
<u>MANUPULATIONS:</u>										
<u>APPROACH & TOUCH:</u>										
no reaction	0	0	0	0	0	0	0	0	0	0
normal	10	9	10	10	10	10	10	10	10	10
increased reaction (jumps away or attacks)	0	1	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	0	0
normal (turns toward site)	9	9	10	10	10	10	10	10	10	10
exaggerated response	1	1	0	0	0	0	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>										
present	6	3	8	3	4	4	7	3	3	4
absent	4	7	2	7	6	6	3	7	7	6
diarrhea	0	0	0	0	0	0	0	0	0	0
<u>URINATION:</u>										
present	10	9	10	10	9	8	9	9	7	9
absent	0	1	0	0	1	2	1	1	3	1

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

TABLE 21

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY FINDINGS
FOR FEMALE RATS

	BASELINE					13-WEEK				
Group	II	IV	VI	VIII	X	II ^a	IV	VI	VIII	X
Dosage (:mg/kg/day)	0	1	5	25	125	0	1	5	25	125
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	9	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	9	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	0	0
normal (turns toward site)	10	10	10	10	10	9	10	10	10	10
exaggerated response	0	0	0	0	0	0	0	0	0	0
<u>IN MOTOR ACTIVITY MONITOR:</u>										
<u>PUPILLARY RESPONSE</u>										
present	10	10	10	10	10	9	10	10	10	10
absent	0	0	0	0	0	0	0	0	0	0
<u>DEFECATION</u>										
present	4	3	7	6	8	3	7	7	5	5
absent	6	7	3	4	2	6	3	3	5	5
diarrhea	0	0	0	0	0	0	0	0	0	0
<u>URINATION:</u>										
present	7	9	10	10	9	7	10	9	9	10
absent	3	1	0	0	1	2	0	1	1	0

^a n=9 due to unscheduled death.

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

TABLE 22

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

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS					
			1	2	3	4	5	6
<u>BASELINE</u>								
I		0	383(34)	318(50)	216(90)	60(67)	35(87)	27(67)
III		1	402(60)	344(56)	312(78) *	163(120) *	83(138)	34(52)
V		5	401(39)	334(44)	254(74)	172(130) *	112(139) *	72(113)
VII		25	398(33)	292(71)	200(108)	146(135) *	68(99)	60(105)
IX		125	402(49)	343(74)	281(121)	164(149) *	90(123)	51(75)
								<u>TOTAL</u>
								1039(202)
								1338(354)
								1346(466)
								1163(430)
								1331(488)
<u>13-WEEK</u>								
I		0	383(42)	327(36)	288(52)	270(55)	226(64)	158(96)
III ^a		1	395(39)	345(27)	295(46)	277(54)	205(108)	127(98)
V		5	390(42)	333(40)	244(46)	209(91)	163(96)	105(111)
VII		25	413(27)	308(64)	228(107)	210(93)	129(85) *	158(77)
IX		125	405(69)	327(69)	275(115)	220(133)	202(128)	168(108)
								1652(280)
								1645(310)
								1443(253)
								1446(364)
								1596(556)

Data arranged as: Mean (Standard Deviation).

^a n=9 due to sensor malfunction.

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

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

TABLE 23

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

ASSESSMENT PERIOD	GROUP	DOSAGE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						TOTAL
<u>BASELINE</u>	II	0	1	2	3	4	5	6	
			370(53)	265(101)	243(120)	241(83)	189(118)	112(92)	1419(381)
	IV	1	389(61)	302(75)	244(90)	207(135)	183(163)	145(158)	1471(599)
	VI	5	364(29)	283(94)	234(80)	256(107)	154(121)	140(124)	1430(372)
	VIII	25	373(45)	259(96)	234(75)	200(69)	153(128)	73(64)	1292(322)
	X	125	367(68)	321(64)	272(88)	236(112)	181(113)	145(116)	1522(442)
<u>13-WEEK</u>	II ^a	0	383(47)	289(44)	237(46)	226(59)	203(39)	202(85)	1540(215)
	IV	1	408(48)	294(69)	246(65)	249(70)	182(61)	150(114)	1529(288)
	VI	5	408(40)	311(58)	211(78)	166(88)	151(77)	170(88)	1418(230)
	VIII	25	407(64)	298(72)	234(58)	193(95)	142(78)	176(66)	1451(321)
	X ^b	125	403(47)	302(62)	241(71)	226(71)	206(89)	153(114)	1531(335)

Data arranged as: Mean (Standard Deviation).

^a n=9 due to unscheduled death.

^b n=9 due to sensor malfunction.

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

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

TABLE 24
MOTOR ACTIVITY ASSESSEMENT:
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	135(19)	139(13)	124(36)	51(50)	21(47)	21(41)	491(141)
III		1	129(26)	129(26)	128(25)	91(65) *	39(51)	23(36)	539(160)
V		5	132(14)	140(17)	131(17)	100(50) *	61(61) *	44(57)	609(156)
VII		25	138(13)	137(7)	108(47)	87(68) *	46(59)	40(53)	556(201)
IX		125	127(26)	136(27)	126(34)	73(50)	44(56)	28(40)	534(162)
<u>13-WEEK</u>									
I		0	141(16)	144(10)	134(13)	137(17)	123(22)	95(50)	773(79)
III ^a		1	142(10)	148(10)	138(16)	133(16)	108(47)	76(54)	745(112)
V		5	139(12)	138(17)	124(19)	109(32)	89(43)	66(60)	665(78)
VII		25	130(16)	129(14)	108(45)	109(43)	73(44) *	87(47)	637(179) *
IX		125	133(22)	134(16)	116(33)	96(45) *	101(57)	88(55)	668(168)

Data arranged as: Mean (Standard Deviation).

^a n=9 due to sensor malfunction.

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

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

TABLE 25

MOTOR ACTIVITY ASSESSEMENT:
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	138(17)	132(32)	120(48)	130(20)	115(54)	82(58)
IV		1	131(28)	127(27)	124(27)	97(48)	85(58)	71(55)
VI		5	137(13)	125(27)	130(32)	122(43)	95(60)	84(67)
VIII		25	138(17)	127(24)	132(20)	127(30)	86(66)	62(52)
X		125	131(26)	138(32)	131(29)	124(49)	94(56)	83(68)
<u>TOTAL</u>								
								717(146)
								635(162)
								692(160)
								673(148)
								702(195)
<u>13-WEEK</u>								
II ^a		0	132(25)	133(14)	128(21)	126(27)	127(21)	121(35)
IV		1	135(24)	136(12)	128(24)	130(20)	117(22)	86(50)
VI		5	125(16)	138(15)	115(29)	100(36)	96(38)	101(41)
VIII		25	135(17)	133(16)	132(20)	108(37)	96(46)	111(29)
X ^b		125	136(11)	134(19)	130(27)	126(27)	111(35)	87(55)
								725(103)

Data arranged as: Mean (Standard Deviation).

^a n=9 due to unscheduled death.

^b n=9 due to sensor malfunction.

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

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

TABLE 26

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 1 mg/kg/day	Group V 5 mg/kg/day	Group VII 25 mg/kg/day	Group IX 125 mg/kg/day
RBC ($\times 10^6/\mu\text{L}$)					
DAY 48	8.33 0.38(10)	8.26 0.35(10)	8.18 0.13(9)	7.90* 0.20(10)	7.78* 0.42(10)
DAY 93	8.57 0.32(10)	8.55 0.37(10)	8.32 0.22(10)	8.12* 0.22(10)	7.76* 0.44(10)
DAY 183	8.71 0.42(10)	--	--	--	8.39 0.47(7)
HGB (g/dL)					
DAY 48	15.1 0.6(10)	15.2 0.7(10)	15.1 0.4(9)	14.8 0.5(10)	14.5 0.7(10)
DAY 93	15.9 0.6(10)	15.9 0.6(10)	15.6 0.5(10)	15.6 0.7(10)	15.0* 0.7(10)
DAY 183	15.4 0.6(10)	--	--	--	15.1 0.3(7)
HCT (%)					
DAY 48	48.3 1.7(10)	48.3 2.2(10)	48.4 1.2(9)	47.0 1.4(10)	46.4 2.4(10)
DAY 93	47.7 1.7(10)	48.0 1.6(10)	47.0 1.5(10)	46.8 1.9(10)	45.5* 2.5(10)
DAY 183	47.8 1.8(10)	--	--	--	46.6 1.6(7)
MCV (fl)					
DAY 48	58.0 1.4(10)	58.5 1.8(10)	59.1 1.2(9)	59.5 1.7(10)	59.7 2.0(10)
DAY 93	55.7 0.9(10)	56.2 1.8(10)	56.5 1.0(10)	57.5* 1.4(10)	58.7* 2.4(10)
DAY 183	54.9 1.6(10)	--	--	--	55.6 1.4(7)
MCH (pg)					
DAY 48	18.2 0.5(10)	18.4 0.7(10)	18.5 0.4(9)	18.7 0.6(10)	18.7 0.5(10)
DAY 93	18.6 0.5(10)	18.6 0.7(10)	18.7 0.5(10)	19.1 0.5(10)	19.4* 0.6(10)
DAY 183	17.7 0.7(10)	--	--	--	18.1 0.8(7)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 1 mg/kg/day	Group V 5 mg/kg/day	Group VII 25 mg/kg/day	Group IX 125 mg/kg/day
MCHC (g/dL)					
DAY 48	31.3 0.5(10)	31.5 0.5(10)	31.3 0.4(9)	31.5 0.7(10)	31.3 0.5(10)
DAY 93	33.3 0.6(10)	33.1 0.5(10)	33.1 0.8(10)	33.3 0.6(10)	33.0 0.7(10)
DAY 183	32.3 0.7(10)	--	--	--	32.5 0.6(7)
RDW (%)					
DAY 48	11.9 0.4(10)	11.5 0.5(10)	11.9 0.6(9)	12.2 0.8(10)	12.9* 0.9(10)
DAY 93	12.8 0.6(10)	12.2 0.5(10)	12.6 0.7(10)	12.7 0.5(10)	13.6 1.8(10)
DAY 183	13.5 0.5(10)	--	--	--	13.3 0.6(7)
ARET (x10 ³ /μL)					
DAY 48	212.6 16.7(10)	206.0 25.6(10)	235.8 44.5(9)	239.6 43.2(10)	262.0* 26.0(10)
DAY 93	172.4 22.7(10)	159.2 21.2(10)	187.0 30.8(10)	192.6 31.2(10)	216.8* 53.6(10)
DAY 183	179.0 24.2(10)	--	--	--	188.4 22.9(7)
PLT (x10 ³ /μL)					
DAY 48	1010 151(6)	1098 20(4)	1054 104(7)	1012 48(5)	950 178(5)
DAY 93	1221 132(9)	1227 109(7)	1199 128(8)	1252 126(8)	1275 209(9)
DAY 183	1145 188(6)	--	--	--	1074 165(7)
WBC (x10 ³ /μL)					
DAY 48	14.18 2.18(10)	15.67 3.75(10)	15.12 3.70(9)	15.46 3.13(10)	16.29 4.01(10)
DAY 93	12.19 3.55(10)	12.45 1.99(10)	11.77 2.58(10)	13.36 3.59(10)	13.89 3.97(10)
DAY 183	13.47 3.28(10)	--	--	--	13.97 2.30(7)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 1 mg/kg/day	Group V 5 mg/kg/day	Group VII 25 mg/kg/day	Group IX 125 mg/kg/day
ANEU ($\times 10^3/\mu\text{L}$)					
DAY 48	1.63 0.55(10)	1.61 0.79(10)	1.96 0.66(9)	2.00 0.68(10)	2.04 0.90(10)
DAY 93	1.86 0.68(10)	1.45 0.33(10)	1.81 1.04(10)	2.48 1.13(10)	2.17 0.79(10)
DAY 183	2.75 1.37(10)	--	--	--	2.49 0.56(7)
ALYM ($\times 10^3/\mu\text{L}$)					
DAY 48	11.97 1.60(10)	13.50 3.21(10)	12.50 3.11(9)	12.84 2.95(10)	13.69 3.35(10)
DAY 93	9.89 3.01(10)	10.55 1.99(10)	9.49 1.45(10)	10.34 2.79(10)	11.26 3.21(10)
DAY 183	9.99 2.56(10)	--	--	--	10.67 1.74(7)
AMON ($\times 10^3/\mu\text{L}$)					
DAY 48	0.30 0.13(10)	0.24 0.10(10)	0.38 0.15(9)	0.29 0.10(10)	0.27 0.11(10)
DAY 93	0.21 0.06(10)	0.24 0.14(10)	0.24 0.12(10)	0.26 0.10(10)	0.21 0.06(10)
DAY 183	0.40 0.14(10)	--	--	--	0.43 0.13(7)
AEOS ($\times 10^3/\mu\text{L}$)					
DAY 48	0.12 0.08(10)	0.11 0.05(10)	0.10 0.05(9)	0.11 0.04(10)	0.12 0.04(10)
DAY 93	0.14 0.07(10)	0.13 0.06(10)	0.14 0.12(10)	0.17 0.14(10)	0.14 0.04(10)
DAY 183	0.17 0.06(10)	--	--	--	0.18 0.05(7)
ABAS ($\times 10^3/\mu\text{L}$)					
DAY 48	0.09 0.05(10)	0.14 0.09(10)	0.10 0.05(9)	0.14 0.05(10)	0.11 0.07(10)
DAY 93	0.04 0.03(10)	0.04 0.03(10)	0.04 0.01(10)	0.04 0.02(10)	0.04 0.01(10)
DAY 183	0.11 0.05(10)	--	--	--	0.14 0.08(7)

TABLE 26 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 1 mg/kg/day	Group V 5 mg/kg/day	Group VII 25 mg/kg/day	Group IX 125 mg/kg/day
ALUC (x10 ³ /μL)					
DAY 48	0.08 0.03(10)	0.07 0.04(10)	0.08 0.02(9)	0.09 0.02(10)	0.07 0.04(10)
DAY 93	0.06 0.03(10)	0.05 0.04(10)	0.05 0.01(10)	0.06 0.03(10)	0.06 0.02(10)
DAY 183	0.05 0.02(10)	--	--	--	0.07 0.02(7)

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 27

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 1 mg/kg/day	Group VI 5 mg/kg/day	Group VIII 25 mg/kg/day	Group X 125 mg/kg/day
RBC ($\times 10^6/\mu\text{L}$)					
DAY 49	8.28 0.29(10)	8.09 0.29(9)	8.14 0.36(10)	8.00 0.41(10)	7.50* 0.43(10)
DAY 94	8.24 0.26(10)	8.28 0.25(10)	8.38 0.31(10)	8.07 0.46(10)	7.66* 0.34(10)
DAY 183	7.76 0.36(9)	--	--	--	7.75 0.30(10)
HGB (g/dL)					
DAY 49	15.6 0.5(10)	15.4 0.5(9)	15.5 0.6(10)	14.9 0.6(10)	14.2* 0.7(10)
DAY 94	16.1 0.5(10)	16.4 0.4(10)	16.5 0.4(10)	15.7 0.7(10)	15.1* 0.7(10)
DAY 183	14.7 0.6(9)	--	--	--	15.1 0.5(10)
HCT (%)					
DAY 49	49.0 1.7(10)	48.1 1.7(9)	48.3 1.7(10)	46.8* 2.2(10)	44.5* 2.5(10)
DAY 94	47.2 1.5(10)	47.9 1.4(10)	48.3 1.8(10)	45.8 2.4(10)	44.6* 2.1(10)
DAY 183	44.0 1.7(9)	--	--	--	45.1 1.9(10)
MCV (fl)					
DAY 49	59.2 0.9(10)	59.5 1.1(9)	59.4 1.6(10)	58.5 1.2(10)	59.4 1.4(10)
DAY 94	57.2 0.9(10)	57.8 0.9(10)	57.7 1.3(10)	56.8 0.8(10)	58.3 1.6(10)
DAY 183	56.8 1.8(9)	--	--	--	58.2 1.1(10)
MCH (pg)					
DAY 49	18.8 0.4(10)	19.1 0.3(9)	19.0 0.4(10)	18.7 0.4(10)	19.0 0.6(10)
DAY 94	19.6 0.3(10)	19.8 0.3(10)	19.7 0.5(10)	19.5 0.5(10)	19.8 0.6(10)
DAY 183	19.0 0.7(9)	--	--	--	19.4 0.3(10)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 1 mg/kg/day	Group VI 5 mg/kg/day	Group VIII 25 mg/kg/day	Group X 125 mg/kg/day
MCHC (g/dL)					
DAY 49	31.8 0.4(10)	32.1 0.3(9)	32.0 0.4(10)	32.0 0.5(10)	32.0 0.5(10)
DAY 94	34.3 0.4(10)	34.3 0.4(10)	34.2 0.5(10)	34.4 0.8(10)	34.0 0.3(10)
DAY 183	33.4 0.3(9)	--	--	--	33.4 0.6(10)
RDW (%)					
DAY 49	11.7 0.6(10)	11.6 0.4(9)	11.8 0.5(10)	11.8 0.4(10)	12.0 0.4(10)
DAY 94	10.9 0.5(10)	11.0 0.4(10)	11.0 0.4(10)	10.8 0.3(10)	11.6* 0.5(10)
DAY 183	11.8 0.5(9)	--	--	--	12.1 0.8(10)
ARET (x10 ³ /μL)					
DAY 49	256.6 44.7(10)	225.4 26.9(9)	249.0 51.4(10)	217.1@ 31.2(10)	240.6 18.0(10)
DAY 94	141.4 31.4(10)	139.0 16.0(10)	155.1 28.4(10)	140.6 19.8(10)	176.6* 39.0(10)
DAY 183	153.5 33.4(9)	--	--	--	164.4 27.0(10)
PLT (x10 ³ /μL)					
DAY 49	973 46(7)	835 175(7)	1095 185(8)	952 181(8)	978 160(5)
DAY 94	1083 130(10)	1025 174(9)	1158 88(7)	1026 190(7)	1068 88(9)
DAY 183	1059 194(7)	--	--	--	957 231(6)
WBC (x10 ³ /μL)					
DAY 49	13.02 4.11(10)	11.83 2.63(9)	13.25 3.38(10)	12.56 2.78(10)	11.10 3.04(10)
DAY 94	10.84 3.92(10)	9.59 2.57(10)	10.57 2.47(10)	9.86 2.61(10)	10.26 1.38(10)
DAY 183	7.29 1.97(9)	--	--	--	8.19 1.73(10)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 1 mg/kg/day	Group VI 5 mg/kg/day	Group VIII 25 mg/kg/day	Group X 125 mg/kg/day
ANEU (x10 ³ /μL)					
DAY 49	1.36 0.66(10)	0.94 0.36(9)	1.50 0.56(10)	1.43 0.82(10)	1.40 0.56(10)
DAY 94	1.28 0.47(10)	1.32 0.81(10)	1.45 0.51(10)	1.76 1.22(10)	1.74 0.68(10)
DAY 183	1.33 0.49(9)	--	--	--	1.43 0.47(10)
ALYM (x10 ³ /μL)					
DAY 49	11.18 3.47(10)	10.50 2.40(9)	11.23 3.25(10)	10.60 2.79(10)	9.25 2.67(10)
DAY 94	9.07 3.39(10)	7.85 2.27(10)	8.70 2.48(10)	7.61 2.12(10)	8.01 1.14(10)
DAY 183	5.55 1.65(9)	--	--	--	6.27 1.67(10)
AMON (x10 ³ /μL)					
DAY 49	0.22 0.15(10)	0.20 0.07(9)	0.23 0.10(10)	0.25 0.13(10)	0.22 0.08(10)
DAY 94	0.18 0.07(10)	0.18 0.09(10)	0.15 0.08(10)	0.23 0.21(10)	0.26 0.09(10)
DAY 183	0.25 0.11(9)	--	--	--	0.29 0.13(10)
AEOS (x10 ³ /μL)					
DAY 49	0.11 0.06(10)	0.09 0.03(9)	0.12 0.04(10)	0.11 0.05(10)	0.10 0.05(10)
DAY 94	0.18 0.07(10)	0.13 0.03(10)	0.17 0.06(10)	0.15 0.06(10)	0.13 0.05(10)
DAY 183	0.09 0.03(9)	--	--	--	0.11 0.05(10)
ABAS (x10 ³ /μL)					
DAY 49	0.09 0.05(10)	0.05 0.02(9)	0.10 0.08(10)	0.08 0.05(10)	0.06 0.04(10)
DAY 94	0.06 0.02(10)	0.06 0.03(10)	0.05 0.05(10)	0.06 0.04(10)	0.06 0.02(10)
DAY 183	0.04 0.04(9)	--	--	--	0.06@ 0.01(10)

TABLE 27 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 1 mg/kg/day	Group VI 5 mg/kg/day	Group VIII 25 mg/kg/day	Group X 125 mg/kg/day
ALUC ($\times 10^3/\mu\text{L}$)					
DAY 49	0.07 0.03(10)	0.05 0.02(9)	0.07 0.03(10)	0.08 0.03(10)	0.07 0.04(10)
DAY 94	0.06 0.04(10)	0.05 0.03(10)	0.04 0.03(10)	0.05 0.04(10)	0.05 0.02(10)
DAY 183	0.03 0.01(9)	--	--	--	0.03 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

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 1 mg/kg/day	Group V 5 mg/kg/day	Group VII 25 mg/kg/day	Group IX 125 mg/kg/day
PT (seconds)					
DAY 93	15.9 0.8(9)	16.1 0.6(10)	15.9 1.1(9)	15.5 0.5(10)	15.9 1.7(9)
APTT (seconds)					
DAY 93	18.2 2.5(9)	20.2 2.1(10)	19.1 1.6(9)	17.7 1.7(10)	19.3 2.1(9)

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

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

TABLE 29

SUMMARY OF COAGULATION VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 1 mg/kg/day	Group VI 5 mg/kg/day	Group VIII 25 mg/kg/day	Group X 125 mg/kg/day
PT (seconds)					
DAY 94	15.3 0.5(10)	14.9 0.6(10)	15.3 0.6(10)	15.2 0.6(10)	14.9 1.0(10)
APTT (seconds)					
DAY 94	15.8 1.8(10)	16.2 2.0(10)	15.0 1.6(10)	15.4 1.7(10)	14.1 2.0(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

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 1 mg/kg/day	Group V 5 mg/kg/day	Group VII 25 mg/kg/day	Group IX 125 mg/kg/day
AST (U/L)					
DAY 48	69 10(10)	69 5(10)	70 6(10)	72 9(10)	69 6(10)
DAY 93	85 12(10)	88 13(9)	114 69(10)	186 152(10)	81 17(10)
DAY 183	147 134(10)	--	--	--	134 51(10)
ALT (U/L)					
DAY 48	33 4(10)	33 5(10)	32 5(10)	33 5(10)	34 7(10)
DAY 93	36 5(10)	42 8(9)	49 44(10)	89 71(10)	44 16(10)
DAY 183	77 91(10)	--	--	--	67 26(10)
SDH (U/L)					
DAY 48	14.1 3.5(10)	13.2 2.8(10)	12.6 2.4(10)	13.2 3.0(10)	13.3 3.5(10)
DAY 93	18.7 3.1(10)	16.9 4.8(10)	17.5 16.3(10)	41.5 38.2(10)	18.4 6.6(10)
DAY 183	24.7 18.0(10)	--	--	--	21.0 6.8(10)
ALKP (U/L)					
DAY 48	131 18(9)	114 21(10)	126 17(9)	135 33(10)	165* 39(10)
DAY 93	109 25(10)	97 18(9)	91 18(10)	110 25(10)	136 35(10)
DAY 183	86 20(10)	--	--	--	86 23(10)
BILI (mg/dL)					
DAY 48	0.11 0.04(10)	0.07* 0.03(10)	0.10 0.03(10)	0.10 0.04(10)	0.07 0.03(10)
DAY 93	0.10 0.03(10)	0.06@ 0.02(9)	0.10 0.04(10)	0.09 0.05(10)	0.09 0.03(10)
DAY 183	0.14 0.05(10)	--	--	--	0.12 0.04(10)

TABLE 30 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 1 mg/kg/day	Group V 5 mg/kg/day	Group VII 25 mg/kg/day	Group IX 125 mg/kg/day
BUN (mg/dL)					
DAY 48	14 2(10)	14 1(10)	14 2(10)	14 1(10)	13 1(10)
DAY 93	13 2(10)	14 2(10)	13 2(10)	15* 2(10)	13 2(10)
DAY 183	18 2(10)	--	--	--	16* 2(10)
CREA (mg/dL)					
DAY 48	0.25 0.06(10)	0.27 0.04(10)	0.28 0.04(10)	0.26 0.02(10)	0.26 0.04(10)
DAY 93	0.42 0.06(10)	0.39 0.08(10)	0.36 0.04(10)	0.37 0.06(10)	0.37 0.04(10)
DAY 183	0.46 0.03(10)	--	--	--	0.41* 0.04(10)
CHOL (mg/dL)					
DAY 48	66 9(10)	53 11(10)	62 12(10)	52* 15(10)	57 11(10)
DAY 93	80 16(10)	57* 9(10)	74 19(10)	66 17(10)	65 15(10)
DAY 183	76 28(10)	--	--	--	79 17(10)
TRIG (mg/dL)					
DAY 48	87 24(10)	74 27(10)	95 50(10)	83 42(10)	43* 21(10)
DAY 93	77 32(10)	67 23(9)	77 28(10)	64 26(10)	37* 18(10)
DAY 183	81 33(10)	--	--	--	95 59(10)
GLUC (mg/dL)					
DAY 48	119 7(10)	115 9(10)	122 10(10)	118 9(10)	122 20(10)
DAY 93	109 28(10)	117 32(10)	114 24(10)	110 29(10)	105 22(10)
DAY 183	129 40(10)	--	--	--	127 31(10)

TABLE 30 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 1 mg/kg/day	Group V 5 mg/kg/day	Group VII 25 mg/kg/day	Group IX 125 mg/kg/day
TP (g/dL)					
DAY 48	6.5 0.3(10)	6.6 0.4(10)	6.6 0.4(10)	6.5 0.3(10)	7.0* 0.4(10)
DAY 93	7.2 0.4(10)	7.0 0.3(9)	7.0 0.5(10)	7.0 0.4(10)	7.6* 0.1(10)
DAY 183	6.9 0.2(10)	--	--	--	6.8 0.1(10)
ALB (g/dL)					
DAY 48	4.2 0.2(10)	4.1 0.3(10)	4.2 0.2(10)	4.2 0.2(10)	4.7* 0.2(10)
DAY 93	4.4 0.2(10)	4.3 0.2(9)	4.3 0.2(10)	4.4 0.3(10)	5.0@ 0.2(10)
DAY 183	4.2 0.2(10)	--	--	--	4.2 0.1(10)
GLOB (g/dL)					
DAY 48	2.4 0.3(10)	2.4 0.2(10)	2.5 0.3(10)	2.3 0.2(10)	2.3 0.3(10)
DAY 93	2.8 0.3(10)	2.6 0.2(9)	2.7 0.3(10)	2.6 0.2(10)	2.6 0.2(10)
DAY 183	2.7 0.2(10)	--	--	--	2.7 0.1(10)
CALC (mg/dL)					
DAY 48	10.8 0.4(10)	10.8 0.2(10)	10.8 0.5(10)	10.5 0.4(10)	10.8 0.4(10)
DAY 93	11.3 0.4(10)	11.3 0.6(10)	11.2 0.6(10)	11.1 0.2(10)	11.4 0.4(10)
DAY 183	11.4 0.5(10)	--	--	--	11.5 0.3(10)
IPHS (mg/dL)					
DAY 48	8.3 0.6(10)	7.9 0.5(10)	8.4 0.7(10)	8.4 1.0(10)	9.2* 0.9(10)
DAY 93	8.1 0.6(10)	8.9 1.4(9)	8.7 0.9(10)	9.2 1.3(10)	9.5* 1.2(10)
DAY 183	8.5 0.8(10)	--	--	--	9.2 1.0(10)

TABLE 30 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 1 mg/kg/day	Group V 5 mg/kg/day	Group VII 25 mg/kg/day	Group IX 125 mg/kg/day
NA (mmol/L)					
DAY 48	148.2 1.3(10)	149.5 4.7(10)	148.2 2.3(10)	148.3 1.2(10)	147.7 1.6(10)
DAY 93	148.4 1.3(10)	149.4 2.2(10)	148.3 3.0(10)	148.3 2.5(10)	148.1 2.4(10)
DAY 183	147.9 1.4(10)	--	--	--	148.4 2.2(10)
K (mmol/L)					
DAY 48	5.87 0.53(10)	5.68 0.47(10)	5.76 0.62(10)	5.52 0.43(10)	5.74 0.34(10)
DAY 93	6.15 0.51(10)	6.16 0.47(9)	6.31 0.52(10)	6.32 0.71(10)	6.31 0.59(10)
DAY 183	6.17 0.45(10)	--	--	--	6.29 0.54(10)
CL (mmol/L)					
DAY 48	102.2 2.1(10)	103.2 3.7(10)	101.5 2.2(10)	101.0 2.1(10)	101.1 2.0(10)
DAY 93	100.7 1.9(10)	101.8 1.8(10)	101.1 1.5(10)	101.2 1.7(10)	100.1 1.5(10)
DAY 183	102.3 2.2(10)	--	--	--	104.1 1.9(10)
PFLU (μ g/mL)					
DAY 93	0.1 0.0(10)	0.1 0.0(10)	0.1 0.0(10)	0.1 0.0(10)	0.4@ 0.0(10)
DAY 183	0.1 0.1(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

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 1 mg/kg/day	Group VI 5 mg/kg/day	Group VIII 25 mg/kg/day	Group X 125 mg/kg/day
AST (U/L)					
DAY 49	72 11(10)	77 15(10)	65 6(10)	91 89(10)	61 9(10)
DAY 94	85 17(10)	119 51(10)	82 18(10)	176 285(10)	93 40(10)
DAY 183	177 176(9)	--	--	--	103 54(10)
ALT (U/L)					
DAY 49	34 8(10)	35 7(10)	29 4(10)	44 41(10)	32 5(10)
DAY 94	40 17(10)	64 46(10)	37 10(10)	75 106(10)	45 16(10)
DAY 183	96 90(9)	--	--	--	58 41(10)
SDH (U/L)					
DAY 49	10.5 2.7(10)	10.5 4.0(10)	7.9 0.9(10)	21.8 41.2(10)	10.0 2.2(10)
DAY 94	16.7 4.4(10)	21.5 8.2(10)	13.6 2.7(10)	44.4 84.1(10)	19.0 10.4(10)
DAY 183	29.2 27.5(9)	--	--	--	17.5 10.4(10)
ALKP (U/L)					
DAY 49	83 16(10)	79 19(10)	79 24(10)	73 28(10)	75 14(10)
DAY 94	51 11(10)	52 13(10)	54 19(10)	49 19(10)	53 10(10)
DAY 183	34 8(9)	--	--	--	38 10(10)
BILI (mg/dL)					
DAY 49	0.15 0.04(10)	0.15 0.03(10)	0.13 0.03(10)	0.14 0.04(10)	0.16 0.03(10)
DAY 94	0.15 0.01(10)	0.15 0.03(10)	0.12 0.03(10)	0.14 0.04(10)	0.17 0.04(10)
DAY 183	0.17 0.07(9)	--	--	--	0.15 0.04(10)

TABLE 31 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 1 mg/kg/day	Group VI 5 mg/kg/day	Group VIII 25 mg/kg/day	Group X 125 mg/kg/day
BUN (mg/dL)					
DAY 49	15 2(10)	16 2(10)	16 2(10)	15 2(10)	15 2(10)
DAY 94	17 2(10)	17 2(10)	17 1(10)	17 4(10)	17 2(10)
DAY 183	17 2(9)	--	--	--	16 3(10)
CREA (mg/dL)					
DAY 49	0.33 0.05(10)	0.35 0.06(10)	0.34 0.06(10)	0.33 0.07(10)	0.31 0.03(10)
DAY 94	0.47 0.06(10)	0.49 0.03(10)	0.44 0.06(10)	0.48 0.10(10)	0.46 0.06(10)
DAY 183	0.52 0.05(9)	--	--	--	0.48 0.06(10)
CHOL (mg/dL)					
DAY 49	77 19(10)	86 16(10)	73 14(10)	105 28(10)	107@ 21(10)
DAY 94	85 19(10)	97 15(10)	79 18(10)	125 45(10)	123 39(10)
DAY 183	134 26(9)	--	--	--	147 67(10)
TRIG (mg/dL)					
DAY 49	44 20(10)	50 20(10)	37 12(10)	43 22(10)	55 46(10)
DAY 94	51 26(10)	66 53(10)	39 11(10)	41 13(10)	42 47(10)
DAY 183	78 14(9)	--	--	--	89 63(10)
GLUC (mg/dL)					
DAY 49	115 10(10)	112 13(10)	116 13(10)	113 5(10)	111 5(10)
DAY 94	101 9(10)	104 12(10)	104 9(10)	106 16(10)	100 5(10)
DAY 183	121 32(9)	--	--	--	104 6(10)

TABLE 31 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 1 mg/kg/day	Group VI 5 mg/kg/day	Group VIII 25 mg/kg/day	Group X 125 mg/kg/day
TP (g/dL)					
DAY 49	7.3 0.3(10)	7.3 0.3(10)	7.0 0.5(10)	7.6 0.5(10)	7.9* 0.4(10)
DAY 94	7.8 0.3(10)	8.0 0.3(10)	7.6 0.5(10)	8.3 0.7(10)	8.6* 0.6(10)
DAY 183	8.5 0.3(9)	--	--	--	8.4 0.4(10)
ALB (g/dL)					
DAY 49	4.9 0.2(10)	4.9 0.2(10)	4.6 0.4(10)	5.0 0.4(10)	5.5@ 0.3(10)
DAY 94	5.2 0.3(10)	5.4 0.3(10)	5.0 0.3(10)	5.5 0.5(10)	5.8* 0.3(10)
DAY 183	5.7 0.3(9)	--	--	--	5.4 0.4(10)
GLOB (g/dL)					
DAY 49	2.4 0.2(10)	2.4 0.2(10)	2.5 0.3(10)	2.6 0.3(10)	2.4 0.2(10)
DAY 94	2.6 0.2(10)	2.6 0.1(10)	2.7 0.3(10)	2.7 0.4(10)	2.8 0.3(10)
DAY 183	2.8 0.1(9)	--	--	--	2.9 0.4(10)
CALC (mg/dL)					
DAY 49	11.3 0.2(10)	11.3 0.4(10)	11.0 0.3(10)	11.4 0.4(10)	11.6 0.5(10)
DAY 94	11.7 0.4(10)	11.5 0.2(10)	11.3 0.4(10)	11.8 0.5(10)	12.2* 0.4(10)
DAY 183	12.4 0.3(9)	--	--	--	12.2 0.3(10)
IPHS (mg/dL)					
DAY 49	7.0 1.3(10)	7.4 1.2(10)	6.8 0.7(10)	6.9 0.5(10)	7.6 1.0(10)
DAY 94	6.8 1.7(10)	5.9 0.8(10)	6.8 0.9(10)	6.7 0.9(10)	7.3 0.5(10)
DAY 183	7.1 1.3(9)	--	--	--	7.4 1.0(10)

TABLE 31 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 1 mg/kg/day	Group VI 5 mg/kg/day	Group VIII 25 mg/kg/day	Group X 125 mg/kg/day
NA (mmol/L)					
DAY 49	145.2 1.4(10)	145.1 1.7(10)	145.1 1.6(10)	144.1 2.4(10)	144.5 1.8(10)
DAY 94	145.6 2.1(10)	145.7 1.3(10)	145.9 1.6(10)	145.5 1.2(10)	146.3 2.5(10)
DAY 183	148.7 1.5(9)	--	--	--	149.6 1.5(10)
K (mmol/L)					
DAY 49	5.74 0.70(10)	5.59 0.48(10)	5.50 0.38(10)	5.36 0.27(10)	5.55 0.38(10)
DAY 94	5.74 0.67(10)	5.54 0.39(10)	5.96 0.36(10)	5.40 0.31(10)	5.95 0.31(10)
DAY 183	5.80 0.55(9)	--	--	--	5.94 0.53(10)
CL (mmol/L)					
DAY 49	101.2 1.6(10)	101.6 1.3(10)	101.9 1.1(10)	100.7 2.0(10)	100.9 1.0(10)
DAY 94	101.1 3.0(10)	101.1 1.8(10)	102.4 1.5(10)	100.5 2.0(10)	100.5 1.9(10)
DAY 183	104.1 1.6(9)	--	--	--	103.9 2.3(10)
PFLU (µg/mL)					
DAY 94	0.1 0.0(10)	0.1 0.1(10)	0.1 0.0(10)	0.2 0.0(10)	0.5@ 0.1(10)
DAY 183	0.1 0.0(9)	--	--	--	0.1 0.0(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 32

SUMMARY OF URINALYSIS VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 1 mg/kg/day	Group V 5 mg/kg/day	Group VII 25 mg/kg/day	Group IX 125 mg/kg/day
VOL (mL)					
DAY 48	14.4 10.5(10)	10.9 5.6(10)	11.7 6.0(10)	13.0 7.9(10)	17.2 5.6(10)
DAY 93	6.8 2.5(10)	6.3 1.8(10)	7.6 4.2(10)	7.8 5.6(10)	21.1@ 13.4(10)
DAY 183	7.5 6.5(10)	--	--	--	7.7 4.1(10)
UOSM (mOsm)					
DAY 48	790 429(10)	841 341(10)	913 313(10)	840 365(10)	605 162(10)
DAY 93	1321 457(10)	1324 323(10)	1293 593(10)	1549 854(10)	703 452(10)
DAY 183	1400 808(9)	--	--	--	1322 590(10)
pH					
DAY 48	7.3 0.3(10)	7.1 0.2(10)	7.1 0.2(10)	7.1 0.4(10)	7.4 0.3(10)
DAY 93	6.8 0.7(10)	6.8 0.4(10)	6.8 0.4(10)	6.8 0.3(10)	7.0 0.4(10)
DAY 183	6.6 0.6(10)	--	--	--	6.6 0.4(10)
URO (EU/dL)					
DAY 48	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)
DAY 93	0.2 0.0(9)	0.2 0.0(10)	0.2 0.0(10)	0.3 0.3(10)	0.2 0.0(10)
DAY 183	0.4 0.3(10)	--	--	--	0.3 0.3(10)
UFLU (µg)					
DAY 93	10.7 4.4(10)	13.0 1.9(10)	38.8@ 10.1(9)	202.4@ 57.9(9)	997.2@ 246.3(10)
DAY 183	9.9 3.1(9)	--	--	--	27.6* 5.1(10)

TABLE 32 (Continued)

SUMMARY OF URINALYSIS VALUES FOR MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 1 mg/kg/day	Group V 5 mg/kg/day	Group VII 25 mg/kg/day	Group IX 125 mg/kg/day
UMTP (mg/dL)					
DAY 48	49 34(10)	48 26(10)	55 34(10)	47 33(10)	43 34(10)
DAY 93	108 87(10)	98 47(10)	81 49(10)	89 53(10)	67 91(10)
DAY 183	161 164(10)	--	--	--	95 91(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 33

SUMMARY OF URINALYSIS VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 1 mg/kg/day	Group VI 5 mg/kg/day	Group VIII 25 mg/kg/day	Group X 125 mg/kg/day
VOL (mL)					
DAY 49	7.2 3.3(10)	7.5 5.8(10)	8.2 6.2(10)	14.4 13.3(10)	8.2 5.2(10)
DAY 94	5.0 4.5(10)	2.8 1.8(9)	4.2 2.5(10)	4.8 3.1(10)	7.7 4.3(10)
DAY 183	8.2 14.1(7)	--	--	--	4.9 4.4(10)
UOSM (mOsm)					
DAY 49	882 281(10)	985 499(10)	1050 509(9)	623 257(10)	954 569(10)
DAY 94	1336 615(10)	1519 598(8)	1317 528(10)	1231 493(10)	1051 714(10)
DAY 183	1477 1104(7)	--	--	--	1445 868(10)
pH					
DAY 49	7.1 0.2(10)	7.0 0.6(10)	6.8 0.3(10)	7.0 0.3(10)	6.9 0.4(10)
DAY 94	6.0 0.3(10)	6.1 0.4(9)	5.9 0.4(10)	6.4 0.3(10)	6.2 0.3(10)
DAY 183	5.7 0.5(7)	--	--	--	6.1 0.5(10)
URO (EU/dL)					
DAY 49	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)
DAY 94	0.2 0.0(10)	0.2 0.0(9)	0.2 0.0(10)	0.2 0.0(10)	0.2 0.0(10)
DAY 183	0.2 0.0(7)	--	--	--	0.3 0.3(10)
UFLU (μg)					
DAY 94	6.0 2.3(8)	5.7 1.4(6)	14.1 3.3(8)	88.0@ 29.0(8)	702.6@ 255.8(9)
DAY 183	11.9 12.4(5)	--	--	--	15.7 3.2(7)

TABLE 33 (Continued)

SUMMARY OF URINALYSIS VALUES FOR FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 1 mg/kg/day	Group VI 5 mg/kg/day	Group VIII 25 mg/kg/day	Group X 125 mg/kg/day
UMTP (mg/dL)					
DAY 49	22 7(10)	34 24(10)	26 18(10)	13 6(10)	46 35(10)
DAY 94	33 23(10)	48 37(9)	30 15(10)	88 147(10)	230 313(10)
DAY 183	172 278(7)	--	--	--	588 1031(10)

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

@ 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	90-Day Time point	3-Month Recovery Time point
I	0	14.8 ± 1.0 ^a	12.4 ± 1.2	11.2 ± 1.8
III ^b	1	14.0 ± 1.7	13.6 ± 1.5	----
V ^b	5	15.9 ± 2.1	13.6 ± 3.0	----
VII ^b	25	14.7 ± 1.1	13.4 ± 2.1	----
IX	125	24.1 ± 3.7 [#]	20.6 ± 2.8 [#]	14.9 ± 2.0 [*]

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

^b Samples were not prepared for analysis from groups III, V and VII at the 90-day recovery time points.

[#] Statistically significant difference from control (p < 0.05) by Jonckheere's Tend test.

^{*} Statistically significant difference from control (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	90-Day Time point	3-Month Recovery Time point
II	0	22.5 ± 2.2 ^a	25.6 ± 3.3	23.8 ± 1.3
IV ^b	1	22.2 ± 1.5	25.4 ± 1.4	----
VI ^b	5	23.8 ± 4.5	27.3 ± 2.1	----
VIII ^b	25	23.2 ± 2.2	29.7 ± 3.3#	----
X	125	29.5 ± 4.4#	39.1 ± 4.7#	27.0 ± 5.6

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

^b Samples were not prepared for analysis from groups IV, VI and VIII at the 90-day recovery time point.

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

TABLE 36

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

Group: Dosage (mg/kg/day)	MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)					
	I 0	III 1	V 5	VII 25	IX 125	
LIVER	14.876 1.770(10)	14.109 1.254(10)	15.575 1.744(10)	17.219# 1.693(10)	21.976# 1.928(10)	
KIDNEYS	3.924 0.463(10)	3.804 0.263(10)	4.087 0.501(10)	4.351# 0.417(10)	4.636# 0.346(10)	
HEART	1.761 0.184(10)	1.832 0.095(10)	1.797 0.187(10)	1.866 0.133(10)	1.916 0.303(10)	
SPLEEN	0.913 0.137(10)	0.842 0.126(10)	0.874 0.171(10)	0.919 0.102(10)	0.963 0.186(10)	
BRAIN	2.186 0.084(10)	2.167 0.105(10)	2.234 0.089(10)	2.175 0.094(10)	2.175 0.069(10)	
THYMUS	0.450 0.134(10)	0.375 0.072(10)	0.480 0.117(10)	0.457 0.131(10)	0.455 0.138(10)	
ADRENAL GLANDS	0.061 0.009(10)	0.048 0.013(10)	0.065 0.011(10)	0.057 0.012(10)	0.062 0.014(10)	
THYROID GLAND	0.024 0.004(10)	0.023 0.004(10)	0.026 0.003(10)	0.026 0.003(10)	0.023 0.003(10)	
TESTES	3.588 0.228(10)	3.500 0.255(10)	3.700 0.442(10)	3.697 0.330(10)	3.552 0.552(10)	
EPIDIDYIMIDES	1.528 0.289(10)	1.549 0.133(10)	1.623 0.160(10)	1.636 0.221(10)	1.456 0.248(10)	
FINAL BODY WEIGHT	552.940 49.145(10)	540.790 37.400(10)	582.650 46.186(10)	564.140 43.119(10)	536.980 31.734(10)	

TABLE 36 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

		MEAN RELATIVE ORGAN WEIGHTS (% of body weight)					
Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125		
LIVER/ FINAL BODY * 100	2.690 0.225(10)	2.609 0.140(10)	2.669 0.148(10)	3.050# 0.124(10)	4.102# 0.410(10)		
KIDNEYS/ FINAL BODY * 100	0.712 0.091(10)	0.707 0.076(10)	0.702 0.069(10)	0.771 0.035(10)	0.867# 0.096(10)		
HEART/ FINAL BODY * 100	0.320 0.035(10)	0.339 0.016(10)	0.308 0.020(10)	0.331 0.013(10)	0.357 0.059(10)		
SPLEEN/ FINAL BODY * 100	0.165 0.021(10)	0.156 0.023(10)	0.149 0.022(10)	0.164 0.020(10)	0.180 0.037(10)		
BRAIN/ FINAL BODY * 100	0.398 0.038(10)	0.402 0.031(10)	0.385 0.030(10)	0.387 0.030(10)	0.406 0.028(10)		
THYMUS/ FINAL BODY * 100	0.081 0.021(10)	0.069 0.010(10)	0.082 0.018(10)	0.081 0.020(10)	0.085 0.025(10)		
ADRENAL GLANDS/ FINAL BODY * 100	0.011 0.002(10)	0.009 0.002(10)	0.011 0.002(10)	0.010 0.002(10)	0.012 0.003(10)		
THYROID GLAND/ FINAL BODY * 100	0.004 0.001(10)	0.004 0.001(10)	0.004 0.001(10)	0.005 0.001(10)	0.004 0.001(10)		
TESTES/ FINAL BODY * 100	0.651 0.048(10)	0.649 0.057(10)	0.635 0.053(10)	0.657 0.054(10)	0.664 0.110(10)		
EPIDIDYMIDES/ FINAL BODY * 100	0.279 0.060(10)	0.287 0.025(10)	0.280 0.032(10)	0.290 0.035(10)	0.273 0.054(10)		

TABLE 36 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

Group: Dosage (mg/kg/day)	MEAN RELATIVE ORGAN WEIGHT (% organ to brain weight ratio)				
	I 0	III 1	V 5	VII 25	IX 125
LIVER/ BRAIN * 100	680.794 80.356(10)	652.386 64.449(10)	697.513 76.846(10)	792.330# 78.215(10)	1011.448# 93.853(10)
KIDNEYS/ BRAIN * 100	179.350 19.034(10)	175.802 13.117(10)	182.593 17.359(10)	200.137# 18.909(10)	213.371# 16.868(10)
HEART/ BRAIN * 100	80.545 7.730(10)	84.719 5.813(10)	80.415 7.364(10)	85.888 6.289(10)	88.139 13.934(10)
SPLEEN/ BRAIN * 100	41.735 5.680(10)	38.817 5.273(10)	39.063 7.279(10)	42.302 4.614(10)	44.283 8.168(10)
THYMUS/ BRAIN * 100	20.511 5.854(10)	17.295 3.170(10)	21.496 5.303(10)	21.087 6.168(10)	20.829 5.858(10)
ADRENAL GLANDS/ BRAIN * 100	2.794 0.360(10)	2.230 0.622(10)	2.901 0.456(10)	2.642 0.553(10)	2.849 0.585(10)
THYROID GLAND/ BRAIN * 100	1.092 0.164(10)	1.065 0.168(10)	1.163 0.101(10)	1.188 0.161(10)	1.071 0.124(10)
TESTES/ BRAIN * 100	164.247 10.716(10)	161.999 15.726(10)	165.628 18.827(10)	170.071 14.477(10)	163.479 26.042(10)
EPIDIDYMIDES/ BRAIN * 100	69.848 12.791(10)	71.552 5.886(10)	72.719 7.299(10)	75.102 8.741(10)	66.885 10.870(10)

TABLE 36 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS

RATS DESIGNATED FOR RECOVERY

Group: Dosage (mg/kg/day)	I 0	IX 125
LIVER	15.779 2.481 (9)	15.067 2.727 (10)
KIDNEYS	3.911 0.428 (9)	3.940 0.520 (10)
HEART	1.799 0.161 (9)	1.841 0.276 (10)
SPLEEN	0.863 0.115 (9)	0.840 0.106 (10)
BRAIN	2.161 0.100 (9)	2.111 0.067 (10)
THYMUS	0.222 0.088 (9)	0.338# 0.056 (10)
ADRENAL GLANDS	0.055 0.009 (9)	0.049 0.010 (10)
THYROID GLAND	0.031 0.005 (9)	0.029 0.005 (10)
TESTES	3.655 0.270 (9)	3.460 0.125 (10)
EPIDIDYMIDES	1.513 0.144 (9)	1.480 0.114 (10)
FINAL BODY WEIGHT	626.311 67.783 (9)	609.860 85.864 (10)

TABLE 36 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS

RATS DESIGNATED FOR RECOVERY

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

Group: Dosage (mg/kg/day)	I 0	IX 125
LIVER/ FINAL BODY * 100	2.510 0.159 (9)	2.462 0.184 (10)
KIDNEYS/ FINAL BODY * 100	0.625 0.027 (9)	0.648 0.046 (10)
HEART/ FINAL BODY * 100	0.289 0.024 (9)	0.302 0.014 (10)
SPLEEN/ FINAL BODY * 100	0.138 0.018 (9)	0.139 0.015 (10)
BRAIN/ FINAL BODY * 100	0.348 0.030 (9)	0.352 0.051 (10)
THYMUS/ FINAL BODY * 100	0.036 0.015 (9)	0.056# 0.007 (10)
ADRENAL GLANDS/ FINAL BODY * 100	0.009 0.002 (9)	0.008 0.001 (10)
THYROID GLAND/ FINAL BODY * 100	0.005 0.001 (9)	0.005 0.001 (10)
TESTES/ FINAL BODY * 100	0.589 0.064 (9)	0.577 0.080 (10)
EPIDIDYIMIDES/ FINAL BODY * 100	0.244 0.032 (9)	0.248 0.045 (10)

TABLE 36 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS

RATS DESIGNATED FOR RECOVERY

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

Group: Dosage (mg/kg/day)	I 0	IX 125
LIVER/ BRAIN * 100	728.243 94.614(9)	714.942 133.730(10)
KIDNEYS/ BRAIN * 100	180.855 17.182(9)	186.766 24.848(10)
HEART/ BRAIN * 100	83.180 5.450(9)	87.334 13.549(10)
SPLEEN/ BRAIN * 100	39.852 4.379(9)	39.856 5.478(10)
THYMUS/ BRAIN * 100	10.361 4.280(9)	16.044# 2.650(10)
ADRENAL GLANDS/ BRAIN * 100	2.554 0.421(9)	2.306 0.468(10)
THYROID GLAND/ BRAIN * 100	1.428 0.267(9)	1.371 0.260(10)
TESTES/ BRAIN * 100	169.421 14.492(9)	163.936 4.527(10)
EPIDIDYMIDES/ BRAIN * 100	70.022 6.365(9)	70.171 5.982(10)

TABLE 36 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR MALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS (10-DAY SACRIFICE)

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
LIVER	10.419 0.940 (5)	10.216 0.733 (5)	10.419 1.444 (5)	10.703 1.004 (5)	14.182 1.684 (5)
FINAL BODY WEIGHT	248.38 16.953 (5)	244.66 11.964 (5)	245.66 23.023 (5)	241.36 17.085 (5)	252.94 17.819 (5)
LIVER/ FINAL BODY * 100	4.193 0.206 (5)	4.174 0.164 (5)	4.232 0.290 (5)	4.433 0.242 (5)	5.593 0.297 (5)

RATS DESIGNATED FOR SATELLITE EVALUATIONS (FINAL SACRIFICE)

Group: Dosage (mg/kg/day)	I 0	III 1	V 5	VII 25	IX 125
LIVER	19.628 4.405 (5)	20.521 3.768 (5)	19.963 3.833 (5)	22.601 3.976 (5)	22.559 3.686 (5)
FINAL BODY WEIGHT	603.040 98.436 (5)	646.340 66.814 (5)	632.480 85.838 (5)	693.840 81.778 (5)	697.940# 65.719 (5)
LIVER/ FINAL BODY * 100	3.232 0.356 (5)	3.157 0.296 (5)	3.139 0.236 (5)	3.241 0.203 (5)	3.220 0.267 (5)

Data summarized as: Mean
Standard Deviation (n)

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

TABLE 37

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

Group: Dosage (mg/kg/day)	MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)					
	II 0	IV 1	VI 5	VIII 25	X 125	
LIVER	7.904 0.849 (10)	8.224 0.982 (10)	8.185 0.845 (10)	9.230# 1.076 (10)	11.513# 0.972 (10)	
KIDNEYS	2.239 0.188 (10)	2.147 0.239 (10)	2.155 0.173 (10)	2.453 0.267 (10)	2.462# 0.265 (10)	
HEART	1.223 0.294 (10)	1.108 0.067 (10)	1.130 0.120 (10)	1.161 0.125 (10)	1.150 0.075 (10)	
SPLEEN	0.579 0.090 (10)	0.549 0.095 (10)	0.622 0.105 (10)	0.574 0.073 (10)	0.609 0.065 (10)	
BRAIN	1.967 0.068 (10)	1.978 0.077 (10)	1.931 0.085 (10)	2.003 0.085 (10)	2.009 0.126 (10)	
THYMUS	0.351 0.074 (10)	0.267 0.068 (10)	0.324 0.082 (10)	0.328 0.060 (10)	0.323 0.074 (10)	
ADRENAL GLANDS	0.076 0.012 (10)	0.063 0.019 (10)	0.070 0.010 (10)	0.065 0.006 (10)	0.073 0.013 (10)	
THYROID GLAND	0.020 0.003 (10)	0.020 0.006 (10)	0.020 0.003 (10)	0.021 0.004 (10)	0.022 0.004 (10)	
OVARIES	0.141 0.018 (10)	0.132 0.025 (10)	0.141 0.033 (10)	0.134 0.024 (10)	0.140 0.025 (10)	
UTERUS	0.704 0.168 (10)	0.779 0.170 (10)	0.738 0.300 (10)	0.780 0.166 (10)	0.808 0.354 (10)	
FINAL BODY WEIGHT	286.830 25.304 (10)	294.600 25.107 (10)	294.090 25.820 (10)	297.520 26.045 (10)	288.960 17.911 (10)	

TABLE 37 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

Group: Dosage (mg/kg/day)	MEAN RELATIVE ORGAN WEIGHTS (% of body weight)					
	II 0	IV 1	VI 5	VIII 25	X 125	
LIVER/ FINAL BODY * 100	2.755 0.158(10)	2.790 0.212(10)	2.784 0.161(10)	3.098# 0.171(10)	3.988# 0.287(10)	
KIDNEYS/ FINAL BODY * 100	0.782 0.043(10)	0.732 0.087(10)	0.734 0.043(10)	0.825 0.056(10)	0.852# 0.064(10)	
HEART/ FINAL BODY * 100	0.426 0.094(10)	0.378 0.032(10)	0.385 0.034(10)	0.390 0.020(10)	0.398 0.018(10)	
SPLEEN/ FINAL BODY * 100	0.201 0.023(10)	0.186 0.025(10)	0.212 0.030(10)	0.194 0.028(10)	0.212 0.028(10)	
BRAIN/ FINAL BODY * 100	0.689 0.049(10)	0.676 0.066(10)	0.660 0.050(10)	0.678 0.064(10)	0.696 0.039(10)	
THYMUS/ FINAL BODY * 100	0.122 0.022(10)	0.091 0.022(10)	0.110 0.025(10)	0.111 0.023(10)	0.112 0.026(10)	
ADRENAL GLANDS/ FINAL BODY * 100	0.027 0.004(10)	0.022* 0.007(10)	0.024 0.003(10)	0.022 0.003(10)	0.025 0.004(10)	
THYROID GLAND/ FINAL BODY * 100	0.007 0.001(10)	0.007 0.002(10)	0.007 0.001(10)	0.007 0.001(10)	0.008 0.002(10)	
OVARIES/ FINAL BODY * 100	0.049 0.005(10)	0.045 0.009(10)	0.048 0.012(10)	0.045 0.008(10)	0.049 0.010(10)	

TABLE 37 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

Group: Dosage (mg/kg/day)	MEAN RELATIVE ORGAN WEIGHTS (% of body weight)				
	II 0	IV 1	VI 5	VIII 25	X 125
UTERUS/ FINAL BODY * 100	0.248 0.064(10)	0.269 0.079(10)	0.255 0.123(10)	0.262 0.049(10)	0.277 0.111(10)
Group: Dosage (mg/kg/day)	MEAN RELATIVE ORGAN WEIGHTS (% organ to brain weight ratio)				
	II 0	IV 1	VI 5	VIII 25	X 125
LIVER/ BRAIN * 100	401.348 34.727(10)	417.043 58.824(10)	423.342 33.481(10)	461.618# 57.204(10)	573.617# 41.766(10)
KIDNEYS/ BRAIN * 100	113.798 8.306(10)	108.831 13.790(10)	111.492 5.931(10)	122.547 12.670(10)	122.384# 7.831(10)
HEART/ BRAIN * 100	62.105 14.598(10)	56.163 4.703(10)	58.463 5.074(10)	58.037 6.592(10)	57.377 4.208(10)
SPLEEN/ BRAIN * 100	29.353 3.943(10)	27.759 4.468(10)	32.243 5.280(10)	28.670 3.645(10)	30.410 3.442(10)
THYMUS/ BRAIN * 100	17.870 3.645(10)	13.466 3.267(10)	16.822 4.325(10)	16.521 3.699(10)	16.006 3.187(10)
ADRENAL GLANDS/ BRAIN * 100	3.862 0.548(10)	3.188 0.905(10)	3.631 0.453(10)	3.260 0.278(10)	3.613 0.522(10)

TABLE 37 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

Group: Dosage (mg/kg/day)	MEAN RELATIVE ORGAN WEIGHTS (% organ to brain weight ratio)					
	II 0	IV 1	VI 5	VIII 25	X 125	
THYROID GLAND/ BRAIN * 100	1.018 0.159(10)	1.019 0.290(10)	1.045 0.144(10)	1.068 0.235(10)	1.081 0.211(10)	
OVARIES/ BRAIN * 100	7.176 0.857(10)	6.672 1.162(10)	7.274 1.569(10)	6.658 1.112(10)	6.994 1.301(10)	
UTERUS/ BRAIN * 100	35.839 8.615(10)	39.442 8.477(10)	38.003 14.926(10)	39.144 9.115(10)	39.878 16.348(10)	

TABLE 37 (CONTINUED)
MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS
RATS DESIGNATED FOR RECOVERY

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

Group: Dosage (mg/kg/day)	II 0	X 125
LIVER	10.309 1.040 (9)	10.339 1.961 (10)
KIDNEYS	2.605 0.277 (9)	2.738 0.541 (10)
HEART	1.332 0.158 (9)	1.234 0.175 (10)
SPLEEN	0.637 0.101 (9)	0.592 0.090 (10)
BRAIN	2.055 0.102 (9)	1.936 0.086 (10)
THYMUS	0.239 0.072 (9)	0.269 0.102 (10)
ADRENAL GLANDS	0.085 0.020 (9)	0.075 0.013 (10)
THYROID GLAND	0.026 0.007 (9)	0.026 0.004 (10)
OVARIES	0.131 0.040 (9)	0.123 0.035 (10)
UTERUS	0.886 0.364 (9)	0.914 0.305 (10)
FINAL BODY WEIGHT	334.033 32.847 (9)	348.920 65.818 (10)

TABLE 37 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS

RATS DESIGNATED FOR RECOVERY

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

Group: Dosage (mg/kg/day)	II 0	X 125
LIVER/ FINAL BODY * 100	3.094 0.248(9)	2.977 0.340(10)
KIDNEYS/ FINAL BODY * 100	0.783 0.079(9)	0.793 0.137(10)
HEART/ FINAL BODY * 100	0.399 0.040(9)	0.357# 0.031(10)
SPLEEN/ FINAL BODY * 100	0.192 0.031(9)	0.174 0.037(10)
BRAIN/ FINAL BODY * 100	0.619 0.052(9)	0.570 0.096(10)
THYMUS/ FINAL BODY * 100	0.072 0.023(9)	0.076 0.018(10)
ADRENAL GLANDS/ FINAL BODY * 100	0.026 0.006(9)	0.022 0.005(10)
THYROID GLAND/ FINAL BODY * 100	0.008 0.002(9)	0.008 0.002(10)
OVARIES/ FINAL BODY * 100	0.039 0.010(9)	0.037 0.013(10)

TABLE 37 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS

RATS DESIGNATED FOR RECOVERY

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

Group: Dosage (mg/kg/day)	II 0	X 125
UTERUS/ FINAL BODY * 100	0.268 0.107(9)	0.278 0.130(10)

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

Group: Dosage (mg/kg/day)	II 0	X 125
LIVER/ BRAIN * 100	501.311 39.253(9)	533.737 96.914(10)
KIDNEYS/ BRAIN * 100	126.765 11.614(9)	141.591 28.381(10)
HEART/ BRAIN * 100	64.848 7.420(9)	63.675 8.079(10)
SPLEEN/ BRAIN * 100	30.944 4.184(9)	30.642 4.777(10)
THYMUS/ BRAIN * 100	11.549 3.111(9)	13.835 4.955(10)
ADRENAL GLANDS/ BRAIN * 100	4.118 0.862(9)	3.882 0.689(10)

TABLE 37 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS

RATS DESIGNATED FOR RECOVERY

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

Group: Dosage (mg/kg/day)	II 0	X 125
THYROID GLAND/ BRAIN * 100	1.261 0.297(9)	1.345 0.220(10)
OVARIES/ BRAIN * 100	6.330 1.813(9)	6.355 1.650(10)
UTERUS/ BRAIN * 100	42.819 15.794(9)	47.502 16.378(10)

TABLE 37 (CONTINUED)

MEAN FINAL BODY AND ORGAN WEIGHTS FOR FEMALE RATS

RATS DESIGNATED FOR SATELLITE EVALUATIONS (10-DAY SACRIFICE)

Group: Dosage (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
LIVER	7.185 0.785 (5)	7.174 0.923 (5)	7.814 0.582 (5)	8.364 1.243 (5)	10.134 1.129 (5)
FINAL BODY WEIGHT	170.54 17.825 (5)	160.44 15.709 (5)	170.74 16.129 (5)	175.58 14.315 (5)	182.52 18.060 (5)
LIVER/ FINAL BODY * 100	4.213 0.118 (5)	4.473 0.355 (5)	4.589 0.282 (5)	4.748 0.424 (5)	5.557 0.344 (5)

RATS DESIGNATED FOR SATELLITE EVALUATIONS (FINAL SACRIFICE)

Group: Dosage (mg/kg/day)	II 0	IV 1	VI 5	VIII 25	X 125
LIVER	12.444 2.922 (5)	11.897 1.637 (5)	12.711 0.553 (5)	13.527 3.301 (5)	12.729 1.305 (5)
FINAL BODY WEIGHT	325.900 46.602 (5)	336.160 29.278 (5)	335.920 44.576 (5)	366.840 53.771 (5)	359.320 44.287 (5)
LIVER/ FINAL BODY * 100	3.784 0.445 (5)	3.537 0.340 (5)	3.828 0.449 (5)	3.651 0.434 (5)	3.567 0.402 (5)

Data summarized as: Mean
Standard Deviation (n)

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

TABLE 38

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)					
		Males					
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
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	10	9	
DILATATION, RIGHT.						1	
LUNGS		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
HEART		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
SKELETAL MUSCLE		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
SPLEEN		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	

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

TABLE 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)					
		Males					
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
AORTA		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
BRAIN		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
SPINAL CORD		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
STOMACH		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
DUODENUM		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
JEJUNUM		(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 38 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
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
MESENTERIC LYMPH NODE		(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 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

TREATMENT	LESION INCIDENCE (Numeric)					
	Males					
	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
SALIVARY GLANDS	(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	10	
MANDIBULAR LYMPH NODE	(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	10	
THYMUS	(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	10	
ADRENAL GLANDS	(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	10	
SCIATIC NERVE	(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	10	
PITUITARY GLAND	(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 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)					
		Males					
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
THYROID GLAND		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
PARATHYROID GLANDS		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
TRACHEA		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
ESOPHAGUS		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
PHARYNX/LARYNX		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
EYE(S) WITH OPTIC NERVE		(10)	(10)	(10)	(10)	(9)	
NO ABNORMALITY DETECTED		10	10	10	10	9	

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

TABLE 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
SKIN		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED ALOPECIA, RIGHT.		10	9 1	10	10	10
PROSTATE		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10
SEMINAL VESICLES		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10
URINARY BLADDER		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED DILATATION.		10	10	9 1	10	10
TESTES		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED SMALL, UNILATERAL. DISCOLORATION, OPAQUE.		9	10	9 1	10	9 1
		1				

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

TABLE 38 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (Numeric)					
	Males					
TREATMENT	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
EPIDIDYMIDES	(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED SMALL, UNILATERAL.	10	10	10	10	9 1	
FEMUR/KNEE JOINT	(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	10	
STERNUM	(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED	10	10	10	10	10	
NOSE	(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 38 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR RECOVERY

LESION	INCIDENCE		
	TREATMENT	Males	
		0 mg/kg I	125 mg/kg IX
LIVER		(10)	(10)
NO ABNORMALITY DETECTED		10	10
KIDNEYS		(10)	(10)
NO ABNORMALITY DETECTED		10	9
CALCULUS\CALCULI, RIGHT			1
LUNGS		(10)	(10)
NO ABNORMALITY DETECTED		10	10
HEART		(10)	(10)
NO ABNORMALITY DETECTED		10	10
SKELETAL MUSCLE		(10)	(10)
NO ABNORMALITY DETECTED		10	10
SPLEEN		(10)	(10)
NO ABNORMALITY DETECTED		10	10

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

TABLE 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS

RATS DESIGNATED FOR RECOVERY

LESION	TREATMENT		INCIDENCE	
			Males	
			0 mg/kg I	125. mg/kg IX
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 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR RECOVERY

LESION	INCIDENCE	
	Males	
TREATMENT	0 mg/kg I	125 mg/kg IX
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 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS

RATS DESIGNATED FOR RECOVERY

LESIONS	TREATMENT	LESION INCIDENCE	
		Males	
		0 mg/kg I	125 mg/kg IX
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 38 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR RECOVERY

LESION	LESION INCIDENCE		
	TREATMENT	Males	
		0 mg/kg I	125 mg/kg IX
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 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS

RATS DESIGNATED FOR RECOVERY

LESION	LESION INCIDENCE	
	Males	
	TREATMENT	0 125 mg/kg I IX
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 38 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR RECOVERY

LESION INCIDENCE	Males		
	TREATMENT	0 mg/kg I	125 mg/kg IX
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 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

TREATMENT	LESION INCIDENCE (Numeric)				
	Males				
	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
LESIONS					
LIVER	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5	5
KIDNEYS	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5	5
LUNGS	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5	5
HEART	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5	5
SKELETAL MUSCLE	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5	5
SPLEEN	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5	5

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

TABLE 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)					
		Males					
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
AORTA		(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	5	
BRAIN		(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	5	
SPINAL CORD		(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	5	
STOMACH		(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	5	
DUODENUM		(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	5	
JEJUNUM		(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	5	

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

TABLE 38 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

LESIONS	LESION INCIDENCE (Numeric)					
	Males					
TREATMENT	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
ILEUM	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
PANCREAS	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
CECUM	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
COLON	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
RECTUM	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
MESENTERIC LYMPH NODE	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	

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

TABLE 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

LESIONS	LESION INCIDENCE (Numeric)					
	Males					
TREATMENT	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
SALIVARY GLANDS	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
MANDIBULAR LYMPH NODE	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
THYMUS	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
ADRENAL GLANDS	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
SCIATIC NERVE	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
PITUITARY GLAND	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	

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

TABLE 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

LESIONS	LESION INCIDENCE (Numeric)					
	Males					
TREATMENT	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
THYROID GLAND	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
PARATHYROID GLANDS	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
TRACHEA	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
ESOPHAGUS	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
PHARYNX/LARYNX	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
EYE(S) WITH OPTIC NERVE	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	

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

TABLE 38 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
SKIN		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
PROSTATE		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
SEMINAL VESICLES		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
URINARY BLADDER		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
TESTES		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
EPIDIDYMIDES		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5

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

TABLE 38 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

TREATMENT	LESION INCIDENCE (Numeric)				
	Males				
	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
LESIONS					
FEMUR/KNEE JOINT	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5	5
STERNUM	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5	5
NOSE	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	5	5	5	5	5

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

TABLE 39

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)					
		Females					
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X	
LIVER		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	10	10	10	10	
KIDNEYS		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	10	10	10	10	
LUNGS		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	10	10	10	10	
HEART		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
NO ABNORMALITY DETECTED LARGE.		1	(10)	(10)	(10)	(10)	
SKELETAL MUSCLE		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	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
N=11 in Group II reflects 1 early death 90 day time period

TABLE 39 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)					
		Females					
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X	
SPLEEN		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	10	10	10	10	
AORTA		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	10	10	10	10	
BRAIN		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	10	10	10	10	
SPINAL CORD		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	10	10	10	10	
STOMACH		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		10	10	10	10	10	
FLUID, RED.		1					

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified
N=11 in Group II reflects 1 early death 90 day time period

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)					
		Females					
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X	
DUODENUM		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	10	10	10	10	
JEJUNUM		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	10	10	10	10	
ILEUM		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	10	10	10	10	
PANCREAS		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	10	10	10	10	
CECUM		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	10	10	10	10	
COLON		(11)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED		11	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
N=11 in Group II reflects 1 early death 90 day time period

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
RECTUM		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
MESENTERIC LYMPH NODE		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
SALIVARY GLANDS		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
MANDIBULAR LYMPH NODE		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
THYMUS		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
ADRENAL GLANDS		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	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
N=11 in Group II reflects 1 early death 90 day time period

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
SCIATIC NERVE		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
PITUITARY GLAND		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
THYROID GLAND		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
PARATHYROID GLANDS		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
TRACHEA		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
ESOPHAGUS		(11)	(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
N=11 in Group II reflects 1 early death 90 day time period

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
ESOPHAGUS		(11)	(10)	(10)	(10)	(10)
PERFORATION.		1				
PHARYNX/LARYNX		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
EYE(S) WITH OPTIC NERVE		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
SKIN		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10
STAIN, RED, NOSE.		1				
MAMMARY GLAND (FEMALE)		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	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
N=11 in Group II reflects 1 early death 90 day time period

TABLE 39 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)				
		Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
OVARIES		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
UTERUS		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
VAGINA		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
URINARY BLADDER		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
FEMUR/KNEE JOINT		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	10	10	10	10
STERNUM		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	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
N=11 in Group II reflects 1 early death 90 day time period

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)				
		Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
NOSE		(11)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		11	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
N=11 in Group II reflects 1 early death 90 day time period

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR RECOVERY

LESION	TREATMENT		Females	
	0 mg/kg II	125 mg/kg X	0 mg/kg II	125 mg/kg X
LIVER			(9)	(10)
NO ABNORMALITY DETECTED			9	10
KIDNEYS			(9)	(10)
NO ABNORMALITY DETECTED			9	10
LUNGS			(9)	(10)
NO ABNORMALITY DETECTED			9	10
HEART			(9)	(10)
NO ABNORMALITY DETECTED			9	10
SKELETAL MUSCLE			(9)	(10)
NO ABNORMALITY DETECTED			9	10
SPLEEN			(9)	(10)
NO ABNORMALITY DETECTED			9	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified
N=9 in Group II reflects 1 early death in 90 day time period

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS

RATS DESIGNATED FOR RECOVERY

LESIONS	LESION INCIDENCE		
	TREATMENT	Females	
		0 mg/kg II	125 mg/kg X
AORTA		(9)	(10)
NO ABNORMALITY DETECTED		9	10
BRAIN		(9)	(10)
NO ABNORMALITY DETECTED		9	10
SPINAL CORD		(9)	(10)
NO ABNORMALITY DETECTED		9	10
STOMACH		(9)	(10)
NO ABNORMALITY DETECTED		9	10
DUODENUM		(9)	(10)
NO ABNORMALITY DETECTED		9	10
JEJUNUM		(9)	(10)
NO ABNORMALITY DETECTED		9	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified
N=9 in Group II reflects 1 early death in 90 day time period

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS

RATS DESIGNATED FOR RECOVERY

LESIONS	TREATMENT		LESION INCIDENCE	
			Females	
			0 mg/kg II	125 mg/kg X
ILEUM			(9)	(10)
NO ABNORMALITY DETECTED			9	10
PANCREAS			(9)	(10)
NO ABNORMALITY DETECTED			9	10
CECUM			(9)	(10)
NO ABNORMALITY DETECTED			9	10
COLON			(9)	(10)
NO ABNORMALITY DETECTED			9	10
RECTUM			(9)	(10)
NO ABNORMALITY DETECTED			9	10
MESENTERIC LYMPH NODE			(9)	(10)
NO ABNORMALITY DETECTED			9	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified
N=9 in Group II reflects 1 early death in 90 day time period

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS

RATS DESIGNATED FOR RECOVERY

LESIONS	TREATMENT	LESION INCIDENCE	
		Females	
		0 mg/kg II	125 mg/kg X
SALIVARY GLANDS		(9)	(10)
NO ABNORMALITY DETECTED		9	10
MANDIBULAR LYMPH NODE		(9)	(10)
NO ABNORMALITY DETECTED		9	10
THYMUS		(9)	(10)
NO ABNORMALITY DETECTED		9	10
ADRENAL GLANDS		(9)	(10)
NO ABNORMALITY DETECTED		9	10
SCIATIC NERVE		(9)	(10)
NO ABNORMALITY DETECTED		9	10
PITUITARY GLAND		(9)	(10)
NO ABNORMALITY DETECTED		8	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
N=9 in Group II reflects 1 early death in 90 day time period

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS

RATS DESIGNATED FOR RECOVERY

LESIONS	TREATMENT		LESION INCIDENCE	
			Females	
			0 mg/kg II	125 mg/kg X
PITUITARY GLAND			(9)	(10)
LARGE.			1	
THYROID GLAND			(9)	(10)
NO ABNORMALITY DETECTED			9	10
PARATHYROID GLANDS			(9)	(10)
NO ABNORMALITY DETECTED			9	10
TRACHEA			(9)	(10)
NO ABNORMALITY DETECTED			9	10
ESOPHAGUS			(9)	(10)
NO ABNORMALITY DETECTED			9	10
PHARYNX/LARYNX			(9)	(10)
NO ABNORMALITY DETECTED			9	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified
N=9 in Group II reflects 1 early death in 90 day time period

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR RECOVERY

LESION	TREATMENT		INCIDENCE	
	0	125	Females	
	mg/kg	mg/kg	II	X
EYE(S) WITH OPTIC NERVE	(9)	(10)		
NO ABNORMALITY DETECTED	9	10		
SKIN	(9)	(10)		
NO ABNORMALITY DETECTED	9	10		
MAMMARY GLAND (FEMALE)	(9)	(10)		
NO ABNORMALITY DETECTED	9	10		
OVARIES	(9)	(10)		
NO ABNORMALITY DETECTED	9	10		
UTERUS	(9)	(10)		
NO ABNORMALITY DETECTED	8	10		
DILATATION.	1			

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified
N=9 in Group II reflects 1 early death in 90 day time period

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS

RATS DESIGNATED FOR RECOVERY

LESIONS	TREATMENT	LESION INCIDENCE	
		Females	
		0 mg/kg II	125 mg/kg X
VAGINA		(9)	(10)
NO ABNORMALITY DETECTED		9	10
URINARY BLADDER		(9)	(10)
NO ABNORMALITY DETECTED		9	10
FEMUR/KNEE JOINT		(9)	(10)
NO ABNORMALITY DETECTED		9	10
STERNUM		(9)	(10)
NO ABNORMALITY DETECTED		9	10
NOSE		(9)	(10)
NO ABNORMALITY DETECTED		9	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified
N-9 in Group II reflects 1 early death in 90 day time period

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
LIVER		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
KIDNEYS		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
LUNGS		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
HEART		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
SKELETAL MUSCLE		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
SPLEEN		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5

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

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

LESIONS	TREATMENT	LESION INCIDENCE (Numeric)					
		Females					
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X	
AORTA		(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	5	
BRAIN		(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	5	
SPINAL CORD		(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	5	
STOMACH		(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	5	
DUODENUM		(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	5	
JEJUNUM		(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED		5	5	5	5	5	

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

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
ILEUM		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
PANCREAS		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
CECUM		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
COLON		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
RECTUM		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
MESENTERIC LYMPH NODE		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5

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

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
SALIVARY GLANDS		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
MANDIBULAR LYMPH NODE		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
THYMUS		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
ADRENAL GLANDS		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
SCIATIC NERVE		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
PITUITARY GLAND		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5

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

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
THYROID GLAND		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
PARATHYROID GLANDS		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
TRACHEA		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
ESOPHAGUS		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
PHARYNX/LARYNX		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
EYE(S) WITH OPTIC NERVE		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5

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

TABLE 39 (CONTINUED)
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

LESIONS	LESION INCIDENCE (Numeric)					
	Females					
TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X	
SKIN	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
MAMMARY GLAND (FEMALE)	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
OVARIES	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
UTERUS	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
VAGINA	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	
URINARY BLADDER	(5)	(5)	(5)	(5)	(5)	
NO ABNORMALITY DETECTED	5	5	5	5	5	

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

TABLE 39 (CONTINUED)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS
RATS DESIGNATED FOR SATELLITE EVALUATIONS

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT	Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
FEMUR/KNEE JOINT		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
STERNUM		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5
NOSE		(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED		5	5	5	5	5

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

TABLE 40

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

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
DIGESTIVE SYSTEM						
LIVER		(10)	(10)	(10)	(10)	(10)
NECROSIS, FOCAL.				1	5	3
INFLAMMATION, SUBACUTE/CHRONIC.		10	9	10	9	8
HYPERTROPHY, HEPATOCELLULAR.						10
FATTY CHANGE, MEDIAN CLEFT.		2	2	2	1	1
FATTY CHANGE, CENTRILOBULAR.						1
PANCREAS		(10)				(10)
NO ABNORMALITY DETECTED		8				8
ATROPHY.		2				2
ESOPHAGUS		(10)				(10)
NO ABNORMALITY DETECTED		10				10
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 40 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)					
		Males					
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
DIGESTIVE SYSTEM							
DUODENUM		(10)				(10)	
NO ABNORMALITY DETECTED		10				10	
JEJUNUM		(10)				(9)	
NO ABNORMALITY DETECTED		10				9	
ILEUM		(10)				(9)	
NO ABNORMALITY DETECTED		10				9	
CECUM		(10)				(9)	
NO ABNORMALITY DETECTED		10				9	
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 40 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
DIGESTIVE SYSTEM						
RECTUM		(10)				(9)
NO ABNORMALITY DETECTED		10				9
SALIVARY GLANDS		(10)				(10)
NO ABNORMALITY DETECTED		10				10

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

TABLE 40 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
URINARY SYSTEM						
KIDNEYS						
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)	(10)
CHRONIC PROGRESSIVE NEPHROPATHY.		5	4	3	1	8
PIGMENT, TUBULAR.		5	6	7	4	1
HYPERTROPHY, TUBULAR.					9	10
HYDRONEPHROSIS, UNILATERAL.					1	1
CYST.					1	
URINARY BLADDER						
NO ABNORMALITY DETECTED		(10)		(1)		(10)
		10		1		10

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

TABLE 40 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)					
		Males					
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
RESPIRATORY SYSTEM							
LUNGS		(10)				(10)	
NO ABNORMALITY DETECTED INFLAMMATION, SUBACUTE/CHRONIC.		9 1				9 1	
TRACHEA		(10)				(10)	
NO ABNORMALITY DETECTED		10				10	
PHARYNX/LARYNX		(10)				(10)	
NO ABNORMALITY DETECTED		10				10	
NOSE		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED DEGENERATION, AMELOBLASTS.		10	10	10	10	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 40 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
CARDIOVASCULAR SYSTEM						
HEART		(10)				(10)
NO ABNORMALITY DETECTED		5				5
CARDIOMYOPATHY		5				5
AORTA		(10)				(10)
NO ABNORMALITY DETECTED		10				10

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

TABLE 40 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
SPLEEN		(10)				(10)
NO ABNORMALITY DETECTED		10				10
THYMUS		(10)				(10)
NO ABNORMALITY DETECTED		10				10
MANDIBULAR LYMPH NODE		(10)				(10)
NO ABNORMALITY DETECTED		10				10
MESENTERIC LYMPH NODE		(10)				(9)
NO ABNORMALITY DETECTED		10				9
BONE MARROW		(10)				(10)
NO ABNORMALITY DETECTED		10				10

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

TABLE 40 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)					
		Males					
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
ENDOCRINE SYSTEM							
PITUITARY GLAND		(9)				(10)	
NO ABNORMALITY DETECTED CYST.		8				10	
THYROID GLAND		(10)	(10)	(10)	(10)	(10)	
NO ABNORMALITY DETECTED ALTERATION, COLLOID.		7	2	1		2	
PARATHYROID GLANDS		3	8	9	10	8	
NO ABNORMALITY DETECTED		(9)				(9)	
ADRENAL GLANDS		9				9	
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 40 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
NERVOUS SYSTEM						
BRAIN		(10)				(10)
NO ABNORMALITY DETECTED		10				10
SPINAL CORD		(10)				(10)
NO ABNORMALITY DETECTED		10				10
SCIATIC NERVE		(10)				(10)
NO ABNORMALITY DETECTED		10				10

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

TABLE 40 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
TREATMENT	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
MUSCULAR AND SKELETAL SYSTEM						
SKELETAL MUSCLE	(10)				(10)	
NO ABNORMALITY DETECTED	10				10	
FEMUR/KNEE JOINT	(10)				(10)	
NO ABNORMALITY DETECTED	10				10	
STERNUM	(10)				(10)	
NO ABNORMALITY DETECTED	10				10	

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

TABLE 40 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
REPRODUCTIVE SYSTEM						
TESTES		(10)	(1)	(1)		(10)
NO ABNORMALITY DETECTED		8				9
DILATATION, SEMINIFEROUS TUBULES, UNILATERAL.				1		1
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, UNILATERAL.				1		
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, BILATERAL.		2				
EPIDIDYIMIDES		(10)				(10)
NO ABNORMALITY DETECTED		9				9
OLIGOSPERMIA/GERM CELL DEBRIS, UNILATERAL.						1
OLIGOSPERMIA/GERM CELL DEBRIS, BILATERAL.		1				
PROSTATE		(10)				(10)
NO ABNORMALITY DETECTED		7				10
INFLAMMATION, SUBACUTE/CHRONIC.		3				
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 40 (CONTINUED)

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

TREATMENT	LESION INCIDENCE (NUMERIC)				
	Males				
	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
LESIONS					
CUTANEOUS SYSTEM					
SKIN	(10)	(1)			(10)
NO ABNORMALITY DETECTED	10	1			10

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

TABLE 40 (CONTINUED)

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

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
TREATMENT	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
SPECIAL SENSES SYSTEM						
EYE(S) WITH OPTIC NERVE	(10)				(10)	
NO ABNORMALITY DETECTED	8				10	
OPTIC NERVE NOT PRESENT.	3				1	
FOLD/ROSETTE, RETINAL.	1					
ADHESION, RETINAL.	1					

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

TABLE 40 (CONTINUED)

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

RATS DESIGNATED FOR RECOVERY

LESIONS	TREATMENT		LESION INCIDENCE	
			Males	
	0 mg/kg I	125 mg/kg IX		
DIGESTIVE SYSTEM				
LIVER	(10)	(10)		
NECROSIS, FOCAL.	3	7		
INFLAMMATION, SUBACUTE/CHRONIC.	9	9		
HYPERPLASIA, BILE DUCT.	5	6		
FATTY CHANGE, MEDIAN CLEFT.	2			

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

TABLE 40 (CONTINUED)

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

RATS DESIGNATED FOR RECOVERY

LESIONS	TREATMENT		LESION INCIDENCE	
			Males	
			0 mg/kg I	125 mg/kg IX
URINARY SYSTEM			(10)	(10)
KIDNEYS			4	3
NO ABNORMALITY DETECTED			6	5
CHRONIC PROGRESSIVE NEPHROPATHY.				1
HYPERPLASIA, TRANSITIONAL CELL.				1
HYDRONEPHROSIS, UNILATERAL.				1
HYDRONEPHROSIS, BILATERAL.				1
CYST.				1

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

TABLE 40 (CONTINUED)

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

RATS DESIGNATED FOR RECOVERY

LESIONS	LESION INCIDENCE		
	TREATMENT	Males	
		0 mg/kg I	125 mg/kg IX
RESPIRATORY SYSTEM		(10)	(10)
NOSE		10	7
NO ABNORMALITY DETECTED			1
ODONTODYSPLASIA.			1
INFLAMMATION, SUBACUTE/CHRONIC.			1
DEGENERATION, AMELOBLASTS.			2

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

TABLE 40 (CONTINUED)

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

RATS DESIGNATED FOR RECOVERY

LESIONS	LESION INCIDENCE		
	TREATMENT	Males	
		0 mg/kg I	125 mg/kg IX
LYMPHATIC AND HEMATOPOIETIC SYSTEM			
THYMUS		(10)	(10)
NO ABNORMALITY DETECTED		10	10

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

TABLE 40 (CONTINUED)

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

RATS DESIGNATED FOR RECOVERY

LESIONS	LESION INCIDENCE		
	TREATMENT	Males	
		0 mg/kg I	125 mg/kg IX
ENDOCRINE SYSTEM		(10)	(10)
THYROID GLAND		3	10
NO ABNORMALITY DETECTED ALTERATION, COLLOID.		7	

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

TABLE 41

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
DIGESTIVE SYSTEM						
LIVER		(11)				(10)
NO ABNORMALITY DETECTED		1				1
INFLAMMATION, SUBACUTE/CHRONIC.		10				6
HYPERPLASIA, BILE DUCT.		2				3
FATTY CHANGE, MEDIAN CLEFT.		2				1
PANCREAS		(11)				(10)
NO ABNORMALITY DETECTED		11				9
INFLAMMATION, SUBACUTE/CHRONIC.						1
ESOPHAGUS		(11)				(10)
NO ABNORMALITY DETECTED		10				10
INFLAMMATION, SUBACUTE/CHRONIC.		1				
LACERATION.		1				
STOMACH		(11)				(10)
NO ABNORMALITY DETECTED		11				10
DUODENUM		(11)				(10)
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
DIGESTIVE SYSTEM						
JEJUNUM		(11)				(10)
NO ABNORMALITY DETECTED		11				10
ILEUM		(11)				(10)
NO ABNORMALITY DETECTED		11				10
CECUM		(11)				(10)
NO ABNORMALITY DETECTED		11				10
COLON		(11)				(10)
NO ABNORMALITY DETECTED		11				10
RECTUM		(11)				(10)
NO ABNORMALITY DETECTED		11				10
SALIVARY GLANDS		(11)				(10)
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
URINARY SYSTEM						
KIDNEYS						
NO ABNORMALITY DETECTED		(11)	(10)	(10)	(10)	(10)
CHRONIC PROGRESSIVE NEPHROPATHY.		7	8	7	7	1
INFLAMMATION, SUBACUTE/CHRONIC.		2	2	3	3	7
HYDRONEPHROSIS, UNILATERAL.		2	1			1
HYDRONEPHROSIS, BILATERAL.		1				1
URINARY BLADDER						
NO ABNORMALITY DETECTED		(11)				(10)
INFLAMMATION, SUBACUTE/CHRONIC.		10				10
		1				

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
RESPIRATORY SYSTEM						
LUNGS		(11)				(10)
NO ABNORMALITY DETECTED		11				10
TRACHEA		(11)				(10)
NO ABNORMALITY DETECTED		11				10
PHARYNX/LARYNX		(11)				(10)
NO ABNORMALITY DETECTED		11				10
NOSE		(11)				(10)
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
CARDIOVASCULAR SYSTEM						
HEART		(11)				(10)
NO ABNORMALITY DETECTED		6				8
CARDIOMYOPATHY:		5				2
AORTA		(11)				(10)
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
SPLEEN		(11)				(10)
NO ABNORMALITY DETECTED		11				10
THYMUS		(11)				(10)
NO ABNORMALITY DETECTED		11				10
MANDIBULAR LYMPH NODE		(11)				(10)
NO ABNORMALITY DETECTED		11				10
MESENTERIC LYMPH NODE		(11)				(10)
NO ABNORMALITY DETECTED		11				10
BONE MARROW		(11)				(10)
NO ABNORMALITY DETECTED		10				10
HYPERPLASIA, GRANULOCYTIC.		1				

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
ENDOCRINE SYSTEM						
PITUITARY GLAND		(11)				(10)
NO ABNORMALITY DETECTED		11				10
THYROID GLAND		(11)				(10)
NO ABNORMALITY DETECTED		11				10
PARATHYROID GLANDS		(9)				(9)
NO ABNORMALITY DETECTED		9				9
ADRENAL GLANDS		(11)				(10)
NO ABNORMALITY DETECTED MINERALIZATION.		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
NERVOUS SYSTEM						
BRAIN		(11)				(10)
NO ABNORMALITY DETECTED		11				10
SPINAL CORD		(11)				(10)
NO ABNORMALITY DETECTED		11				10
SCIATIC NERVE		(11)				(10)
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
MUSCULAR AND SKELETAL SYSTEM						
SKELETAL MUSCLE		(11)				(10)
NO ABNORMALITY DETECTED INFLAMMATION, SUBACUTE/CHRONIC.		11				9 1
FEMUR/KNEE JOINT		(11)				(10)
NO ABNORMALITY DETECTED		11				10
STERNUM		(11)				(10)
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	Females					
	TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
REPRODUCTIVE SYSTEM						
OVARIES		(11)				(10)
NO ABNORMALITY DETECTED		11				10
UTERUS		(11)				(10)
NO ABNORMALITY DETECTED		11				10
MAMMARY GLAND (FEMALE)		(11)				(8)
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (NUMERIC)					
	Females					
TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X	
CUTANEOUS SYSTEM						
SKIN	(11)				(10)	
NO ABNORMALITY DETECTED	11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)				
	Females				
TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
SPECIAL SENSES SYSTEM					
EYE(S) WITH OPTIC NERVE	(11)				(10)
NO ABNORMALITY DETECTED OPTIC NERVE NOT PRESENT. FOLD/ROSETTE, RETINAL.	11				9 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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

RATS DESIGNATED FOR RECOVERY

LESIONS	LESION INCIDENCE		
	TREATMENT	Females	
		0 mg/kg II	125 mg/kg X
DIGESTIVE SYSTEM		(9)	(10)
LIVER		3	2
NO ABNORMALITY DETECTED		1	6
NECROSIS, FOCAL.		3	1
INFLAMMATION, SUBACUTE/CHRONIC.		1	1
HYPERPLASIA, BILE DUCT.		2	2
FATTY CHANGE, MEDIAN CLEFT.			
ANGIECTASIS.			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=9 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

RATS DESIGNATED FOR RECOVERY

LESION INCIDENCE	Females	
	0 mg/kg II	125 mg/kg X
TREATMENT		
LESIONS		
URINARY SYSTEM	(9)	(10)
KIDNEYS	4	2
	5	8
		1

NO ABNORMALITY DETECTED
CHRONIC PROGRESSIVE NEPHROPATHY.
HYDRONEPHROSIS, BILATERAL.

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=9 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS

RATS DESIGNATED FOR RECOVERY

LESION	INCIDENCE		
	TREATMENT	0 mg/kg II	125 mg/kg X
ENDOCRINE SYSTEM			
PITUITARY GLAND		(1)	1
NO ABNORMALITY DETECTED			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=9 IN GROUP II DUE TO EARLY DEATH

TABLE 41 (CONTINUED)
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
RATS DESIGNATED FOR RECOVERY

LESIONS	LESION INCIDENCE		
	TREATMENT	0 mg/kg II	125 mg/kg X
REPRODUCTIVE SYSTEM			
UTERUS		(1)	1
DILATATION.			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=9 IN GROUP II DUE TO EARLY DEATH

TABLE 42

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

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
DIGESTIVE SYSTEM						
LIVER		(10)	(10)	(10)	(10)	(10)
NECROSIS, FOCAL. minimal total observations per lesion				1 1	5 5	3 3
INFLAMMATION, SUBACUTE/CHRONIC. minimal total observations per lesion		10 10	9 9	10 10	9 9	8 8
HYPERTROPHY, HEPATOCELLULAR. minimal mild total observations per lesion						4 6 10
FATTY CHANGE, MEDIAN CLEFT. minimal mild total observations per lesion		2 2	2 2	1 1 2	1 1	1 1
FATTY CHANGE, CENTRILOBULAR. minimal total observations per lesion						1 1

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

TABLE 42 (CONTINUED)
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NON-NEOPLASTIC LESIONS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
DIGESTIVE SYSTEM		(10)				(10)
PANCREAS		8				8
NO ABNORMALITY DETECTED		2				2
ATROPHY.		2				2
minimal						
total observations per lesion		(10)				(10)
ESOPHAGUS		10				10
NO ABNORMALITY DETECTED		(10)				(10)
STOMACH		10				10
NO ABNORMALITY DETECTED		(10)				(10)
DUODENUM		10				10
NO ABNORMALITY DETECTED		(10)				(9)
JEJUNUM		10				9
NO ABNORMALITY DETECTED		(10)				

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

TABLE 42 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
DIGESTIVE SYSTEM						
ILEUM		(10)				(9)
NO ABNORMALITY DETECTED		10				9
CECUM		(10)				(9)
NO ABNORMALITY DETECTED		10				9
COLON		(10)				(10)
NO ABNORMALITY DETECTED		10				10
RECTUM		(10)				(9)
NO ABNORMALITY DETECTED		10				9
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 42 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
URINARY SYSTEM						
KIDNEYS						
NO ABNORMALITY DETECTED		(10)	(10)	(10)	(10)	(10)
CHRONIC PROGRESSIVE NEPHROPATHY.						
minimal		5	4	3	1	
total observations per lesion		5	6	7	4	8
PIGMENT, TUBULAR.		5	6	7	4	8
minimal						1
total observations per lesion						1
HYPERTROPHY, TUBULAR.						
minimal					9	10
total observations per lesion					9	10
HYDRONEPHROSIS, UNILATERAL.						
minimal						1
total observations per lesion						1
CYST.						
minimal					1	
total observations per lesion					1	
URINARY BLADDER		(10)		(1)		(10)
NO ABNORMALITY DETECTED		10		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 42 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
RESPIRATORY SYSTEM						
LUNGS		(10)				(10)
NO ABNORMALITY DETECTED		9				9
INFLAMMATION, SUBACUTE/CHRONIC.						
minimal		1				1
total observations per lesion		1				1
TRACHEA		(10)				(10)
NO ABNORMALITY DETECTED		10				10
PHARYNX/LARYNX		(10)				(10)
NO ABNORMALITY DETECTED		10				10
NOSE		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	5
DEGENERATION, AMELOBLASTS.						
minimal						2
mild						3
total observations per lesion						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 42 (CONTINUED)

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

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
CARDIOVASCULAR SYSTEM						
HEART		(10)				(10)
NO ABNORMALITY DETECTED		5				5
CARDIOMYOPATHY, minimal		5				5
total observations per lesion		5				5
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 42 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
SPLEEN		(10)				(10)
NO ABNORMALITY DETECTED		10				10
THYMUS		(10)				(10)
NO ABNORMALITY DETECTED		10				10
MANDIBULAR LYMPH NODE		(10)				(10)
NO ABNORMALITY DETECTED		10				10
MESENTERIC LYMPH NODE		(10)				(9)
NO ABNORMALITY DETECTED		10				9
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 42 (CONTINUED)
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NON-NEOPLASTIC LESIONS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (NUMERIC)						
	TREATMENT	Males					
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
ENDOCRINE SYSTEM							
PITUITARY GLAND		(9)				(10)	
NO ABNORMALITY DETECTED		8				10	
cyst.		1					
minimal		1					
total observations per lesion		(10)	(10)	(10)	(10)	(10)	
THYROID GLAND							
NO ABNORMALITY DETECTED		7	2	1		2	
ALTERATION, COLLOID.		3	7	9	10	3	
minimal			1			2	
mild						1	
moderate						2	
severe						1	
total observations per lesion		3	8	9	10	8	

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

TABLE 42 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
TREATMENT	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
ENDOCRINE SYSTEM						
PARATHYROID GLANDS	(9)				(9)	
NO ABNORMALITY DETECTED	9				9	
ADRENAL GLANDS	(10)				(10)	
NO ABNORMALITY DETECTED	10				10	

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

TABLE 42 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
NERVOUS SYSTEM						
BRAIN		(10)				(10)
NO ABNORMALITY DETECTED		10				10
SPINAL CORD		(10)				(10)
NO ABNORMALITY DETECTED		10				10
SCIATIC NERVE		(10)				(10)
NO ABNORMALITY DETECTED		10				10

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

TABLE 42 (CONTINUED)

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

TREATMENT	LESION INCIDENCE (NUMERIC)					
	Males					
	0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX	
MUSCULAR AND SKELETAL SYSTEM						
SKELETAL MUSCLE	(10)				(10)	
NO ABNORMALITY DETECTED	10				10	
FEMUR/KNEE JOINT	(10)				(10)	
NO ABNORMALITY DETECTED	10				10	
STERNUM	(10)				(10)	
NO ABNORMALITY DETECTED	10				10	

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

TABLE 42 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
REPRODUCTIVE SYSTEM						
TESTES		(10)		(1)		(10)
NO ABNORMALITY DETECTED		8				9
DILATATION, SEMINIFEROUS TUBULES, UNILATERAL.						
moderate				1		
total observations per lesion				1		
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, UNILATERAL.						
mild				1		
moderate						1
total observations per lesion						1
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, BILATERAL.						
minimal		1				
severe		1				
total observations per lesion		2				

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

TABLE 42 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
REPRODUCTIVE SYSTEM						
EPIDIDYIMIDES		(10)				(10)
NO ABNORMALITY DETECTED		9				9
OLIGOSPERMIA/GERM CELL DEBRIS, UNILATERAL. severe						1
total observations per lesion		1				1
OLIGOSPERMIA/GERM CELL DEBRIS, BILATERAL. severe		1				
total observations per lesion		1				
PROSTATE		(10)				(10)
NO ABNORMALITY DETECTED		7				10
INFLAMMATION, SUBACUTE/CHRONIC. minimal		3				
total observations per lesion		3				
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 42 (CONTINUED)

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

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Males				
		0 mg/kg I	1 mg/kg III	5 mg/kg V	25 mg/kg VII	125 mg/kg IX
CUTANEOUS SYSTEM						
SKIN		(10)	(1)			(10)
NO ABNORMALITY DETECTED		10	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 42 (CONTINUED)

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

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)					
		Males					
		0	1	5	25	125	
		mg/kg I	mg/kg III	mg/kg V	mg/kg VII	mg/kg IX	
SPECIAL SENSES SYSTEM							
EYE(S) WITH OPTIC NERVE		(10)				(10)	
NO ABNORMALITY DETECTED		8				10	
OPTIC NERVE NOT PRESENT.		3				1	
FOLD/ROSETTE, RETINAL.							
minimal		1					
total observations per lesion		1					
ADHESION, RETINAL.							
minimal		1					
total observations per lesion		1					

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

TABLE 42 (CONTINUED)

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

LESIONS	LESION INCIDENCE		
	TREATMENT	Males	
		0 mg/kg I	125 mg/kg IX
DIGESTIVE SYSTEM		(10)	(10)
LIVER			
NECROSIS, FOCAL, minimal		2	6
mild		1	1
total observations per lesion		3	7
INFLAMMATION, SUBACUTE/CHRONIC.			
minimal		8	9
mild		1	
total observations per lesion		9	9
HYPERPLASIA, BILE DUCT.			
minimal		5	6
total observations per lesion		5	6
FATTY CHANGE, MEDIAN CLEFT.			
minimal		2	
total observations per lesion		2	

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

TABLE 42 (CONTINUED)

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

LESIONS	LESION INCIDENCE		
	TREATMENT	Males	
		0 mg/kg I	125 mg/kg IX
URINARY SYSTEM		(10)	(10)
KIDNEYS			
NO ABNORMALITY DETECTED		4	3
CHRONIC PROGRESSIVE NEPHROPATHY.			
minimal		6	5
total observations per lesion		6	5
HYPERPLASIA, TRANSITIONAL CELL.			
minimal			1
total observations per lesion			1
HYDRONEPHROSIS, UNILATERAL.			
minimal			1
total observations per lesion			1
HYDRONEPHROSIS, BILATERAL.			
minimal			1
total observations per lesion			1
CYST.			
minimal			1
total observations per lesion			1

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

TABLE 42 (CONTINUED)

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

RATS DESIGNATED FOR RECOVERY

LESIONS	LESION INCIDENCE		
	TREATMENT	Males	
		0 mg/kg I	125 mg/kg IX
RESPIRATORY SYSTEM			
NOSE		(10)	(10)
NO ABNORMALITY DETECTED		10	7
ODONTODYSPLASIA,			1
moderate			1
total observations per lesion			1
INFLAMMATION, SUBACUTE/CHRONIC,			1
mild			1
total observations per lesion			1
DEGENERATION, AMELOBLASTS,			2
minimal			2
total observations per lesion			2

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

TABLE 42 (CONTINUED)

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

LESIONS	LESION INCIDENCE		
	TREATMENT	Males	
		0 mg/kg I	125 mg/kg IX
LYMPHATIC AND HEMATOPOIETIC SYSTEM			
THYMUS		(10)	(10)
NO ABNORMALITY DETECTED		10	10

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

TABLE 42 (CONTINUED)
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NON-NEOPLASTIC LESIONS
RATS DESIGNATED FOR RECOVERY

LESIONS	LESION INCIDENCE		
	TREATMENT	Males	
		0 mg/kg I	125 mg/kg IX
ENDOCRINE SYSTEM		(10)	(10)
THYROID GLAND		3	6
NO ABNORMALITY DETECTED		5	2
ALTERATION, COLLOID.		1	2
minimal		1	2
mild		7	10
moderate			
total observations per lesion			

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

TABLE 43

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

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)					
		Females					
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X	
DIGESTIVE SYSTEM							
LIVER		(11)				(10)	
NO ABNORMALITY DETECTED		1				1	
INFLAMMATION, SUBACUTE/CHRONIC.		10				6	
minimal		10				6	
total observations per lesion							
HYPERPLASIA, BILE DUCT.		2				3	
minimal		2				3	
total observations per lesion							
FATTY CHANGE, MEDIAN CLEFT.		2				1	
minimal		2				1	
total observations per lesion							
PANCREAS		(11)				(10)	
NO ABNORMALITY DETECTED		11				9	
INFLAMMATION, SUBACUTE/CHRONIC.							
minimal						1	
total observations per lesion						1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
DIGESTIVE SYSTEM						
ESOPHAGUS		(11)				(10)
NO ABNORMALITY DETECTED		10				10
INFLAMMATION, SUBACUTE/CHRONIC.		1				
severe		1				
total observations per lesion		1				
LACERATION.						
STOMACH		(11)				(10)
NO ABNORMALITY DETECTED		11				10
DUODENUM		(11)				(10)
NO ABNORMALITY DETECTED		11				10
JEJUNUM		(11)				(10)
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
DIGESTIVE SYSTEM						
ILEUM		(11)				(10)
NO ABNORMALITY DETECTED		11				10
CECUM		(11)				(10)
NO ABNORMALITY DETECTED		11				10
COLON		(11)				(10)
NO ABNORMALITY DETECTED		11				10
RECTUM		(11)				(10)
NO ABNORMALITY DETECTED		11				10
SALIVARY GLANDS		(11)				(10)
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)					
		Females					
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X	
URINARY SYSTEM							
KIDNEYS							
NO ABNORMALITY DETECTED							
CHRONIC PROGRESSIVE NEPHROPATHY.							
minimal							
total observations per lesion							
INFLAMMATION, SUBACUTE/CHRONIC.							
minimal							
total observations per lesion							
HYDRONEPHROSIS, UNILATERAL.							
minimal							
total observations per lesion							
HYDRONEPHROSIS, BILATERAL.							
minimal							
total observations per lesion							
URINARY BLADDER							
NO ABNORMALITY DETECTED							
INFLAMMATION, SUBACUTE/CHRONIC.							
minimal							
total observations per lesion							

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
		Females				
RESPIRATORY SYSTEM						
LUNGS		(11)				(10)
NO ABNORMALITY DETECTED		11				10
TRACHEA		(11)				(10)
NO ABNORMALITY DETECTED		11				10
PHARYNX/LARYNX		(11)				(10)
NO ABNORMALITY DETECTED		11				10
NOSE		(11)				(10)
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
CARDIOVASCULAR SYSTEM						
HEART		(11)				(10)
NO ABNORMALITY DETECTED		6				8
CARDIOMYOPATHY, minimal		5				2
total observations per lesion		5				2
AORTA		(11)				(10)
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NON-NEOPLASTIC LESIONS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
LYMPHATIC AND HEMATOPOIETIC SYSTEM						
SPLEEN		(11)				(10)
NO ABNORMALITY DETECTED		11				10
THYMUS		(11)				(10)
NO ABNORMALITY DETECTED		11				10
MANDIBULAR LYMPH NODE		(11)				(10)
NO ABNORMALITY DETECTED		11				10
MESENTERIC LYMPH NODE		(11)				(10)
NO ABNORMALITY DETECTED		11				10
BONE MARROW		(11)				(10)
NO ABNORMALITY DETECTED		10				10
HYPERPLASIA, GRANULOCYTIC. mild		1				
total observations per lesion		1				

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
ENDOCRINE SYSTEM		(11)				(10)
PITUITARY GLAND		11				10
NO ABNORMALITY DETECTED		(11)				(10)
THYROID GLAND		11				10
NO ABNORMALITY DETECTED		(9)				(9)
PARATHYROID GLANDS		9				9
NO ABNORMALITY DETECTED		(11)				(10)
ADRENAL GLANDS		11				9
NO ABNORMALITY DETECTED						1
MINERALIZATION, minimal						1
total observations per lesion						

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NON-NEOPLASTIC LESIONS
RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT	Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
NERVOUS SYSTEM		(11)				(10)
BRAIN		11				10
NO ABNORMALITY DETECTED		(11)				(10)
SPINAL CORD		11				10
NO ABNORMALITY DETECTED		(11)				(10)
SCIATIC NERVE		11				10
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)					
		Females					
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X	
MUSCULAR AND SKELETAL SYSTEM							
SKELETAL MUSCLE		(11)				(10)	
NO ABNORMALITY DETECTED		11				9	
INFLAMMATION, SUBACUTE/CHRONIC, minimal						1	
total observations per lesion						1	
FEMUR/KNEE JOINT		(11)				(10)	
NO ABNORMALITY DETECTED		11				10	
STERNUM		(11)				(10)	
NO ABNORMALITY DETECTED		11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

RATS DESIGNATED FOR SUBCHRONIC TOXICITY

LESIONS	LESION INCIDENCE (NUMERIC)					
	Females					
TREATMENT	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X	
REPRODUCTIVE SYSTEM	(11)				(10)	
OVARIES	11				10	
NO ABNORMALITY DETECTED	(11)				(10)	
UTERUS	11				10	
NO ABNORMALITY DETECTED	(11)				(8)	
MAMMARY GLAND (FEMALE)	11				8	
NO ABNORMALITY DETECTED	11					

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

TREATMENT	LESION INCIDENCE (NUMERIC)				
	Females				
	0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
LESIONS					
CUTANEOUS SYSTEM					
SKIN	(11)				(10)
NO ABNORMALITY DETECTED	11				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
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC)				
		Females				
		0 mg/kg II	1 mg/kg IV	5 mg/kg VI	25 mg/kg VIII	125 mg/kg X
SPECIAL SENSES SYSTEM						
EYE(S) WITH OPTIC NERVE		(11)				(10)
NO ABNORMALITY DETECTED		11				9
OPTIC NERVE NOT PRESENT.						1
FOLD/ROSETTE, RETINAL.						1
minimal						1
total observations per lesion						

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=11 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

RATS DESIGNATED FOR RECOVERY

LESIONS	LESION INCIDENCE		
	TREATMENT	0 mg/kg II	125 mg/kg X
		Females	
DIGESTIVE SYSTEM		(9)	(10)
LIVER		3	2
NO ABNORMALITY DETECTED		1	
NECROSIS, FOCAL, minimal		1	
total observations per lesion			
INFLAMMATION, SUBACUTE/CHRONIC, minimal		3	6
total observations per lesion		3	6
HYPERPLASIA, BILE DUCT, minimal		1	1
total observations per lesion		1	1
FATTY CHANGE, MEDIAN CLEFT, minimal		1	1
mild		2	
total observations per lesion			
ANGIECTASIS, minimal		1	1
total observations per lesion		2	2

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=9 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

LESIONS	LESION INCIDENCE		
	TREATMENT	Females	
		0 mg/kg II	125 mg/kg X
URINARY SYSTEM		(9)	(10)
KIDNEYS		4	2
NO ABNORMALITY DETECTED		5	5
CHRONIC PROGRESSIVE NEPHROPATHY.		5	3
minimal			8
mild			1
total observations per lesion			1
HYDRONEPHROSIS, BILATERAL.			
minimal			
total observations per lesion			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=9 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)

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

LESIONS	LESION INCIDENCE		
	TREATMENT	Females	
		0 mg/kg II	125 mg/kg X
ENDOCRINE SYSTEM			(1)
PITUITARY GLAND			1
NO ABNORMALITY DETECTED			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=9 IN GROUP II DUE TO EARLY DEATH

TABLE 43 (CONTINUED)
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS
NON-NEOPLASTIC LESIONS
RATS DESIGNATED FOR RECOVERY

LESIONS	LESION INCIDENCE		
	TREATMENT	Females	
		0 mg/kg II	125 mg/kg X
REPRODUCTIVE SYSTEM			
UTERUS			(1)
DILATATION. mild total observations per lesion			1 1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
N=9 IN GROUP II DUE TO EARLY DEATH

FIGURES

FIGURES

EXPLANATORY NOTES

Critical Dates

- Day 91 • Last day of test substance administration for rats designated for satellite bleeds and 3-month recovery.
- Last day of non-fasted body weight and food consumption data collection for rats designated for the 90-day exposure period.
 - Last day of food consumption data collection for rats designated for satellite bleeds in the 1, 5, and 25 mg/kg/day dose groups.
- Day 92 Last day of test substance administration for male rats designated for the 90-day exposure period.
- Day 93 • Last day of test substance administration for female rats designated for the 90-day exposure period.
- Male rats designated for the 90-day exposure period were sacrificed.
- Day 94 Female rats designated for 90-day exposure period were sacrificed.
- Day 175 Rats designated for satellite bleeds were sacrificed
- Day 182 Last day of non-fasted body weight and food consumption data collection for rats designated for the 3-month recovery period.
- Day 183 Male and female rats designated for the 3-month recovery period were sacrificed.

FIGURE 1

MEAN BODY WEIGHTS OF MALE RATS

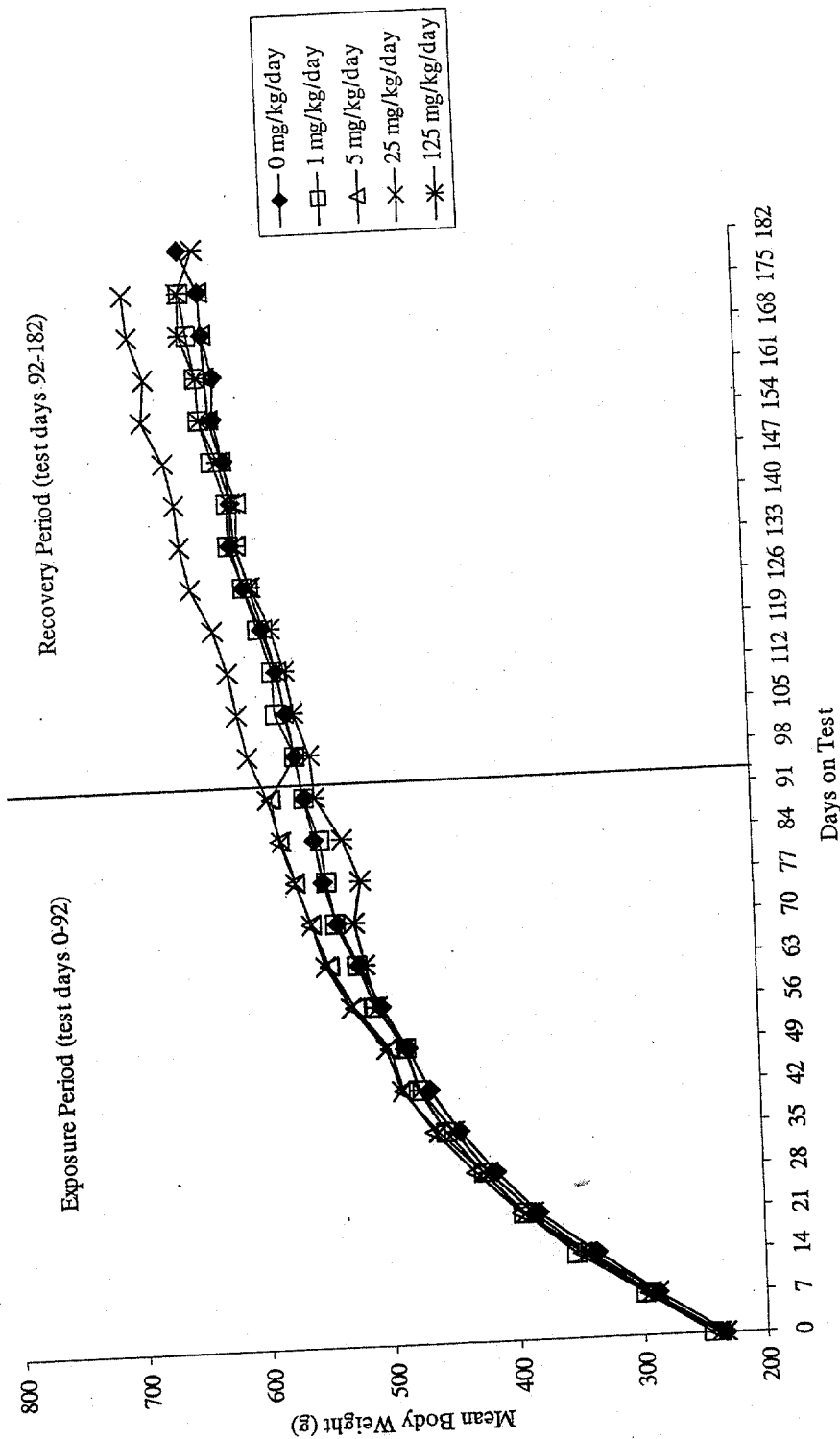


FIGURE 2
MEAN BODY WEIGHTS OF FEMALE RATS

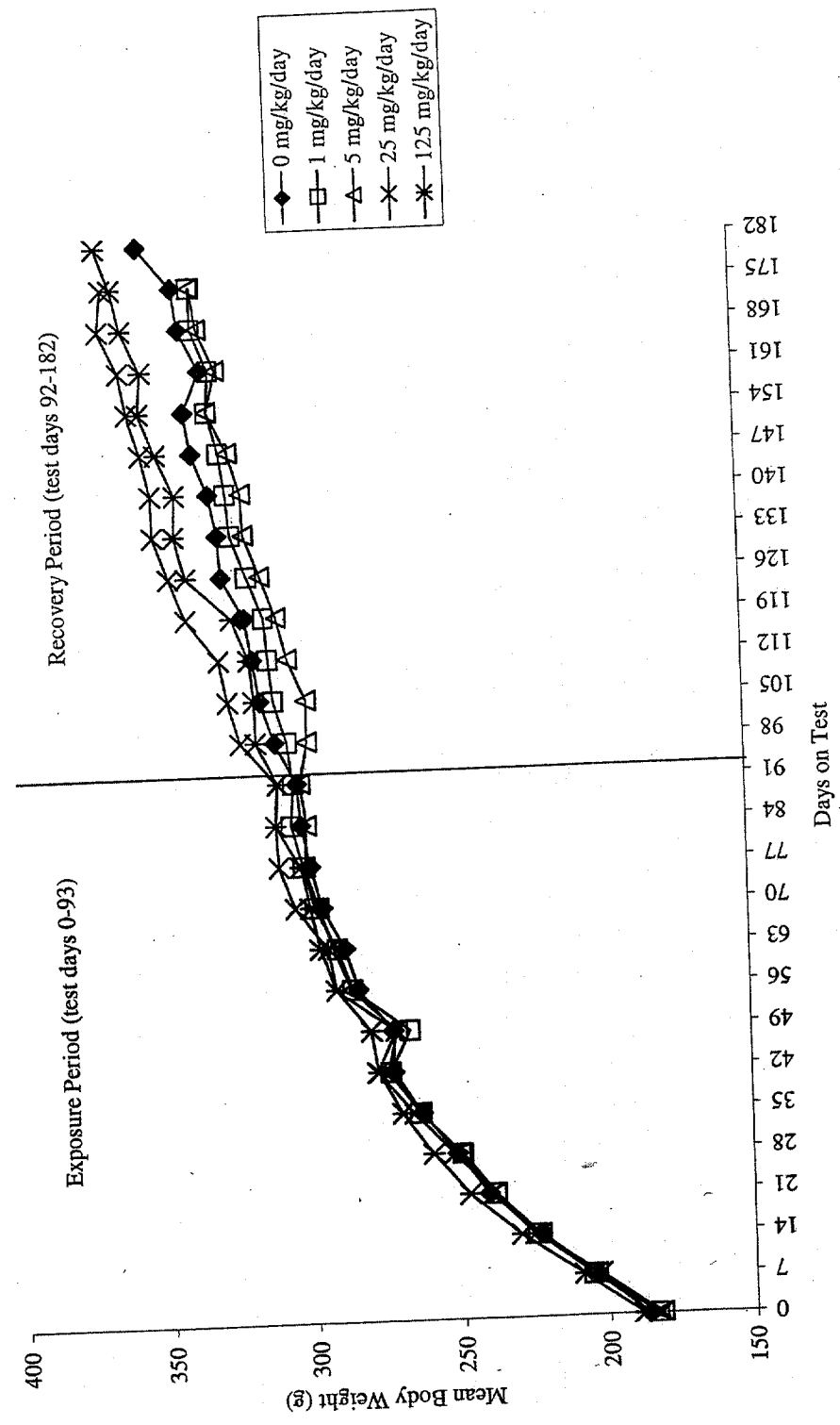
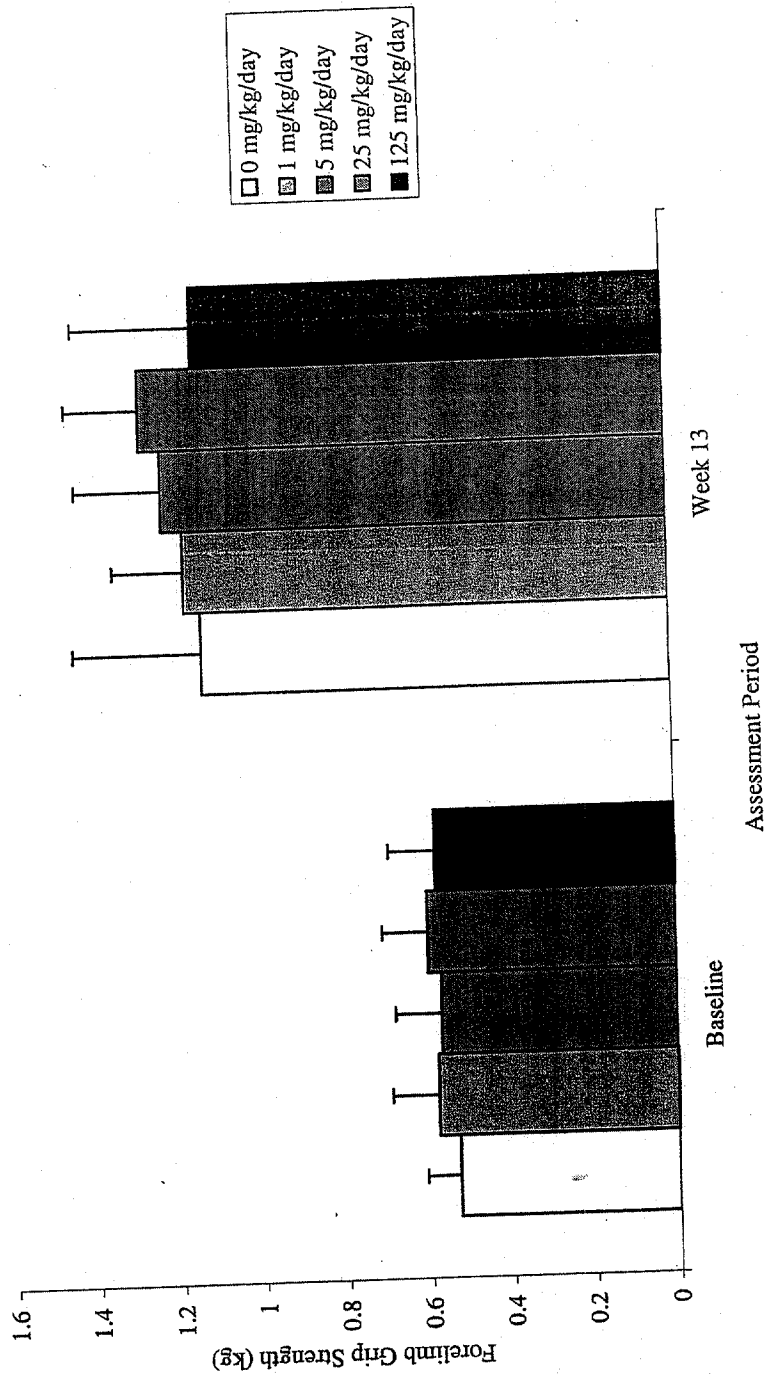


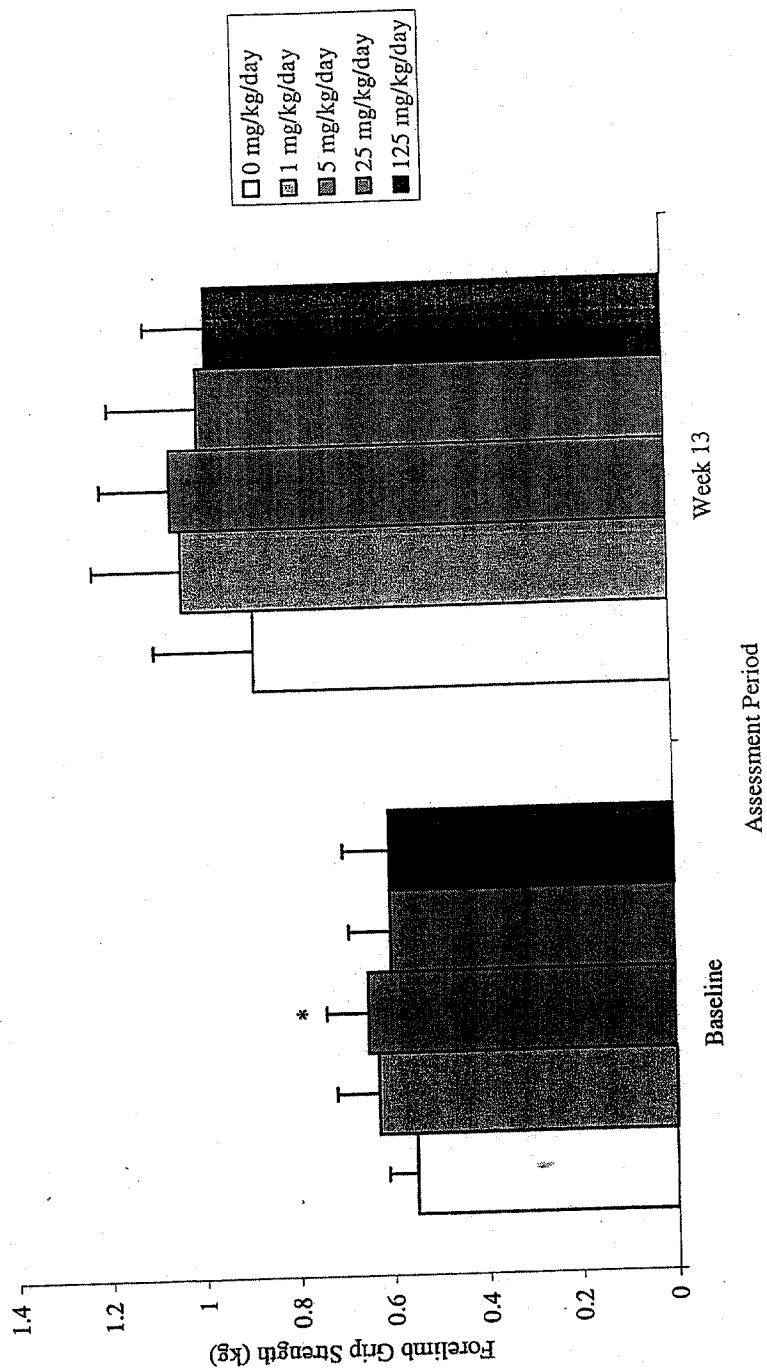
FIGURE 3
MEAN FORELIMB GRIP STRENGTH FOR MALE RATS



Error bars represent standard deviation

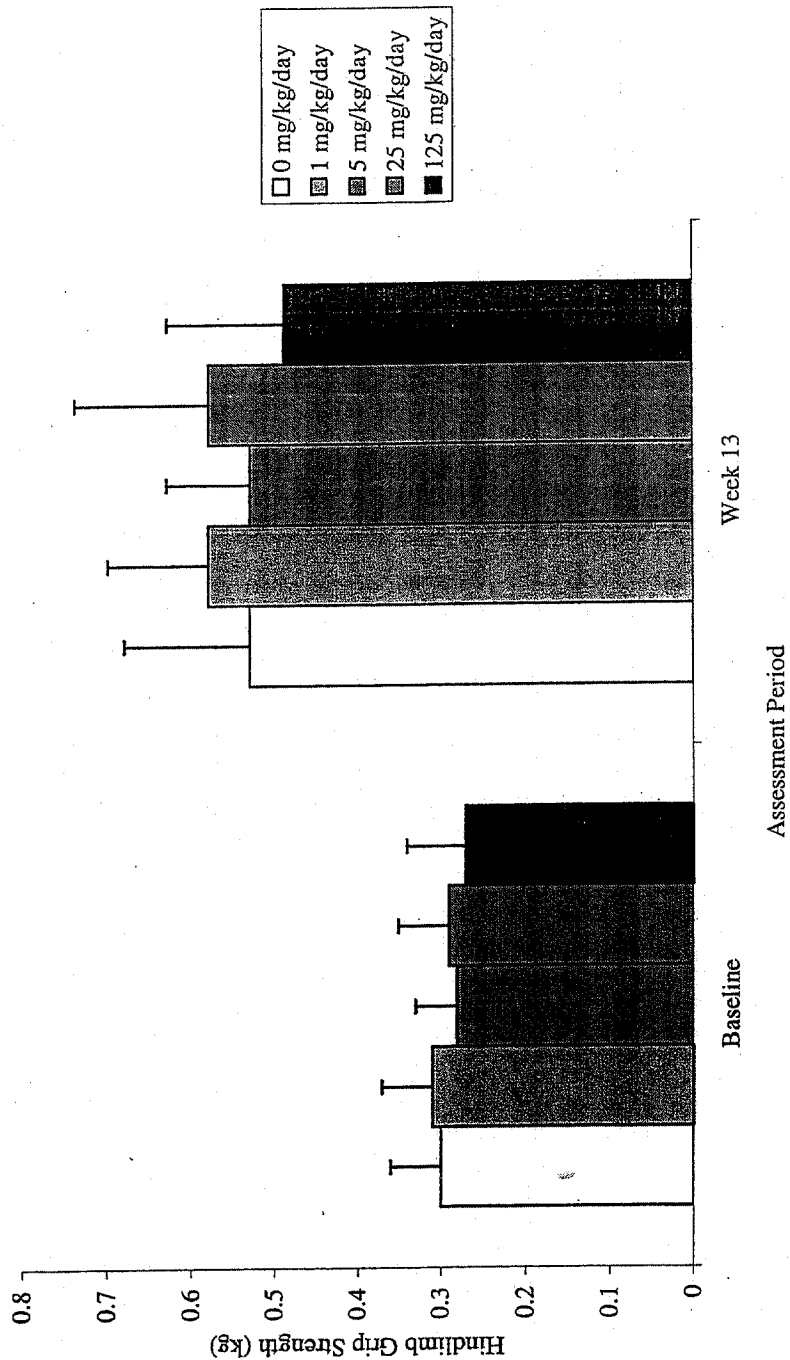
FIGURE 4

MEAN FORELIMB GRIP STRENGTH FOR FEMALE RATS



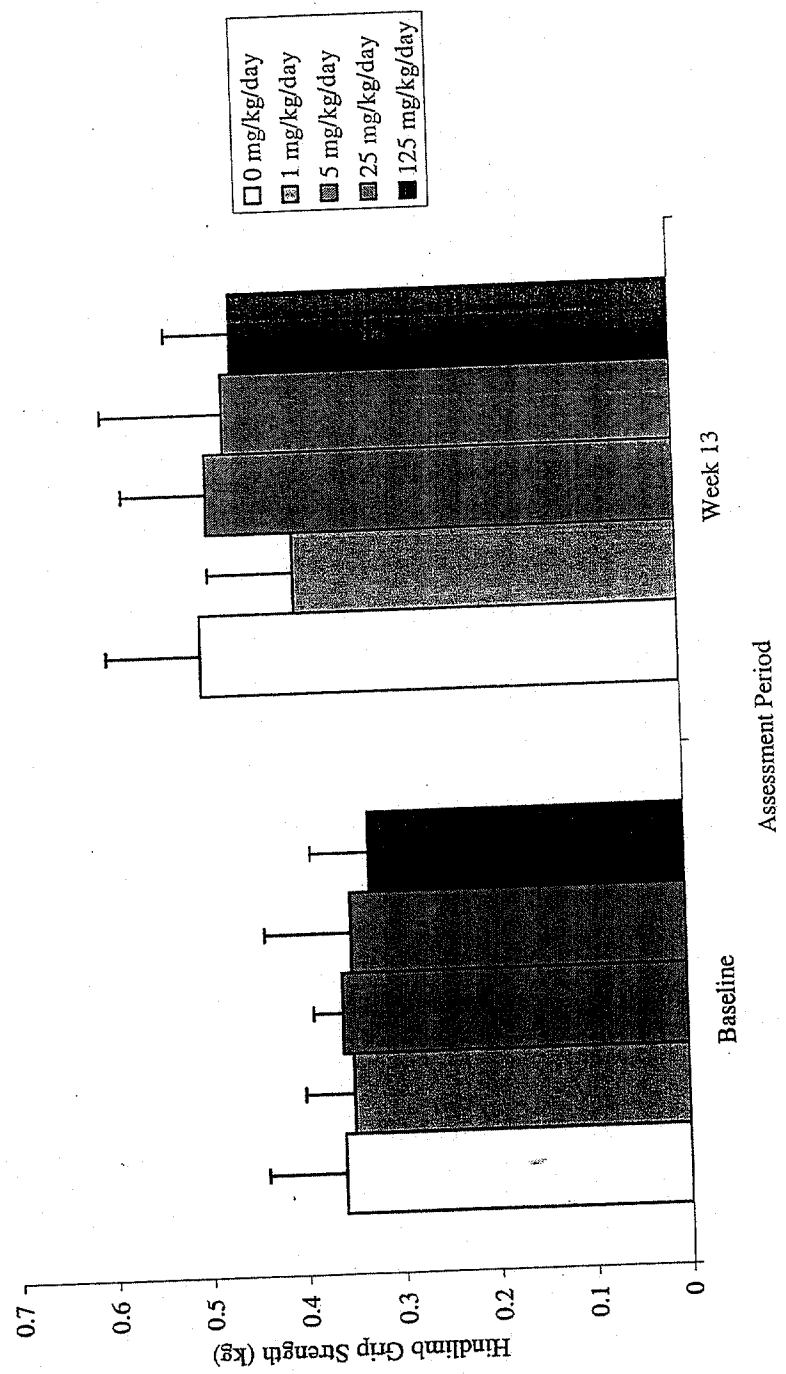
Error bars represent standard deviation
* Statistically significant difference from control at $p < 0.05$.

FIGURE 5
MEAN HINDLIMB GRIP STRENGTH FOR MALE RATS



Error bars represent standard deviation

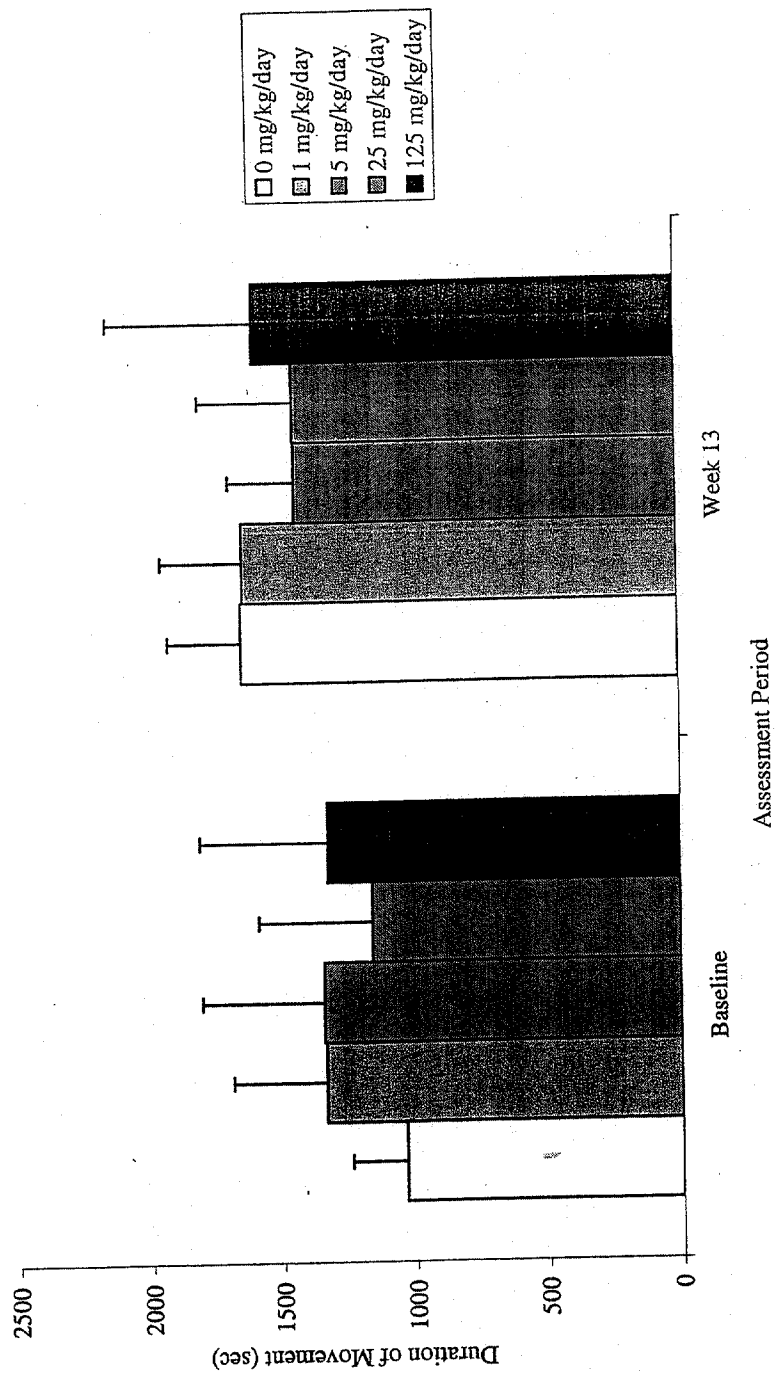
FIGURE 6
MEAN HINDLIMB GRIP STRENGTH FOR FEMALE RATS



Error bars represent standard deviation

FIGURE 7

MEAN TOTAL DURATION OF MOVEMENT FOR MALE RATS



Error bars represent standard deviation

FIGURE 8
MEAN TOTAL DURATION OF MOVEMENT FOR FEMALE RATS

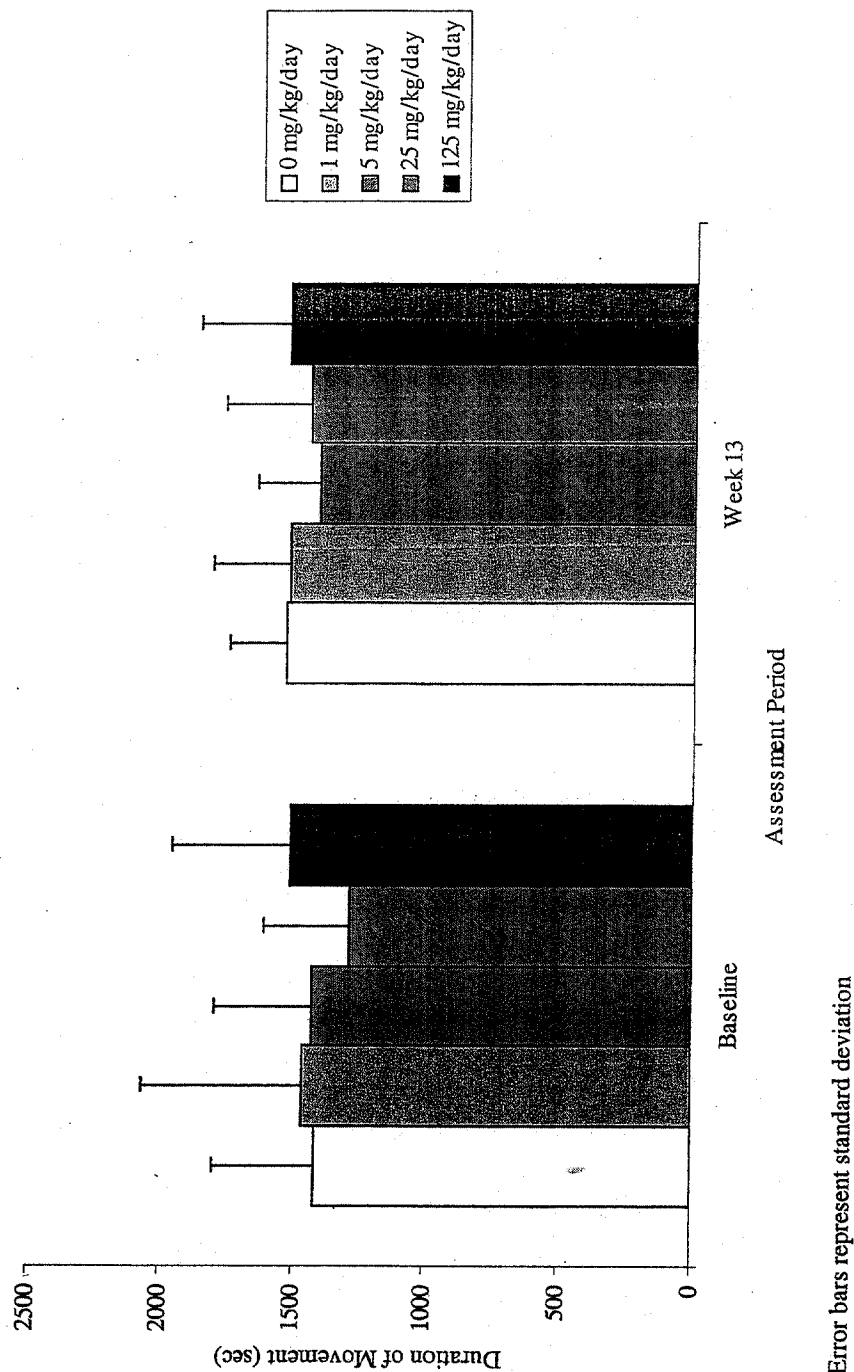
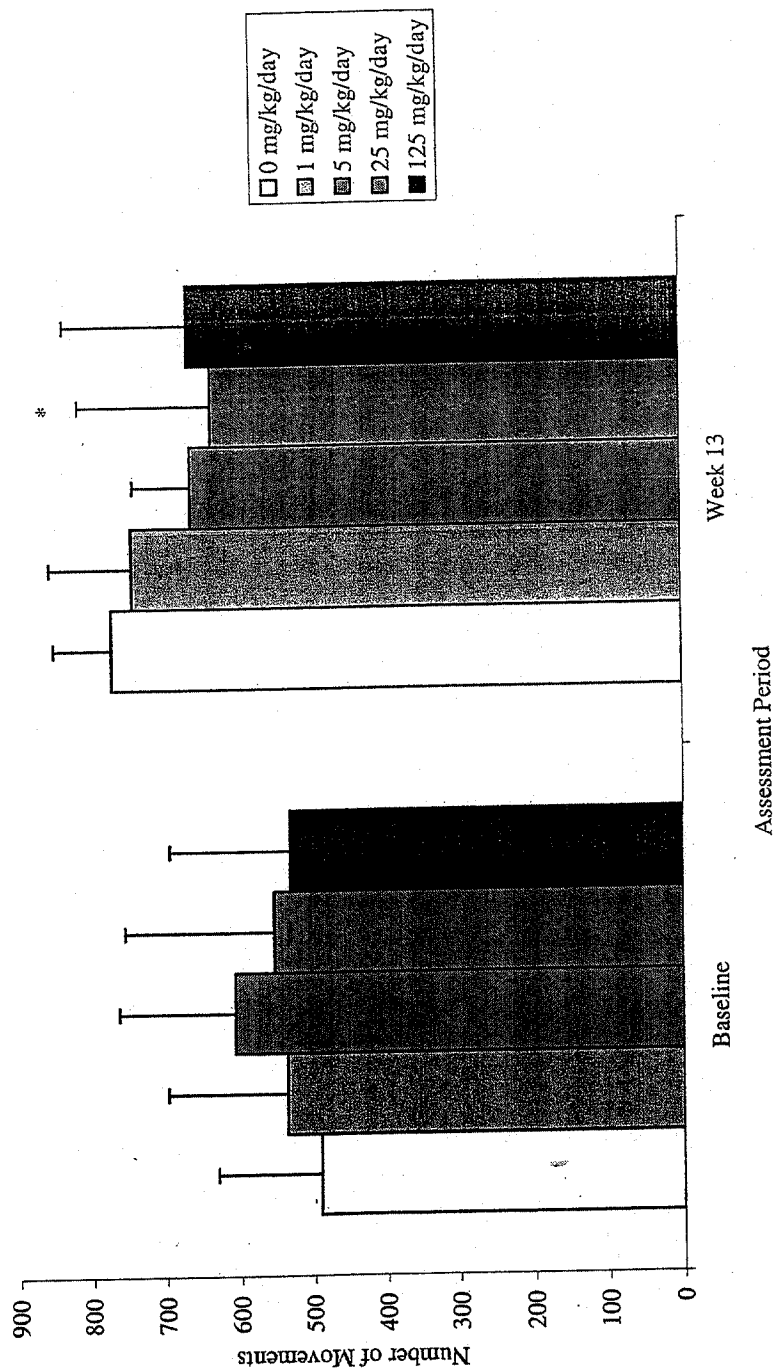
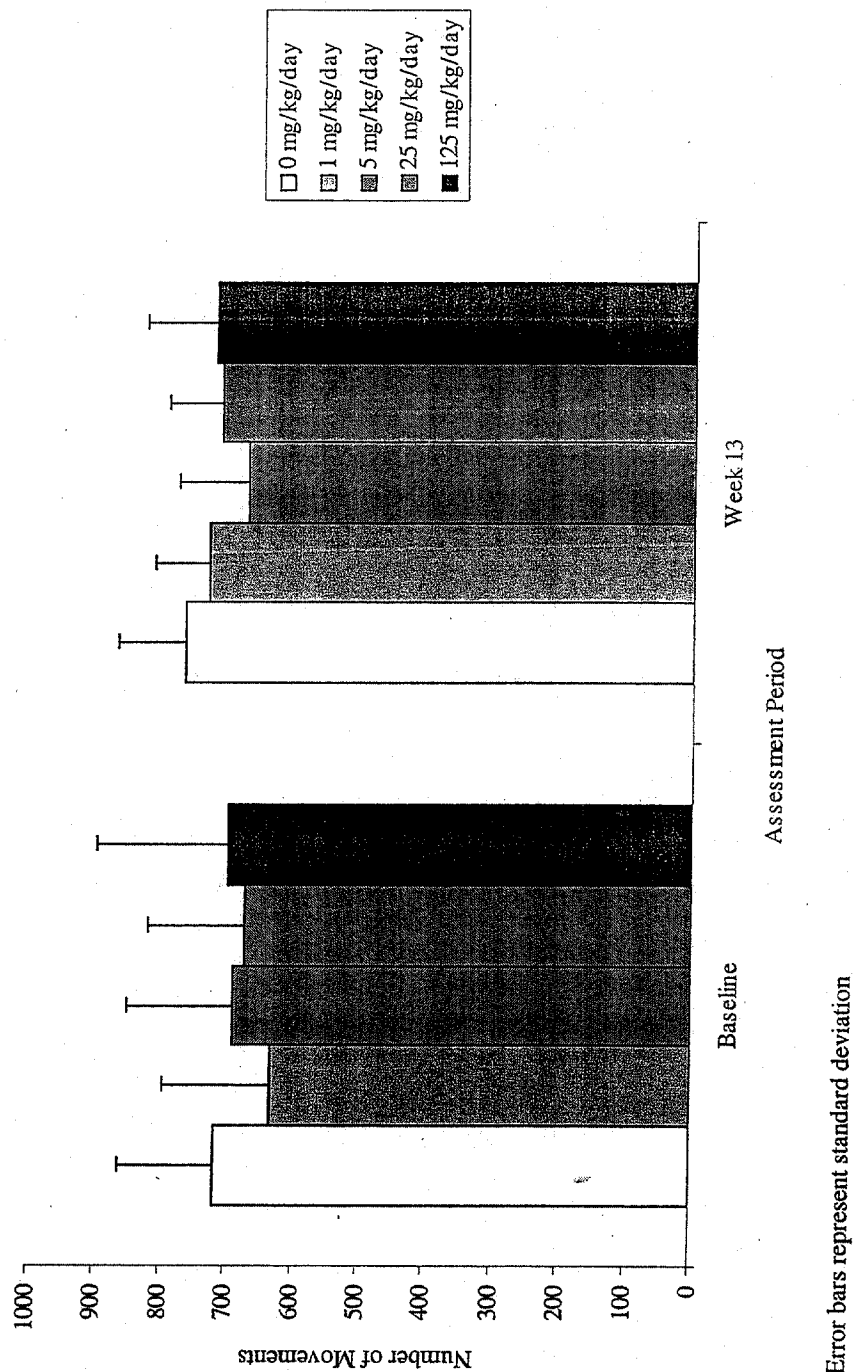


FIGURE 9
MEAN TOTAL NUMBER OF MOVEMENTS FOR MALE RATS



Error bars represent standard deviation.
* Statistically significant difference from control at p<0.05.

FIGURE 10
MEAN TOTAL NUMBER OF MOVEMENTS FOR FEMALE RATS



APPENDICES

APPENDICES

EXPLANATORY NOTES

Critical Dates

- Day 91 • Last day of test substance administration for rats designated for satellite bleeds and 3-month recovery.
 - Last day of non-fasted body weight and food consumption data collection for rats designated for the 90-day exposure period.
 - Last day of food consumption data collection for rats designated for satellite bleeds in the 1, 5, and 25 mg/kg/day dose groups.
- Day 92 Last day of test substance administration for male rats designated for the 90-day exposure period.
- Day 93 • Last day of test substance administration for female rats designated for the 90-day exposure period.
 - Male rats designated for the 90-day exposure period were sacrificed.
- Day 94 Female rats designated for 90-day exposure period were sacrificed.
- Day 175 Rats designated for satellite bleeds were sacrificed
- Day 182 Last day of non-fasted body weight and food consumption data collection for rats designated for the 3-month recovery period.
- Day 183 Male and female rats designated for the 3-month recovery period were sacrificed.

Note

mg/kg = mg/kg/day

APPENDIX A
ANALYTICAL DATA

Table I. Homogeneity and Stability of [REDACTED] in Dosing Suspensions

Sample Type	mg/ml [REDACTED]	Percent Nominal
	Nominal	Measured
Test Day 1/-6		
<u>Homogeneity</u>		
CONTROL	0.00	ND(A)
TOP	0.20	0.163
MIDDLE	0.20	0.164
BOTTOM	0.20	0.161
		Mean(B): 0.163±0.002 C.V. 1%
TOP	1.0	0.803
MIDDLE	1.0	0.857
BOTTOM	1.0	0.890
		Mean(B): 0.850±0.04 C.V. 5%
TOP	5.0	4.55
MIDDLE	5.0	4.80
BOTTOM	5.0	4.61
		Mean(B): 4.65±0.13 C.V. 3%
TOP	25.0	19.9(C)
MIDDLE	25.0	21.9
BOTTOM	25.0	22.9
		Mean(B): 21.6±1.5 C.V. 7%
<u>Stability</u>		
5 HOUR(D)	0.20	0.167
	1.0	0.818
	5.0	4.14
	25.0	21.8
7-DAY REFRIGERATED	0.2	0.161
	0.2	0.173
		Mean(E): 0.167±0.01 C.V. 5%
5 HOUR(D)	0.2	0.158(C)

(A) Denotes not detected.

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

(C) Duplicate reanalysis of original sample support original analysis and are not reported.

(D) Stability samples held 5 hours a room temperature.

(E) The average measured concentration, average percent of nominal (in parentheses), standard deviation, and coefficient of variation of duplicate samples.

Table I. Homogeneity and Stability of [REDACTED] in Dosing Suspensions (continued)

Sample Type	mg/mL Nominal	Measured	Percent Nominal
Test Day 4(F)			
<u>Homogeneity</u>			
CONTROL	0.00	ND(A)	----
TOP	1.0	0.944	94.4
MIDDLE	1.0	0.884	88.4
BOTTOM	1.0	0.836 (C)	83.6
		Mean(B): 0.888±0.05	(88.8%)
		C.V. 6%	
TOP	5.0	4.43	88.6
MIDDLE	5.0	4.37	87.4
BOTTOM	5.0	4.72 (C)	94.4
		Mean(B): 4.51±0.19	(90.2%)
		C.V. 4%	
TOP	25.0	22.2	88.8
MIDDLE	25.0	22.7	90.8
BOTTOM	25.0	24.2	96.8
		Mean(B): 23.0±1.0	(92.0%)
		C.V. 5%	
<u>Stability</u>			
5 HOUR(D)			
	1.0	0.854(G)	85.4
	5.0	4.75	95.0
	25.0	24.0	96.0
7-DAY REFRIGERATED			
TOP	1.0	0.900	90.0
MIDDLE	1.0	0.864	86.4
BOTTOM	1.0	0.859	85.9
		Mean(B): 0.874±0.02	(87.4%)
		C.V. 3%	
#1	5.0	4.46	89.2
#2	5.0	4.44	88.8
		Mean(E): 4.45±0.01	(89.0%)
		C.V. 0.2%	
#1	25.0	24.2	96.8
#2	25.0	23.9	95.6
		Mean(E): 24.1±0.21	(96.4%)
		C.V. 1%	
5 HOUR(D)			
	1.0	0.904(H)	90.4
	5.0	4.21(H)	84.2
	25.0	21.2(H)	84.8

- (A) Denotes not detected.
 (B) The average measured concentration, average percent of nominal (in parentheses), standard deviation, and coefficient of variation of top, middle, and bottom.
 (C) Duplicate reanalysis of original sample support original analysis and are not reported..
 (D) Stability samples held 5 hours a room temperature.
 (E) The average measured concentration, average percent of nominal (in parentheses), standard deviation, and coefficient of variation for duplicate samples.
 (F) Samples analyzed in a previous study [REDACTED]
 (G) Mean result of all reported analyses except for one duplicate repeat sample. Aliquot error caused result to be low.
 (H) Mean result of duplicate re-sampling from the original diluted sample. Original result was lower than expected due to aliquot error.

Table II. Concentration Verification of [REDACTED] in Dosing Solutions

Preparation Day	mg/ml [REDACTED]		Percent
Sample Type	Nominal	Measured	Nominal
Test Day 42			
<u>Concentration Verification</u> ^(A)			
Control	0.0	ND ^(B)	---
	0.2-1(O)	0.153	76.5
	0.2-1(1)	0.158	79.0
	0.2-1(2)	<u>0.158</u>	79.0
	<i>mean</i> ^(C) :	0.156	78.0
	0.2-2(O)	0.167	83.5
	0.2-2(1)	0.170	85.0
	0.2-2(2)	<u>0.169</u>	84.5
	<i>mean</i> ^(C) :	0.169	84.5
	<i>Mean</i> ^(D) :	0.163 ± 0.01	(81.5)
		C.V. 6%	
	1.0-1(O)	0.718	71.8
	1.0-1(1)	0.757	75.7
	1.0-1(2)	<u>0.773</u>	77.3
	<i>mean</i> ^(C) :	0.749	74.9
	1.0-2(O)	0.764	76.4
	1.0-2(1)	0.779	77.9
	1.0-2(2)	<u>0.784</u>	78.4
	<i>mean</i> ^(C) :	0.776	77.6
	<i>Mean</i> ^(D) :	0.763 ± 0.02	(76.3)
		C.V. 3%	
	5.0-1(O)	3.89	77.8
	5.0-1(1)	3.82	76.4
	5.0-1(2)	<u>3.89</u>	77.8
	<i>mean</i> ^(C) :	3.87	77.3
	5.0-2(1)	3.89	77.8
	5.0-2(2)	<u>3.93</u>	78.6
	<i>mean</i> ^(E) :	3.91	78.2
	<i>Mean</i> ^(D) :	3.89 ± 0.03	(77.8)
		C.V. 1%	
	25.0-1(1)	19.4	77.6
	25.0-1(2)	<u>19.4</u>	77.6
	<i>mean</i> ^(E) :	19.4	77.6
	25.0-2(1)	19.3	77.2
	25.0-2(2)	<u>18.8</u>	75.2
	<i>mean</i> ^(E) :	19.1	76.2
	<i>Mean</i> ^(D) :	19.3 ± 0.21	(77.2)
		C.V. 1%	

(A) Duplicate samples (-1, -2) per level were analyzed. Mean, S.D. and C.V. calculated to verify uniformity of mixture.

(B) Denotes not detected.

(C) Mean result of the original analysis [(O)], and duplicate reanalysis of the original sample [(1), (2)].

(D) The average measured concentration, average percent of nominal (in parentheses), standard deviation, and coefficient of variation for duplicate samples

(E) Mean result of duplicate reanalysis on the original submitted sample [(1), (2)]. Original analysis not reported due to aliquot error.

Table II. Concentration Verification of [REDACTED] in Dosing Solutions (continued)

Preparation Day	mg/mL		Percent
Sample Type	Nominal	Measured	Nominal
Test Day 45			
Concentration Verification ^(A)			
Control	0.0	ND ^(B)	----
	0.2-1(O)	0.065	32.5
	0.2-1(1)	0.067	33.5
	0.2-1(2)	<u>0.065</u>	32.5
	mean ^(C) :	0.066	33.0
	0.2-2(O)	0.081	40.5
	0.2-2(1)	0.083	41.5
	0.2-2(2)	<u>0.084</u>	42.0
	mean ^(C) :	0.083	41.5
	Mean ^(D) :	0.075 ± 0.01	(37.5)
		C.V. 13%	
	1.0-1(O)	0.662	66.2
	1.0-1(1)	0.678	67.8
	1.0-1(2)	<u>0.687</u>	68.7
	mean ^(C) :	0.676	67.6
	1.0-2(O)	0.646	64.6
	1.0-2(1)	0.657	65.7
	1.0-2(2)	<u>0.665</u>	66.5
	mean ^(C) :	0.656	65.6
	Mean ^(D) :	0.666 ± 0.01	(66.6)
		C.V. 2%	
	5.0-1(O)	2.13	42.6
	5.0-1(1)	2.27	45.4
	5.0-1(2)	<u>2.21</u>	44.2
	mean ^(C) :	2.20	44.0
	5.0-2(O)	2.26	45.2
	5.0-2(1)	2.36	47.2
	5.0-2(2)	<u>2.33</u>	46.6
	mean ^(C) :	2.32	46.4
	Mean ^(D) :	2.26 ± 0.09	(45.2)
		C.V. 4%	
	25.0-1(1)	8.31	33.2
	25.0-1(2)	<u>8.36</u>	33.4
	mean ^(E) :	8.34	33.4
	25.0-2(1)	8.76	35.0
	25.0-2(2)	<u>8.52</u>	34.1
	mean ^(E) :	8.64	34.6
	Mean ^(D) :	8.49 ± 0.21	(34.0)
		C.V. 3%	

(A) Duplicate samples (-1, -2) per level were analyzed. Mean, S.D. and C.V. calculated to verify uniformity of mixture.

(B) Denotes not detected.

(C) Mean result of the original analysis [(O)], and duplicate reanalysis of the original sample [(1), (2)].

(D) The average measured concentration, average percent of nominal (in parentheses), standard deviation, and coefficient of variation for duplicate samples.

(E) Mean result of duplicate reanalysis on the original submitted sample [(1), (2)]. Original analysis not reported due to aliquot error.

Table II. Concentration Verification of [REDACTED] in Dosing Solutions (continued)

Preparation Day	mg/ml		Percent
Sample Type	Nominal	Measured	Nominal
Test Day 48 ^(F)			
<u>Concentration Verification</u> ^(A)			
Control	0.0	ND ^(B)	----
	0.2-1	0.197	98.5
	0.2-2	<u>0.219</u>	109.5
	<i>Mean</i> ^(D) :	<i>0.208 ± 0.02</i>	<i>(104.0)</i>
		<i>C.V. 7%</i>	
	1.0-1	0.865	86.5
	1.0-2	<u>0.948</u>	94.8
	<i>Mean</i> ^(D) :	<i>0.907 ± 0.06</i>	<i>(90.7)</i>
		<i>C.V. 6%</i>	
	5.0-1	3.93	78.6
	5.0-2	<u>3.90</u>	78.0
	<i>Mean</i> ^(D) :	<i>3.92 ± 0.02</i>	<i>(78.3)</i>
		<i>C.V. 1%</i>	
	25.0-1	21.9	87.6
	25.0-2	<u>22.5</u>	90.0
	<i>Mean</i> ^(D) :	<i>22.2 ± 0.42</i>	<i>(88.8)</i>
		<i>C.V. 2%</i>	
Test Day 52			
<u>Concentration Verification</u> ^(A)			
Control	0.0	ND ^(B)	----
	0.2-1	0.174	87.0
	0.2-2	<u>0.184</u>	92.0
	<i>Mean</i> ^(D) :	<i>0.179 ± 0.01</i>	<i>(89.5)</i>
		<i>C.V. 4%</i>	
	1.0-1	0.845	84.5
	1.0-2	<u>0.895</u>	89.5
	<i>Mean</i> ^(D) :	<i>0.870 ± 0.04</i>	<i>(87.0)</i>
		<i>C.V. 4%</i>	
	5.0-1	4.22	84.4
	5.0-2	<u>4.16</u>	83.2
	<i>Mean</i> ^(D) :	<i>4.19 ± 0.04</i>	<i>(83.8)</i>
		<i>C.V. 1%</i>	
	25.0-1	23.5	94.0
	25.0-2	<u>22.3</u>	89.2
	<i>Mean</i> ^(D) :	<i>22.9 ± 0.85</i>	<i>(91.6)</i>
		<i>C.V. 4%</i>	

(A) Duplicate samples (-1, -2) per level were analyzed. Mean, S.D. and C.V. calculated to verify uniformity of mixture.

(B) Denotes not detected.

(D) The average measured concentration, average percent of nominal (in parentheses), standard deviation, and coefficient of variation for duplicate samples.

(F) Suspension not dosed to animals.

Table II. Concentration Verification of [REDACTED] in Dosing Solutions (continued)

Preparation Day	mg/mL		Percent
Sample Type	Nominal	Measured	Nominal
Test Day 56			
<u>Concentration Verification</u> ^(A)			
Control	0.0	ND(B)	----
	0.2-1	0.167	83.5
	0.2-2	<u>0.189</u>	94.5
	<i>Mean</i> ^(D) :	<i>0.178 ± 0.02</i>	<i>(89.0)</i>
		<i>C.V. 9%</i>	
	1.0-1	0.964	96.4
	1.0-2	<u>0.950</u>	95.0
	<i>Mean</i> ^(D) :	<i>0.957 ± 0.01</i>	<i>(95.7)</i>
		<i>C.V. 1%</i>	
	5.0-1	4.41	88.2
	5.0-2	<u>4.31</u>	86.2
	<i>Mean</i> ^(D) :	<i>4.36 ± 0.07</i>	<i>(87.2)</i>
		<i>C.V. 2%</i>	
	25.0-1	22.8	91.2
	25.0-2	<u>21.4</u>	85.6
	<i>Mean</i> ^(D) :	<i>22.1 ± 0.99</i>	<i>(88.4)</i>
		<i>C.V. 4%</i>	
Test Day 58			
<u>Concentration Verification</u> ^(A)			
Control	0.0	ND(B)	----
	0.2-1	0.174	87.0
	0.2-2	<u>0.150</u>	75.0
	<i>Mean</i> ^(D) :	<i>0.162 ± 0.02</i>	<i>(81.0)</i>
		<i>C.V. 10%</i>	
	1.0-1	0.945	94.5
	1.0-2	<u>0.937</u>	93.7
	<i>Mean</i> ^(D) :	<i>0.941 ± 0.01</i>	<i>(94.1)</i>
		<i>C.V. 1%</i>	
	5.0-1	4.48	89.6
	5.0-2	<u>4.17</u>	83.4
	<i>Mean</i> ^(D) :	<i>4.33 ± 0.22</i>	<i>(86.5)</i>
		<i>C.V. 5%</i>	
	25.0-1	22.5	90.0
	25.0-2	<u>22.1</u>	88.4
	<i>Mean</i> ^(D) :	<i>22.3 ± 0.28</i>	<i>(89.2)</i>
		<i>C.V. 1%</i>	

(A) Duplicate samples (-1, -2) per level were analyzed. Mean, S.D. and C.V. calculated to verify uniformity of mixture.

(B) Denotes not detected.

(D) The average measured concentration, average percent of nominal (in parentheses), standard deviation, and coefficient of variation for duplicate samples.

Table II. Concentration Verification of [REDACTED] in Dosing Solutions (continued)

Preparation Day	mg/ml [REDACTED]	Percent
Sample Type	Nominal	Nominal
Test Day 65		
Concentration Verification ^(A)		
Control	0.0	ND ^(B)

	0.2-1(O)	0.158
	0.2-1(1)	0.158
	0.2-1(2)	0.162
	mean ^(C) :	0.159
	0.2-2(O)	0.148
	0.2-2(1)	0.149
	0.2-2(2)	0.153
	mean ^(C) :	0.150
	Mean ^(D) :	0.155 ± 0.01
		C.V. 4%
	1.0-1	0.832
	1.0-2	0.898
	Mean ^(D) :	0.865 ± 0.05
		C.V. 5%
	5.0-1	4.32
	5.0-2	4.40
	Mean ^(D) :	4.36 ± 0.06
		C.V. 1%
	25.0-1	20.8
	25.0-2	20.5
	Mean ^(D) :	20.7 ± 0.21
		C.V. 1%

(A) Duplicate samples (-1, -2) per level were analyzed. Mean, S.D. and C.V. calculated to verify uniformity of mixture.

(B) Denotes not detected.

(C) Mean result of the original analysis [(O)], and duplicate reanalysis of the original sample [(1), (2)].

(D) The average measured concentration, average percent of nominal (in parentheses), standard deviation, and coefficient of variation for duplicate samples.

Table II. Concentration Verification of [REDACTED] in Dosing Solutions (continued)

Preparation Day	mg/mL		Percent
Sample Type	Nominal	Measured	Nominal
Test Day 91			
Concentration Verification ^(A)			
Control	0.0	ND ^(B)	---
	0.2-1	0.162	81.0
	0.2-2	<u>0.165</u>	82.5
	Mean ^(D) :	0.164 ± 0.002	(82.0)
		C.V. 1%	
	1.0-1(O)	0.781	78.1
	1.0-1(1)	0.744	74.4
	1.0-1(2)	<u>0.754</u>	75.4
	mean ^(C) :	0.760	76.0
	1.0-2	<u>0.863</u>	86.3
	Mean ^(D) :	0.812 ± 0.07	(81.2)
		C.V. 9%	
	5.0-1(O)	3.90	78.0
	5.0-1(1)	4.07	81.4
	5.0-1(2)	<u>3.91</u>	78.2
	mean ^(C) :	3.96	79.2
	5.0-2(O)	3.81	76.2
	5.0-2(1)	3.98	79.6
	5.0-2(2)	<u>3.90</u>	78.0
	mean ^(C) :	3.90	78.0
	Mean ^(D) :	3.93 ± 0.04	(78.6)
		C.V. 1%	
	25.0-1(O)	19.1	76.4
	25.0-1(1)	20.3	81.2
	25.0-1(2)	<u>20.2</u>	80.8
	mean ^(C) :	19.9	76.4
	25.0-2(O)	18.8	75.2
	25.0-2(1)	18.9	75.6
	25.0-2(2)	<u>18.4</u>	73.6
	mean ^(C) :	18.7	74.8
	Mean ^(D) :	19.3 ± 0.85	(77.2)
		C.V. 4%	

(A) Duplicate samples (-1,-2) per level were analyzed. Mean, S.D. and C.V. calculated to verify uniformity of mixture.

(B) Denotes not detected.

(C) Mean result of the original analysis [(O)], and duplicate reanalysis of the original sample [(1), (2)].

(D) The average measured concentration, average percent of nominal (in parentheses), standard deviation, and coefficient of variation for duplicate samples.

Table II. Concentration Verification of [REDACTED] in Dosing Solutions (continued)

Preparation Day Sample Type	mg/mL Nominal	Measured	Percent Nominal
Test Day 63			
<u>Concentration Verification(A)</u>			
Control	0.0	ND(B)	----
	0.2-1	0.190	95.0
	0.2-2	<u>0.192</u>	96.0
	<i>Mean(C):</i>	<i>0.191 ± 0.001</i>	(95.5)
		<i>C.V. 1%</i>	
	1.0-1	0.784	78.4
	1.0-2	<u>0.792</u>	79.2
	<i>Mean(C):</i>	<i>0.788 ± 0.01</i>	(78.8)
		<i>C.V. 1%</i>	
	5.0-1	4.12	82.4
	5.0-2	<u>4.08</u>	81.8
	<i>Mean(C):</i>	<i>4.10 ± 0.03</i>	(82.0)
		<i>C.V. 1%</i>	
	25.0-1	23.0	92.0
	25.0-2	<u>21.4</u>	85.6
	<i>Mean(C):</i>	<i>22.2 ± 1.1</i>	(88.8)
		<i>C.V. 5%</i>	
Test Day 73			
<u>Concentration Verification(B)</u>			
Control	0.0	ND(C)	----
	0.2-1	0.176	88.0
	0.2-2	<u>0.155</u>	77.5
	<i>Mean(C):</i>	<i>0.166 ± 0.01</i>	(82.8)
		<i>C.V. 9%</i>	
	1.0-1	0.980	98.0
	1.0-2	<u>1.03</u>	103.0
	<i>Mean(C):</i>	<i>1.01 ± 0.04</i>	(101.0)
		<i>C.V. 4%</i>	
	5.0-1	4.57	91.4
	5.0-2	<u>4.60</u>	92.0
	<i>Mean(D):</i>	<i>4.59 ± 0.02</i>	(91.8)
		<i>C.V. 0.4%</i>	
	25.0-1	23.3	93.2
	25.0-2	<u>24.4</u>	97.6
	<i>Mean(C):</i>	<i>23.9 ± 0.78</i>	(95.6)
		<i>C.V. 3%</i>	

(A) Duplicate samples (-1, -2) per level were analyzed. Mean, S.D. and C.V. calculated to verify uniformity of mixture.

(B) Denotes not detected.

(D) The average measured concentration, average percent of nominal (in parentheses), standard deviation, and coefficient of variation for duplicate samples.

Figure 1
Representative Analytical Calibration Curve

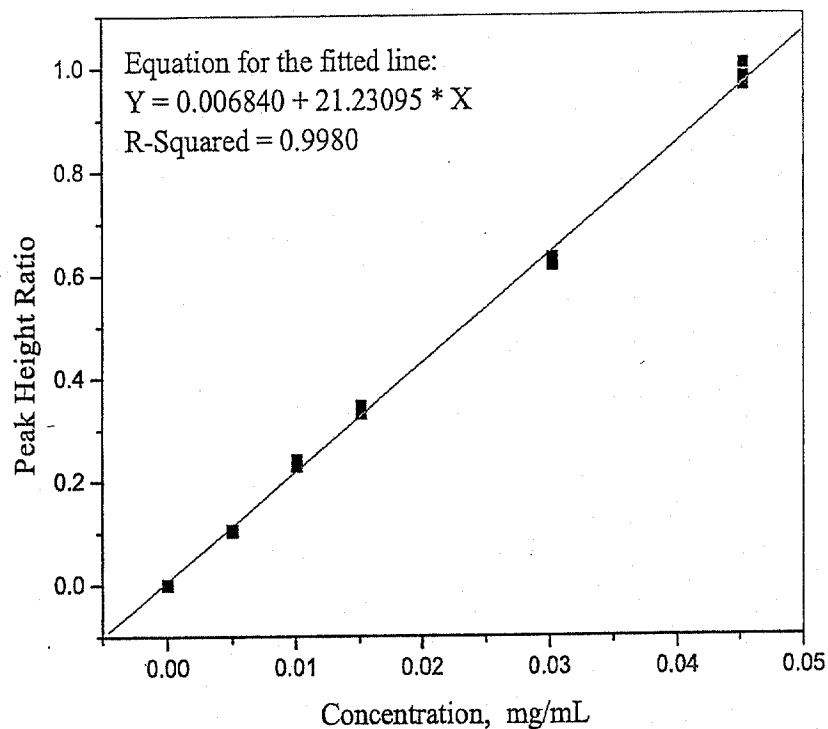


Figure 1: Calibration curve showing linear fit (line) to replicate peak height ratio measurements (squares) for calibration solutions of [REDACTED] diluted over a concentration range of 0.0050 to 0.0453 mg/mL with the 0 mg/mL control diluted sample was used as the zero.

Figure 2
Representative High Performance Liquid Chromatography Chromatograms

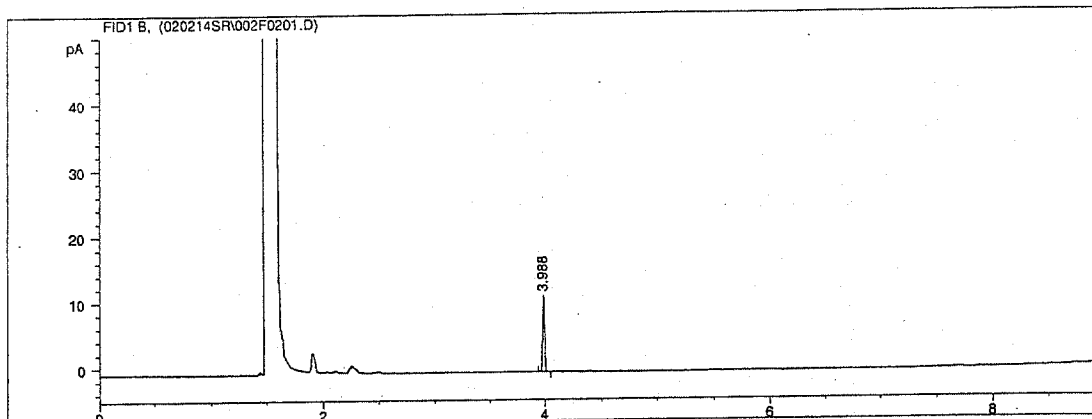


Figure 2a: Representative HPLC chromatogram of 0 mg/mL (control) sample with internal standard [REDACTED] added. Retention time for [REDACTED] is approximately 3.5 minutes. Retention time for internal standard is approximately 3.9 minutes.

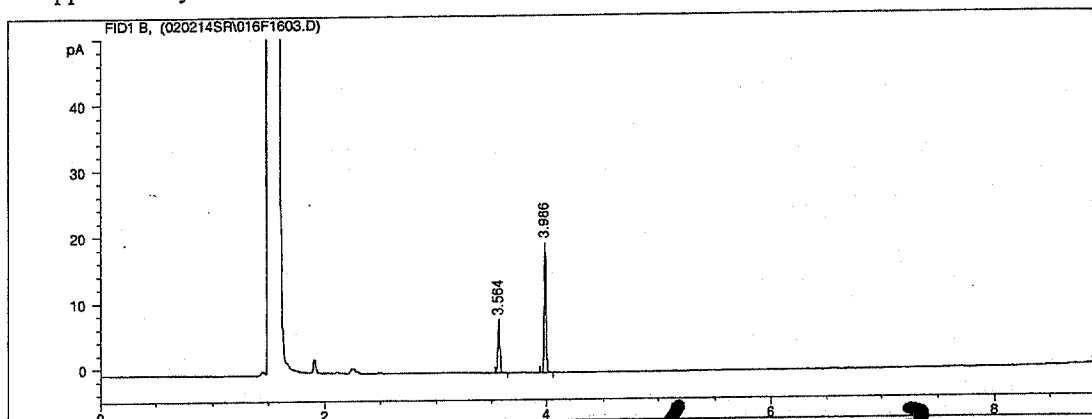


Figure 2b: Representative HPLC chromatogram of 5.0 mg/mL [REDACTED] dosing solution diluted to a nominal concentration of 0.03 mg/mL. The measured concentration of the representative solution is 4.85 mg/mL.

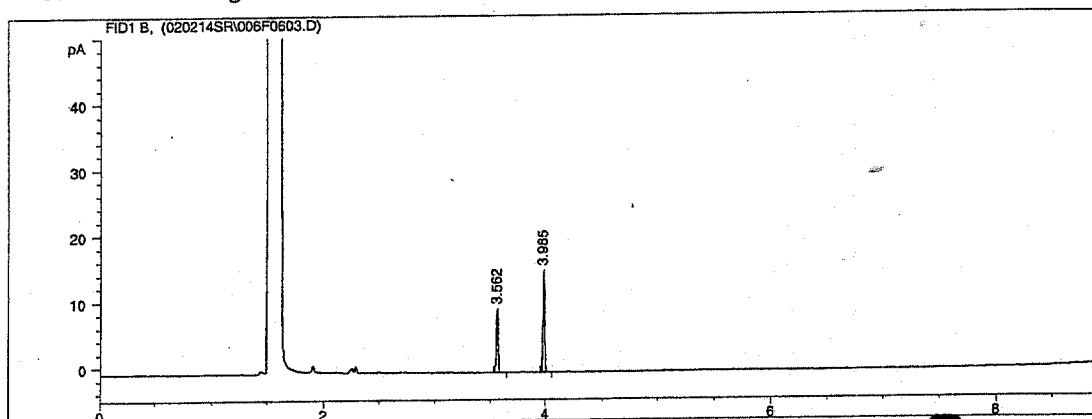


Figure 2c: Representative HPLC chromatogram of 0.0302 mg/mL [REDACTED] analytical reference solution.