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May 11, 2004

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Office of Pollution Prevention and Toxics
United States Environmental Protection Agency
1201 Constitution Avenue, NW
Washington DC 20002

8EHQ-04-15570

Subject: **Low DCPD Resin Oil (CASRN 68477-54-3) – TSCA Section 8(e) Notice OECD 422 – Combined Repeated Dose Toxicity Study and Reproductive / Developmental Toxicity Screening Test in Rats**

Dear Sir or Madam:

Equistar Chemicals, LP (Equistar) hereby submits this letter pursuant to Section 8(e) of the Toxic Substances Control Act (TSCA) and EPA's 1991 Section 8(e) Reporting Guide because it includes findings that EPA may consider reportable. In a combined repeated dose toxicity study and reproductive/developmental toxicity screening test, male rats exposed to 375 mg/kg/bwt/day of Low DCPD Resin Oil (CASRN 68477-54-3; *Distillates, petroleum, steam-cracked, C_{8-12} fraction*) exhibited increased incidence of minimal thyroid follicular cell hypertrophy. Additionally, there was a decrease in mean pup weights in the offspring of male and female rats exposed to this same dose. Equistar has not made a determination as to whether a significant risk of injury to health or the environment is actually presented by these findings.

A copy of the draft report is enclosed for your review and a final report will be forwarded upon its availability.

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Low DCPD Resin Oil was tested pursuant to the American Chemistry Council Olefins Panel's test plan for the Resin Oils and Cyclodiene Concentrates Category under the High Production Volume Chemical Challenge Program.[1] The Low DCPD Resin Oil stream, which typically contains less than 0.5% DCPD, is produced as a C_{8-12} distillate of a pyrolysis gasoline stream. The primary components are vinyl aromatics.

Should you have any questions or require additional details, please do not hesitate to call me at 713-309-2136. I may also be reached by facsimile at 713-951-1574 or by e-mail at patrick.gibson@lyondell.com.

Contain No CBI

Sincerely,

Patrick R. Gibson

Patrick Gibson
Product Safety Specialist - Regulatory
Corporate TSCA Coordinator
Equistar Chemicals, LP

8804000014 3

Enclosure

275268

Cc: Dr. W. Claude White
TSCA 8(e) Files

[1] The test plan is available at http://www.epa.gov/chemrtk/olefins/olefintp.pdf

Study Title

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats

Volume 1 of 2

TEST GUIDELINES: U.S. EPA Health Effects Test Guidelines
OPPTS 870.3650 (2000)

OECD Guideline for the Testing of Chemicals
Section 4: Health Effects, Number 422 (1996)

AUTHOR: Linda A. Malley, Ph.D., D.A.B.T.

STUDY COMPLETED ON: <IS>

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

LABORATORY PROJECT ID: DuPont-13041

WORK REQUEST NUMBER: 14295

SERVICE CODE NUMBER: 1422

SPONSOR: American Chemistry Council
1300 Wilson Boulevard
Arlington, Virginia 22209
U.S.A.

SPONSOR STUDY NUMBER: OLF-92.0-HPV789-DHL

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are consistent with the OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM(98)17 except for the items documented below. The items listed do not impact the validity of the study.

The test substance was characterized by the Sponsor prior to the initiation of this study. Although the analysis was not conducted according to Good Laboratory Practice Standards, it was not considered to have affected the validity of the study since confirmatory analyses conducted by Haskell Laboratory were similar to the results obtained by the Sponsor.

A sample of the test substance was not retained at Haskell Laboratory due to its potential to form peroxides. Since peroxide formation can result in an explosive hazard, the remaining test substance and empty container were safely discarded after the report was completed.

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

Sponsor: American Chemistry Council
1300 Wilson Boulevard
Arlington, Virginia 22209
U.S.A.

Study Director: _____ _____
Linda A. Malley, Ph.D., D.A.B.T. Date
Senior Research Toxicologist
E.I. du Pont de Nemours and Company

QUALITY ASSURANCE STATEMENT

Haskell Sample Number(s):

25429

Dates of Inspections:

Protocol: August 19, 2003
Conduct: September 24,25, 2003; October 1,9,22, 2003
Records, Reports: December 1-4,11, 2003; January 11-16,18-21, 2004; February 22,24, 2004

Dates Findings Reported to:

Study Director: August 20, 2003; September 24,25, 2003; October 1,9,22, 2003; December 4,11,17, 2003; January 16,21, 2004; February 25, 2004

Management: September 24,25, 2003; October 1,9,22, 2003; December 4,17, 2003; January 16,21, 2004; February 25, 2004

Reported by: _____ _____

Kimberly B. Brebner
Staff Quality Assurance Auditor

Date

CERTIFICATION

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

Analytical Evaluation by: _____ _____
Janet C. Maslanka, B.S. Date
Senior Staff Chemist

_____ _____
Vladimir Čapka, Ph.D. Date
Research Chemist

Clinical Pathology Evaluation by: _____ _____
Nancy E. Everds, D.V.M., Diplomate A.C.V.P. Date
Principal Research Clinical Pathologist and Manager

Anatomic Pathology Evaluation by: _____ _____
Greg P. Sykes, V.M.D. Diplomate A.C.V.P., Date
A.C.L.A.M., A.B.T.
Veterinary Pathologist

Anatomic Pathology Evaluation Peer Review by: _____ _____
Peter C. Mann, D.V.M., Diplomate A.C.V.P. Date
Veterinary Pathologist

Statistical Analysis by: _____ _____
John W. Green, Ph.D., Ph.D. Date
Principal Research Statistician

Approved by: _____ _____
Eve Mylchreest, Ph.D. Date
Management

Issued by Study Director: _____ _____

Linda A. Malley, Ph.D., D.A.B.T. Date
Senior Research Toxicologist

This report was accepted by the Sponsor.

Sponsor: _____ _____

Elizabeth J. Moran, Ph.D., D.A.B.T. Date
Sponsor Representative

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STUDY INFORMATION

CA Index Name: Distillates (petroleum), steam-cracked, C8-12 fraction

Synonyms/Codes:
- Low DCPD Resin Oil
- Low Dicyclopentadiene Resin Oil
- Lyondell Resin Oil – 90 (LRO-90)
- Steam-cracked aromatic naptha
- ARF
- Aromatic Resin Feedstock
- H-25429

Haskell Number: 25429

CAS Registry Number: 68477-54-3

Composition: (provided by the sponsor)

0.0005 wt %	Benzene
0.0074 wt %	BHT (Butylated Hydroxytoluene)
0.01 wt %	Ethylbenzene
0.29 wt %	meta-, ortho-, and para- Xylene
0.52 wt %	Styrene
0.68 wt %	DCPD (Dicyclopentadiene)
0.92 wt %	123HEMMI (1,2,3-Trimethylbenzene)
1.8 wt %	1,3,5-Trimethylbenzene
1.47 wt %	Naphthalene
2.71 wt %	alpha-, cis-beta-, and trans-beta- Methyl Styrene
6.45 wt %	1,2,4-trimethylbenzene
8.35 wt %	Methyl Indenes (total)
13.68 wt %	Indene
17.29 wt %	meta-, ortho-, and para- Vinyl Toluene

The balance of the composition is expected to consist of other hydrocarbons with carbon range primarily 8 to 10, mainly aromatics and olefins, with some paraffins.

Physical Characteristics: Colorless - light yellow liquid

Stability: The test substance appeared to be stable under the conditions of the study.

Sponsor: American Chemistry Council
1300 Wilson Boulevard
Arlington, Virginia 22209
U.S.A.

Study Initiated/Completed: September 2, 2003 / (see report cover page)

STUDY PERSONNEL

Study Director:	Linda A. Malley, Ph.D., D.A.B.T.
Management:	Jeanette M. Erhardt, Ph.D.
Developmental, Reproductive, and Neurobehavioral Toxicology Management:	Eve Mylchreest, Ph.D.
Primary Technician:	Joseph F. Aschiero
Management:	Janice L. Connell, M.S., B.A., C.I.H.
Analytical Chemist:	Janet C. Maslanka, B.S.
Management:	Gary W. Jepson, Ph.D.
Analytical Chemist (Test Substance Characterization Evaluation):	Vladimir Capka, Ph.D.
Management:	Gary W. Jepson, Ph.D.
Neurobehavioral Toxicologist:	Linda A. Malley, Ph.D., D.A.B.T.
Management:	Jeanette M. Erhardt, Ph.D.
Clinical Pathologist:	Nancy E. Everds, D.V.M., Diplomate A.C.V.P.
Management:	Jeanette M. Erhardt, Ph.D.
Anatomic Pathologist:	Greg P. Sykes, V.M.D., Diplomate A.C.V.P., A.C.L.A.M., A.B.T.
Peer Review Anatomic Pathologist:	Peter C. Mann, D.V.M., Diplomate A.C.V.P.
Management:	Scott E. Loveless, Ph.D.
Statistical Analysis:	John W. Green, Ph.D., Ph.D. Julia L. Reynolds, M.S.
Management:	Janice L. Connell, M.S., B.A., C.I.H.
Toxicology Report Preparation:	Sean M. Callaghan, B.A.
Management:	Kim D. Birkmeyer, M.S.
Laboratory Veterinarian:	Thomas W. Mayer, D.V.M., Diplomate A.C.L.A.M.
Management:	Janice L. Connell, M.S., B.A., C.I.H.

SUMMARY

Groups of 12 young, adult, male or nulliparous female Crl:CD®(IGS)BR rats were administered an oral gavage dose of 0, 35, 125, or 375 mg/kg/day Low DCPD Resin Oil once daily for 29 or 30 days, respectively. Satellite groups of 12 young, nulliparous female rats were administered an oral gavage dose of 0, 35, 125, or 375 mg/kg/day once daily during a premating period of approximately 2 weeks, during cohabitation (up to 2 weeks), a gestation period of approximately 3 weeks, and a lactation period of approximately 4 days. Body weights, clinical signs, and food consumption were recorded throughout the study. After approximately 30 days, blood samples were collected from all male rats and all subchronic female rats for measurement of hematology, coagulation, and clinical chemistry parameters. A neurobehavioral test battery, consisting of motor activity and functional observational battery assessments, was conducted on all male rats and subchronic female rats during the pretest period in order to obtain baseline measurements, and following approximately 4 weeks of test substance administration.

On test days 30 and 31 respectively, all subchronic males and females were sacrificed and underwent gross necropsy. Selected tissues from the control and 375 mg/kg/day groups, and target organs (liver, kidneys, thyroid gland) from all groups were processed for histopathology and examined.

Following the 2-week premating period, each satellite female was paired with a male of the same respective dosage group during a 2-week cohabitation period. Measurements of body weight, food consumption, and clinical signs of toxicity in satellite females were conducted throughout premating, cohabitation (with the exception of food consumption), gestation, and lactation. After postpartum day 4, lactating females and nonpregnant females were sacrificed, selected organs were weighed, and selected tissues were evaluated microscopically. Offspring were weighed and evaluated for external abnormalities at birth and on lactation days 1 and 4, and were sacrificed on postnatal day 4.

Test substance-related increases in the incidences of stained fur, and/or wet fur were observed in males, subchronic females, and satellite females following administration of 375 mg/kg/day Low DCPD Resin Oil. Stained and/or wet fur were also occasionally observed in males, subchronic females, and satellite females administered 125 mg/kg/day. These clinical signs were not present during either the detailed clinical observations in an open field arena, or during the FOB evaluation.

Test substance-related decreases in body weight and/or weight gain were observed in males, subchronic females, and satellite females administered 375 mg/kg/day of the test substance. In addition, instances of decreased body weight and/or weight gain were also observed in males administered 125 mg/kg/day of the test substance. Test substance-related decreases in food consumption and food efficiency occurred in 125 mg/kg/day and above males, and in 375 mg/kg/day subchronic females, which correlated with the decreased body weight and weight gain.

No test substance-related effects or statistically significant trends in mating index, fertility index, gestation length, number of implantation sites, implantation efficiency, pre-implantation loss,

post-implantation loss, or number of *corpora lutea* were observed for any dosage of the test substance.

Test substance-related decreases in mean pup weight were observed in offspring from the 375 mg/kg/day group. No effects were observed on the number of pups born, number of pups born alive, sex ratio, gestation index, external abnormalities, or litter survival for postnatal days 0-4 in the offspring from any dosage group.

No test substance-related effects on forelimb grip strength, hindlimb grip strength, hindlimb splay, rearing, body temperature, motor activity, or FOB parameters were observed in the males or subchronic female rats administered any dosage of the test substance.

There were no adverse, statistically significant, or treatment-related changes in hematological, coagulation, or clinical chemistry parameters in male or subchronic female rats.

Administration of 35, 125, or 375 mg/kg/day of the test substance for approximately 30 days produced a dose-related increase in renal tubular hyaline droplets in male rats; however, hyaline droplet nephropathy was not observed. Increased hyaline droplets were not observed in females. The hyaline droplet accumulation in male rats was not considered to be an adverse effect of the test substance. Also, renal tubular hyaline droplet accumulation is species and sex specific, and is not predictive of an effect on other species.

Minimal to mild hepatocellular hypertrophy, and associated increases in liver weight parameters were observed in 375 mg/kg/day males, and in 125 and 375 mg/kg/day females; however, this change is considered to be secondary to enzyme induction as a pharmacological response to a xenobiotic, and was not considered to be adverse.

Minimal thyroid follicular hypertrophy was observed in 375 mg/kg/day males, which was considered to be test substance-related and potentially adverse.

Thymus weight was decreased in 125 and 375 mg/kg/day males, and in 375 mg/kg/day females. However, there was no corresponding microscopic effect on the thymus.

No morphological changes were detected in reproductive tissues for the satellite females administered any dosage of the test substance.

The no-observed-effect level (NOEL) and the no-observed-adverse-effect level (NOAEL) for offspring is 125 mg/kg/day based on decreased pup body weight at 375 mg/kg/day.

The NOEL and NOAEL for reproduction is 375 mg/kg/day based on the absence of effects on mating index, fertility index, number of implantation sites, implantation efficiency, pre-implantation loss, post-implantation loss, number of *corpora lutea*, and absence of morphological changes in the reproductive organs of males and females at the highest dose tested.

The NOEL and NOAEL for neurobehavioral parameters is 375 mg/kg/day in males and females, the highest dosage tested.

The NOEL and NOAEL for systemic toxicity was 35 mg/kg/day in males and 35 mg/kg/day in females based on decreased body weight, weight gain, food consumption, and food efficiency (males) at 125 mg/kg/day and above; and on clinical signs of toxicity at 125 mg/kg/day and above in males and females. The low-observed-effect level (LOEL) in males and females was 125 mg/kg/day based on clinical signs of toxicity observed at 125 mg/kg/day and above.

The NOEL for pathology was considered to be 35 mg/kg/day in subchronic females based on hepatocellular hypertrophy observed in subchronic females at 125 mg/kg/day and above. A NOEL was not determined in males based on an increased incidence of renal tubular hyaline droplets at all dosage levels. The NOAEL in males was considered to be 125 mg/kg/day based on thyroid follicular hypertrophy at 375 mg/kg/day. The NOAEL in females was considered to be 375 mg/kg/day based on the absence of adverse morphological effects observed at any dosage. The LOEL in males was considered to be 35 mg/kg/day based on the renal tubular hyaline droplets at all dose levels. The LOEL in females was 125 mg/kg/day based on hepatocellualr hypertrophy at 125 mg/kg/day and above.

Parameters	NOEL (mg/kg/day)	NOAEL (mg/kg/day)	LOEL (mg/kg/day)
Systemic	35 M 35 F	35 M 35 F	125 M 125 F
Neurobehavioral	375 M 375 F	375 M 375 F	- -
Pathology	- 35 F	125 M 375 F	35 M 125 F
Reproductive	375 M 375 F	375 M 375 F	- -
Developmental (Pups)	125	125	375

M = Males; F = Females

INTRODUCTION

Low Dicyclopentadiene Resin Oil (Low DCPD Resin Oil) was evaluated for potential toxicity using a combined repeated dose toxicity/reproduction/developmental toxicity study. The purpose of this study was to evaluate the potential effects of Low DCPD Resin Oil when administered by gavage to male and female rats for a minimum of 28 consecutive days. General toxicity, clinical pathology, neurobehavioral activity, gross pathology, and histopathology were evaluated.

In addition, a satellite group was used to evaluate the potential effects of Low DCPD Resin Oil during premating (approximately 2 weeks), gestation (approximately 3 weeks), and lactation through day 4. In the satellite group, gonadal function, mating behavior, fertility, implantation, development of the conceptus, parturition, gross pathology, and histopathology were evaluated.

Prior to conducting the main study, a range-finding study was conducted in time-mated pregnant female rats.[1] Dose levels for the main study were selected based on the results of the range-finding study.

STUDY DESIGN

A. Treatment Groups and Dose Levels

Main Subchronic[a]				Satellite[b]		Dosage
Group Male	Number of Males	Group Female	Number of Females	Group Females	Number of Females	mg/kg/day
I	12	II	12	II-0	12	0 (Control)
III	12	IV	12	IV-0	12	35 (Low)
V	12	VI	12	VI-0	12	125 (Medium)
VII	12	VIII	12	VIII-0	12	375 (High)

a Main study males and females (general toxicity and neurotoxicity endpoints)
b Satellite females (reproductive and developmental toxicity endpoints)

Study Parameters	Frequency
Clinical Observations • Predosing Observations (Subchronic and Satellite)[a] • Mortality/Moribundity Checks (Subchronic and Satellite)[b] • Detailed Clinical Observations (Subchronic)[c]	 • Daily prior to dosing • Twice daily (a.m. and p.m.) • Pretest, and Days 8, 15, 22, and 29 (1-2 hour post-dosing)
Body Weights	• Study Days 1, 8, 15, 22, and 29 and at scheduled sacrifice (Subchronic) • Days 1, 8, and 15 – Premating (Satellite) • Weekly – Mating (Satellite) • Daily - Gestation (Satellite) • Days 0 and 4 - Lactation (Satellite)
Food Consumption	• Study Days 1, 8, 15, 22, and 29 (Subchronic) Food consumption was discontinued for males upon cohabitation • Days 1, 8, and 15 – Premating (Satellite) • Days 0, 7, 14, and 21 - Gestation (Satellite) • Days 0 and 4 - Lactation (Satellite)
Functional Observational Battery (Subchronic)	Pretest and Study Day 29-30
Motor Activity (Subchronic)	Pretest and Study Day 29-30
Clinical Pathology (Subchronic)	Study Day 30-31
Necropsy • Subchronic Males • Subchronic Females • Pregnant Satellite Rats • Satellite Rats that did not deliver a litter • Pups • Satellite Rats with no Evidence of Mating	Sacrifice Schedule • Study Day 30 • Study Day 31 • Lactation Day 4 • Gestation Day 27 (approximately) • Lactation Day 4 • Study Day 43 (approximately)

a Predosing Clinical Observations – Immediately prior to dosing, each rat was individually handled and examined for abnormal behavior and appearance. Clinical abnormalities or No Abnormalities Detected (NAD) were recorded.

b Mortality/Moribundity Checks – All rats were examined at cage-site twice daily. One of the cage-site examinations occurred in the afternoon, at least 1-2 hours after dosing was completed. Abnormal clinical signs were noted by exception.

c Detailed Clinical Observations were recorded in the study database for all rats in the Main study, listing either clinical abnormalities or "NAD." During treatment, when these rats were scheduled for detailed clinical observation evaluations, detailed clinical observations evaluations were performed and recorded first, predosing observations were then performed and recorded, and then the rats were dosed.

MATERIALS AND METHODS

A. Test Guidelines

The study design complies with the following test guidelines:

- Office of Prevention, Pesticides and Toxic Substances (OPPTS) U.S. Environmental Protection Agency (EPA) (2000). OPPTS 870.3650 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. *Health Effects Test Guidelines.*

- Organisation for Economic Co-Operation and Development (OECD) (1996). 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. *Guideline for the Testing of Chemicals.*

B. Route of Administration

The test substance was administered by oral intubation (gavage) to ensure maximal exposure and provide for comparison with other similar substances that have or were tested by oral gavage administration. The vehicle control substance was also administered by oral gavage. The degree of the test substance or vehicle absorption by the test system was deemed beyond the scope and objectives of the study.

C. Duration of the Study

The start date of the study was defined as the day the study protocol was signed by the Study Director. The experimental start date was defined as the first day of dosing (test day 1). The experimental termination date of the main study was defined as the in-life completion phase at Haskell Laboratory. The completion date of the study was defined as the date the final report is signed by the Study Director at Haskell Laboratory.

D. Test Substance

1. Identification:

Chemical Name:	Low Dicyclopentadiene Resin Oil
Other Name Used in this Report:	Low DCPD Resin Oil
CAS Registry Number:	68477-54-3
Haskell Sample Number:	25429
Lot Number:	Not applicable
Purity:	Not applicable
Color:	Colorless-light yellow
Form:	Liquid
Supplier for Low DCPD Resin Oil:	Equistar Chemicals, LP
Vehicle:	Corn oil
Supplier for Corn Oil:	Mazola®
Lot Number/Expiration Date for Corn Oil:	Oct2103B/Oct2103

The test substance was supplied as a liquid, stored at or below 70° F, and protected from light and air.

2. Characterization

The test substance was characterized by the supplier.

3. Stability

Stability of the test substance was established by analyses at 2 time points. Aliquots were taken after the end of the range-finding study, which served as the beginning of the study analysis for the main study. Aliquots were taken again near the end of the current study. The results of these analyses were reported as test substance stability. The stability samples were analyzed by gas chromatography using flame-ionization detection (FID). Two peaks of the major component(s) were compared to an internal standard to determine a ratio. Two calibration curves were prepared from these ratios, and the samples were evaluated based on the calibration curves. The results were averaged and reported as the concentration of the test substance. The samples were analyzed by Haskell Laboratory's Analytical Chemistry Group on the day the samples were collected. Details regarding the analytical method used were documented in the Analytical Chemistry Group study reports.[2,3]

E. Vehicle

Corn oil was used as test substance vehicle. The corn oil was purchased from reliable commercial vendors by Haskell Laboratory and was not expected to contain any contaminants that would interfere with the conduct of the study. The corn oil was assumed to be stable under the conditions of the study. Corn oil was stored refrigerated.

F. Degree of Absorption

For the purposes of this study, clinical signs of toxicity and other manifestations of toxic effects were considered to indicate uptake of the test substance. No attempt was made to establish the actual systemic dose each rat received. All treatment-related effects were therefore reported as a function of the administered dose(s).

G. Dosing Formulation Preparation, Sampling, and Analysis

For the preparation of dosing formulations, the test substance purity was considered 100%.

Dosing formulations of the test substance were prepared daily by adding the corn oil to the measured amount of test substance and stirring to establish uniformity.

Near the beginning of the study, 4 samples (approximately 3 mL per sample) were collected from each formulation, and were analyzed for homogeneity/concentration verification, and 5-hour stability at room temperature. Near the middle and end of the dosing period, duplicate samples were taken from all formulations and analyzed for concentration verification.

The remaining formulation samples after dosing were stored refrigerated, and discarded when the final results from the analysis were accepted.

The samples were mixed and diluted with chloroform. The resulting solution was analyzed by gas chromatography using FID detection.

1. Sample Submittal

On September 10, 2003, dosing formulations containing Low DCPD Resin Oil at the concentrations of 17.5, 62.5, and 187.5 mg/mL were collected. These samples were analyzed to determine homogeneity/concentration verification and 5-hour room temperature stability. Dosing formulations from the same levels were collected on October 1, 2003 and October 15, 2003 and analyzed for concentration verification. A 0 mg/mL (control) sample was collected and submitted with each sampling.

All dosing formulation samples were collected on the same day the formulations were prepared. They were analyzed when received or when reanalysis was necessary.

2. Recovery Sample Analysis

Concurrent with dosing formulation analyses, recovery of Low DCPD Resin Oil from spiked Mazola corn oil was tested at the targeted low-level, mid-level and high-level to confirm the analytical method. Low DCPD Resin Oil was weighed, then diluted with 3 mL of Mazola® corn oil. All recovery samples were then mixed for dispersion of the Low DCPD Resin Oil in the corn oil. The samples were then processed and analyzed in the same manner as the dosing samples at similar concentrations.

3. Dosing Formulation Treatment

Each dosing sample (3 mL) was diluted to 50 mL with chloroform to dissolve the Mazola® corn oil and the Low DCPD Resin Oil in the formulation. The dosing samples were analyzed after further dilution with chloroform to an expected concentration of approximately 0.735, 0.750, 0.788 mg/mL prior to analysis. Before all final dilutions, the internal standard (refer to Calibration and Quantitation Section) at the approximate concentration of 0.075 mg/mL, and the 0 mg/mL sample (initial dilution) were added to each test sample to give an equivalent final concentration of the matrix (corn oil diluted with chloroform) and internal standard in all samples.

4. Chromatographic Conditions

Instrument:	Hewlett-Packard Model 6890 GC
Column:	DB-1, 30 m x 0.25 mm ID, 0.25 μm film thickness
Injector:	Split, 180°C
Detector:	Flame Ionization Detector (FID); 280°C
Carrier Gas:	Helium (2.7 mL/min)
Split ratio:	10:1
Injection Volume:	3 microliter
Oven Program:	Gradient
Initial Temperature:	65°C
Initial Time:	0.50 min.
Level 1 Rate:	20°C/min.
Level 1 Temperature:	85°C
Level 1 Time:	0.00 min.
Level 2 Rate:	40°C/min.
Level 2 Temperature:	250°C
Level 2 Time:	1.00 min.
Total run time:	6.63 min.

5. Calibration and Quantitation

A separate sample of the Low DCPD Resin Oil (H-25429, 100.0%) was used as an analytical reference for the analysis. A stock solution was prepared in chloroform. Calibration solutions of approximately 0.25 to 1.00 mg/mL were prepared in chloroform from this solution. A stock solution of the internal standard (toluene, 99.5% pure, Fluka/Chemika) was prepared in chloroform and added to each calibration standard and test solution to give a final concentration of approximately 0.075 mg/mL. The ratio of each peak area for Low DCPD Resin Oil and for the internal standard from replicate gas chromatography (GC) analysis of these solutions was used to construct calibration curves by least squares regression. Measured concentrations for each sample were determined by applying the peak area ratios from replicate injections of each sample to the respective calibration curve. The measured concentration for each peak in the Low DCPD Resin Oil was averaged and the percentage of the nominal was reported as the results.

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.

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 as the baseline for comparing the corresponding stability results.

H. Test Species

Fifty-six male and 112 female (nulliparous) Crl:CD®(SD)IGS BR rats were obtained from Charles River Laboratories, Inc. (Raleigh, North Carolina) on August 28, 2003. The rats were approximately 8-10 weeks old at study start. The weight range was 114.8 g–165.3 g on the day after arrival. The Crl:CD®(SD)IGS BR rat was selected on the bases of extensive experience with this strain at Haskell Laboratory and its suitability with respect to longevity, sensitivity, and low incidence of spontaneous diseases.

I. Animal Husbandry

1. Identification

Each rat was assigned an animal number and an individual cage identification number. The animal number was tattooed on the tail of each rat. The animal number and cage identification number were both included on the cage label.

2. Housing Environment

Rats were housed singly in stainless steel, wire-mesh cages, suspended above cage boards, except as described in the next 2 paragraphs. Each cage rack contained only rats of 1 gender.

During cohabitation, males designated for subchronic toxicity were cohoused with the satellite females in their respective groups until evidence of copulation was observed or 2 weeks had elapsed.

Females in the satellite group were housed in polycarbonate pans with bedding (Bed-o-Cobs®) from gestation day 19 or the end of the cohabitation period (if evidence of copulation was not detected) until sacrifice.

Animal rooms were targeted at a temperature of 22° ± 3°C and a relative humidity of 40%-60%. Animal rooms were artificially illuminated (fluorescent light) on an approximate 12-hour light/dark cycle.

3. Food and Water

All rats were provided tap water (United Water Delaware) *ad libitum*. They were fed PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002 (chunk chow) *ad libitum*.

4. Animal Health Monitoring

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.

- Food 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 was 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 was administered by the attending laboratory animal veterinarian and data are maintained separately from study records. Evaluation of these data did not indicate any conditions that affected the validity of the study.

J. Quarantine and Pretest Procedures

Upon arrival at Haskell Laboratory, all rats were housed 1 per cage, sexes separate, in quarantine. The rats were:

- quarantined for a minimum of 6 days.
- identified temporarily by cage identification.
- weighed at least 3 times during quarantine.
- observed with respect to weight gain and any gross signs of disease or injury during the entire 12-day pretest period.

The rats were released from quarantine by the laboratory animal veterinarian or designee on the bases of acceptable body weights and absence of clinical signs.

K. Assignment to Groups

Rats of each sex were selected for use on study on the bases of adequate body weight gain and freedom from any clinical signs of disease or injury. They were distributed by computerized, stratified randomization into study groups as described in the Study Design, so that there were no statistically significant differences among group body weight means within a sex. The weight variation on test day 1 did not exceed ± 20% of the mean for each sex.

Rats that were not assigned to a test group were released for other laboratory purposes or were sacrificed by carbon dioxide asphyxiation and discarded without pathological evaluation.

L. Dose Selection

In a range-finding study, 6 time-mated, presumed pregnant female rats per group were administered Low DCPD Resin Oil once daily during gestation days 12-19 at dosages of 0, 100,

375, or 750 mg/kg/day.[1] Test substance-related reductions in body weight, weight gain, and food consumption occurred in rats administered 375 or 750 mg/kg/day. Maternal animals in the 750 mg/kg/day group had test substance-related increased incidences of salivation and wet and/or stained fur. A test substance-related reduction in placental weight occurred in rats administered 750 mg/kg/day. Test substance-related reductions in fetal weight occurred at 750 mg/kg/day. Based on these effects in the range-finding study, the dosages selected by the sponsor for the main study were 0, 35, 125, and 375 mg/kg/day.

M. Administration of Dosing Formulations

The test substance was administered once daily by gavage at a dose volume of 2 mL/kg. Females designated for the subchronic toxicity study (main group) were dosed for 30 days. Females designated for the reproduction study (satellite group) were dosed during the premating period (approximately 2 weeks), the mating period until evidence of copulation was observed (up to 2 weeks), the gestation period (approximately 3 weeks), and days 0-4 of lactation (if delivery was in progress at the time of dosing, the female was not administered the dose). Females showing no evidence of copulation continued to be dosed after the end of the cohabitation period until sacrifice. Males were dosed during the premating period (approximately 2 weeks), during the mating period until evidence of copulation was observed, and subsequently until sacrifice (29 days). Control rats were dosed with corn oil (2 mL/kg).

Individual dosages were based on the most recently recorded weight.

N. Clinical Observations and Mortality

Clinical Observations were recorded throughout the test period for all rats. Moribund rats were sacrificed and necropsied.

1. Predosing Observations – Main Subchronic Study and Satellite Study

Prior to dosing, or at the time of dosing, each rat was individually handled and examined for abnormal behavior and appearance. Clinical abnormalities or No Abnormalities Detected (NAD) were recorded in the study database for each rat prior to dosing.

2. Morbidity/Mortality Checks – Main Subchronic Study and Satellite Study

During the test period, cage-site examinations to detect moribund or dead rats and abnormal behavior and/or appearance among rats were conducted at least twice daily throughout the study. One of the cage-site examinations occurred in the afternoon, at least 1-2 hours after dosing was completed. Abnormal clinical signs were noted by exception.

3. Detailed Clinical Observations – Main Subchronic Study

Rats in the Main Study underwent a detailed clinical observation evaluation during pretest, and on days 8, 15, 22, and 29. During the treatment period, when these rats were scheduled for detailed

clinical observation evaluations, detailed clinical observations evaluations were performed and recorded first, predosing observations were performed and recorded, and then the rats were dosed.

Each rat was individually handled and examined for abnormal behavior and appearance in a standardized arena. The detailed clinical observations included (but are not limited to) evaluation of fur, skin, eyes, mucous membranes, occurrence of secretions and excretions, autonomic nervous system activity (lacrimation, piloerection, and unusual respiratory pattern), changes in gait, posture, response to handling, presence of clonic, tonic, stereotypical, or bizarre behavior. Clinical Observations were recorded in the study database for all rats in the Main study, listing either clinical abnormalities or "NAD."

O. Body Weights and Body Weight Gains

1. Subchronic Toxicity Animals

All main study rats were weighed on day 1, 8, 15, 22, and 29 and at scheduled sacrifice. In addition, rats undergoing functional observational battery and motor activity evaluations were weighed on the days of those observations.

2. Satellite Study

Satellite female rats were weighed according to the following schedule:

- Premating period – Days 1, 8, and 15
- Mating – Weekly
- Gestation – Daily (Weights collected on gestation days other than 0, 7, 14, and 21 were used to calculate dosages, and were not included in the summary tables.)
- Lactation – Days 0 and 4

P. Food Consumption and Food Efficiency

The amount of food consumed by each rat over the weighing interval was determined by weighing each feeder at the beginning of the interval and subtracting the diet remaining and the amount of spillage from the feeder at the end of the interval. From these determinations, mean daily food consumption (g/day) was calculated. Mean food efficiency was calculated by dividing the amount of weight gain by the amount of food consumed for a given interval of test days.

1. Main Subchronic Study

Food consumption was measured on days 1, 8, 15, 22, and 29 for each rat on the main study (food consumption in males was discontinued upon cohabitation).

2. Satellite Study

Satellite female rats had food consumption measured according to the following schedule:

- Premating period – Days 1, 8, and 15
- Gestation – Days 0, 7, 14, and 21
- Lactation – Days 0 and 4

Food consumption was not measured during cohabitation.

Q. Neurobehavioral Evaluations

Prior to initiation of dosing, all rats designated for subchronic toxicity and approximately 8 extra rats per sex were evaluated in the Fuctional Observational Battery (FOB) test to establish their baseline FOB parameters. The FOB was performed again on males and subchronic females on test days 29 and 30, respectively. The week 4 assessment for males was conducted approximately 22-25 hours after the dose was administered on test day 28, and was conducted before the dose was administered on test day 29. The week 4 assessment for females was conducted approximately 22-25 hours after the dose administered on test day 29 and was conducted before the dose administered on test day 30.

In order to accommodate the Neurotoxicology testing facility, the functional observational battery (FOB) and motor activity (MA) assessments were conducted in 2 replicates per sex over a 2-day period for baseline and a 2-day period for the week 4 FOB. Replicate designations were not reported in the final report, but were recorded in the study records. Assignment to a given replicate was counterbalanced across all groups within a sex.

For all the following assessments, the experimenter was unaware of the group designation of the animal.

1. Functional Observational Battery (FOB)

FOB testing consisted of a series of quantified behavioral observations conducted in a sequence that proceeds from the least interactive to the most interactive. (See Appendix A.)

During the FOB assessments, each rat was evaluated in 3 "environments:" 1) inside the home cage; 2) upon removal from the home cage and while being handled; and 3) in a standard "open field" arena (approximately 85 x 59 x 20 cm). The animal's actual home cage was not amenable to transport between the housing room and neurobehavioral laboratory areas. Therefore, for the purposes of the FOB, the "home cage" was defined as the cage on the transport rack to which an individual animal was assigned and to which the rats have been acclimated and undisturbed for a period of at least 10 minutes.

Inside the home cage, the presence of the following was recorded, if and when observed:

- palpebral closure
- writhing
- circling
- biting
- unusual changes in body posture
- gait/coordination

During removal from the home cage and handling, each rat was assessed for:

- fur appearance
- ease of removal
- ease of handling
- muscle tone
- the presence of
  - vocalizations
  - piloerection
  - bite marks
  - palpebral closure
  - lacrimation
  - exophthalmus
  - salivation

In the open field arena, the rats were evaluated for:

- unusual responses in
  - arousal
  - grooming
  - gait/coordination
  - posture
  - rate of respiration
  - ease of respiration
  - righting reflex
  - the number of rearing movements
- the presence of
  - convulsions
  - tremors
  - muscle fasciculation
  - muscle spasms
  - diarrhea
  - polyuria
  - palpebral closure
  - vocalizations

While in the standard arena, simple assessments of sensory function were made, including:

- response to
  - approach/touch
  - auditory stimulus
  - tail pinch

The presence or absence of pupillary constriction assessed after a beam of light is directed into each eye was measured immediately prior to removing the rats from the motor activity chambers because the darkened room in which the apparatus was located facilitates observing the response. The presence of diarrhea and polyuria on the cage boards below the motor activity cages was also evaluated following each motor activity session.

The remainder of FOB testing involved standardized or calibrated devices. Fore- and hindlimb grip strength was measured by a strain gauge device (Chatillon® -Digital Force gauge) (3 trials per animal per session). Hindlimb splay was assessed by inking the hind paws and releasing the rat from a height of approximately 32 cm onto a piece of paper that covered a padded surface. Heel to heel distance was measured from the inked impressions and recorded.

Rectal body temperature was measured with a YSI Precision™ 4000 Thermometer and temperature probe.

2. Motor Activity (MA)

Motor activity sessions were conducted on the same animals, the same day as FOB assessments, following the FOB assessments. Rats were individually tested in 1 of 30 nominally identical, automated activity monitors (Coulbourn®). Groups 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, total motor activity over a 60-minute time period, as well as for 6 successive 10-minute blocks.

3. Test Facility Positive Control Data

Procedures and data describing the effects of acrylamide, carbaryl, d-amphetamine, and trimethyltin are presented in 5 separate reports.[4,5,6,7,8] These positive control studies are the basis of training certification for the study personnel 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.

R. Clinical Pathology Evaluation

A clinical pathology evaluation was conducted on all main subchronic study males and females 30 and 31 days after initiation of the study, respectively. These animals were fasted overnight (at least 15 hours). Blood samples for hematology and clinical chemistry measurements were collected from the orbital sinus of each animal while the animal was under carbon dioxide anesthesia. Blood samples for coagulation parameters 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 because further tests were not required to support experimental findings. Bone marrow smears were prepared at sacrifice from all surviving animals. Bone marrow smears were stained with Wright's stain, but analysis was not necessary to support experimental findings.

1. Hematology and Coagulation

Blood samples were evaluated for quality by visual examination prior to analysis. Complete blood counts, including reticulocytes, were determined on a Bayer® Advia 120 hematology analyzer or determined from microscopic evaluation of the blood smear. Wright-stained blood smears from all animals were examined microscopically for confirmation of automated results and

evaluation of cellular morphology. Blood smears, stained with new methylene blue, were prepared from each animal undergoing a hematology evaluation, but were not needed for examination. Coagulation times were determined on a Sysmex® CA-1000 Coagulation Analyzer.

The following parameters were determined:

red blood cell count
hemoglobin
hematocrit
mean corpuscular volume
mean corpuscular hemoglobin
mean corpuscular hemoglobin concentration
red cell distribution width
absolute reticulocyte count

prothrombin time
activated partial thromboplastin time

platelet count
white blood cell count
differential white blood cell count
microscopic blood smear examination

2. Clinical Chemistry

Serum clinical chemistry parameters were determined on a Roche Diagnostics (BMC)/Hitachi® 717 clinical chemistry analyzer.

The following parameters were determined:

aspartate aminotransferase
alanine aminotransferase
sorbitol dehydrogenase
alkaline phosphatase
total bilirubin
urea nitrogen
creatinine
cholesterol
triglycerides

glucose
total protein
albumin
globulin
calcium
inorganic phosphorus
sodium
potassium
chloride

S. Reproductive Assessment

1. Breeding

After 2 weeks of treatment with the test substance, each satellite female was continually housed on a 1:1 basis with a randomly selected subchronic male of the same treatment level in the male's cage. On the day copulation was confirmed, the satellite female was transferred back to individual cage housing. Mating pairs were cohoused until evidence of copulation was observed (designated as day 0 of gestation), or until 2 weeks had elapsed. Once daily, each female was examined for an intravaginal copulation plug or sperm in vaginal lavage sample, either 1 of which was considered evidence of copulation. The day evidence of copulation was observed was

designated as day 0 of gestation. Cageboard was examined for the presence of a cageboard plug(s). The presence of cageboard plugs, vaginal plugs, and/or sperm was recorded.

2. Gestation Procedures – Satellite Study

After they were transferred into polycarbonate pans (on day 19 of gestation (GD 19) for mated females, or at the end of the cohabitation period for females without evidence of copulation), female rats were observed at least twice daily for signs of delivery and pups.

3. Lactation Procedures – Satellite Study

The day when delivery was complete was designated day 0 postpartum, lactation day 0 (LD 0). At each examination period, pups were individually handled and examined for abnormal behavior and appearance; any dead, missing, or abnormal pups were recorded. Any pups found dead or which were euthanized in moribund condition were examined externally to the extent possible and discarded.

a. Day 0 Postpartum (Lactation Day 0)

Live and dead pups in each litter were counted as soon as possible after delivery was completed. Live pups in each litter were individually weighed and sex determined. Any clinical abnormalities in pups were recorded.

b. Days 1 and 4 Postpartum (Lactation Days 1 and 4)

Pups in each litter were counted by sex, individually weighed, and any clinical abnormalities in pups were recorded. On lactation day 4, all offspring were evaluated for external alterations, and euthanized by decapitation.

T. Anatomic Pathology Evaluation

1. Rats Designated for Subchronic Toxicity

On test days 30 and 31, respectively, male and female subchronic rats were sacrificed and necropsied. The 48 male rats in the subchronic study were also used as the P_1 males in the Reproductive/Developmental Toxicity Screening Test discussed below.

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

The following tissues were collected from subchronic toxicity rats:

Digestive System[a]
- liver
- esophagus
- stomach
- duodenum
- jejunum
- ileum [a]
- cecum
- colon
- rectum
- tongue
- pancreas

Urinary System
- kidneys
- urinary bladder

Respiratory System
- lungs
- trachea
- nose
- pharynx/larynx

Cardiovascular System
- heart
- aorta

Hematopoietic System
- spleen
- thymus
- mediastinal lymph node
- mandibular lymph node
- mesenteric lymph node
- bone marrow [b]

Endocrine System
- pituitary gland
- parathyroid gland
- thyroid gland
- adrenal glands

Nervous System
- brain (three sections)
- spinal cord (three levels)
- eyes (with optic nerve)
- sciatic nerve

Musculoskeletal System
- femur/knee joint
- sternum
- skeletal muscle

Reproductive System

Male
- testes
- epididymides
- prostate
- seminal vesicles
- coagulating glands

Female
- ovaries (with oviducts)[c]
- cervix
- uterus[c]
- vagina

Integumentary System
- skin
- salivary glands
- lacrimal glands
- mammary gland[d]

Miscellaneous
- gross observations[e]

a. Including Peyer's patches.
b. Bone marrow was collected with the femur and sternum.
c. The uteri of females in the satellite groups were examined for the presence and number of implantation sites, and the number of *corpora lutea* in the ovaries was determined.
d. Females only.
e. Gross observations made at necropsy for which histopathology was not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) were generally not collected.

The following tissues were weighed from rats sacrificed by design in the 28-day subchronic toxicity study: liver, kidneys, lungs, adrenal glands, thymus, spleen, brain, heart, testes, epididymides, ovaries, and uterus. Organ weight/final body weight and organ weight/brain weight ratios were calculated.

Gross lesions that were diagnosed at necropsy 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.

With regards to Peyer's patches, a microscopic diagnosis of "Peyer's patch not present (present elsewhere)" was used when Peyer's patches were absent from the ileum but present elsewhere in

the intestines. A diagnosis of "Peyer's patch not present" was used when there were no Peyer's patches in any of the 6 sections of intestine. Neither diagnosis was used when a Peyer's patch was present in the ileum.

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, sectioned approximately 5-6 microns thick, stained with hematoxylin and eosin (H&E), and examined microscopically by a veterinary pathologist.

All collected tissues from control and high-dose (375 mg/kg/day) subchronic toxicity study rats received a full histopathological examination. Liver (males and females), thyroid gland (males only), kidneys (males only), and gross lesions were examined from the low- (35 mg/kg/day) and mid-dose (125 mg/kg/day) subchronic toxicity study rats.

2. Rats Designated for Reproductive Evaluations

a. P_1 Adults

P_1 adults included the male rats from the subchronic toxicity study (main study) and a separate population of satellite female rats that included 12 rats per dose level. P_1 males (Groups I, III, V, and VII) received gross and microscopic examinations as described for the subchronic toxicity study. All satellite females (Groups II-0, IV-0, VI-0, and VIII-0) received a gross pathological examination that included recording the number of ovarian *corpora lutea* and uterine implantation sites. Rats were sacrificed by carbon dioxide anesthesia and exsanguination.

The same tissues collected from female rats in the subchronic toxicity study were collected from the satellite females at necropsy. Tissue fixation and processing were also the same as for the subchronic study. Microscopic evaluation of the satellite female rats was limited to the reproductive organs of the 4 females with impaired reproductive performance, including 2 Group II-0 rats (animal numbers 94 and 118), 1 Group VI-0 rat (animal number 78), and 1 Group VIII-0 rat (animal number 127).

Similarly, the reproductive organs from the P_1 males that cohabited with these females were also examined. All tissues from the Group I rats (animal numbers 36 and 44), which cohabited with females 94 and 118, respectively, and the Group VII rat (animal number 40), which cohabited with female animal number 127, were examined as prescribed for the subchronic toxicity study. Only the reproductive organs of the Group V rat (animal number 9), which cohabited with female animal number 78, were examined. The gross and microscopic findings of the P_1 males are included in the subchronic toxicity tables and appendices.

Satellite female rats had the following organs weighed at necropsy: liver, kidneys, lung, ovaries, and uterus. Organ weight/final body weight ratios were calculated.

b. Pups

All offspring surviving to postnatal day 4 were examined as described in sections S.3.b. (Reproductive Assessment, Days 1 and 4 Postpartum), and euthanized by decapitation. Pups

found dead or which were euthanized in moribund condition were examined to the extent possible and discarded.

U. Data Analyses

1. Reproductive Function Calculations

The following table lists the indices of reproductive functions that were calculated for the P_1 adults.

Mating Index (%)	=	$\frac{\text{Number Copulated}^{a}}{\text{Number Cohabited}}$	x 100
Fertility Index (%)	=	$\frac{\text{Number Pregnant}^{b}}{\text{Number Copulated}^{a}}$	x 100
Gestation Index (%)	=	$\frac{\text{Number of Litters with at Least One Live Pup}}{\text{Number of Litters}}$	x 100
Implantation Efficiency (%)[c]	=	$\frac{\text{Number of Pups Born}}{\text{Number of Implantation Sites}}$	x 100
Pups Born Alive (%)[c]	=	$\frac{\text{Number of Pups Born Alive}}{\text{Number of Pups Born}}$	x 100
Viability Index (%)[c,d]	=	$\frac{\text{Number of Pups Alive Day 4 Preculling}}{\text{Number of pups born alive}}$	x 100
Preimplantation Loss[e]	=	$\frac{\text{Number of } corpora\ lutea - \text{Number of implantation sites}}{\text{Number of } corpora\ lutea}$	
Postimplantation Loss[e]	=	$\frac{\text{Number of implantation sites} - \text{Number of pups}}{\text{Number of implantation sites}}$	

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

2. Summary Data for Body Weight, Weight Gain, Food Consumption, and Food Efficiency

Body weight data for subchronic males, subchronic females, and satellite females were summarized weekly. Body weight gain, food consumption, and food efficiency data for subchronic males were summarized over weekly intervals, and for the intervals of days 1-15, 15-29, and 1-29 so that any potential effects from cohabitation on these parameters could be evaluated. Body weight gain, food consumption, and food efficiency data for subchronic females and satellite females were summarized over weekly intervals and for test days 1-29 (subchronic females), test days 1-15 of premating (satellite females), test days 0-21 of gestation (satellite females), and test days 0-4 of lactation (satellite females).

3. Statistical Methods

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Gestation Length Implantation Site Numbers Implantation Efficiency Mean Number of Pups per Litter Percent Born Alive 0-4 Day Viability Viability Index Number of *Corpora Lutea* Sex Ratio Pre-implantation Loss Post-implantation Loss Organ Weights	Test for lack of trend[9]	Sequential application[10] of the Jonckheere-Terpstra trend test[11]	Preliminary tests for pairwise comparison
	OR[a]		
	Levene's test for homogeneity[12] and Shapiro-Wilk test[13] for normality[b]	One-way analysis of variance[14] followed with Dunnett's test[15, 16, 17]	Kruskal-Wallis test[18] followed with Dunn's test[19]
Food Efficiency	None	One-way analysis of variance[14] followed with Dunnett's test[15]	
Incidence of Clinical Observations Incidence of FOB Descriptive Parameters Mating Index Fertility Index Gestation Index	None	Cochran-Armitage test for trend[14][c]	
Clinical Pathology[d]	Levene's test for homogeneity[12] and Shapiro-Wilk test[13] for normality[b]	One-way analysis of variance[14] followed with Dunnett's test[15, 16, 17]	Kruskal-Wallis test[18] followed with Dunn's test[19]

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Mean Pup Weights (Covariates: litter size, sex ratio)	None	Linear contrast of the least square means[20]	None

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

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

c If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test[21] with a Bonferroni correction was used.

d When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that data. When an individual observation was recorded as being greater than a certain value, calculations were performed on the recorded value. For example, if specific gravity was reported as >1.083, 1.083 was used for any calculations performed with that data.

a. Statistical Analysis of Neurobehavioral Data (Appendix GG)

- Statistical Analysis of Motor Activity

Motor activity (number and duration of movements) was done by repeated measures ANOVA[22] with day and bin (epoch) as repeated factors, with bin nested within day, possibly after a normalizing, variance stabilizing transformation. Since bin had more than two levels, consideration was given to the variance-covariance structure in testing for significance of treatment effects overall or within a single day or bin. Where the correlations between observations on the same subject in different bins on the same day appear to vary as separation in time increases (a real possibility), either a Huynh-Feldt or Greenhouse-Geisser adjustment was made or an alternative variance-covariance structure (e.g., unstructured,[20] auto-regressive,[23] heterogeneous auto-regressive,[23] or heterogeneous compound symmetry[20]) was used that reflected this varying correlation. Assessment of the need for such an adjustment or alternative variance-covariance structure can be done using Mauchly's criterion[24] for sphericity, through inspection of the sample variance-covariance matrix, or through the use of variance-covariance diagnostics described in Hocking *et al.*,[25] Green and Hocking,[23] Grynovicki and Green,[26] and Searle *et al.*[27]

The responses were assessed for normality using the Shapiro-Wilk[13] test applied to the residuals from the ANOVA model and appropriate plots. If the data was judged non-normal, then a normalizing transformation is sought. If no such transformation can be found, then separate analyses for the responses from each day and bin were done. If no normality problem was found or was resolved by a transformation, then Levene's test[12] for variance homogeneity was done. If significant variance heterogeneity was found from this test and appropriate plots, then a normalizing, variance-stabilizing transformation was sought. If none was found, then separate analyses for the responses from each day and bin were done.

In the context of this repeated measures ANOVA, linear contrasts[28] were estimated to determine treatment effects. A linear contrast for dose trend was estimated as were individual comparisons of treatments to control. This was done on each day, averaging across bins, and in each bin. To control the false positive rate associated with these comparisons, adjustments to the p-values were made based on the significance (or lack thereof) of the Dose-by-Day and Dose-by-Day-by-Bin interactions, and the test for linear trend in the dose-response.

In addition, a repeated measures analysis was done of the daily sums over bins of the responses from each animal. Such sums (or, equivalently so far as conclusions are concerned, averages) were more likely to be normally distributed than were the individual responses, so that separate analyses by each time point was less likely. These data were analyzed by the same method described below for grip strength.

- Statistical Analysis of Grip Strength, Foot Splay, Body Temperature, and Rearing

These endpoints were analyzed by repeated measures ANOVA with day as the only repeated factors, possibly after a normalizing, variance stabilizing transformation. Since day has only 2 levels, the Greenhouse-Geisser[29] conditions were automatically satisfied and no special treatment of the variance-covariance matrix or the tests for treatment effects was needed. Normality and variance homogeneity were evaluated as above, analogous actions were taken where significant non-normality or variance heterogeneity is encountered, and tests for treatment effects were conducted as above, except that bin was not a consideration.

b. Trend Test

For each parameter analyzed with a trend test, the test was applied to the data sequentially. If a significant dose-response was detected, data from the top dose group was excluded and the test repeated until no significant trend was detected.[10]

c. Litter Parameters

For litter parameters, the proportion of affected fetuses per litter or the litter mean was used as the experimental unit for statistical evaluation.[30]

d. Level of Significance

The level of significance selected was $p < 0.05$ for trend tests Levene's, Shapiro-Wilk, Kruskal-Wallis, Dunn's, and linear contrasts. Where the data were tied and the standard large sample version of Jonckheere's test[11] was not applicable, exact p values were calculated using permutation methodology.[31]

RESULTS AND DISCUSSION

A. Test Substance Characterization
(Appendix B)

Non-GLP method development was performed to determine feasibility of characterization of Low DCPD Resin Oil test substance (Haskell Number 25429). The purpose of this method development was also to adjust the sponsor-provided analytical method to instrumentation being used at the performing laboratory. The method provided by the sponsor as well as the final analytical method used to generate the preliminary feasibility data at the performing laboratory are in Appendix B. The sponsor also provided the initial lot analysis of the test substance with the associated chromatogram. Both, the sponsor's analysis and the chromatogram are in Appendix B. Low DCPD Resin Oil test substance was analyzed by gas chromatography (GC) using flame-ionization detection (FID). The representative chromatogram for the test substance is in Appendix B. Because of the insufficient resolution of p-vinyltoluene, m-vinyltoluene and 1,2,4-trimethylbenzene in the test substance chromatogram, the sponsor has decided to use the supplier-provided analysis for the test substance characterization.

Based on the relative agreement between the chromatographic profiles of the test substance received at the testing facility (Haskell Number 25429) and the chromatogram provided by the sponsor, as well as in the corresponding percent composition values for m-vinyltoluene, p-vinyltoluene, indene, and 1,2,4-trimethylbenzene, we believe that the intended test substance was received at the testing facility.

B. Analytical Evaluation of Dosing Formulations
(Appendix C)

1. Chromatography for Dosing Formulations

The concentration of the Low DCPD Resin Oil was expressed as the average value of the concentration for the components from 2 peak areas. Low DCPD Resin Oil eluted from the GC column as resolved peaks with retention times of approximately 2.7 minutes (2.5 minutes/old column) and 3.0 minutes (2.7 minutes/old column). The 2 peak areas represent the components as follows: at 2.7 minutes, the meta-vinyl toluene, ortho-vinyl toluene, para-vinyl toluene, and 1,2,4-trimethylbenzene components and at 3.0 minutes, the indene component. Each peak area was evaluated separately using the internal standard (1.7 minutes or 1.4 minutes/old column) peak area to form a ratio. Respective calibration curves were prepared with this ratio and the samples were evaluated. The concentration of the Low DCPD Resin Oil was expressed as the average value of the concentration for the components from the 2 peak areas. Representative GC chromatograms are shown in Appendix C, Figures 2(a - d). Test substance was not detected in the 0 mg/mL control.

2. Recovery Samples

Detailed analytical results of recovery samples are summarized in Appendix C, Table I. The variability of the analytical method was demonstrated by the coefficients of variation of the recovery results at each targeted dosing concentration over the course of the study. The measured concentrations of Low DCPD Resin Oil for the 17.5 mg/mL level (approximately 14.5 mg/mL used) were 106.3%, 110.3%, and 99.3% of nominal (mean percent recovery = 105.3% ± 5.6, C.V. = 5%). The measured concentrations of Low DCPD Resin Oil for the 62.5 mg/mL level (approximately 53.1 mg/mL used) were 108.4%, 103.0%, and 94.3% of nominal (mean percent recovery = 101.9% ± 7.1, C.V. = 7%). The measured concentrations of Low DCPD Resin Oil for the 187.5 mg/mL level (approximately 189.0 mg/mL used) were 107.5%, 90.7%, and 92.8% of nominal (mean percent recovery = 97.0% ± 9.2, C.V. = 9%). Based on these data, the analytical method performed satisfactory for the all concentrations in the study.

3. Homogeneity/Concentration Verification and Stability Samples from Dosing Formulations

Analytical results from dosing formulations collected on September 10, 2003 and analyzed for homogeneity/concentration verification and stability are shown in Appendix C, Table II and Summary Table 1.

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

Preparation Day Sample Type	Nominal mg/mL	Measured T,M,B[a] mg/mL	Mean (T,M,B) % Nominal	C.V. (%)	Stability[b] % Nominal
10-Sept-03 Homogeneity	0	ND[c]	---	---	---
	17.5	18.1, 17.6, 18.8	104.0	3	101.1
	62.5	68.6, 68.9, 65.8	108.5	3	97.1
	187.5	215, 203, 210	111.5	3	104.5

a Mean results for the analysis of the top (T), middle (M), and bottom (B) samples.
b Samples held 5 hours at room temperature, covered, and not stirred.
c Denotes none detected.

The data for samples collected on September 10, 2003 indicate that the test substance was homogeneously mixed in the vehicle at all levels (C.V.'s = 3, 3, and 3, respectively). The test substance was at the targeted concentration in the samples (± 11.5% of nominal) and was stable in the vehicle when held 5 hours at room temperature.

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

4. Concentration Verification Samples from Dosing Formulations

Analytical results from dosing formulations prepared October 1, 2003 and October 15, 2003 and analyzed for concentration verification are shown in Appendix C, Table III and Summary Table 1.

The following table summarizes the results for all concentration verification analyses.

Preparation Day	Nominal mg/mL	Measured[a] mg/mL	Average % Nominal	CV %
1-Oct-2003	0	ND[b]	---	---
	17.5	17.9, 19.2	106.3	5
	62.5	61.3, 66.0[c]	101.9	5
	187.5	214[c], 182	105.6	11
15-Oct-2003	0	ND[b]	---	---
	17.5	20.3, 19.1	112.6	4
	62.5	55.1, 56.7	89.4	2
	187.5	170[d], 162	88.5	3

a Duplicate samples per level were analyzed. C.V. calculated to verify uniformity of mixture.
b Denotes none detected.
c Mean result of duplicate reanalysis of the original sample. Original analysis not reported due to error in preparation for analysis.
d Mean result of original analysis and duplicate reanalysis of the original sample.

The data for samples collected on October 1, 2003 indicate that the test substance was uniformly mixed in the vehicle at all levels (C.V.'s = 5, 5, and 11, respectively) and that the test substance was at the targeted concentration (± 6.3% of nominal). The CV of 11% for the 187.5 mg/mL level was an indication of analytical variability in the analysis and was not due to the mixing of the test substance in the vehicle. This variability was indicated by the analysis of the recovery samples at this level during the study (CV = 9).

The data for samples collected on October 15, 2003 indicate that the test substance was uniformly mixed in the vehicle at all levels (C.V.'s = 4, 2, and 3, respectively) and that the test substance was at the targeted concentration (± 12.6% of nominal).

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

5. Summary of Analytical Evaluation of Dosing Formulations

Data from the analysis of the samples at the start of the study indicate that the test substance was mixed homogeneously, was at the targeted levels, and stable under the conditions of study. The data for the concentration verification indicated that the test substance was mixed uniformly in the vehicle and at the targeted concentration during the study. Test substance was not found in the 0 mg/mL samples.

C. Test Substance Stability Analyses (Appendices D and E)

Samples of the test substance were analyzed near the beginning and end of the study. These analyses indicated that the Low DCPD Resin Oil was stable over the course of the study.

The average of the Low DCPD Resin Oil was 95.2% ± 2.6 and 100.3% ± 3.6 for samples analyzed on July 1, 2003 and October 20, 2003. This work was reported in analytical reports Dupont-13355[2] and Dupont-13877,[3] (Appendix D and E, respectively). The Low DCPD Resin Oil was reported by the sponsor to be 100.0%. The difference between the sponsor reported value and the experimental data represent analytical variability.

In-Life Toxicology Results

A. Clinical Observations and Mortality in Subchronic Males and Females

1. Subchronic Males:

a. Predosing Clinical Observations (Table 2, Appendix F)

No test substance-related or statistically significant differences in the incidences of clinical signs occurring prior to daily dosage administration were observed for any dosage in male rats.

b. Postdosing Clinical Observations (Table 3, Appendix F)

Following administration of the test substance, male rats in the 375 mg/kg/day Low DCPD Resin Oil group had test substance-related, statistically significant increases in the incidences of stained chin and wet chin. Single instances of stained chin lasting 1-2 days for each incidence were observed in the 6 affected males. Single incidences of wet chin lasting 1-13 days were observed in the 7 affected males administered 325 mg/kg/day.

In addition, the incidences of stained chin and wet chin were increased (not statistically significant) in males administered 125 mg/kg/day. Single incidences of stained chin lasting only 1 day were observed in 1 affected male and single incidences of wet chin lasting only 1 day were observed in 2 affected males administered 125 mg/kg/day.

c. Detailed Clinical Observations (Table 4, Appendix G)

No test substance-related or statistically significant differences in the incidences of clinical signs in an open field arena were observed for any dosage in male rats.

d. Mortality

Unscheduled mortality did not occur during the study.

2. Subchronic Females

a. Predosing Clinical Observations (Table 5, Appendix H)

No test substance-related or statistically significant differences in the incidences of clinical signs occurring prior to daily dosage administration were observed for any dosage in female rats.

b. Postdosing Clinical Observations (Table 6, Appendix H)

Following daily administration of the test substance, female rats in the 375 mg/kg/day Low DCPD Resin Oil group had test substance-related, statistically significant increases in the incidences of stained chin and wet chin. The incidences of stained chin all occurred on the first day of dosing, and were not observed subsequently. Two animals each had 1 instance of wet chin, lasting only 1 day. However, 3 of the animals affected with wet chin had episodes that lasted 7-18 days. One female in the 125 mg/kg/day group also exhibited wet chin that lasted for 11 days.

c. Detailed Clinical Observations (Table 7, Appendix I)

No test substance-related or statistically significant differences in the incidences of clinical signs observed in an open field arena were observed for any dosage in female rats.

d. Mortality

Unscheduled mortality did not occur during the study.

B. Body Weight and Weight Gain in Subchronic Males and Females

1. Subchronic Males (Tables 8-9, Appendix J)

Test substance-related, statistically significant decreases in body weight and weight gain were observed in males administered 125 or 375 mg/kg/day. Body weight was significantly decreased on test day 22 for 375 mg/kg/day males, and was 10% lower than the control value on test day 29. Weight gain in 375 mg/kg/day males was significantly decreased for the intervals of test days 1-8, 8-15, 15-22, 1-15, and 1-29. Mean weight gain was 24%, 25%, and 24% lower than the control values for the intervals of test days 1-15, 15-29, and 1-29, respectively.

Body weight was also significantly decreased on test day 22 for 125 mg/kg/day males, and was 7% lower than the control value on test day 29. Weight gain for 125 mg/kg/day males was also significantly decreased during the intervals of test days 1-8, 8-15, 15-22, 1-15, and 1-29. Mean weight gain was 26% and 16% lower than the control values for the intervals of test days 1-15 and 1-29, respectively.

No test substance-related effects or statistically significant differences on body weight or weight gain were observed in males administered 35 mg/kg/day Low DCPD Resin Oil.

2. Subchronic Females (Tables 10-11, Appendix K)

Test substance-related, statistically significant decreases in body weight and weight gain were observed in 375 mg/kg/day females for test day 29, and over the interval of test days 1-29. Body weight was 5% lower than the control value on test day 29, and weight gain over the interval of test days 1-29 was 14% lower compared to the mean control value. No test substance-related effects or statistically significant trends in body weight or weight gain were observed in females administered 35 or 125 mg/kg/day of Low DCPD Resin Oil.

C. Food Consumption and Food Efficiency in Subchronic Males and Females

1. Males During Premating (Tables 12-13, Appendix L)

Test substance-related, statistically significant decreases in food consumption and food efficiency were observed in 125 and 375 mg/kg/day males. Food consumption was significantly decreased in 375 mg/kg/day males during test days 1-8, 8-15, and was decreased 10% compared to the control value over the interval of test days 1-15. Food consumption was also significantly decreased in 125 mg/kg/day males during test days 1-8, 8-15, and was decreased 12% compared to the control value over the interval of test days 1-15. Food consumption was transiently decreased in the 35 mg/kg/day males during test days 8-15, however, there were no effects on body weight or weight gain in this group, and therefore, the transient decrease was not considered to be adverse.

Food efficiency was significantly decreased in 375 mg/kg/day males during test days 1-8, 8-15, and was decreased 15% compared to the control value over the interval of test days 1-15. Food efficiency was also significantly decreased in 125 mg/kg/day males during test days 1-8, and was decreased 16% compared to the control value over the interval of test days 1-15. No test substance-related or statistically significant differences in food efficiency were observed in males administered 35 mg/kg/day or below.

2. Subchronic Females (Tables 14-15, Appendix M)

Test substance-related, statistically significant decreases in food consumption and food efficiency were observed in 375 mg/kg day females. Food consumption was significantly decreased in 375 mg/kg/day females during test days 1-8, 8-15, 15-22, 22-29, and was decreased 8% compared to the control value over the interval of test days 1-29. Females in the 125 mg/kg/day group had transiently decreased food consumption during test days 1-8 only. Since food consumption for 125 mg/kg/day females over the interval of test days 1-29 was similar to the control value, the transient decrease during test days 1-8 was not considered to be adverse.

No test substance-related effects or statistically significant effects on food consumption were observed in subchronic females administered 35 mg/kg/day Low DCPD Resin Oil. In addition, no test substance-related effects or statistically significant effects on food efficiency were observed in subchronic females for any dosage.

D. Clinical Signs and Mortality in Satellite Females

1. Predosing Clinical Observations During Premating and Cohabitation (Table 16, Appendix N)

There were no test substance-related clinical observations prior to daily dosage administration during the premating period.

2. Postdosing Clinical Observations During Premating and Cohabitation (Table 17, Appendix N)

Following administration of the test substance, female rats in the 375 mg/kg/day Low DCPD Resin Oil group had test substance-related, statistically significant increases in the incidence of wet chin. In addition, 1 female in the 375 mg/kg/day group also had stained chin. Each of the 3 dams affected with wet chin had 1 episode lasting 5-12 days. Stained chin was observed in 1 animal, once, lasting only 1 day.

3. Predosing Clinical Observations During Gestation (Table 18, Appendix O)

Female rats administered 375 mg/kg/day Low DCPD Resin Oil had a statistically significant increase in the incidence of stained perineum observed prior to the daily administration of the test substance during the gestation period. This sign was transient in one animal, being observed only on gestation days 1-2, and was observed for gestation days 0-21 in a second animal.

4. Postdosing Clinical Observations During Gestation (Table 19, Appendix O)

Following administration of the test substance, female rats in the 375 mg/kg/day Low DCPD Resin Oil group had a test substance-related, statistically significant increase in the incidence of wet chin following dosing. Each affected rat only had 1 episode of wet chin lasting 3-19 days. In addition, 1 rat in the 125 mg/kg/day group also had 1 episode of wet chin that lasted only 1 day.

5. Predosing Clinical Observations During Lactation (Table 20, Appendix P)

One female rat administered 375 mg/kg/day Low DCPD Resin Oil had a single episode of stained perineum on lactation days 0-4 observed prior to the daily administration of the test substance during the lactation period.

6. Postdosing Clinical Observations During Lactation (Table 21, Appendix P)

Following daily administration of the dosing formulations, no test substance-related clinical signs of toxicity were observed in satellite females.

7. Mortality

Unscheduled mortality did not occur during the study.

E. Mean Body Weights and Body Weight Gains in Satellite Females

1. Satellite Females During Premating (Tables 22-23, Appendix Q)

Statistically significant, test substance-related decreases in body weight and weight gain were observed in 375 mg/kg/day satellite females during the premating period. Body weight was significantly decreased 4% and 3% for test days 8 and 15, respectively. A statistically significant, decrease (31%) in body weight gain occurred during test days 1-8. However, over the interval of test days 1-15, body weight gain of 375 mg/kg/day satellite females was only 14% lower than the control value (not statistically significant).

2. Satellite Females During Gestation (Tables 24-25, Appendix R-S)

Test substance-related, statistically significant decreases in body weight and weight gain occurred in 375 mg/kg/day satellite females during gestation days 0, 7, 14, and 21, and over the interval of gestation days 0-21 respectively. Body weight of 375 mg/kg/day satellite females was decreased 4%, 5%, 6%, and 6% compared to the control values for test days 0, 7, 14, and 21, respectively. Body weight gain for 375 mg/kg/day females was decreased 9% compared to the control value over the interval of test days 0-21. The decreased body weight and weight gain correlated with decreased body weight and weight gain during the premating period and in subchronic females; therefore, they were considered to be test substance related and adverse. No test substance-related effects or statistically significant trends in body weight or weight gain were observed in females administered 125 mg/kg/day or below.

3. Satellite Females During Lactation (Tables 26-27, Appendix T)

Test substance-related, statistically significant decreases in body weight occurred in 125 and 375 mg/kg/day satellite females on lactation days 0 and 4. Body weights were 7%, and 7% lower than the control value for 125 and 375 mg/kg/day females on lactation day 0. Body weights were 8% and 7% lower than the control value for 125 and 375 mg/kg/day on lactation day 4. However, no test substance-related effects occurred on body weight gain during lactation days 0-4. No test substance-related or statistically significant effects were observed in body weight or weight gain during the lactation period for dosages of 35 mg/kg/day and below.

F. Mean Food Consumption and Food Efficiency in Satellite Females

1. Satellite Females During Premating (Tables 28-29, Appendix U)

No test substance-related trends or statistically significant differences on food consumption or food efficiency were observed in females administered any dosage of Low DCPD Resin Oil during premating.

2. Satellite Females During Gestation (Tables 30-31, Appendix V)

No test substance-related trends or statistically significant differences on food consumption or food efficiency were observed in females administered any dosage of Low DCPD Resin Oil during gestation.

3. Satellite Females During Lactation (Tables 32-33, Appendix W)

No test substance-related trends or statistically significant differences on food consumption or food efficiency were observed in females administered any dosage of Low DCPD Resin Oil during lactation.

G. Summary of Clinical Observations, Body Weight, and Food Consumption Data in Subchronic Males, Subchronic Females, and Satellite Females

1. Summary of Clinical Observations in Subchronic Males, Subchronic Females, and Satellite Females

Test substance-related increases in the incidences of stained fur, and/or wet fur were observed in males, subchronic females, and satellite females following administration of 375 mg/kg/day Low DCPD Resin Oil. Stained and/or wet fur were also occasionally observed in males, subchronic females, and satellite females administered 125 mg/kg/day. These clinical signs were not present during either the detailed clinical observations in an open field arena or during the FOB evaluation.

2. Summary of Body Weight Data in Subchronic Males, Subchronic Females, and Satellite Females

Test substance-related decreases in body weight and/or weight gain were observed in males, subchronic females, and satellite females administered 375 mg/kg/day of the test substance. In addition, instances of decreased body weight and/or weight gain were also observed in males administered 125 mg/kg/day of the test substance and in satellite females during lactation.

3. Summary of Food Consumption Data in Subchronic Males, Subchronic Females and Satellite Females

Test substance-related decreases in food consumption and food efficiency were observed in 125 mg/kg/day and above males, and in 375 mg/kg/day subchronic females, which correlated with the decreased body weight and weight gain noted above.

H. Reproductive Indices (Table 34, Appendices X-Y)

No test substance-related effects or statistically significant trends in mating index, fertility index, gestation length, number of implantation sites, implantation efficiency, pre-implantation loss, post-implantation loss, or number of *corpora lutea* were observed for any dosage of the test substance.

I. Offspring Data

1. Clinical Observations in Offspring (Table 35, Appendix Z)

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

2. Litter Size, Sex Ratio and Pup Survival (Table 36, Appendix AA)

No statistically significant trends were observed on the number of pups born, number of pups born alive, sex ratio, gestation index, or litter survival for postnatal days 0-4 in the offspring from any dosage group. The mean percent of pups born alive in the 375 mg/kg/day group was significantly lower than the control group (98.1% born alive in the 375 mg/kg/day group compared to 100% for the control group) due to 3 litters in which 1 pup per litter was born dead. In addition, there was a trend toward decreased litter survival for postnatal days 0-4 due to mortality of 5 pups in the litter produced by animal number 95 (375 mg/kg/day group) that died between lactation days 0 and 1. The litter size for this dam was 19 pups compared to a group mean of 14.9 pups and a control mean of 13.6 pups. The pups from the affected litter were also small with weights ranging from 3.6 g to 4.9 g compared to a group mean of 6.0 g and a control mean of 6.7 g. These data suggest that the pup mortality between lactation days 0 and 1 for the litter produced by animal number 95 could be due to the large litter size. In addition, fetal mortality did not occur in a range-finding study [(1)] at dosages up to 750 mg/kg/day.

3. Pup Weights (Table 37, Appendix BB)

Test substance-related, statistically significant decreases in mean pup weight were observed for the 375 mg/kg/day group on postnatal days 0, 1, and 4 (10%, 13%, and 15%, respectively).

4. Summary of Offspring Data

Test substance-related decreases in mean pup weight were observed in offspring from the 375 mg/kg/day group. No effects were observed on the number of pups born, number of pups born alive, sex ratio, gestation index, external abnormalities, or litter survival for postnatal days 0-4 in the offspring from any dosage group.

J. Neurobehavioral Observations in Males and Subchronic Females

1. Grip Strength, Hindlimb Splay, Rearing, and Body Temperature (Tables 38-39, Figures 1-6, Appendix CC)

No test substance-related effects or statistically significant differences were observed in forelimb grip strength, hindlimb grip strength, hindlimb splay, body temperature (males), or rearing during the baseline or week 4 evaluations in either males or subchronic females administered any dosage of Low DCPD Resin Oil. During the week 4 evaluation, body temperature for females was significantly increased compared to the control value. However, the mean was within the historical control range 34.0-36.8°C and, therefore, this statistical difference was not considered to be test substance-related.

2. Functional Observational Battery (Tables 40-41, Appendix DD)

No test substance-related or statistically significant differences in any of the 38 FOB parameters were observed during the baseline or week 4 evaluations in either males or subchronic females administered any dosage of Low DCPD Resin Oil.

3. Motor Activity (Tables 42-45, Figures 7-10, Appendices EE-FF)

No test substance-related effects or statistically significant differences in duration of movements or number of movements were observed in the male or subchronic female rats administered any dosage of the test substance.

4. Summary of Neurobehavioral Data

No test substance-related effects on forelimb grip strength, hindlimb grip strength, hindlimb splay, rearing, body temperature, motor activity, or FOB parameters were observed in the male or subchronic female rats administered any dosage of the test substance.

K. Clinical Pathology Data

1. Hematology
(Tables 46-47, Appendix HH)

There were no adverse changes in hematologic parameters in male or female rats. The following treatment-related changes in mean hematologic parameters were not considered to be adverse:

- Red cell distribution width and reticulocyte count were minimally increased in female rats dosed with 375 mg/kg/day at test day 31 (means were 105% and 134% of control group means, respectively). In addition, more polychromatophilic red cells were noted on peripheral blood smears from rats in this group. These 3 changes indicated that red cell production was minimally increased. However, because this process did not affect the red cell mass, it was considered to be non-adverse.

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

- Increased reticulocytes in male rats dosed with 125 mg/kg/day at test day 30.
- Decreased monocytes in female rats dosed with 35 mg/kg/day at test day 31.

2. Coagulation
(Tables 48-49, Appendix HH)

There were no statistically significant or treatment-related changes in coagulation parameters in male or female rats.

3. Clinical Chemistry
(Tables 50-51, Appendix HH)

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

- Creatinine was minimally increased in males dosed with 125 or 375 mg/kg/day, and in females dosed with 375 mg/kg/day (means were 117%, 117%, and 126% of control group means, respectively). These changes were possibly due to treatment. Increased creatinine may be caused by decreased glomerular filtration of creatinine. However, in this study, other markers of decreased glomerular filtration (urea nitrogen and phosphorus) were unaffected by treatment. Histologically, there were increased renal tubular hyaline droplets in male rats only dosed with 35, 125, or 375 mg/kg/day. However, on 2 related studies with similar compounds,[32,33] there were no increases in serum creatinine values, although renal tubular hyaline droplets were more pronounced. Therefore, although increased creatinine was possibly due to treatment, it was considered to be non-adverse because of the lack of changes in correlative clinical pathology parameters, and the lack of other relevant adverse effects on the kidney.

- Glucose was minimally decreased in males dosed with 125 or 375 mg/kg/day (means were 93% and 88% of control group mean). These changes were possibly due to treatment at 375 mg/kg/day. However, the range of individual animal data was similar across the control and treated groups; thus, this change was not considered to be adverse.

- Albumin was minimally increased in males dosed with 375 mg/kg/day (mean was 104% of control group mean). This change was considered to be unrelated to treatment due to the similar range of values across all dose groups.

Bilirubin was minimally decreased in females dosed with 375 mg/kg/day (mean was 82% of control group mean). In this group, there was histologic evidence of enzyme induction (centrilobular hypertrophy), and liver weights were increased. Decreased bilirubin was likely to be secondary to enzyme induction, as a result of a physiologic response to dosing of a xenobiotic. Therefore, these changes were considered to be non-adverse.

4. Summary of Clinical Pathology Data

In conclusion, dosing of the test substance to rats for 4 weeks resulted in the following clinical pathology changes: minimally increased production of red cells (increased red cell distribution width, reticulocytes, and polychromasia) in females dosed with 375 mg/kg/day, minimally decreased glucose in males dosed with 375 mg/kg/day, minimally increased creatinine in males and females dosed with 375 mg/kg/day, and minimally decreased serum bilirubin in females dosed with 375 mg/kg/day. All of these effects were considered to be non-adverse.

Therefore, under the conditions of this study and for the clinical pathology parameters measured, the no-adverse-effect level was 375 mg/kg/day for males and females, based on the lack of adverse effects at any dose.

Anatomic Pathology Evaluation in Subchronic Males And Females

A. Mortality

There were no test substance-related deaths. All 96 rats survived until the scheduled sacrifice date.

B. Organ Weight Data
(Tables 52-53, Appendix II)

In the subchronic toxicity study, test substance-related increases in liver weights and decreases in thymus weights were observed in males and females. Since mean final body weights were decreased in both males and females, in a dose-related pattern, mean absolute organ weights were often decreased as well. Therefore, mean organ weight/body weight ratios (% body weight) were most useful in determining test substance-related organ weight effects. Treatment-related body weight effects are presented elsewhere in this report.

Test Substance-Related Effects on Mean Absolute and Relative Organ Weights In Male and Female Rats

	Male				Female			
Dose (mg/kg/day):	0	35	125	375	0	35	125	375
Final Body Weight (grams)	387.8	379.3	358.8#	348.0#	243.3	239.3	234.2	228.4#
Liver								
absolute wt. (grams)	12.0	11.9	11.4	12.3	7.35	7.66	7.70	7.91
liver wt./body wt. x 100	3.09	3.14	3.17	3.53#	3.01	3.19	3.29#	3.46#
liver wt./brain wt. x 100	595	597	562	621	394	413	423	426
Thymus								
absolute wt. (grams)	0.50	0.49	0.42#	0.38#	0.44	0.41	0.42	0.38
thymus wt./body wt. x 100	0.13	0.13	0.12#	0.11#	0.18	0.17	0.18	0.16
thymus wt./brain wt. x 100	25.0	24.4	20.6#	19.2#	23.5	22.3	22.9	20.3

Trend test (Jonckheere-Terpstra) significant
- Underlined values were interpreted to be test-substance related weight effects.
Values are rounded off from data included in tables 52-53.

1. Liver

Liver weight parameters were increased in the high-dose males and the mid- and high-dose females. Mean relative liver (liver/body) weights were increased 14% in high-dose males, 15% in high-dose females, and 9% in mid-dose females, as compared to their respective controls. Each of these increases was statistically significant by the trend test. These liver weight effects corresponded to treatment-related hepatocellular hypertrophy at the same dose levels (see Microscopic Findings).

2. Thymus

A decrease in mean relative thymus (thymus/body) weight was observed in mid-dose males and high-dose males and females, but was not considered indicative of toxicity to the thymus. While decreases in mean absolute and mean relative (thymus/brain) thymus weights in treated groups appeared to parallel decreases in mean final body weights, the thymus effect exceeded the body weight effect at these dose levels. Mean relative thymus weight (thymus/body weight) was decreased 11% in mid-dose males, 16% in high-dose males, and 9% in high-dose females, as compared to the respective control means (calculated from Tables 52-53). The decreased thymic weight parameters were statistically significant in males but not females. Since there was no corresponding microscopic effect on the thymus (see Microscopic Findings), it is likely that this thymus weight effect was largely due to a disproportionate loss of mediastinal thymus-associated fat as compared to total body fat. Therefore, the thymus was not considered to be a target organ.

3. Other

All other individual and mean organ weight differences were considered to be spurious and unrelated to test substance administration or directly related to lower body weights. Due to the decrease in mean final body weights, there were associated decreases in the mean absolute weights of some body-weight sensitive organs (e.g., heart and spleen). Similarly, there were increases in the mean relative organ to body weight ratio (organ weight/body weight) of body-weight insensitive organs (e.g., kidneys, adrenals, brain, testes).

4. Kidney

Kidney weights were not affected by test substance administration in male and female rats.

In males, mean absolute and mean relative kidney (kidney/brain) weights were only marginally increased (3% and 5%, respectively) at the high-dose, as compared to controls. While the mean relative kidney (kidney/body) weight was significantly increased 15% at the high-dose, the increase was largely due to the 10% decrease in mean final body weight. A statistically significant decrease (7%) in mean final body weight in the mid-dose males was responsible for the increase (6%) in mean relative kidney (kidney/body) weight

Similarly, in females, mean absolute and mean relative kidney (kidney/brain) weights were unchanged at the high-dose, as compared to controls. While the mean relative kidney (kidney/body) weight was increased a statistically significant 7% at the high-dose, the increase was entirely due to the 6% decrease in mean final body weight. Small decreases in mean final body weights in the low- and mid-dose females (2% and 4%, respectively) contributed to the statistically significant increases (6% and 8%, respectively) in mean relative kidney (kidney/body) weights.

5. Adrenal

Adrenal gland weights were not affected by test substance administration in male and female rats.

Although mean relative adrenal (adrenal/body) weights were increased a statistically significant 11% in both mid- and high-dose females, relative to the control value, the difference was

considered a reflection of the lower mean final body weights and not an adrenal gland effect. Mean absolute adrenal weights were increased only 7% and 6% in the mid- and high-dose females, respectively. Also, there was no test substance-related microscopic effect in the adrenals (see Microscopic Findings). Adrenal gland weight parameters were similar in all male dose groups; adrenal glands were not weighed in the satellite females.

Mean Absolute and Relative Kidney and Adrenal Gland Weights In Male and Female Rats

	Male				Female			
Dose (mg/kg/day):	0	35	125	375	0	35	125	375
Final Body Weight (grams)	387.8	379.3	358.8#	348.0#	243.3	239.3	234.2	228.4#
Kidney								
absolute wt. (grams)	3.20	3.17	3.15	3.30	1.87	1.94	1.94	1.87
kidney wt./body wt. x 100	0.83	0.84	0.88#	0.95#	0.77	0.81#	0.83#	0.82#
kidney wt./brain wt. x 100	159	159	155	167	100	105	106	101
Adrenal								
absolute wt. (grams)	0.060	0.061	0.057	0.055	0.068	0.066	0.073	0.072
adrenal wt./body wt. x 100	0.016	0.016	0.016	0.016	0.028	0.027	0.031#	0.031#
adrenal wt./brain wt. x 100	3.01	3.05	2.82	2.78	3.64	3.54	4.02	3.86

Trend test (Jonckheere-Terpstra) significant
- Underlined values were interpreted to be test-substance related weight effects.
Values are rounded off from data included in tables 52-53.

C. Gross Observations
(Tables 55-56, Appendix JJ)

There were no test substance-related gross observations in the 28-day subchronic toxicity study. All gross observations at necropsy were interpreted to be naturally occurring background lesions that are typical of rats of this age and strain.

D. Microscopic Observations
(Tables 58-59, Appendix JJ)

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

Test Substance-Related Effects on the Incidence of Microscopic Findings In Male and Female Rats

	Male				Female			
Dose (mg/kg/day):	0	35	125	375	0	35	125	375
Number of Rats:	12	12	12	12	12	12	12	12
Kidney								
Hyaline droplets, increased	0	12	12	12	0	-	-	0
Liver								
Hypertrophy, hepatocyte, centrilobular	0	0	0	10	0	0	3	12
Thyroid Gland								
Hypertrophy, follicular cell	2	3	2	4	0	-	-	1

- underlined values were interpreted to be test-substance related increases in microscopic findings.

1. Kidney

An increase in hyaline droplets within the epithelium of the proximal convoluted tubule (PCT) of kidneys was observed in all male rats exposed to the test substance. The increase in PCT hyaline droplets was graded as minimal to moderate and was dose related. In the 375 mg/kg/day males (12 rats), most cases (11 rats) were graded as mild while one was graded as moderate; in the 125 mg/kg/day males (12 rats), 10 cases were graded as mild, 2 were graded as minimal; in the 35 mg/kg/day males (12 rats), all cases were graded as minimal. In this 28-day study, there were no cases graded as severe (grade 4) since the hyaline droplet accumulation did not produce renal tubular cell degeneration and necrosis (i.e., hyaline droplet nephropathy). The increase in hyaline droplets observed in this study was not considered to be adverse.

Small quantities of hyaline droplets are a normal finding in the cytoplasm of the renal proximal convoluted tubular epithelium in male rats. They consist of phagolysosomes containing the poorly hydrolysable low molecular weight protein, $\alpha_{2\mu}$ globulin. Normally, approximately 50 mg of this globulin are produced daily in the male rat liver and passed into the glomerular filtrate. More than half of the globulin is reabsorbed by the lining cells of the PCT. Several xenobiotics, including unleaded gasoline and d-limonene, increase the accumulation of hyaline droplets in the PCT by binding to the $\alpha_{2\mu}$ globulin. Excessive accumulation of these hyaline droplets leads to a nephropathy characterized by degeneration and necrosis of tubular epithelium, increased chronic progressive nephropathy with secondary epithelial proliferation, and, potentially following long-term exposure, neoplasia. Since female rats, and most other species including mice, dogs, monkeys, and humans, do not produce significant quantities of the $\alpha_{2\mu}$ globulin, experimental findings related to hyaline droplet accumulation in male rats are not relevant to other species.[34]

2. Liver

In the liver, hypertrophy of centrilobular hepatocytes was observed in all (12 of 12) high-dose females, a few (3 of 12) mid-dose females, and most (10/12) high-dose males. The hypertrophy was graded mild (grade 2) in all high-dose females and minimal (grade 1) in all high-dose males and mid-dose females. Microscopically, hepatocellular hypertrophy was characterized by an increased amount of finely granular eosinophilic cytoplasm within centrilobular hepatocytes. There was no histomorphologic evidence of hepatocellular damage, and hepatic serum enzyme

levels were not elevated (see Clinical Pathology section). Thus, hepatocellular hypertrophy (and the associated increase in liver weights) was considered a test substance-related pharmacological response to the metabolism of a xenobiotic and not adverse.

3. Thyroid

A marginally increased incidence of thyroid follicular cell hypertrophy was present in male rats given 375 mg/kg/day of the test substance. All cases were graded minimal. Follicular cell hypertrophy was characterized by low columnar follicular epithelium with a finely granular or vacuolated cytoplasm. Follicles were decreased in size, irregular in shape, and contained decreased amounts of normal pink colloid. The presence of minimal hypertrophy in 2 of 12 male control rats demonstrated the background incidence of this physiological change in males. The 1 case of minimal follicular hypertrophy observed in a high-dose female was considered to be within the range of normal findings in control rats.

An increase in the incidence and severity of thyroid follicular cell hypertrophy is indicative of altered thyroid gland homeostasis. Although the follicular cell response observed in this study (minimal hypertrophy) was within the range of normal physiological response, the effect is potentially proliferative and adverse, especially in the rat. Since follicular cell hypertrophy is consistent with several different mechanisms of altered thyroid gland homeostasis, the specific cause of the hypertrophic response in this study is not clear. In rats, a common cause of thyroid follicular cell hypertrophy is an increase in the rate of hepatic thyroxine (T_4) glucuronidation and subsequent biliary excretion.[35] An increased rate of T_4 excretion results in lower T_4 blood levels which triggers an increase in the release of pituitary-derived thyroid stimulating hormone (TSH), resulting in thyroid follicular cell hypertrophy. Many inducers of hepatic cytochrome P450 isoenzymes in the rat are known to secondarily cause thyroid follicular cell hypertrophy by this mechanism. In this study, the presence of test substance-related hepatocellular hypertrophy in the males and females demonstrates that hepatocellular enzyme systems have been induced and that T_4 excretion may have been secondarily increased. Due to differences in T_4 half-life, thyroglobulin binding, and the ease of UDP-glucuronyl-transferase induction, rats are much more susceptible than humans to secondary thyroid follicular cell hypertrophy.[35]

4. Other

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

E. Anatomical Pathology Conclusions for Subchronic Toxicity Evaluation

Exposure to 35, 125, and 375 mg/kg/day of the test substance for approximately 30 days produced a dose-related increase in renal tubular hyaline droplets in male rats. Hyaline droplet nephropathy was not observed. Increased hyaline droplets were not observed in females. Minimal to mild hepatocellular hypertrophy was observed in most males and females given 375 mg/kg/day and in a few females given 125 mg/kg/day. An associated increase in liver weight parameters was observed in high-dose males and females and mid-dose females. A slight increase in the incidence of minimal thyroid follicular hypertrophy was observed in male rats given 375 mg/kg/day of the test substance. Thymus weight was decreased in 125 and 375 mg/kg/day

males and in 375 mg/kg/day females; however, the decreased weight was not considered adverse since there was no corresponding microscopic effect on the thymus.

The hyaline droplet accumulation in male rats was not considered to be an adverse effect in these animals, and it is considered species and sex specific and not predictive of an effect in other species. The hepatocellular hypertrophy and slightly increased liver weights in both sexes was consistent with enzyme induction as a pharmacological response to a xenobiotic and was not considered to be adverse. The thyroid effect, although marginal, was regarded as potentially adverse.

Under the conditions of this study, the NOAEL for pathology for male rats was 125 mg/kg/day based on the increase in thyroid follicular hypertrophy. The NOAEL for pathology for female rats was 375 mg/kg/day, based on the finding of only non-adverse hepatocellular hypertrophy in females given 125 and 375 mg/kg/day of the test substance.

Anatomic Pathology Evaluation In Satellite Females

A. Mortality

In the P_1 adult generation, there was no test substance-related effect on mortality. There were no deaths among the 48 males (subchronic toxicity study) or 48 satellite females.

B. Organ Weight Data
(Table 54, Appendix KK)

Data for the P_1 males is presented with the subchronic toxicity study since those males were cohabited with the P_1 female satellite groups for production of the F_1 offspring.

In the satellite P_1 females, a test substance-related organ weight increase was observed in the liver of rats given 375 mg/kg/day. At the high-dose, the mean relative liver (liver/body) weight was increased 13% over the control mean. A marginal increase (5%) in the mean relative liver (liver/body) weight in the mid-dose satellite females was considered to be similar to the controls. In the subchronic study, the mid-dose females had a statistically significant 9% increase that was interpreted to be test substance-related.

Test Substance-Related Effects on Mean Absolute and Relative Organ Weights In P_1 Female Rats (Satellite Groups)

	Female			
Dose (mg/kg/day):	0	35	125	375
Final Body Weight (grams)	326.7	317.9	301.9#	304.2#
Liver				
absolute wt. (grams)	13.7	13.1	13.4	14.4
liver wt./body wt. x 100	4.19	4.12	4.41	4.72#

Trend test (Jonckheere-Terpstra) significant
- Underlined values were interpreted to be test-substance related weight effects.

All other individual and mean organ weight differences were considered to be spurious and unrelated to test substance administration or directly related to lower body weights.

C. Gross Observations
(Table 57, Appendix LL)

Data for the P_1 males is presented with the subchronic toxicity study.

No test substance-related gross observations were observed in the P_1 females (satellite females). All gross observations at necropsy were interpreted to be naturally occurring background lesions that are typical of rats of this age and strain.

D. Microscopic Findings
(Table 60, Appendices MM)

Microscopic examination of P_1 adults included examination of the reproductive organs of the four cohabiting pairs that failed to produce litters (i.e., reproductive failures). The affected pairs included 2 Group I/II-0 pairs (male animal number 36 and female animal number 94; male animal number 44 and female animal number 118), 1 Group V/VI-0 pair (male animal number 9 and female animal number 78), and 1 Group VII/VIII-0 pairs (male animal number 40 and female animal number 127).

Microscopic examination of the reproductive organs of the 4 non-producing pairs did not reveal any changes that would account for the failure to produce litters. Based on pathology, and an incidence that was not dose-related, the failure to produce litters by these 4 pairs was not test substance-related.

E. Anatomical Pathology Conclusions for Reproductive Toxicity

For pathology, the NOAEL was 375 mg/kg/day (the highest dose level) for the female satellite groups based on the finding of only a pharmacological, non-adverse, increase in liver weight parameters in the 375 mg/kg/day dose group.

The pathology results of the P_1 male rats are included in the subchronic toxicity study.

CONCLUSIONS

Test substance-related increases in the incidences of stained fur, and/or wet fur were observed in males, subchronic females, and satellite females following administration of 375 mg/kg/day Low DCPD Resin Oil. Stained and/or wet fur were also occasionally observed in males, subchronic females, and satellite females administered 125 mg/kg/day. These clinical signs were not present during either the detailed clinical observations in an open field arena or during the FOB evaluation.

Test substance-related decreases in body weight and/or weight gain were observed in males, subchronic females, and satellite females administered 375 mg/kg/day of the test substance. In addition, instances of decreased body weight and/or weight gain were also observed in males administered 125 mg/kg/day of the test substance. Test substance-related decreases in food consumption and food efficiency occurred in 125 mg/kg/day and above males, and in 375 mg/kg/day subchronic females which correlated with the decreased body weight and weight gain.

No test substance-related effects or statistically significant trends in mating index, fertility index, gestation length, number of implantation sites, implantation efficiency, pre-implantation loss, post implantation loss, or number of *corpora lutea* were observed for any dosage of the test substance.

Test substance-related decreases in mean pup weight were observed in offspring from the 375 mg/kg/day group. No effects were observed on the number of pups born, number of pups born alive, sex ratio, gestation index, external abnormalities, or litter survival for postnatal days 0-4 in the offspring from any dosage group.

No test substance-related effects on forelimb grip strength, hindlimb grip strength, hindlimb splay, rearing, body temperature, motor activity, or FOB parameters were observed in the males or subchronic female rats administered any dosage of the test substance.

There were no adverse, statistically significant, or treatment-related changes in hematological, coagulation, or clinical chemistry parameters in male or subchronic female rats.

Administration of 35, 125, or 375 mg/kg/day of the test substance for approximately 30 days produced a dose-related increase in renal tubular hyaline droplets in male rats, however, hyaline droplet nephropathy was not observed. Increased hyaline droplets were not observed in females. The hyaline droplet accumulation in male rats was not considered to be an adverse effect of the test substance. Renal tubular hyaline droplet association is species and sex specific, and is not predictive of an effect on other species.

Minimal to mild hepatocellular hypertrophy and associated increases in liver weight parameters were observed in 375 mg/kg/day males, and in 125 and 375 mg/kg/day females; however, this change is considered to be secondary to enzyme induction as a pharmacological response to a xenobiotic, and was not considered to be adverse.

Minimal thyroid follicular hypertrophy was observed in 375 mg/kg/day males, which was considered to be test substance-related and potentially adverse.

Thymus weight was decreased in 125 and 375 mg/kg/day males, and in 375 mg/kg/day females. However, there was no corresponding microscopic effect on the thymus.

No morphological changes were detected in reproductive tissues for the satellite females administered any dosage of the test substance.

The no-observed-effect level (NOEL) and the no-observed-adverse-effect level (NOAEL) for offspring is 125 mg/kg/day based on decreased pup body weight at 375 mg/kg/day.

The NOEL and NOAEL for reproduction is 375 mg/kg/day based on the absence of effects on mating index, fertility index, number of implantation sites, implantation efficiency, pre-implantation loss, post-implantation loss, number of *corpora lutea*, and absence of morphological changes in the reproductive organs of males and females at the highest dose tested.

The NOEL and NOAEL for neurobehavioral parameters is 375 mg/kg/day in males and females, the highest dosage tested.

The NOEL and NOAEL for systemic toxicity was 35 mg/kg/day in males and females based on decreased body weight, weight gain, food consumption, and food efficiency (males) at 125 mg/kg/day and above; and on clinical signs of toxicity in 125 mg/kg/day and above males and females.

The NOEL for pathology was considered to be 35 mg/kg/day in subchronic females based on hepatocellular hypertrophy observed in subchronic females at 125 mg/kg/day and above. A NOEL was not determined in males based on an increased incidence of renal tubular hyaline droplets at all dosage levels. The NOAEL in males was considered to be 125 mg/kg/day based on thyroid follicular hypertrophy at 375 mg/kg/day. The NOAEL in females was considered to be 375 mg/kg/day based on the absence of adverse morphological effects observed at any dosage.

RECORDS AND SAMPLE STORAGE

All original records will be retained at Haskell Laboratory, E.I. du Pont de Nemours and Company, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware. Preserved wet tissues, paraffin blocks, histological slides, blood smears, and bone marrow smears will be retained at Haskell Laboratory.

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TABLES

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

Summary of Hematology Values

RBC - red blood cell count
HGB - hemoglobin
HCT - hematocrit
MCV - mean corpuscular volume
MCH - mean corpuscular hemoglobin
MCHC - mean corpuscular hemoglobin concentration
RDW - red cell distribution width
ARET - absolute reticulocyte count
PLT - platelet count
WBC - white blood cell count
ANEU - absolute neutrophil (all forms)
ALYM - absolute lymphocyte
AMON - absolute monocyte
AEOS - absolute eosinophil
ABAS - absolute basophil
ALUC - absolute large unstained cell
NRBC - nucleated red blood cell count
NC - not calculated or not calculable
\- - no data

Summary of Coagulation Values

PT - prothrombin time
APTT - activated partial thromboplastin time

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

NOTES:

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

TABLE 1

SUMMARY OF DOSING FORMUALTION ANALYSES

	Dosing Concentration of Low DCPD Resin Oil (mg/mL)		
Nominal:	**17.5**	**62.5**	**187.5**
Homogeneity Samples 10-Sept-2003			
Top	18.1 (103.4) [a]	68.6 (109.8)	215 (114.7)
Middle	17.6 (100.6)	68.9 (110.2)	203 (108.3)
Bottom	18.8 (107.4)	65.8 (105.3)	210 (112.0)
Average Measured Conc. [b]	**18.2**	**67.8**	**209**
Average Percent Nominal	**(104.0)**	**(108.5)**	**(111.5)**
Standard Deviation [b]	**± 0.60**	**± 1.7**	**± 6.0**
Coefficient of Variation [b]	**3%**	**3%**	**3%**
Stability Samples 5 Hour Room Temperature	17.7 (101.1)	60.7 (97.1)	196 (104.5)
Concentration Verification 1-Oct-2003			
#1	17.9 (102.3)	61.3 (98.1)	214[c] (114.1)
#2	19.2 (109.7)	66.0[c] (105.6)	182 (97.1)
Average Measured Conc. [d]	**18.6**	**63.7**	**198**
Average Percent Nominal	**(106.3)**	**(101.9)**	**(105.6)**
Standard Deviation [d]	**± 0.92**	**± 3.3**	**± 23**
Coefficient of Variation [d]	**5%**	**5%**	**11%**
Concentration Verification 15-Oct-2003			
#1	20.3 (116.0)	55.1 (88.2)	170[e] (90.7)
#2	19.1 (109.1)	56.7 (90.7)	162 (86.4)
Average Measured Conc. [d]	**19.7**	**55.9**	**166**
Average Percent Nominal	**(112.6)**	**(89.4)**	**(88.5)**
Standard Deviation [d]	**± 0.84**	**± 1.1**	**± 5.7**
Coefficient of Variation [d]	**4%**	**2%**	**3%**

a Numbers in parentheses are the respective percent of nominal values.
b Statistics based on the average measured concentration (mg/mL) of the top, middle and bottom of each dosing level.
c Mean result of duplicate reanalysis of the sample. Original analysis was not reported due to aliquot error for the analysis.
d Statistics based on the average measured concentration (mg/mL) of duplicate samples of each dosing level.
e Mean result of the original analysis and duplicate reanalysis of the sample.

TABLE 2

SUMMARY OF CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS (PREDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	I	III	V	VII
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
OBSERVATION				
ALOPECIA	1	0	0	0

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 3

SUMMARY OF CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS (POSTDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	I	III	V	VII
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
OBSERVATION				
STAINED CHIN	0	0	1	6*
WET CHIN	0	0	2	7*

*Statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 4

SUMMARY OF DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	I	III	V	VII
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
PRETEST OBSERVATIONS				
RATS WITH CLINICAL SIGNS	0	0	0	0
DOSING PERIOD OBSERVATIONS				
ALOPECIA	1	0	0	0

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 5

SUMMARY OF CLINICAL OBSERVATIONS IN SUBCHRONIC FEMALE RATS (PREDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II	IV	VI	VIII
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
OBSERVATION				
ALOPECIA	2	0	2	1

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 6

SUMMARY OF CLINICAL OBSERVATIONS IN SUBCHRONIC FEMALE RATS (POSTDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II	IV	VI	VIII
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
OBSERVATION				
STAINED CHIN	0	0	0	4*
WET CHIN	0	0	1	5*

Statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 7

SUMMARY OF DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC FEMALE RATS

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II	IV	VI	VIII
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
PRETEST OBSERVATIONS				
RATS WITH CLINICAL SIGNS	0	0	0	0
DOSING PERIOD OBSERVATIONS				
ALOPECIA	2	0	2	1

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 8

MEAN BODY WEIGHTS (grams) OF SUBCHRONIC MALE RATS

	MEAN BODY WEIGHTS (g)			
Group:	I	III	V	VII
CONCENTRATION(MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
DAYS ON TEST				
1	256.7(10.7)	255.8(10.1)	253.9(10.1)	254.7(10.9)
8	302.6(13.0)	301.7(10.5)	287.0(12.3)	288.2(12.7)
15	349.0(17.7)	343.1(13.6)	322.5(16.7)	325.2(14.2)
22	385.0(20.5)	375.6(13.7)	349.8(15.9)*	348.9(17.7)*
29	418.0(24.3)	411.1(17.0)	388.9(19.7)	377.3(18.3)

Data summarized as Mean (Standard Deviation)

* Statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

TABLE 9

MEAN BODY WEIGHT GAINS (grams) OF SUBCHRONIC MALE RATS

	MEAN BODY WEIGHT GAINS (g)			
Group:	I	III	V	VII
CONCENTRATION(MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
DAYS ON TEST				
1-8	45.9(5.2)	45.9(3.2)	33.1(5.5)*	33.5(4.8)*
8-15	46.5(6.4)	41.4(6.9)	35.5(9.2)*	37.0(4.8)*
15-22	36.0(4.6)	32.5(4.8)	27.4(4.9)*	23.7(5.8)*
22-29	32.9(7.2)	35.5(5.7)	39.1(7.5)	28.4(7.1)
1-15[a]	92.4(10.0)	87.3(8.2)	68.6(12.2)*	70.5(7.8)*
15-29[b]	68.9(10.4)	68.0(9.7)	66.4(8.6)	52.0(7.8)
1-29	161.3(17.6)	155.3(12.4)	135.0(16.8)*	122.6(13.1)*

Data summarized as Mean (Standard Deviation)

* Statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

a Premating period
b Cohabitation period

TABLE 10

MEAN BODY WEIGHTS (grams) OF SUBCHRONIC FEMALE RATS

MEAN BODY WEIGHTS (g)

Group:	II	IV	VI	VIII
CONCENTRATION(MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
DAYS ON TEST				
Day 1	192.9(8.8)	190.6(12.1)	190.4(12.0)	189.2(12.1)
Day 8	212.8(11.0)	208.2(12.6)	205.9(12.1)	207.7(14.4)
Day 15	231.6(17.1)	226.8(14.0)	224.6(16.8)	220.5(16.3)
Day 22	245.2(18.1)	241.6(13.1)	241.2(17.6)	235.9(16.7)
Day 29	257.5(20.8)	255.4(15.3)	252.2(19.5)	244.7(14.5)*

Data summarized as Mean (Standard Deviation)

* Statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

TABLE 11

MEAN BODY WEIGHT GAINS (grams) OF SUBCHRONIC FEMALE RATS

	MEAN BODY WEIGHT GAINS (g)			
Group:	II	IV	VI	VIII
CONCENTRATION(MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
DAYS ON TEST				
1-8	19.9(4.6)	17.6(7.8)	15.4(2.9)	18.5(6.1)
8-15	18.8(8.4)	18.6(6.9)	18.7(8.1)	12.8(5.2)
15-22	13.6(5.8)	14.8(5.0)	16.7(6.5)	15.5(7.7)
22-29	12.2(4.7)	13.8(6.2)	11.0(6.3)	8.8(5.4)
1-29	64.6(12.7)	64.8(11.4)	61.8(14.0)	55.6(9.2)*

Data summarized as Mean (Standard Deviation)

* Statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

TABLE 12

MEAN DAILY FOOD CONSUMPTION (grams/day) OF SUBCHRONIC MALE RATS DURING PREMATING

	MEAN DAILY FOOD CONSUMED PER RAT (g)			
Group:	I	III	V	VII
CONCENTRATION(MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
DAYS ON TEST				
1-8	24.7(1.8)	24.1(1.5)	22.2(1.4)*	22.0(1.3)*
8-15	26.6(2.2)	24.6(1.4)*	23.3(1.5)*	24.2(1.6)*
1-15	25.7(1.9)	24.3(1.3)	22.7(1.2)*	23.1(1.4)*

Data summarized as Mean (Standard Deviation)

* Statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

TABLE 13

MEAN FOOD EFFICIENCY (grams weight gained/grams food consumed) OF SUBCHRONIC MALE RATS DURING PREMATING

	MEAN FOOD EFFICIENCY (g WT GAIN/g FOOD CONSUMED)			
Group:	I	III	V	VII
CONCENTRATION(MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
DAYS ON TEST				
1-8	0.266(0.032)	0.273(0.021)	0.213(0.027)*	0.217(0.026)*
8-15	0.249(0.021)	0.240(0.035)	0.216(0.049)	0.218(0.021)*
1-15	0.257(0.022)	0.257(0.024)	0.215(0.033)*	0.218(0.018)*

Data summarized as Mean (Standard Deviation)

* Statistically significant differences at $p<0.05$ by One Way Analysis of Variance and Dunnett/Tamhane-Dunnett's test.

TABLE 14

MEAN DAILY FOOD CONSUMPTION (grams/day) OF SUBCHRONIC FEMALE RATS

	MEAN DAILY FOOD CONSUMED PER RAT (g)			
Group:	II	IV	VI	VIII
CONCENTRATION(MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
DAYS ON TEST				
1-8	18.4(1.6)	17.6(0.9)	16.9(1.6)*	16.6(1.3)*
8-15	19.7(2.1)	19.4(1.3)	18.9(2.0)	18.0(1.4)*
15-22	18.8(1.6)	18.6(1.4)	18.7(1.9)	17.2(1.3)*
22-29	18.0(1.7)	18.5(1.6)	17.6(1.7)	16.8(0.9)*
1-29	18.7(1.7)	18.5(1.1)	18.0(1.6)	17.2(1.1)*

Data summarized as Mean (Standard Deviation)

* Statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

TABLE 15

MEAN FOOD EFFICIENCY (grams weight gained/grams food consumed) OF SUBCHRONIC FEMALE RATS

MEAN FOOD EFFICIENCY (g WT GAIN/g FOOD CONSUMED)

Group:	II	IV	VI	VIII
CONCENTRATION(MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
DAYS ON TEST				
1-8	0.154(0.030)	0.142(0.063)	0.131(0.025)	0.158(0.046)
8-15	0.134(0.055)	0.136(0.046)	0.137(0.054)	0.102(0.041)
15-22	0.102(0.041)	0.113(0.035)	0.128(0.049)	0.126(0.062)
22-29	0.096(0.033)	0.106(0.046)	0.086(0.048)	0.075(0.045)
1-29	0.122(0.018)	0.125(0.020)	0.122(0.022)	0.116(0.018)

Data summarized as Mean (Standard Deviation)

There were no statistically significant differences at $p<0.05$ by One Way Analysis of Variance and Dunnett/Tamhane-Dunnett's test.

TABLE 16

SUMMARY OF CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING PREMATING AND COHABITATION (PREDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
OBSERVATION				
ALOPECIA	1	1	1	2

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 17

SUMMARY OF CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING PREMATING AND COHABITATION (POSTDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
OBSERVATION				
STAINED CHIN	0	0	0	1
WET CHIN	0	0	0	3*

Statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 18

SUMMARY OF CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING GESTATION (PREDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	11	12	12	11
OBSERVATION				
ALOPECIA	2	5	2	4
CAGEBOARD PLUGS	8	9	4	7
SPERM POSITIVE	8	9	6	7
STAINED PERINEUM	0	0	0	2*
VAGINAL PLUG	3	3	6	4

*Statistically significant trends by Cochran-Armitage test; $p < 0.05$.
This table contains data from females with evidence of copulation observed.

TABLE 19

SUMMARY OF CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING GESTATION (POSTDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	11	12	12	11
OBSERVATION				
WET CHIN	0	0	1	3*

*Statistically significant trends by Cochran-Armitage test; $p < 0.05$.

This table contains data from females with evidence of copulation observed.

TABLE 20

SUMMARY OF CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING LACTATION (PREDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	10	12	11	11
OBSERVATION				
ALOPECIA	2	5	3	4
STAINED PERINEUM	0	0	0	1

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 21

SUMMARY OF CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING LACTATION (POSTDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	10	12	11	11
OBSERVATION				
No Abnormalities Detected	10	12	11	11

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 22

MEAN BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING PREMATING

	MEAN BODY WEIGHTS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
DAYS ON TEST				
1	192.3(8.0)	197.2(11.4)	189.2(7.2)	190.3(7.3)
8	209.3(9.7)	213.5(14.7)	204.9(8.4)	202.0(8.3)*
15	225.9(12.1)	232.0(16.3)	215.4(11.8)	219.3(6.4)*

Data summarized as Mean (Standard Deviation)

* Statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

TABLE 23

MEAN BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS DURING PREMATING

	MEAN BODY WEIGHT GAINS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
DAYS ON TEST				
1-8	17.0(5.6)	16.3(7.5)	15.6(3.9)	11.7(4.0)*
8-15	16.6(6.7)	18.6(4.3)	10.5(5.5)	17.3(6.5)
1-15	33.6(8.6)	34.9(9.8)	26.2(6.9)	29.0(5.2)

Data summarized as Mean (Standard Deviation)

* Statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

TABLE 24

MEAN BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING GESTATION

	MEAN BODY WEIGHTS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	9	12	11	11
GESTATION DAYS				
0	239.7(16.4)	241.5(15.3)	230.0(11.6)	229.2(10.1)*
7	280.8(21.0)	278.8(15.5)	266.9(15.4)	265.6(9.4)*
14	321.3(21.2)	317.9(16.3)	303.5(23.4)	303.0(9.5)*
21	405.0(36.4)	407.9(19.8)	390.6(30.1)	379.6(19.7)*

Data summarized as Mean (Standard Deviation)

* Statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

TABLE 25

MEAN BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS DURING GESTATION

	MEAN BODY WEIGHT GAINS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	9	12	11	11
GESTATION DAYS				
0-7	41.1(7.4)	37.3(8.1)	36.9(6.4)	36.4(5.0)
7-14	40.5(4.4)	39.1(8.8)	36.7(10.2)	37.4(7.3)
14-21	83.7(18.5)	90.1(11.1)	87.0(11.0)	76.6(16.6)
0-21	165.3(27.4)	166.5(18.3)	160.6(21.0)	150.4(16.5)*

Data summarized as Mean (Standard Deviation)

* Statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

TABLE 26

MEAN BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING LACTATION

	MEAN BODY WEIGHTS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	10	12	11	11
LACTATION DAYS				
0	310.3(23.8)	305.3(15.5)	288.8(20.3)*	289.1(15.7)*
4	328.9(21.0)	317.9(25.3)	304.0(19.6)*	305.2(15.4)*

Data summarized as Mean (Standard Deviation)

* Statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

TABLE 27

MEAN BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS DURING LACTATION

	MEAN BODY WEIGHT GAINS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	10	12	11	11
LACTATION DAYS				
0-4	18.6(8.4)	12.6(26.5)	15.1(8.1)	16.1(12.6)

Data summarized as Mean (Standard Deviation)

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

TABLE 28

MEAN DAILY FOOD CONSUMPTION (grams/day) OF SATELLITE FEMALE RATS DURING PREMATING

	MEAN DAILY FOOD CONSUMED PER RATS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
DAYS ON TEST				
1-8	17.5(1.1)	18.3(1.4)	16.5(1.2)	16.9(1.0)
8-15	19.9(1.4)	19.9(1.7)	17.8(1.5)	19.5(1.7)
1-15	18.7(1.1)	19.1(1.5)	17.2(1.2)	18.2(1.3)

Data summarized as Mean (Standard Deviation)

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

TABLE 29

MEAN FOOD EFFICIENCY (grams weight gained/grams food consumed) OF SATELLITE FEMALE RATS DURING PREMATING

	MEAN FOOD EFFICIENCY (g WT GAIN/g FOOD CONSUMED)			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	12	12	12	12
DAYS ON TEST				
1-8	0.139(0.046)	0.125(0.052)	0.135(0.035)	0.098(0.031)
8-15	0.118(0.044)	0.132(0.024)	0.083(0.042)	0.126(0.045)
1-15	0.128(0.032)	0.129(0.028)	0.109(0.027)	0.114(0.019)

Data summarized as Mean (Standard Deviation)

There were no statistically significant differences at $p<0.05$ by One Way Analysis of Variance and Dunnett/Tamhane-Dunnett's test.

TABLE 30

MEAN DAILY FOOD CONSUMPTION (grams/day) OF SATELLITE FEMALE RATS DURING GESTATION

	MEAN DAILY FOOD CONSUMED PER RATS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	9	12	11	11
GESTATION DAYS				
0-7	24.1(2.6)	23.5(1.7)	22.2(2.9)	22.8(1.6)
7-14	25.6(2.3)	24.8(2.0)	23.6(3.7)	24.5(1.3)
14-21	25.9(2.5)	24.8(1.5)	24.4(2.2)	24.7(1.4)
0-21	25.2(2.4)	24.4(1.4)	23.4(2.8)	24.0(1.2)

Data summarized as Mean (Standard Deviation)

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

TABLE 31

MEAN FOOD EFFICIENCY (grams weight gained/grams food consumed) OF SATELLITE FEMALE RATS DURING GESTATION

MEAN FOOD EFFICIENCY (g WT GAIN/g FOOD CONSUMED)

GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	9	12	11	11
GESTATION DAYS				
0-7	0.243(0.030)	0.226(0.043)	0.237(0.026)	0.229(0.032)
7-14	0.227(0.026)	0.226(0.047)	0.221(0.035)	0.219(0.048)
14-21	0.458(0.072)	0.519(0.055)	0.512(0.061)	0.442(0.083)
0-21	0.311(0.031)	0.325(0.028)	0.328(0.025)	0.299(0.035)

Data summarized as Mean (Standard Deviation)

There were no statistically significant differences at $p<0.05$ by One Way Analysis of Variance and Dunnett/Tamhane-Dunnett's test.

TABLE 32

MEAN DAILY FOOD CONSUMPTION (grams/day) OF SATELLITE FEMALE RATS DURING LACTATION

	MEAN DAILY FOOD CONSUMED PER RAT (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	10	12	11	11
LACTATION DAYS				
0-4	33.8(5.3)	30.7(8.8)	33.5(13.8)	30.7(6.2)

Data summarized as Mean (Standard Deviation)

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

TABLE 33

MEAN FOOD EFFICIENCY (grams weight gained/grams food consumed) OF SATELLITE FEMALE RATS DURING LACTATION

	MEAN FOOD EFFICIENCY (g WT GAIN/g FOOD CONSUMED)			
GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	10	12	11	11
LACTATION DAYS				
0-4	0.138(0.060)	-0.006(0.449)	0.117(0.066)	0.138(0.134)

Data summarized as Mean (Standard Deviation)

There were no statistically significant differences at $p<0.05$ by One Way Analysis of Variance and Dunnett/Tamhane-Dunnett's test.

TABLE 34

SUMMARY OF REPRODUCTIVE INDICES: F_1 GENERATION

MATERNAL GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
MATING INDEX (%)	100.0	100.0	100.0	91.7
(# copulated/cohoused)	(12/12)	(12/12)	(12/12)	(11/12)
FERTILITY INDEX (%)	83.3	100.0	91.7	100.0
(# pregnant/copulated)	(10/12)	(12/12)	(11/12)	(11/11)
GESTATION LENGTH (days)[a]	22.3	22.3	22.3	22.2
NUMBER OF IMPLANTATION SITES				
per pregnant female	15	16	15	16
Standard deviation (# in group)	2(10)	1(12)	2(11)	2(11)
IMPLANTATION EFFICIENCY (%)	90.5	92.6	91.7	95.3
Standard deviation (# in group)	15.0(10)	7.8(12)	8.0(11)	5.2(11)
NUMBER OF CORPORA LUTEA				
per pregnant female	16	17	17	17
Standard deviation (# in group)	3(10)	1(12)	2(11)	2(11)
PRE-IMPLANTATION LOSS	0.1	0.1	0.1	0.1
Standard deviation (# in group)	0.1(10)	0.1(12)	0.1(11)	0.1(11)
POST-IMPLANTATION LOSS	0.1	0.1	0.1	0.1
Standard deviation (# in group)	0.1(10)	0.1(12)	0.1(11)	0.0(11)

There were no statistically significant trends in mating or fertility indices by Cochran-Armitage test; $p < 0.05$.

There were no statistically significant trends in gestation length, number of implantation sites, implantation efficiency, number of corpora lutea, pre-implantation loss or post-implantation loss by Jonckheere's Terpstra test; $p<0.05$.

a Gestation length could not be calculated for those females that were pregnant for which no evidence of copulation was observed.

TABLE 35

SUMMARY OF PUP CLINICAL OBSERVATIONS: F_1 GENERATION

MATERNAL GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	10	12	11	11
OBSERVATIONS IN All PUPS				
SMALL WHOLE BODY	0	1 (1)	0	1 (1)
TOTAL NUMBER OF SIGNS	0	1	0	1
NUMBER OF LITTERS AFFECTED	0	1	0	1
TOTAL NUMBER OF LITTERS	10	12	11	11
OBSERVATIONS IN MALE PUPS				
TOTAL NUMBER OF SIGNS	0	0	0	0
NUMBER OF LITTERS AFFECTED	0	0	0	0
TOTAL NUMBER OF LITTERS	10	12	11	11
OBSERVATIONS IN FEMALE PUPS				
SMALL WHOLE BODY	0	1 (1)	0	1 (1)
TOTAL NUMBER OF SIGNS	0	1	0	1
NUMBER OF LITTERS AFFECTED	0	1	0	1
TOTAL NUMBER OF LITTERS	10	12	11	11

There were no statistically significant trends by Cochran-Armitage test; $p<0.05$.

Numbers outside the parenthesis are the number of pups affected; the numbers in parenthesis are the number of litters affected.

TABLE 36

MEAN PUP NUMBERS AND SURVIVAL: F_1 GENERATION

MATERNAL GROUP:	II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	0	35	125	375
N:	10	12	11	11
MEAN NUMBER OF PUPS/LITTER				
Born	13.6	14.5	13.9	14.9
Born Alive	13.6	14.5	13.9	14.6
Day 1	13.6	14.5	13.8	14.2
Day 4	13.6	14.5	13.8	14.2
MEAN NUMBER OF MALE PUPS/LITTER				
Born	7.2	6.7	6.5	8.7
Born Alive	7.2	6.7	6.5	8.5
Day 1	7.2	6.7	6.5	8.2
Day 4	7.2	6.7	6.5	8.2
MEAN NUMBER OF FEMALE PUPS/LITTER				
Born	6.4	7.8	7.4	6.2
Born Alive	6.4	7.8	7.4	6.2
Day 1	6.4	7.8	7.3	6.0
Day 4	6.4	7.8	7.3	6.0
Sex Ratio (males)	0.53	0.46	0.48	0.59
Gestation Index[a]	100.0	100.0	100.0	100.0
Mean % Born Alive	100.0	100.0	100.0	98.1*
0-4 Day Viability	100.0	100.0	99.5	97.6

a Percent litters delivered having at least 1 live pup.

* Statistically significant trends by Jonckheere-Terpstra test at $p < 0.05$.

There were no statistically significant trends in gestation index by Cochran-Armitage test; $p < 0.05$.

There were no statistically significant trends in number of pups, sex ratio, or day 0-4 viability by Jonckheere-Terpstra trend test at $p<0.05$.

Statistics were performed on combined pups per litter only. Male and female data are presented for information only.

TABLE 37

MEAN PUP WEIGHTS: F_1 GENERATION

Maternal Group:	II-0	IV-0	VI-0	VIII-0
Concentration (mg/kg/day):	0	35	125	375
N:	10	12	11	11
		MEAN PUP WEIGHTS		
Day 0	6.7(0.7)	6.4(0.5)	6.5(0.5)	6.0(0.7)*
Day 1	7.5(0.9)	7.2(0.6)	7.2(0.5)	6.5(0.9)*
Day 4	11.2(1.8)	10.2(1.2)	10.4(0.9)	9.5(1.4)*
		MEAN MALE PUP WEIGHTS		
Day 0	6.9(0.7)	6.7(0.5)	6.7(0.5)	6.2(0.8)
Day 1	7.8(0.8)	7.5(0.6)	7.4(0.5)	6.7(1.0)
Day 4	11.5(1.8)	10.4(1.2)	10.7(0.9)	9.7(1.5)
		MEAN FEMALE PUP WEIGHTS		
Day 0	6.5(0.7)	6.3(0.5)	6.3(0.4)	5.8(0.6)
Day 1	7.3(0.8)	7.1(0.5)	7.0(0.5)	6.3(0.9)
Day 4	10.8(1.8)	10.0(1.1)	10.2(0.9)	9.1(1.3)

Data were summarized as Mean (Standard Deviation).

* Statistically significant trends by linear contrast of least square means; $p < 0.05$.

Statistics were performed on combined pups per litter only. Male and female data are presented for information only.

TABLE 38

MEAN FORELIMB AND HINDLIMB GRIP STRENGTH, REARING, HINDLIMB SPLAY, BODY WEIGHT AND BODY TEMPERATURE FOR MALE RATS

ASSESSMENT PERIOD	GROUP	CONCENTRATION (mg/kg/day)	FORELIMB GRIP STRENGTH [Mean of 3 trials] (kg)	HINDLIMB GRIP STRENGTH [Mean of 3 trials] (kg)	REARING (Number)	HINDLIMB SPLAY (cm)	BODY WEIGHT (g)	BODY TEMPERATURE (°C)
Baseline								
	I	0	0.44 (0.08)	0.33 (0.07)	4 (4)	6.0 (1.2)	216.0 (6.9)	35.0 (0.3)
	III	35	0.49 (0.11)	0.31 (0.07)	5 (3)	6.3 (1.3)	215.5 (8.8)	34.8 (0.5)
	V	125	0.47 (0.12)	0.34 (0.07)	5 (3)	6.7 (0.9)	215.8 (8.3)	35.0 (0.5)
	VII	375	0.49 (0.11)	0.32 (0.05)	6 (3)	7.3 (1.9)	217.2 (9.0)	34.8 (0.5)
Week 4								
	I	0	0.97 (0.20)	0.54 (0.08)	3 (3)	7.8 (1.9)	418.0 (24.3)	34.8 (0.7)
	III	35	1.04 (0.16)	0.53 (0.04)	3 (2)	8.1 (1.5)	411.1 (17.0)	34.7 (0.2)
	V	125	1.07 (0.26)	0.55 (0.10)	3 (3)	8.4 (1.9)	388.9 (19.7)	35.2 (0.6)
	VII	375	1.01 (0.18)	0.55 (0.07)	5 (3)	7.8 (2.6)	377.3 (18.3)	34.5 (0.5)

Data arranged as : Mean (Standard Deviation)

Statistical Methods: Shapiro-Wilk's and Levene's tests were performed. Repeated measures analysis of variance with linear contrasts or Jonckheere's trend test were used to identify which concentration groups, if any, were significantly different from control.

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

TABLE 39

MEAN FORELIMB AND HINDLIMB GRIP STRENGTH, REARING, HINDLIMB SPLAY, BODY WEIGHT AND BODY TEMPERATURE FOR FEMALE RATS

ASSESSMENT PERIOD	GROUP	CONCENTRATION (mg/kg/day)	FORELIMB GRIP STRENGTH [Mean of 3 trials] (kg)	HINDLIMB GRIP STRENGTH [Mean of 3 trials] (kg)	REARING (Number)	HINDLIMB SPLAY (cm)	BODY WEIGHT (g)	BODY TEMPERATURE (°C)
Baseline								
	II	0	0.46 (0.08)	0.35 (0.05)	6 (4)	5.4 (1.0)	179.4 (7.4)	35.1 (0.6)
	IV	35	0.49 (0.14)	0.35 (0.06)	5 (2)	4.9 (1.1)	179.0 (9.3)	35.4 (0.7)
	VI	125	0.45 (0.07)	0.32 (0.05)	7 (2)	4.4 (1.2)	178.5 (9.5)	35.5 (0.6)
	VIII	375	0.43 (0.13)	0.35 (0.08)	6 (4)	5.6 (1.7)	176.0 (10.2)	35.4 (0.6)
Week 4								
	II	0	0.94 (0.20)	0.53 (0.06)	6 (3)	5.4 (1.1)	259.5 (22.3)	35.9 (0.7)
	IV	35	0.91 (0.18)	0.52 (0.09)	6 (4)	5.2 (1.5)	255.8 (13.0)	36.0 (0.6)
	VI	125	0.95 (0.18)	0.48 (0.06)	6 (3)	4.8 (1.7)	249.4 (18.6)	36.1 (0.6)
	VIII	375	0.87 (0.19)	0.52 (0.06)	6 (4)	6.0 (2.1)	245.3 (15.1)	36.6 (0.4) *

Data arranged as : Mean (Standard Deviation)

Statistical Methods: Shapiro-Wilk's and Levene's tests were performed. Repeated measures analysis of variance with linear contrasts or Jonckheere's trend test were used to identify which concentration groups, if any, were significantly different from control.

* Statistically significant difference compared to control at $p<0.05$.

TABLE 40

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS FOR MALE RATS

	BASELINE				WEEK 4			
GROUP	I	III	V	VII	I	III	V	VII
CONCENTRATION (mg/kg/day)	0	35	125	375	0	35	125	375
NUMBER EXAMINED	12	12	12	12	12	12	12	12
HOME CAGE:								
POSTURE:								
limbs spread out or lying on one side	0	0	0	0	0	0	0	0
curled up,	5	6	1	4	3	2	1	2
sitting, standing or rearing normally, alert	7	6	11	8	9	10	11	10
jumping	0	0	0	0	0	0	0	0
PALPEBRAL CLOSURE:								
eyelids wide open	7	6	11	8	9	11	12	10
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
rat appears to be sleeping	5	6	1	4	3	1	0	2
WRITHING:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
CIRCLING:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
BITING:								
absent	12	12	12	12	12	12	12	12
biting others	0	0	0	0	0	0	0	0
biting cage	0	0	0	0	0	0	0	0
self mutilation	0	0	0	0	0	0	0	0
GAIT/COORDINATION:								
normal	12	12	12	12	12	12	12	12
unbalanced, swaying, uncoordinated	0	0	0	0	0	0	0	0
ataxic	0	0	0	0	0	0	0	0
unable to move	0	0	0	0	0	0	0	0
REMOVAL FROM CAGE:								
EASE OF REMOVAL:								
too easy (rat sits quietly, no resistance)	0	0	0	0	0	0	0	0
some resistance (rears, follows observer's hand)	12	12	12	12	12	12	12	12
difficult (runs around cage, may attack)	0	0	0	0	0	0	0	0

TABLE 40 (CONTINUED)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS FOR MALE RATS

	BASELINE				WEEK 4			
GROUP	I	III	V	VII	I	III	V	VII
CONCENTRATION (mg/kg/day)	0	35	125	375	0	35	125	375
NUMBER EXAMINED	12	12	12	12	12	12	12	12
EASE OF HANDLING:								
too easy	0	0	0	0	0	0	0	0
easy (alert, limbs pulled up against body)	12	12	12	12	12	12	12	12
difficult	0	0	0	0	0	0	0	0
MUSCLE TONE:								
limp	0	0	0	0	0	0	0	0
normal	12	12	12	12	12	12	12	12
rigid	0	0	0	0	0	0	0	0
VOCALIZATIONS:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
PILOERECTION:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
BITE MARKS ON TAIL/PAWS:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
PALPEBRAL CLOSURE:								
none	12	12	12	12	12	12	12	12
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
FUR APPEARANCE:								
normal	12	12	12	12	12	12	12	12
slightly soiled	0	0	0	0	0	0	0	0
very soiled, crusty	0	0	0	0	0	0	0	0
LACRIMATION:								
none	12	12	12	12	12	12	12	12
slight	0	0	0	0	0	0	0	0
severe	0	0	0	0	0	0	0	0
SALIVATION:								
none	12	12	12	12	12	12	12	12
slight (wet chin)	0	0	0	0	0	0	0	0
severe (active salivation, drooling)	0	0	0	0	0	0	0	0

TABLE 40 (CONTINUED)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS FOR MALE RATS

	BASELINE				WEEK 4			
GROUP	I	III	V	VII	I	III	V	VII
CONCENTRATION (mg/kg/day)	0	35	125	375	0	35	125	375
NUMBER EXAMINED	12	12	12	12	12	12	12	12
EXOPTHALAMUS:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
OPEN FIELD:								
RIGHTING REFLEX:								
present	12	12	12	12	12	12	12	12
slow	0	0	0	0	0	0	0	0
absent	0	0	0	0	0	0	0	0
RESPIRATION EASE:								
normal	12	12	12	12	12	12	12	12
labored breathing	0	0	0	0	0	0	0	0
RATE OF RESPIRATION:								
slow	0	0	0	0	0	0	0	0
normal	12	12	12	12	12	12	12	12
rapid	0	0	0	0	0	0	0	0
POSTURE:								
normal	12	12	12	12	12	12	12	12
abnormal	0	0	0	0	0	0	0	0
CONVULSIONS:								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
TREMORS:								
none	12	12	12	12	12	12	12	12
slight - paws	0	0	0	0	0	0	0	0
mild - limbs	0	0	0	0	0	0	0	0
severe - multiple sites	0	0	0	0	0	0	0	0
MUSCLE SPASMS:								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
MUSCLE FASCICULATION:								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0

TABLE 40 (CONTINUED)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS FOR MALE RATS

	BASELINE				WEEK 4			
GROUP	I	III	V	VII	I	III	V	VII
CONCENTRATION (mg/kg/day)	0	35	125	375	0	35	125	375
NUMBER EXAMINED	12	12	12	12	12	12	12	12
GROOMING:								
normal or none	12	12	12	12	12	12	12	12
repetitive, stereotypy	0	0	0	0	0	0	0	0
GAIT/COORDINATION:								
normal	12	12	12	12	12	12	12	12
unbalanced, swaying, uncoordinated	0	0	0	0	0	0	0	0
ataxic	0	0	0	0	0	0	0	0
unable to move	0	0	0	0	0	0	0	0
AROUSAL:								
very low (stupor, little or no responsiveness)	0	0	0	0	0	0	0	0
low	0	1	0	0	0	2	1	1
normal (alert, exploratory movements)	12	11	12	12	12	10	10	11
high (slight excitement, tense, sudden movements)	0	0	0	0	0	0	1	0
VOCALIZATIONS:								
present	0	0	0	0	0	0	0	0
absent	11	12	12	12	11	12	12	12
vocalizes only when handled	1	0	0	0	1	0	0	0
PALPEBRAL CLOSURE:								
none	12	12	12	12	12	12	12	12
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
DIARRHEA:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
POLYURIA:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
MANIPULATIONS:								
APPROACH & TOUCH:								
no reaction	0	0	0	0	0	0	0	0
normal	12	12	12	12	12	12	12	12
increased reaction (jumps away or attacks)	0	0	0	0	0	0	0	0

TABLE 40 (CONTINUED)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS FOR MALE RATS

	BASELINE				WEEK 4			
GROUP	I	III	V	VII	I	III	V	VII
CONCENTRATION (mg/kg/day)	0	35	125	375	0	35	125	375
NUMBER EXAMINED	12	12	12	12	12	12	12	12
AUDITORY STIMULUS:								
no reaction	0	0	0	0	0	0	0	0
normal reaction (rat flinches or flicks ear)	12	12	12	12	12	12	12	12
exaggerated reaction (rat jumps, flips)	0	0	0	0	0	0	0	0
TAIL PINCH:								
no response	0	0	0	0	0	0	0	0
normal (turns toward site)	12	11	12	12	11	12	11	12
exaggerated response	0	1	0	0	1	0	1	0
IN MOTOR ACTIVITY MONITOR:								
PUPILLARY RESPONSE:								
present	12	12	12	12	12	12	12	12
absent	0	0	0	0	0	0	0	0
DIARRHEA:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
POLYURIA:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
ADDITIONAL FINDINGS:								
HEAD SHAKE								
present	0	0	0	0	0	1	0	0
absent	12	12	12	12	12	11	12	12

Statistical Methods: Cochran-Armitage test for trend.

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

TABLE 41

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS FOR FEMALE RATS

	BASELINE				WEEK 4			
GROUP	II	IV	VI	VIII	II	IV	VI	VIII
CONCENTRATION (mg/kg/day)	0	35	125	375	0	35	125	375
NUMBER EXAMINED	12	12	12	12	12	12	12	12
HOME CAGE:								
POSTURE:								
limbs spread out or lying on one side	0	0	0	0	0	0	0	0
curled up	4	2	2	2	1	0	1	1
sitting, standing or rearing normally, alert	8	10	10	10	11	12	11	11
jumping	0	0	0	0	0	0	0	0
PALPEBRAL CLOSURE:								
eyelids wide open	8	11	10	10	12	12	12	11
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
rat appears to be sleeping	4	1	2	2	0	0	0	1
WRITHING:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
CIRCLING:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
BITING:								
absent	12	12	12	12	12	12	12	12
biting others	0	0	0	0	0	0	0	0
biting cage	0	0	0	0	0	0	0	0
self mutilation	0	0	0	0	0	0	0	0
GAIT/COORDINATION:								
normal	12	12	12	12	12	12	12	12
unbalanced, swaying, uncoordinated	0	0	0	0	0	0	0	0
ataxic	0	0	0	0	0	0	0	0
unable to move	0	0	0	0	0	0	0	0
REMOVAL FROM CAGE:								
EASE OF REMOVAL:								
too easy (rat sits quietly, no resistance)	0	0	0	0	0	0	0	0
some resistance (rears, follows observer's hand)	12	12	12	12	12	12	12	12
difficult (runs around cage, may attack)	0	0	0	0	0	0	0	0

TABLE 41 (CONTINUED)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS FOR FEMALE RATS

	BASELINE				WEEK 4			
GROUP	II	IV	VI	VIII	II	IV	VI	VIII
CONCENTRATION (mg/kg/day)	0	35	125	375	0	35	125	375
NUMBER EXAMINED	12	12	12	12	12	12	12	12
EASE OF HANDLING:								
too easy	0	0	0	0	0	0	0	0
easy (alert, limbs pulled up against body)	12	12	12	12	12	12	12	12
difficult	0	0	0	0	0	0	0	0
MUSCLE TONE:								
limp	0	0	0	0	0	0	0	0
normal	12	12	12	12	12	12	12	12
rigid	0	0	0	0	0	0	0	0
VOCALIZATIONS:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
PILOERECTION:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
BITE MARKS ON TAIL/PAWS:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
PALPEBRAL CLOSURE:								
none	12	12	12	12	12	12	12	12
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
FUR APPEARANCE:								
normal	12	12	12	12	12	12	12	12
slightly soiled	0	0	0	0	0	0	0	0
very soiled, crusty	0	0	0	0	0	0	0	0
LACRIMATION:								
none	12	12	12	12	12	12	12	12
slight	0	0	0	0	0	0	0	0
severe	0	0	0	0	0	0	0	0
SALIVATION:								
none	12	12	12	12	12	12	12	12
slight (wet chin)	0	0	0	0	0	0	0	0
severe (active salivation, drooling)	0	0	0	0	0	0	0	0

TABLE 41 (CONTINUED)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS FOR FEMALE RATS

	BASELINE				WEEK 4			
GROUP	II	IV	VI	VIII	II	IV	VI	VIII
CONCENTRATION (mg/kg/day)	0	35	125	375	0	35	125	375
NUMBER EXAMINED	12	12	12	12	12	12	12	12
EXOPTHALAMUS:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
OPEN FIELD:								
RIGHTING REFLEX:								
present	12	12	12	12	12	12	12	12
slow	0	0	0	0	0	0	0	0
absent	0	0	0	0	0	0	0	0
RESPIRATION EASE:								
normal	12	12	12	12	12	12	12	12
labored breathing	0	0	0	0	0	0	0	0
RATE OF RESPIRATION:								
slow	0	0	0	0	0	0	0	0
normal	12	12	12	12	12	12	12	12
rapid	0	0	0	0	0	0	0	0
POSTURE:								
normal	12	12	12	12	12	12	12	12
abnormal	0	0	0	0	0	0	0	0
CONVULSIONS:								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
TREMORS:								
none	12	12	12	12	12	12	12	12
slight - paws	0	0	0	0	0	0	0	0
mild - limbs	0	0	0	0	0	0	0	0
severe - multiple sites	0	0	0	0	0	0	0	0
MUSCLE SPASMS:								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
MUSCLE FASCICULATION:								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0

TABLE 41 (CONTINUED)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS FOR FEMALE RATS

	BASELINE				WEEK 4			
GROUP	II	IV	VI	VIII	II	IV	VI	VIII
CONCENTRATION (mg/kg/day)	0	35	125	375	0	35	125	375
NUMBER EXAMINED	12	12	12	12	12	12	12	12
GROOMING:								
normal or none	12	12	12	12	12	12	12	12
repetitive, stereotypy	0	0	0	0	0	0	0	0
GAIT/COORDINATION:								
normal	12	12	12	12	12	12	12	12
unbalanced, swaying, uncoordinated	0	0	0	0	0	0	0	0
ataxic	0	0	0	0	0	0	0	0
unable to move	0	0	0	0	0	0	0	0
AROUSAL:								
very low (stupor, little or no responsiveness)	0	0	0	0	0	0	0	0
low	1	0	0	0	2	1	1	3
normal (alert, exploratory movements)	11	12	12	11	10	11	11	8
high (slight excitement, tense, sudden movements)	0	0	0	1	0	0	0	1
VOCALIZATIONS:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
vocalizes only when handled	0	0	0	0	0	0	0	0
PALPEBRAL CLOSURE:								
none	12	12	12	12	12	12	12	12
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
DIARRHEA:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
POLYURIA:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
MANIPULATIONS:								
APPROACH & TOUCH:								
no reaction	0	0	0	0	0	0	0	0
normal	12	12	12	12	12	12	11	12
increased reaction (jumps away or attacks)	0	0	0	0	0	0	1	0

TABLE 41 (CONTINUED)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS FOR FEMALE RATS

	BASELINE				WEEK 4			
GROUP	II	IV	VI	VIII	II	IV	VI	VIII
CONCENTRATION (mg/kg/day)	0	35	125	375	0	35	125	375
NUMBER EXAMINED	12	12	12	12	12	12	12	12
AUDITORY STIMULUS:								
no reaction	0	0	0	0	0	0	0	0
normal reaction (rat flinches or flicks ear)	12	12	12	11	12	12	12	11
exaggerated reaction (rat jumps, flips)	0	0	0	1	0	0	0	1
TAIL PINCH:								
no response	0	0	0	0	0	0	0	0
normal (turns toward site)	12	12	11	12	12	12	12	12
exaggerated response	0	0	1	0	0	0	0	0
IN MOTOR ACTIVITY MONITOR:								
PUPILLARY RESPONSE:								
normal	12	12	12	12	12	12	12	12
abnormal	0	0	0	0	0	0	0	0
DIARRHEA:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
POLYURIA:								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
ADDITIONAL FINDINGS:								
HEAD SHAKE								
present	0	0	0	0	0	0	1	0
absent	12	12	12	12	12	12	11	12

Statistical Methods: Cochran-Armitage test for trend.

There were no statistically trends at $p < 0.05$.

TABLE 42

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

ASSESSMENT PERIOD	GROUP	CONCENTRATION (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
BASELINE			**1**	**2**	**3**	**4**	**5**	**6**	**TOTAL**
	I	0	391(56)	292(73)	169(104)	85(96)	46(89)	12(34)	994(349)
	III	35	393(41)	279(59)	133(103)	41(65)	17(48)	6(6)	868(259)
	V	125	409(35)	334(56)	215(69)	92(101)	39(76)	12(30)	1101(249)
	VII	375	385(56)	270(78)	192(111)	102(123)	30(56)	5(10)	982(328)
WEEK 4			**1**	**2**	**3**	**4**	**5**	**6**	**TOTAL**
	I	0	386(57)	282(50)	177(93)	142(107)	68(98)	64(94)	1118(334)
	III	35	386(50)	299(51)	187(107)	96(85)	59(60)	18(39)	1045(285)
	V	125	385(54)	304(50)	175(95)	133(125)	79(102)	76(95)	1152(340)
	VII	375	358(41)	273(52)	160(110)	117(102)	66(88)	19(20)	993(286)

Data arranged as: Mean (Standard Deviation).

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

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

TABLE 43

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

ASSESSMENT PERIOD	GROUP	CONCENTRATION (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
BASELINE			**1**	**2**	**3**	**4**	**5**	**6**	**TOTAL**
	II	0	344(50)	270(57)	192(104)	128(98)	86(82)	62(75)	1081(270)
	IV	35	379(52)	305(57)	248(95)	175(72)	92(79)	57(68)	1255(276)
	VI	125	362(79)	307(79)	251(92)	144(98)	84(112)	96(108)	1243(465)
	VIII	375	385(33)	337(63)	246(104)	165(95)	140(94)	70(70)	1343(332)
WEEK 4			**1**	**2**	**3**	**4**	**5**	**6**	**TOTAL**
	II	0	357(49)	279(67)	203(56)	186(99)	130(86)	70(55)	1224(260)
	IV	35	397(50)	313(50)	248(68)	205(78)	176(66)	180(104)	1519(289)
	VI	125	383(86)	318(90)	239(113)	177(124)	165(110)	122(82)	1405(380)
	VIII	375	407(51)	300(64)	190(93)	128(102)	83(105)	107(106)	1215(343)

Data arranged as: Mean (Standard Deviation).

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

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

TABLE 44

MOTOR ACTIVITY ASSESSMENT: NUMBER OF MOVEMENTS FOR MALE RATS

ASSESSMENT PERIOD	GROUP	CONCENTRATION (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
BASELINE			**1**	**2**	**3**	**4**	**5**	**6**	**TOTAL**
	I	0	131(22)	140(13)	91(44)	57(50)	28(47)	12(31)	460(127)
	III	35	144(17)	135(20)	84(38)	28(38)	13(27)	8(5)	411(83)
	V	125	139(17)	141(21)	124(25)	64(50)	24(42)	10(18)	501(113)
	VII	375	141(14)	137(13)	101(46)	54(57)	26(46)	6(9)	466(134)
WEEK 4			**1**	**2**	**3**	**4**	**5**	**6**	**TOTAL**
	I	0	137(25)	126(20)	105(39)	78(55)	44(55)	43(53)	533(182)
	III	35	149(20)	146(16)	106(51)	56(47)	39(38)	13(21)	508(148)
	V	125	137(14)	137(11)	91(47)	71(64)	45(54)	44(51)	525(188)
	VII	375	149(19)	141(18)	89(47)	68(51)	43(52)	18(17)	507(141)

Data arranged as: Mean (Standard Deviation).

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

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

TABLE 45

MOTOR ACTIVITY ASSESSMENT: NUMBER OF MOVEMENTS FOR FEMALE RATS

ASSESSMENT PERIOD	GROUP	CONCENTRATION (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						
BASELINE			**1**	**2**	**3**	**4**	**5**	**6**	**TOTAL**
	II	0	137(14)	137(10)	111(38)	86(53)	66(59)	53(57)	589(182)
	IV	35	135(14)	135(22)	120(37)	106(35)	66(52)	45(49)	607(143)
	VI	125	139(16)	139(12)	133(25)	95(44)	53(57)	58(53)	617(133)
	VIII	375	136(13)	133(19)	116(32)	103(45)	89(54)	53(49)	630(145)
WEEK 4			**1**	**2**	**3**	**4**	**5**	**6**	**TOTAL**
	II	0	147(22)	138(16)	124(19)	113(50)	79(45)	62(45)	662(150)
	IV	35	134(21)	133(13)	125(18)	113(37)	115(29)	102(46)	722(96)
	VI	125	138(19)	136(14)	115(32)	99(54)	99(58)	83(47)	670(111)
	VIII	375	135(14)	136(15)	110(35)	86(55)	52(57)	67(55)	584(121)

Data arranged as: Mean (Standard Deviation).

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

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

TABLE 46

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

	Group I 0 mg/kg/day	Group III 35 mg/kg/day	Group V 125 mg/kg/day	Group VII 375 mg/kg/day
RBC ($x10^6/\mu L$)				
DAY 30	8.04	8.08	8.35	8.25
	0.25(12)	0.32(12)	0.45(12)	0.30(12)
HGB (g/dL)				
DAY 30	15.5	15.6	15.8	15.7
	0.6(12)	0.5(12)	0.4(12)	0.6(12)
HCT (%)				
DAY 30	48.1	48.2	49.1	48.9
	1.6(12)	1.2(12)	1.8(12)	1.8(12)
MCV (fl)				
DAY 30	59.9	59.7	58.8	59.4
	2.1(12)	2.0(12)	1.6(12)	2.1(12)
MCH (pg)				
DAY 30	19.3	19.3	18.9	19.0
	0.6(12)	0.8(12)	0.7(12)	0.7(12)
MCHC (g/dL)				
DAY 30	32.2	32.3	32.2	32.0
	0.4(12)	0.4(12)	0.5(12)	0.3(12)
RDW (%)				
DAY 30	11.2	11.2	11.2	11.3
	0.7(12)	0.4(12)	0.4(12)	0.6(12)
ARET ($x10^3/\mu L$)				
DAY 30	190.7	208.4	227.8*	206.5
	27.1(12)	18.3(12)	30.6(12)	35.7(12)
PLT ($x10^3/\mu L$)				
DAY 30	1124	1192	1113	1086
	119(11)	156(10)	110(9)	117(10)
WBC ($x10^3/\mu L$)				
DAY 30	13.73	13.67	13.18	13.65
	2.42(12)	2.24(12)	2.99(12)	3.30(12)
ANEU ($x10^3/\mu L$)				
DAY 30	1.95	2.28	2.12	2.30
	0.45(12)	0.68(12)	0.58(12)	0.82(12)
ALYM ($x10^3/\mu L$)				
DAY 30	11.18	10.80	10.50	10.79
	2.19(12)	1.73(12)	2.47(12)	2.76(12)

TABLE 46 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

	Group I 0 mg/kg/day	Group III 35 mg/kg/day	Group V 125 mg/kg/day	Group VII 375 mg/kg/day
AMON ($x10^3/\mu L$)				
DAY 30	0.32	0.31	0.28	0.30
	0.08(12)	0.08(12)	0.07(12)	0.11(12)
AEOS ($x10^3/\mu L$)				
DAY 30	0.12	0.14	0.13	0.11
	0.05(12)	0.06(12)	0.06(12)	0.08(12)
ABAS ($x10^3/\mu L$)				
DAY 30	0.07	0.07	0.07	0.06
	0.04(12)	0.02(12)	0.02(12)	0.03(12)
ALUC ($x10^3/\mu L$)				
DAY 30	0.09	0.08	0.09	0.09
	0.04(12)	0.03(12)	0.04(12)	0.05(12)

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 47

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 35 mg/kg/day	Group VI 125 mg/kg/day	Group VIII 375 mg/kg/day
RBC ($x10^6/\mu L$)				
DAY 31	7.88	7.81	7.85	7.58
	0.39(11)	0.26(12)	0.36(10)	0.23(12)
HGB (g/dL)				
DAY 31	15.7	15.7	15.5	15.2
	0.6(11)	0.4(12)	0.4(10)	0.5(12)
HCT (%)				
DAY 31	47.1	47.3	47.4	46.1
	2.2(11)	1.3(12)	1.6(10)	1.3(12)
MCV (fl)				
DAY 31	59.8	60.6	60.5	60.8
	1.4(11)	2.0(12)	1.7(10)	1.8(12)
MCH (pg)				
DAY 31	19.9	20.0	19.8	20.1
	0.6(11)	0.6(12)	0.7(10)	0.6(12)
MCHC (g/dL)				
DAY 31	33.4	33.1	32.8	33.0
	0.6(11)	0.5(12)	0.5(10)	0.5(12)
RDW (%)				
DAY 31	10.6	10.7	10.9	11.1*
	0.2(11)	0.3(12)	0.5(10)	0.5(12)
ARET ($x10^3/\mu L$)				
DAY 31	180.6	184.4	187.3	241.2*
	37.2(11)	41.2(12)	51.0(10)	61.4(12)
PLT ($x10^3/\mu L$)				
DAY 31	1195	1128	1163	1160
	116(6)	182(9)	162(6)	176(9)
WBC ($x10^3/\mu L$)				
DAY 31	10.69	9.81	10.24	10.22
	2.20(11)	2.46(12)	1.92(10)	2.47(12)
ANEU ($x10^3/\mu L$)				
DAY 31	1.10	1.24	1.18	1.38
	0.38(11)	0.44(12)	0.55(10)	0.45(12)
ALYM ($x10^3/\mu L$)				
DAY 31	9.05	8.17	8.59	8.40
	2.13(11)	2.22(12)	1.77(10)	2.40(12)

TABLE 47 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 35 mg/kg/day	Group VI 125 mg/kg/day	Group VIII 375 mg/kg/day
AMON ($x10^3/\mu L$)				
DAY 31	0.25	0.17*	0.22	0.19
	0.07(11)	0.08(12)	0.05(10)	0.07(12)
AEOS ($x10^3/\mu L$)				
DAY 31	0.13	0.11	0.12	0.11
	0.09(11)	0.05(12)	0.06(10)	0.04(12)
ABAS ($x10^3/\mu L$)				
DAY 31	0.06	0.05	0.06	0.05
	0.03(11)	0.04(12)	0.03(10)	0.03(12)
ALUC ($x10^3/\mu L$)				
DAY 31	0.09	0.08	0.08	0.08
	0.04(11)	0.05(12)	0.02(10)	0.03(12)

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 48

SUMMARY OF COAGULATION VALUES FOR MALE RATS

	Group I 0 mg/kg/day	Group III 35 mg/kg/day	Group V 125 mg/kg/day	Group VII 375 mg/kg/day
PT (seconds)				
DAY 30	15.2 0.7(12)	15.5 1.2(12)	16.4 2.1(12)	16.1 2.2(12)
APTT (seconds)				
DAY 30	17.5 2.0(12)	17.5 2.3(12)	17.3 1.8(12)	17.2 1.8(12)

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 49

SUMMARY OF COAGULATION VALUES FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 35 mg/kg/day	Group VI 125 mg/kg/day	Group VIII 375 mg/kg/day
PT (seconds)				
DAY 31	14.6 0.7(12)	13.9 0.8(12)	14.4 1.5(12)	14.8 0.7(12)
APTT (seconds)				
DAY 31	15.7 2.2(12)	15.0 2.0(12)	15.7 1.7(12)	16.1 1.9(12)

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 50

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

	Group I 0 mg/kg/day	Group III 35 mg/kg/day	Group V 125 mg/kg/day	Group VII 375 mg/kg/day
AST (U/L)				
DAY 30	89	92	90	83
	13(12)	22(12)	9(12)	12(12)
ALT (U/L)				
DAY 30	31	31	29	32
	5(12)	7(12)	4(12)	6(12)
SDH (U/L)				
DAY 30	12.6	15.3	15.7	13.9
	3.1(12)	4.5(12)	3.6(12)	2.5(12)
ALKP (U/L)				
DAY 30	164	161	181	157
	23(12)	36(12)	46(12)	35(12)
BILI (mg/dL)				
DAY 30	0.12	0.10	0.12	0.12
	0.02(12)	0.03(12)	0.03(12)	0.04(12)
BUN (mg/dL)				
DAY 30	12	11	12	12
	2(12)	2(12)	1(12)	1(12)
CREA (mg/dL)				
DAY 30	0.29	0.30	0.34*	0.34*
	0.03(12)	0.05(12)	0.06(12)	0.03(12)
CHOL (mg/dL)				
DAY 30	51	49	53	56
	8(12)	6(12)	10(12)	12(12)
TRIG (mg/dL)				
DAY 30	61	55	63	61
	19(12)	22(12)	30(12)	31(12)
GLUC (mg/dL)				
DAY 30	107	101	99*	94*
	10(12)	7(12)	5(12)	8(12)
TP (g/dL)				
DAY 30	6.5	6.5	6.7	6.8
	0.3(12)	0.3(12)	0.3(12)	0.3(12)
ALB (g/dL)				
DAY 30	4.5	4.5	4.6	4.7*
	0.2(12)	0.1(12)	0.2(12)	0.2(12)

TABLE 50 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

	Group I 0 mg/kg/day	Group III 35 mg/kg/day	Group V 125 mg/kg/day	Group VII 375 mg/kg/day
GLOB (g/dL)				
DAY 30	2.1 0.2(12)	2.1 0.2(12)	2.0 0.2(12)	2.1 0.2(12)
CALC (mg/dL)				
DAY 30	10.9 0.2(12)	10.8 0.3(12)	10.9 0.3(12)	11.0 0.3(12)
IPHS (mg/dL)				
DAY 30	9.0 0.7(12)	8.9 0.7(12)	9.1 0.6(12)	8.8 0.7(12)
NA (mmol/L)				
DAY 30	149.8 1.7(12)	150.4 1.9(12)	151.0 2.0(12)	151.2 1.4(12)
K (mmol/L)				
DAY 30	5.91 0.36(12)	5.97 0.37(12)	5.94 0.46(12)	6.10 0.41(12)
CL (mmol/L)				
DAY 30	103.3 1.2(12)	103.4 2.4(12)	102.7 1.4(12)	103.2 1.4(12)

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 51

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 35 mg/kg/day	Group VI 125 mg/kg/day	Group VIII 375 mg/kg/day
AST (U/L)				
DAY 31	88	84	84	85
	12(12)	13(12)	13(12)	20(12)
ALT (U/L)				
DAY 31	27	26	25	27
	4(12)	6(12)	7(12)	5(12)
SDH (U/L)				
DAY 31	13.6	12.6	13.5	11.9
	3.8(12)	3.8(12)	3.9(12)	4.8(12)
ALKP (U/L)				
DAY 31	87	94	92	99
	21(12)	21(12)	23(12)	24(12)
BILI (mg/dL)				
DAY 31	0.17	0.15	0.14	0.14*
	0.02(12)	0.03(12)	0.02(12)	0.04(12)
BUN (mg/dL)				
DAY 31	15	13	14	14
	2(12)	2(12)	2(12)	1(12)
CREA (mg/dL)				
DAY 31	0.35	0.34	0.39	0.44*
	0.05(12)	0.05(12)	0.05(12)	0.08(12)
CHOL (mg/dL)				
DAY 31	68	72	72	80
	13(12)	11(12)	26(12)	16(12)
TRIG (mg/dL)				
DAY 31	36	35	27	31
	10(12)	9(12)	7(12)	10(12)
GLUC (mg/dL)				
DAY 31	106	105	108	101
	18(12)	7(12)	16(12)	9(12)
TP (g/dL)				
DAY 31	7.2	7.2	7.1	7.2
	0.4(12)	0.3(12)	0.4(12)	0.4(12)
ALB (g/dL)				
DAY 31	4.9	5.0	4.9	5.0
	0.3(12)	0.2(12)	0.3(12)	0.3(12)

TABLE 51 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 35 mg/kg/day	Group VI 125 mg/kg/day	Group VIII 375 mg/kg/day
GLOB (g/dL)				
DAY 31	2.2	2.2	2.2	2.2
	0.2(12)	0.2(12)	0.1(12)	0.2(12)
CALC (mg/dL)				
DAY 31	10.9	10.9	11.1	10.9
	0.4(12)	0.2(12)	0.4(12)	0.4(12)
IPHS (mg/dL)				
DAY 31	7.4	7.2	7.9	7.4
	0.7(12)	0.9(12)	1.3(12)	0.9(12)
NA (mmol/L)				
DAY 31	146.8	147.2	147.3	146.8
	1.3(12)	1.3(12)	1.1(12)	1.6(12)
K (mmol/L)				
DAY 31	5.84	5.87	6.11	5.91
	0.31(12)	0.40(12)	0.50(12)	0.45(12)
CL (mmol/L)				
DAY 31	103.0	103.4	103.6	103.7
	1.2(12)	1.0(12)	2.0(12)	0.8(12)

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 52

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT MALE

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

Group:	I	III	V	VII
Dosage(mg/kg/day)	0	35	125	375
Final Body Weight	387.8	379.3	358.8#	348.0#
	21.2(12)	14.2(12)	18.4(12)	16.0(12)
Liver	11.993	11.925	11.368	12.292
	1.059(12)	1.035(12)	0.887(12)	1.109(12)
Kidneys	3.200	3.170	3.147	3.298
	0.288(12)	0.196(12)	0.239(12)	0.263(12)
Lungs	1.757	1.745	1.729	1.658
	0.083(12)	0.160(12)	0.173(12)	0.153(12)
Heart	1.462	1.381	1.341#	1.284#
	0.123(12)	0.142(12)	0.083(12)	0.127(12)
Spleen	0.724	0.694	0.645#	0.618#
	0.088(12)	0.093(12)	0.086(12)	0.053(12)
Thymus	0.503	0.486	0.417#	0.380#
	0.078(12)	0.054(12)	0.040(12)	0.051(12)
Adrenal Glands	0.060	0.061	0.057	0.055
	0.008(11)	0.009(12)	0.008(12)	0.008(12)
Testes	3.249	3.211	3.128	3.153
	0.209(12)	0.198(12)	0.156(12)	0.190(12)

TABLE 52 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT MALE

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

Group:	I	III	V	VII
Dosage(mg/kg/day)	0	35	125	375
Epididymides	1.086	1.128	1.086	1.061
	0.106(12)	0.069(12)	0.046(12)	0.078(12)
Brain	2.019	1.997	2.026	1.981
	0.079(12)	0.072(12)	0.064(12)	0.053(12)

TABLE 52 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT MALE

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

Group:	I	III	V	VII
Dosage(mg/kg/day)	0	35	125	375
Liver/Final Body * 100	3.092	3.141	3.167	3.528#
	0.187(12)	0.196(12)	0.142(12)	0.209(12)
Kidneys/Final Body * 100	0.826	0.836	0.877#	0.947#
	0.068(12)	0.051(12)	0.055(12)	0.055(12)
Lungs/Final Body * 100	0.454	0.460	0.482	0.477
	0.028(12)	0.033(12)	0.038(12)	0.044(12)
Heart/Final Body * 100	0.377	0.364	0.374	0.369
	0.027(12)	0.033(12)	0.025(12)	0.030(12)
Spleen/Final Body * 100	0.187	0.183	0.180	0.178
	0.022(12)	0.024(12)	0.028(12)	0.016(12)
Thymus/Final Body * 100	0.130	0.128	0.116#	0.109#
	0.022(12)	0.014(12)	0.011(12)	0.013(12)
Adrenal Glands/Final Body * 100	0.016	0.016	0.016	0.016
	0.002(11)	0.002(12)	0.002(12)	0.002(12)
Testes/Final Body * 100	0.840	0.848	0.873	0.908#
	0.069(12)	0.060(12)	0.051(12)	0.067(12)

TABLE 52 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT MALE

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

Group:	I	III	V	VII
Dosage(mg/kg/day)	0	35	125	375
Epididymides/Final Body * 100	0.280	0.297	0.303#	0.305#
	0.023(12)	0.012(12)	0.016(12)	0.022(12)
Brain/Final Body * 100	0.522	0.527	0.566#	0.570#
	0.039(12)	0.020(12)	0.035(12)	0.027(12)

TABLE 52 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT MALE

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

Group:	I	III	V	VII
Dosage(mg/kg/day)	0	35	125	375
Liver/Brain * 100	594.942	597.494	562.083	620.757
	59.436(12)	50.024(12)	54.787(12)	55.912(12)
Kidneys/Brain * 100	158.706	158.876	155.400	166.591
	15.436(12)	10.220(12)	12.167(12)	13.720(12)
Lungs/Brain * 100	87.074	87.398	85.476	83.784
	4.710(12)	7.268(12)	9.907(12)	8.210(12)
Heart/Brain * 100	72.470	69.245	66.236#	64.893#
	6.143(12)	7.637(12)	4.632(12)	7.121(12)
Spleen/Brain * 100	35.832	34.702	31.899#	31.212#
	4.268(12)	3.940(12)	4.618(12)	2.717(12)
Thymus/Brain * 100	25.003	24.356	20.580#	19.178#
	4.222(12)	2.746(12)	1.904(12)	2.657(12)
Adrenal Glands/Brain * 100	3.011	3.048	2.819	2.775
	0.374(11)	0.451(12)	0.443(12)	0.438(12)
Testes/Brain * 100	161.037	161.035	154.503	159.335
	11.119(12)	12.399(12)	9.032(12)	11.301(12)

TABLE 52 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT MALE

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

Group:	I	III	V	VII
Dosage(mg/kg/day)	0	35	125	375
Epididymides/Brain * 100	53.842 5.747(12)	56.547 3.777(12)	53.653 3.230(12)	53.590 3.963(12)

Note:

Trend test (Jonckheere-Terpstra) significant

TABLE 53

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT FEMALE

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

Group:	II	IV	VI	VIII
Dosage(mg/kg/day)	0	35	125	375
Final Body Weight	243.3	239.3	234.2	228.4#
	20.0(12)	11.1(12)	17.1(12)	15.2(12)
Liver	7.348	7.656	7.699	7.908
	0.907(12)	0.868(12)	0.677(12)	0.723(12)
Kidneys	1.871	1.942	1.938	1.870
	0.191(12)	0.147(12)	0.174(12)	0.227(12)
Lungs	1.425	1.365	1.374	1.385
	0.139(12)	0.098(12)	0.111(12)	0.154(12)
Heart	0.943	0.938	0.911	0.874
	0.121(12)	0.110(12)	0.098(12)	0.105(12)
Spleen	0.494	0.506	0.482	0.477
	0.059(12)	0.069(12)	0.065(12)	0.074(12)
Thymus	0.439	0.414	0.418	0.377#
	0.117(12)	0.057(12)	0.100(12)	0.107(12)
Adrenal Glands	0.068	0.066	0.073	0.072
	0.013(12)	0.007(12)	0.008(12)	0.009(12)
Ovaries	0.121	0.127	0.130	0.125
	0.011(12)	0.016(12)	0.024(12)	0.021(12)

TABLE 53 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT FEMALE

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

Group:	II	IV	VI	VIII
Dosage(mg/kg/day)	0	35	125	375
Uterus	0.547	0.638	0.574	0.657
	0.183(12)	0.225(12)	0.123(12)	0.266(12)
Brain	1.863	1.857	1.822	1.855
	0.064(12)	0.094(12)	0.093(12)	0.072(12)

TABLE 53 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT FEMALE

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

Group:	II	IV	VI	VIII
Dosage(mg/kg/day)	0	35	125	375
Liver/Final Body * 100	3.014	3.193	3.286#	3.464#
	0.216(12)	0.237(12)	0.130(12)	0.224(12)
Kidneys/Final Body * 100	0.768	0.812#	0.827#	0.818#
	0.034(12)	0.056(12)	0.028(12)	0.076(12)
Lungs/Final Body * 100	0.588	0.571	0.589	0.610
	0.058(12)	0.031(12)	0.056(12)	0.097(12)
Heart/Final Body * 100	0.387	0.392	0.390	0.383
	0.032(12)	0.037(12)	0.044(12)	0.043(12)
Spleen/Final Body * 100	0.203	0.212	0.206	0.209
	0.023(12)	0.029(12)	0.021(12)	0.029(12)
Thymus/Final Body * 100	0.180	0.173	0.178	0.164
	0.044(12)	0.024(12)	0.035(12)	0.040(12)
Adrenal Glands/Final Body * 100	0.028	0.027	0.031#	0.031#
	0.004(12)	0.003(12)	0.003(12)	0.003(12)
Ovaries/Final Body * 100	0.050	0.053	0.055	0.055
	0.004(12)	0.006(12)	0.008(12)	0.008(12)

TABLE 53 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT FEMALE

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

Group:	II	IV	VI	VIII
Dosage(mg/kg/day)	0	35	125	375
Uterus/Final Body * 100	0.223	0.268	0.245	0.290
	0.065(12)	0.098(12)	0.050(12)	0.130(12)
Brain/Final Body * 100	0.770	0.778	0.780	0.815#
	0.058(12)	0.055(12)	0.048(12)	0.052(12)

TABLE 53 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT FEMALE

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

Group:	II	IV	VI	VIII
Dosage(mg/kg/day)	0	35	125	375
Liver/Brain * 100	394.222	412.890	422.881	426.322
	45.041(12)	47.811(12)	35.163(12)	36.258(12)
Kidneys/Brain * 100	100.362	104.775	106.327	100.792
	8.674(12)	9.526(12)	7.900(12)	11.821(12)
Lungs/Brain * 100	76.513	73.642	75.405	74.645
	6.940(12)	5.968(12)	4.836(12)	7.967(12)
Heart/Brain * 100	50.592	50.635	50.088	47.102
	6.212(12)	6.577(12)	5.564(12)	5.519(12)
Spleen/Brain * 100	26.528	27.229	26.497	25.782
	3.158(12)	3.283(12)	3.576(12)	4.521(12)
Thymus/Brain * 100	23.534	22.287	22.904	20.296
	6.041(12)	2.904(12)	5.071(12)	5.586(12)
Adrenal Glands/Brain * 100	3.637	3.538	4.023	3.858
	0.619(12)	0.384(12)	0.360(12)	0.465(12)
Ovaries/Brain * 100	6.484	6.843	7.125	6.757
	0.477(12)	0.874(12)	1.199(12)	1.180(12)

TABLE 53 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT FEMALE

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

Group:	II	IV	VI	VIII
Dosage(mg/kg/day)	0	35	125	375
Uterus/Brain * 100	29.215	34.653	31.579	35.486
	9.051(12)	13.573(12)	6.879(12)	14.336(12)

Note:

Trend test (Jonckheere-Terpstra) significant

TABLE 54

MEAN FINAL BODY AND ORGAN WEIGHTS - SATELLITE ADULT FEMALE

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

Group:	II-0	IV-0	VI-0	VIII-0
Dosage(mg/kg/day)	0	35	125	375
Final Body Weight	326.7	317.9	301.9#	304.2#
	19.8(12)	25.3(12)	20.0(12)	15.1(12)
Liver	13.703	13.147	13.356	14.355
	1.713(12)	1.745(12)	1.957(12)	1.398(12)
Kidneys	2.299	2.248	2.197	2.321
	0.189(12)	0.168(12)	0.268(12)	0.223(12)
Lungs	1.515	1.543	1.431	1.502
	0.112(12)	0.169(12)	0.108(12)	0.088(12)
Ovaries	0.137	0.132	0.125	0.133
	0.023(12)	0.018(12)	0.021(12)	0.020(12)
Uterus	0.829	0.710	0.686	0.667
	0.334(12)	0.088(12)	0.140(12)	0.115(12)

TABLE 54 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SATELLITE ADULT FEMALE

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

Group:	II-0	IV-0	VI-0	VIII-0
Dosage(mg/kg/day)	0	35	125	375
Liver/Final Body * 100	4.191	4.122	4.412	4.716#
	0.429(12)	0.346(12)	0.446(12)	0.369(12)
Kidneys/Final Body * 100	0.704	0.710	0.728	0.762#
	0.042(12)	0.060(12)	0.073(12)	0.053(12)
Lungs/Final Body * 100	0.464	0.491	0.475	0.495
	0.030(12)	0.099(12)	0.036(12)	0.035(12)
Ovaries/Final Body * 100	0.042	0.042	0.041	0.044
	0.007(12)	0.007(12)	0.006(12)	0.007(12)
Uterus/Final Body * 100	0.255	0.224	0.227	0.219
	0.106(12)	0.027(12)	0.045(12)	0.034(12)

Note:

Trend test (Jonckheere-Terpstra) significant

TABLE 55

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS - SUBCHRONIC ADULTS

SITE/LESION:	GROUP DESIGNATION:	I	III	V	VII
	DOSE (mg/kg/day):	0	35	125	375
	NUMBER IN GROUP:	12	12	12	12
KIDNEYS					
DILATATION		0	1	0	2

NOTE:
- INCIDENCES REFLECT THE NUMBER OF ANIMALS WITH A GIVEN LESION.

TABLE 56

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS - SUBCHRONIC ADULTS

SITE/LESION:	GROUP DESIGNATION:	II	IV	VI	VIII
	DOSE (mg/kg/day):	0	35	125	375
	NUMBER IN GROUP:	12	12	12	12
UTERUS					
DILATATION		0	0	0	1
SKIN					
ALOPECIA		0	0	0	1

NOTE:
- INCIDENCES REFLECT THE NUMBER OF ANIMALS WITH A GIVEN LESION.

TABLE 57

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS - SATELLITE ADULTS

SITE/LESION:	GROUP DESIGNATION:	II-0	IV-0	VI-0	VIII-0
	DOSE (mg/kg/day):	0	35	125	375
	NUMBER IN GROUP:	12	12	12	12
KIDNEYS					
DILATATION		1	0	0	0
UTERUS					
FLUID		2	0	0	0

NOTE:
- INCIDENCES REFLECT THE NUMBER OF ANIMALS WITH A GIVEN LESION.

TABLE 58

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: I DOSE (mg/kg/day): 0 NUMBER IN GROUP: 12	GROUP DESIGNATION: III DOSE (mg/kg/day): 35 NUMBER IN GROUP: 12	GROUP DESIGNATION: V DOSE (mg/kg/day): 125 NUMBER IN GROUP: 12	GROUP DESIGNATION: VII DOSE (mg/kg/day): 375 NUMBER IN GROUP: 12
DIGESTIVE SYSTEM					
LIVER		12	12	12	12
FATTY CHANGE, MEDIAN CLEFT		3 (-,3,-,-,-)	2 (-,2,-,-,-)	-	1 (-,1,-,-,-)
HEMATOPOIESIS, INCREASED EXTRAMEDULLARY		2 (-,2,-,-,-)	-	1 (-,1,-,-,-)	4 (-,4,-,-,-)
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR		-	-	-	10 (,1, , ,) (-,0,-,-,-)
INFLAMMATION, SUBACUTE/CHRONIC		12 (,1, , ,) (-,1,1,-,-)	12 (,1, , ,) (-,2,-,-,-)	11 (,1, , ,) (-,1,-,-,-)	12 (,1, , ,) (-,2,-,-,-)
NECROSIS, COAGULATIVE, FOCAL		2 (-,1,1,-,-)	-	-	-
PANCREAS		12	0	0	12
TONGUE		12	0	0	12
ESOPHAGUS		12	0	0	12
DEGENERATION, MYOFIBER, FOCAL		-	-	-	1 (-,1,-,-,-)
INFLAMMATION, MUSCULAR, FOCAL		-	-	-	1 (-,1,-,-,-)
STOMACH		12	0	0	12
EROSION/ULCER, GLANDULAR		1 (-,1,-,-,-)	-	-	-
DUODENUM		12	0	0	12
JEJUNUM		12	0	0	12
ILEUM		12	0	0	12
PEYER'S PATCH NOT PRESENT		3 (3,-,-,-,-)	-	-	1 (1,-,-,-,-)
PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)		9 (9,-,-,-,-)	-	-	9 (9,-,-,-,-)

TABLE 58 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: I	III	V	VII
	DOSE (mg/kg/day):	0	35	125	375
	NUMBER IN GROUP:	12	12	12	12
DIGESTIVE SYSTEM (Cont'd)					
CECUM		12	0	0	12
CELLULARITY INCREASED, LAMINA PROPRIA		2 (-,-,2,-,-)	-	-	3 (-,1,2,-,-)
COLON		12	0	0	12
RECTUM		12	0	0	12
URINARY SYSTEM					
KIDNEYS		12	12	12	12
AGGREGATES, LYMPHOID		1 (-,1,-,-,-)	2 (-,2,-,-,-)	1 (-,1,-,-,-)	1 (-,1,-,-,-)
CYST		1 (-,-,1,-,-)	-	-	1 (-,-,1,-,-)
HYALINE DROPLETS, INCREASED		-	12 (,1, , ,) (-,2,-,-,-)	12 (, ,1, ,) (-,2,0,-,-)	12 (, ,1, ,) (-,-,1,1,-)
HYDRONEPHROSIS, BILATERAL		-	1 (-,1,-,-,-)	-	1 (-,-,1,-,-)
HYDRONEPHROSIS, UNILATERAL		2 (-,-,2,-,-)	1 (-,-,1,-,-)	1 (-,1,-,-,-)	1 (-,-,1,-,-)
INFARCT		-	-	1 (-,1,-,-,-)	-
NEPHROPATHY, CHRONIC PROGRESSIVE		4 (-,4,-,-,-)	5 (-,5,-,-,-)	5 (-,5,-,-,-)	6 (-,6,-,-,-)
URINARY BLADDER		12	0	0	12
AGGREGATES, LYMPHOID		1 (-,1,-,-,-)	-	-	1 (-,1,-,-,-)

TABLE 58 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS - SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: I	III	V	VII
	DOSE (mg/kg/day):	0	35	125	375
	NUMBER IN GROUP:	12	12	12	12
RESPIRATORY SYSTEM					
NOSE		12	0	0	12
INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE)		11 (-,3,8,-,-)	-	-	11 (-,3,7,1,-)
PHARYNX/LARYNX		12	0	0	12
DEGENERATION, MYOFIBER, FOCAL		1 (-,1,-,-,-)	-	-	-
TRACHEA		12	0	0	12
LUNGS		12	0	0	12
HEMORRHAGE		7 (-,7,-,-,-)	-	-	6 (-,5,1,-,-)
HISTIOCYTOSIS, ALVEOLAR		3 (-,3,-,-,-)	-	-	4 (-,3,1,-,-)
HYPERTROPHY, VASCULAR MEDIAL		1 (-,-,1,-,-)	-	-	-
INFLAMMATION, ALVEOLAR		4 (-,2,2,-,-)	-	-	6 (-,5,1,-,-)
INFLAMMATION, SUBACUTE/CHRONIC, PERIVASCULAR		1 (-,1,-,-,-)	-	-	-
CARDIOVASCULAR SYSTEM					
HEART		12	0	0	12
INFLAMMATION, SUBACUTE/CHRONIC		4 (-,3,1,-,-)	-	-	1 (-,1,-,-,-)
AORTA		12	0	0	12
HEMATOPOIETIC SYSTEM					
BONE MARROW		12	0	0	12

TABLE 58 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS - SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: I	III	V	VII
		DOSE (mg/kg/day): 0	35	125	375
		NUMBER IN GROUP: 12	12	12	12
HEMATOPOIETIC SYSTEM (Cont'd)					
THYMUS		12	0	0	12
HEMORRHAGE		10 (,1, , ,) (-,0,-,-,-)	-	-	10 (, , , ,) (-,9,1,-,-)
SPLEEN		12	0	0	12
HEMATOPOIESIS, INCREASED EXTRAMEDULLARY		-	-	-	1 (-,1,-,-,-)
MANDIBULAR LYMPH NODE		12	0	0	12
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS		3 (-,2,1,-,-)	-	-	6 (-,5,1,-,-)
MEDIASTINAL LYMPH NODE		11	0	0	12
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS		7 (-,5,2,-,-)	-	-	10 (-,7,3,-,-)
INFLAMMATION, SUBACUTE/CHRONIC, MEDIASTINAL		1 (-,1,-,-,-)	-	-	-
MESENTERIC LYMPH NODE		12	0	0	12
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS		1 (-,1,-,-,-)	-	-	2 (-,1,1,-,-)
ENDOCRINE SYSTEM					
PITUITARY GLAND		12	0	0	12
CYST		-	-	-	1 (-,-,1,-,-)
HYPERPLASIA, CRANIOPHARYNGEAL		-	-	-	1 (-,-,1,-,-)
ADRENAL GLANDS		12	0	0	12
THYROID GLAND		12	12	12	12
ECTOPIC THYMUS TISSUE		2 (2,-,-,-,-)	-	1 (1,-,-,-,-)	1 (1,-,-,-,-)
HYPERTROPHY, FOLLICULAR CELL		2 (-,2,-,-,-)	3 (-,3,-,-,-)	2 (-,2,-,-,-)	4 (-,4,-,-,-)
PARATHYROID GLAND		11	0	0	10

TABLE 58 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS - SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: I	III	V	VII
	DOSE (mg/kg/day):	0	35	125	375
	NUMBER IN GROUP:	12	12	12	12
NERVOUS SYSTEM					
BRAIN		12	0	0	12
SPINAL CORD		12	0	0	12
SCIATIC NERVE		12	0	0	12
EYES		12	0	0	12
FOLD/ROSETTE, RETINAL		1 (-,1,-,-,-)	-	-	-
INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE)		9 (-,8,1,-,-)	-	-	9 (-,6,3,-,-)
OPTIC NERVE NOT PRESENT, UNILATERAL		2 (2,-,-,-,-)	-	-	2 (2,-,-,-,-)
MUSCULOSKELETAL SYSTEM					
FEMUR/KNEE JOINT		12	0	0	12
STERNUM		12	0	0	12
SKELETAL MUSCLE		12	0	0	12
REPRODUCTIVE SYSTEM					
TESTES		12	0	1	12
EPIDIDYMIDES		12	0	1	12
AGGREGATES, LYMPHOID		4 (-,4,-,-,-)	-	1 (-,1,-,-,-)	7 (-,7,-,-,-)
PROSTATE		12	0	1	12
AGGREGATES, LYMPHOID		7 (-,5,1,1,-)	-	-	5 (-,2,3,-,-)
INFLAMMATION, SUBACUTE/CHRONIC		-	-	-	1 (-,-,1,-,-)

TABLE 58 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS - SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: I	III	V	VII
	DOSE (mg/kg/day):	0	35	125	375
	NUMBER IN GROUP:	12	12	12	12
REPRODUCTIVE SYSTEM (Cont'd)					
SEMINAL VESICLES		12	0	1	12
COAGULATING GLANDS		12	0	1	12
INTEGUMENTARY SYSTEM					
SKIN		12	0	0	12
SALIVARY GLANDS		12	0	0	12
DEGENERATION/NECROSIS, FOCAL (PAROTID GLAND)		2 (-,2,-,-,-)	-	-	-
EXORBITAL LACRIMAL GLANDS		12	0	0	12
AGGREGATES, LYMPHOID		2 (-,2,-,-,-)	-	-	-
MISCELLANEOUS					
OTHER		0	0	0	0
CAUSE OF DEATH		12	0	0	12
SACRIFICED BY DESIGN		12 (1, , , ,) (2,-,-,-,-)	-	-	12 (1, , , ,) (2,-,-,-,-)
TOTAL ANIMALS WITH PRIMARY TUMORS		0	0	0	0
TOTAL ANIMALS WITH BENIGN TUMORS		0	0	0	0
TOTAL ANIMALS WITH MALIGNANT TUMORS		0	0	0	0

TABLE 58 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS - SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	I	III	V	VII
		DOSE (mg/kg/day):	0	35	125	375
		NUMBER IN GROUP:	12	12	12	12

NOTES:

- THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- LESION GRADES: P = PRESENT; 1 = MINIMAL; 2 = MILD; 3 = MODERATE; 4 = SEVERE.
- LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. DOUBLE DIGIT NUMBERS ARE EXPRESSED VERTICALLY, FOR EXAMPLE: (,1, ,1,1) MEANS NO LESIONS (-,0,6,1,5) WERE GRADED "PRESENT", 10 LESIONS WERE "MINIMAL", 6 LESIONS WERE "MILD", 11 LESIONS WERE "MODERATE", AND 15 LESIONS WERE "SEVERE".

TABLE 59

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: II	IV	VI	VIII
		DOSE (mg/kg/day): 0	35	125	375
		NUMBER IN GROUP: 12	12	12	12
DIGESTIVE SYSTEM					
LIVER		12	12	12	12
FATTY CHANGE, MEDIAN CLEFT		-	4 (-,4,-,-,-)	-	-
HEMATOPOIESIS, INCREASED EXTRAMEDULLARY		1 (-,1,-,-,-)	1 (-,1,-,-,-)	1 (-,1,-,-,-)	-
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR		-	-	3 (, , , ,) (-,3,-,-,-)	12 (, ,1, ,) (-,-,2,-,-)
INFLAMMATION, SUBACUTE/CHRONIC		10 (,1, , ,) (-,0,-,-,-)	11 (,1, , ,) (-,1,-,-,-)	12 (,1, , ,) (-,2,-,-,-)	12 (,1, , ,) (-,2,-,-,-)
NECROSIS, COAGULATIVE, FOCAL		-	1 (-,1,-,-,-)	-	-
PANCREAS		12	0	0	12
AGGREGATES, LYMPHOID		-	-	-	1 (-,1,-,-,-)
TONGUE		12	0	0	12
ESOPHAGUS		12	0	0	12
DEGENERATION, MYOFIBER, FOCAL		2 (-,2,-,-,-)	-	-	1 (-,-,1,-,-)
INFLAMMATION, SUBACUTE/CHRONIC		-	-	-	1 (-,1,-,-,-)
STOMACH		12	0	0	12
DUODENUM		12	0	0	12
JEJUNUM		12	0	0	12
ILEUM		12	0	0	12
PEYER'S PATCH NOT PRESENT		1 (1,-,-,-,-)	-	-	6 (6,-,-,-,-)
PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)		7 (7,-,-,-,-)	-	-	5 (5,-,-,-,-)

TABLE 59 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: DOSE (mg/kg/day): NUMBER IN GROUP:	II 0 12	IV 35 12	VI 125 12	VIII 375 12
DIGESTIVE SYSTEM ((Cont'd)						
CECUM			12	0	0	12
CELLULARITY INCREASED, LAMINA PROPRIA			-	-	-	1 (-,1,-,-,-)
COLON			12	0	0	12
RECTUM			12	0	0	12
URINARY SYSTEM						
KIDNEYS			12	0	0	12
AGGREGATES, LYMPHOID			6 (-,6,-,-,-)	-	-	2 (-,2,-,-,-)
MINERALIZATION			1 (-,1,-,-,-)	-	-	-
NEPHROPATHY, CHRONIC PROGRESSIVE			5 (-,5,-,-,-)	-	-	4 (-,4,-,-,-)
URINARY BLADDER			12	0	0	12
AGGREGATES, LYMPHOID			1 (-,1,-,-,-)	-	-	1 (-,1,-,-,-)
RESPIRATORY SYSTEM						
NOSE			12	0	0	12
PHARYNX/LARYNX			12	0	0	12
TRACHEA			12	0	0	12
AGGREGATES, LYMPHOID			-	-	-	1 (-,1,-,-,-)
INFLAMMATION, SUBACUTE/CHRONIC			1 (-,1,-,-,-)	-	-	-

TABLE 59 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: II	IV	VI	VIII
	DOSE (mg/kg/day):	0	35	125	375
	NUMBER IN GROUP:	12	12	12	12
RESPIRATORY SYSTEM (Cont'd)					
LUNGS		12	0	0	12
HEMORRHAGE		7 (-,6,1,-,-)	-	-	1 (-,1,-,-,-)
HISTIOCYTOSIS, ALVEOLAR		3 (-,3,-,-,-)	-	-	1 (-,1,-,-,-)
INFLAMMATION, ALVEOLAR		-	-	-	1 (-,1,-,-,-)
INFLAMMATION, SUBACUTE/CHRONIC, PERIVASCULAR		2 (-,2,-,-,-)	-	-	-
CARDIOVASCULAR SYSTEM					
HEART		12	0	0	12
INFLAMMATION, SUBACUTE/CHRONIC		2 (-,2,-,-,-)	-	-	-
AORTA		12	0	0	12
HEMATOPOIETIC SYSTEM					
BONE MARROW		12	0	0	12
THYMUS		12	0	0	12
HEMORRHAGE		5 (-,5,-,-,-)	-	-	5 (-,5,-,-,-)
SPLEEN		12	0	0	12
HEMATOPOIESIS, INCREASED EXTRAMEDULLARY		1 (-,1,-,-,-)	-	-	-
MANDIBULAR LYMPH NODE		12	0	0	12
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS		2 (-,2,-,-,-)	-	-	2 (-,2,-,-,-)
MEDIASTINAL LYMPH NODE		12	0	0	10
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS		9 (-,4,5,-,-)	-	-	6 (-,3,3,-,-)
MESENTERIC LYMPH NODE		12	0	0	12

TABLE 59 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: II	IV	VI	VIII
	DOSE (mg/kg/day):	0	35	125	375
	NUMBER IN GROUP:	12	12	12	12
ENDOCRINE SYSTEM					
PITUITARY GLAND		12	0	0	12
ADRENAL GLANDS		12	0	0	12
THYROID GLAND		12	0	0	12
ECTOPIC THYMUS TISSUE		1 (1,-,-,-,-)	-	-	1 (1,-,-,-,-)
HYPERTROPHY, FOLLICULAR CELL		-	-	-	1 (-,1,-,-,-)
PARATHYROID GLAND		12	0	0	12
NERVOUS SYSTEM					
BRAIN		12	0	0	12
SPINAL CORD		12	0	0	12
SCIATIC NERVE		12	0	0	12
EYES		12	0	0	12
FOLD/ROSETTE, RETINAL		1 (-,1,-,-,-)	-	-	4 (-,4,-,-,-)
INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE)		9 (-,7,2,-,-)	-	-	7 (-,3,4,-,-)
LENS NOT PRESENT, UNILATERAL		-	-	-	1 (1,-,-,-,-)
NEOVASCULARIZATION, CORNEAL		-	-	-	1 (-,1,-,-,-)
OPTIC NERVE NOT PRESENT, UNILATERAL		2 (2,-,-,-,-)	-	-	3 (3,-,-,-,-)
MUSCULOSKELETAL SYSTEM					
FEMUR/KNEE JOINT		12	0	0	12

TABLE 59 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: II	IV	VI	VIII
	DOSE (mg/kg/day):	0	35	125	375
	NUMBER IN GROUP:	12	12	12	12
MUSCULOSKELETAL SYSTEM (Cont'd)					
STERNUM		12	0	0	12
SKELETAL MUSCLE		12	0	0	12
REPRODUCTIVE SYSTEM					
OVARIES		12	0	0	12
UTERUS		12	0	0	12
CERVIX		12	0	0	12
VAGINA		12	0	0	12
ESTRUS STAGE: ESTRUS		2 (2,-,-,-,-)	-	-	6 (6,-,-,-,-)
ESTRUS STAGE: METESTRUS		6 (6,-,-,-,-)	-	-	2 (2,-,-,-,-)
ESTRUS STAGE: PROESTRUS		4 (4,-,-,-,-)	-	-	4 (4,-,-,-,-)
INFLAMMATION, SUBACUTE/CHRONIC		1 (-,-,-,1,-)	-	-	-
INTEGUMENTARY SYSTEM					
SKIN		12	0	0	12
SALIVARY GLANDS		12	0	0	12
FOCUS OF CELLULAR ALTERATION, BASOPHILIC (PAROTID GLAND)		-	-	-	1 (-,1,-,-,-)
EXORBITAL LACRIMAL GLANDS		12	0	0	12
AGGREGATES, LYMPHOID		1 (-,1,-,-,-)	-	-	-
MAMMARY GLAND		12	0	0	12

TABLE 59 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: II	IV	VI	VIII
	DOSE (mg/kg/day):	0	35	125	375
	NUMBER IN GROUP:	12	12	12	12
MISCELLANEOUS					
OTHER					
SKIN: NO ABNORMALITIES DETECTED		0/-	0/-	0/-	1/1 (1,-,-,-,-)
CAUSE OF DEATH					
SACRIFICED BY DESIGN		12/12 (1, , , ,) (2,-,-,-,-)	0/-	0/-	12/12 (1, , , ,) (2,-,-,-,-)
TOTAL ANIMALS WITH PRIMARY TUMORS		0	0	0	0
TOTAL ANIMALS WITH BENIGN TUMORS		0	0	0	0
TOTAL ANIMALS WITH MALIGNANT TUMORS		0	0	0	0

NOTES:

- THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- LESION GRADES: P = PRESENT; 1 = MINIMAL; 2 = MILD; 3 = MODERATE; 4 = SEVERE.
- LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. DOUBLE DIGIT NUMBERS ARE EXPRESSED VERTICALLY, FOR EXAMPLE: (,1, ,1,1) MEANS NO LESIONS WERE GRADED "PRESENT", 10 LESIONS WERE "MINIMAL", 6 LESIONS WERE "MILD", 11 LESIONS WERE "MODERATE", AND 15 LESIONS WERE "SEVERE".
  (-,0,6,1,5)

TABLE 60

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SATELLITE ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	II-0	IV-0	VI-0	VIII-0
		DOSE (mg/kg/day):	0	35	125	375
		NUMBER IN GROUP:	12	12	12	12
REPRODUCTIVE SYSTEM						
OVARIES			2	0	1	1
UTERUS			2	0	1	1
CERVIX			2	0	1	1
VAGINA			2	0	1	1
ESTRUS STAGE: DIESTRUS			-	-	-	1 (1,-,-,-,-)
ESTRUS STAGE: ESTRUS			2 (2,-,-,-,-)	-	-	-
ESTRUS STAGE: METESTRUS			-	-	1 (1,-,-,-,-)	-
MISCELLANEOUS						
CAUSE OF DEATH			2	0	1	1
SACRIFICED BY DESIGN			2 (2,-,-,-,-)	-	1 (1,-,-,-,-)	1 (1,-,-,-,-)
TOTAL ANIMALS WITH PRIMARY TUMORS			0	0	0	0
TOTAL ANIMALS WITH BENIGN TUMORS			0	0	0	0
TOTAL ANIMALS WITH MALIGNANT TUMORS			0	0	0	0

NOTES:
- THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- LESION GRADES: P = PRESENT; 1 = MINIMAL; 2 = MILD; 3 = MODERATE; 4 = SEVERE.
- LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. FOR EXAMPLE: (-,1,2,-,-) MEANS NO LESIONS WERE GRADED "PRESENT" (NON-GRADED LESIONS), 1 LESION WAS GRADED "MINIMAL", 2 LESIONS WERE GRADED "MILD", NO LESIONS WERE GRADED "MODERATE" AND NO LESIONS WERE GRADED "SEVERE".

FIGURES

FIGURE 1

MEAN FORELIMB GRIP STRENGTH FOR MALE RATS

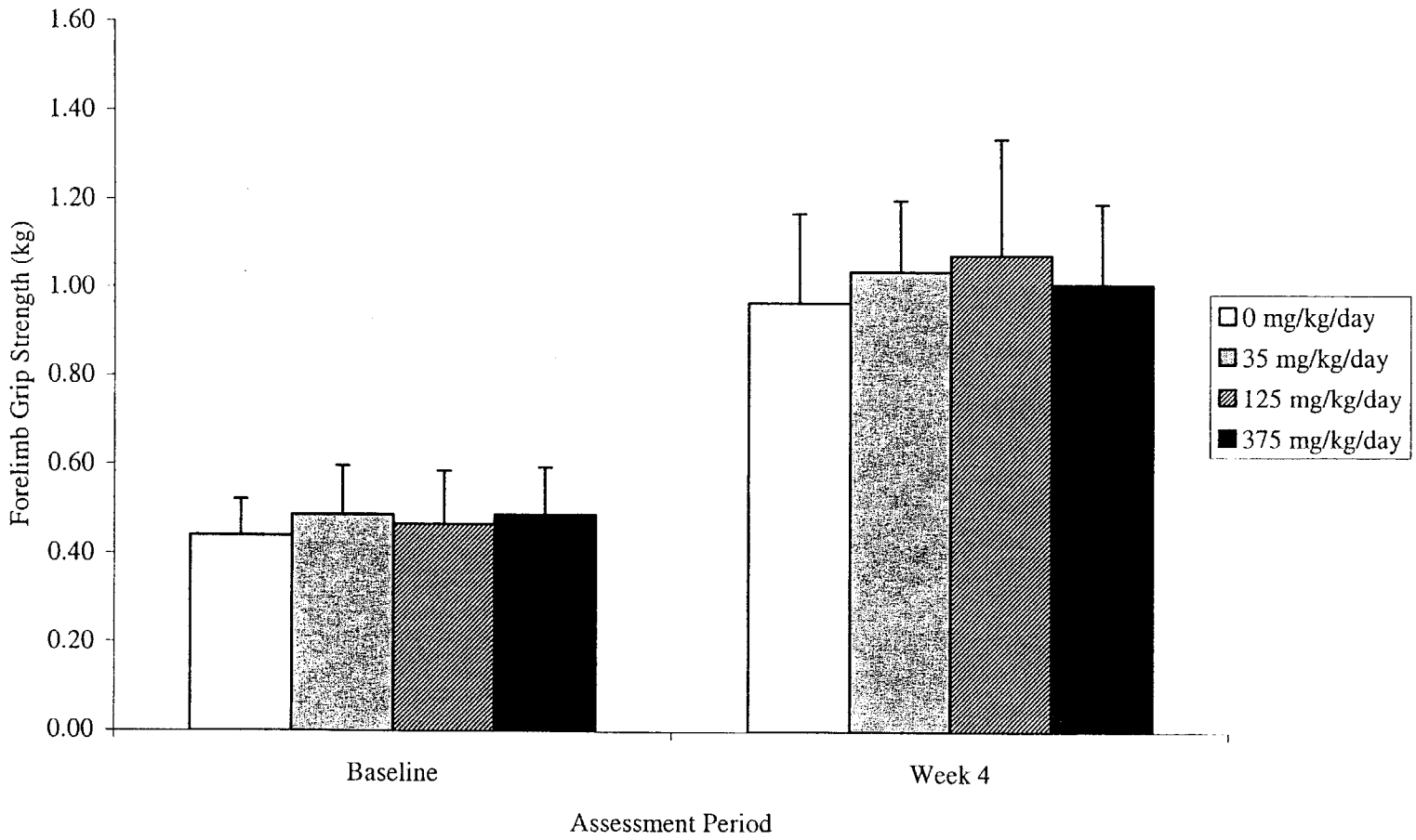


FIGURE 2

MEAN FORELIMB GRIP STRENGTH FOR FEMALE RATS

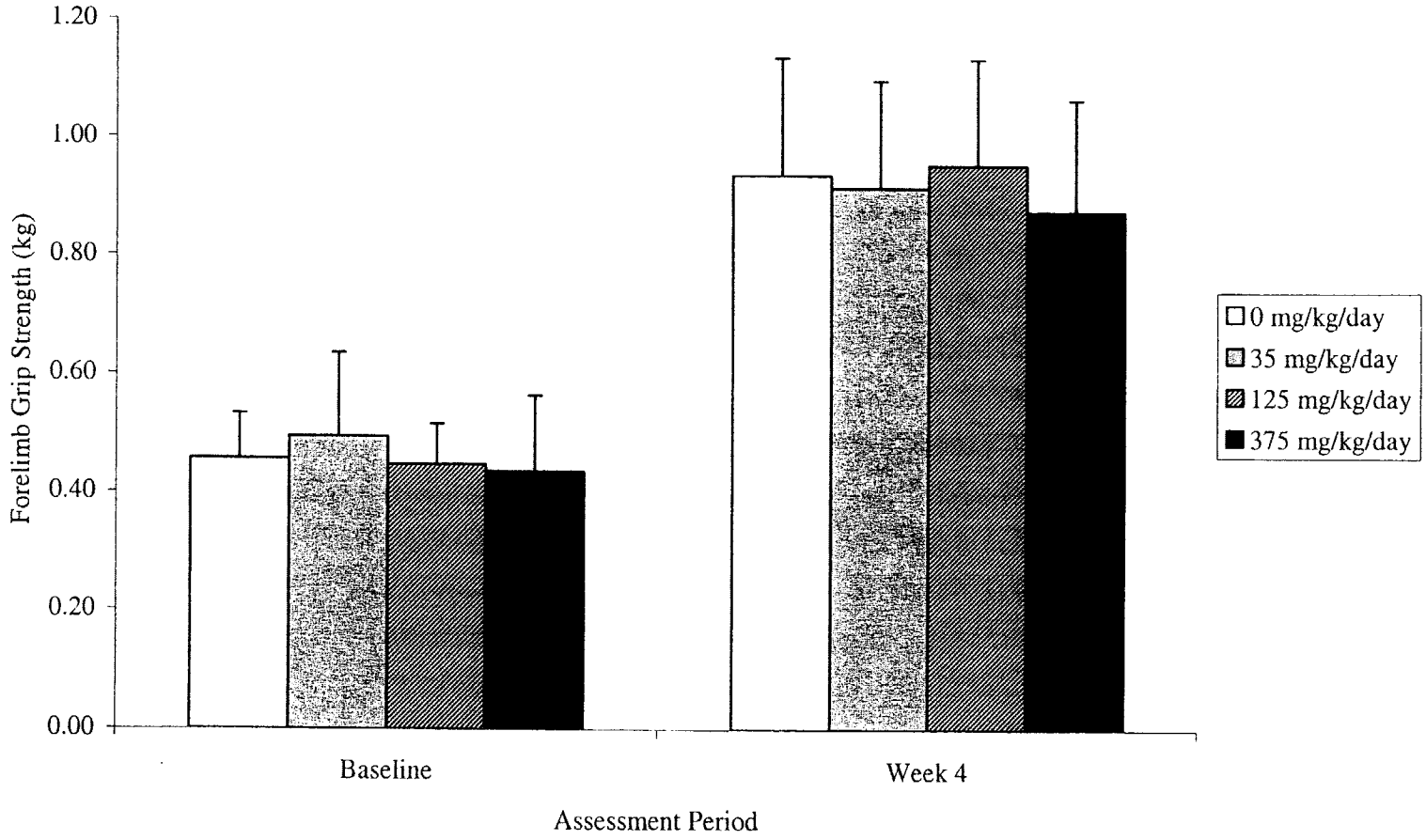


FIGURE 3

MEAN HINDLIMB GRIP STRENGTH FOR MALE RATS

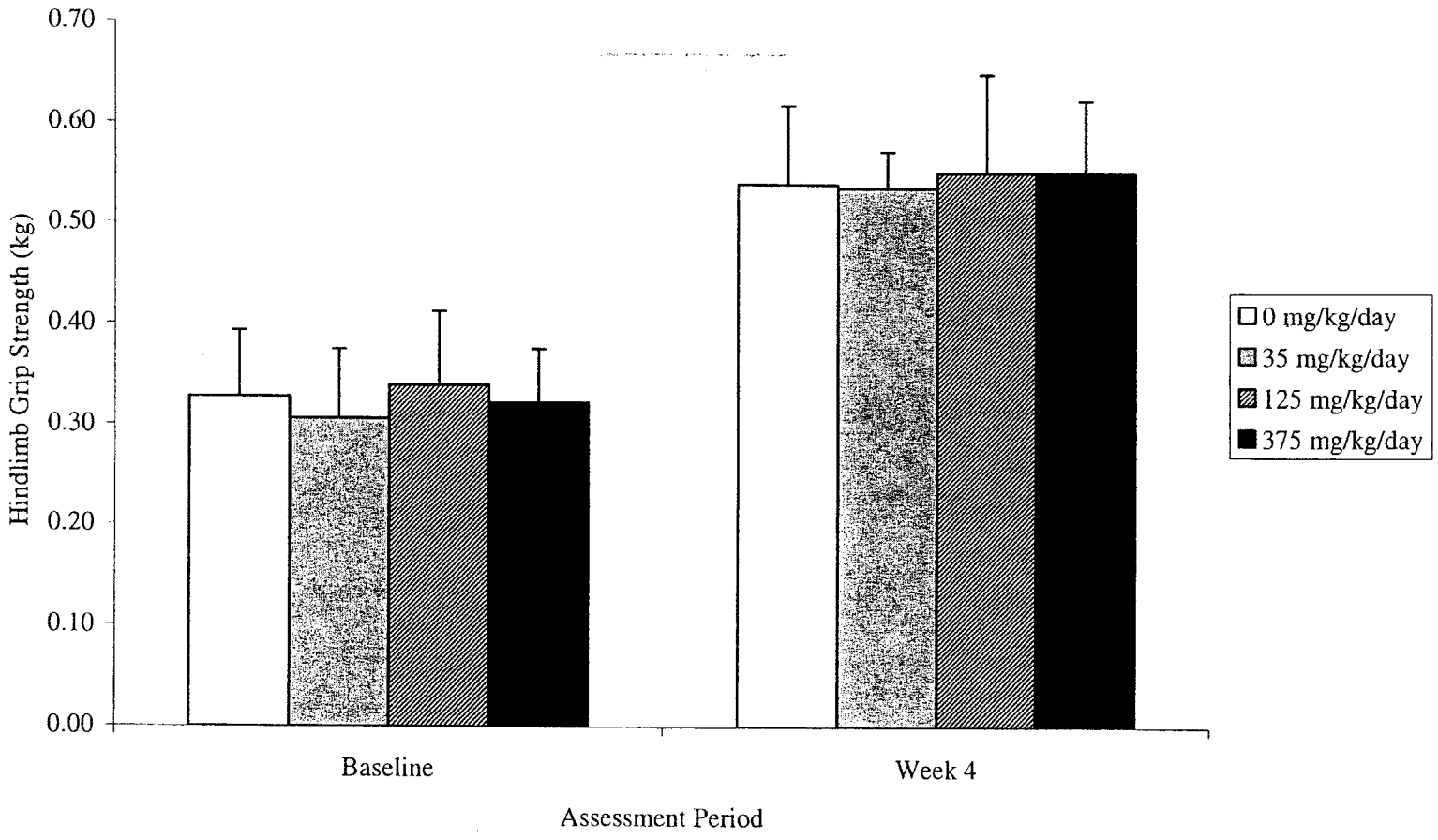


FIGURE 4

MEAN HINDLIMB GRIP STRENGTH FOR FEMALE RATS

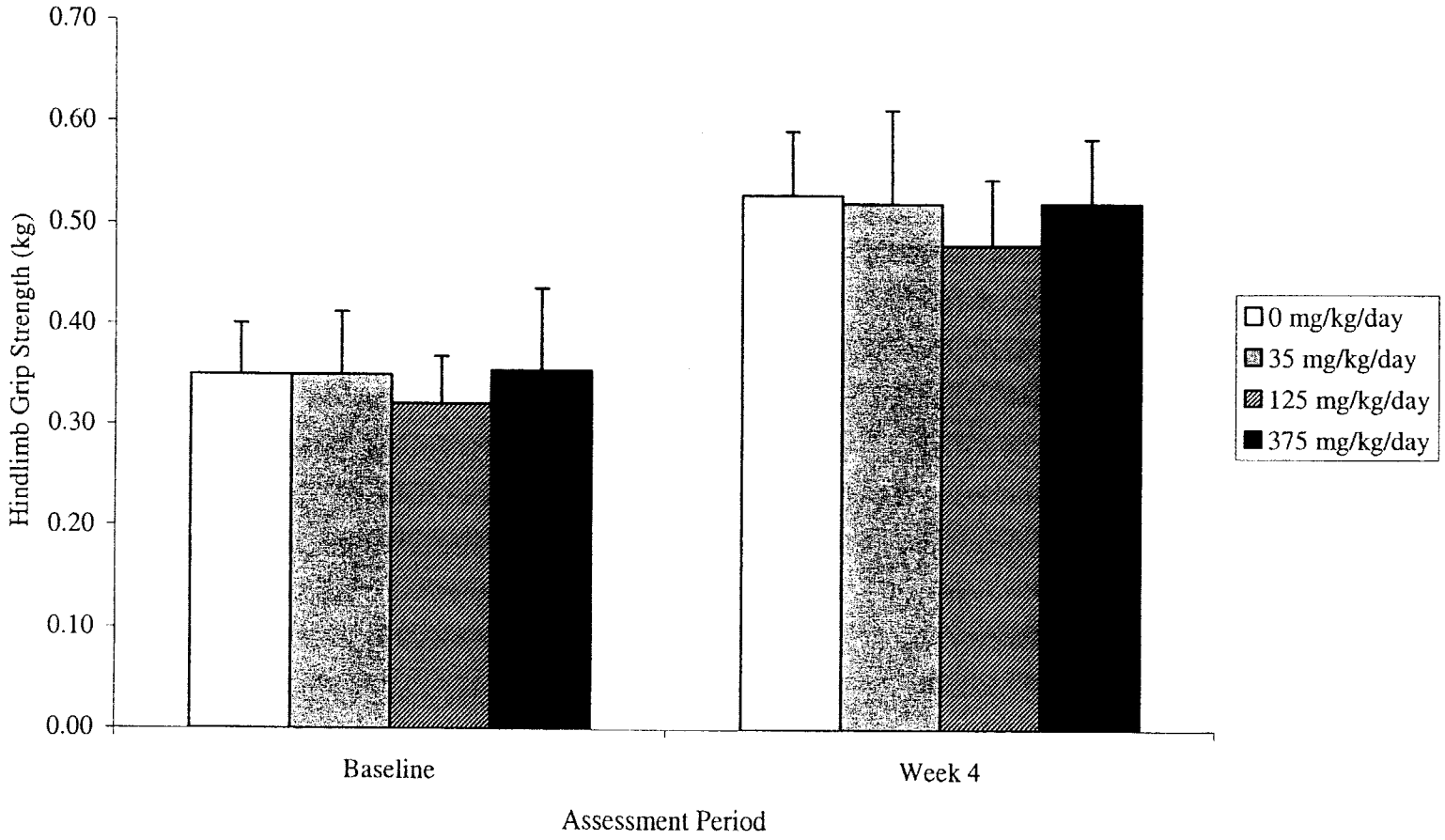


FIGURE 5

MEAN HINDLIMB FOOT SPLAY FOR MALE RATS

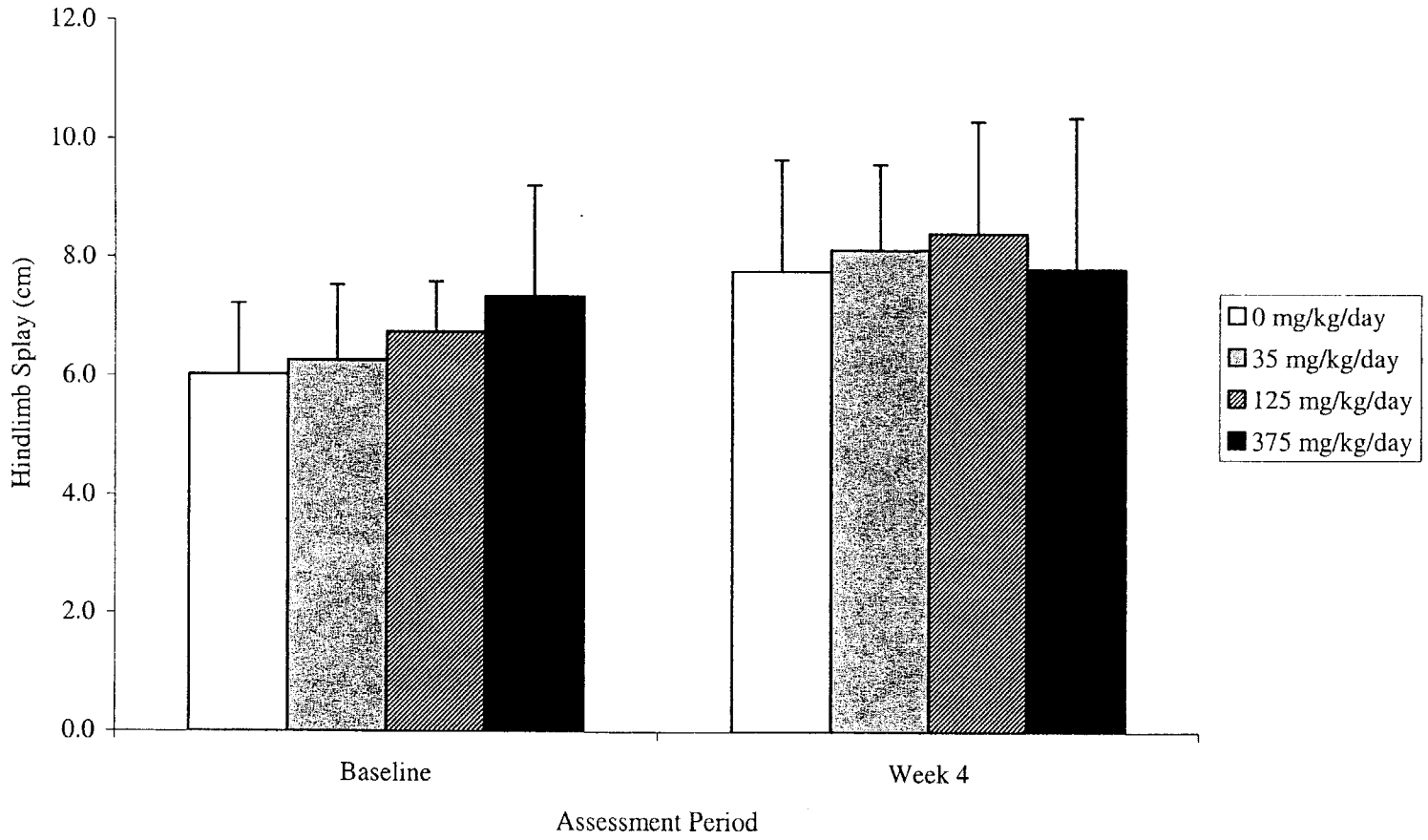


FIGURE 6

MEAN HINDLIMB FOOT SPLAY FOR FEMALE RATS

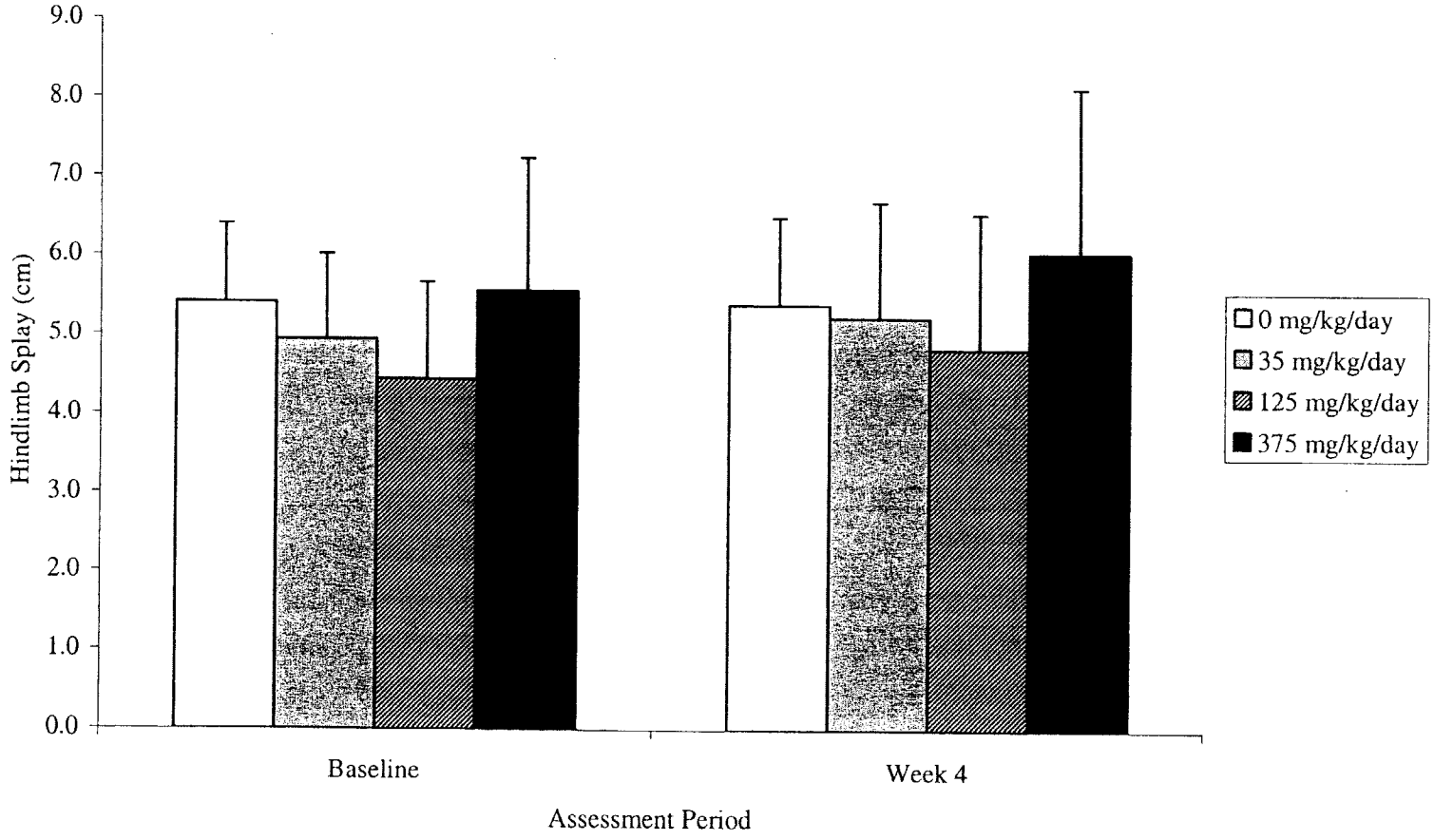


FIGURE 7

MEAN TOTAL DURATION OF MOVEMENT FOR MALE RATS

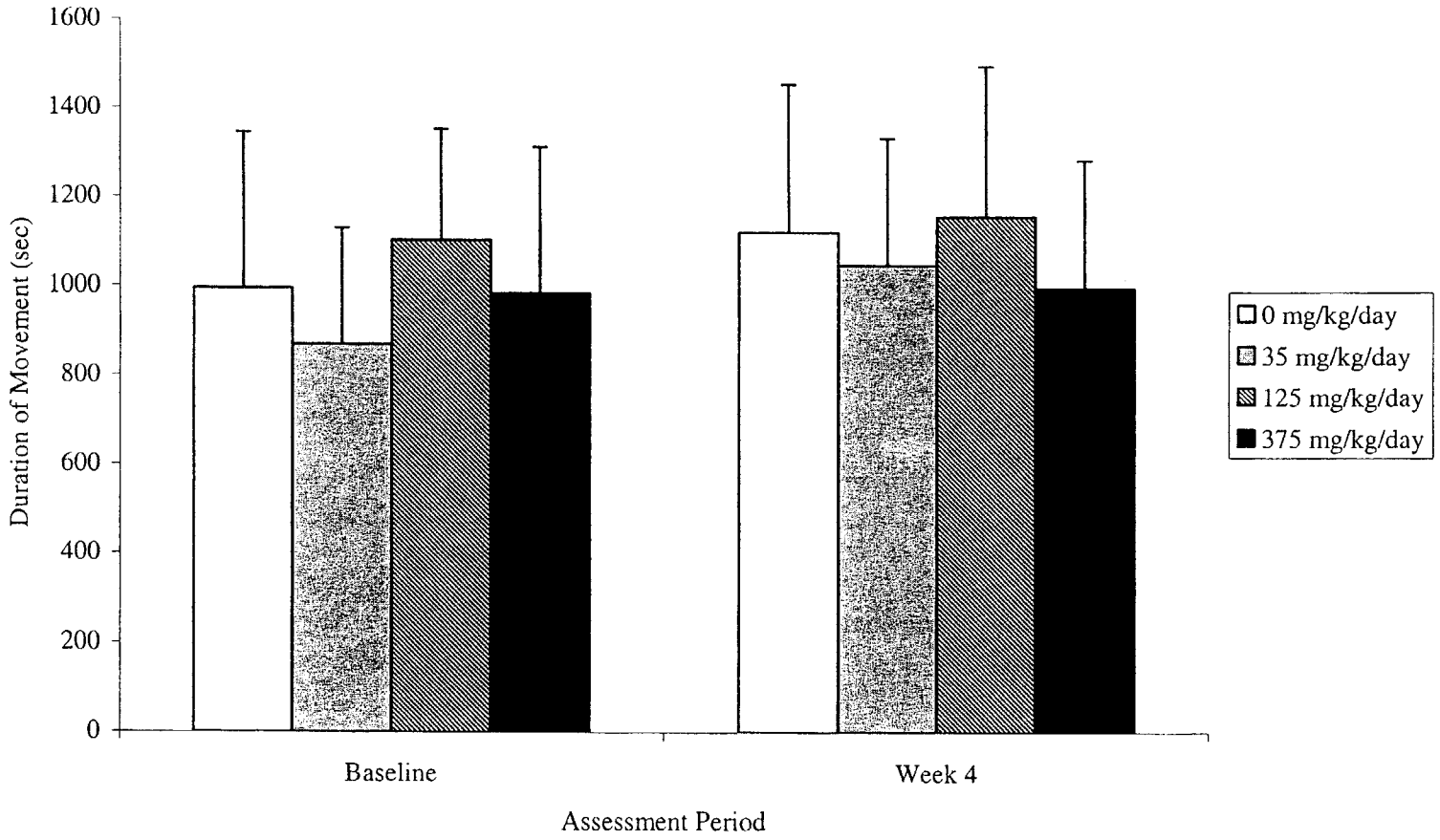


FIGURE 8

MEAN TOTAL DURATION OF MOVEMENT FOR FEMALE RATS

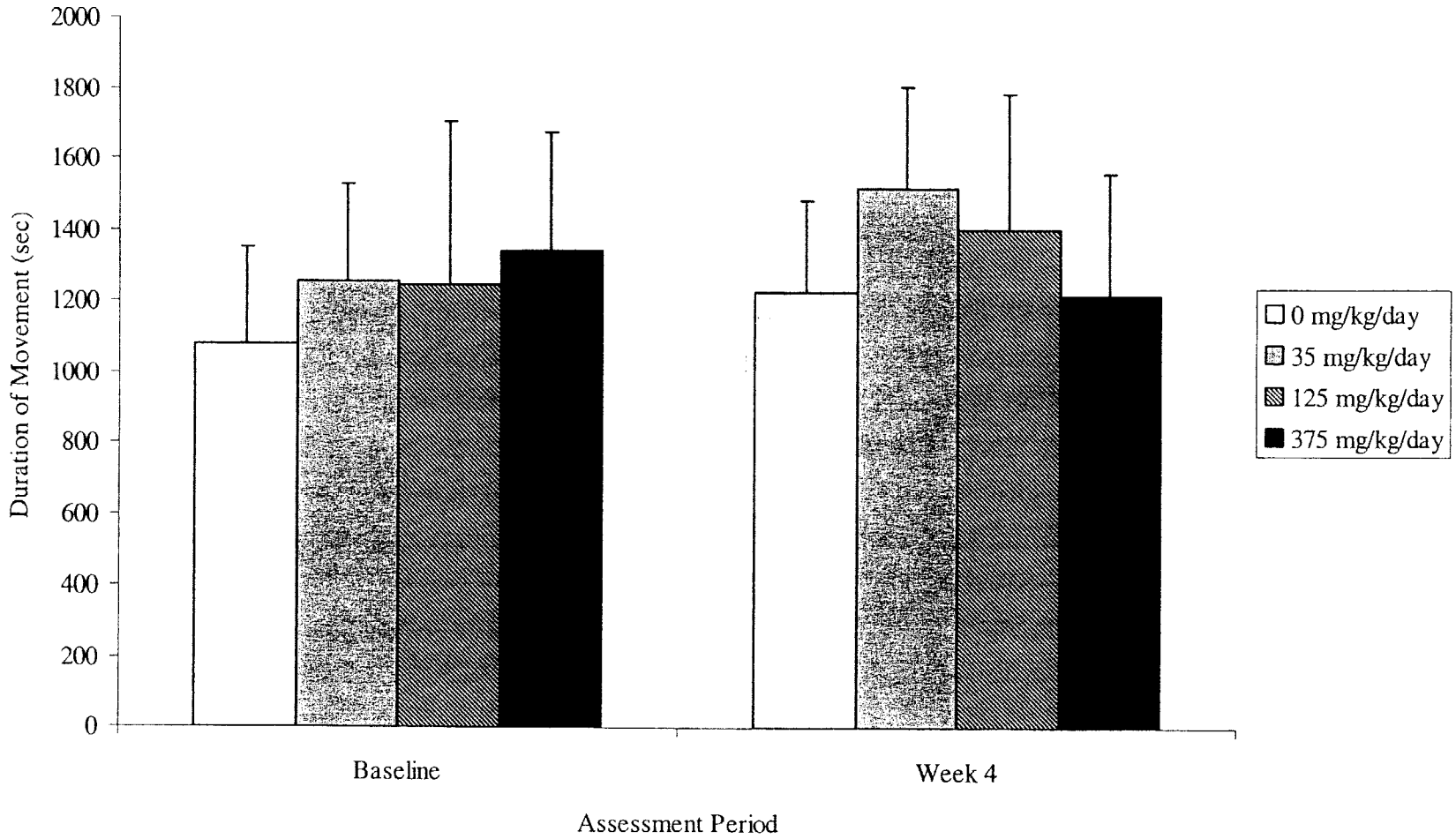


FIGURE 9

MEAN TOTAL NUMBER OF MOVEMENTS FOR MALE RATS

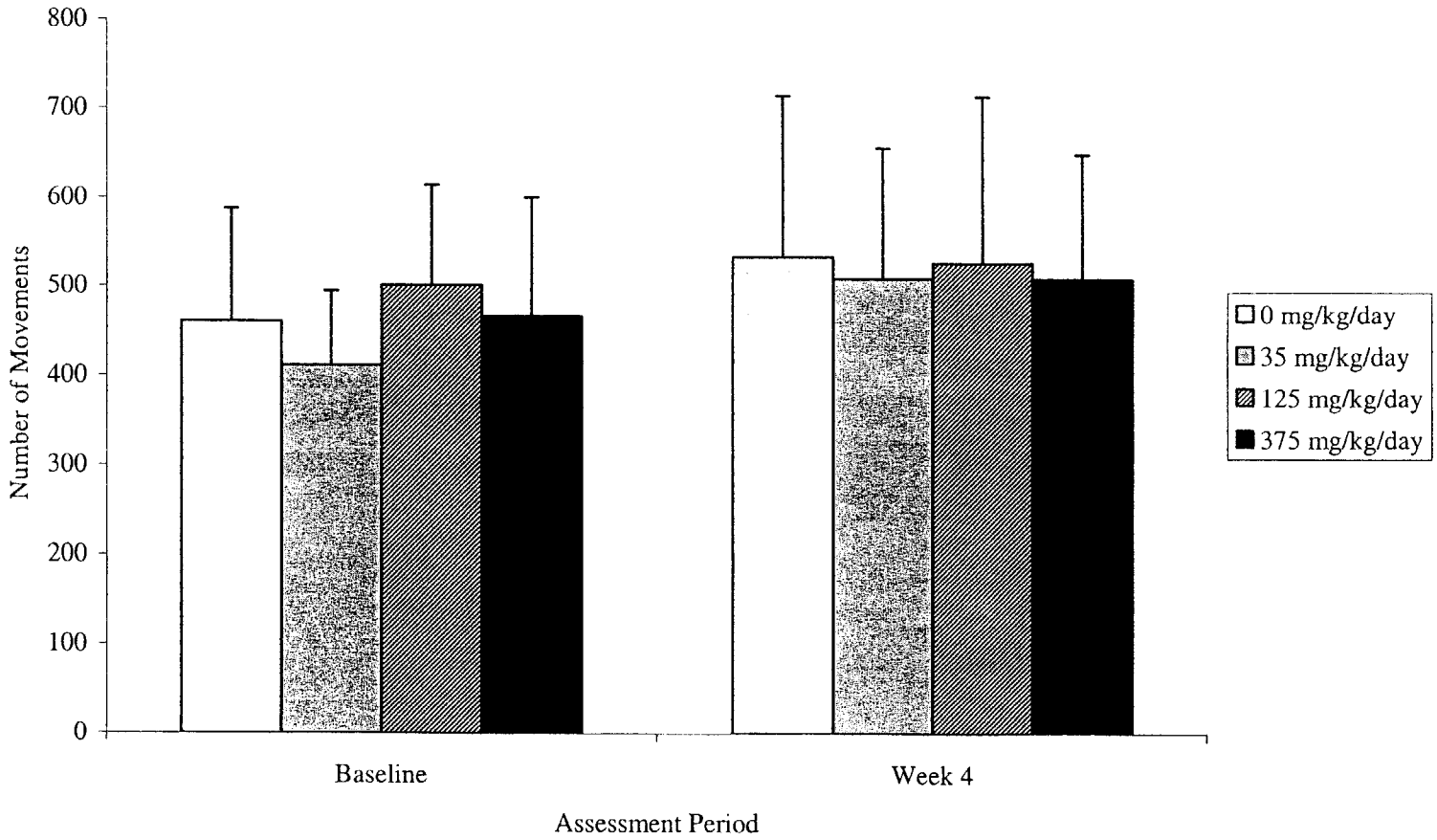
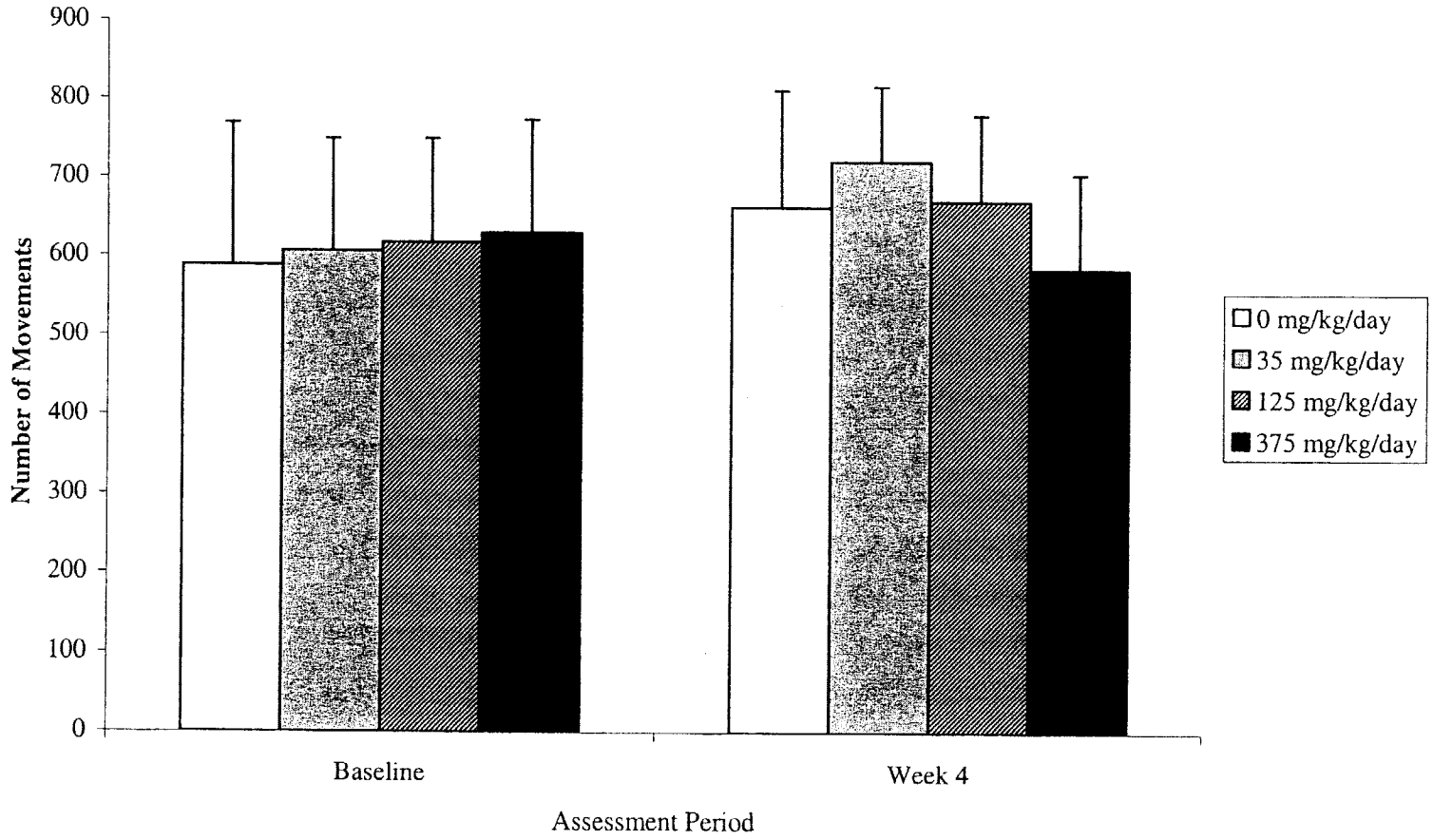


FIGURE 10

MEAN TOTAL NUMBER OF MOVEMENTS FOR FEMALE RATS



APPENDICES

APPENDIX A

Protocol and Protocol Amendments

DuPont-13041

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats

Work Request Number 14295

Service Code 1422

Protocol

Haskell Animal Welfare Committee Number: DGRT-153GP
ACC Reference Number: OLF-92.0-HPV789-DHL

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-13041

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Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-13041

INTRODUCTION AND PURPOSE

Low Dicyclopentadiene Resin Oil (low DCPD resin oil) will be evaluated for potential toxicity using a combined repeated dose toxicity/reproduction/developmental toxicity study. The purpose of this study is to evaluate the potential effects of low DCPD resin oil when administered by gavage to male and female rats for a minimum of 28 consecutive days. General toxicity, clinical pathology, neurobehavioral activity, gross pathology, and histopathology will be evaluated.

In addition, a satellite group will be used to evaluate the potential effects of low DCPD resin oil during premating (approximately 2 weeks), gestation (approximately 3 weeks), and lactation through day 4. In the satellite group, gonadal function, mating behavior, fertility, implantation, development of the conceptus, parturition, gross pathology, and histopathology will be evaluated.

Prior to conducting the main study, a range-finding study will be conducted in time-mated pregnant female rats. Dose levels for the main study will be selected based on the results of the range-finding study.

SPONSOR AND TEST FACILITY

The sponsor of this study is the American Chemistry Council, 1300 Wilson Boulevard, Arlington, Virginia 22209. Sponsor approval of the study protocol will be indicated by the signature of the sponsor's representative on the protocol.

The testing facility will be the DuPont Haskell Laboratory for Health and Environmental Sciences (1090 Elkton Road, Newark, Delaware 19714-0050) using Haskell Laboratory Standard Operating Procedures (SOPs) and animal facilities.

REGULATORY COMPLIANCE

Except as documented in the study records, the main study performed at Haskell Laboratory will be conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are consistent with the OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM(98)17.[1,2] The study design is based on Organisation for Economic Cooperation and Development (OECD), Guidelines for Testing of Chemicals, Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test, Guideline No. 422 (1996)[3] and the EPA Health Effects Guideline OPPTS 870.3650 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test.[4] Areas of noncompliance will be documented in the final report.

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-13041

STUDY DESIGN

Treatment Groups and Dose Levels

Main Subchronic[a]				Satellite[b]		Dosage
Group Male[a]	Number of Males	Group Female[a]	Number of Females	Group Females[b]	Number of Females	mg/kg/day
I	12	II	12	II-0	12	0 (Control)
III	12	IV	12	IV-0	12	35 (Low)
V	12	VI	12	VI-0	12	125 (Medium)
VII	12	VIII	12	VIII-0	12	375 (High)

a Main study males and females (general toxicity and neurotoxicity endpoints)
b Satellite females (reproductive and developmental toxicity endpoints)

Study Parameters	Frequency
Clinical Observations	
• Predosing Observations (Main and Satellite)[a]	• Daily prior to dosing
• Mortality/Moribundity Checks (Main and Satellite)[b]	• Twice daily (a.m. and p.m.)
• Detailed Clinical Observations (Main)[c]	• Pretest, and Days 8, 15, 22, and 29
Body Weights	• Study Days 1, 8, 15, 22, and 29 and at scheduled sacrifice (Main) • Days 1, 8, and 15 – Premating (Satellite) • Weekly – Mating (Satellite) • Daily - Gestation (Satellite) • Days 0 and 4 - Lactation (Satellite)
Food Consumption	• Study Days 1, 8, 15, 22 and 29 (Main) Food consumption will be discontinued for males upon cohabitation • Days 1, 8, and 15 – Premating (Satellite) • Days 0, 7, 14, and 21 - Gestation (Satellite) • Days 0 and 4 - Lactation (Satellite)
Functional Observational Battery (Main)	Pretest and Study Day 29-30
Motor Activity (Main)	Pretest and Study Day 29-30
Clinical Pathology (Main)	Study Day 30-31
Necropsy	Sacrifice Schedule
• Main Males	• Study Day 30
• Main Females	• Study Day 31
• Pregnant Satellite Rats	• Lactation Day 4
• Satellite Rats that did not deliver a litter	• Gestation Day 27 (approximately)
• Pups	• Lactation Day 4
• Satellite Rats with no Evidence of Mating	• Study Day 43 (approximately)

a Predosing Clinical Observations – Immediately prior to dosing, each rat will be individually handled and examined for abnormal behavior and appearance. Clinical abnormalities or No Abnormalities Detected (NAD) will be recorded in the study database for each rat prior to dosing.

b Mortality/Moribundity Checks – All rats will be examined at cage-site twice daily. One of the cage-site examinations will occur in the afternoon, at least 1-2 hours after dosing has been completed. Abnormal clinical signs will be noted by exception and recorded in the study database.

c Detailed Clinical Observations will be recorded in the study database for all rats in the Main study, listing either clinical abnormalities or "NAD." During treatment, when these rats are scheduled for detailed clinical observation evaluations, detailed clinical observations evaluations will be performed and recorded first, predosing observations will then be performed and recorded, and the rats will then be dosed.

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and
Reproductive/Developmental Toxicity Screening Test in Rats DuPont-13041

MATERIALS AND METHODS

A. Route of Administration

The test substance will be administered by oral intubation (gavage) to ensure maximal exposure and provide for comparison with other similar substances that have or will be tested by oral gavage administration. The vehicle control substance will also be administered by oral gavage. The degree of the test substance or vehicle absorption by the test system is deemed beyond the scope and objectives of the study.

B. Duration of the Study

The start date of the study will be defined as the day the study protocol is signed by the Study Director. The experimental start date will be defined as the first day of dosing (test day 1). The experimental termination date of the main study will be defined as the in-life completion phase at Haskell Laboratory. The completion date of the study will be defined as the date the final report is signed by the Study Director at Haskell Laboratory.

C. Test Substance

1. Identification:

Chemical Name:	Low Dicyclopentadiene Resin Oil
Other Name Used in this Protocol:	Low DCPD Resin Oil
CAS Registry Number:	68477-54-3
Haskell Sample Number:	25429
Lot Number:	Not applicable
Purity:	Not applicable
Color:	Colorless-light yellow
Form:	Liquid
Supplier for Low DCPD Resin Oil:	Equistar Chemicals, LP
Vehicle:	Corn oil
Supplier for Corn Oil:	Mazola®
Lot Number/Expiration Date for Corn Oil:	Oct2103B/Oct2103

The test substance will be supplied as a liquid, stored at or below 70° F, and protected from light and air. Corn oil will be stored refrigerated.

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-13041

D. Test Substance Characterization

The test substance will be characterized by the supplier.

1. Test Substance Stability

Stability of the test substance will be established by analyses at 2 time points. Aliquots will be taken after the end of the range-finding study, which will serve as the beginning of the study analysis for the main study. Aliquots will be taken again near the end of the current of study. The results of these analyses will be reported as test substance stability. The stability samples will be analyzed by gas chromatography using FID detection. Two peaks of the major component(s) will be compared to an internal standard to determine a ratio. Two calibration curves will be prepared from these ratios, and the samples will be evaluated based on the calibration curves. The results will then be averaged and reported as the concentration of the test substance. The samples will be analyzed by Haskell Laboratory's Analytical Chemistry Group on the day the samples are collected. Details regarding the analytical method used will be documented in the Analytical Chemistry Group study report.

E. Vehicle

Corn oil will be used as test substance vehicle. The corn oil will be purchased from reliable commercial vendors by Haskell Laboratory and is not expected to contain any contaminants that would interfere with the conduct of the study. The corn oil will be assumed to be stable under the conditions of the study.

F. Degree of Absorption

For the purposes of this study, clinical signs of toxicity and other manifestations of toxic effects will be considered to indicate uptake of the test substance. No attempt will be made to establish the actual systemic dose each rat received. All treatment-related effects will therefore be reported as a function of the administered dose(s).

G. Dosing Formulation Preparation and Sampling

For the preparation of dosing formulations, the test substance purity will be considered 100%.

Dosing formulations of the test substance will be prepared daily with corn oil by adding the corn oil to the measured amount of test material and stirring to establish uniformity.

Near the beginning of the study, 4 samples (approximately 3 mL) will be collected from each formulation, and will be analyzed for homogeneity/concentration verification, and 5-hour stability at room temperature. Near the middle and end of the dosing period, duplicate samples will be taken from all formulations and analyzed for concentration verification.

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and
Reproductive/Developmental Toxicity Screening Test in Rats DuPont-13041

The remaining formulation samples after dosing will be stored refrigerated, and discarded when the final results from the analysis have been accepted. Whenever samples are collected, a sample of the vehicle will also be collected and analyzed.

The samples will be mixed and diluted with chloroform. The resulting solution will be analyzed by gas chromatography using FID detection. The samples will be analyzed by the Haskell Laboratory Analytical Chemistry Group on the day the samples are collected. Details regarding the analytical method used will be documented in the Analytical Chemistry Group study records and the final report.

H. Test System

Approximately 56 male and 112 female (nulliparous) Crl:CD®(SD)IGS BR rats will be obtained from Charles River Laboratories, Inc (Raleigh, North Carolina). The rats will be approximately 8-10 weeks old at study start. This age corresponds to an estimated weight range of 200-325 g according to the vendor. Since the exact weight range for the animals in this study is not available prior to issuing the protocol, the exact weight range will be recorded in the raw data and stated in the final report. The Crl:CD®(SD)IGS BR rat has been selected on the bases of extensive experience with this strain at Haskell Laboratory and its suitability with respect to longevity, sensitivity, and low incidence of spontaneous diseases.

I Animal Husbandry

1. Identification

Each rat will be assigned an animal number and an individual cage identification number. The animal number will be tattooed on the tail of each rat. The animal number and cage identification number will both be included on the cage label.

2. Housing Environment

Rats will be housed singly in stainless steel, wire-mesh cages, suspended above cage boards, except as described in the next 2 paragraphs. Each cage rack will contain only rats of one gender.

During cohabitation, males designated for subchronic toxicity will be cohoused with the satellite females in their respective groups until evidence of copulation is observed.

Females in the satellite group will be housed in polycarbonate pans with bedding (Bed-o-Cobs®) from gestation day 19 or the end of the cohabitation period (if evidence of copulation was not detected) until sacrifice.

Animal rooms will be targeted at an acceptable temperature of 22° ± 3°C and maintained at an acceptable relative humidity of 30-70% (targeted at 40-60%). Animal rooms will be artificially illuminated (fluorescent light) on an approximate 12-hour light/dark cycle.

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-13041

3. Feed and Water

All rats will be provided tap water (United Water Delaware) ad libitum. They will be fed PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002 (chunk chow) ad libitum.

4. Animal Health Monitoring

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. Data are maintained separately from study records and may be included in the final report at the discretion of the study director.

J. Disposition of Moribund Animals or Animals Found Dead

During any portion of the main study, if a rat is determined to be moribund in the judgment of the Study Director, the consulting veterinarian, or their designee, the affected animal will be euthanized by carbon dioxide asphyxiation as soon as practical and will be subjected to a gross necropsy and tissue collection.

K. Quarantine and Pretest Procedures

Upon arrival at Haskell Laboratory, all rats will be housed 1 per cage, sexes separate, in quarantine. The rats will be:

- quarantined for a minimum of 6 days.
- identified temporarily by cage identification.
- weighed at least 3 times during quarantine.

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and
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- observed with respect to weight gain and any gross signs of disease or injury during the entire pretest period (approximately 12 days).

The rats will be released from quarantine by the laboratory animal veterinarian or designee on the bases of acceptable body weights and clinical signs.

Rats that are accidentally killed or removed from study during the pretest period will be discarded without necropsy. Rats that are found dead or sacrificed *in extremis* during the pretest period will undergo a gross pathological examination to check for the presence of disease. Dependent upon these findings, further diagnostic procedures may be employed at the discretion of the study director, a pathologist, or the laboratory animal veterinarian. The results will not be reported in the final report unless considered significant to the evaluation of the study.

L. Assignment to Groups

Rats of each sex will be selected for use on study on the bases of adequate body weight gain and freedom from any clinical signs of disease or injury. They will be distributed by computerized, stratified randomization into study groups as designated in the Study Design, so that there are no statistically significant differences among group body weight means within a sex. To the extent possible, the weight variation on test day 1 will not exceed ± 20% of the mean for each sex.

After assignment to groups, each rat will be housed individually. At study start (test day 1) the rats will be approximately 8-10 weeks of age.

Rats that have not been assigned to a test group will be released for other laboratory purposes or be sacrificed by carbon dioxide asphyxiation and discarded without pathological evaluation, at the discretion of the Study Director.

M. Dose Selection

Individual dosages for the main study were determined in consultation with the Sponsor and were based on the results of the range-finding study.

N. Administration of Dosing Solutions

The test substance will be administered once daily by gavage at a dose volume of 2 mL/kg. Females designated for the subchronic toxicity study (main group) will be dosed for a minimum of 28 days. Females designated for the reproduction study (satellite group) will be dosed during the premating period (approximately 2 weeks), the mating period until evidence of copulation is observed (up to 2 weeks), the gestation period (approximately 3 weeks), and days 0-4 of lactation (if delivery is in progress at the time of dosing, the female will not be administered the dose). Females showing no evidence of copulation will continue to be dosed after the end of the cohabitation period until sacrifice. Males will be dosed during the premating period (approximately 2 weeks), during the mating period until evidence of copulation is observed, and

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subsequently until sacrifice (a minimum of 28 days total). Control rats will be dosed with corn oil (2 mL/kg) for a minimum of 28 days.

Individual dosages will be based on the most recently recorded weight.

O. Body Weights

1. Main Subchronic Study

All main study rats will be weighed on day 1, 8, 15, 22, and 29 and at scheduled sacrifice unless experimental findings or special scheduling situations warrant a change in the weighing schedule. In addition, rats undergoing functional observational battery and motor activity evaluations will be weighed on the days of those observations; however those weights will be included only in the appendix of the final report.

2. Satellite Study

Satellite female rats will be weighed according to the following schedule:

- Premating period – Days 1, 8, and 15
- Mating – Weekly
- Gestation – Daily
- Lactation – Days 0 and 4

P. Food Consumption and Food Efficiency

The amount of feed consumed by each rat over the weighing interval will be determined by weighing each feeder at the beginning of the interval and subtracting the diet remaining and the amount of spillage from the feeder at the end of the interval. From these determinations, mean daily feed consumption (g/day) will be calculated. Mean food efficiency will be calculated by dividing the amount of weight gain by the amount of food consumed for a given interval of test days.

1. Main Subchronic Study

Feed consumption will be measured on day 1, 8, 15, 22, and 29 for each rat on the main study (food consumption in males will be discontinued upon cohabitation).

2. Satellite Study

Satellite female rats will have feed consumption measured according to the following schedule:

- Premating period – Days 1, 8, and 15
- Gestation – Days 0, 7, 14, and 21
- Lactation – Days 0 and 4

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Feed consumption will not be measured during cohabitation.

Q. Clinical Observations and Mortality

Clinical Observations will be recorded throughout the test period for all rats. Moribund rats will be sacrificed and necropsied. Databases used for collection of clinical observation data will be documented in the study records.

1. Predosing Observations – Main Subchronic Study and Satellite Study

Prior to dosing, or at the time of dosing, each rat will be individually handled and examined for abnormal behavior and appearance. Clinical abnormalities or No Abnormalities Detected (NAD) will be recorded in the study database for each rat prior to dosing.

2. Morbidity/Mortality Checks – Main Subchronic Study and Satellite Study

During the test period, cage-site examinations to detect moribund or dead rats and abnormal behavior and/or appearance among rats will be conducted at least twice daily throughout the study. Moribund rats will be sacrificed and necropsied. One of the cage-site examinations will occur in the afternoon, at least 1-2 hours after dosing has been completed. Abnormal clinical signs will be noted by exception and will be recorded in the study database.

3. Detailed Clinical Observations – Main Subchronic Study

Rats in the Main Study will undergo a detailed clinical observation evaluation during pretest, and on days 8, 15, 22, and 29. During the treatment period, when these rats are scheduled for detailed clinical observation evaluations, detailed clinical observations evaluations will be performed and recorded first, predosing observations will then be performed and recorded, and the rats will then be dosed.

Each rat will be individually handled and examined for abnormal behavior and appearance in a standardized arena. The detailed clinical observations will include (but are not limited to) evaluation of fur, skin, eyes, mucous membranes, occurrence of secretions and excretions, autonomic nervous system activity (lacrimation, piloerection, and unusual respiratory pattern), changes in gait, posture, response to handling, presence of clonic, tonic, stereotypical, or bizarre behavior. Clinical Observations will be recorded in the study database for all rats in the Main study, listing either clinical abnormalities or "NAD."

R. Neurobehavioral Evaluations – Main Subchronic Study

For all the following assessments, the experimenter will be unaware of the group designation of the animal.

In order to accommodate the Neurotoxicology testing facility, the functional observational battery (FOB) and motor activity (MA) assessments will be conducted in 2 replicates per sex

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over a one-day period for baseline and a one-day period for the week 4 FOB. Replicate designations will not be reported in the final report, but will be recorded in the study records. Assignment to a given replicate will be counter balanced across all groups within a sex.

Prior to initiation of dosing, all rats designated for subchronic toxicity and approximately 8 extra rats per sex will be evaluated in the FOB test to establish their baseline FOB parameters. The FOB will be performed again on the rats designated for subchronic toxicity after a minimum of 28 days after initiation of test substance administration. Rats will be administered the daily dose after neurobehavioral evaluations are performed.

1. Functional Observational Battery (FOB)

FOB testing will consist of a series of quantified behavioral observations conducted in a sequence that proceeds from the least interactive to the most interactive. (See Appendix A.)

During the FOB assessments, each rat will be evaluated in three "environments:" 1) inside the home cage; 2) upon removal from the home cage and while being handled; and 3) in a standard "open field" arena (approximately 85 x 59 x 20 cm). The animal's actual home cage is not amenable to transport between the housing room and neurobehavioral laboratory areas. Therefore, for the purposes of the FOB, the "home cage" is defined as the cage on the transport rack to which an individual animal is assigned and to which the rats have been acclimated and undisturbed for a period of at least 10 minutes.

Inside the home cage, the presence of the following will be recorded, if and when observed:

- palpebral closure
- writhing
- circling
- biting
- unusual changes in body posture
- gait/coordination

During removal from the home cage and handling, each rat will be assessed for:

- fur appearance
- ease of removal
- ease of handling
- muscle tone
- the presence of
  - vocalizations
  - piloerection
  - bite marks
  - palpebral closure
  - lacrimation
  - exophthalmus
  - salivation

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In the open field arena, the rats will be evaluated for:

- unusual responses in
  - arousal
  - grooming
  - gait/coordination
  - posture
  - rate of respiration
  - ease of respiration
  - righting reflex
  - the number of rearing movements
- the presence of
  - convulsions
  - tremors
  - muscle fasciculation
  - muscle spasms
  - diarrhea
  - polyuria
  - palpebral closure
  - vocalizations

While in the standard arena, simple assessments of sensory function will be made, including:

- response to
  - approach/touch
  - auditory stimulus
  - tail pinch
  - the presence or absence of pupillary constriction assessed after a beam of light is directed into each eye.
  - pupillary constriction measured immediately prior to removing the rats from the motor activity chambers because the darkened room in which the apparatus is located facilitates observing the response.
  - the presence of diarrhea and polyuria on the cageboards below the motor activity cages will also be evaluated following each motor activity session.

The remainder of FOB testing involves standardized or calibrated devices. Fore- and hindlimb grip strength will be measured by a strain gauge device (Chatillon® -Digital Force gauge) (3 trials per animal per session). Hindlimb splay will be assessed by inking the hind paws and releasing the rat from a height of approximately 32 cm onto a piece of paper that covers a padded surface. Heel to heel distance will be measured from the inked impressions and recorded.

Rectal body temperature will be recorded with a YSI Precision™ 4000 Thermometer and temperature probe.

2. Motor Activity (MA)

Motor activity sessions will be conducted on the same animals, the same day as FOB assessments, following the FOB assessments. Rats will be individually tested in one of 30 nominally identical, automated activity monitors (Coulbourn®). Groups will be counterbalanced across the monitors and time of day to the fullest extent possible. The infrared monitoring device enables measurement of two dependent variables, duration of movement and number of movements. A continuous movement is counted as one movement regardless of duration. Each test session will be 60 minutes in duration, and the results will be expressed for

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the total session, total motor activity over a 60-minute time period, as well as for 6 successive 10-minute blocks.

S. Clinical Pathology Evaluation

A clinical pathology evaluation will be conducted on all rats designated for subchronic toxicity at the time of scheduled sacrifice. These rats will be fasted overnight. Blood samples for hematology and clinical chemistry measurements will be collected from the orbital sinus of each animal while the animal is under light carbon dioxide anesthesia. Blood samples for coagulation parameters will be collected at sacrifice from the abdominal *vena cava* of each animal while the animal is under carbon dioxide anesthesia. Additional blood collected from the *vena cava* will be placed in a serum tube, processed to serum, and frozen at approximately -80°C. Serum may be used for additional testing as documented by protocol amendment, or will be discarded when the final report issues. Bone marrow smears will be prepared at the final sacrifice from all surviving animals and will be evaluated if warranted by experimental findings.

At the discretion of the Study Director or clinical pathologist, additional samples for selected clinical pathology tests may be collected from animals showing clinical evidence of toxicity or sacrificed *in extremis*.

1. Hematology and Coagulation

Blood samples will be evaluated for quality by visual examination prior to analysis.

The following hematology and coagulation parameters will be determined:

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

In addition, blood smears, stained with new methylene-blue, will be prepared from each animal undergoing a hematology evaluation and will be examined, if required, to substantiate or clarify the results of hematology findings.

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2. Clinical Chemistry

The following clinical chemistry parameters will be 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

T. Reproductive Assessment

1. Breeding

After 2 weeks of treatment with the test substance, each satellite female will be continually housed on a 1:1 basis with a randomly selected subchronic male of the same treatment level in the male's cage. On the day copulation is confirmed, the satellite female will be transferred back to individual cage housing. Mating pairs will be cohoused until evidence of copulation is observed (designated as day 0 of gestation), or until two weeks have elapsed. Once daily, each female will be examined for an intravaginal copulation plug or sperm in vaginal lavage sample, either one of which will be considered evidence of copulation. The day evidence of copulation is observed will be designated as day 0 of gestation. Cageboard will be examined for the presence of a cageboard plug(s). The presence of cageboard plugs, vaginal plugs, and/or sperm will be recorded.

2. Gestation Procedures – Satellite Study

After they are transferred into polycarbonate pans (on day 19 of gestation (GD 19) for mated females, or at the end of the cohabitation period for females without evidence of copulation), female rats will be observed at least twice daily for signs of delivery and pups.

3. Lactation Procedures – Satellite Study

The day when delivery is complete is designated day 0 postpartum (LD 0). At each examination period, pups will be individually handled and examined for abnormal behavior and appearance; any dead, missing, or abnormal pups will be recorded. Any pups found dead or which are euthanized in moribund condition will be examined to the extent possible and discarded.

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a. Day 0 Postpartum (Lactation Day 0)

Live and dead pups in each litter will be counted as soon as possible after delivery is completed. Live pups in each litter will be individually weighed and sex determined. Any clinical abnormalities in pups will be recorded.

b. Days 1 and 4 Postpartum (Lactation Day 1 and 4)

Pups in each litter will be counted by sex, individually weighed, and any clinical abnormalities in pups will be recorded. On LD4, all offspring will be evaluated for external alterations, and euthanized by decapitation.

U. Anatomic Pathology Evaluation

1. Pretest

See Section K. Pretest Period.

2. Adult Rats

All rats found dead, accidentally killed, sacrificed *in extremis*, or sacrificed by design will undergo a gross evaluation and the tissues listed below will be collected. Rats will be euthanatized by carbon dioxide asphyxiation and exsanguination. Rats in the Main Study only will be fasted after 3 p.m. on the afternoon before their scheduled sacrifice; rats in the Satellite Study will not be fasted before sacrifice. The order of sacrifice for scheduled deaths will be random among all treatment groups within a sex. Bone marrow smears will be prepared at the final sacrifice from all surviving animals and will be evaluated if warranted by experimental findings.

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The following tissues will be collected from rats that are found dead or accidentally killed (tissue integrity permitting), sacrificed *in extremis*, or sacrificed by design including satellite females.

Digestive System[a]
liver
esophagus
stomach
duodenum
jejunum
ileum
cecum
colon
rectum
tongue
pancreas

Urinary System
kidneys
urinary bladder

Respiratory System
lungs
trachea
nose
pharynx/larynx

Cardiovascular System
heart
aorta

Hematopoietic System
spleen
thymus
mediastinal lymph node
mandibular lymph node
mesenteric lymph node
bone marrow[b]

Endocrine System
pituitary gland
parathyroid gland
thyroid gland
adrenal glands

Nervous System
brain (3 sections)
spinal cord (3 levels)
eyes (with optic nerve)
sciatic nerve

Musculoskeletal System
femur/knee joint
sternum
skeletal muscle

Reproductive System
Male
testes
epididymides
prostate
seminal vesicles
coagulating glands
Female[c]
ovaries (with oviducts)
cervix
uterus
vagina

Integumentary System
skin
salivary glands
lacrimal glands
mammary gland (females only)

Miscellaneous
gross observations[d]

a Peyer's patches will be collected from sections of the digestive tract.
b Bone marrow will be collected with the femur and sternum.
c Females in the satellite groups will be examined for the presence and number of uterine implantation sites and ovarian *corpora lutea*.
d Gross observations made at necropsy for which histopathology is not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) will generally not be collected.

All tissues will be placed in the appropriate fixative.

For rats in the Main subchronic study that are sacrificed by design, the following organs will be weighed: liver, kidneys, lungs, adrenal glands, thymus, spleen, brain, heart, and testes and epididymides and/or ovaries and uterus. For rats in the Satellite study, the following organs will be weighed and trimmed: liver, kidney, lungs, ovaries and uterus. Relative organ weights (percent of final body weight; ratio to brain weight) will be calculated. Final body weights determined just prior to necropsy will be used in the assessment of organ weight changes.

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Organs from rats found dead, sacrificed *in extremis*, or accidentally killed may be weighed at the discretion of the pathologist or Study Director.

Histologic examination of all the tissues in the table above will be conducted on rats designated for subchronic toxicity from the high-treatment and control group animals. Examination of tissues from the remaining groups will be limited to relevant gross lesions and those tissues that demonstrate treatment-related histologic effects in the high-treatment group.

Gross lesions and tissues listed from satellite females will be collected and saved for possible future histopathology. The uteri of all mated females will be examined for the number of implantation sites and the ovaries will be examined for the number of *corpora lutea*. The uteri of mated females that did not deliver litters will be visually examined for implantation sites in order to verify pregnancy status. In the event that histopathology is considered necessary for satellite females that deliver a litter, it will be addressed in a protocol amendment. All preserved reproductive tissues from animals with impaired reproductive performance (e.g., failure to mate, conceive, sire, deliver healthy offspring, or nurse) will be examined microscopically.

Paraffin-embedded tissues will be sectioned approximately 5-6 microns thick, stained with hematoxylin and eosin, and examined microscopically by a veterinary pathologist. Selected gross observations for which a microscopic diagnosis would not be additive (e.g., osteoarthritis, pododermatitis, tail chronic dermatitis, calculus, and deformities of the teeth, toe, tail, or ear pinna) will be saved, but will generally not be processed for microscopic evaluation. Rats found dead or sacrificed *in extremis* will be histologically examined in a similar manner in an attempt to determine cause of death or morbidity.

Additional procedures to identify and/or clarify histologic features of lesions may be performed at the discretion of the pathologist and will be documented in the final report.

3. Pups

All offspring surviving to postnatal day 4 will be evaluated for external alterations and euthanized by decapitation. Pups found dead or which are euthanized in moribund condition will be examined to the extent possible and discarded.

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DATA ANALYSES

The following table lists the indices of reproductive function that will be calculated for the P_1 adults.

Reproductive Function Calculations

Mating Index (%)	=	Number Copulated[a] / Number Cohabited	x 100
Fertility Index (%)	=	Number Pregnant[b] / Number Copulated[a]	x 100
Gestation Index (%)	=	Number of Litters with at Least One Live Pup / Number of Litters	x 100
Implantation Efficiency (%)[c]	=	Number of Pups Born / Number of Implantation Sites	x 100
Pups Born Alive (%)[c]	=	Number of Pups Born Alive / Number of Pups Born	x 100
Viability Index (%)[c,d]	=	Number of Pups Alive Day 4 Preculling / Number of pups born alive	x 100
Preimplantation Loss[e]	=	Number of corpora lutea – Number of implantation sites / Number of implantation sites	
Postimplantation Loss[e]	=	Number of implantation sites – Number of pups / Number of pups	

a Evidence of copulation = intravaginal or cageboard copulatory plug and/or sperm in vaginal lavage sample, found dead pregnant, or delivery of a litter.
b Including those found dead pregnant during gestation.
c To be determined for each litter. Mean and standard deviation for each dose level will be calculated.
d Excluding litters sacrificed due to death of dam during lactation.
e Restricted to pregnant dams.

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Statistical Methods

	Method of Statistical Analysis		
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Food Efficiency Gestation Length Implantation Site Numbers Implantation Efficiency Preimplantation Loss Postimplantation Loss Mean Number of Pups Per Litter Percent Born Alive Sex Ratio 0-4 Day Viability Number of *Corpora Lutea* Organ Weight	Test for lack of trend[7]	Sequential application[6] of the Jonckheere-Terpstra trend test[7]	Preliminary tests for pairwise comparison
	OR[a]		
	Levene's test for homogeneity[8] and Shapiro-Wilk test[9] for normality[b]	One-way analysis of variance[10] and Dunnett's test[11,12,13]	Kruskall-Wallis test[14] and Dunn's test[15]
Incidence of Clinical Observations Incidence of Descriptive Functional Observational Battery Parameters Mating Index Fertility Index Gestation Index	None	Cochran-Armitage test for trend[10][c]	
Grip Strength Foot Splay Body Temperature Rearing	Bartlett's test[16] for homogeneity of variances	One-way analysis of variance[10] and Dunnett's test[11,12,13]	Kruskall-Wallis test[14] and Dunn's test[15]
Motor Activity[d]	Levene's test for homogeneity[8] and Shapiro-Wilk test[9] for normality[b]	Repeated measures analysis of variance followed by contrasts[17]	Sequential application[6] of the Jonckheere-Terpstra trend test[7]
Clinical Pathology[e]	Levene's test for homogeneity[8] and Shapiro-Wilk test[9] for normality[b]	One-way analysis of variance[10] followed with Dunnett's test[11,12,13]	Kruskal-Wallis test[14] followed with Dunn's test[15]
Mean Pup Weights (Covariates: litter size, sex ratio)	None	Linear contrast of least squares means[18]	Dunn's test[15]
Incidence of Microscopic Lesions	None	None	

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

b If the Shapiro-Wilk test is not significant but Levene's test is significant, a robust version of Dunnett's test will be used. If the Shapiro-Wilk test is significant, Kruskal-Wallis test is followed with Dunn's test.

c If the incidence is not significant, but a significant lack of fit occurs, then Fisher's Exact test[19] with a Bonferroni correction is used.

d Test day and 10-minute intervals will be used as repeated-measure factors.

e When an individual observation is recorded as being less than a certain value, calculations are performed on half the recorded value. For example, if bilirubin is reported as <0.1, 0.05 is used for any calculations performed with that data. When an individual observation is recorded as being greater than a certain value, calculations are performed on the recorded value. For example, if specific gravity is reported as >1.083, 1.083 was used for any calculations performed with that data.

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For each parameter analyzed with a trend test, the test will be applied to the data sequentially. If a significant dose-response is detected, data from the top dose group will be excluded and the test repeated until no significant trend is detected.[6] For litter parameters, the proportion of affected fetuses per litter or the litter mean will be used as the experimental unit for statistical evaluation.[20] The level of significance selected is $p < 0.05$. Additional statistical tests will be used, and other parameters analyzed, if deemed necessary.

Where the data are tied and the standard large sample version of Jonckheere's test[7] is not applicable, exact p values will be calculated using permutation methodology.[21]

SPECIAL SAFETY AND HANDLING PROCEDURES

The test substance will be dispensed, mixed, and sampled in a chemical fume hood. Laboratory personnel will wear Racal respirators while mixing, dosing, and sampling the test material or the formulations containing the test material.

HUMANE TREATMENT OF ANIMALS

In so far as is consistent with the scientific objectives of the study, experiments and procedures performed by Haskell Laboratory personnel have been designed to minimize pain and distress inflicted upon the experimental animals. If the animals appear in pain, distress, or become moribund, laboratory guidelines will apply. Haskell Laboratory SOPs will apply for animals found dead or *in extremis*. Guidelines concerning the humane treatment of animals are reviewed and maintained by the Haskell Animal Welfare Committee (HAWC).

RECORDS AND SAMPLE STORAGE

All original records will be retained at Haskell Laboratory, E. I. du Pont de Nemours and Company, Newark, Delaware or at Iron Mountain Records Management, 200 Todds Lane, Wilmington, Delaware. Preserved wet tissues, paraffin blocks, slides, blood smears and bone marrow smears will be retained at Haskell Laboratory. A sample of the test substance will be collected for archive purposes and retained at Haskell Laboratory.

CHANGES IN THE PROTOCOL

Changes in the protocol will be documented in protocol amendments signed by the Study Director and Sponsor's representative.

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FINAL REPORT

A final report will be written and will be reviewed by the Haskell Quality Assurance Unit (prior to sponsor review). The report will include but is not limited to:

- a GLP compliance statement
- detailed information about the test substance
- analytical report(s)
- vehicle control
- test system and animal husbandry
- protocol and amendments

The study results will include:

- body weights/weight gain
- food consumption/food efficiency
- clinical signs of toxicity
- reproduction, gestation, and lactation parameters
- neurobehavioral evaluations - functional observational battery and motor activity
- clinical pathology
- pathology
- a discussion of study results
- conclusions
- robust summary

A draft of the Haskell Laboratory final report will be submitted to the American Chemistry Council prior to finalization of the report.

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PROTOCOL APPENDIX A

FUNCTIONAL OBSERVATIONAL BATTERY SCORING SYSTEM

(comments are provided for guidance and not intended to be all-inclusive)

HOME CAGE OBSERVATIONS

POSTURE:	-2	=	limbs spread out or lying on one side
	-1	=	curled up, often asleep or sitting with head hung down
	0	=	sitting, standing or rearing normally, alert
	1	=	jumping
PALPEBRAL CLOSURE:	0	=	eyelids wide open
	-1	=	eyelids drooping (ptosis)
	-2	=	eyelids completely shut
	S	=	rat appears to be sleeping
WRITHING:	1	=	present
	0	=	absent
CIRCLING:	1	=	present
	0	=	absent
BITING:	0	=	none
	1	=	biting others
	2	=	biting cage
	3	=	self mutilation
GAIT/ COORDINATION ABNORMALITIES:	0	=	normal
	1	=	unbalanced, swaying, uncoordinated
	2	=	ataxic (unable to coordinate voluntary muscles, dragging limbs, hopping)
	3	=	unable to move

OUTSIDE THE HOME CAGE (REMOVING FROM CAGE)

EASE OF REMOVAL:	-1	=	too easy (rat sits quietly, no resistance)
	0	=	some resistance (rears, follows observer's hand)
	1	=	difficult (runs around cage, may be aggressive)
EASE OF HANDLING:	-1	=	too easy
	0	=	easy (alert, limbs pulled up against body)
	1	=	difficult
MUSCLE TONE:	-1	=	limp
	0	=	normal
	1	=	rigid
VOCALIZATIONS:	1	=	present
	0	=	absent
PILOERECTION:	1	=	present
	0	=	absent
BITE MARKS ON TAIL/PAWS:	1	=	present
	0	=	absent
PALPEBRAL CLOSURE:	0	=	none
	-1	=	eyelids drooping (ptosis)
	-2	=	eyelids completely shut
FUR APPEARANCE:	0	=	normal
	-1	=	slightly soiled
	-2	=	very soiled, crusty

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-13041

LACRIMATION:	0	=	none
	1	=	slight
	2	=	severe
SALIVATION:	0	=	none
	1	=	slight (wet chin)
	2	=	severe (active salivation, drooling)
EXOPHTHALMUS:	1	=	present
	0	=	absent

OPEN FIELD ARENA (IN FREE ROAMING SPACE)

RIGHTING REFLEX:	0	=	present
	-1	=	slow
	-2	=	absent
RESPIRATION EASE:	0	=	absent
	1	=	labored breathing (add description)
RATE OF RESPIRATION:	-1	=	slow
	0	=	normal
	1	=	rapid
POSTURE	0	=	normal
	1	=	abnormal (add description)
CONVULSIONS:	0	=	none
	1	=	present- violent involuntary series of muscle contractions; may be accompanied by pupillary dilation, vomiting, salivation, defecation, urination, chewing, and / or loss of consciousness (add description)
TREMORS:	0	=	none
	1	=	slight- localized to fingers or paws
	2	=	mild- limbs (note forelimb, hindlimb, or both)
	3	=	severe- multiple locations (list)
MUSCLE FASCICULATION:	0	=	none
	1	=	present- rippling of muscle or skin
MUSCLE SPASMS:	0	=	none
	1	=	present- twitching of a muscle or group of muscles
GROOMING:	0	=	normal or none
	1	=	repetitive, stereotypy
GAIT/ COORDINATION ABNORMALITIES:	0	=	normal
	1	=	unbalanced, swaying, uncoordinated
	2	=	ataxic (unable to coordinate voluntary muscles, dragging limbs, hopping)
	3	=	unable to move
AROUSAL (level of activity):	-2	=	very slow (stupor, little or no responsiveness)
	-1	=	low (some exploratory movements with periods of immobility)
	0	=	normal (alert, exploratory movements)
	1	=	high (slight excitement, tense, sudden movements)
VOCALIZATIONS:	0	=	absent
	1	=	present
	2	=	vocalizes only when handled
PALPEBRAL CLOSURE:	0	=	none
	-1	=	eyelids drooping (ptosis)
	-2	=	eyelids completely shut

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-13041

DIARRHEA:	0	=	absent
	1	=	present
POLYURIA:	0	=	absent
	1	=	present
REARING:	#	=	the number of times both forelimbs are lifted off the cageboard

MANIPULATIONS IN OPEN FIELD ARENA (FREE ROAMING SPACE)

APPROACH & TOUCH:	-1	=	no reaction
	0	=	normal
	1	=	increased reaction (jumps away or attacks)
AUDITORY STIMULUS:	-1	=	no reaction
	0	=	normal reaction (rat flinches or flicks ear)
	1	=	exaggerated reaction (rat jumps, flips)
TAIL PINCH:	-1	=	no response
	0	=	normal (turns toward site)
	1	=	exaggerated response (vocalizations, rapid turning)

IN MOTOR ACTIVITY MONITOR

PUPILLARY RESPONSE:	0	=	present
	1	=	absent
DIARRHEA:	0	=	absent
	1	=	present
POLYURIA:	0	=	absent
	1	=	present

ADDITIONAL OBSERVATIONS WHICH ARE NOTED ONLY IF PRESENT:

SNIFFING:	=	focuses on one item for a prolonged period of time.
HEAD WEAVING:	=	movement of the head from side to side or up and down (head bobbing) without other major movements
STRAUB TAIL	=	tail stiff and held in a vertical position for a prolonged period
SYNCOPE	=	abrupt loss of consciousness (fainting), loss of responsiveness to external stimulation
STEREOTYPIC BEHAVIOR	=	any other repetitive behavior (add description)

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and
Reproductive/Developmental Toxicity Screening Test in Rats DuPont-13041

PROTOCOL APPENDIX B

STUDY FUNCTIONS AND STUDY PERSONNEL

Study Function	Study Personnel
Study Director:	Linda A. Malley, Ph.D., D.A.B.T. Senior Research Toxicologist
Analytical Chemistry Evaluation:	Janet C. Maslanka, B.S. Analytical Chemist
Neurobehavior Evaluation:	Linda A. Malley, Ph.D., D.A.B.T. Neurotoxicologist
Clinical Pathology Evaluation:	Nancy E. Everds, D.V.M., Diplomate A.C.V.P. Clinical Pathologist
Anatomic Pathology Evaluation:	Gregory P. Sykes, V.M.D., Diplomate A.C.V.P., A.C.L.A.M., A.B.T. Veterinary Pathologist

Study Dates

Baseline FOB/MA	September 4-5, 2003
Baseline Detailed Clinical Observations	September 8, 2003
Initiation of test substance administration	September 10, 2003
Co-house males with satellite females	September 24, 2003
Week 4 FOB/MA	October 8-9, 2003
Clinical pathology	October 9-10, 2003
Sacrifice of main study males and females	October 9-10, 2003
Start sacrifice for repro satellite females and females with no pups	October 17, 2003 (Approximately)
Proposed delivery of audited draft report to sponsor	March 2, 2004

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-13041

SIGNATURES

Approved by: Linda A. Malley 02-Sept-03

Linda A. Malley, Ph.D., D.A.B.T.
Study Director
Developmental, Reproductive, and Neurobehavioral Toxicology
DuPont Haskell Laboratory
Date

11-Sept-03

Elizabeth Moran, Ph.D.
Sponsor Representative
Date

cc:	J.M. Lewis	M.K. Vaillancourt	K.B. Brebner
	E. Mylchreest	N.E. Everds	J.C. Hamill
	D.L. Tyler	D.M. Hoban	J.W. Green
	S.E. Karr	G.P. Sykes	C.R. Kee
	N.P. Betts	S.W. Records	M.M. Wilford
	P. Mukerji	L.J. Lewis	R.L. Poore
	J.C. Maslanka	S.R. Frame	S.C. Craven
	D.A. Vick		

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and
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Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and
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Work Request Number 14295
Service Code Number 1422
PROTOCOL AMENDMENT 1

The protocol is amended as follows:

1. P. 19-21, Data Analyses, replace with the following:

Data Analyses

1. Reproductive Function Calculations

The following table lists the indices of reproductive functions that were calculated for the P_1 adults.

Mating Index (%)	=	$\frac{\text{Number Copulated}^a}{\text{Number Cohabited}}$	x100
Fertility Index (%)	=	$\frac{\text{Number Pregnant}^b}{\text{Number Copulated}^a}$	x100
Gestation Index (%)	=	$\frac{\text{Number of Litters with at Least One Live Pup}}{\text{Number of Litters}}$	x100
Implantation Efficiency (%)[c]	=	$\frac{\text{Number of Pups Born}}{\text{Number of Implantation Sites}}$	x100
Pups Born Alive (%)[c]	=	$\frac{\text{Number of Pups Born Alive}}{\text{Number of Pups Born}}$	x100
Viability Index (%)[c,d]	=	$\frac{\text{Number of Pups Alive Day 4 Preculling}}{\text{Number of pups born alive}}$	x100
Preimplantation Loss[e]	=	$\frac{\text{Number of } corpora\ lutea - \text{Number of implantation sites}}{\text{Number of } corpora\ lutea}$	
Postimplantation Loss[e]	=	$\frac{\text{Number of implantation sites} - \text{Number of pups}}{\text{Number of implantation sites}}$	

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

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PROTOCOL AMENDMENT 1 (Continued)

2. Summary Data for Body Weight, Weight Gain, Food Consumption, and Food Efficiency

Body weight data for subchronic males, subchronic females, and satellite females were summarized weekly. Body weight gain, food consumption, and food efficiency data for subchronic males were summarized over weekly intervals, and for the intervals of days 1-15, 15-29, and 1-29 so that any potential effects from cohabitation on these parameters could be evaluated. Body weight gain, food consumption, and food efficiency data for subchronic females and satellite females were summarized over weekly intervals and for test days 1-29 (subchronic females), test days 1-15 of premating (satellite females), test days 0-21 of gestation (satellite females), and test days 0-4 of lactation (satellite females).

3. Statistical Methods

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Gestation Length Implantation Site Numbers Implantation Efficiency Mean Number of Pups per Litter Percent Born Alive 0-4 Day Viability Viability Index Number of *Corpora Lutea* Sex Ratio Pre-implantation Loss Post-implantation Loss Organ Weights	Test for lack of trend	Sequential application of the Jonckheere-Terpstra trend test	Preliminary tests for pairwise comparison
	OR[a]		
	Levene's test for homogeneity and Shapiro-Wilk test for normality[b]	One-way analysis of variance followed with Dunnett's test	Kruskal-Wallis test followed with Dunn's test
Food Efficiency	None	One-way analysis of variance followed with Dunnett's test	
Incidence of Clinical Observations Incidence of FOB Descriptive Parameters Mating Index Fertility Index Gestation Index	None	Cochran-Armitage test for trend	

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		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Clinical Pathology[d]	Levene's test for homogeneity and Shapiro-Wilk test for normality[b]	One-way analysis of variance followed with Dunnett's test	Kruskal-Wallis test followed with Dunn's test
Mean Pup Weights (Covariates litter size, sex ratio)	None	Linear contrast of the least square means	None

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

a. Statistical Analysis of Motor Activity

Motor activity (number and duration of movements) is done by repeated measures ANOVA with day and bin (epoch) as repeated factors, with bin nested within day, possibly after a normalizing, variance stabilizing transformation. Since bin has more than two levels, consideration must be given to the variance-covariance structure in testing for significance of treatment effects overall or within a single day or bin. Where the correlations between observations on the same subject in different bins on the same day appear to vary as separation in time increases (a real possibility), either a Huynh-Feldt or Greenhouse-Geisser adjustment is made or an alternative variance-covariance structure (e.g., unstructured, auto-regressive, heterogeneous auto-regressive, or heterogeneous compound symmetry) is used that reflects this varying correlation. Assessment of the need for such an adjustment or alternative variance-covariance structure can be done using Mauchly's criterion for sphericity, through inspection of the sample variance-covariance matrix, or through the use of variance-covariance diagnostics described in Hocking *et al.*, Green and Hocking, Grynovicki and Green, and Searle *et al.*.

The responses are assessed for normality using the Shapiro-Wilk test applied to the residuals from the ANOVA model and appropriate plots. If the data are judged non-normal, then a normalizing transformation is sought. If no such transformation can be found, then separate analyses for the responses from each day and bin are done. If no normality problem is found or is resolved by a transformation, then Levene's test for variance homogeneity is done. If significant variance heterogeneity is found from this test and appropriate plots, then a Low normalizing, variance-stabilizing transformation is sought. If none is found, then separate analyses for the responses from each day and bin are done.

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In the context of this repeated measures ANOVA, linear contrasts are estimated to determine treatment effects. A linear contrast for dose trend is estimated as are individual comparisons of treatments to control. This is done on each day, averaging across bins, and in each bin. To control the false positive rate associated with these comparisons, adjustments to the p-values are made based on the significance (or lack thereof) of the Dose-by-Day and Dose-by-Day-by-Bin interactions, and the test for linear trend in the dose-response.

In addition, a repeated measures analysis is done of the daily sums over bins of the responses from each animal. Such sums (or, equivalently so far as conclusions are concerned, averages) are more likely to be normally distributed than are the individual responses, so that separate analyses by each time point are less likely. These data are analyzed by the same method described below for grip strength.

b. Statistical Analysis of Grip Strength, Foot Splay, Body Temperature, and Rearing

These endpoints are analyzed by repeated measures ANOVA with day as the only repeated factors, possibly after a normalizing, variance stabilizing transformation. Since day has only two levels, the Greenhouse-Geisser conditions are automatically satisfied and no special treatment of the variance-covariance matrix or the tests for treatment effects is needed. Normality and variance homogeneity are evaluated as above, analogous actions are taken where significant non-normality or variance heterogeneity is encountered, and tests for treatment effects are conducted as above, except that bin is not a consideration.

c. Trend Test

For each parameter analyzed with a trend test, the test was applied to the data sequentially. If a significant dose-response was detected, data from the top dose group was excluded and the test repeated until no significant trend was detected.

d. Litter Parameters

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

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PROTOCOL AMENDMENT 1 (Continued)

e. Level of Significance

The level of significance selected was $p < 0.05$ for trend tests Levene's, Shapiro-Wilk, Kruskal-Wallis, Dunn's, and linear contrasts. Where the data were tied and the standard large sample version of Jonckheere's test was not applicable, exact p values were calculated using permutation methodology.

Rationale: At the request of the sponsor, the Data Analyses section was expanded and rewritten to provide additional details for analysis of the data. In addition, the denominators for pre-implantation loss and post-implantation loss were corrected.

2. Pages 11-12, Section R, second paragraph, first sentence, change to:"... will be conducted in 2 replicates per sex over a two-day period for baseline and a two-day period for the week 4 FOB.

Rationale: The original protocol incorrectly stated that the assessment periods would occur on one day instead of 2 days.

3. Page 21, Record and Sample Storage, remove the last sentence pertaining to an archive sample of the test substance.

Rationale: The test substance has the potential to form peroxides which can be an explosive hazard. Therefore, an archive sample cannot be retained, and the container must be discarded safely.

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PROTOCOL AMENDMENT 1 (Continued)

4. Reference #3, p.22, change to: The OECD Guideline for the Testing of Chemicals Section 4: (422) Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (1996).

Rationale: The reference in the original protocol was incorrect.

Approved by: _____ _____
Linda A. Malley, Ph.D. Date
Study Director
Developmentsl, Reproductive, and Neurobehavioral Toxicology
DuPont Haskell Laboratory

_____ _____
Elizabeth Moran, Ph.D. Date
Sponsor Representative

APPENDIX B

Test Substance Characterization

APPENDIX B

Supplemental information for the Test Substance characterization.

1. Analytical method provided by the sponsor. Inserted as received from the sponsor (17 pages).
2. Table 1. Composition of Low DCPD Resin Oil Test Substance (H# 25429, inserted as received from the sponsor).
3. Figure 1. Chromatogram of Low DCPD Resin Oil Test Substance (H# 25429, inserted as received from the sponsor, 3 pages).
4. Analytical method developed at Haskell Laboratory.
5. Figure 2. Representative chromatogram of Low DCPD Resin Oil Test Substance (H# 25429) analyzed at Haskell Laboratory.
6. Table 2. Composition of selected components of Low DCPD Resin Oil test substance.

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MANUAL ANALYTICAL PROCEDURE MANUAL		REVISION DATE APRIL 1995
DOCUMENT TITLE REACTIVES IN AROMATIC RESIN FEEDSTOCK BY GAS CHROMATOGRAPHY		
DOCUMENT NUMBER CHO-LYON-5852 M	DOCUMENT AUTHOR K. W. LOVELL	APPROVERS SIGNATURE

PURPOSE

This procedure describes the GC method for determining reactive content in Lyondell Resin Oil.

SCOPE

Lyondell Resin Oil is analyzed using an instrument equipped with a splitter assembly, flame ionization detector and a 100 meter x 0.32 m ID x 1 micron thickness methyl silicone capillary column. Nelson Analytical software integrates and translates data which is transferred via computer link to the operating units. The dynamic range for this analysis is 0.0005 wt% to 50.0 wt%.

REFERENCES/DEFINITIONS

1. Reference: RJH-01-85, RJH-05-85, RJH-06-85, RJH-07-85, RJH-10-85, RJH-12-85, RJH-13-85, RJH-14-85, RJH-15-85, RJH-16-85, RJH-17-85, RJH-18-85, RJH-26-85, RJH-27-85, RJH-30-85, RJH-31-85, RJH-07-86, KWL-03-93.
2. Original procedure written by C. M. Copeland and J. D. Winter.
3. Revised by R. J. Haynal in December 1984.
4. Revised in January 1992 by Ken Lovell, A. Bettes, E. Foger, J. A. McCormick, and R. J. Haynal.
5. Revised in June 1993 to convert to ISO 9002 formatting.
6. Revised in April 1995 to update Review Statement.

RESPONSIBILITY

The area Technician is responsible for ensuring procedure is followed.

QUALITY CRITICAL

This procedure is Quality Critical because it is used for product certification and by various units in process control.

HSE CRITICAL

Use care when handling samples. Follow all laboratory safety procedures. Minimum safety protection requirements are lab coat, safety glasses and gloves. Do not inhale vapors or dust and avoid skin contact or ingestion. For additional information refer to the MSDS No.'s provided below.

Benzene	MSDS No. D-AP7594
Hydrogen	MSDS No. D-AP1139
Lyondell Resin Oil	MSDS No. D-AP1446 (LRO-90)

REVIEW

This procedure will be reviewed for accuracy and completeness at least every three years by the Analytical Group.

TRAINING

Training on this procedure will be accomplished during the initial training of employees. In the event of a new procedure, or an existent procedure being changed to different work position, follow-up training will be administered to all affected personnel. The training will be performed by a trainer of the procedure and/or testing position. Before the procedure may be actually used in the production process, the employee must successfully complete the training to meet the Position Verification Guidelines.

PROCEDURE/POLICY

1. Varian 3400 Gas Chromatograph or equivalent:
   a. Flame Ionization Detector
   b. Injector with Varian 1075 Splitter Assembly.
   c. 100M x 0.32 mm ID x 1 micron film thickness
      (Supplied by Supelco Inc./Reference Lot #C217402)
   d. Fritted injection liners - Varian Part #16-000830-1
2. Hamilton syringe - 1.0µL size.
3. Nelson Analytical Interface and Associated software.

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[illegible]

1. Temperature programming

   Initial column temperature 85°C

   Initial hold time 63 min

Prgm	Final Temp	Rate	Hold Time/min	Total Time
1	115°C	3.0°	0/0	73
2	180°C	15.0°		
10.0	87.33			
3	230°C	5.0	10.0	107.33

2. Injector Temperature 200°C
3. Detector Temperature 220°C
4. Flow Parameters
   a. linear viscosity 23.0 cm/sec @ 100°C
   b. splitter exit 100 mL/min
   c. make-up 30 mL/min
5. Flame gases
   a. air 360 mL/min
   b. hydrogen 30 mL/min
6. Miscellaneous
   a. detector range 10^{-11}
   b. attenuation 16
   c. sample size 0.3µL (2,000,000 area counts)

[illegible]

1. Chromatographic Grade Helium (ALPHAGAZ)
2. Chromatographic Grade Hydrogen (ALPHAGAZ)
3. Chromatographic Grade Air

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See CHO-LAB-0604 for calibration procedure.

1. Samples are received in a glass do-pack container. Use proper hand protection when handling and injecting sample.
2. Download correct Nelson chromatography method and identify sample.
3. Activate the proper instrument method.
4. Prepare syringe by flushing sample several times then use appropriate sample size to achieve 3 million area counts (0.3µL with 0.1µL of air and wipe needle)
5. When instrument is equilibrated the "Ready" will appear, inject the sample and push start. The GC will auto-start the Nelson Interface.
6. Nelson chromatography will integrate and format for reporting.

All calculations are handled by Nelson Analytical Software.

Log reactives and 2,6 ditert'ary buty' 1 methyl phenol (BHT) as follows:

a.	Benzene	Log to 2 places.
b.	C7 & Lighter	Log all peaks that elute before toluene including benzene and toluene. Log to 2 places.
c.	Named Reactives	Styrene, a-methyl styrene, cis-B-methyl styrene, meta-vinyl-toluene, trans-B-methyl-indene, total methyl styrene dicyclopentadiene, indene, total methyl-indene (which includes methyl-indene4) and all peaks in between. Log to 2 places.
d.	SS Partial Reactives	Par R1, 2, 3, 4, 5, 6, 14, 15, 19, 20 Log to 2 places.
e.	SS Total Reactives	Tot R7, 8, 9, 10, 11, 12, 13, 16, 17, 18. Log to 2 places.
f.	Total Reactives	Named reactives + ss partial reactives + ss total reactives. Log to 2 places.
g.	BHT	Log BHT to 4 places.

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PRECISION

Repeatability and reproducibility are on SOC data collected for Styrene. Indene and Naphthalene and should not exceed 3.0% relative to retention blend value. Total reactive content is used for Marketing sales and should not exceed 1.0% relative to the retention blend value.

APPENDICES

Attachment I	Nelson Method
Attachment II	GC Chromatogram
Attachment III	Precision Data

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ATTACHMENT I

NELSON METHOD

Lyondell Petrochemical Company

DOCUMENT NUMBER CHO-LYON-5852	REVISION NUMBER 4
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Method file name : Q:AY010
Default Sample Name: 0125|LRO PROD STD
Operator: GC2
Date-time: 03-14-1993 03:37:19 version: 501

ACQUISITION PARAMETERS

SINGLE OR DUAL CHANNEL (1 OR 2)	1
RUN TIME (minutes)	107.00
END TIME FOR PLOTS (default=RUN TIME)	107.00
SOLVENT DELAY TIME (minutes)	0.00
PEAK DETECTION THRESHOLD (microv/sec)	0.01
Area Threshold	5.00
MINIMUM PEAK WIDTH (seconds)	5.00
TIME FOR ONE SAMPLE (seconds)	0.30
NUMBER OF REAL TIME CRT PAGES TO PLOT (0 TO 99)	0.00
REAL TIME PLOT FULL SCALE FOR CH.0 (millivolts)	1.00
REAL TIME FULL SCALE FOR CH.1 (millivolts)	200.00
HARD COPY REAL TIME PLOT	NO
AUTO ZERO REAL TIME PLOT	YE
Pre Version 4 method	NO
RECORD AREA TABLES ON DISK	NO
RECORD RAW DATA	YE
NUMBER OF CRT PAGES FOR REPLOT (1 TO 99)	0
VERTICAL SCALE FACTOR FOR REPLOT (units of largest peak)	1.00
OFFSET FOR THE REPLOT (millivolts)	0.00
PUT NAMES ON REPLOT?	YE
AREA PERCENT REPORT	NO
EXTERNAL STANDARD REPORT	NO
INTERNAL STANDARD REPORT	NO
FINAL REPORT AREA REJECT (microvolt-sec)	0.00
LINK TO USER PROGRAM	YE
FORCE DROP LINE INTEGRATION	NO
FORCE COMMON BASE LINE	NO
FULL SCALE RANGE FOR A.D.C. (3=1VOLT, 1=2VOLT, 0=10VOLT)	0
AREA REJECT FOR REFERENCE PEAKS?	99999.00
% RET TIME WINDOW FOR REFERENCE PEAKS	0.00
RET TIME WINDOW IN SECONDS FOR REF. PEAKS	0.00
AREA OR PEAK HEIGHT QUANTITATION (0 OR 1)	0
GROUP REPORT	NO
NUMBER OF CALIBRATION LEVELS (1 TO 6)	1
LIST COMPONENTS NOT FOUND IN SAMPLE?	YE
INCLUDE UNKNOWN PEAKS IN REPORTS?	YE
UPDATE RESPONSE FACTORS WITH REPLACEMENT (0) OR AVERAGE (1)	1
DEFAULT DILUTION FACTOR	1.00
DEFAULT SAMPLE WEIGHT	1.00
DEFAULT AMOUNT INJECTED	1.00
DEFAULT AMOUNT OF INTERNAL STANDARD	1.00
GPC MW DISTRIBUTION	NO
SIMULATED DISTILLATION REPORT	NO

LINK TO PROGRAM : CUSER
SAVE RAW DATA IN : AY01
Response factor for unknowns= 1
Component Units = WT%
Number of Components = 42

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Lyondell Petrochemical Company

DOCUMENT NUMBER	REVISION NUMBER
CHO-LYON-5852	4
PAGE 8 OF 17	REVISION DATE JUNE 1993

Method:Q:AY010

No.	Component Name	Ret Time	Tol	Fit Type	Resp Fact	RF #
1.	BENZENE	10.70	0.50	2	1.0000	1
2.	TOLUENE	15.40	0.50	2	1.0000	1
3.	ETHYLBENZENE	23.70	0.50	2	1.0000	1
4.	P+M-XYLENE'S	24.70	0.50	2	1.0000	1
5.	STYRENE	27.30	0.50	2	1.0000	1
6.	O-XYLENE	28.05	0.50	2	1.0000	1
7.	a-M-STYRENE	45.05	0.50	2	1.0000	1
8.	UNK C9 ALKBZ	45.17	0.50	2	1.0000	1
9.	c-B-MS	48.00	0.50	2	1.0000	1
10.	m-V-TOL	48.75	0.50	2	1.0000	1
11.	o-V-TOL	49.15	0.30	2	1.0000	1
12.	PSEUDOCUMENE	49.60	0.20	2	1.0000	1
13.	p-V-TOL	50.00	0.30	2	1.0000	1
14.	tbMS + 123HEMMI	58.20	0.50	2	1.0000	1
15.	DCPD	61.40	0.50	2	1.0000	1
16.	UNK INDAN	61.84	0.50	2	1.0000	1
17.	INDENE	64.63	0.50	2	1.0000	1
18.	SS PAR R1	65.12	0.50	2	1.0000	1
19.	SS PAR R2	65.42	0.50	2	1.0000	1
20.	SS PAR R3	72.93	0.50	2	1.0000	1
21.	SS PAR R4	73.26	0.50	2	1.0000	1
22.	SS PAR R5	73.80	0.50	2	1.0000	1
23.	SS PAR R6	74.10	0.50	2	1.0000	1
24.	SS TOT R7	74.30	0.50	2	1.0000	1
25.	SS TOT R8	75.05	0.50	2	1.0000	1
26.	SS TOT R9	75.25	0.50	2	1.0000	1
27.	SS TOT R10	75.72	0.50	2	1.0000	1
28.	SS TOT R11	75.90	0.50	2	1.0000	1
29.	SS TOT R12	76.23	0.50	2	1.0000	1
30.	SS TOT R13	76.95	0.50	2	1.0000	1
31.	SS PAR R14	77.60	0.50	2	1.0000	1
32.	SS PAR R15	77.80	0.50	2	1.0000	1
33.	SS TOT R16	78.12	0.50	2	1.0000	1
34.	SS TOT R17	78.45	0.50	2	1.0000	1
35.	SS TOT R18	78.64	0.50	2	1.0000	1
36.	SSPAR R19/20	79.30	0.50	2	1.0000	1
37.	M-INDEN 1	79.90	0.50	2	1.0000	1
38.	M-INDEN 2	80.32	0.50	2	1.0000	1
39.	M-INDEN 3	80.44	0.50	2	1.0000	1
40.	M-INDEN 4	80.90	0.50	2	1.0000	1
41.	NAPHTHALENE	82.34	0.50	2	1.0000	1
42.	BHT	100.40	0.20	2	1.0600	1

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DOCUMENT NUMBER	REVISION NUMBER
CHO-LYON-5852	4
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Method: Q:AY010

Event #	Time	Event
1	24.50	EPD-
2	25.05	EPD+
3	57.28	EPD-
4	58.79	EPD+

Event Explanations

1 to 8	(C/O)	relay (Close/Open)
AT	(D/H)	Area Threshold (Double/Halve)
FBA		Force Baseline at All peak starts
BF	(D/H)	Bunching Factor (Double/Halve)
DP	(+/-)	Force Dropline integration (on/off)
FB		Force Baseline at peak start
COM		Common Baseline for next Peaks
CBT	(+/-)	Common Baseline Test (on/off)
PEN	(+/-)	End peaks on Baseline Penetration (o
EPD	(+/-)	End-of-Peak Detection (on/off)
END		End Peak at this Time
EXP	(+/-)	Expo Skim (on/off)
HF	(+/-)	Project Horizontal baseline Forward
HR		Project Horizontal baseline Rearward
NEG	(+/-)	Negative Peak Detection (on/off)
NT	(D/H)	Noise Threshold (Double/Halve)
PD	(+/-)	Peak Detection (on/off)
SKIM		Force straight line peak skim
SPT		Split Peak at this Time
VI		Read vial number after injection

Examples: 1C = relay #1 Closed EXP+ = Expo Skim

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CHO-LYON-5852	4
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ATTACHMENT II

GC CHROMATOGRAM

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DOCUMENT NUMBER	REVISION NUMBER
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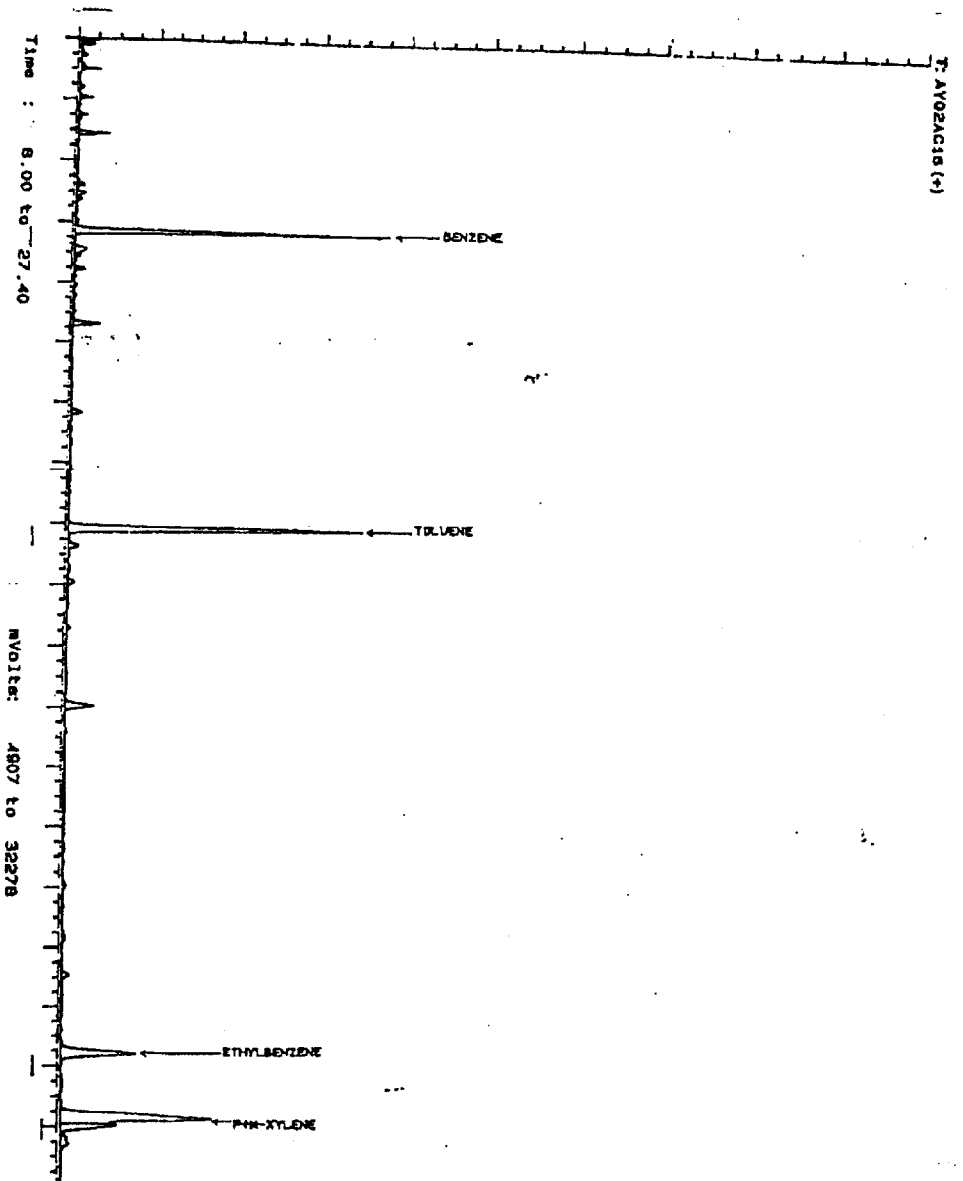

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DOCUMENT NUMBER CHO-LYON-5852	REVISION NUMBER 4
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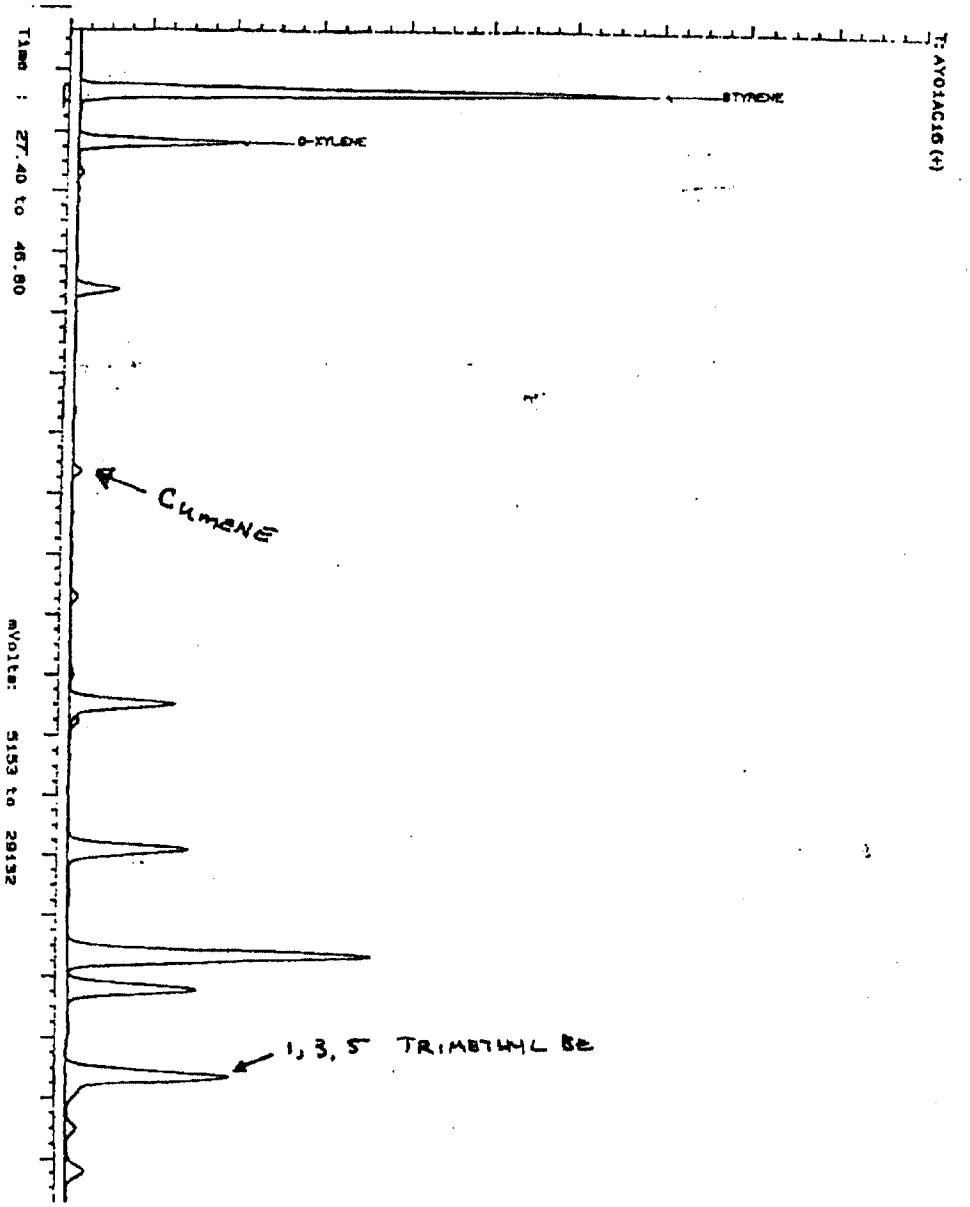

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DOCUMENT NUMBER CHO-LYON-5852	REVISION NUMBER 4
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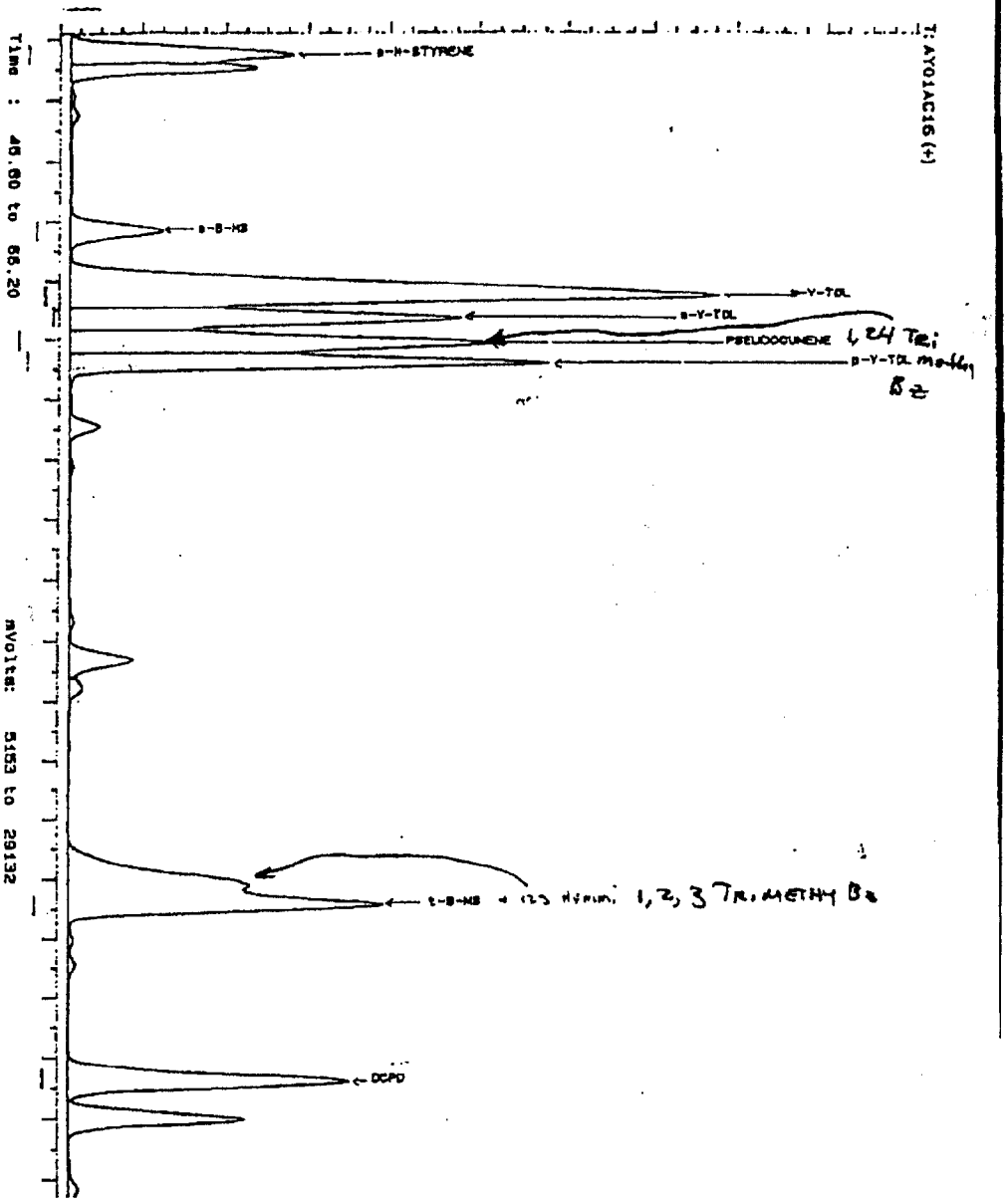

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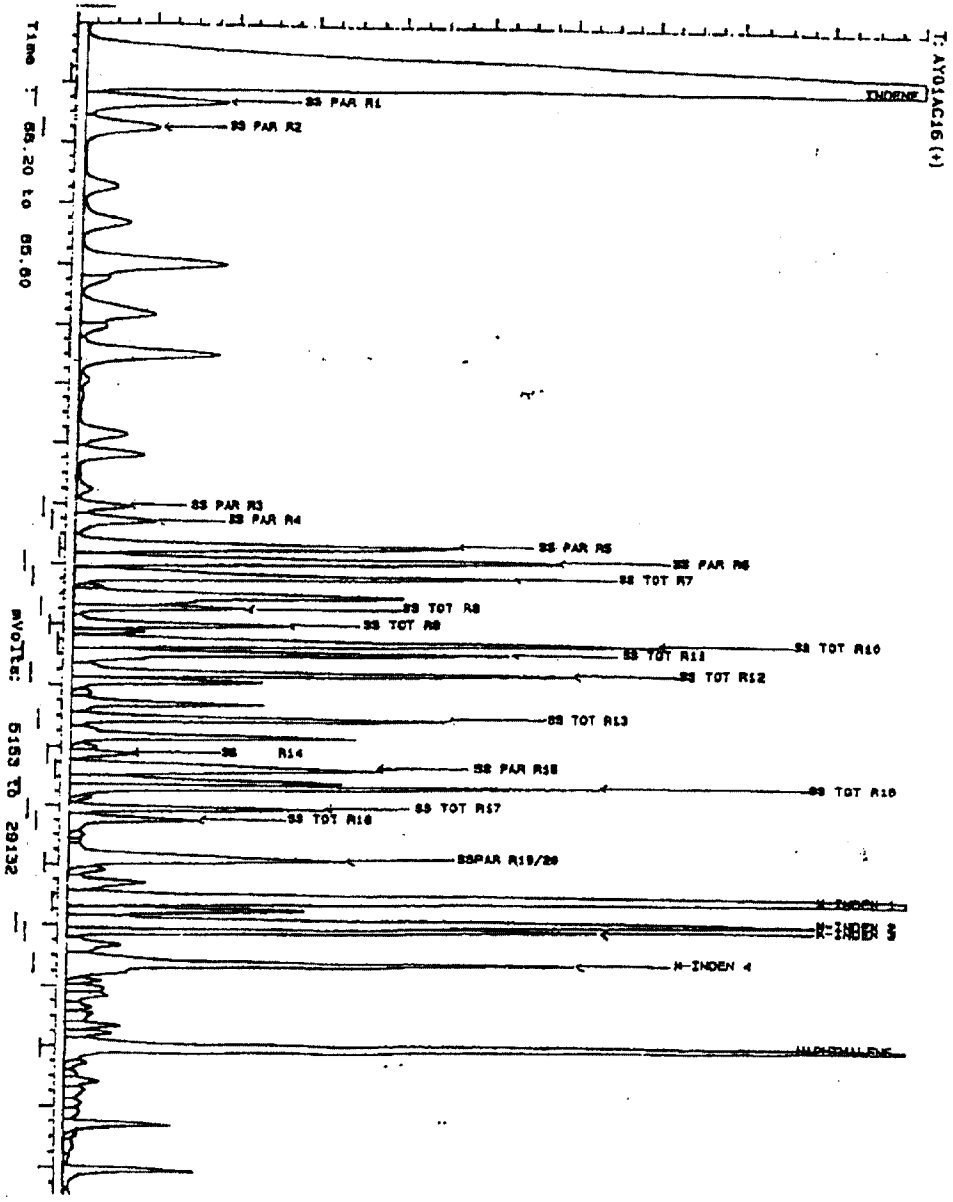
DOCUMENT NUMBER CHO-LYON-5552	REVISION NUMBER 4
PAGE 14 OF 17	REVISION DATE JUNE 1993



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DOCUMENT NUMBER CHO-LYON-5852	REVISION NUMBER 4
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ATTACHMENT III
PRECISION DATA

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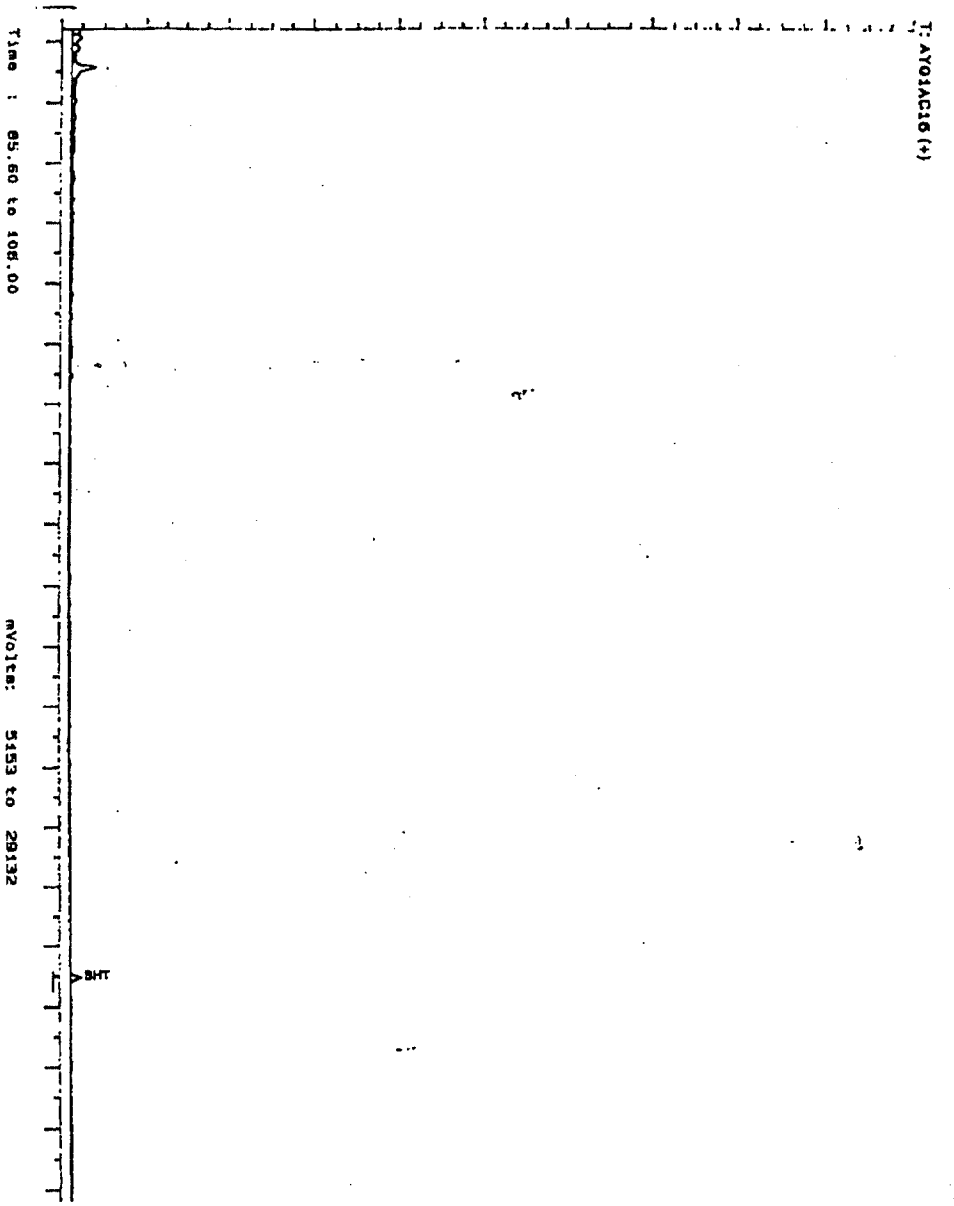
DOCUMENT NUMBER	REVISION NUMBER
CHO-LYON-5852	4
PAGE 16 OF 17	REVISION DATE JUNE 1993



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DOCUMENT NUMBER CHO-LYON-5852	REVISION NUMBER 4
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Component	Styrene	Indene	Naphthalene	Total Reactives
	3.98	13.29	4.74	66.43
	3.93	13.11	4.71	66.41
	4.25	13.08	4.87	65.32
	3.98	13.16	4.71	66.31
	3.98	13.11	4.68	66.35
	4.05	13.25	4.56	66.37
	4.14	13.45	4.68	66.69
	3.76	12.98	4.83	66.35
	4.04	13.29	4.68	66.65
	3.84	13.03	4.83	66.05
	3.95	13.22	4.75	66.63
	4.01	13.14	4.68	66.08
	4.08	13.20	4.63	66.36
	4.01	13.22	4.74	66.51
	3.98	13.20	4.75	66.52
	3.98	13.19	4.72	66.49
	3.94	13.10	4.79	66.47
	3.94	13.14	4.79	66.43
	3.77	12.83	4.83	66.06
	3.98	13.10	4.72	66.08
	4.11	13.27	4.71	66.65
Mean wt%	3.98	13.16	4.73	66.34
SD	0.11	0.12	0.07	0.30
Rel SD %	2.83	0.88	1.55	0.46

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Table 1

Manufacturer's characterization of the "Low DCPD Resin Oil" test substance that was submitted for testing in the American Chemistry Council Olefins Panel's HPV program – for the Resin Oils and Cyclodiene Dimer Concentrates Category. The test substance was sent on about February 10, 2003, to the EMBSI and Haskell Labs (received on February 27, 2003).

Low DCPD Resin Oil HPV SAMPLE	15:15	2/10/2003
Determinant	**Result**	**Units**
BENZENE	0.0005	WT%
C1-C7	0	WT%
TOLUENE	0	WT%
ETHYLBENZENE	0.01	WT%
P+M-XYLENE'S	0.11	WT%
STYRENE	0.52	WT%
O-XYLENE	0.18	WT%
1,3,5-TRIMETHYLBENZENE	1.8	WT%
alpha-METHYL STYRENE	1.1	WT%
cis-beta-METHYL STYRENE	0.55	WT%
meta-VINYL TOLUENE	10.04	WT%
ortho-VINYL TOLUENE	2.98	WT%
PSEUDOCUMENE	6.45	WT%
para-VINYL TOLUENE	4.27	WT%
trans- beta METHYL STYRENE	1.06	WT%
123HEMMI	0.92	WT%
DCPD	0.68	WT%
INDENE	13.68	WT%
METHYL INDENES (TOTAL)	8.35	WT%
NAPHTHALENE	1.47	WT%
BHT	0.0074	WT%
Total	54.1705	

Additional Comment: The manufacturer's characterization of the Low DCPD Resin Oil test substance identifies and quantifies the major resin-forming components in the complex mixture. The identified components are primarily aromatic hydrocarbons, with a carbon range of C8 through C10. These components account for about 54 wt% of the mixture. The balance of the composition is expected to consist primarily of other C8 through C10 hydrocarbons (mainly aromatics and lesser amounts of paraffins and olefins). The chromatogram generated by the manufacturer's GC analysis of the test substance indicates more than 100 peaks (corresponding to unidentified hydrocarbon species in the mixture) that have retention times similar to the identified aromatics. The individual unknown peaks are quantified on the chromatogram and the individual values range from less than 0.01 wt % to as much as about 2.2 wt%. The Low DCPD Resin Oil is produced as a distillate fraction with a boiling range of about 335 to 410 degrees F.

Figure 1

Manufacturer-supplied chromatogram of the " Low DCPD Resin Oil" test substance that was submitted for testing in the American Chemistry Council Olefins Panel's HPV program – for the Resin Oils and Cyclodiene Dimer Concentrates Category. The test substance was sent on about February 10, 2003, to the EMBSI and Haskell Labs (received on February 27, 2003).

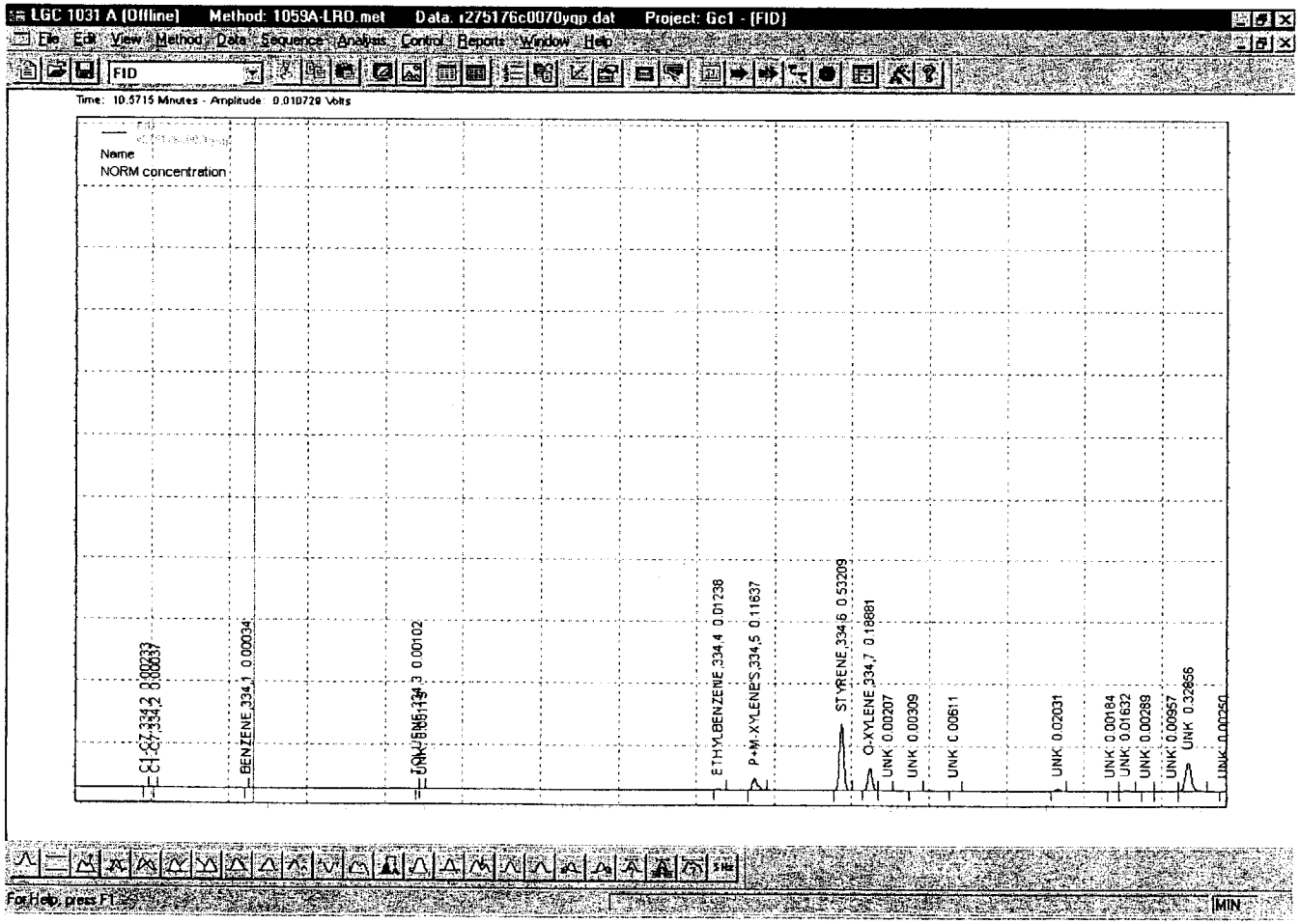


Figure 1 (continued)

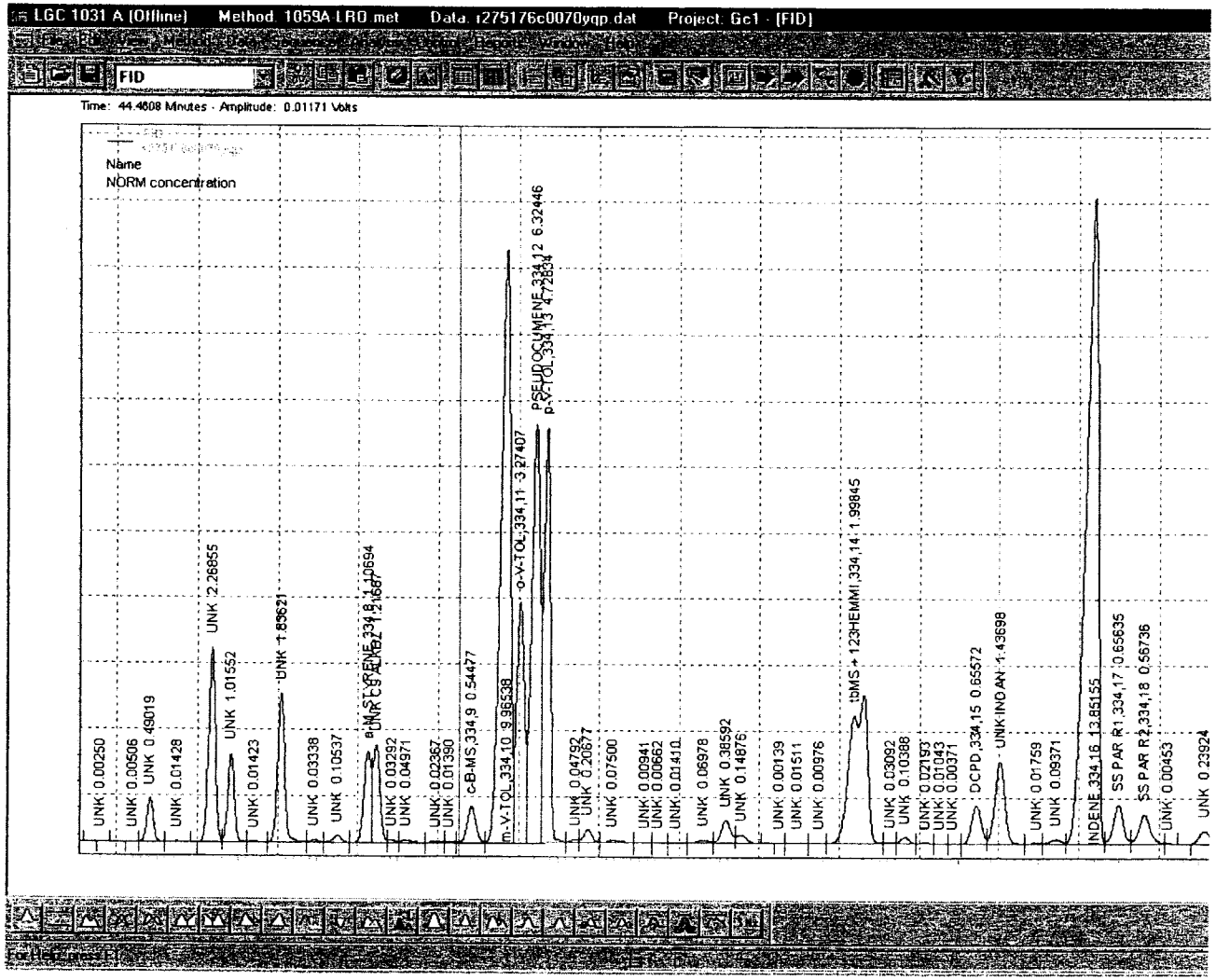
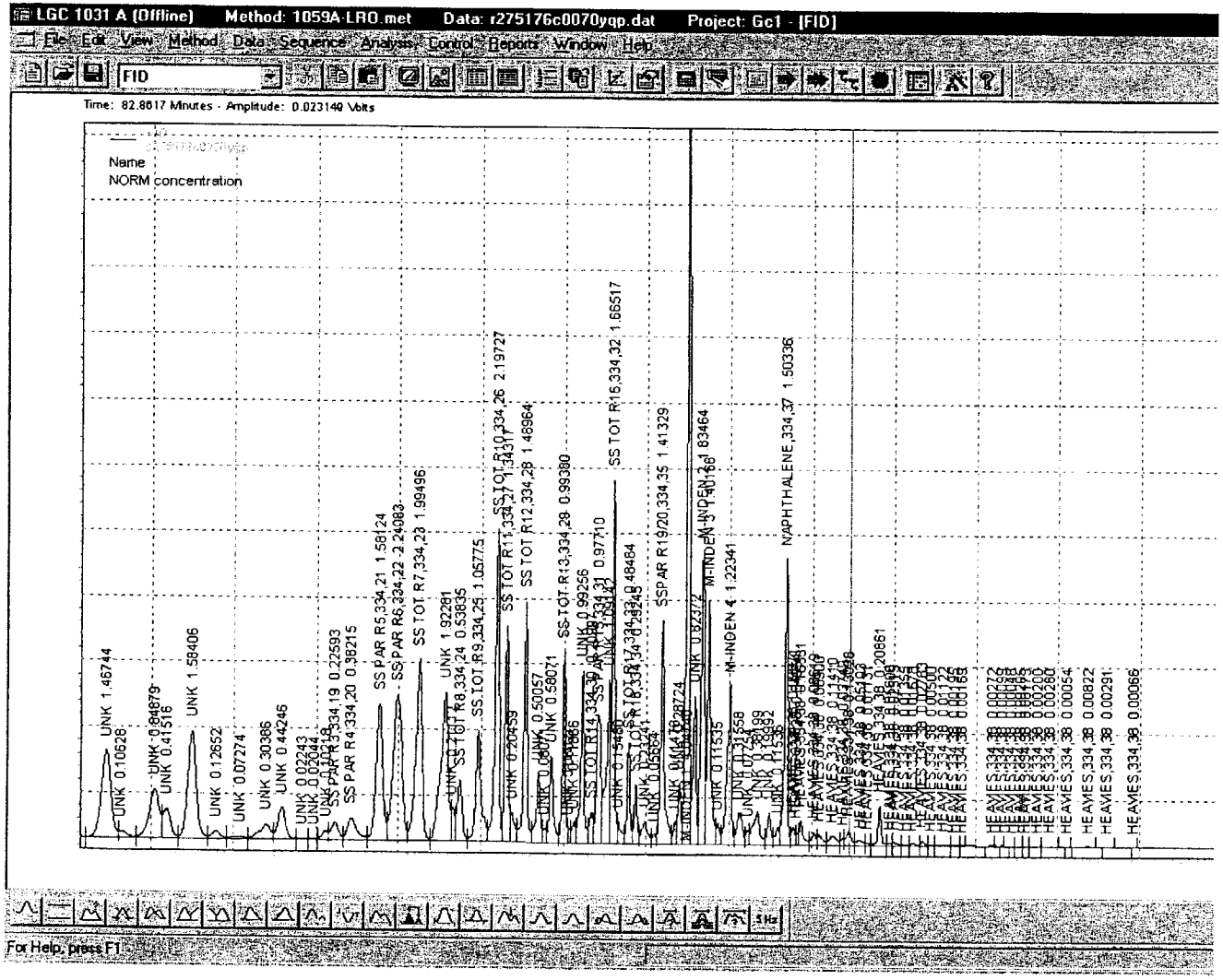


Figure 1 (continued)



Analytical method used at Haskell Laboratory:

The method used for analysis of Low DCPD Resin Oil was based on the method provided by the sponsor (see above).

The instrument and the experimental conditions pertaining to the GC analysis are summarized below:

Instrument:	Hewlett Packard HP6890 gas chromatograph with 7683 autosampler
GC Column:	Supelco SPB-1, 100 m length, 0.23 mm internal diameter, 1.0 µm film thickness
Carrier Gas:	Helium
Injector Temperature:	200°C
Pressure:	24.9 psi
Split Ratio:	52.1:1
Wash Solvent A:	chloroform
Syringe Size:	5 µL
Injection Volume:	0.1 µL
Carrier Gas Flow Rate:	1.8 mL/min, constant flow mode
Initial Temperature:	85°C, hold for 63 minutes, then increase at 3°C/min to Final Temperature 1
Final Temperature 1:	115°C, increase at 15°C/min to Final Temperature 2
Final Temperature 2:	230°C, hold at Final Temperature 2 for 2 minutes
Run Time:	99.33 min
Detector:	Flame Ionization Detector (FID)
Detector Temperature:	220°C
Hydrogen Flow:	40 mL/min
Air Flow:	450 mL/min
Makeup Gas Type:	Helium

Figure 2

Representative chromatogram of Low DCPD Resin Oil Test Substance (in order to avoid overlapping labels, not all the peaks were annotated).

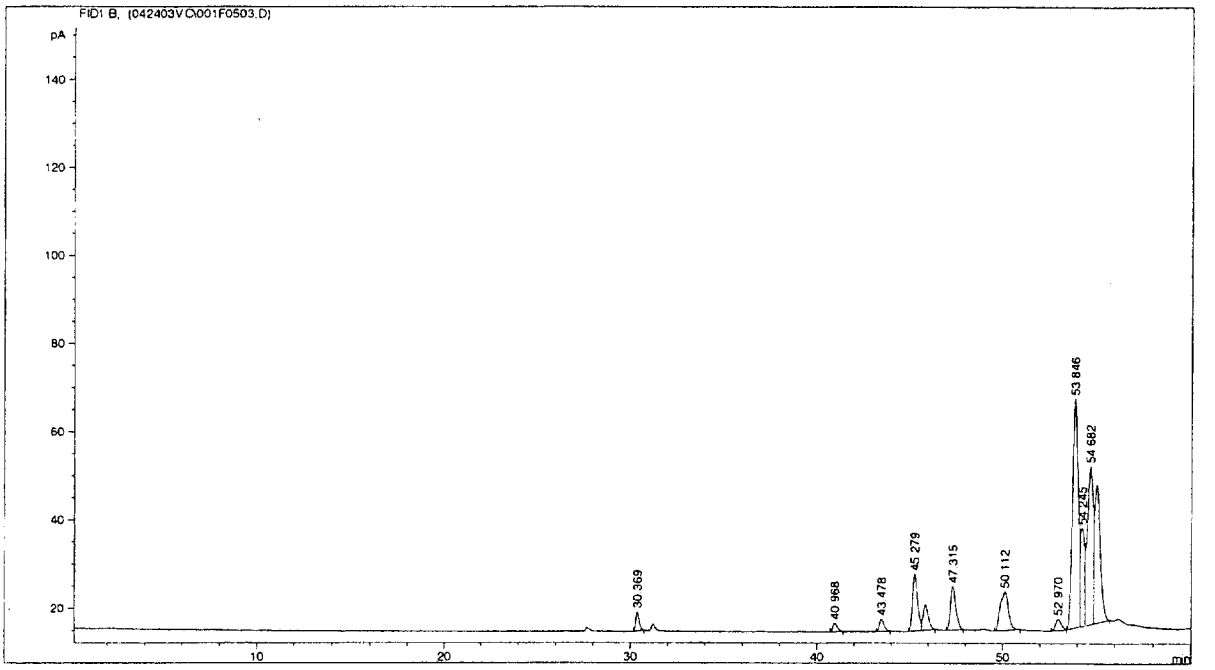


Figure 2 (continued)

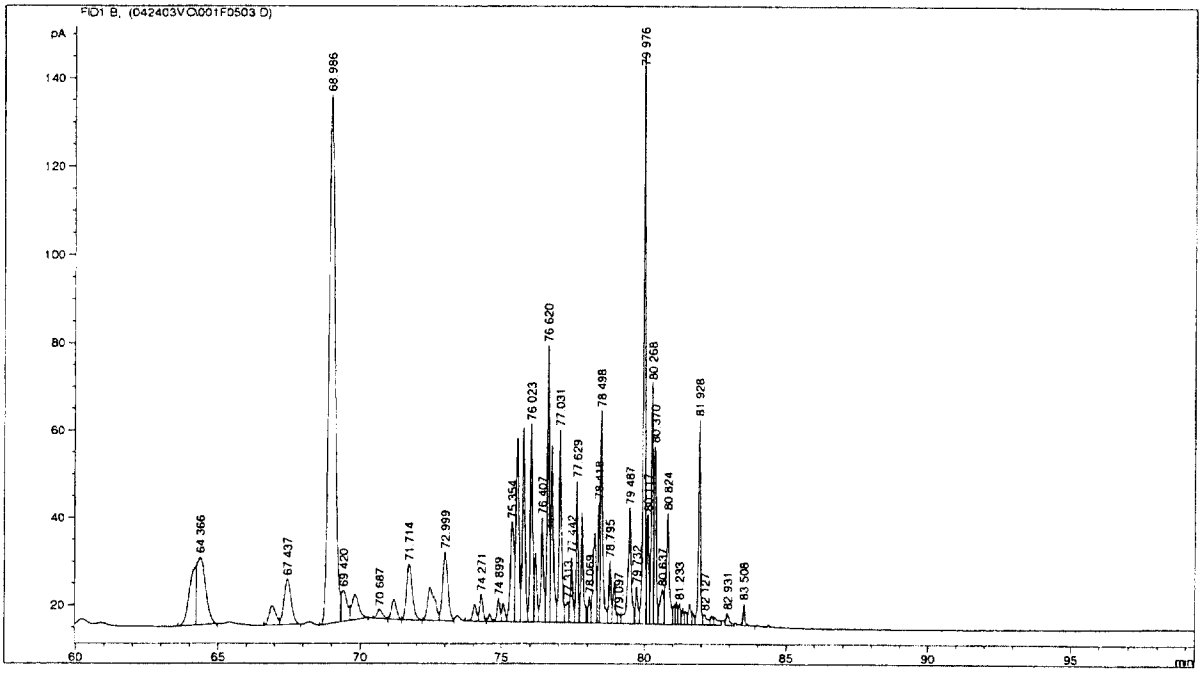


Table 2

Retention times and composition of representative components in the chromatogram in Figure 2.

Retention Time (min)	Component Name[a]	Area %	Supplier's Composition (%)
53.846	m-vinyltoluene	8.52	10.04
55.682	1,2,4-trimethylbenzene	5.77	6.45
55.026	p-vinyltoluene	5.08	4.27
68.986	indene	14.38	13.68

[a] Components identified based on Sponsor-provided gas chromatographic profile

APPENDIX C

Dosing Formulation Analysis

Table I. Recovery of Low DCPD Resin Oil Added to Dosing Vehicle

Sample Type	mg/mL Low DCPD Resin Oil		Percent
	Nominal	Measured	Nominal
RECOVERY[A]	14.4	15.3	106.3
RECOVERY[B]	14.5	16.0	110.3
RECOVERY[D]	14.5	14.4[C]	99.3
		Mean	***105.3 ±5.6, C.V. 5%***
RECOVERY[A]	52.2	56.6	108.4
RECOVERY[B]	52.8	54.4[C]	103.0
RECOVERY[D]	54.4	51.3[C]	94.3
		Mean	***101.9 ±7.1, C.V. 7%***
RECOVERY[A]	188.9	203	107.5
RECOVERY[B]	189.6	172	90.7
RECOVERY[D]	188.5	175[E]	92.8
		Mean	***97.0 ±9.2, C.V. 9%***

(A) Processed with homogeneity/concentration verification samples from dosing prepared September 10, 2003.

(B) Processed with concentration verification samples from dosing prepared October 1, 2003.

(C) Mean result of duplicate reanalysis of the original sample. Original result is not reported due to aliquot error for analysis.

(D) Processed with concentration verification samples from dosing prepared October 15, 2003.

(E) Mean result of original analysis and duplicate reanalysis of the original sample.

Table II. Homogeneity and Stability of Low DCPD Resin Oil in Dosing Formulations

Sample Type	mg/mL Low DCPD Resin Oil		Percent
	Nominal	Measured	Nominal
10-Sept-2003			
Homogeneity			
CONTROL	0.00	ND(A)	----
TOP	17.5	18.1	103.4
MIDDLE	17.5	17.6	100.6
BOTTOM	17.5	18.8	107.4
		Mean*(B): *18.2 ± 0.60	***(104.0%)***
		C.V. 3%	
TOP	62.5	68.6	109.8
MIDDLE	62.5	68.9	110.2
BOTTOM	62.5	65.8	105.3
		Mean*(B): *67.8 ± 1.7	***(108.5%)***
		C.V. 3%	
TOP	187.5	215	114.7
MIDDLE	187.5	203	108.3
BOTTOM	187.5	210	112.0
		Mean*(B): *209 ± 6.0	***(111.5%)***
		C.V. 3%	
Stability(C)			
	17.5	17.7	101.1
	62.5	60.7	97.1
	187.5	196	104.5

(A) Denotes not detected.

(B) The average measured concentration, average percent of nominal (in parentheses and based on average measured), standard deviation, and coefficient of variation of top, middle, and bottom (mean result, n=3).

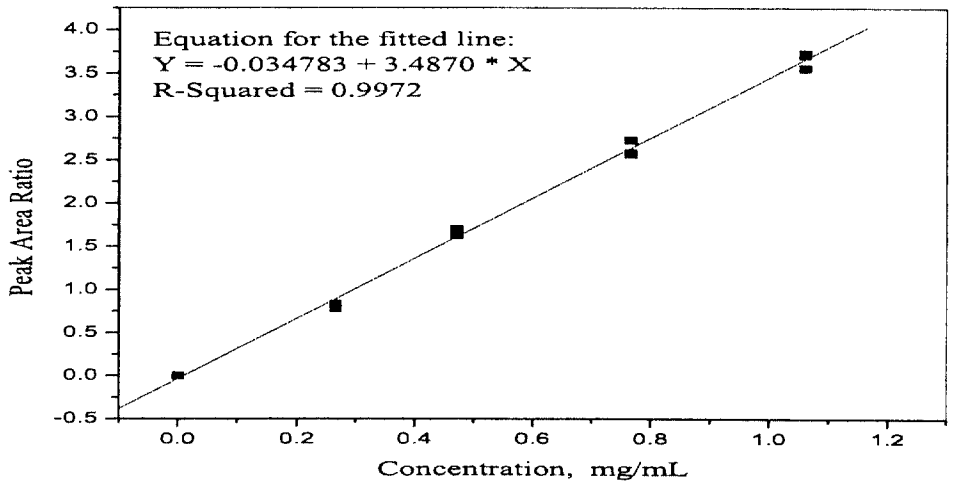
(C) Stability samples held 5 hours at room temperature, covered and not stirred.

Table III. Concentration Verification of Low DCPD Resin Oil in Dosing Suspensions

Sample Type	mg/mL Low DCPD Resin Oil Nominal	Measured	Percent Nominal
1-Oct-2003			
Concentration Verification			
CONTROL	0.00	ND(A)	----
#1	17.5	17.9	102.3
#2	17.5	19.2	109.7
		Mean(B): 18.6 ± 0.92	***(106.3%)***
		C.V. 5%	
#1	62.5	61.3	98.1
#2	62.5	66.0(C)	105.6
		Mean(D): 63.7 ± 3.3	***(101.9%)***
		C.V. 5%	
#1	187.5	214(C)	114.1
#2	187.5	182	97.1
		Mean(D): 198 ± 23	***(105.6%)***
		C.V. 11%	
15-Oct-2003			
Concentration Verification			
CONTROL	0.00	ND(A)	----
#1	17.5	20.3	116.0
#2	17.5	19.1	109.1
		Mean(B): 19.7 ± 0.84	***(112.6%)***
		C.V. 4%	
#1	62.5	55.1	88.2
#2	62.5	56.7	90.7
		Mean(B): 55.9 ± 1.1	***(89.4%)***
		C.V. 2%	
#1	187.5	170(E)	90.7
#2	187.5	162	86.4
		Mean(D): 166± 5.7	***(88.5%)***
		C.V. 3%	

(A) Denotes not detected.
(B) The average measured concentration, average percent of nominal (in parentheses and based on averaged measured), standard deviation, and coefficient of variation of duplicate samples.
(C) The average measured concentration, average percent of nominal of duplicate reanalysis of the original sample. Original analysis was not acceptable due to aliquot error in the analysis.
(D) The average measured concentration, average percent of nominal (in parentheses and based on average measured), standard deviation, and coefficient of variation of the average of duplicate samples including the average of a duplicate reanalysis of the original sample.
(E) The average measured concentration, average percent of nominal of the original analysis and duplicate reanalysis of the original sample.

Figure 1
Representative Analytical Calibration Curve



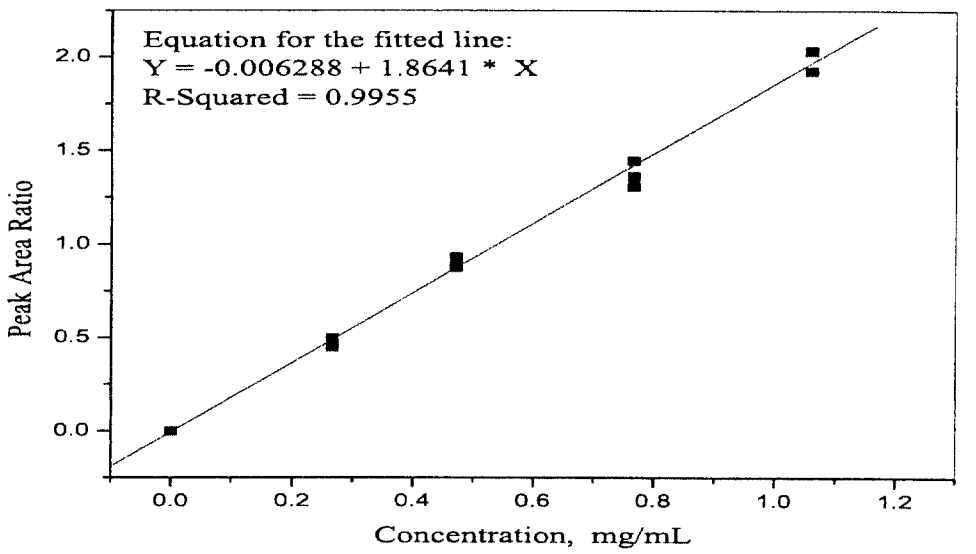


Figure 1: Calibration curve showing linear fit (line) to replicate peak height ratio (squares) for calibration solutions of Low DCPD Resin Oil diluted over a concentration range of 0.2651 to 1.0602 mg/mL based on peak areas ratio at (a) 1st peak (2.5 or 2.7 minutes) and (b) 2nd peak. (2.7 or 3.0 minutes).

Figure 2
Representative Gas Chromatography Chromatograms

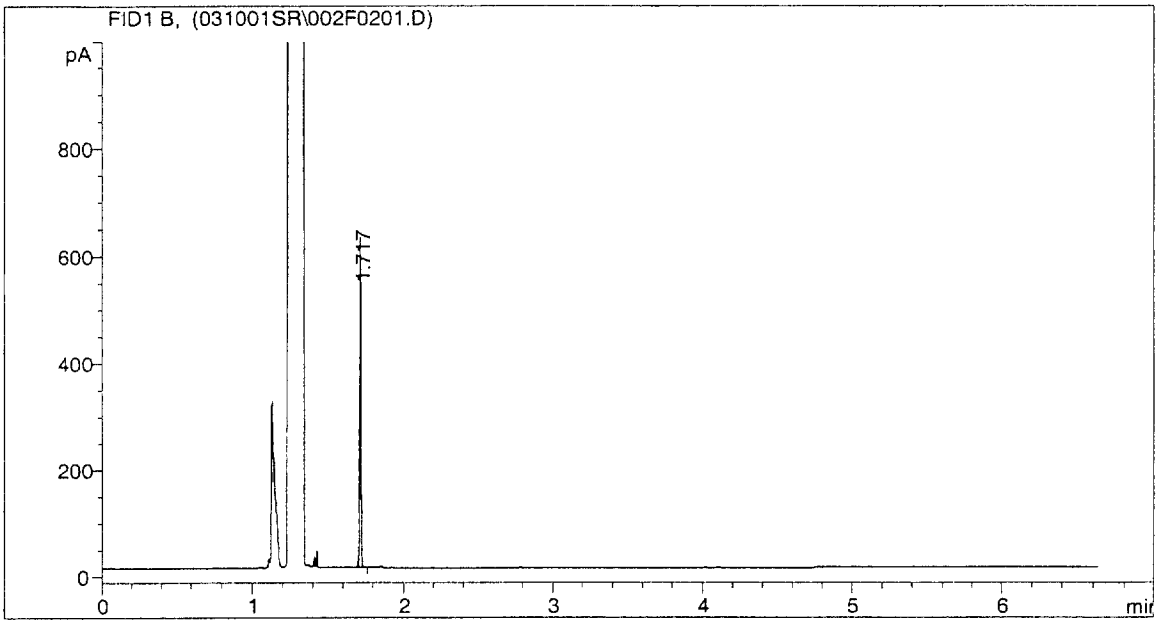


Figure 2a: Representative GC chromatogram of the 0 mg/mL (control) sample. Retention time for the 2 peaks used for the Low DCPD Resin Oil are approximately 2.7 minutes and 3.0 minutes. The internal standard peak retention time is approximately 1.7 minutes.

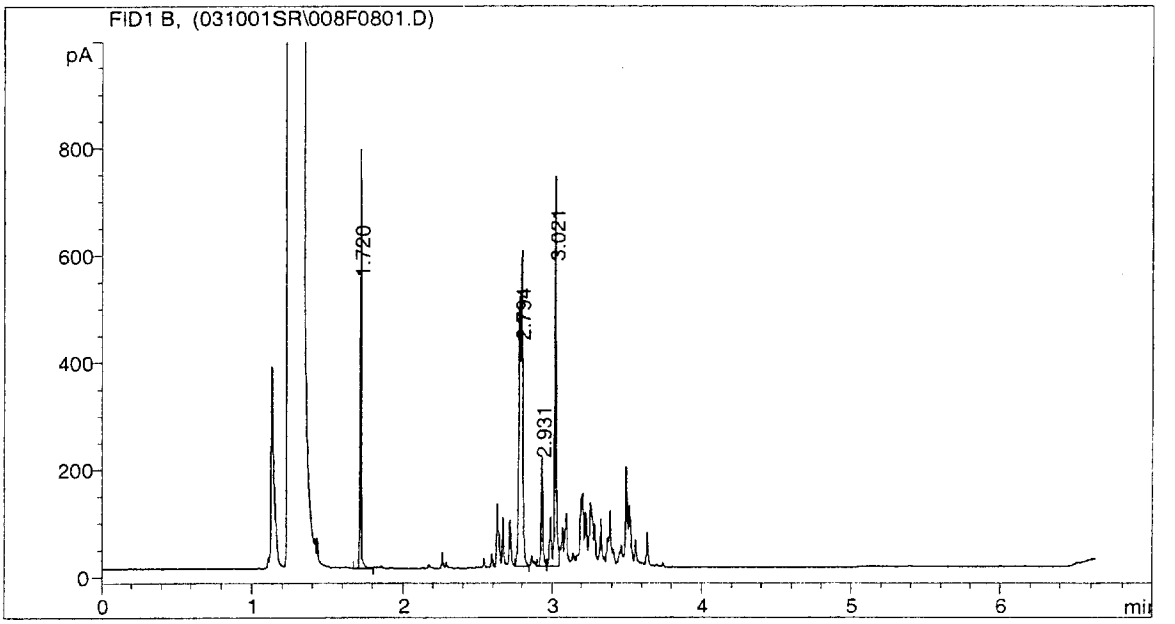


Figure 2b: Representative GC chromatogram of 17.5 mg/mL Low DCPD Resin Oil dosing formulation diluted to a nominal concentration of 0.735 mg/mL. The mean measured concentration of the representative solution is 19.7 mg/mL.

Figure 2 (continued)
Representative Gas Chromatography Chromatograms

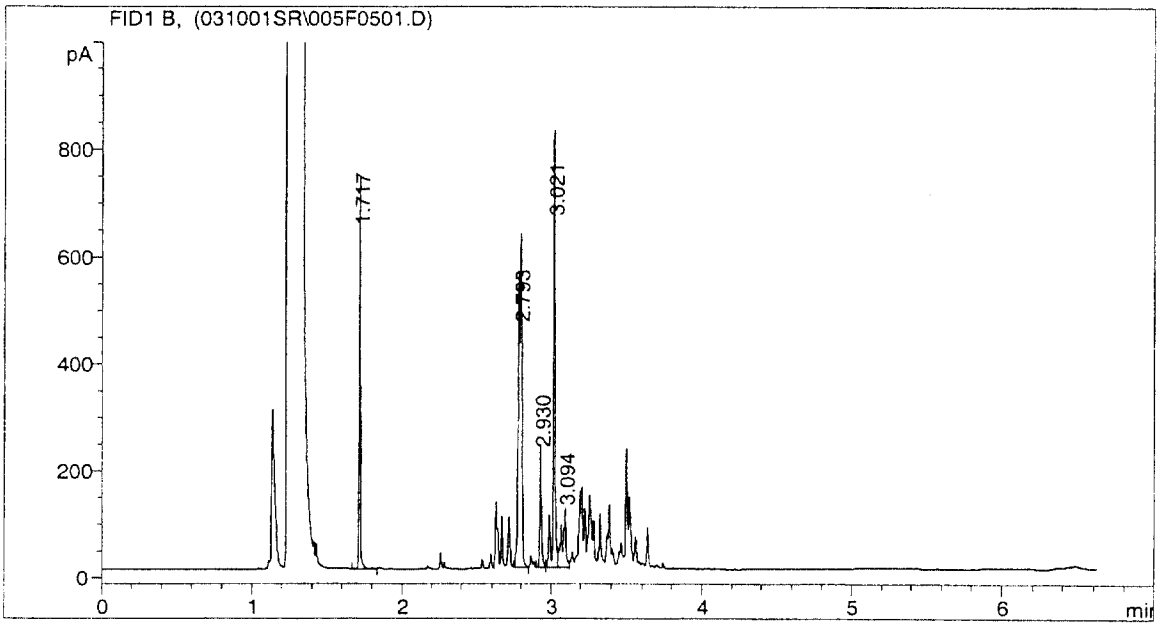


Figure 2c: Representative GC chromatogram of 0.7956 mg/mL Low DCPD Resin Oil analytical reference solution.

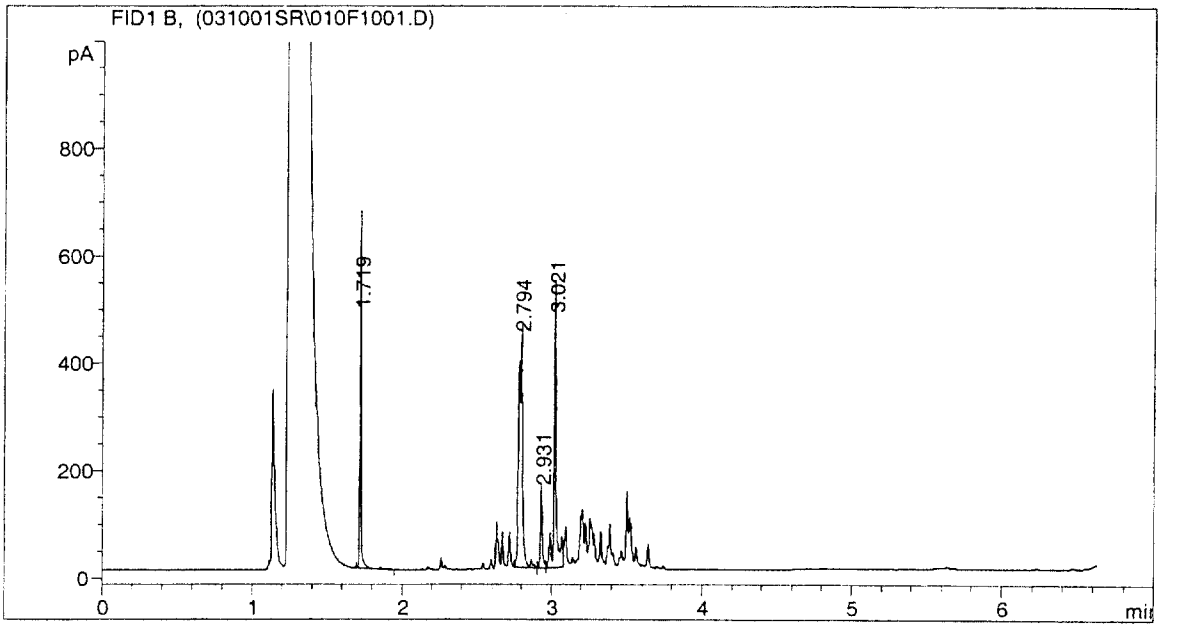


Figure 2d: Representative GC chromatogram of 14.5 mg/mL spiked dosing formulation diluted to nominal concentration of 0.609 mg/mL of Low DCPD Resin Oil. The measured concentration of the representative solution is 16.0 mg/mL.

APPENDIX D

Pre-Study Stability Report

TEST SUBSTANCE STABILITY OF LOW DICYCLOPENTADIENE RESIN OIL (LOW DCPD RESIN OIL)

Medical Research Project Number:	5672
Haskell Sample Number:	H-25429
Analytical Report Number:	Dupont-13355

SUMMARY

At the end of the Low DCPD Resin Oil Developmental pilot study (MR 14295/SC840), a sample of Low DCPD Resin Oil was received on June 24, 2003, and analyzed July 1, 2003. The percentage of Low DCPD Resin Oil was measured to be 95.2% ± 2.6 with a range of 93.2 to 98.2% for replicate analyses (n = 3). Sponsor reported Low DCPD Resin Oil content of 100% when the Low DCPD Resin Oil was received

SIGNATURES:

Analysis by: Sheila A. Riley — 3-Nov. 2003
Sheila A. Riley, Chemistry Associate — Date

Report by: Janet C. Maslanka — 3-Nov-2003
Janet C. Maslanka, Analytical Staff Chemist — Date

Date issued: 3-Nov-2003

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METHODS

Analysis of Low DCPD Resin Oil was performed by gas chromatography (GC). This two major peaks in the GC analysis of the Low DCPD Resin Oil were used for the quantitation of the samples.

SAMPLE PREPARATION & ANALYSIS

For the analysis, aliquots (0.0109, 0.0112, 0.0111 grams) of Low DCPD Resin Oil were dissolved in chloroform (10 mL) to give nominal concentrations of 1090, 1120, and 1110 ppm after the addition of the internal standard (refer to Calibration and Quantitation Section) and analyzed according to the method below.

INSTRUMENT & CONDITIONS

Instrument:	Hewlett-Packard Model 6890 GC
Column:	DB-1, 30 m x 0.25 mm ID, 0.25 μm film thickness
Injector:	Split, 180°C
Detector:	Flame Ionization Detector (FID); 280°C
Carrier Gas:	Helium (2.7 mL/min)
Split ratio:	10:1
Injection Volume:	3 microliter
Oven Program:	Gradient
Initial Temperature:	65°C
Initial Time:	0.50 min.
Level 1 Rate:	20°C/min.
Level 1 Temperature:	85°C
Level 1 Time:	0.00 min.
Level 2 Rate:	40°C/min.
Level 2 Temperature:	250°C
Level 2 Time:	1.00 min.
Total run time:	6.63 min.

CALIBRATION & QUANTITATION

A separate sample of the Low DCPD Resin Oil (H-25429, 100.0%) was used as an analytical reference for the analysis. A stock solution was prepared in chloroform. Calibration solutions of approximately 520 to 1230 ppm were prepared in chloroform from this solution. A stock solution of the internal standard (toluene, Fluka Chemika, 99.5% pure) was prepared in chloroform and added to each calibration standard and test solution to give a final concentration of approximately 73 ppm. The ratio of each peak area (2) for Low DCPD Resin Oil and for the internal standard from replicate GC analysis of these solutions were used to construct a calibration curve by least squares regression. Measured concentrations for each purity solution were determined by applying the peak area ratios from replicate injections of each sample to the respective calibration curve. The measured concentration for each peak in the Low DCPD Resin Oil was averaged and the % nominal reported as the results.

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RESULTS

Low DCPD Resin Oil eluted from the GC column as resolved peaks with retention time of approximately 2.8 and 3.0 minutes. The peak area was used with the internal standard peak area to form a ratio for calculating the amount of Low DCPD Resin Oil in the test substance from both peaks. The measured concentration from both peaks was averaged and the % nominal calculated based on this average. Sponsor reported the test substance as 100.0% when the sample was received.

Table 1. The percent of active ingredient (a.i.) in the Low DCPD Resin Oil sample analyzed July 1, 2003.

	ppm Low DCPD Resin Oil		Percent
Aliquot	Targeted	Measured	Nominal
1	1090	1070	98.2
2	1120	1055	94.2
3	1110	1035	93.2
Average Percent Nominal			**95.2**
Standard Deviation			**± 2.6**
Coefficient of Variation			**3%**

APPENDIX E

Post-Study Stability Report

TEST SUBSTANCE STABILITY OF LOW DICYCLOPENTADIENE RESIN OIL (LOW DCPD RESIN OIL)

Medical Research Project Number:	5672
Haskell Sample Number:	H-25429
Analytical Report Number:	Dupont-13877

SUMMARY

A sample of Low DCPD Resin Oil was received on October14, 2003, and analyzed October 20, 2003. The percentage of Low DCPD Resin Oil was measured to be 100.3% ± 3.6 with a range of 96.3 to 103.3% for replicate analyses (n = 3). Sponsor reported Low DCPD Resin Oil content of 100% when the Low DCPD Resin Oil was received

SIGNATURES:

Analysis by: Sheila A. Riley — 18, Feb. 2004
Sheila A. Riley, Chemistry Associate — Date

Report by: Janet C. Maslanka — 18-Feb-2004
Janet C. Maslanka, Senior Staff Chemist — Date

Date issued: 18-Feb-2004

Dupont-13877 page 2 of 3

METHODS

Analysis of Low DCPD Resin Oil was performed by gas chromatography (GC). The two major peaks in the GC analysis of the Low DCPD Resin Oil were used for the quantitation of the samples.

SAMPLE PREPARATION & ANALYSIS

For the analysis, aliquots (0.0689, 0.0700, 0.0638 grams) of Low DCPD Resin Oil were dissolved in chloroform (10 mL) to give nominal concentrations of 6890, 7000, and 6380 ppm. The samples were further diluted with chloroform to a final concentration of 689, 700, and 638 ppm after the addition of the internal standard (refer to Calibration and Quantitation Section) and analyzed according to the method below.

INSTRUMENT & CONDITIONS

Instrument:	Hewlett-Packard Model 6890 GC
Column:	DB-1, 30 m x 0.25 mm ID, 0.25 µm film thickness
Injector:	Split, 180°C
Detector:	Flame Ionization Detector (FID); 280°C
Carrier Gas:	Helium (2.7 mL/min)
Split ratio:	10:1
Injection Volume:	3 microliter
Oven Program:	Gradient
Initial Temperature:	65°C
Initial Time:	0.50 min.
Level 1 Rate:	20°C/min.
Level 1 Temperature:	85°C
Level 1 Time:	0.00 min.
Level 2 Rate:	40°C/min.
Level 2 Temperature:	250°C
Level 2 Time:	1.00 min.
Total run time:	6.63 min.

CALIBRATION & QUANTITATION

A separate sample of the Low DCPD Resin Oil (H-25429, 100.0%) was used as an analytical reference for the analysis. A stock solution was prepared in chloroform. Calibration solutions of approximately 329 to 1053 ppm were prepared in chloroform from this solution. A stock solution of the internal standard (toluene, Fluka Chemika, 99.5% pure) was prepared in chloroform and added to each calibration standard and test solution to give a final concentration of approximately 73 ppm. The ratio of each peak area (2) for Low DCPD Resin Oil and for the internal standard from replicate GC analysis of these solutions were used to construct a calibration curve by least squares regression. Measured concentrations for each purity solution were determined by applying the peak area ratios from replicate injections of each sample to the respective calibration curve. The measured concentration for each peak in the Low DCPD Resin Oil was averaged and the % nominal reported as the results.

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RESULTS

Low DCPD Resin Oil eluted from the GC column as resolved peaks with retention time of approximately 2.7 and 3.0 minutes. The peak area was used with the internal standard peak area to form a ratio for calculating the amount of Low DCPD Resin Oil in the test substance from both peaks. The measured concentration from both peaks was averaged and the % nominal calculated based on this average. Sponsor reported the test substance as 100.0% when the sample was received.

Table 1. The percent of active ingredient (a.i.) in the Low DCPD Resin Oil sample analyzed October 20, 2003.

	ppm Low DCPD Resin Oil		Percent
Aliquot	Targeted	Measured	Nominal
1	689	712	103.3
2	700	674	96.3
3	638	646	101.2
Average Percent Nominal			**100.3**
Standard Deviation			**± 3.6**
Coefficient of Variation			**4%**

APPENDIX F

Individual Clinical Observations and Mortality Data in Subchronic Male Rats

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating period
Test Days 15-29 = Cohabitation period

Post dosing clinical observations were recorded by exception. A "-" indicates that no signs were present for a given animal.

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA

IN SUBCHRONIC MALE RATS (PREDOSING)

GROUP: I CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
1	ALOPECIA BOTH FRONT PAW(S)	22	30
	ALOPECIA BOTH FRONT LEG(S)	28	30
	SACRIFICED BY DESIGN TEST DAY 30		
8	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
10	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
12	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
13	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
22	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
31	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
36	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
41	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
44	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
45	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
54	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA

IN SUBCHRONIC MALE RATS (PREDOSING)

GROUP: III CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
3	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
5	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
14	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
18	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
20	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
26	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
35	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
46	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
48	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
50	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
55	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
56	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA

IN SUBCHRONIC MALE RATS (PREDOSING)

GROUP: V CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
4	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
9	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
25	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
28	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
30	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
32	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
37	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
38	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
43	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
47	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
49	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
51	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA

IN SUBCHRONIC MALE RATS (PREDOSING)

GROUP: VII CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
2	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
6	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
11	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
16	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
19	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
21	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
27	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
33	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
39	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
40	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
52	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		
53	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 30		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS (POSTDOSING)

GROUP: I CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
1	-		
8	-		
10	-		
12	-		
13	-		
22	-		
31	-		
36	-		
41	-		
44	-		
45	-		
54	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS (POSTDOSING)

GROUP: III CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
3	-		
5	-		
14	-		
18	-		
20	-		
26	-		
35	-		
46	-		
48	-		
50	-		
55	-		
56	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS (POSTDOSING)

GROUP: V CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
4	-		
9	WET CHIN	29	29
25	-		
28	WET CHIN	29	29
30	-		
32	STAINED CHIN BROWN	15	15
37	-		
38	-		
43	-		
47	-		
49	-		
51	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS (POSTDOSING)

GROUP: VII CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
2	-		
6	STAINED CHIN BROWN	15	15
11	STAINED CHIN BROWN	1	1
	WET CHIN	28	28
16	-		
19	WET CHIN	17	19
21	STAINED CHIN BROWN	1	1
27	WET CHIN	13	20
	STAINED CHIN BROWN	22	23
33	WET CHIN	24	24
39	-		
40	WET CHIN	9	9
52	WET CHIN	1	13
	STAINED CHIN BROWN	16	16
53	STAINED CHIN BROWN	1	1
	WET CHIN	29	29

APPENDIX G

Individual Detailed Clinical Observations in Subchronic Male Rats

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating period
Test Days 15-29 = Cohabitation period

Detailed clinical observations were conducted during the pretest period and on test days 8, 15, 22, and 29.

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

GROUP: I CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
1	ALOPECIA BOTH FRONT PAW(S)	22	29
	ALOPECIA BOTH FRONT LEG(S)	29	29
8	NO ABNORMALITIES DETECTED		
10	NO ABNORMALITIES DETECTED		
12	NO ABNORMALITIES DETECTED		
13	NO ABNORMALITIES DETECTED		
22	NO ABNORMALITIES DETECTED		
31	NO ABNORMALITIES DETECTED		
36	NO ABNORMALITIES DETECTED		
41	NO ABNORMALITIES DETECTED		
44	NO ABNORMALITIES DETECTED		
45	NO ABNORMALITIES DETECTED		
54	NO ABNORMALITIES DETECTED		

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

GROUP: III CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
3	NO ABNORMALITIES DETECTED		
5	NO ABNORMALITIES DETECTED		
14	NO ABNORMALITIES DETECTED		
18	NO ABNORMALITIES DETECTED		
20	NO ABNORMALITIES DETECTED		
26	NO ABNORMALITIES DETECTED		
35	NO ABNORMALITIES DETECTED		
46	NO ABNORMALITIES DETECTED		
48	NO ABNORMALITIES DETECTED		
50	NO ABNORMALITIES DETECTED		
55	NO ABNORMALITIES DETECTED		
56	NO ABNORMALITIES DETECTED		

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

GROUP: V CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
4	NO ABNORMALITIES DETECTED		
9	NO ABNORMALITIES DETECTED		
25	NO ABNORMALITIES DETECTED		
28	NO ABNORMALITIES DETECTED		
30	NO ABNORMALITIES DETECTED		
32	NO ABNORMALITIES DETECTED		
37	NO ABNORMALITIES DETECTED		
38	NO ABNORMALITIES DETECTED		
43	NO ABNORMALITIES DETECTED		
47	NO ABNORMALITIES DETECTED		
49	NO ABNORMALITIES DETECTED		
51	NO ABNORMALITIES DETECTED		

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

GROUP: VII CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
2	NO ABNORMALITIES DETECTED		
6	NO ABNORMALITIES DETECTED		
11	NO ABNORMALITIES DETECTED		
16	NO ABNORMALITIES DETECTED		
19	NO ABNORMALITIES DETECTED		
21	NO ABNORMALITIES DETECTED		
27	NO ABNORMALITIES DETECTED		
33	NO ABNORMALITIES DETECTED		
39	NO ABNORMALITIES DETECTED		
40	NO ABNORMALITIES DETECTED		
52	NO ABNORMALITIES DETECTED		
53	NO ABNORMALITIES DETECTED		

APPENDIX H

Individual Clinical Observations and Mortality Data in Subchronic Female Rats

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC FEMALE RATS

EXPLANATORY NOTES

Notes

Post dosing clinical observations were recorded by exception. A "-" indicates that no signs were present for a given animal.

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA

IN SUBCHRONIC FEMALE RATS (PREDOSING)

GROUP: II CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
69	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
89	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
101	ALOPECIA BOTH FRONT PAW(S)	28	31
	ALOPECIA BOTH FRONT LEG(S)	28	31
	SACRIFICED BY DESIGN TEST DAY 31		
112	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
113	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
123	ALOPECIA BOTH FRONT LEG(S)	5	31
	SACRIFICED BY DESIGN TEST DAY 31		
126	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
144	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
152	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
155	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
162	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
163	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA

IN SUBCHRONIC FEMALE RATS (PREDOSING)

GROUP: IV CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
71	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 31		
75	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 31		
83	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 31		
107	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 31		
119	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 31		
120	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 31		
128	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 31		
138	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 31		
145	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 31		
149	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 31		
160	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 31		
164	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 31		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA

IN SUBCHRONIC FEMALE RATS (PREDOSING)

GROUP: VI CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
62	ALOPECIA BOTH FRONT PAW(S)	8	31
	ALOPECIA BOTH FRONT LEG(S)	8	31
	SACRIFICED BY DESIGN TEST DAY 31		
79	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
99	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
135	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
142	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
143	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
147	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
150	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
153	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
154	ALOPECIA BOTH FRONT PAW(S)	10	28
	ALOPECIA RIGHT FRONT PAW(S)	29	31
	SACRIFICED BY DESIGN TEST DAY 31		
156	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
161	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA

IN SUBCHRONIC FEMALE RATS (PREDOSING)

GROUP: VIII CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
67	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
68	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
70	ALOPECIA BOTH HIND QUARTERS	22	31
	ALOPECIA LEFT FRONT LEG(S)	22	23
	ALOPECIA BOTH FRONT LEG(S)	24	31
	ALOPECIA UNDERBODY	28	31
	SACRIFICED BY DESIGN TEST DAY 31		
76	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
77	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
84	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
88	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
114	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
129	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
146	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
151	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
159	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA

IN SUBCHRONIC FEMALE RATS (POSTDOSING)

GROUP: II CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
69	-		
89	-		
101	-		
112	-		
113	-		
123	-		
126	-		
144	-		
152	-		
155	-		
162	-		
163	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA

IN SUBCHRONIC FEMALE RATS (POSTDOSING)

GROUP: IV CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
71	-		
75	-		
83	-		
107	-		
119	-		
120	-		
128	-		
138	-		
145	-		
149	-		
160	-		
164	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA

IN SUBCHRONIC FEMALE RATS (POSTDOSING)

GROUP: VI CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
62	-		
79	-		
99	-		
135	WET CHIN	20	30
142	-		
143	-		
147	-		
150	-		
153	-		
154	-		
156	-		
161	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA

IN SUBCHRONIC FEMALE RATS (POSTDOSING)

GROUP: VIII CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
67	-		
68	-		
70	WET CHIN	13	30
76	-		
77	WET CHIN	19	27
84	STAINED CHIN BROWN	1	1
	WET CHIN	20	26
88	STAINED CHIN BROWN	1	1
	WET CHIN	24	24
114	-		
129	-		
146	STAINED CHIN BROWN	1	1
151	-		
159	STAINED CHIN BROWN	1	1
	WET CHIN	13	13

APPENDIX I

Individual Detailed Clinical Observations in Subchronic Female Rats

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC FEMALE RATS

EXPLANATORY NOTES

Notes

Detailed clinical observations were conducted during the pretest period and on test days 8, 15, 22, and 29.

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN
SUBCHRONIC FEMALE RATS

GROUP: II CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
69	NO ABNORMALITIES DETECTED		
89	NO ABNORMALITIES DETECTED		
101	ALOPECIA BOTH FRONT PAW(S)	29	29
	ALOPECIA BOTH FRONT LEG(S)	29	29
112	NO ABNORMALITIES DETECTED		
113	NO ABNORMALITIES DETECTED		
123	ALOPECIA BOTH FRONT LEG(S)	8	29
126	NO ABNORMALITIES DETECTED		
144	NO ABNORMALITIES DETECTED		
152	NO ABNORMALITIES DETECTED		
155	NO ABNORMALITIES DETECTED		
162	NO ABNORMALITIES DETECTED		
163	NO ABNORMALITIES DETECTED		

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN
SUBCHRONIC FEMALE RATS

GROUP: IV CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
71	NO ABNORMALITIES DETECTED		
75	NO ABNORMALITIES DETECTED		
83	NO ABNORMALITIES DETECTED		
107	NO ABNORMALITIES DETECTED		
119	NO ABNORMALITIES DETECTED		
120	NO ABNORMALITIES DETECTED		
128	NO ABNORMALITIES DETECTED		
138	NO ABNORMALITIES DETECTED		
145	NO ABNORMALITIES DETECTED		
149	NO ABNORMALITIES DETECTED		
160	NO ABNORMALITIES DETECTED		
164	NO ABNORMALITIES DETECTED		

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC FEMALE RATS

GROUP: VI CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
62	ALOPECIA BOTH FRONT PAW(S)	8	29
	ALOPECIA BOTH FRONT LEG(S)	8	29
79	NO ABNORMALITIES DETECTED		
99	NO ABNORMALITIES DETECTED		
135	NO ABNORMALITIES DETECTED		
142	NO ABNORMALITIES DETECTED		
143	NO ABNORMALITIES DETECTED		
147	NO ABNORMALITIES DETECTED		
150	NO ABNORMALITIES DETECTED		
153	NO ABNORMALITIES DETECTED		
154	ALOPECIA BOTH FRONT PAW(S)	15	22
	ALOPECIA RIGHT FRONT PAW(S)	29	29
156	NO ABNORMALITIES DETECTED		
161	NO ABNORMALITIES DETECTED		

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN
SUBCHRONIC FEMALE RATS

GROUP: VIII CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
67	NO ABNORMALITIES DETECTED		
68	NO ABNORMALITIES DETECTED		
70	ALOPECIA BOTH HIND QUARTERS	22	29
	ALOPECIA LEFT FRONT LEG(S)	22	22
	ALOPECIA BOTH FRONT LEG(S)	29	29
	ALOPECIA UNDERBODY	29	29
76	NO ABNORMALITIES DETECTED		
77	NO ABNORMALITIES DETECTED		
84	NO ABNORMALITIES DETECTED		
88	NO ABNORMALITIES DETECTED		
114	NO ABNORMALITIES DETECTED		
129	NO ABNORMALITIES DETECTED		
146	NO ABNORMALITIES DETECTED		
151	NO ABNORMALITIES DETECTED		
159	NO ABNORMALITIES DETECTED		

APPENDIX J

Individual Body Weights and Body Weight Gains of Subchronic Male Rats

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS
OF SUBCHRONIC MALE RATS

EXPLANATORY NOTES

Notes

Test Days 1-14 = Premating period
Test Days 15-29 = Cohabitation period

Day 30 data are presented for information only, and are not included in the summary tables, and were not analyzed statistically.

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC MALE RATS

GROUP: I CONCENTRATION: 0 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	30
ANIMAL #	MEAN BODY WEIGHT (grams)					
1	255.1	287.4	325.6	356.2	382.1	354.9
8	250.7	291.6	334.6	370.1	410.8	384.1
10	265.5	308.6	353.8	386.3	424.5	394.3
12	253.2	302.3	353.4	389.7	424.8	397.3
13	248.4	296.1	345.5	386.4	421.5	386.9
22	255.3	301.9	344.7	375.4	399.3	377.3
31	256.6	305.4	349.9	382.6	420.9	387.1
36	237.1	282.2	324.8	360.9	390.0	360.4
41	261.8	313.3	352.1	394.1	425.1	397.6
44	262.6	310.2	364.8	407.4	450.9	414.6
45	252.5	300.6	347.7	379.1	398.4	369.4
54	281.1	331.2	391.3	432.3	467.2	429.3

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
1	32.3	38.2	30.6	25.9	127.0
8	40.9	43.0	35.5	40.7	160.1
10	43.1	45.2	32.5	38.2	159.0
12	49.1	51.1	36.3	35.1	171.6
13	47.7	49.4	40.9	35.1	173.1
22	46.6	42.8	30.7	23.9	144.0
31	48.8	44.5	32.7	38.3	164.3
36	45.1	42.6	36.1	29.1	152.9
41	51.5	38.8	42.0	31.0	163.3
44	47.6	54.6	42.6	43.5	188.3
45	48.1	47.1	31.4	19.3	145.9
54	50.1	60.1	41.0	34.9	186.1

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC MALE RATS

GROUP: III CONCENTRATION: 35 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	30
ANIMAL #	MEAN BODY WEIGHT (grams)					
3	258.1	306.9	354.8	382.3	417.6	385.3
5	250.7	298.3	336.6	365.9	398.2	366.9
14	273.0	318.2	360.1	387.7	414.1	381.0
18	248.6	291.8	338.3	365.3	398.0	370.5
20	254.5	300.9	324.8	356.2	387.3	364.1
26	250.6	299.9	348.5	387.3	424.9	397.0
35	246.3	294.3	331.6	367.3	409.2	369.6
46	274.5	318.6	361.9	399.4	444.7	406.6
48	240.1	283.3	324.0	356.2	384.1	357.6
50	257.8	300.5	343.9	377.8	417.4	381.7
55	259.6	310.9	358.6	387.2	422.5	386.9
56	255.7	296.5	333.9	374.8	415.2	384.2

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
3	48.8	47.9	27.5	35.3	159.5
5	47.6	38.3	29.3	32.3	147.5
14	45.2	41.9	27.6	26.4	141.1
18	43.2	46.5	27.0	32.7	149.4
20	46.4	23.9	31.4	31.1	132.8
26	49.3	48.6	38.8	37.6	174.3
35	48.0	37.3	35.7	41.9	162.9
46	44.1	43.3	37.5	45.3	170.2
48	43.2	40.7	32.2	27.9	144.0
50	42.7	43.4	33.9	39.6	159.6
55	51.3	47.7	28.6	35.3	162.9
56	40.8	37.4	40.9	40.4	159.5

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC MALE RATS

GROUP: V CONCENTRATION: 125 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	30
ANIMAL #	MEAN BODY WEIGHT (grams)					
4	248.7	276.0	298.7	326.7	352.8	324.5
9	246.4	273.0	298.3	327.5	371.1	337.4
25	268.1	298.1	337.2	359.0	400.9	365.2
28	254.2	293.7	340.4	375.6	419.3	390.9
30	254.6	286.1	333.4	354.1	395.0	368.4
32	272.7	303.3	337.7	362.0	404.4	368.2
37	249.9	280.3	300.7	332.8	368.9	344.5
38	258.4	301.6	332.7	362.1	397.4	363.2
43	237.1	272.1	315.2	349.8	381.8	357.4
47	251.2	284.9	329.3	356.7	411.8	378.9
49	244.0	272.6	309.9	333.6	373.4	344.8
51	261.2	302.0	335.9	358.2	389.9	361.6

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
4	27.3	22.7	28.0	26.1	104.1
9	26.6	25.3	29.2	43.6	124.7
25	30.0	39.1	21.8	41.9	132.8
28	39.5	46.7	35.2	43.7	165.1
30	31.5	47.3	20.7	40.9	140.4
32	30.6	34.4	24.3	42.4	131.7
37	30.4	20.4	32.1	36.1	119.0
38	43.2	31.1	29.4	35.3	139.0
43	35.0	43.1	34.6	32.0	144.7
47	33.7	44.4	27.4	55.1	160.6
49	28.6	37.3	23.7	39.8	129.4
51	40.8	33.9	22.3	31.7	128.7

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC MALE RATS

GROUP: VII CONCENTRATION: 375 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	30
ANIMAL #	MEAN BODY WEIGHT (grams)					
2	255.5	287.9	327.3	340.1	385.1	356.6
6	247.6	281.8	322.6	345.8	375.6	355.8
11	242.2	274.9	307.0	327.5	363.0	333.5
16	245.9	287.2	326.6	356.7	388.4	355.2
19	241.7	270.4	309.3	325.1	351.2	321.9
21	257.2	284.6	323.2	350.8	375.7	349.5
27	261.9	300.2	329.4	356.9	385.3	355.1
33	247.6	283.2	325.7	351.4	377.7	346.4
39	260.1	288.9	320.7	349.7	378.0	346.9
40	252.1	284.8	319.1	337.0	354.1	333.7
52	266.0	294.6	327.5	351.3	371.5	336.7
53	278.7	319.9	364.4	394.3	421.6	384.5

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
2	32.4	39.4	12.8	45.0	129.6
6	34.2	40.8	23.2	29.8	128.0
11	32.7	32.1	20.5	35.5	120.8
16	41.3	39.4	30.1	31.7	142.5
19	28.7	38.9	15.8	26.1	109.5
21	27.4	38.6	27.6	24.9	118.5
27	38.3	29.2	27.5	28.4	123.4
33	35.6	42.5	25.7	26.3	130.1
39	28.8	31.8	29.0	28.3	117.9
40	32.7	34.3	17.9	17.1	102.0
52	28.6	32.9	23.8	20.2	105.5
53	41.2	44.5	29.9	27.3	142.9

APPENDIX K

Individual Body Weights and Body Weight Gains of Subchronic Female Rats

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF SUBCHRONIC FEMALE RATS

EXPLANATORY NOTES

Notes

Day 31 data are presented for information only, and are not included in the summary tables, and were not analyzed statistically.

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC FEMALE RATS

GROUP: II CONCENTRATION: 0 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	31
ANIMAL #	MEAN BODY WEIGHT (grams)					
69	194.8	207.6	235.3	251.7	257.4	248.2
89	207.8	223.8	254.0	270.7	290.9	270.8
101	194.9	218.6	236.4	246.1	253.7	246.4
112	190.0	207.2	213.7	235.8	247.4	232.0
113	185.1	205.3	216.8	235.2	246.9	232.4
123	196.7	218.7	240.3	250.2	262.4	250.7
126	194.7	218.4	233.8	241.1	254.9	234.5
144	198.2	226.6	248.8	261.9	278.0	261.6
152	171.7	187.7	198.2	202.0	206.9	193.7
155	187.8	202.7	215.1	231.7	250.1	235.1
162	195.2	217.7	250.9	259.5	274.1	257.5
163	197.9	219.8	236.0	256.9	267.0	256.6

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
69	12.8	27.7	16.4	5.7	62.6
89	16.0	30.2	16.7	20.2	83.1
101	23.7	17.8	9.7	7.6	58.8
112	17.2	6.5	22.1	11.6	57.4
113	20.2	11.5	18.4	11.7	61.8
123	22.0	21.6	9.9	12.2	65.7
126	23.7	15.4	7.3	13.8	60.2
144	28.4	22.2	13.1	16.1	79.8
152	16.0	10.5	3.8	4.9	35.2
155	14.9	12.4	16.6	18.4	62.3
162	22.5	33.2	8.6	14.6	78.9
163	21.9	16.2	20.9	10.1	69.1

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC FEMALE RATS

GROUP: IV CONCENTRATION: 35 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	31
ANIMAL #	MEAN BODY WEIGHT (grams)					
71	175.6	194.0	215.7	237.5	243.8	232.6
75	208.4	228.2	256.8	268.1	286.9	265.5
83	203.5	217.1	242.9	254.4	265.8	251.8
107	203.0	218.8	227.5	233.1	249.1	237.0
119	178.7	209.3	223.3	237.6	254.1	234.6
120	192.9	194.6	205.5	222.4	240.0	233.5
128	198.3	212.4	224.3	242.9	252.1	232.7
138	194.8	213.3	236.8	251.7	274.7	249.0
145	170.2	187.0	213.4	232.5	236.7	228.6
149	186.2	217.5	228.9	241.8	247.4	233.6
160	194.2	210.9	230.4	251.5	268.6	243.8
164	181.7	195.0	216.3	225.3	245.3	228.7

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
71	18.4	21.7	21.8	6.3	68.2
75	19.8	28.6	11.3	18.8	78.5
83	13.6	25.8	11.5	11.4	62.3
107	15.8	8.7	5.6	16.0	46.1
119	30.6	14.0	14.3	16.5	75.4
120	1.7	10.9	16.9	17.6	47.1
128	14.1	11.9	18.6	9.2	53.8
138	18.5	23.5	14.9	23.0	79.9
145	16.8	26.4	19.1	4.2	66.5
149	31.3	11.4	12.9	5.6	61.2
160	16.7	19.5	21.1	17.1	74.4
164	13.3	21.3	9.0	20.0	63.6

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC FEMALE RATS

GROUP: VI CONCENTRATION: 125 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	31
ANIMAL #	MEAN BODY WEIGHT (grams)					
62	187.9	208.4	230.8	253.2	269.6	240.5
79	200.2	218.5	244.8	266.5	276.6	259.0
99	190.9	204.8	216.6	235.3	243.6	228.1
135	182.1	197.5	218.9	233.5	248.4	225.9
142	194.9	209.6	231.7	251.2	270.0	250.1
143	184.3	201.8	213.9	231.4	243.1	227.2
147	182.2	194.5	214.5	226.9	228.8	211.0
150	171.1	183.3	185.0	203.7	214.0	202.5
153	203.8	215.0	227.5	229.0	242.8	229.7
154	210.5	224.7	249.1	259.4	275.4	252.7
156	201.6	217.8	235.6	251.9	264.6	250.0
161	175.8	194.6	226.5	252.9	249.7	233.8

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
62	20.5	22.4	22.4	16.4	81.7
79	18.3	26.3	21.7	10.1	76.4
99	13.9	11.8	18.7	8.3	52.7
135	15.4	21.4	14.6	14.9	66.3
142	14.7	22.1	19.5	18.8	75.1
143	17.5	12.1	17.5	11.7	58.8
147	12.3	20.0	12.4	1.9	46.6
150	12.2	1.7	18.7	10.3	42.9
153	11.2	12.5	1.5	13.8	39.0
154	14.2	24.4	10.3	16.0	64.9
156	16.2	17.8	16.3	12.7	63.0
161	18.8	31.9	26.4	-3.2	73.9

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC FEMALE RATS

GROUP: VIII CONCENTRATION: 375 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	31
ANIMAL #	MEAN BODY WEIGHT (grams)					
67	189.1	198.7	218.0	228.9	242.4	222.8
68	193.7	218.2	233.8	251.9	256.0	239.0
70	195.4	221.4	243.6	239.7	256.6	237.6
76	202.6	218.6	229.3	243.3	248.8	238.3
77	185.2	197.1	202.0	221.0	231.2	210.0
84	201.7	222.1	231.5	253.5	250.4	240.5
88	174.1	191.5	208.6	227.8	240.6	218.1
114	175.3	194.1	199.4	207.6	220.8	204.2
129	212.1	232.9	244.9	264.6	273.0	255.9
146	181.3	191.9	202.5	223.6	230.5	214.8
151	179.7	196.8	208.6	221.9	233.3	222.9
159	179.7	209.0	223.3	247.4	253.3	236.1

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
67	9.6	19.3	10.9	13.5	53.3
68	24.5	15.6	18.1	4.1	62.3
70	26.0	22.2	-3.9	16.9	61.2
76	16.0	10.7	14.0	5.5	46.2
77	11.9	4.9	19.0	10.2	46.0
84	20.4	9.4	22.0	-3.1	48.7
88	17.4	17.1	19.2	12.8	66.5
114	18.8	5.3	8.2	13.2	45.5
129	20.8	12.0	19.7	8.4	60.9
146	10.6	10.6	21.1	6.9	49.2
151	17.1	11.8	13.3	11.4	53.6
159	29.3	14.3	24.1	5.9	73.6

APPENDIX L

Individual Food Consumption by Subchronic Male Rats During Premating

INDIVIDUAL FOOD CONSUMPTION BY SUBCHRONIC MALE RATS DURING PREMATING

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating period
Test Days 15-29 = Cohabitation period

Food consumption was not determined during or following the cohabitation period.

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC MALE RATS DURING PREMATING

GROUP: I CONCENTRATION: 0 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #			
1	24.1	26.6	25.4
8	23.8	24.8	24.3
10	26.6	26.4	26.5
12	27.6	29.6	28.6
13	24.6	27.0	25.8
22	23.6	24.1	23.9
31	24.0	26.3	25.2
36	22.3	24.1	23.2
41	24.9	25.7	25.3
44	23.9	29.4	26.6
45	22.9	24.9	23.9
54	28.1	30.6	29.3

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC MALE RATS DURING PREMATING

GROUP: III CONCENTRATION: 35 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #			
3	25.3	26.4	25.9
5	26.0	24.2	25.1
14	25.4	25.5	25.5
18	22.2	24.8	23.5
20	24.2	22.1	23.1
26	23.6	26.5	25.1
35	26.1	25.4	25.7
46	25.2	25.7	25.4
48	21.7	22.4	22.1
50	23.1	23.6	23.4
55	22.7	23.5	23.1
56	23.2	24.5	23.8

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC MALE RATS DURING PREMATING

GROUP: V CONCENTRATION: 125 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #			
4	22.7	21.6	22.1
9	20.6	22.7	21.6
25	21.8	23.2	22.5
28	22.7	24.9	23.8
30	22.1	25.2	23.6
32	22.6	22.8	22.7
37	22.9	20.7	21.8
38	24.3	25.3	24.8
43	21.6	23.1	22.3
47	21.8	24.7	23.2
49	19.0	21.6	20.3
51	24.0	24.0	24.0

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC MALE RATS DURING PREMATING

GROUP: VII CONCENTRATION: 375 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #			
2	21.6	24.0	22.8
6	22.1	24.3	23.2
11	21.0	22.1	21.5
16	21.9	24.5	23.2
19	20.6	23.1	21.8
21	21.7	23.9	22.8
27	22.7	22.7	22.7
33	22.6	25.2	23.9
39	22.5	24.0	23.2
40	20.4	23.5	21.9
52	21.6	24.7	23.2
53	25.5	28.4	27.0

APPENDIX M

Individual Food Consumption by Subchronic Female Rats

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC FEMALE RATS

GROUP: II CONCENTRATION: 0 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #					
69	16.9	18.4	18.3	16.9	17.6
89	19.0	21.7	19.7	18.9	19.8
101	17.5	18.6	17.5	16.9	17.6
112	19.4	20.9	20.0	17.6	19.5
113	17.0	17.4	17.4	16.4	17.0
123	18.6	21.3	18.1	19.1	19.3
126	19.7	20.8	18.4	18.3	19.3
144	20.5	22.9	21.0	19.9	21.0
152	15.5	16.1	15.9	13.9	15.3
155	17.1	17.6	17.9	18.5	17.8
162	18.7	20.9	20.2	19.3	19.8
163	20.6	20.3	21.2	19.8	20.5

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC FEMALE RATS

GROUP: IV CONCENTRATION: 35 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #					
71	18.4	19.4	19.5	19.3	19.2
75	18.2	19.9	18.1	19.0	18.8
83	18.2	20.5	20.0	20.0	19.7
107	17.1	18.1	17.2	17.5	17.5
119	17.7	17.7	17.3	16.8	17.4
120	15.9	16.9	16.5	17.4	16.7
128	19.0	21.4	19.5	19.3	19.8
138	18.6	19.9	19.9	20.9	19.8
145	17.0	20.5	18.7	15.3	17.9
149	17.4	18.9	17.4	17.9	17.9
160	17.5	19.9	21.0	20.3	19.7
164	16.6	19.6	18.1	18.1	18.1

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC FEMALE RATS

GROUP: VI CONCENTRATION: 125 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #					
62	17.3	18.7	21.0	20.3	19.3
79	17.2	20.6	19.6	18.2	18.9
99	16.1	18.3	16.6	17.8	17.2
135	17.2	18.6	18.7	17.6	18.0
142	18.3	21.3	20.9	19.5	20.0
143	16.2	17.1	17.7	16.2	16.8
147	14.9	18.2	17.1	15.3	16.4
150	13.6	14.6	15.0	15.0	14.5
153	18.5	19.2	18.3	18.9	18.7
154	19.5	22.0	20.3	18.3	20.0
156	17.7	18.6	18.7	18.8	18.4
161	16.3	20.0	20.3	15.6	18.1

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC FEMALE RATS

GROUP: VIII CONCENTRATION: 375 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #					
67	14.5	17.1	16.0	15.7	15.8
68	17.4	18.2	17.3	16.9	17.4
70	17.0	18.8	15.7	17.5	17.3
76	16.8	18.6	17.0	16.7	17.3
77	16.1	18.7	18.0	17.4	17.6
84	18.6	19.0	18.9	17.2	18.4
88	16.2	19.0	18.6	17.9	17.9
114	16.3	17.1	16.1	16.7	16.6
129	18.8	20.6	19.4	17.0	18.9
146	14.9	15.4	15.9	14.5	15.2
151	15.6	16.4	16.0	16.7	16.2
159	17.0	17.4	17.4	17.5	17.3

APPENDIX N

Individual Clinical Observations in Satellite Female Rats During Premating and Cohabitation

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING PREMATING AND COHABITATION

EXPLANATORY NOTES

Notes

Test Days 1-15	=	Premating Period
Test Days 15-29	=	Cohabitation Period

This appendix contains data for females during the premating and cohabitation periods. Postdosing clinical observations were recorded by exception. A "-" indicates that no signs were present for a given animal.

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING AND COHABITATION (PREDOSING)

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
57	NO ABNORMALITIES DETECTED		
59	NO ABNORMALITIES DETECTED		
72	NO ABNORMALITIES DETECTED		
82	NO ABNORMALITIES DETECTED		
87	NO ABNORMALITIES DETECTED		
90	ALOPECIA RIGHT FRONT LEG(S)	5	6
	ALOPECIA BOTH FRONT LEG(S)	7	15
91	NO ABNORMALITIES DETECTED		
94	NO ABNORMALITIES DETECTED		
109	NO ABNORMALITIES DETECTED		
118	NO ABNORMALITIES DETECTED		
121	NO ABNORMALITIES DETECTED		
132	NO ABNORMALITIES DETECTED		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING AND COHABITATION (PREDOSING)

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
60	NO ABNORMALITIES DETECTED		
64	NO ABNORMALITIES DETECTED		
100	NO ABNORMALITIES DETECTED		
102	NO ABNORMALITIES DETECTED		
103	NO ABNORMALITIES DETECTED		
105	NO ABNORMALITIES DETECTED		
106	NO ABNORMALITIES DETECTED		
115	NO ABNORMALITIES DETECTED		
116	NO ABNORMALITIES DETECTED		
117	ALOPECIA BOTH FRONT LEG(S)	6	15
140	NO ABNORMALITIES DETECTED		
165	NO ABNORMALITIES DETECTED		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING AND COHABITATION (PREDOSING)

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
61	NO ABNORMALITIES DETECTED		
78	NO ABNORMALITIES DETECTED		
85	NO ABNORMALITIES DETECTED		
86	NO ABNORMALITIES DETECTED		
97	NO ABNORMALITIES DETECTED		
104	NO ABNORMALITIES DETECTED		
110	NO ABNORMALITIES DETECTED		
122	NO ABNORMALITIES DETECTED		
130	NO ABNORMALITIES DETECTED		
131	ALOPECIA BOTH FRONT LEG(S)	6	15
137	NO ABNORMALITIES DETECTED		
157	NO ABNORMALITIES DETECTED		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING AND COHABITATION (PREDOSING)

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
63	NO ABNORMALITIES DETECTED		
65	NO ABNORMALITIES DETECTED		
66	NO ABNORMALITIES DETECTED		
73	ALOPECIA BOTH FRONT PAW(S)	1	15
	ALOPECIA BOTH FRONT LEG(S)	1	15
81	ALOPECIA BOTH FRONT PAW(S)	2	15
	ALOPECIA BOTH FRONT LEG(S)	7	15
92	NO ABNORMALITIES DETECTED		
95	NO ABNORMALITIES DETECTED		
96	NO ABNORMALITIES DETECTED		
125	NO ABNORMALITIES DETECTED		
127	NO ABNORMALITIES DETECTED		
133	NO ABNORMALITIES DETECTED		
166	NO ABNORMALITIES DETECTED		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING AND COHABITATION (POSTDOSING)

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
57	-		
59	-		
72	-		
82	-		
87	-		
90	-		
91	-		
94	-		
109	-		
118	-		
121	-		
132	-		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING AND COHABITATION (POSTDOSING)

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
60	-		
64	-		
100	-		
102	-		
103	-		
105	-		
106	-		
115	-		
116	-		
117	-		
140	-		
165	-		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING AND COHABITATION (POSTDOSING)

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
61	-		
78	-		
85	-		
86	-		
97	-		
104	-		
110	-		
122	-		
130	-		
131	-		
137	-		
157	-		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING AND COHABITATION (POSTDOSING)

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
63	-		
65	WET CHIN	9	20
66	-		
73	-		
81	-		
92	WET CHIN	1	9
95	-		
96	-		
125	-		
127	WET CHIN	19	23
133	-		
166	STAINED CHIN BROWN	1	1

APPENDIX O

Individual Clinical Observations in Satellite Female Rats During Gestation

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING GESTATION

EXPLANATORY NOTES

Note

This Appendix contains data from females with evidence of copulation observed (gestation days 0-21).

Postdosing clinical observations were recorded by exception. A "-" indicates that no signs were present for a given animal.

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (PREDOSING)

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
57	VAGINAL PLUG	0	0
59	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
72	VAGINAL PLUG	0	0
82	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
87	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
90	ALOPECIA BOTH FRONT LEG(S)	0	18
	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
94	VAGINAL PLUG	0	0
109	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
118	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
121	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA RIGHT FRONT LEG(S)	12	18
132	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (PREDOSING)

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
60	VAGINAL PLUG	0	0
64	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
100	VAGINAL PLUG	0	0
102	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
103	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
105	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA RIGHT FRONT PAW(S)	4	4
	ALOPECIA RIGHT FRONT LEG(S)	4	4
	ALOPECIA BOTH FRONT PAW(S)	5	21
	ALOPECIA BOTH FRONT LEG(S)	5	21
106	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA RIGHT FRONT PAW(S)	4	5
	ALOPECIA BOTH FRONT PAW(S)	6	22
115	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
116	ALOPECIA BOTH FRONT LEG(S)	0	21
	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
117	ALOPECIA BOTH FRONT LEG(S)	0	21
	ALOPECIA BOTH FRONT PAW(S)	0	21
	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
140	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
165	VAGINAL PLUG	0	0
	ALOPECIA BOTH FRONT PAW(S)	9	21
	ALOPECIA BOTH FRONT LEG(S)	9	21

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (PREDOSING)

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
61	VAGINAL PLUG	0	0
78	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
85	VAGINAL PLUG	0	0
86	VAGINAL PLUG	0	0
97	VAGINAL PLUG	0	0
	ALOPECIA BOTH FRONT PAW(S)	16	21
	ALOPECIA BOTH FRONT LEG(S)	18	21
104	SPERM POSITIVE	0	0
110	SPERM POSITIVE	0	0
122	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
130	VAGINAL PLUG	0	0
131	ALOPECIA BOTH FRONT LEG(S)	0	22
	VAGINAL PLUG	0	0
	ALOPECIA BOTH FRONT PAW(S)	1	22
137	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
157	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (PREDOSING)

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
63	VAGINAL PLUG	0	0
65	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	STAINED PERINEUM YELLOW	1	2
	ALOPECIA BOTH HIND QUARTERS	9	21
	ALOPECIA LEFT SIDE(S)	17	21
66	STAINED PERINEUM YELLOW	0	21
73	ALOPECIA BOTH FRONT PAW(S)	0	21
	ALOPECIA BOTH FRONT LEG(S)	0	21
	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
81	ALOPECIA BOTH FRONT PAW(S)	0	22
	ALOPECIA BOTH FRONT LEG(S)	0	22
	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
92	VAGINAL PLUG	0	0
95	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA BOTH FRONT LEG(S)	12	21
	ALOPECIA UNDERBODY	21	21
96	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
125	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
133	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
166	VAGINAL PLUG	0	0

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (POSTDOSING)

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
57	-		
59	-		
72	-		
82	-		
87	-		
90	-		
94	-		
109	-		
118	-		
121	-		
132	-		

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (POSTDOSING)

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
60	-		
64	-		
100	-		
102	-		
103	-		
105	-		
106	-		
115	-		
116	-		
117	-		
140	-		
165	-		

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (POSTDOSING)

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
61	-		
78	-		
85	-		
86	-		
97	-		
104	-		
110	-		
122	-		
130	-		
131	WET CHIN	9	9
137	-		
157	-		

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (POSTDOSING)

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
63	-		
65	WET CHIN	0	18
66	WET CHIN	3	5
73	-		
81	-		
92	WET CHIN	1	3
95	-		
96	-		
125	-		
133	-		
166	-		

APPENDIX P

Individual Clinical Observations and Mortality Data in Satellite Female Rats During Lactation

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN SATELLITE FEMALE RATS DURING LACTATION

EXPLANATORY NOTES

Notes

Test days for animal fates are determined from the initiation of test substance administration.

This appendix contains data from females that delivered a litter (lactation days 0-4).

Post dosing clinical observations were recorded by exception. A "-" indicates that no signs were present for a given animal.

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (PREDOSING)

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
57	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
59	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		
72	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
82	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 48		
87	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 42		
90	ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 44	0	4
91	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 49		
109	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 42		
121	ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 49	4	4
132	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (PREDOSING)

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
60	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 44		
64	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 42		
100	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 45		
102	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
103	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
105	ALOPECIA BOTH FRONT PAW(S)	0	4
	ALOPECIA BOTH FRONT LEG(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 43		
106	ALOPECIA BOTH FRONT PAW(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 44		
115	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 42		
116	ALOPECIA BOTH FRONT LEG(S)	0	4
	ALOPECIA BOTH FRONT PAW(S)	3	4
	SACRIFICED BY DESIGN TEST DAY 47		
117	ALOPECIA BOTH FRONT LEG(S)	0	4
	ALOPECIA BOTH FRONT PAW(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 47		
140	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
165	ALOPECIA BOTH FRONT PAW(S)	0	4
	ALOPECIA BOTH FRONT LEG(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 45		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (PREDOSING)

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
61	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 45		
85	ALOPECIA BOTH FRONT PAW(S)	1	4
	SACRIFICED BY DESIGN TEST DAY 45		
86	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 45		
97	ALOPECIA BOTH FRONT PAW(S)	0	4
	ALOPECIA BOTH FRONT LEG(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 45		
104	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
110	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
122	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 44		
130	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 45		
131	ALOPECIA BOTH FRONT LEG(S)	0	4
	ALOPECIA BOTH FRONT PAW(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 46		
137	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
157	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 44		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (PREDOSING)

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
63	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 44		
65	ALOPECIA BOTH HIND QUARTERS	0	4
	ALOPECIA LEFT SIDE(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 46		
66	STAINED PERINEUM YELLOW	0	4
	SACRIFICED BY DESIGN TEST DAY 45		
73	ALOPECIA BOTH FRONT PAW(S)	0	4
	ALOPECIA BOTH FRONT LEG(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 43		
81	ALOPECIA BOTH FRONT PAW(S)	0	4
	ALOPECIA BOTH FRONT LEG(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 44		
92	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
95	ALOPECIA BOTH FRONT LEG(S)	0	4
	ALOPECIA UNDERBODY	0	4
	SACRIFICED BY DESIGN TEST DAY 42		
96	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
125	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 45		
133	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 45		
166	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 45		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (POSTDOSING)

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
57	-		
59	-		
72	-		
82	-		
87	-		
90	-		
91	-		
94	-		
109	-		
121	-		
132	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (POSTDOSING)

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
60	-		
64	-		
100	-		
102	-		
103	-		
105	-		
106	-		
115	-		
116	-		
117	-		
140	-		
165	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (POSTDOSING)

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
61	-		
85	-		
86	-		
97	-		
104	-		
110	-		
122	-		
130	-		
131	-		
137	-		
157	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (POSTDOSING)

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
63	-		
65	-		
66	-		
73	-		
81	-		
92	-		
95	-		
96	-		
125	-		
133	-		
166	-		

APPENDIX Q

Individual Body Weights and Body Weight Gains of Satellite Females During Premating

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF SATELLITE FEMALE RATS DURING PREMATING

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating period

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS DURING PREMATING

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

DAYS ON TEST:	1	8	15
ANIMAL #	MEAN BODY WEIGHT (grams)		
57	197.9	208.6	221.2
59	195.6	211.7	234.3
72	199.6	219.2	236.9
82	198.4	222.9	245.4
87	186.8	206.6	223.6
90	172.4	190.7	210.1
91	188.5	212.2	226.0
94	191.2	204.1	210.7
109	189.4	194.7	212.5
118	202.2	221.6	236.6
121	189.9	210.6	215.7
132	196.0	209.2	237.9

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #			
57	10.7	12.6	23.3
59	16.1	22.6	38.7
72	19.6	17.7	37.3
82	24.5	22.5	47.0
87	19.8	17.0	36.8
90	18.3	19.4	37.7
91	23.7	13.8	37.5
94	12.9	6.6	19.5
109	5.3	17.8	23.1
118	19.4	15.0	34.4
121	20.7	5.1	25.8
132	13.2	28.7	41.9

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS DURING PREMATING

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

DAYS ON TEST:	1	8	15
ANIMAL #	MEAN BODY WEIGHT (grams)		
60	191.0	210.3	226.7
64	205.5	220.9	243.4
100	200.8	220.2	235.9
102	205.1	210.2	230.6
103	198.7	217.0	232.2
105	202.6	214.8	228.7
106	207.5	230.6	245.0
115	172.5	178.9	196.4
116	212.5	228.3	249.9
117	189.6	222.5	248.8
140	197.7	215.2	239.8
165	182.5	192.6	207.0

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)		
60	19.3	16.4	35.7
64	15.4	22.5	37.9
100	19.4	15.7	35.1
102	5.1	20.4	25.5
103	18.3	15.2	33.5
105	12.2	13.9	26.1
106	23.1	14.4	37.5
115	6.4	17.5	23.9
116	15.8	21.6	37.4
117	32.9	26.3	59.2
140	17.5	24.6	42.1
165	10.1	14.4	24.5

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS DURING PREMATING

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

DAYS ON TEST:	1	8	15
ANIMAL #	MEAN BODY WEIGHT (grams)		
61	199.1	213.3	224.9
78	185.9	198.7	200.6
85	181.3	192.1	197.4
86	178.4	194.8	200.0
97	189.7	205.4	212.2
104	189.2	211.9	219.1
110	181.9	194.8	209.3
122	186.1	208.8	221.4
130	189.2	200.5	217.2
131	190.8	207.9	220.3
137	198.2	215.0	236.2
157	200.9	215.1	226.0

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)		
61	14.2	11.6	25.8
78	12.8	1.9	14.7
85	10.8	5.3	16.1
86	16.4	5.2	21.6
97	15.7	6.8	22.5
104	22.7	7.2	29.9
110	12.9	14.5	27.4
122	22.7	12.6	35.3
130	11.3	16.7	28.0
131	17.1	12.4	29.5
137	16.8	21.2	38.0
157	14.2	10.9	25.1

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS DURING PREMATING

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

DAYS ON TEST:	1	8	15
ANIMAL #	MEAN BODY WEIGHT (grams)		
63	186.6	195.5	215.5
65	192.0	199.9	215.0
66	194.8	211.9	220.4
73	192.6	198.5	220.0
81	186.3	197.6	225.0
92	185.4	196.9	217.9
95	196.3	203.6	230.7
96	171.4	184.0	204.3
125	192.2	207.9	218.8
127	199.4	210.4	220.0
133	192.9	204.7	218.6
166	193.7	212.7	224.8

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)		
63	8.9	20.0	28.9
65	7.9	15.1	23.0
66	17.1	8.5	25.6
73	5.9	21.5	27.4
81	11.3	27.4	38.7
92	11.5	21.0	32.5
95	7.3	27.1	34.4
96	12.6	20.3	32.9
125	15.7	10.9	26.6
127	11.0	9.6	20.6
133	11.8	13.9	25.7
166	19.0	12.1	31.1

Study Title

Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats

Volume 2 of 2

TEST GUIDELINES: U.S. EPA Health Effects Test Guidelines
OPPTS 870.3650 (2000)

OECD Guideline for the Testing of Chemicals
Section 4: Health Effects, Number 422 (1996)

AUTHOR: Linda A. Malley, Ph.D., D.A.B.T.

STUDY COMPLETED ON: <IS>

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LABORATORY PROJECT ID: DuPont-13041

WORK REQUEST NUMBER: 14295

SERVICE CODE NUMBER: 1422

SPONSOR: American Chemistry Council
1300 Wilson Boulevard
Arlington, Virginia 22209
U.S.A.

SPONSOR STUDY NUMBER: OLF-92.0-HPV789-DHL

APPENDIX R

Individual Body Weights of Satellite Female Rats During Gestation

INDIVIDUAL BODY WEIGHTS OF SATELLITE FEMALE RATS DURING GESTATION

EXPLANATORY NOTES

Abbreviations

NLD = No litter delivered; data excluded from statistical analysis.
- = No Data

a = Evidence of copulation was not observed, but animal delivered a litter.
b = Evidence of copulation was not observed, and the animal did not deliver a litter.

INDIVIDUAL BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING GESTATION

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

GESTATION DAYS:	0	1	2	3	4	5	6
ANIMAL NUMBER							
57	239.2	245.7	248.3	257.2	256.5	264.1	270.2
59	238.9	247.4	248.9	259.0	262.4	270.2	277.8
72	255.1	262.1	271.6	278.3	287.7	297.1	298.9
82	267.6	285.6	280.9	290.5	295.4	302.8	307.3
87	224.4	239.0	248.3	256.0	266.2	271.2	277.2
90	219.8	230.1	232.2	235.3	244.8	244.6	250.6
91 a	-	-	-	-	-	-	-
94(NLD)	220.6	236.1	243.8	250.6	259.0	259.8	265.4
109	220.2	227.9	235.5	232.9	242.7	244.8	253.1
118(NLD)	237.5	249.8	258.9	260.1	264.7	271.9	277.3
121	251.1	260.5	266.5	270.6	277.8	287.6	291.0
132	241.4	248.7	257.8	261.0	272.5	274.6	280.6

GESTATION DAYS:	7	8	9	10	11	12	13
ANIMAL NUMBER							
57	272.3	277.4	282.8	289.4	290.6	304.9	299.3
59	281.0	285.3	282.5	298.4	304.5	308.4	318.7
72	303.3	310.0	316.9	324.8	327.8	335.2	337.0
82	312.1	316.9	319.7	330.8	332.7	338.4	352.9
87	275.7	283.3	288.5	299.6	304.8	312.6	314.9
90	250.6	260.6	260.4	266.9	277.0	277.7	279.9
91 a	-	-	-	-	-	-	-
94(NLD)	273.0	286.6	287.3	299.7	299.2	291.7	299.9
109	252.1	264.6	264.7	268.9	279.2	283.5	287.8
118(NLD)	283.9	289.6	293.2	308.1	306.1	296.9	300.3
121	293.9	297.7	302.6	309.1	314.3	324.3	321.0
132	286.6	292.2	302.4	310.9	314.7	315.3	322.6

INDIVIDUAL BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING GESTATION

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

GESTATION DAYS:	14	15	16	17	18	19	20
ANIMAL NUMBER							
57	307.5	312.8	327.1	335.8	346.1	364.1	371.4
59	321.7	335.3	339.2	354.2	372.8	386.9	402.4
72	348.0	354.2	366.8	384.1	400.5	413.7	439.1
82	350.0	354.8	364.3	370.8	394.2	404.8	431.4
87	321.4	335.9	339.7	356.7	375.8	392.4	399.7
90	286.1	291.0	295.5	311.3	312.6	317.6	327.5
91 a	-	-	-	-	-	-	-
94(NLD)	301.9	309.5	305.5	304.4	313.7	316.9	314.9
109	298.8	304.9	310.9	323.5	345.7	361.1	365.5
118(NLD)	298.3	300.8	296.8	296.2	294.0	295.5	304.1
121	331.3	340.3	347.9	359.0	372.9	390.4	406.5
132	326.9	333.2	331.6	345.9	362.4	384.4	393.8

GESTATION DAYS:	21
ANIMAL NUMBER	
57	360.1
59	414.0
72	437.0
82	447.9
87	424.2
90	339.0
91 a	-
94(NLD)	320.7
109	385.5
118(NLD)	306.9
121	426.9
132	410.5

INDIVIDUAL BODY WEIGHTS (grams) OF SATELLITE
FEMALE RATS DURING GESTATION

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

GESTATION DAYS:	0	1	2	3	4	5	6
ANIMAL NUMBER							
60	237.3	240.3	254.1	260.7	260.9	262.8	270.2
64	243.0	258.7	260.6	272.2	277.7	282.2	286.7
100	251.4	256.4	266.7	269.2	272.9	282.3	283.7
102	234.6	242.6	247.1	249.0	250.6	258.9	261.6
103	235.1	249.9	257.5	259.5	261.7	270.2	277.0
105	239.2	241.8	246.5	260.0	265.2	268.1	269.0
106	251.5	252.3	262.7	273.3	272.4	271.3	278.7
115	205.4	213.9	220.1	224.7	232.0	241.9	241.7
116	264.7	272.9	275.9	280.7	283.8	286.4	288.9
117	259.7	264.9	275.3	284.0	280.0	290.0	291.9
140	243.0	246.3	254.4	265.4	269.4	279.6	278.9
165	232.5	234.2	239.9	245.0	249.7	254.1	257.1

GESTATION DAYS:	7	8	9	10	11	12	13
ANIMAL NUMBER							
60	277.8	290.3	291.3	298.3	303.9	313.7	306.6
64	295.6	297.2	306.5	312.7	319.2	321.7	328.3
100	294.2	293.6	297.8	304.1	310.0	314.0	316.0
102	259.5	268.7	268.3	280.5	280.6	287.2	290.4
103	273.1	277.7	281.1	289.0	298.9	303.1	304.9
105	277.7	289.3	296.0	297.6	308.3	315.1	318.7
106	283.2	288.2	295.2	301.3	307.5	315.5	319.4
115	250.8	258.5	264.0	273.1	275.1	283.7	291.4
116	292.0	304.0	301.6	311.1	315.0	312.9	325.5
117	298.3	298.4	304.0	310.4	318.1	314.3	321.6
140	282.9	287.5	299.0	301.1	314.1	322.1	324.7
165	260.3	269.9	278.3	282.1	284.1	293.5	299.2

INDIVIDUAL BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING GESTATION

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

GESTATION DAYS:	14	15	16	17	18	19	20
ANIMAL NUMBER							
60	302.7	306.9	318.1	329.3	343.9	357.8	368.6
64	333.3	342.4	348.9	363.8	386.6	403.7	417.1
100	320.9	330.1	339.2	354.7	363.3	382.9	393.5
102	292.5	306.7	310.9	319.3	336.6	353.4	349.2
103	316.1	327.7	331.7	345.7	360.6	358.9	378.0
105	332.6	337.0	348.5	365.2	379.9	396.6	412.1
106	327.9	334.5	338.7	353.0	366.3	379.1	391.9
115	294.4	298.5	308.5	325.3	340.8	359.6	370.1
116	328.8	332.9	347.4	351.6	369.4	381.4	398.4
117	333.3	336.6	346.4	360.9	374.2	394.7	408.3
140	333.0	325.9	333.9	351.9	366.6	380.2	392.0
165	298.9	311.0	321.9	334.9	350.9	374.0	380.3

GESTATION DAYS:	21
ANIMAL NUMBER	
60	385.1
64	444.2
100	407.3
102	375.9
103	394.9
105	429.6
106	408.4
115	385.9
116	415.7
117	420.9
140	416.3
165	411.0

INDIVIDUAL BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING GESTATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

GESTATION DAYS:	0	1	2	3	4	5	6
ANIMAL NUMBER							
61	244.6	249.0	260.2	263.4	268.2	273.8	279.1
78(NLD)	202.0	218.3	221.7	231.3	237.5	239.5	252.4
85	217.1	225.8	228.2	234.8	235.0	242.3	242.9
86	221.4	231.0	239.4	247.3	246.1	253.3	257.9
97	217.5	226.6	231.3	229.8	235.8	239.5	242.8
104	225.3	233.6	236.3	238.7	242.5	246.6	246.4
110	218.1	222.6	227.7	233.4	239.4	240.7	247.1
122	228.6	232.6	240.1	240.1	248.0	252.2	260.5
130	230.3	235.2	240.4	244.1	251.0	258.5	262.0
131	245.3	255.9	251.8	268.6	268.5	279.0	281.0
137	248.3	257.2	257.7	269.0	272.0	278.2	280.4
157	233.0	238.4	243.0	249.2	252.9	254.3	256.6

GESTATION DAYS:	7	8	9	10	11	12	13
ANIMAL NUMBER							
61	284.4	283.0	293.7	300.5	300.9	312.2	312.2
78(NLD)	251.6	259.3	259.6	266.8	265.1	257.5	266.9
85	250.6	255.7	255.5	264.5	271.8	281.4	277.9
86	265.7	267.7	276.3	284.2	286.0	294.2	295.2
97	248.4	253.8	255.4	263.8	267.8	273.5	273.2
104	254.1	254.4	256.7	263.5	266.6	277.4	280.9
110	259.0	249.3	260.4	265.9	268.3	280.2	280.5
122	260.2	262.4	270.6	271.9	280.3	275.9	285.5
130	269.5	272.0	281.3	284.9	293.6	300.1	300.7
131	292.6	296.0	299.3	305.5	313.2	328.2	328.0
137	289.1	300.1	304.3	312.5	325.8	337.7	336.4
157	261.9	261.9	270.6	274.3	282.3	287.5	293.4

INDIVIDUAL BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING GESTATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

GESTATION DAYS:	14	15	16	17	18	19	20
ANIMAL NUMBER							
61	313.8	327.3	335.5	348.5	360.3	376.1	393.2
78(NLD)	271.8	272.5	276.0	274.7	280.7	284.6	279.8
85	284.7	294.8	308.0	316.5	328.1	348.4	359.6
86	297.5	306.8	320.4	327.1	343.2	360.4	366.2
97	278.8	289.9	289.7	304.8	316.2	326.2	338.0
104	281.4	289.9	295.0	306.3	319.2	335.3	347.5
110	294.6	296.5	302.2	318.3	327.6	343.4	357.5
122	291.5	289.2	296.5	314.8	328.6	342.2	350.4
130	305.9	314.5	325.2	337.5	354.9	375.6	376.0
131	339.1	351.0	360.4	376.0	391.4	416.6	437.5
137	352.3	358.6	370.9	388.3	407.3	421.5	435.8
157	299.3	302.8	309.2	329.4	341.1	347.3	358.7

GESTATION DAYS:	21
ANIMAL NUMBER	
61	413.1
78(NLD)	274.2
85	371.1
86	378.9
97	352.5
104	369.4
110	378.8
122	375.4
130	407.0
131	414.1
137	459.3
157	376.5

INDIVIDUAL BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING GESTATION

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

GESTATION DAYS:	0	1	2	3	4	5	6
ANIMAL NUMBER							
63	229.3	236.9	243.0	246.6	249.7	253.2	260.5
65	222.7	232.9	242.0	244.8	249.9	257.3	257.8
66	235.8	243.7	243.1	251.2	255.2	260.4	262.2
73	223.7	227.3	235.2	243.0	247.3	250.1	249.7
81	239.4	239.1	245.3	253.8	256.6	262.3	257.0
92	220.4	231.9	231.6	240.4	244.7	253.3	254.8
95	226.0	235.4	246.1	256.1	261.0	259.4	264.0
96	208.8	215.4	224.8	235.0	232.5	232.7	241.3
125	242.1	249.8	254.9	259.6	264.1	267.7	269.7
127(NLD),b	-	-	-	-	-	-	-
133	232.9	243.9	241.9	250.0	251.6	256.9	259.0
166	240.4	248.1	257.4	258.2	262.2	273.2	278.5

GESTATION DAYS:	7	8	9	10	11	12	13
ANIMAL NUMBER							
63	261.5	267.6	274.0	279.4	286.1	293.9	297.3
65	265.0	272.6	280.7	283.8	287.3	290.8	296.7
66	268.8	274.1	278.4	285.4	284.4	295.2	295.1
73	253.6	259.1	267.0	272.6	280.4	282.1	290.5
81	268.2	271.6	272.8	281.8	281.0	292.5	297.5
92	257.2	266.2	266.4	277.8	286.8	284.3	292.9
95	267.2	274.3	275.2	288.0	292.1	300.4	307.1
96	251.4	252.2	256.5	258.9	268.0	270.2	273.4
125	278.3	279.5	284.4	286.4	294.6	301.9	300.5
127(NLD),b	-	-	-	-	-	-	-
133	268.9	268.7	268.9	274.7	283.2	288.7	285.9
166	281.7	283.7	290.8	294.6	306.2	310.8	309.6

INDIVIDUAL BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING GESTATION

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

GESTATION DAYS:	14	15	16	17	18	19	20
ANIMAL NUMBER							
63	305.3	317.1	330.7	345.6	359.3	368.9	373.4
65	304.4	307.6	321.7	330.1	342.5	357.8	366.9
66	299.5	307.4	320.2	331.3	348.2	362.8	370.2
73	302.0	297.4	305.3	319.6	334.5	338.8	347.6
81	301.7	308.8	317.2	327.6	344.2	353.5	358.0
92	300.3	306.3	312.8	323.5	343.4	357.8	373.0
95	312.9	322.9	336.9	346.9	367.7	385.7	361.9
96	282.3	290.6	289.3	302.1	308.9	322.2	333.5
125	308.0	318.6	329.9	338.8	356.2	372.4	383.6
127(NLD),b	-	-	-	-	-	-	-
133	296.4	308.1	317.6	326.8	341.1	356.9	366.6
166	319.9	335.0	347.1	353.6	371.7	392.4	407.7

GESTATION DAYS:	21
ANIMAL NUMBER	
63	396.7
65	379.4
66	385.3
73	362.8
81	382.1
92	390.0
95	353.7
96	353.4
125	377.1
127(NLD),b	-
133	373.7
166	421.6

APPENDIX S

Individual Body Weight Gains of Satellite Female Rats During Gestation

INDIVIDUAL BODY WEIGHT GAINS OF SATELLITE
FEMALE RATS DURING GESTATION

EXPLANATORY NOTES

Abbreviations

NLD = No litter delivered; data excluded from statistical analysis.
- = No Data

a = Evidence of copulation was not observed, but animal delivered a litter.
b = Evidence of copulation was not observed, and the animal did not deliver a litter.

INDIVIDUAL BODY WEIGHT GAINS (grams) OF
SATELLITE FEMALE RATS DURING GESTATION

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NUMBER				
57	33.1	35.2	52.6	120.9
59	42.1	40.7	92.3	175.1
72	48.2	44.7	89.0	181.9
82	44.5	37.9	97.9	180.3
87	51.3	45.7	102.8	199.8
90	30.8	35.5	52.9	119.2
91 a	-	-	-	-
94(NLD)	52.4	28.9	18.8	100.1
109	31.9	46.7	86.7	165.3
118(NLD)	46.4	14.4	8.6	69.4
121	42.8	37.4	95.6	175.8
132	45.2	40.3	83.6	169.1

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NUMBER				
60	40.5	24.9	82.4	147.8
64	52.6	37.7	110.9	201.2
100	42.8	26.7	86.4	155.9
102	24.9	33.0	83.4	141.3
103	38.0	43.0	78.8	159.8
105	38.5	54.9	97.0	190.4
106	31.7	44.7	80.5	156.9
115	45.4	43.6	91.5	180.5
116	27.3	36.8	86.9	151.0
117	38.6	35.0	87.6	161.2
140	39.9	50.1	83.3	173.3
165	27.8	38.6	112.1	178.5

INDIVIDUAL BODY WEIGHT GAINS (grams) OF
SATELLITE FEMALE RATS DURING GESTATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NUMBER				
61	39.8	29.4	99.3	168.5
78(NLD)	49.6	20.2	2.4	72.2
85	33.5	34.1	86.4	154.0
86	44.3	31.8	81.4	157.5
97	30.9	30.4	73.7	135.0
104	28.8	27.3	88.0	144.1
110	40.9	35.6	84.2	160.7
122	31.6	31.3	83.9	146.8
130	39.2	36.4	101.1	176.7
131	47.3	46.5	75.0	168.8
137	40.8	63.2	107.0	211.0
157	28.9	37.4	77.2	143.5

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NUMBER				
63	32.2	43.8	91.4	167.4
65	42.3	39.4	75.0	156.7
66	33.0	30.7	85.8	149.5
73	29.9	48.4	60.8	139.1
81	28.8	33.5	80.4	142.7
92	36.8	43.1	89.7	169.6
95	41.2	45.7	40.8	127.7
96	42.6	30.9	71.1	144.6
125	36.2	29.7	69.1	135.0
127(NLD),b	-	-	-	-
133	36.0	27.5	77.3	140.8
166	41.3	38.2	101.7	181.2

APPENDIX T

Individual Body Weights and Body Weight Gains of Satellite Female Rats During Lactation

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF SATELLITE FEMALE RATS DURING LACTATION

EXPLANATORY NOTES

Abbreviations

- = No Data

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS
DURING LACTATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

LACTATION DAYS:	0	4
ANIMAL NUMBER	MEAN BODY WEIGHT (grams)	
57	305.4	323.8
59	302.9	318.6
72	348.4	365.8
82	338.9	358.9
87	316.0	336.6
90	286.4	303.3
91	298.1	310.5
94	-	-
109	270.6	306.5
118	-	-
121	330.6	333.9
132	305.8	331.4

LACTATION DAYS:	0-4
ANIMAL NUMBER	MEAN BODY WEIGHT GAINS (grams)
57	18.4
59	15.7
72	17.4
82	20.0
87	20.6
90	16.9
91	12.4
94	-
109	35.9
118	-
121	3.3
132	25.6

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS DURING LACTATION

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

LACTATION DAYS:	0	4
ANIMAL NUMBER	MEAN BODY WEIGHT (grams)	
60	330.3	305.6
64	321.6	339.3
100	319.1	319.7
102	278.1	312.1
103	299.9	333.2
105	315.1	324.1
106	300.3	249.5
115	285.4	298.8
116	299.3	327.6
117	313.5	337.8
140	308.2	340.2
165	292.7	326.7

LACTATION DAYS:	0-4
ANIMAL NUMBER	MEAN BODY WEIGHT GAINS (grams)
60	-24.7
64	17.7
100	0.6
102	34.0
103	33.3
105	9.0
106	-50.8
115	13.4
116	28.3
117	24.3
140	32.0
165	34.0

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS
DURING LACTATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

LACTATION DAYS:	0	4
ANIMAL NUMBER	MEAN BODY WEIGHT (grams)	
61	294.6	319.6
78	-	-
85	275.9	298.6
86	295.0	306.2
97	266.3	274.2
104	281.1	289.6
110	251.2	280.0
122	285.8	303.5
130	297.1	309.3
131	307.5	323.3
137	326.6	342.1
157	295.9	297.2

LACTATION DAYS:	0-4
ANIMAL NUMBER	MEAN BODY WEIGHT GAINS (grams)
61	25.0
78	-
85	22.7
86	11.2
97	7.9
104	8.5
110	28.8
122	17.7
130	12.2
131	15.8
137	15.5
157	1.3

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS DURING LACTATION

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

LACTATION DAYS:	0	4
ANIMAL NUMBER	MEAN BODY WEIGHT (grams)	
63	290.5	325.1
65	300.4	311.3
66	285.4	305.7
73	281.5	296.0
81	294.5	307.7
92	294.0	306.6
95	251.6	287.5
96	283.1	273.6
125	287.7	311.2
127	-	-
133	295.7	304.8
166	316.0	327.8

LACTATION DAYS:	0-4
ANIMAL NUMBER	MEAN BODY WEIGHT GAINS (grams)
63	34.6
65	10.9
66	20.3
73	14.5
81	13.2
92	12.6
95	35.9
96	-9.5
125	23.5
127	-
133	9.1
166	11.8

APPENDIX U

Individual Food Consumption by Satellite Female Rats During Premating

INDIVIDUAL FOOD CONSUMPTION BY SATELLITE FEMALE RATS DURING PREMATING

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating period
Test Days 15-29 = Cohabitation period

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SATELLITE FEMALE RATS DURING PREMATING

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL NUMBER			
57	16.0	17.8	16.9
59	17.7	21.8	19.8
72	16.1	19.3	17.7
82	18.2	18.0	18.1
87	18.3	19.2	18.7
90	15.7	19.1	17.4
91	17.8	20.4	19.1
94	18.1	19.0	18.5
109	17.0	21.0	19.0
118	18.8	20.5	19.6
121	17.1	19.6	18.4
132	19.1	22.6	20.9

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SATELLITE FEMALE RATS DURING PREMATING

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL NUMBER			
60	18.4	20.0	19.2
64	18.7	20.7	19.7
100	18.0	19.1	18.6
102	17.8	18.9	18.4
103	17.7	18.9	18.3
105	17.4	18.0	17.7
106	19.5	21.4	20.4
115	16.0	17.3	16.7
116	20.4	21.8	21.1
117	20.3	21.9	21.1
140	19.4	22.5	20.9
165	16.3	18.6	17.4

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SATELLITE FEMALE RATS DURING PREMATING

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL NUMBER			
61	15.6	19.1	17.3
78	16.6	17.3	17.0
85	16.9	17.9	17.4
86	16.7	16.8	16.7
97	15.0	16.0	15.5
104	15.9	16.2	16.0
110	16.6	18.6	17.6
122	16.1	17.8	17.0
130	15.2	16.5	15.8
131	19.2	21.1	20.1
137	17.8	19.2	18.5
157	16.9	17.3	17.1

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SATELLITE FEMALE RATS DURING PREMATING

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL NUMBER			
63	15.5	17.6	16.5
65	15.1	17.1	16.1
66	17.1	17.9	17.5
73	17.0	20.2	18.6
81	17.0	20.3	18.6
92	16.1	19.2	17.6
95	16.7	20.4	18.6
96	16.5	21.7	19.1
125	18.5	22.6	20.6
127	17.2	17.8	17.5
133	18.5	20.5	19.5
166	17.6	19.1	18.3

APPENDIX V

Individual Food Consumption by Satellite Female Rats During Gestation

INDIVIDUAL FOOD CONSUMPTION BY FEMALE RATS
DURING GESTATION

EXPLANATORY NOTES

Abbreviations

- = No Data
NLD = No litter delivered; data excluded from statistical analysis.

a = Evidence of copulation was not observed, but animal delivered a litter.
b = Evidence of copulation was not observed, and the animal did not deliver a litter.

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SATELLITE FEMALE RATS DURING GESTATION

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NUMBER				
57	21.7	22.5	23.2	22.5
59	26.0	26.4	26.2	26.2
72	23.3	26.5	27.4	25.7
82	27.6	28.0	27.5	27.7
87	25.5	27.4	29.8	27.6
90	19.6	21.9	21.5	21.0
91 a	-	-	-	-
94(NLD)	26.3	26.8	22.4	25.2
109	21.9	23.7	24.1	23.2
118(NLD)	24.5	24.3	18.1	22.3
121	24.9	25.7	26.7	25.8
132	26.3	27.9	26.5	26.9

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SATELLITE FEMALE RATS DURING GESTATION

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NUMBER				
60	24.8	25.9	23.5	24.7
64	26.2	27.2	26.6	26.7
100	23.3	24.7	24.5	24.2
102	20.7	21.4	24.6	22.2
103	22.6	22.7	21.5	22.3
105	22.6	26.0	27.0	25.2
106	22.8	25.2	25.5	24.5
115	22.3	24.2	24.3	23.6
116	23.5	23.5	23.8	23.6
117	23.4	22.8	26.2	24.1
140	26.9	28.4	25.1	26.8
165	23.0	25.1	24.7	24.3

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SATELLITE FEMALE RATS DURING GESTATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NUMBER				
61	23.9	23.5	23.9	23.8
78(NLD)	24.5	23.3	18.4	22.1
85	21.4	21.6	24.7	22.5
86	23.2	25.3	24.8	24.4
97	17.7	20.2	20.5	19.5
104	20.2	19.9	24.7	21.6
110	22.7	22.4	23.7	22.9
122	21.3	21.8	22.6	21.9
130	20.1	23.1	23.9	22.4
131	27.5	30.4	28.0	28.6
137	26.3	30.1	28.0	28.1
157	20.1	20.8	23.3	21.4

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SATELLITE FEMALE RATS DURING GESTATION

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NUMBER				
63	21.4	23.2	23.8	22.8
65	20.6	22.6	24.4	22.5
66	21.3	24.6	25.9	24.0
73	21.4	24.0	23.1	22.8
81	23.0	24.1	25.0	24.0
92	21.6	24.3	25.1	23.7
95	24.2	24.1	22.0	23.4
96	23.4	24.7	23.8	24.0
125	25.4	27.4	26.0	26.3
127(NLD),b	-	-	-	-
133	24.2	24.2	25.8	24.7
166	24.1	26.4	26.4	25.6

APPENDIX W

Individual Food Consumption by Satellite Female Rats During Lactation

INDIVIDUAL FOOD CONSUMPTION BY FEMALE RATS
DURING LACTATION

EXPLANATORY NOTES

Abbreviations

- = No Data

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SATELLITE FEMALE RATS DURING LACTATION

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

LACTATION DAYS:	0-4
ANIMAL NUMBER	
57	30.4
59	27.1
72	40.1
82	34.9
87	41.4
90	25.9
91	31.9
94	-
109	34.4
118	-
121	32.4
132	39.2

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SATELLITE FEMALE RATS DURING LACTATION

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

LACTATION DAYS:	0-4
ANIMAL NUMBER	
60	17.4
64	31.0
100	28.4
102	35.2
103	34.7
105	30.9
106	9.6
115	33.0
116	36.5
117	39.8
140	37.6
165	34.4

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SATELLITE FEMALE RATS DURING LACTATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

LACTATION DAYS:	0-4
ANIMAL NUMBER	
61	31.3
78	-
85	31.2
86	29.8
97	23.5
104	28.2
110	30.8
122	34.6
130	27.9
131	73.8
137	34.1
157	23.6

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SATELLITE FEMALE RATS DURING LACTATION

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

LACTATION DAYS:	0-4
ANIMAL NUMBER	
63	36.6
65	32.9
66	28.4
73	28.8
81	32.1
92	34.8
95	19.4
96	26.8
125	41.8
127	-
133	23.8
166	31.9

APPENDIX X

Individual Mating Data and Gestation Length: P_1 Generation

INDIVIDUAL MATING DATA AND GESTATION LENGTH: P_1 GENERATION

EXPLANATORY NOTES

Abbreviation

-- = No Data

INDIVIDUAL MATING DATA AND GESTATION LENGTH: P_1 GENERATION

GROUPS: II-0,I CONCENTRATION: 0 MG/KG/DAY

FEMALE ANIMAL#	MALE #1 ANIMAL#	PLUG OBSERVED	MALE #2 ANIMAL#	PLUG OBSERVED	LITTER PRODUCED	GESTATION LENGTH(days)
57	1	+			+	22
59	8	+			+	23
72	10	+			+	22
82	12	+			+	23
87	13	+			+	22
90	22	+			+	22
91	31	-			+	--
94	36	+			-	--
109	41	+			+	22
118	44	+			-	--
121	45	+			+	22
132	54	+			+	23

INDIVIDUAL MATING DATA AND GESTATION LENGTH: P_1 GENERATION

GROUPS: IV-0,III CONCENTRATION: 35 MG/KG/DAY

FEMALE ANIMAL#	MALE #1 ANIMAL#	PLUG OBSERVED	MALE #2 ANIMAL#	PLUG OBSERVED	LITTER PRODUCED	GESTATION LENGTH(days)
60	3	+			+	22
64	5	+			+	22
100	14	+			+	22
102	18	+			+	23
103	20	+			+	23
105	26	+			+	22
106	35	+			+	23
115	46	+			+	22
116	48	+			+	22
117	50	+			+	22
140	55	+			+	22
165	56	+			+	22

INDIVIDUAL MATING DATA AND GESTATION LENGTH: P_1 GENERATION

GROUPS: VI-0,V CONCENTRATION: 125 MG/KG/DAY

FEMALE ANIMAL#	MALE #1 ANIMAL#	PLUG OBSERVED	MALE #2 ANIMAL#	PLUG OBSERVED	LITTER PRODUCED	GESTATION LENGTH(days)
61	4	+			+	22
78	9	+			-	--
85	25	+			+	22
86	28	+			+	22
97	30	+			+	22
104	32	+			+	22
110	37	+			+	22
122	38	+			+	23
130	43	+			+	22
131	47	+			+	23
137	49	+			+	22
157	51	+			+	23

INDIVIDUAL MATING DATA AND GESTATION LENGTH: P_1 GENERATION

GROUPS: VIII-0,VII CONCENTRATION: 375 MG/KG/DAY

FEMALE ANIMAL#	MALE #1 ANIMAL#	PLUG OBSERVED	MALE #2 ANIMAL#	PLUG OBSERVED	LITTER PRODUCED	GESTATION LENGTH(days)
63	2	+			+	22
65	6	+			+	22
66	11	+			+	22
73	16	+			+	22
81	19	+			+	23
92	21	+			+	23
95	27	+			+	22
96	33	+			+	22
125	39	+			+	22
127	40	-			-	--
133	52	+			+	22
166	53	+			+	22

APPENDIX Y

Number of Pups Born, Number of Implantation Sites, Number of *Corporea Lutea*, and Implantation Efficiency

NUMBER OF PUPS BORN, NUMBER OF IMPLANTATION SITES, NUMBER OF *CORPORA LUTEA*, AND IMPLANTATION EFFICIENCY

EXPLANATORY NOTES

Abbreviations:

NLD = No litter delivered.

NUMBER OF PUPS BORN, NUMBER OF IMPLANTATION SITES, NUMBER OF *CORPORA LUTEA*, AND IMPLANTATION EFFICIENCY

Groups: II-0 DOSE: 0 MG/KG/DAY

Animal Number	Number Of Pups Born	Number Of Implantation Sites	Number Of *Corpora Lutea*	Implantation Efficiency (%)
57	12	13	13	92.3
59	16	16	17	100.0
72	15	17	19	88.2
82	13	14	14	92.9
87	15	15	15	100.0
90	5	10	11	50.0
91	16	16	19	100.0
94	NLD	-	NLD	NLD
109	15	15	15	100.0
118	NLD	-	NLD	NLD
121	15	16	16	93.8
132	14	16	16	87.5

Groups: IV-0 DOSE: 35 MG/KG/DAY

Animal Number	Number Of Pups Born	Number Of Implantation Sites	Number Of *Corpora Lutea*	Implantation Efficiency (%)
60	12	13	15	92.3
64	15	16	16	93.8
100	13	15	15	86.7
102	12	15	18	80.0
103	13	17	17	76.5
105	17	17	17	100.0
106	15	16	16	93.8
115	15	15	15	100.0
116	16	16	16	100.0
117	15	16	19	93.8
140	15	16	16	93.8
165	16	16	18	100.0

NUMBER OF PUPS BORN, NUMBER OF IMPLANTATION SITES, NUMBER OF *CORPORA LUTEA*, AND IMPLANTATION EFFICIENCY

Groups: VI-0 DOSE: 125 MG/KG/DAY

Animal Number	Number Of Pups Born	Number Of Implantation Sites	Number Of *Corpora Lutea*	Implantation Efficiency (%)
61	15	15	19	100.0
78	NLD	NLD	NLD	NLD
85	13	13	14	100.0
86	12	13	16	92.3
97	13	13	14	100.0
104	13	15	15	86.7
110	15	17	18	88.2
122	12	15	16	80.0
130	16	17	17	94.1
131	16	18	22	88.9
137	17	17	17	100.0
157	11	14	15	78.6

Groups: VIII-0 DOSE: 375 MG/KG/DAY

Animal Number	Number Of Pups Born	Number Of Implantation Sites	Number Of *Corpora Lutea*	Implantation Efficiency (%)
63	17	17	17	100.0
65	14	16	17	87.5
66	16	16	17	100.0
73	14	15	15	93.3
81	13	14	14	92.9
92	14	14	17	100.0
95	19	20	22	95.0
96	12	14	16	85.7
125	16	17	18	94.1
127	NLD	NLD	NLD	NLD
133	13	13	13	100.0
166	16	16	18	100.0

APPENDIX Z

Individual Litter Clinical Observations: F_1 Generation

INDIVIDUAL LITTER CLINICAL OBSERVATIONS: F_1 GENERATION

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	LACTATION DAY	SIGN INCIDENCE	OBSERVATIONS
57	NO ABNORMALITIES DETECTED		
59	NO ABNORMALITIES DETECTED		
72	NO ABNORMALITIES DETECTED		
82	NO ABNORMALITIES DETECTED		
87	NO ABNORMALITIES DETECTED		
90	NO ABNORMALITIES DETECTED		
91	NO ABNORMALITIES DETECTED		
109	NO ABNORMALITIES DETECTED		
121	NO ABNORMALITIES DETECTED		
132	NO ABNORMALITIES DETECTED		

INDIVIDUAL LITTER CLINICAL OBSERVATIONS: F_1 GENERATION

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

ANIMAL NUMBER	LACTATION DAY	SIGN INCIDENCE	OBSERVATIONS
60	NO ABNORMALITIES DETECTED		
64	NO ABNORMALITIES DETECTED		
100	NO ABNORMALITIES DETECTED		
102	DAY 0	1 OF 12	SMALL WHOLE BODY
	DAY 1	1 OF 12	SMALL WHOLE BODY
	DAY 4	1 OF 12	SMALL WHOLE BODY
	LITTER SUMMARY:	1	SMALL WHOLE BODY
103	NO ABNORMALITIES DETECTED		
105	NO ABNORMALITIES DETECTED		
106	NO ABNORMALITIES DETECTED		
115	NO ABNORMALITIES DETECTED		
116	NO ABNORMALITIES DETECTED		
117	NO ABNORMALITIES DETECTED		
140	NO ABNORMALITIES DETECTED		
165	NO ABNORMALITIES DETECTED		

INDIVIDUAL LITTER CLINICAL OBSERVATIONS: F_1 GENERATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

ANIMAL NUMBER	LACTATION DAY	SIGN INCIDENCE	OBSERVATIONS
61	NO ABNORMALITIES DETECTED		
85	NO ABNORMALITIES DETECTED		
86	NO ABNORMALITIES DETECTED		
97	NO ABNORMALITIES DETECTED		
104	NO ABNORMALITIES DETECTED		
110	NO ABNORMALITIES DETECTED		
122	NO ABNORMALITIES DETECTED		
130	NO ABNORMALITIES DETECTED		
131	NO ABNORMALITIES DETECTED		
137	NO ABNORMALITIES DETECTED		
157	NO ABNORMALITIES DETECTED		

INDIVIDUAL LITTER CLINICAL OBSERVATIONS: F_1 GENERATION

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

ANIMAL NUMBER	LACTATION DAY	SIGN INCIDENCE	OBSERVATIONS
63	NO ABNORMALITIES DETECTED		
65	NO ABNORMALITIES DETECTED		
66	NO ABNORMALITIES DETECTED		
73	NO ABNORMALITIES DETECTED		
81	DAY 0	1 OF 13	SMALL WHOLE BODY
	DAY 1	1 OF 13	SMALL WHOLE BODY
	DAY 4	1 OF 13	SMALL WHOLE BODY
	LITTER SUMMARY:	1	SMALL WHOLE BODY
92	NO ABNORMALITIES DETECTED		
95	NO ABNORMALITIES DETECTED		
96	NO ABNORMALITIES DETECTED		
125	NO ABNORMALITIES DETECTED		
133	NO ABNORMALITIES DETECTED		
166	NO ABNORMALITIES DETECTED		

APPENDIX AA

Individual Pup Survival: F_1 Generation

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

EXPLANATORY NOTES

Abbreviations

- = No Data

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

NUMBER OF PUPS

ANIMAL NUMBER	BORN	BORN ALIVE	DAY 1	DAY 4
57	12	12	12	12
59	16	16	16	16
72	15	15	15	15
82	13	13	13	13
87	15	15	15	15
90	5	5	5	5
91	16	16	16	16
94	-	-	-	-
109	15	15	15	15
118	-	-	-	-
121	15	15	15	15
132	14	14	14	14

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL NUMBER	BORN	BORN ALIVE	DAY 1	DAY 4
57	8	8	8	8
59	10	10	10	10
72	6	6	6	6
82	4	4	4	4
87	9	9	9	9
90	3	3	3	3
91	8	8	8	8
94	-	-	-	-
109	8	8	8	8
118	-	-	-	-
121	10	10	10	10
132	6	6	6	6

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

NUMBER OF FEMALE PUPS

ANIMAL NUMBER	BORN	BORN ALIVE	DAY 1	DAY 4
57	4	4	4	4
59	6	6	6	6
72	9	9	9	9
82	9	9	9	9
87	6	6	6	6
90	2	2	2	2
91	8	8	8	8
94	-	-	-	-
109	7	7	7	7
118	-	-	-	-
121	5	5	5	5
132	8	8	8	8

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

NUMBER OF PUPS

ANIMAL NUMBER	SEX RATIO (MALES)	% BORN ALIVE	0-4 DAY VIABILITY
57	0.67	100.0	100.0
59	0.63	100.0	100.0
72	0.40	100.0	100.0
82	0.31	100.0	100.0
87	0.60	100.0	100.0
90	0.60	100.0	100.0
91	0.50	100.0	100.0
94	-	-	-
109	0.53	100.0	100.0
118	-	-	-
121	0.67	100.0	100.0
132	0.43	100.0	100.0

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL NUMBER	% BORN ALIVE	0-4 DAY VIABILITY
57	100.0	100.0
59	100.0	100.0
72	100.0	100.0
82	100.0	100.0
87	100.0	100.0
90	100.0	100.0
91	100.0	100.0
94	-	-
109	100.0	100.0
118	-	-
121	100.0	100.0
132	100.0	100.0

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

NUMBER OF FEMALE PUPS

ANIMAL NUMBER	% BORN ALIVE	0-4 DAY VIABILITY
57	100.0	100.0
59	100.0	100.0
72	100.0	100.0
82	100.0	100.0
87	100.0	100.0
90	100.0	100.0
91	100.0	100.0
94	-	-
109	100.0	100.0
118	-	-
121	100.0	100.0
132	100.0	100.0

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

	NUMBER OF PUPS			
ANIMAL NUMBER	BORN	BORN ALIVE	DAY 1	DAY 4
60	12	12	12	12
64	15	15	15	15
100	13	13	13	13
102	12	12	12	12
103	13	13	13	13
105	17	17	17	17
106	15	15	15	15
115	15	15	15	15
116	16	16	16	16
117	15	15	15	15
140	15	15	15	15
165	16	16	16	16

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL NUMBER	BORN	BORN ALIVE	DAY 1	DAY 4
60	8	8	8	8
64	7	7	7	7
100	1	1	1	1
102	5	5	5	5
103	7	7	7	7
105	10	10	10	10
106	7	7	7	7
115	10	10	10	10
116	6	6	6	6
117	5	5	5	5
140	8	8	8	8
165	6	6	6	6

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

NUMBER OF FEMALE PUPS

ANIMAL NUMBER	BORN	BORN ALIVE	DAY 1	DAY 4
60	4	4	4	4
64	8	8	8	8
100	12	12	12	12
102	7	7	7	7
103	6	6	6	6
105	7	7	7	7
106	8	8	8	8
115	5	5	5	5
116	10	10	10	10
117	10	10	10	10
140	7	7	7	7
165	10	10	10	10

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

NUMBER OF PUPS

ANIMAL NUMBER	SEX RATIO (MALES)	% BORN ALIVE	0-4 DAY VIABILITY
60	0.67	100.0	100.0
64	0.47	100.0	100.0
100	0.08	100.0	100.0
102	0.42	100.0	100.0
103	0.54	100.0	100.0
105	0.59	100.0	100.0
106	0.47	100.0	100.0
115	0.67	100.0	100.0
116	0.38	100.0	100.0
117	0.33	100.0	100.0
140	0.53	100.0	100.0
165	0.38	100.0	100.0

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL NUMBER	% BORN ALIVE	0-4 DAY VIABILITY
60	100.0	100.0
64	100.0	100.0
100	100.0	100.0
102	100.0	100.0
103	100.0	100.0
105	100.0	100.0
106	100.0	100.0
115	100.0	100.0
116	100.0	100.0
117	100.0	100.0
140	100.0	100.0
165	100.0	100.0

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: IV-0 CONCENTRATION: 35 MG/KG/DAY

NUMBER OF FEMALE PUPS

ANIMAL NUMBER	% BORN ALIVE	0-4 DAY VIABILITY
60	100.0	100.0
64	100.0	100.0
100	100.0	100.0
102	100.0	100.0
103	100.0	100.0
105	100.0	100.0
106	100.0	100.0
115	100.0	100.0
116	100.0	100.0
117	100.0	100.0
140	100.0	100.0
165	100.0	100.0

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

NUMBER OF PUPS

ANIMAL NUMBER	BORN	BORN ALIVE	DAY 1	DAY 4
61	15	15	15	15
78	-	-	-	-
85	13	13	13	13
86	12	12	12	12
97	13	13	13	13
104	13	13	13	13
110	15	15	15	15
122	12	12	12	12
130	16	16	16	16
131	16	16	16	16
137	17	17	16	16
157	11	11	11	11

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL NUMBER	BORN	BORN ALIVE	DAY 1	DAY 4
61	7	7	7	7
78	-	-	-	-
85	8	8	8	8
86	6	6	6	6
97	3	3	3	3
104	6	6	6	6
110	7	7	7	7
122	10	10	10	10
130	9	9	9	9
131	5	5	5	5
137	5	5	5	5
157	6	6	6	6

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

NUMBER OF FEMALE PUPS

ANIMAL NUMBER	BORN	BORN ALIVE	DAY 1	DAY 4
61	8	8	8	8
78	-	-	-	-
85	5	5	5	5
86	6	6	6	6
97	10	10	10	10
104	7	7	7	7
110	8	8	8	8
122	2	2	2	2
130	7	7	7	7
131	11	11	11	11
137	12	12	11	11
157	5	5	5	5

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

NUMBER OF PUPS

ANIMAL NUMBER	SEX RATIO (MALES)	% BORN ALIVE	0-4 DAY VIABILITY
61	0.47	100.0	100.0
78	-	-	-
85	0.62	100.0	100.0
86	0.50	100.0	100.0
97	0.23	100.0	100.0
104	0.46	100.0	100.0
110	0.47	100.0	100.0
122	0.83	100.0	100.0
130	0.56	100.0	100.0
131	0.31	100.0	100.0
137	0.29	100.0	94.1
157	0.55	100.0	100.0

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL NUMBER	% BORN ALIVE	0-4 DAY VIABILITY
61	100.0	100.0
78	-	-
85	100.0	100.0
86	100.0	100.0
97	100.0	100.0
104	100.0	100.0
110	100.0	100.0
122	100.0	100.0
130	100.0	100.0
131	100.0	100.0
137	100.0	100.0
157	100.0	100.0

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: VI-0 CONCENTRATION: 125 MG/KG/DAY

NUMBER OF FEMALE PUPS

ANIMAL NUMBER	% BORN ALIVE	0-4 DAY VIABILITY
61	100.0	100.0
78	-	-
85	100.0	100.0
86	100.0	100.0
97	100.0	100.0
104	100.0	100.0
110	100.0	100.0
122	100.0	100.0
130	100.0	100.0
131	100.0	100.0
137	100.0	91.7
157	100.0	100.0

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

NUMBER OF PUPS

ANIMAL NUMBER	BORN	BORN ALIVE	DAY 1	DAY 4
63	17	17	17	17
65	14	14	14	14
66	16	16	16	16
73	14	14	14	14
81	13	13	13	13
92	14	13	13	13
95	19	19	14	14
96	12	12	12	12
125	16	16	16	16
127	-	-	-	-
133	13	12	12	12
166	16	15	15	15

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL NUMBER	BORN	BORN ALIVE	DAY 1	DAY 4
63	10	10	10	10
65	10	10	10	10
66	7	7	7	7
73	10	10	10	10
81	8	8	8	8
92	8	7	7	7
95	8	8	5	5
96	6	6	6	6
125	11	11	11	11
127	-	-	-	-
133	6	5	5	5
166	12	11	11	11

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

NUMBER OF FEMALE PUPS

ANIMAL NUMBER	BORN	BORN ALIVE	DAY 1	DAY 4
63	7	7	7	7
65	4	4	4	4
66	9	9	9	9
73	4	4	4	4
81	5	5	5	5
92	6	6	6	6
95	11	11	9	9
96	6	6	6	6
125	5	5	5	5
127	-	-	-	-
133	7	7	7	7
166	4	4	4	4

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

NUMBER OF PUPS

ANIMAL NUMBER	SEX RATIO (MALES)	% BORN ALIVE	0-4 DAY VIABILITY
63	0.59	100.0	100.0
65	0.71	100.0	100.0
66	0.44	100.0	100.0
73	0.71	100.0	100.0
81	0.62	100.0	100.0
92	0.57	92.9	100.0
95	0.42	100.0	73.7
96	0.50	100.0	100.0
125	0.69	100.0	100.0
127	-	-	-
133	0.46	92.3	100.0
166	0.75	93.8	100.0

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL NUMBER	% BORN ALIVE	0-4 DAY VIABILITY
63	100.0	100.0
65	100.0	100.0
66	100.0	100.0
73	100.0	100.0
81	100.0	100.0
92	87.5	100.0
95	100.0	62.5
96	100.0	100.0
125	100.0	100.0
127	-	-
133	83.3	100.0
166	91.7	100.0

INDIVIDUAL PUP SURVIVAL: F_1 GENERATION

GROUP: VIII-0 CONCENTRATION: 375 MG/KG/DAY

NUMBER OF FEMALE PUPS

ANIMAL NUMBER	% BORN ALIVE	0-4 DAY VIABILITY
63	100.0	100.0
65	100.0	100.0
66	100.0	100.0
73	100.0	100.0
81	100.0	100.0
92	100.0	100.0
95	100.0	81.8
96	100.0	100.0
125	100.0	100.0
127	-	-
133	100.0	100.0
166	100.0	100.0

APPENDIX BB

Individual Pup Weights: F_1 Generation

INDIVIDUAL PUP WEIGHTS: F_1 GENERATION

EXPLANATORY NOTES

Abbreviations

Blank Spaces = No Data

INDIVIDUAL PUP WEIGHTS (grams): F_1 GENERATION
Lactation Day 0

Group: II-0 Dose: 0 mg/kg/day

Animal Number	Pup Sex	PUP NUMBER 1	2	3	4	5	6	7	8	9	10
57	♂	7.5	6.9	6.8	6.9	7.2	6.0	6.7	7.1		
	♀	6.4	6.0	6.3	6.8						
59	♂	7.1	7.1	5.0	7.3	7.4	6.4	6.9	6.6	6.3	7.3
	♀	6.5	5.7	5.9	6.2	6.4	5.7				
72	♂	7.0	6.1	7.5	7.0	6.5	6.8				
	♀	7.0	6.8	6.0	6.1	6.1	6.8	6.4	6.4	6.2	
82	♂	8.1	8.0	8.1	7.5						
	♀	7.3	7.0	6.8	7.6	7.4	7.6	7.0	7.0	7.4	
87	♂	7.1	6.6	6.7	6.5	7.4	7.0	6.5	7.0	6.4	
	♀	6.2	5.8	5.7	6.9	6.5	6.5				
90	♂	7.4	8.0	7.1							
	♀	7.0	7.2								
91	♂	6.0	5.9	5.6	5.7	5.8	5.9	6.0	5.8		
	♀	6.1	5.3	6.1	5.3	5.4	5.6	5.8	5.4		
94	♂										
	♀										
109	♂	6.8	6.2	6.7	6.2	6.5	6.2	6.5	6.2		
	♀	6.5	6.3	6.1	6.2	6.1	6.1	6.0			
118	♂										
	♀										
121	♂	6.6	7.2	6.7	6.3	6.5	6.1	6.9	6.5	6.1	6.6
	♀	5.5	5.7	5.5	6.1	6.2					
132	♂	8.1	7.9	8.6	8.3	8.0	6.7				
	♀	7.4	7.7	7.2	8.1	7.7	7.9	7.9	7.3		

INDIVIDUAL PUP WEIGHTS (grams): F_1 GENERATION
Lactation Day 0

Group: IV-0 Dose: 35 mg/kg/day

Animal Number	Pup Sex	PUP NUMBER 1	2	3	4	5	6	7	8	9	10	11	12
60	♂	6.7	6.6	7.1	5.2	6.2	6.5	5.8	6.7				
	♀	5.1	5.8	5.5	5.7								
64	♂	6.1	6.1	6.4	5.8	6.2	6.2	5.4					
	♀	5.8	6.1	5.7	5.8	5.9	6.2	5.8	5.7				
100	♂	6.7											
	♀	5.7	6.7	6.6	6.2	6.2	6.1	5.9	6.6	6.2	6.5	6.3	5.7
102	♂	7.9	7.7	7.9	8.2	8.0							
	♀	7.1	7.4	7.4	7.5	7.4	7.3	3.0					
103	♂	7.1	6.7	7.1	7.9	6.7	7.7	7.4					
	♀	7.5	7.4	6.8	7.3	7.0	7.2						
105	♂	6.7	6.7	7.1	6.9	6.7	6.4	6.6	6.7	6.5	6.7		
	♀	6.3	6.3	5.7	5.9	6.2	5.9	6.2					
106	♂	6.9	7.2	6.9	7.2	6.7	6.8	7.2					
	♀	6.5	6.2	5.8	7.1	6.6	6.9	5.8	6.9				
115	♂	6.0	6.6	6.0	6.2	6.6	5.8	6.4	6.4	6.3	5.8		
	♀	6.4	6.5	5.7	6.1	6.3							
116	♂	6.6	6.1	6.8	5.7	6.0	6.3						
	♀	6.2	5.9	6.5	6.4	6.5	5.8	6.0	6.1	6.5	5.9		
117	♂	7.0	6.4	7.0	6.3	6.4							
	♀	6.0	6.2	6.8	5.9	6.3	5.7	5.8	5.9	6.3	6.1		
140	♂	6.6	7.1	7.1	7.3	7.3	7.3	6.2	6.7				
	♀	6.6	6.7	6.8	6.4	6.4	7.1	6.9					
165	♂	6.6	6.1	6.3	6.2	6.2	6.4						
	♀	5.2	5.2	5.8	5.8	5.9	5.7	6.0	5.4	6.3	5.9		

INDIVIDUAL PUP WEIGHTS (grams): F_1 GENERATION
Lactation Day 0

Group: VI-0 Dose: 125 mg/kg/day

Animal Number	Pup Sex	PUP NUMBER 1	2	3	4	5	6	7	8	9	10	11	12
61	♂	6.0	5.5	5.4	6.2	6.2	6.4	6.4					
	♀	6.3	5.8	6.2	5.9	5.9	6.1	5.5	5.4				
78	♂												
	♀												
85	♂	6.5	6.3	6.3	6.8	6.2	6.5	6.6	6.9				
	♀	6.5	6.4	6.1	5.8	6.7							
86	♂	6.7	6.1	5.5	6.8	6.5	6.7						
	♀	6.2	6.1	6.0	6.2	6.2	6.1						
97	♂	6.3	6.4	6.1									
	♀	6.0	5.3	5.7	6.1	5.7	6.0	6.0	5.6	5.6	5.1		
104	♂	6.3	6.8	6.8	7.1	7.1	6.8						
	♀	6.5	6.5	6.6	6.6	6.5	6.3	6.7					
110	♂	6.9	6.9	6.0	6.8	6.5	6.7	6.5					
	♀	6.3	5.8	6.0	6.2	6.2	6.3	6.0	6.2				
122	♂	7.4	7.0	7.3	7.4	7.0	6.7	7.1	6.7	7.2	6.9		
	♀	6.1	6.8										
130	♂	6.6	5.9	6.4	6.8	6.2	6.5	5.8	7.7	6.2			
	♀	6.7	5.9	5.7	5.7	5.8	6.3	5.4					
131	♂	7.9	8.1	7.1	7.3	7.2							
	♀	6.8	6.6	6.9	6.8	6.9	6.6	7.2	6.4	6.9	6.9	7.5	
137	♂	6.6	6.0	7.5	6.8	6.3							
	♀	6.1	6.5	6.0	6.1	6.1	5.8	6.2	4.0	6.2	5.9	6.1	6.2
157	♂	7.9	7.3	7.4	7.7	7.6	7.5						
	♀	7.3	7.1	7.1	7.0	7.1							

INDIVIDUAL PUP WEIGHTS (grams): F_1 GENERATION
Lactation Day 0

Group: VIII-0 Dose: 375 mg/kg/day

Animal Number	Pup Sex	PUP NUMBER 1	2	3	4	5	6	7	8	9	10	11
63	♂	5.7	6.0	5.7	5.8	6.0	6.0	5.8	5.5	6.1	5.5	
	♀	5.4	5.5	5.5	5.1	5.2	5.3	5.5				
65	♂	6.2	5.8	6.0	5.8	6.1	5.9	6.1	5.8	5.6	6.2	
	♀	5.4	5.7	5.7	5.7							
66	♂	5.8	4.7	5.5	6.0	5.8	6.0	5.7				
	♀	5.4	5.6	5.8	5.3	5.8	5.8	5.5	5.6	5.7		
73	♂	5.8	6.3	5.5	6.6	5.9	6.0	6.4	5.6	5.4	5.9	
	♀	5.6	5.6	5.5	5.7							
81	♂	8.1	7.1	8.0	7.2	7.8	8.1	8.1	7.9			
	♀	7.5	7.5	7.0	7.5	3.5						
92	♂	7.1	7.0	7.4	7.5	5.9	6.3	6.2				
	♀	6.6	7.0	6.2	6.6	6.4	6.1					
95	♂	4.6	4.5	4.5	4.8	4.9	4.9	4.3	4.3			
	♀	4.4	4.0	4.6	4.6	4.6	4.6	4.2	3.6	4.0	4.7	4.1
96	♂	6.7	6.4	6.3	6.5	6.1	6.2					
	♀	5.8	5.1	5.9	6.2	6.1	5.4					
125	♂	5.8	5.5	5.8	5.9	6.0	5.7	6.3	5.8	5.2	5.7	5.7
	♀	5.8	5.2	6.1	5.4	5.5						
127	♂											
	♀											
133	♂	6.4	6.1	6.0	6.9	6.2						
	♀	5.9	5.9	5.9	6.2	5.5	6.2	6.0				
166	♂	7.4	5.2	6.9	7.5	6.9	7.2	7.2	6.5	6.5	6.4	6.2
	♀	5.9	7.0	6.4	6.4							

INDIVIDUAL PUP WEIGHTS (grams): F_1 GENERATION
Lactation Day 1

Group: II-0 Dose: 0 mg/kg/day

Animal Number	Pup Sex	PUP NUMBER 1	2	3	4	5	6	7	8	9	10
57	♂	8.5	7.7	7.6	7.6	7.8	7.8	6.6	7.3		
	♀	7.3	6.7	6.8	6.8						
59	♂	6.0	4.8	7.5	7.7	7.2	8.0	8.0	7.4	6.8	8.2
	♀	6.2	7.3	5.8	6.5	6.8	7.2				
72	♂	8.1	7.5	7.5	7.9	8.2	6.8				
	♀	6.8	7.6	6.6	6.9	6.7	7.3	7.7	6.7	7.8	
82	♂	8.9	9.1	9.0	9.3						
	♀	8.5	8.0	7.7	8.5	8.0	8.6	8.5	8.3	7.7	
87	♂	7.1	8.3	7.7	7.8	7.8	7.0	8.0	7.8	7.4	
	♀	7.9	6.8	7.6	7.9	7.0	6.3				
90	♂	8.6	9.2	8.6							
	♀	8.6	8.2								
91	♂	6.4	6.3	6.9	6.5	6.3	6.7	6.8	6.5		
	♀	6.3	6.1	6.4	6.7	6.8	5.9	6.3	5.9		
94	♂										
	♀										
109	♂	6.6	7.4	6.9	7.2	6.8	7.1	7.2	6.7		
	♀	6.5	7.3	6.8	6.4	7.5	6.5	6.6			
118	♂										
	♀										
121	♂	7.4	7.1	6.8	7.8	8.0	8.0	7.5	6.9	7.9	7.4
	♀	6.0	6.1	6.9	6.7	6.9					
132	♂	8.9	9.1	9.1	7.4	9.4	8.8				
	♀	8.7	8.5	8.2	8.7	8.3	9.1	8.0	8.9		

INDIVIDUAL PUP WEIGHTS (grams): F_1 GENERATION
Lactation Day 1

Group: IV-0 Dose: 35 mg/kg/day

Animal Number	Pup Sex	PUP NUMBER 1	2	3	4	5	6	7	8	9	10	11	12
60	♂	8.9	5.8	7.9	8.0	7.2	6.9	7.9	7.3				
	♀	7.0	7.0	6.0	6.6								
64	♂	6.9	7.0	6.9	6.6	6.5	6.1	6.5					
	♀	6.7	6.1	6.8	6.9	6.5	6.2	6.2	6.4				
100	♂	8.1											
	♀	8.0	8.0	7.3	6.7	8.0	7.7	7.4	7.2	7.4	7.1	7.5	7.7
102	♂	8.9	8.6	8.9	9.0	8.8							
	♀	7.9	8.1	8.1	8.5	8.5	3.6	8.2					
103	♂	8.6	7.8	7.8	8.5	8.4	7.5	7.6					
	♀	8.5	7.6	8.0	8.1	8.4	8.2						
105	♂	7.3	7.1	7.6	6.8	7.3	7.6	7.1	7.6	7.5	7.3		
	♀	6.8	6.9	7.0	6.8	6.2	7.3	6.3					
106	♂	7.0	7.1	7.7	7.5	7.5	7.2	7.5					
	♀	6.3	7.3	7.2	7.7	6.8	6.8	7.4	6.5				
115	♂	6.8	7.6	6.8	7.0	7.5	6.8	7.0	7.5	7.5	7.4		
	♀	7.1	6.9	6.8	7.5	7.4							
116	♂	6.7	7.4	6.5	7.3	6.5	6.4						
	♀	6.6	7.4	6.8	7.2	6.8	7.3	6.5	6.6	6.8	6.9		
117	♂	7.8	7.5	7.6	6.9	8.2							
	♀	7.1	7.0	6.5	6.5	7.2	7.9	6.5	6.5	6.9	7.3		
140	♂	6.8	7.3	7.7	7.2	7.6	7.6	8.0	7.6				
	♀	7.0	7.7	6.9	7.5	6.8	7.0	7.3					
165	♂	7.5	6.8	6.9	6.4	6.8	6.6						
	♀	6.3	5.9	6.4	7.1	5.8	6.0	6.7	6.7	6.6	6.5		

INDIVIDUAL PUP WEIGHTS (grams): F_1 GENERATION
Lactation Day 1

Group: VI-0 Dose: 125 mg/kg/day

Animal Number	Pup Sex	PUP NUMBER 1	2	3	4	5	6	7	8	9	10	11
61	♂	7.6	6.4	6.8	7.2	6.7	6.0	6.8				
	♀	6.5	6.8	6.7	6.8	6.1	6.9	6.1	6.9			
78	♂											
	♀											
85	♂	7.5	7.4	7.0	7.6	7.8	7.2	7.6	7.0			
	♀	7.2	6.5	7.3	7.6	7.6						
86	♂	7.4	7.1	7.2	7.9	6.4	7.6					
	♀	6.8	7.2	7.3	7.0	7.1	7.5					
97	♂	7.3	7.3	6.6								
	♀	6.2	6.0	6.5	5.8	6.8	6.4	7.0	7.1	6.6	6.6	
104	♂	7.5	7.8	7.3	7.7	7.4	6.7					
	♀	7.1	7.0	7.1	7.4	6.9	7.2	6.9				
110	♂	6.8	6.7	6.3	6.8	6.9	7.4	6.6				
	♀	6.6	6.6	6.0	6.3	6.7	6.5	6.3	6.3			
122	♂	8.3	8.2	7.9	8.3	7.6	7.7	8.0	7.8	8.2	8.1	
	♀	7.9	7.3									
130	♂	6.9	7.5	7.6	6.7	6.9	6.9	6.2	6.9	6.5		
	♀	6.1	6.5	6.4	6.3	6.3	7.0	5.9				
131	♂	7.4	7.8	7.8	8.7	7.9						
	♀	7.3	7.1	7.0	8.0	7.4	7.9	7.0	7.7	8.0	7.4	7.6
137	♂	7.3	7.4	7.1	7.2	7.2						
	♀	6.6	6.8	7.0	6.8	6.5	6.6	7.0	6.6	7.1	6.8	7.0
157	♂	8.2	8.6	7.9	8.4	8.7	8.3					
	♀	7.8	7.7	8.0	7.8	7.9						

INDIVIDUAL PUP WEIGHTS (grams): F_1 GENERATION
Lactation Day 1

Group: VIII-0 Dose: 375 mg/kg/day

Animal Number	Pup Sex	PUP NUMBER 1	2	3	4	5	6	7	8	9	10	11
63	♂	6.8	6.3	6.2	6.3	6.5	6.4	6.0	6.3	6.0	5.5	
	♀	5.2	6.0	5.8	5.8	5.9	6.1	5.6				
65	♂	7.0	6.4	7.0	6.7	6.6	6.9	6.7	6.9	6.9	6.1	
	♀	6.4	6.2	6.4	6.6							
66	♂	7.0	6.1	6.4	5.7	6.4	6.2	4.8				
	♀	5.6	6.1	6.2	6.0	5.8	5.9	6.0	6.4	5.8		
73	♂	7.2	7.2	6.3	6.5	6.3	7.1	6.8	6.4	6.0	7.0	
	♀	6.3	6.3	6.4	6.4							
81	♂	8.2	8.7	7.9	8.3	8.6	8.4	7.6	8.6			
	♀	8.2	8.1	8.1	7.7	4.0						
92	♂	6.6	7.5	8.2	7.4	7.1	8.1	7.6				
	♀	7.3	6.9	6.8	7.2	7.9	7.4					
95	♂	4.3	4.0	4.6	4.7	4.5						
	♀	4.3	4.0	4.6	4.0	3.8	4.0	4.5	3.4	4.6		
96	♂	7.7	7.8	7.1	7.5	7.6	7.6					
	♀	6.1	7.7	6.8	6.9	6.9	6.1					
125	♂	6.5	6.5	5.7	6.2	6.3	6.5	6.2	6.3	6.2	6.6	6.6
	♀	5.9	5.8	6.6	6.6	6.1						
127	♂											
	♀											
133	♂	6.8	6.6	7.3	6.0	7.0						
	♀	6.8	6.8	7.0	6.6	6.1	5.7	6.0				
166	♂	6.9	7.4	6.7	8.0	6.0	8.2	7.4	7.5	6.7	7.3	7.0
	♀	6.7	6.8	6.5	7.2							

INDIVIDUAL PUP WEIGHTS (grams): F_1 GENERATION
Lactation Day 4

Group: II-0 Dose: 0 mg/kg/day

Animal Number	Pup Sex	PUP NUMBER 1	2	3	4	5	6	7	8	9	10
57	♂	11.0	10.5	11.7	11.8	10.0	10.5	11.5	11.8		
	♀	11.0	10.3	10.0	9.9						
59	♂	8.1	9.4	7.9	10.0	10.8	10.4	10.9	7.9	6.5	9.8
	♀	7.6	10.6	9.6	9.0	7.7	6.5				
72	♂	9.8	11.4	11.5	10.8	10.9	11.2				
	♀	10.3	10.8	10.4	10.1	10.3	9.1	11.3	11.4	9.5	
82	♂	13.5	14.3	13.7	13.8						
	♀	11.0	13.4	12.4	11.8	12.5	12.6	12.7	12.5	11.8	
87	♂	12.4	12.2	12.8	11.9	12.4	12.9	13.1	11.6	12.7	
	♀	10.1	11.6	12.2	10.0	10.5	12.0				
90	♂	15.2	14.2	14.3							
	♀	14.3	14.0								
91	♂	9.4	10.1	9.2	9.2	9.9	10.4	8.8	9.9		
	♀	9.5	9.3	9.6	8.7	10.0	10.0	9.3	8.4		
94	♂										
	♀										
109	♂	10.6	9.4	9.9	9.7	9.9	10.0	9.8	9.4		
	♀	9.4	9.5	9.4	9.6	10.4	9.5	8.6			
118	♂										
	♀										
121	♂	11.4	10.7	10.8	10.4	9.7	10.4	11.5	10.3	10.9	11.0
	♀	10.2	8.7	10.0	9.1	9.9					
132	♂	13.2	13.1	13.2	13.1	12.9	11.8				
	♀	13.8	12.4	12.8	12.6	12.9	13.0	12.0	13.2		

INDIVIDUAL PUP WEIGHTS (grams): F_1 GENERATION
Lactation Day 4

Group: IV-0 Dose: 35 mg/kg/day

Animal Number	Pup Sex	PUP NUMBER 1	2	3	4	5	6	7	8	9	10	11	12
60	♂	10.6	9.9	10.2	9.4	9.3	10.4	10.4	7.8				
	♀	9.3	8.2	9.5	9.2								
64	♂	9.6	10.2	10.2	9.6	10.4	8.5	9.6					
	♀	10.1	10.0	9.1	9.9	9.5	9.1	9.6	9.5				
100	♂	11.5											
	♀	10.7	11.3	11.2	11.2	12.0	10.4	11.2	11.5	10.9	10.6	12.0	9.8
102	♂	12.8	13.0	12.7	13.2	12.5							
	♀	12.4	12.1	12.1	12.9	11.5	5.2	11.6					
103	♂	12.1	11.0	11.4	11.6	11.7	11.0	11.5					
	♀	11.7	11.9	11.7	10.8	11.8	12.1						
105	♂	9.5	10.3	9.6	9.9	9.6	10.1	9.5	10.9	9.4	9.9		
	♀	9.2	8.8	9.1	8.5	8.5	8.8	9.2					
106	♂	8.4	8.6	7.9	8.3	8.3	8.6	8.0					
	♀	7.7	7.9	8.2	7.5	8.1	8.4	7.9	7.9				
115	♂	10.6	10.4	11.7	10.8	9.6	10.6	9.8	10.4	10.1	8.7		
	♀	10.2	10.1	9.9	10.6	10.9							
116	♂	9.3	10.9	11.0	9.6	8.9	9.0						
	♀	10.9	9.3	10.2	10.4	9.6	9.7	10.8	10.5	10.7	9.7		
117	♂	11.8	11.4	11.9	12.2	10.7							
	♀	10.2	11.7	10.4	10.8	10.6	11.4	10.5	10.5	10.3	12.1		
140	♂	10.3	10.4	10.7	11.7	10.1	10.8	11.3	10.9				
	♀	9.9	10.8	10.2	10.6	9.8	11.0	10.4					
165	♂	9.4	9.3	9.8	9.4	9.5	9.4						
	♀	8.7	9.8	9.4	8.0	9.3	8.3	8.6	9.5	8.5	9.0		

INDIVIDUAL PUP WEIGHTS (grams): F_1 GENERATION
Lactation Day 4

Group: VI-0 Dose: 125 mg/kg/day

Animal Number	Pup Sex	PUP NUMBER 1	2	3	4	5	6	7	8	9	10	11
61	♂	9.9	11.3	10.7	9.2	10.4	9.5	9.1				
	♀	10.2	10.0	9.0	9.4	9.5	9.1	10.7	9.5			
78	♂											
	♀											
85	♂	10.1	11.4	10.4	11.7	10.2	10.5	10.3	10.1			
	♀	9.2	10.7	10.2	9.0	10.5						
86	♂	9.3	12.1	12.0	11.8	11.7	10.6					
	♀	11.4	10.7	11.5	11.0	10.9	11.5					
97	♂	9.8	10.1	10.1								
	♀	9.1	8.7	9.6	9.5	9.0	9.3	9.1	9.4	9.2	9.8	
104	♂	10.4	11.0	9.6	10.6	10.3	10.3					
	♀	10.2	9.7	9.9	10.5	9.3	9.8	10.1				
110	♂	10.2	10.4	9.4	8.8	10.0	9.1	9.2				
	♀	8.7	7.6	9.3	9.4	9.5	9.5	9.5	8.8			
122	♂	12.6	12.5	12.1	13.1	12.7	11.9	12.8	11.9	12.8	12.2	
	♀	12.0	11.4									
130	♂	10.1	9.7	9.5	9.2	9.2	9.7	8.5	9.2	8.9		
	♀	9.0	9.0	8.8	10.0	8.8	9.8	9.0				
131	♂	11.0	10.8	10.3	11.1	12.9						
	♀	11.2	10.7	11.4	11.5	10.5	10.8	11.1	11.3	10.3	9.6	10.3
137	♂	9.8	10.5	10.6	10.9	11.7						
	♀	10.9	9.4	10.0	10.9	10.0	10.4	9.9	10.2	9.5	10.1	10.6
157	♂	12.1	11.8	11.7	11.4	11.3	11.7					
	♀	11.2	11.5	10.7	10.7	11.2						

INDIVIDUAL PUP WEIGHTS (grams): F_1 GENERATION
Lactation Day 4

Group: VIII-0 Dose: 375 mg/kg/day

Animal Number	Pup Sex	PUP NUMBER 1	2	3	4	5	6	7	8	9	10	11
63	♂	9.2	9.0	9.6	9.3	9.7	9.0	8.6	9.2	9.1	8.8	
	♀	8.8	8.7	7.7	9.2	9.0	7.9	9.1				
65	♂	10.4	10.1	9.6	9.5	10.1	10.1	9.9	7.9	9.6	9.8	
	♀	9.5	9.2	9.8	9.4							
66	♂	8.4	7.4	9.4	9.0	8.0	8.8	10.0				
	♀	9.3	8.9	7.7	8.7	8.4	9.0	7.8	9.1	7.8		
73	♂	10.3	7.8	8.3	8.3	9.1	9.4	8.9	9.4	9.5	9.9	
	♀	8.8	9.4	8.8	9.3							
81	♂	12.3	10.8	11.0	12.0	12.3	12.0	11.1	12.0			
	♀	5.9	11.6	11.2	11.4	11.3						
92	♂	12.0	9.8	12.3	11.2	11.3	11.1	12.4				
	♀	10.6	11.6	11.4	10.9	10.8	11.2					
95	♂	5.4	6.9	6.4	6.8	6.7						
	♀	6.6	5.9	7.0	6.4	6.6	6.0	6.5	6.2	5.0		
96	♂	11.1	11.4	11.4	11.3	11.3	11.6					
	♀	9.2	10.5	11.5	9.5	10.6	10.6					
125	♂	9.8	9.3	8.5	8.2	9.7	9.0	10.0	8.9	9.3	9.7	8.1
	♀	9.7	8.6	7.9	9.3	9.0						
127	♂											
	♀											
133	♂	9.7	10.3	9.4	9.2	8.9						
	♀	9.0	9.4	8.5	8.9	9.6	8.6	9.4				
166	♂	11.2	10.3	10.7	10.6	10.9	11.0	10.6	11.0	10.4	8.7	7.7
	♀	6.8	8.7	8.5	10.1							

APPENDIX CC

Individual Forelimb and Hindlimb Grip Strength, Hindlimb Splay, Body Weight, and Body Temperature

Individual Forelimb and Hindlimb Grip Strength, Hindlimb Splay, Body Weight, and Body Temperature

BASELINE

			FORELIMB GRIP STRENGTH (kg)				HINDLIMB GRIP STRENGTH (kg)						
ANIMAL	SEX	DOSAGE (mg/kg/day)	TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	HINDLIMB SPLAY (cm)	BODY WEIGHT (grams)	BODY TEMPERATURE (°C)
1	M	0	0.28	0.36	0.46	0.37	0.41	0.41	0.22	0.35	6.9	214.2	35.3
8	M	0	0.47	0.31	0.34	0.37	0.51	0.47	0.37	0.45	5.9	209.6	35.0
10	M	0	0.52	0.60	0.65	0.59	0.28	0.30	0.27	0.28	7.4	220.6	34.6
12	M	0	0.46	0.42	0.39	0.42	0.26	0.24	0.36	0.29	6.2	209.8	34.8
13	M	0	0.46	0.46	0.68	0.53	0.35	0.30	0.30	0.32	3.6	212.7	35.1
22	M	0	0.31	0.29	0.31	0.30	0.36	0.47	0.47	0.43	4.4	212.7	35.3
31	M	0	0.51	0.46	0.60	0.52	0.27	0.26	0.27	0.27	5.5	220.7	35.3
36	M	0	0.46	0.46	0.31	0.41	0.32	0.27	0.31	0.30	6.4	206.1	34.3
41	M	0	0.45	0.67	0.30	0.47	0.37	0.31	0.34	0.34	7.6	227.0	35.2
44	M	0	0.55	0.42	0.44	0.47	0.45	0.34	0.36	0.38	6.3	217.2	35.4
45	M	0	0.53	0.46	0.33	0.44	0.30	0.25	0.27	0.27	6.9	213.0	35.0
54	M	0	0.41	0.41	0.34	0.39	0.25	0.23	0.27	0.25	5.1	228.4	35.2
3	M	35	0.60	0.61	0.66	0.62	0.23	0.23	0.32	0.26	7.5	217.3	35.4
5	M	35	0.42	0.37	0.60	0.46	0.20	0.26	0.39	0.28	7.2	207.6	34.4
14	M	35	0.29	0.57	0.49	0.45	0.56	0.40	0.35	0.44	5.0	230.7	35.6
18	M	35	0.41	0.51	0.32	0.41	0.29	0.18	0.13	0.20	5.1	209.0	35.2
20	M	35	0.54	0.80	0.61	0.65	0.33	0.34	0.29	0.32	5.7	218.3	34.3
26	M	35	0.31	0.30	0.49	0.37	0.39	0.37	0.36	0.37	5.6	213.5	35.1
35	M	35	0.42	0.37	0.50	0.43	0.31	0.26	0.29	0.29	6.5	206.3	34.9
46	M	35	0.49	0.80	0.80	0.70	0.39	0.40	0.30	0.36	5.9	230.4	35.4
48	M	35	0.59	0.48	0.48	0.52	0.27	0.20	0.30	0.26	5.6	202.8	34.3
50	M	35	0.32	0.32	0.54	0.39	0.22	0.22	0.24	0.23	8.2	220.7	34.3
55	M	35	0.42	0.34	0.48	0.41	0.34	0.28	0.47	0.36	4.5	215.1	34.6
56	M	35	0.32	0.45	0.56	0.44	0.31	0.30	0.30	0.30	8.3	213.7	34.5

Individual Forelimb and Hindlimb Grip Strength, Hindlimb Splay, Body Weight, and Body Temperature

BASELINE

ANIMAL	SEX	DOSAGE (mg/kg/day)	FORELIMB GRIP STRENGTH (kg) TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	HINDLIMB GRIP STRENGTH (kg) TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	HINDLIMB SPLAY (cm)	BODY WEIGHT (grams)	BODY TEMPERATURE (°C)
4	M	125	0.54	0.63	0.56	0.58	0.28	0.41	0.49	0.39	6.7	213.8	35.5
9	M	125	0.43	0.45	0.31	0.40	0.32	0.26	0.31	0.30	8.1	209.4	35.3
25	M	125	0.35	0.32	0.31	0.33	0.27	0.36	0.28	0.30	5.5	229.9	34.9
28	M	125	0.53	0.30	0.37	0.40	0.42	0.38	0.52	0.44	7.0	208.9	35.1
30	M	125	0.34	0.50	0.70	0.51	0.32	0.34	0.25	0.30	7.6	212.7	34.8
32	M	125	0.31	0.27	0.38	0.32	0.26	0.22	0.29	0.26	5.6	226.4	34.7
37	M	125	0.46	0.46	0.67	0.53	0.46	0.31	0.38	0.38	7.0	214.5	35.2
38	M	125	0.44	0.66	0.58	0.56	0.34	0.34	0.31	0.33	7.9	219.5	34.7
43	M	125	0.72	0.65	0.76	0.71	0.48	0.41	0.55	0.48	6.4	199.8	34.9
47	M	125	0.40	0.48	0.68	0.52	0.34	0.37	0.37	0.36	6.1	217.9	36.2
49	M	125	0.45	0.34	0.35	0.38	0.35	0.22	0.20	0.26	6.0	213.3	34.4
51	M	125	0.38	0.30	0.44	0.37	0.25	0.33	0.21	0.26	6.9	223.3	34.6
2	M	375	0.51	0.51	0.57	0.53	0.27	0.42	0.21	0.30	7.9	213.8	34.3
6	M	375	0.43	0.38	0.36	0.39	0.43	0.30	0.35	0.36	7.4	207.2	34.9
11	M	375	0.51	0.48	0.55	0.51	0.31	0.30	0.31	0.31	8.7	206.6	35.1
16	M	375	0.33	0.42	0.59	0.45	0.25	0.27	0.22	0.25	7.5	205.9	34.6
19	M	375	0.37	0.57	0.51	0.48	0.29	0.24	0.34	0.29	8.3	209.2	34.3
21	M	375	0.62	0.70	0.61	0.64	0.33	0.43	0.43	0.40	7.2	220.4	34.6
27	M	375	0.52	0.49	0.41	0.47	0.38	0.40	0.42	0.40	9.5	229.1	34.3
33	M	375	0.56	0.64	0.47	0.56	0.28	0.24	0.39	0.30	3.5	218.0	35.3
39	M	375	0.46	0.50	0.36	0.44	0.29	0.37	0.32	0.33	9.3	223.4	35.2
40	M	375	0.30	0.23	0.21	0.25	0.42	0.44	0.31	0.39	7.6	214.5	34.6
52	M	375	0.41	0.70	0.77	0.63	0.24	0.29	0.27	0.27	7.3	226.1	35.7
53	M	375	0.54	0.56	0.42	0.51	0.29	0.26	0.28	0.28	3.8	231.6	34.2

Individual Forelimb and Hindlimb Grip Strength, Hindlimb Splay, Body Weight, and Body Temperature

BASELINE

ANIMAL	SEX	DOSAGE (mg/kg/day)	FORELIMB GRIP STRENGTH (kg) TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	HINDLIMB GRIP STRENGTH (kg) TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	HINDLIMB SPLAY (cm)	BODY WEIGHT (grams)	BODY TEMPERATURE (°C)
69	F	0	0.44	0.46	0.30	0.40	0.33	0.35	0.35	0.34	5.2	176.5	34.9
89	F	0	0.51	0.51	0.55	0.52	0.34	0.45	0.30	0.36	3.7	193.2	35.4
101	F	0	0.51	0.41	0.61	0.51	0.45	0.46	0.44	0.45	6.4	182.7	34.6
112	F	0	0.30	0.52	0.57	0.46	0.28	0.47	0.35	0.37	3.6	178.6	35.4
113	F	0	0.55	0.65	0.70	0.63	0.28	0.38	0.38	0.35	6.0	175.3	34.3
123	F	0	0.45	0.51	0.44	0.47	0.38	0.33	0.30	0.34	6.7	191.4	34.7
126	F	0	0.36	0.33	0.44	0.38	0.41	0.30	0.37	0.36	4.9	180.9	35.2
144	F	0	0.41	0.61	0.49	0.50	0.27	0.22	0.38	0.29	5.7	176.7	34.8
152	F	0	0.36	0.33	0.56	0.42	0.31	0.26	0.25	0.27	5.9	165.9	35.3
155	F	0	0.37	0.36	0.48	0.40	0.23	0.43	0.42	0.36	6.0	173.7	35.6
162	F	0	0.43	0.45	0.30	0.39	0.27	0.24	0.31	0.27	4.8	176.3	36.2
163	F	0	0.26	0.41	0.48	0.38	0.34	0.42	0.43	0.40	6.0	181.4	34.4
71	F	35	0.46	0.36	0.35	0.39	0.33	0.38	0.50	0.40	4.4	165.6	34.9
75	F	35	0.56	0.61	0.44	0.54	0.44	0.30	0.22	0.32	5.5	189.7	34.9
83	F	35	0.33	0.35	0.42	0.37	0.43	0.53	0.44	0.47	6.3	190.4	35.4
107	F	35	0.68	0.64	0.75	0.69	0.35	0.41	0.39	0.38	5.5	187.1	34.9
119	F	35	0.70	0.68	0.80	0.73	0.39	0.32	0.36	0.36	6.2	169.8	35.7
120	F	35	0.74	0.66	0.53	0.64	0.32	0.32	0.34	0.33	4.3	183.3	35.1
128	F	35	0.43	0.18	0.20	0.27	0.48	0.41	0.31	0.40	4.3	188.3	37.0
138	F	35	0.50	0.51	0.60	0.54	0.21	0.29	0.27	0.26	6.0	182.6	35.5
145	F	35	0.48	0.55	0.57	0.53	0.22	0.28	0.32	0.27	3.6	164.4	34.4
149	F	35	0.41	0.52	0.40	0.44	0.32	0.36	0.51	0.40	5.0	177.2	35.4
160	F	35	0.34	0.47	0.40	0.40	0.34	0.28	0.42	0.35	5.4	176.4	35.6
164	F	35	0.30	0.37	0.49	0.39	0.31	0.29	0.27	0.29	2.8	172.9	35.8

Individual Forelimb and Hindlimb Grip Strength, Hindlimb Splay, Body Weight, and Body Temperature

BASELINE

ANIMAL	SEX	DOSAGE (mg/kg/day)	FORELIMB GRIP STRENGTH (kg) TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	HINDLIMB GRIP STRENGTH (kg) TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	HINDLIMB SPLAY (cm)	BODY WEIGHT (grams)	BODY TEMPERATURE (°C)
62	F	125	0.73	0.45	0.38	0.52	0.41	0.30	0.27	0.33	5.1	177.9	35.1
79	F	125	0.49	0.47	0.41	0.46	0.36	0.41	0.33	0.37	3.1	185.9	35.5
99	F	125	0.43	0.34	0.43	0.40	0.19	0.22	0.34	0.25	3.2	187.9	35.8
135	F	125	0.43	0.27	0.30	0.33	0.25	0.22	0.28	0.25	5.5	167.6	35.5
142	F	125	0.57	0.67	0.47	0.57	0.37	0.35	0.30	0.34	5.1	178.2	34.3
143	F	125	0.31	0.54	0.41	0.42	0.36	0.30	0.31	0.32	4.0	174.3	35.6
147	F	125	0.36	0.51	0.41	0.43	0.35	0.34	0.35	0.35	4.1	172.3	35.8
150	F	125	0.54	0.38	0.59	0.50	0.31	0.29	0.41	0.34	2.7	163.6	34.8
153	F	125	0.56	0.38	0.52	0.49	0.33	0.24	0.32	0.30	5.5	188.7	36.6
154	F	125	0.40	0.41	0.37	0.39	0.49	0.33	0.32	0.38	6.9	192.0	35.4
156	F	125	0.51	0.33	0.59	0.48	0.31	0.38	0.43	0.37	4.5	185.5	35.8
161	F	125	0.35	0.40	0.35	0.37	0.22	0.29	0.26	0.26	3.6	167.8	36.3
67	F	375	0.57	0.56	0.51	0.55	0.34	0.35	0.33	0.34	4.5	179.3	35.4
68	F	375	0.35	0.46	0.47	0.43	0.31	0.36	0.36	0.34	4.3	175.7	35.1
70	F	375	0.36	0.40	0.58	0.45	0.31	0.37	0.45	0.38	4.8	182.3	35.2
76	F	375	0.54	0.51	0.54	0.53	0.25	0.35	0.31	0.30	7.3	187.3	35.0
77	F	375	0.72	0.69	0.68	0.70	0.78	0.45	0.41	0.55	8.3	171.3	35.0
84	F	375	0.36	0.37	0.57	0.43	0.35	0.46	0.34	0.38	4.9	192.7	34.5
88	F	375	0.19	0.21	0.20	0.20	0.20	0.31	0.26	0.26	5.3	163.3	34.5
114	F	375	0.41	0.58	0.43	0.47	0.41	0.41	0.52	0.45	6.9	163.5	36.0
129	F	375	0.43	0.43	0.46	0.44	0.22	0.37	0.40	0.33	8.2	188.4	35.7
146	F	375	0.35	0.22	0.27	0.28	0.23	0.31	0.23	0.26	4.9	175.4	35.3
151	F	375	0.40	0.38	0.41	0.40	0.24	0.43	0.43	0.37	3.8	167.7	36.4
159	F	375	0.30	0.35	0.37	0.34	0.24	0.23	0.42	0.30	3.4	165.1	36.4

Individual Forelimb and Hindlimb Grip Strength, Hindlimb Splay, Body Weight, and Body Temperature

WEEK 4

			FORELIMB GRIP STRENGTH (kg)				HINDLIMB GRIP STRENGTH (kg)						
ANIMAL	SEX	DOSAGE (mg/kg/day)	TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	HINDLIMB SPLAY (cm)	BODY WEIGHT (grams)	BODY TEMPERATURE (°C)
1	M	0	0.79	0.86	0.86	0.84	0.69	0.47	0.53	0.56	8.2	382.1	35.6
8	M	0	0.76	1.34	1.50	1.20	0.58	0.48	0.50	0.52	5.0	410.8	34.9
10	M	0	1.12	1.09	1.39	1.20	0.57	0.48	0.50	0.52	9.5	424.5	33.5
12	M	0	0.62	0.79	0.81	0.74	0.42	0.35	0.43	0.40	7.9	424.8	33.6
13	M	0	0.78	0.71	0.61	0.70	0.51	0.51	0.49	0.50	5.5	421.5	34.4
22	M	0	0.59	0.70	0.67	0.65	0.52	0.56	0.49	0.52	6.5	399.3	35.7
31	M	0	1.10	1.13	1.34	1.19	0.66	0.55	0.54	0.58	8.8	420.9	35.1
36	M	0	0.91	1.14	1.13	1.06	0.44	0.51	0.51	0.49	7.4	390.0	34.5
41	M	0	1.05	1.18	1.20	1.14	0.42	0.62	0.61	0.55	6.2	425.1	35.1
44	M	0	0.93	0.79	1.30	1.01	0.81	0.70	0.70	0.74	8.8	450.9	35.4
45	M	0	1.03	1.14	0.87	1.01	0.51	0.49	0.53	0.51	11.9	398.4	34.7
54	M	0	0.89	0.76	0.88	0.84	0.47	0.62	0.62	0.57	7.4	467.2	34.8
3	M	35	0.95	1.12	0.95	1.01	0.50	0.46	0.61	0.52	7.3	417.6	34.7
5	M	35	1.20	1.11	1.24	1.18	0.56	0.55	0.54	0.55	8.4	398.2	34.6
14	M	35	0.83	0.73	0.60	0.72	0.57	0.53	0.46	0.52	7.4	414.1	34.6
18	M	35	1.11	0.87	1.05	1.01	0.52	0.56	0.51	0.53	7.6	398.0	34.8
20	M	35	1.01	1.40	1.65	1.35	0.50	0.58	0.70	0.59	7.5	387.3	34.8
26	M	35	0.80	1.05	1.17	1.01	0.56	0.59	0.55	0.57	6.9	424.9	34.8
35	M	35	1.17	0.85	0.87	0.96	0.50	0.46	0.47	0.48	8.5	409.2	34.6
46	M	35	1.34	1.15	1.24	1.24	0.56	0.53	0.64	0.58	8.9	444.7	34.9
48	M	35	1.05	0.93	0.82	0.93	0.59	0.50	0.47	0.52	7.3	384.1	34.5
50	M	35	0.90	0.89	1.19	0.99	0.65	0.42	0.39	0.49	9.1	417.4	35.1
55	M	35	1.02	1.20	0.70	0.97	0.49	0.56	0.47	0.51	12.0	422.5	34.4
56	M	35	1.00	0.99	1.18	1.06	0.63	0.55	0.52	0.57	6.6	415.2	35.1

Individual Forelimb and Hindlimb Grip Strength, Hindlimb Splay, Body Weight, and Body Temperature

WEEK 4

ANIMAL	SEX	DOSAGE (mg/kg/day)	FORELIMB GRIP STRENGTH (kg) TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	HINDLIMB GRIP STRENGTH (kg) TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	HINDLIMB SPLAY (cm)	BODY WEIGHT (grams)	BODY TEMPERATURE (°C)
4	M	125	1.15	1.30	0.99	1.15	0.45	0.47	0.52	0.48	5.9	352.8	35.3
9	M	125	1.29	1.05	1.28	1.21	0.40	0.60	0.47	0.49	6.9	371.1	35.0
25	M	125	0.67	0.77	0.68	0.71	0.36	0.46	0.48	0.43	5.6	400.9	35.0
28	M	125	0.70	0.74	0.68	0.71	0.73	0.65	0.56	0.65	8.0	419.3	34.8
30	M	125	1.08	1.00	1.11	1.06	0.49	0.51	0.58	0.53	8.8	395.0	34.9
32	M	125	1.47	1.51	1.08	1.35	0.33	0.32	0.43	0.36	8.6	404.4	34.4
37	M	125	1.47	1.48	1.34	1.43	0.79	0.67	0.63	0.70	11.6	368.9	36.0
38	M	125	1.05	1.44	1.50	1.33	0.53	0.69	0.69	0.64	11.9	397.4	35.8
43	M	125	1.34	1.20	1.37	1.30	0.63	0.60	0.52	0.58	8.8	381.8	34.3
47	M	125	0.75	0.84	0.61	0.73	0.50	0.77	0.49	0.59	8.5	411.8	35.4
49	M	125	1.07	0.94	0.88	0.96	0.62	0.64	0.60	0.62	8.0	373.4	35.4
51	M	125	0.81	1.09	0.94	0.95	0.51	0.54	0.59	0.55	8.3	389.9	36.0
2	M	375	0.89	1.07	1.07	1.01	0.54	0.55	0.57	0.55	10.8	385.1	34.8
6	M	375	0.85	1.30	1.07	1.07	0.57	0.64	0.58	0.60	5.2	375.6	34.8
11	M	375	1.08	1.14	1.06	1.09	0.43	0.53	0.42	0.46	10.5	363.0	34.4
16	M	375	1.07	1.22	1.06	1.12	0.45	0.57	0.56	0.53	7.6	388.4	34.4
19	M	375	1.01	0.99	1.10	1.03	0.56	0.72	0.70	0.66	11.6	351.2	33.5
21	M	375	1.30	1.31	1.21	1.27	0.71	0.82	0.57	0.70	8.9	375.7	34.1
27	M	375	1.20	1.28	1.12	1.20	0.47	0.61	0.58	0.55	9.6	385.3	34.6
33	M	375	0.99	1.14	0.96	1.03	0.54	0.52	0.52	0.53	3.2	377.7	33.8
39	M	375	1.05	1.19	0.85	1.03	0.45	0.56	0.55	0.52	7.5	378.0	34.3
40	M	375	0.51	0.62	0.77	0.63	0.51	0.63	0.63	0.59	5.2	354.1	34.5
52	M	375	1.00	0.80	0.68	0.83	0.47	0.46	0.56	0.50	7.2	371.5	35.4
53	M	375	0.66	0.78	0.82	0.75	0.42	0.49	0.51	0.47	6.2	421.6	35.1

Individual Forelimb and Hindlimb Grip Strength, Hindlimb Splay, Body Weight, and Body Temperature

WEEK 4

			FORELIMB GRIP STRENGTH (kg)				HINDLIMB GRIP STRENGTH (kg)						
ANIMAL	SEX	DOSAGE (mg/kg/day)	TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	HINDLIMB SPLAY (cm)	BODY WEIGHT (grams)	BODY TEMPERATURE (°C)
69	F	0	0.91	0.81	0.67	0.80	0.62	0.58	0.56	0.59	5.7	260.1	35.1
89	F	0	1.03	1.15	1.09	1.09	0.66	0.67	0.50	0.61	6.7	289.8	35.5
101	F	0	0.73	1.29	0.89	0.97	0.45	0.61	0.59	0.55	3.9	261.0	35.1
112	F	0	1.21	1.05	0.92	1.06	0.43	0.48	0.51	0.47	4.1	250.4	36.2
113	F	0	0.98	1.14	0.94	1.02	0.52	0.32	0.37	0.40	4.9	249.0	35.4
123	F	0	0.97	0.35	0.36	0.56	0.60	0.57	0.62	0.60	5.5	272.3	36.3
126	F	0	1.28	0.84	1.29	1.14	0.58	0.52	0.66	0.59	4.3	255.8	36.6
144	F	0	0.77	0.76	0.97	0.83	0.46	0.46	0.57	0.50	5.3	280.8	35.9
152	F	0	0.68	0.55	0.68	0.64	0.53	0.43	0.53	0.50	5.5	201.5	36.2
155	F	0	0.88	1.16	0.75	0.93	0.56	0.49	0.62	0.56	7.9	250.3	36.0
162	F	0	1.24	0.78	0.85	0.96	0.46	0.53	0.51	0.50	5.3	269.9	35.2
163	F	0	1.24	1.26	1.22	1.24	0.46	0.41	0.58	0.48	5.5	272.9	37.3
71	F	35	1.04	0.77	0.85	0.89	0.52	0.40	0.50	0.47	4.0	251.5	36.4
75	F	35	0.80	0.90	0.80	0.83	0.43	0.58	0.54	0.52	7.1	282.0	36.8
83	F	35	1.15	1.17	1.04	1.12	0.76	0.76	0.61	0.71	6.6	268.7	35.3
107	F	35	0.76	0.69	0.67	0.71	0.45	0.46	0.47	0.46	3.4	249.7	36.2
119	F	35	0.84	1.08	1.10	1.01	0.54	0.53	0.49	0.52	4.9	244.0	36.1
120	F	35	0.66	0.58	0.84	0.69	0.53	0.41	0.56	0.50	6.3	246.5	35.2
128	F	35	0.69	0.61	0.48	0.59	0.35	0.54	0.59	0.49	3.3	254.0	35.8
138	F	35	0.90	1.13	1.60	1.21	0.35	0.43	0.40	0.39	7.3	269.2	36.0
145	F	35	0.80	0.90	1.03	0.91	0.53	0.42	0.40	0.45	5.2	240.7	35.9
149	F	35	1.02	1.17	0.83	1.01	0.74	0.58	0.74	0.69	4.2	249.7	35.5
160	F	35	0.70	1.11	1.15	0.99	0.48	0.54	0.61	0.54	6.4	268.1	35.6
164	F	35	1.19	1.13	0.74	1.02	0.42	0.61	0.47	0.50	4.0	245.1	37.1

Individual Forelimb and Hindlimb Grip Strength, Hindlimb Splay, Body Weight, and Body Temperature

WEEK 4

			FORELIMB GRIP STRENGTH (kg)				HINDLIMB GRIP STRENGTH (kg)						
ANIMAL	SEX	DOSAGE (mg/kg/day)	TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	TRIAL 1	TRIAL 2	TRIAL 3	MEAN OF 3 TRIALS	HINDLIMB SPLAY (cm)	BODY WEIGHT (grams)	BODY TEMPERATURE (°C)
62	F	125	1.13	1.49	1.10	1.24	0.61	0.61	0.44	0.55	3.5	249.1	36.1
79	F	125	0.79	1.17	1.17	1.04	0.42	0.56	0.58	0.52	3.6	277.8	35.5
99	F	125	1.09	0.93	0.77	0.93	0.50	0.43	0.38	0.44	3.6	244.1	36.1
135	F	125	0.75	0.78	0.72	0.75	0.52	0.42	0.54	0.49	6.9	246.8	36.1
142	F	125	0.84	0.68	0.61	0.71	0.31	0.33	0.43	0.36	3.5	265.3	36.0
143	F	125	0.74	0.95	0.83	0.84	0.41	0.45	0.36	0.41	3.3	241.5	36.5
147	F	125	0.94	1.03	0.81	0.93	0.41	0.49	0.42	0.44	7.4	231.4	36.4
150	F	125	1.20	1.26	0.98	1.15	0.42	0.56	0.44	0.47	6.0	212.7	34.5
153	F	125	0.77	0.63	0.95	0.78	0.50	0.60	0.50	0.53	4.1	236.7	36.3
154	F	125	1.35	1.21	1.14	1.23	0.37	0.47	0.47	0.44	7.8	275.1	36.2
156	F	125	0.98	1.10	0.82	0.97	0.51	0.63	0.56	0.57	4.7	261.0	36.8
161	F	125	0.95	0.85	0.80	0.87	0.52	0.56	0.51	0.53	3.5	250.8	36.4
67	F	375	0.74	1.05	1.13	0.97	0.53	0.60	0.74	0.62	4.9	237.6	36.5
68	F	375	1.05	1.01	0.63	0.90	0.38	0.51	0.49	0.46	7.3	261.2	36.5
70	F	375	0.97	1.10	1.26	1.11	0.59	0.54	0.56	0.56	3.3	258.6	36.9
76	F	375	0.78	0.78	0.61	0.72	0.48	0.50	0.35	0.44	8.2	256.9	36.2
77	F	375	0.87	0.55	0.89	0.77	0.49	0.45	0.47	0.47	8.7	229.1	36.3
84	F	375	0.65	0.60	0.77	0.67	0.56	0.58	0.63	0.59	6.0	258.2	35.8
88	F	375	0.75	0.77	1.05	0.86	0.46	0.52	0.48	0.49	4.4	237.6	36.5
114	F	375	0.71	0.75	0.74	0.73	0.55	0.61	0.67	0.61	8.2	220.0	36.5
129	F	375	1.19	1.14	1.30	1.21	0.50	0.61	0.47	0.53	8.9	265.9	37.2
146	F	375	0.64	0.71	0.66	0.67	0.46	0.52	0.51	0.50	4.6	230.6	37.1
151	F	375	0.85	0.78	0.57	0.73	0.41	0.54	0.41	0.45	4.3	236.9	37.1
159	F	375	1.03	1.17	1.19	1.13	0.43	0.61	0.45	0.50	3.7	251.3	36.2

APPENDIX DD

Individual Functional Observational Battery Assessment

INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY ASSESSMENT

EXPLANATORY NOTES

INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY SCORING SYSTEM

Home Cage Observations:

POSTURE:	-2	=	limbs spread out or lying on one side
	-1	=	curled up, often asleep, or sitting with head hung down
	0	=	sitting, standing or rearing normally, alert
	1	=	jumping
PALPEBRAL CLOSURE:	-2	=	eyelids completely shut
	-1	=	eyelids drooping (ptosis)
	0	=	eyelids wide open
	S	=	rat appears to be sleeping
WRITHING:	0	=	absent
	1	=	present
CIRCLING:	0	=	absent
	1	=	present
BITING:	0	=	absent
	1	=	biting others
	2	=	biting cage
	3	=	self mutilation
GAIT/COORDINATION:	3	=	unable to move
	2	=	ataxic (unable to coordinate voluntary muscles, dragging limbs, hopping)
	1	=	unbalanced, swaying, uncoordinated
	0	=	normal

Outside the Home Cage (Removing from Cage):

EASE OF REMOVAL:	-1	=	too easy (rat sits quietly, no resistance)
	0	=	some resistance (rears, follows observer's hand)
	1	=	difficult (runs around cage, may attack)
EASE OF HANDLING:	-1	=	too easy
	0	=	easy (alert, limbs pulled up against body)
	1	=	difficult
MUSCLE TONE:	-1	=	limp
	0	=	normal
	1	=	rigid
VOCALIZATIONS:	0	=	absent
	1	=	present
PILOERECTION:	0	=	absent
	1	=	present
BITE MARKS ON TAIL/PAWS:	0	=	absent
	1	=	present
PALPEBRAL CLOSURE:	-2	=	eyelids completely shut
	-1	=	eyelids drooping (ptosis)
	0	=	none
FUR APPEARANCE:	-2	=	very soiled, crusty
	-1	=	slightly soiled
	0	=	normal

INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY ASSESSMENTS

EXPLANATORY NOTES (Continued)

INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY SCORING SYSTEM (Continued)

Outside the Home Cage (Removing from Cage): (Continued)

LACRIMATION:	0	=	none
	1	=	slight
	2	=	severe
SALIVATION:	0	=	none
	1	=	slight (wet chin)
	2	=	severe (active salivation, drooling)
EXOPHTHALMUS:	0	=	absent
	1	=	present

Open Field Area (in Free-Roaming Space):

RIGHTING REFLEX:	-2	=	absent
	-1	=	slow
	0	=	present
EASE OF RESPIRATION:	0	=	absent
	1	=	labored breathing (add description)
RATE OF RESPIRATION:	-1	=	slow
	0	=	normal
	1	=	rapid
POSTURE:	0	=	normal
	1	=	abnormal (add description)
CONVULSIONS:	0	=	none
	1	=	present - violent involuntary series of muscle contractions; may be accompanied by pupillary dilation, vomiting, salivation, defecation, urination, chewing, and/or loss of consciousness (add description)
TREMORS:	0	=	none
	1	=	slight - localized to fingers or paws
	2	=	mild - limbs (note forelimb, hindlimb, or both)
	3	=	severe - multiple locations (list)
MUSCLE SPASMS:	0	=	none
	1	=	present - twitching of a muscle or group of muscles
MUSCLE FASCICULATION:	0	=	none
	1	=	present - rippling of muscle or skin
GROOMING:	0	=	normal or none
	1	=	repetitive, stereotypy
GAIT/COORDINATION:	3	=	unable to move
	2	=	ataxic (unable to coordinate voluntary muscles, dragging limbs, hopping)
	1	=	unbalanced, swaying, uncoordinated
	0	=	normal
AROUSAL:	-2	=	very slow (stupor, little or no responsiveness)
	-1	=	low (some exploratory movements with periods of immobility)
	0	=	normal (alert, exploratory movements)
	1	=	high (slight excitement, tense, sudden movements)

INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY ASSESSMENTS

EXPLANATORY NOTES (Continued)

INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY SCORING SYSTEM (Continued)

Open Field Area (in Free-Roaming Space): (Continued)

VOCALIZATIONS:	0	=	absent
	1	=	present
	2	=	vocalizes only when handled
PALPEBRAL CLOSURE:	-2	=	eyelids completely shut
	-1	=	eyelids drooping (ptosis)
	0	=	none
DIARRHEA:	0	=	absent
	1	=	present
POLYURIA:	0	=	absent
	1	=	present
REARING:	#	=	the number of times both forelimbs are lifted off the cageboard

Manipulations in Open Field Area (Free-Roaming Space):

APPROACH & TOUCH:	-1	=	no reaction
	0	=	normal
	1	=	increased reaction (jumps away or attacks)
AUDITORY STIMULUS:	-1	=	no reaction
	0	=	normal reaction (rat flinches or flicks ear)
	1	=	exaggerated reaction (rat jumps, flips)
TAIL PINCH:	-1	=	no response
	0	=	normal (turns toward site)
	1	=	exaggerated response (vocalizations, rapid turning)

Motor Activity Monitor:

PUPILLARY RESPONSE:	0	=	present
	1	=	absent
DIARRHEA:	0	=	absent
	1	=	present
POLYURIA:	0	=	absent
	1	=	present

Individual Functional Battery Assessment

	HOME CAGE						OUTSIDE THE HOME CAGE											OPEN FIELD AREA																MANIPU-LATIONS			MOTOR ACTIVITY		
Animal Number	POSTURE	PALPEBRAL CLOSURE	WRITHING	CIRCLING	BITING	GAIT/COORDINATION	EASE OF REMOVAL	EASE OF HANDLING	MUSCLE TONE	VOCALIZATIONS	PILOERECTION	BITE MARKS ON TAIL/PAWS	PALPEBRAL CLOSURE	FUR APPEARANCE	LACRIMATION	SALIVATION	EXOPHTHALMUS	RIGHTING REFLEX	EASE OF RESPIRATION	RATE OF RESPIRATION	POSTURE	CONVULSIONS	TREMORS	MUSCLE SPASMS	MUSCLE FASCICULATION	GROOMING	GAIT/COORDINATION	AROUSAL	VOCALIZATIONS	PALPEBRAL CLOSURE	DIARRHEA	POLYURIA	REARING	APPROACH & TOUCH	AUDITORY STIMULUS	TAIL PINCH	PUPILLARY RESPONSE	DIARRHEA	POLYURIA
Male, Group I - 0 mg/kg/day - BASELINE																																							
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
8	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11	0	0	0	0	0	0
22	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
41	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	4	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
45	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Male, Group III - 35 mg/kg/day - BASELINE																																							
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
5	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	1	0	0	0
14	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	0	0	0	0	0	0
20	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	1	0	0	0	0	0	0
48	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	0	0	0	0	0	0
50	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
55	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0

Individual Functional Battery Assessment

	HOME CAGE						OUTSIDE THE HOME CAGE											OPEN FIELD AREA																MANIPU-LATIONS			MOTOR ACTIVITY		
Animal Number	POSTURE	PALPEBRAL CLOSURE	WRITHING	CIRCLING	BITING	GAIT/COORDINATION	EASE OF REMOVAL	EASE OF HANDLING	MUSCLE TONE	VOCALIZATIONS	PILOERECTION	BITE MARKS ON TAIL/PAWS	PALPEBRAL CLOSURE	FUR APPEARANCE	LACRIMATION	SALIVATION	EXOPHTHALMUS	RIGHTING REFLEX	EASE OF RESPIRATION	RATE OF RESPIRATION	POSTURE	CONVULSIONS	TREMORS	MUSCLE SPASMS	MUSCLE FASCICULATION	GROOMING	GAIT/COORDINATION	AROUSAL	VOCALIZATIONS	PALPEBRAL CLOSURE	DIARRHEA	POLYURIA	REARING	APPROACH & TOUCH	AUDITORY STIMULUS	TAIL PINCH	PUPILLARY RESPONSE	DIARRHEA	POLYURIA
Male, Group V - 125 mg/kg/day - BASELINE																																							
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11	0	0	0	0	0	0
9	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
Male, Group VII - 375 mg/kg/day - BASELINE																																							
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
16	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
19	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
33	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0
53	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0

Individual Functional Battery Assessment

	HOME CAGE						OUTSIDE THE HOME CAGE											OPEN FIELD AREA																MANIPU-LATIONS			MOTOR ACTIVITY		
Animal Number	POSTURE	PALPEBRAL CLOSURE	WRITHING	CIRCLING	BITING	GAIT/COORDINATION	EASE OF REMOVAL	EASE OF HANDLING	MUSCLE TONE	VOCALIZATIONS	PILOERECTION	BITE MARKS ON TAIL/PAWS	PALPEBRAL CLOSURE	FUR APPEARANCE	LACRIMATION	SALIVATION	EXOPHTHALMUS	RIGHTING REFLEX	EASE OF RESPIRATION	RATE OF RESPIRATION	POSTURE	CONVULSIONS	TREMORS	MUSCLE SPASMS	MUSCLE FASCICULATION	GROOMING	GAIT/COORDINATION	AROUSAL	VOCALIZATIONS	PALPEBRAL CLOSURE	DIARRHEA	POLYURIA	REARING	APPROACH & TOUCH	AUDITORY STIMULUS	TAIL PINCH	PUPILLARY RESPONSE	DIARRHEA	POLYURIA
Female, Group II - 0 mg/kg/day - BASELINE																																							
69	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0	0	0	0	0
101	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
112	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
113	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	0	0	0	0	0	0
123	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0
126	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	0	0	0	0	0	0
144	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
152	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	4	0	0	0	0	0	0
155	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
162	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
163	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Female, Group IV - 35 mg/kg/day - BASELINE																																							
71	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
119	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
128	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
138	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
145	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
149	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
160	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
164	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0

Individual Functional Battery Assessment

	HOME CAGE						OUTSIDE THE HOME CAGE											OPEN FIELD AREA																MANIPU-LATIONS			MOTOR ACTIVITY		
Animal Number	POSTURE	PALPEBRAL CLOSURE	WRITHING	CIRCLING	BITING	GAIT/COORDINATION	EASE OF REMOVAL	EASE OF HANDLING	MUSCLE TONE	VOCALIZATIONS	PILOERECTION	BITE MARKS ON TAIL/PAWS	PALPEBRAL CLOSURE	FUR APPEARANCE	LACRIMATION	SALIVATION	EXOPHTHALMUS	RIGHTING REFLEX	EASE OF RESPIRATION	RATE OF RESPIRATION	POSTURE	CONVULSIONS	TREMORS	MUSCLE SPASMS	MUSCLE FASCICULATION	GROOMING	GAIT/COORDINATION	AROUSAL	VOCALIZATIONS	PALPEBRAL CLOSURE	DIARRHEA	POLYURIA	REARING	APPROACH & TOUCH	AUDITORY STIMULUS	TAIL PINCH	PUPILLARY RESPONSE	DIARRHEA	POLYURIA
Female, Group VI - 125 mg/kg/day - BASELINE																																							
62	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
79	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
135	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0	0	0	0	0
142	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	1	0	0	0
143	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
147	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0	0	0	0	0
150	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	0	0	0	0	0	0
153	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0
154	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0
156	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0
161	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0
Female, Group VIII - 375 mg/kg/day - BASELINE																																							
67	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	15	0	0	0	0	0	0
76	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	1	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
114	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
129	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
146	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
151	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
159	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0

Individual Functional Battery Assessment

	HOME CAGE						OUTSIDE THE HOME CAGE											OPEN FIELD AREA																MANIPU-LATIONS			MOTOR ACTIVITY		
Animal Number	POSTURE	PALPEBRAL CLOSURE	WRITHING	CIRCLING	BITING	GAIT/COORDINATION	EASE OF REMOVAL	EASE OF HANDLING	MUSCLE TONE	VOCALIZATIONS	PILOERECTION	BITE MARKS ON TAIL/PAWS	PALPEBRAL CLOSURE	FUR APPEARANCE	LACRIMATION	SALIVATION	EXOPHTHALMUS	RIGHTING REFLEX	EASE OF RESPIRATION	RATE OF RESPIRATION	POSTURE	CONVULSIONS	TREMORS	MUSCLE SPASMS	MUSCLE FASCICULATION	GROOMING	GAIT/COORDINATION	AROUSAL	VOCALIZATIONS	PALPEBRAL CLOSURE	DIARRHEA	POLYURIA	REARING	APPROACH & TOUCH	AUDITORY STIMULUS	TAIL PINCH	PUPILLARY RESPONSE	DIARRHEA	POLYURIA
Male, Group I - 0 mg/kg/day - WEEK 4																																							
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	3	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	1	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
41	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
44	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
54	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Male, Group III - 35 mg/kg/day - WEEK 4																																							
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
35 [a]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0
55	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
56	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0

a Head shake

Individual Functional Battery Assessment

	HOME CAGE						OUTSIDE THE HOME CAGE											OPEN FIELD AREA																MANIPU-LATIONS			MOTOR ACTIVITY		
Animal Number	POSTURE	PALPEBRAL CLOSURE	WRITHING	CIRCLING	BITING	GAIT/COORDINATION	EASE OF REMOVAL	EASE OF HANDLING	MUSCLE TONE	VOCALIZATIONS	PILOERECTION	BITE MARKS ON TAIL/PAWS	PALPEBRAL CLOSURE	FUR APPEARANCE	LACRIMATION	SALIVATION	EXOPHTHALMUS	RIGHTING REFLEX	EASE OF RESPIRATION	RATE OF RESPIRATION	POSTURE	CONVULSIONS	TREMORS	MUSCLE SPASMS	MUSCLE FASCICULATION	GROOMING	GAIT/COORDINATION	AROUSAL	VOCALIZATIONS	PALPEBRAL CLOSURE	DIARRHEA	POLYURIA	REARING	APPROACH & TOUCH	AUDITORY STIMULUS	TAIL PINCH	PUPILLARY RESPONSE	DIARRHEA	POLYURIA
Male, Group V - 125 mg/kg/day - WEEK 4																																							
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	10	0	0	1	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
38	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
Male, Group VII - 375 mg/kg/day - WEEK 4																																							
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
21	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	2	0	0	0	0	0	0
52	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0

Individual Functional Battery Assessment

	HOME CAGE						OUTSIDE THE HOME CAGE											OPEN FIELD AREA																MANIPU-LATIONS			MOTOR ACTIVITY		
Animal Number	POSTURE	PALPEBRAL CLOSURE	WRITHING	CIRCLING	BITING	GAIT/COORDINATION	EASE OF REMOVAL	EASE OF HANDLING	MUSCLE TONE	VOCALIZATIONS	PILOERECTION	BITE MARKS ON TAIL/PAWS	PALPEBRAL CLOSURE	FUR APPEARANCE	LACRIMATION	SALIVATION	EXOPHTHALMUS	RIGHTING REFLEX	EASE OF RESPIRATION	RATE OF RESPIRATION	POSTURE	CONVULSIONS	TREMORS	MUSCLE SPASMS	MUSCLE FASCICULATION	GROOMING	GAIT/COORDINATION	AROUSAL	VOCALIZATIONS	PALPEBRAL CLOSURE	DIARRHEA	POLYURIA	REARING	APPROACH & TOUCH	AUDITORY STIMULUS	TAIL PINCH	PUPILLARY RESPONSE	DIARRHEA	POLYURIA
Female, Group II - 0 mg/kg/day - WEEK 4																																							
69	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11	0	0	0	0	0	0
101	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0
112	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0	0	0	0	0
113	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0
123	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	3	0	0	0	0	0	0
126	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
144	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
152	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	4	0	0	0	0	0	0
155	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
162	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0
163	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
Female, Group IV - 35 mg/kg/day - WEEK 4																																							
71	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	1	0	0	0	0	0	0
119	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
128	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	13	0	0	0	0	0	0
138	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0
145	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
149	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	0	0	0	0	0	0
160	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0
164	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0

Individual Functional Battery Assessment

	HOME CAGE						OUTSIDE THE HOME CAGE											OPEN FIELD AREA																MANIPU-LATIONS			MOTOR ACTIVITY		
Animal Number	POSTURE	PALPEBRAL CLOSURE	WRITHING	CIRCLING	BITING	GAIT/COORDINATION	EASE OF REMOVAL	EASE OF HANDLING	MUSCLE TONE	VOCALIZATIONS	PILOERECTION	BITE MARKS ON TAIL/PAWS	PALPEBRAL CLOSURE	FUR APPEARANCE	LACRIMATION	SALIVATION	EXOPHTHALMUS	RIGHTING REFLEX	EASE OF RESPIRATION	RATE OF RESPIRATION	POSTURE	CONVULSIONS	TREMORS	MUSCLE SPASMS	MUSCLE FASCICULATION	GROOMING	GAIT/COORDINATION	AROUSAL	VOCALIZATIONS	PALPEBRAL CLOSURE	DIARRHEA	POLYURIA	REARING	APPROACH & TOUCH	AUDITORY STIMULUS	TAIL PINCH	PUPILLARY RESPONSE	DIARRHEA	POLYURIA
Female, Group VI - 125 mg/kg/day - WEEK 4																																							
62	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	2	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
135	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0
142	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
143	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
147	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
150	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0	0	0	0	0
153	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0
154	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	1	0	0	0	0	0
156 [a]	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0
161	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
Female, Group VIII - 375 mg/kg/day - WEEK 4																																							
67	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	12	0	0	0	0	0	0
76	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	3	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	4	0	0	0	0	0	0
114	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0
129	-1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	1	0	0	0	0
146	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	0
151	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	0	0	0	0	0	0
159	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0

a Head shake

APPENDIX EE

Individual Motor Activity: Duration of Movement

Individual Motor Activity: Duration of Movement (sec)

Animal Number	Successive 10-Minute Intervals 1	2	3	4	5	6	Total
Male, Group I - 0 mg/kg/day - BASELINE							
1	291	171	173	14	2	0	651
8	346	234	3	11	7	0	601
10	418	342	118	0	0	0	878
12	437	375	254	308	275	117	1766
13	512	373	377	183	1	17	1463
22	369	235	110	82	173	3	972
31	425	356	247	53	0	0	1081
36	384	335	182	4	8	0	913
41	362	184	6	1	0	0	553
44	351	351	173	93	2	0	970
45	376	273	184	85	1	0	919
54	417	276	200	185	78	1	1157
Male, Group III - 35 mg/kg/day - BASELINE							
3	375	248	120	1	3	9	756
5	456	332	313	103	0	2	1206
14	405	324	108	1	3	4	845
18	395	298	12	3	7	20	735
20	410	307	83	0	14	0	814
26	413	239	64	7	0	2	725
35	339	264	143	3	2	2	753
46	366	227	95	8	1	8	705
48	471	366	348	208	167	0	1560
50	371	155	14	98	2	9	649
55	379	332	151	0	0	7	869
56	340	251	142	56	1	7	797
Male, Group V - 125 mg/kg/day - BASELINE							
4	415	351	281	340	248	105	1740
9	463	411	261	53	14	1	1203
25	393	387	133	142	8	0	1063
28	376	305	194	91	1	0	967
30	416	321	278	30	0	7	1052
32	447	350	110	0	0	0	907
37	341	256	163	6	1	6	773
38	384	285	150	9	0	9	837
43	392	302	205	189	119	13	1220
47	424	294	324	145	1	0	1188
49	456	444	204	0	3	1	1108
51	404	304	278	100	70	2	1158
Male, Group VII - 375 mg/kg/day - BASELINE							
2	399	295	292	18	0	0	1004
6	313	170	259	206	157	2	1107
11	438	358	122	1	6	10	935
16	380	240	182	16	0	0	818
19	447	315	207	223	0	0	1192
21	335	290	296	172	3	0	1096
27	375	105	64	2	2	6	554
33	465	390	344	262	69	0	1530
39	284	243	56	3	0	0	586
40	427	304	310	314	124	34	1513
52	348	243	17	0	0	4	612
53	404	285	149	2	0	0	840

Individual Motor Activity: Duration of Movement (sec)

Animal Number	Successive 10-Minute Intervals 1	2	3	4	5	6	Total
Female, Group II - 0 mg/kg/day - BASELINE							
69	290	203	161	108	205	128	1095
89	274	189	140	138	133	182	1056
101	386	340	406	223	228	108	1691
112	314	248	196	224	139	196	1317
113	374	334	202	73	45	0	1028
123	263	247	233	292	156	87	1278
126	332	281	241	253	49	2	1158
144	394	215	47	57	27	12	752
152	341	234	134	1	0	9	719
155	420	344	27	0	0	7	798
162	371	337	213	76	4	9	1010
163	363	272	304	87	41	2	1069
Female, Group IV - 35 mg/kg/day - BASELINE							
71	396	312	315	239	234	157	1653
75	442	344	286	154	133	4	1363
83	327	232	284	154	70	4	1071
107	405	331	305	269	52	2	1364
119	351	340	314	80	2	19	1106
120	411	348	271	212	60	0	1302
128	322	295	213	186	193	112	1321
138	309	164	124	159	4	6	766
145	436	372	343	263	158	169	1741
149	329	286	261	199	144	55	1274
160	455	300	5	22	1	140	923
164	366	332	253	157	52	14	1174
Female, Group VI - 125 mg/kg/day - BASELINE							
62	417	365	274	257	237	283	1833
79	479	405	394	326	304	274	2182
99	295	181	181	27	3	0	687
135	299	235	98	131	29	5	797
142	349	299	211	39	5	166	1069
143	364	266	269	198	201	45	1343
147	316	259	241	201	178	28	1223
150	204	193	95	74	8	5	579
153	436	394	358	196	5	205	1594
154	461	347	294	130	2	94	1328
156	342	371	301	3	4	42	1063
161	387	369	292	144	27	0	1219
Female, Group VIII - 375 mg/kg/day - BASELINE							
67	314	202	103	228	92	94	1033
68	387	285	239	197	183	144	1435
70	408	371	333	252	184	104	1652
76	361	398	315	219	290	43	1626
77	399	352	290	73	7	3	1124
84	374	368	173	141	213	192	1461
88	420	336	299	110	21	4	1190
114	393	400	375	317	204	11	1700
129	366	348	294	171	168	76	1423
146	356	260	31	1	101	0	749
151	426	413	326	237	218	166	1786
159	417	308	177	35	0	0	937

Individual Motor Activity: Duration of Movement (sec)

Animal Number	Successive 10-Minute Intervals 1	2	3	4	5	6	Total
Male, Group I - 0 mg/kg/day - WEEK 4							
8	378	283	71	2	0	1	735
10	429	225	15	1	4	0	674
12	452	329	271	218	283	292	1845
13	507	337	281	153	6	14	1298
22	401	191	161	257	102	191	1303
1	332	224	224	269	216	115	1380
31	387	306	193	65	0	17	968
36	338	346	285	177	59	9	1214
41	357	327	130	7	0	10	831
44	294	279	74	300	7	0	954
45	365	269	278	147	143	102	1304
54	388	265	141	102	0	12	908
Male, Group III - 35 mg/kg/day - WEEK 4							
3	403	315	164	161	21	1	1065
5	424	358	234	182	123	137	1458
14	366	294	69	17	14	1	761
18	438	309	67	6	2	13	835
20	410	346	309	206	151	32	1454
26	399	283	243	0	61	0	986
35	294	223	236	178	87	2	1020
46	297	234	251	99	9	7	897
48	447	323	323	136	83	21	1333
50	368	210	4	1	0	2	585
55	417	347	75	0	0	1	840
56	366	343	270	165	158	0	1302
Male, Group V - 125 mg/kg/day - WEEK 4							
4	432	368	258	167	135	272	1632
9	452	287	30	0	10	9	788
25	356	275	116	0	1	0	748
28	322	195	290	264	201	154	1426
30	428	309	293	284	103	200	1617
32	368	303	173	135	280	62	1321
37	317	280	255	189	207	165	1413
38	300	263	136	238	7	0	944
43	363	307	29	6	0	2	707
47	414	356	88	0	0	30	888
49	450	341	214	308	8	5	1326
51	417	364	213	0	0	17	1011
Male, Group VII - 375 mg/kg/day - WEEK 4							
2	327	300	178	98	51	3	957
6	311	271	237	175	100	3	1097
11	381	287	252	171	11	0	1102
16	331	243	150	193	145	51	1113
19	317	188	207	228	255	39	1234
21	360	282	210	156	191	39	1238
27	294	259	119	4	0	21	697
33	409	412	385	306	28	48	1588
39	383	269	131	5	0	2	790
40	406	267	23	24	1	1	722
52	381	236	7	42	3	4	673
53	401	258	21	0	1	21	702

Individual Motor Activity: Duration of Movement (sec)

Animal Number	Successive 10-Minute Intervals 1	2	3	4	5	6	Total
Female, Group II - 0 mg/kg/day - WEEK 4							
69	282	221	144	182	158	25	1012
89	288	194	158	262	148	112	1162
101	404	377	276	295	48	75	1475
112	341	235	232	241	131	151	1331
113	348	216	270	223	246	31	1334
123	372	260	195	42	0	71	940
126	325	320	209	179	108	76	1217
144	431	358	165	251	214	6	1425
152	314	194	89	19	66	22	704
155	413	354	221	49	3	1	1041
162	370	307	251	307	211	99	1545
163	397	313	230	177	222	167	1506
Female, Group IV - 35 mg/kg/day - WEEK 4							
71	373	319	253	282	199	219	1645
75	430	294	354	210	238	269	1795
83	371	279	144	97	194	189	1274
107	390	320	200	8	112	1	1031
119	378	225	155	210	231	57	1256
120	450	370	267	181	256	302	1826
128	344	302	259	252	160	176	1493
138	316	270	225	241	99	24	1175
145	361	288	284	219	92	186	1430
149	410	367	256	256	274	209	1772
160	480	411	366	245	95	326	1923
164	462	316	209	254	164	203	1608
Female, Group VI - 125 mg/kg/day - WEEK 4							
62	422	202	283	107	43	5	1062
79	492	296	106	351	312	64	1621
99	294	277	186	171	163	159	1250
135	407	411	257	117	2	1	1195
142	386	286	299	328	301	168	1768
143	359	251	216	50	2	153	1031
147	271	261	249	291	239	86	1397
150	224	199	57	9	153	72	714
153	505	478	449	64	90	262	1848
154	461	409	385	311	216	227	2009
156	371	409	264	261	206	99	1610
161	399	342	118	69	258	169	1355
Female, Group VIII - 375 mg/kg/day - WEEK 4							
67	324	203	145	92	2	22	788
68	390	290	221	123	8	10	1042
70	377	293	200	143	49	18	1080
76	449	385	31	361	299	20	1545
77	420	250	284	90	0	2	1046
84	421	287	241	145	146	222	1462
88	406	329	308	156	128	10	1337
114	429	286	97	11	2	182	1007
129	418	296	255	198	109	245	1521
146	310	271	142	1	3	84	811
151	473	451	289	210	250	255	1928
159	468	264	61	5	0	213	1011

APPENDIX FF

Individual Motor Activity: Number of Movements

Individual Motor Activity: Number of Movements

Animal Number	Successive 10-Minute Intervals 1	2	3	4	5	6	Total
Male, Group I - 0 mg/kg/day - BASELINE							
1	140	124	95	21	3	0	383
8	160	155	6	16	12	3	352
10	112	156	66	3	2	1	340
12	130	143	100	155	140	110	778
13	79	124	120	81	4	18	426
22	135	140	89	75	109	4	552
31	118	128	135	46	2	0	429
36	156	154	120	7	5	0	442
41	138	145	10	3	5	3	304
44	144	142	130	80	5	3	504
45	136	152	100	68	4	0	460
54	123	121	125	128	50	5	552
Male, Group III - 35 mg/kg/day - BASELINE							
3	145	125	86	3	4	10	373
5	120	144	121	67	5	6	463
14	146	148	88	1	7	5	395
18	130	138	15	3	11	19	316
20	149	134	81	1	18	0	383
26	146	136	60	10	2	6	360
35	162	160	111	5	6	4	448
46	176	157	64	11	2	9	419
48	133	152	129	112	96	1	623
50	121	90	19	65	2	11	308
55	138	124	117	1	0	11	391
56	161	113	112	59	4	8	457
Male, Group V - 125 mg/kg/day - BASELINE							
4	130	132	128	133	137	67	727
9	118	129	136	47	15	1	446
25	155	126	112	112	4	4	513
28	158	172	141	78	2	0	551
30	131	142	154	46	0	5	478
32	133	146	82	0	1	2	364
37	161	113	92	11	3	5	385
38	161	169	113	19	0	12	474
43	134	126	128	137	67	12	604
47	131	138	158	94	2	3	526
49	112	118	98	0	4	1	333
51	141	175	149	91	47	5	608
Male, Group VII - 375 mg/kg/day - BASELINE							
2	152	144	134	35	0	0	465
6	165	109	154	133	128	6	695
11	130	125	62	3	9	8	337
16	143	137	99	15	3	5	402
19	134	141	134	110	0	0	519
21	136	147	139	92	6	1	521
27	154	119	58	4	5	13	353
33	124	145	145	134	54	1	603
39	151	148	46	5	0	1	351
40	119	144	145	118	110	31	667
52	155	131	24	0	1	6	317
53	129	148	76	2	1	3	359

Individual Motor Activity: Number of Movements

Animal Number	Successive 10-Minute Intervals 1	2	3	4	5	6	Total
Female, Group II - 0 mg/kg/day - BASELINE							
69	139	134	93	92	133	130	721
89	136	141	126	129	120	145	797
101	123	147	135	110	148	84	747
112	151	150	143	147	134	140	865
113	125	125	89	64	22	2	427
123	115	140	139	144	117	64	719
126	157	147	123	143	45	5	620
144	135	119	47	32	13	14	360
152	162	144	101	6	0	13	426
155	133	138	39	2	3	16	331
162	132	128	138	58	7	16	479
163	131	131	154	103	45	6	570
Female, Group IV - 35 mg/kg/day - BASELINE							
71	120	138	129	122	148	121	778
75	126	149	131	119	78	5	608
83	161	134	154	113	56	12	630
107	147	165	157	138	50	2	659
119	135	145	130	51	7	17	485
120	144	121	125	116	43	5	554
128	146	143	114	107	118	104	732
138	132	128	103	122	6	8	499
145	128	137	134	139	128	127	793
149	134	138	116	126	117	62	693
160	108	73	14	22	1	67	285
164	133	147	137	100	34	15	566
Female, Group VI - 125 mg/kg/day - BASELINE							
62	134	145	156	148	133	140	856
79	119	129	151	137	125	126	787
99	156	124	132	39	7	0	458
135	124	133	84	89	30	14	474
142	156	143	154	50	6	123	632
143	123	146	118	114	142	41	684
147	147	132	149	116	110	34	688
150	155	155	115	95	11	13	544
153	157	131	148	88	10	104	638
154	120	154	109	126	10	78	597
156	131	126	113	7	10	18	405
161	151	155	167	135	36	1	645
Female, Group VIII - 375 mg/kg/day - BASELINE							
67	148	118	81	138	73	83	641
68	142	172	152	164	126	105	861
70	130	116	133	122	112	74	687
76	139	136	129	146	170	44	764
77	125	133	123	66	10	5	462
84	130	129	126	100	138	135	758
88	123	126	133	90	18	6	496
114	128	107	125	123	116	14	613
129	158	148	158	118	110	48	740
146	153	136	43	5	88	2	427
151	117	111	104	120	104	114	670
159	143	159	89	46	0	0	437

Individual Motor Activity: Number of Movements

Animal Number	Successive 10-Minute Intervals 1	2	3	4	5	6	Total
Male, Group I - 0 mg/kg/day - WEEK 4							
8	165	130	56	6	3	5	365
10	129	102	20	4	7	2	264
12	143	142	110	123	128	143	789
13	83	89	117	91	5	8	393
22	154	118	130	152	90	138	782
1	148	119	156	145	136	83	787
31	107	105	116	31	2	23	384
36	138	149	147	96	34	11	575
41	165	152	105	6	2	14	444
44	158	141	72	126	10	3	510
45	118	123	131	90	113	72	647
54	132	141	97	64	3	13	450
Male, Group III - 35 mg/kg/day - WEEK 4							
3	164	145	117	94	8	2	530
5	122	122	117	95	74	74	604
14	166	153	54	19	21	4	417
18	109	145	43	4	1	6	308
20	167	161	143	118	85	27	701
26	150	143	126	0	33	2	454
35	153	143	147	107	72	7	629
46	178	166	163	61	9	7	584
48	140	144	121	80	53	21	559
50	138	131	7	3	1	5	285
55	140	122	64	0	0	2	328
56	157	173	166	92	109	2	699
Male, Group V - 125 mg/kg/day - WEEK 4							
4	120	151	122	102	78	119	692
9	126	142	17	1	5	7	298
25	139	129	77	4	5	4	358
28	155	121	170	136	121	115	818
30	121	130	132	136	68	74	661
32	139	118	88	87	126	39	597
37	148	149	149	104	120	132	802
38	162	141	74	168	8	2	555
43	143	145	24	9	1	5	327
47	140	149	49	1	1	11	351
49	119	127	88	108	7	9	458
51	133	139	105	1	0	9	387
Male, Group VII - 375 mg/kg/day - WEEK 4							
2	141	144	118	83	31	2	519
6	196	180	147	116	78	3	720
11	131	154	135	103	10	1	534
16	131	138	94	140	100	50	653
19	134	122	85	86	137	42	606
21	140	149	127	90	128	37	671
27	157	146	83	6	0	18	410
33	136	128	128	125	22	21	560
39	159	154	87	13	1	5	419
40	167	135	18	31	4	3	358
52	148	114	12	19	5	8	306
53	142	129	30	1	5	22	329

Individual Motor Activity: Number of Movements

Animal Number	Successive 10-Minute Intervals 1	2	3	4	5	6	Total
Female, Group II - 0 mg/kg/day - WEEK 4							
69	120	130	108	107	93	26	584
89	193	170	138	167	110	130	908
101	143	136	127	149	26	50	631
112	151	158	142	162	136	122	871
113	131	109	128	127	121	20	636
123	131	146	126	42	3	79	527
126	148	146	148	151	78	53	724
144	120	121	92	116	79	14	542
152	141	136	88	27	61	41	494
155	142	139	128	39	10	3	461
162	170	142	143	151	111	80	797
163	169	128	119	118	116	124	774
Female, Group IV - 35 mg/kg/day - WEEK 4							
71	145	143	126	126	115	137	792
75	118	138	134	109	126	139	764
83	157	134	113	104	145	119	772
107	148	144	128	14	88	2	524
119	130	144	90	126	149	66	705
120	125	117	124	98	151	123	738
128	156	141	149	167	128	131	872
138	163	144	141	140	90	25	703
145	126	113	125	112	69	113	658
149	127	134	144	135	145	122	807
160	87	107	97	95	85	118	589
164	129	140	123	126	90	127	735
Female, Group VI - 125 mg/kg/day - WEEK 4							
62	145	142	159	87	48	8	589
79	103	144	58	159	142	53	659
99	161	149	108	125	121	133	797
135	141	123	109	91	6	3	473
142	124	128	149	153	153	130	837
143	161	126	131	37	5	90	550
147	133	143	105	147	141	66	735
150	165	154	66	18	121	85	609
153	112	116	144	49	37	147	605
154	128	135	129	166	149	101	808
156	142	116	130	125	117	59	689
161	139	156	90	34	148	123	690
Female, Group VIII - 375 mg/kg/day - WEEK 4							
67	147	139	102	72	7	35	502
68	164	154	167	125	4	12	626
70	123	134	104	92	60	15	528
76	135	121	46	142	167	18	629
77	126	144	121	51	2	5	449
84	138	122	132	96	115	141	744
88	143	144	129	136	54	11	617
114	124	143	87	14	4	102	474
129	141	159	147	135	81	127	790
146	140	141	98	4	10	95	488
151	112	113	127	150	114	102	718
159	122	112	58	11	1	135	439

APPENDIX GG

Details of the Statistical Analysis Conducted on the Neurobehavioral Data

DETAILS OF THE STATISTICAL ANALYSIS CONDUCTED ON THE NEUROBEHAVIORAL DATA

EXPLANATORY NOTES

Abbreviations

NumDF	=	Numerator degrees of freedom
DenDF	=	Denominator degrees of freedom
CovParm	=	Covariance parameter
DY	=	Day
DS	=	Dose
DY1	=	Baseline evaluation
DY2	=	Week 4 evaluation
REML	=	Restricted maximum likelihood
Std Err	=	Standard error
AR(1)	=	Autorecessive order 1
ProbF	=	Probablitity of getting an F value that large
Jonc	=	Value of test statistic
ZC	=	Standardized value of test statistic
ZCCF	=	Standardized value of test statistic with continuity correction factor
P1UPCF	=	p value for upward trend
P2DNCF	=	p value for downward trend
SIGNIF	=	Significant
*	=	Statisically significant at $p < 0.05$
B	=	Bin (10-minute interval)
V	=	Versus

DETAILS OF THE STATISTICAL ANALYSIS CONDUCTED ON THE NEUROBEHAVIORAL DATA

In the tables of repeated measures results below, the term 'Estimate' refers to a standardized linear contrast. It is difficult to interpret this other than in terms of the sign (positive trend means an increasing trend, positive dose 1 vs. x means dose x exceeds dose 1) and significance is relative to the standard error provided. The significance of the estimate is given numerically and, where significant at the 0.05 level, shown with an asterisk in the SIGNIF column.

Rows are shown for Dose trend at each day or day-bin combination. The existence of a significant or non-significant trend in the dose means for the indicated day-bin combination affects how the significance of comparisons of treatments to control are computed. For example, if the DOSE*DAY and DOSE*BIN(DAY) interactions are not significant and the dose-trend on a given day or day-bin combination is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if the named interactions are not significant, the tests for dose-trend are adjusted for the number of such combinations tested. No other use of these dose trends is made.

In the tables of Jonckheere test results below, the label Day D, Bin B, Hidose x refers to a Jonckheere test applied to the data from day D and Bin B with all doses up to and including dose x. If the test with dose x is significant at the 0.05 level, then a test is shown for dose x-1. If this test is not significant, there is no need for further testing and none is shown.

A repeated measures ANOVA, possibly on a transformed response, is the preferred method of analysis. However, if neither a normalizing, variance-stabilizing transform nor a biologically feasible alternative variance-covariance structure was found that produced a normal, homogeneous set of residuals, then a non-parametric analysis was done.

Duration of Movement

Male

CovParm	Estimate
Variance	*2.9077*
AR(1)	*0.01673*
Residual	*11.6238*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
DAY	*1*	*109*	*7.59*	*0.0069*	*DAY*	*
BIN(DAY)	*10*	*442*	*185.32*	*<.0001*	*BIN(DAY)*	*
DOSE	*3*	*59*	*0.71*	*0.5501*	*DOSE*	
*DAY*DOSE*	*3*	*108*	*0.32*	*0.8090*	*DAY*DOSE*	
*DOSE*BIN(DAY)*	*30*	*442*	*0.74*	*0.8425*	*DOSE*BIN(DAY)*	

MALE, sqrttime, reml, ar(1), FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DS	*-0.2156*	*3.0190*	*-0.07*	*0.9433*	
DY 1, DS TREND	*1.3842*	*3.6359*	*0.38*	*0.7046*	
DY 1, DS 1 vs 2	*-0.9642*	*1.1496*	*-0.84*	*0.4045*	
DY 1, DS 1 vs 3	*0.8407*	*1.1499*	*0.73*	*0.4671*	
DY 1, DS 1 vs 4	*-0.1402*	*1.1496*	*-0.12*	*0.9033*	
DY 2, DS TREND	*-1.8154*	*3.6368*	*-0.50*	*0.6192*	
DY 2, DS 1 vs 2	*-0.7130*	*1.1496*	*-0.62*	*0.5371*	
DY 2, DS 1 vs 3	*0.07146*	*1.1499*	*0.06*	*0.9506*	
DY 2, DS 1 vs 4	*-0.8666*	*1.1499*	*-0.75*	*0.4536*	
DY 1, B 1, DS TREND	*-0.02983*	*5.4188*	*-0.01*	*0.9956*	
DY 1, B 1, DS 1 v 2	*0.1054*	*1.7135*	*0.06*	*0.9510*	
DY 1, B 1, DS 1 v 3	*0.5014*	*1.7137*	*0.29*	*0.7701*	
DY 1, B 1, DS 1 v 4	*-0.1419*	*1.7135*	*-0.08*	*0.9340*	
DY 1, B 2, DS TREND	*-0.4804*	*5.4188*	*-0.09*	*0.9294*	
DY 1, B 2, DS 1 v 2	*-0.3431*	*1.7135*	*-0.20*	*0.8414*	
DY 1, B 2, DS 1 v 3	*1.2750*	*1.7137*	*0.74*	*0.4575*	
DY 1, B 2, DS 1 v 4	*-0.6995*	*1.7135*	*-0.41*	*0.6834*	
DY 1, B 3, DS TREND	*7.1591*	*5.4188*	*1.32*	*0.1875*	
DY 1, B 3, DS 1 v 2	*-1.3329*	*1.7135*	*-0.78*	*0.4373*	
DY 1, B 3, DS 1 v 3	*2.4852*	*1.7137*	*1.45*	*0.1481*	
DY 1, B 3, DS 1 v 4	*1.1137*	*1.7135*	*0.65*	*0.5162*	
DY 1, B 4, DS TREND	*3.5006*	*5.4188*	*0.65*	*0.5188*	
DY 1, B 4, DS 1 v 2	*-3.0710*	*1.7135*	*-1.79*	*0.0741*	
DY 1, B 4, DS 1 v 3	*0.3378*	*1.7137*	*0.20*	*0.8439*	
DY 1, B 4, DS 1 v 4	*0.03062*	*1.7135*	*0.02*	*0.9858*	
DY 1, B 5, DS TREND	*-1.2249*	*5.4188*	*-0.23*	*0.8213*	
DY 1, B 5, DS 1 v 2	*-1.7563*	*1.7135*	*-1.02*	*0.3062*	
DY 1, B 5, DS 1 v 3	*-0.2039*	*1.7137*	*-0.12*	*0.9054*	
DY 1, B 5, DS 1 v 4	*-0.9258*	*1.7135*	*-0.54*	*0.5894*	
DY 1, B 6, DS TREND	*-0.6193*	*5.4188*	*-0.11*	*0.9091*	
DY 1, B 6, DS 1 v 2	*0.6129*	*1.7135*	*0.36*	*0.7208*	
DY 1, B 6, DS 1 v 3	*0.6490*	*1.7137*	*0.38*	*0.7052*	

Duration of Movement

Male (continued)

DY 1, B 6, DS 1 v 4	*-0.2185*	*1.7135*	*-0.13*	*0.8986*
DY 2, B 1, DS TREND	*-2.0859*	*5.4194*	*-0.38*	*0.7006*
DY 2, B 1, DS 1 v 2	*0.01445*	*1.7135*	*0.01*	*0.9933*
DY 2, B 1, DS 1 v 3	*-0.02540*	*1.7137*	*-0.01*	*0.9882*
DY 2, B 1, DS 1 v 4	*-0.6820*	*1.7137*	*-0.40*	*0.6909*
DY 2, B 2, DS TREND	*-0.6668*	*5.4194*	*-0.12*	*0.9022*
DY 2, B 2, DS 1 v 2	*0.5032*	*1.7135*	*0.29*	*0.7692*
DY 2, B 2, DS 1 v 3	*0.6469*	*1.7137*	*0.38*	*0.7061*
DY 2, B 2, DS 1 v 4	*-0.2701*	*1.7137*	*-0.16*	*0.8748*
DY 2, B 3, DS TREND	*-3.4262*	*5.4194*	*-0.63*	*0.5278*
DY 2, B 3, DS 1 v 2	*0.1309*	*1.7135*	*0.08*	*0.9392*
DY 2, B 3, DS 1 v 3	*-0.1158*	*1.7137*	*-0.07*	*0.9462*
DY 2, B 3, DS 1 v 4	*-1.0598*	*1.7137*	*-0.62*	*0.5368*
DY 2, B 4, DS TREND	*-2.7765*	*5.4194*	*-0.51*	*0.6088*
DY 2, B 4, DS 1 v 2	*-2.4658*	*1.7135*	*-1.44*	*0.1512*
DY 2, B 4, DS 1 v 3	*-1.5695*	*1.7137*	*-0.92*	*0.3605*
DY 2, B 4, DS 1 v 4	*-1.2243*	*1.7137*	*-0.71*	*0.4756*
DY 2, B 5, DS TREND	*0.8863*	*5.4194*	*0.16*	*0.8702*
DY 2, B 5, DS 1 v 2	*0.5522*	*1.7135*	*0.32*	*0.7475*
DY 2, B 5, DS 1 v 3	*0.6862*	*1.7137*	*0.40*	*0.6891*
DY 2, B 5, DS 1 v 4	*0.2507*	*1.7137*	*0.15*	*0.8838*
DY 2, B 6, DS TREND	*-2.8230*	*5.4194*	*-0.52*	*0.6028*
DY 2, B 6, DS 1 v 2	*-3.0128*	*1.7135*	*-1.76*	*0.0798*
DY 2, B 6, DS 1 v 3	*0.8065*	*1.7137*	*0.47*	*0.6383*
DY 2, B 6, DS 1 v 4	*-2.2141*	*1.7137*	*-1.29*	*0.1974*

There was a normality problem in the residuals so an analysis was performed on SQRT(*response*).

If the DOSE*DAY and DOSE*BIN(DAY) interactions are not significant and the dose-trend on a given day or day-bin combination is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if the named interactions are not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Duration of Movement

Female

CovParm	Estimate
Variance	*1162.45*
AR(1)	*0.04326*
Residual	*4656.81*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
DAY	*1*	*113*	*3.96*	*0.0491*	*DAY*	*
BIN(DAY)	*10*	*442*	*125.76*	*<.0001*	*BIN(DAY)*	*
DOSE	*3*	*62.8*	*1.42*	*0.2451*	*DOSE*	
*DAY*DOSE*	*3*	*113*	*2.30*	*0.0807*	*DAY*DOSE*	
*DOSE*BIN(DAY)*	*30*	*442*	*1.09*	*0.3452*	*DOSE*BIN(DAY)*	

FEMALE, mo_time, reml, ar(1), FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*51.8971*	*61.6202*	*0.84*	*0.4029*	
DY 1, DS TREND	*127.92*	*74.0509*	*1.73*	*0.0883*	
DY 1, DS 1 vs 2	*28.8540*	*23.4068*	*1.23*	*0.2216*	
DY 1, DS 1 vs 3	*26.3147*	*23.4239*	*1.12*	*0.2649*	
DY 1, DS 1 vs 4	*43.4856*	*23.4067*	*1.86*	*0.0672*	
DY 2, DS TREND	*-24.1234*	*74.1005*	*-0.33*	*0.7457*	
DY 2, DS 1 vs 2	*48.9297*	*23.4067*	*2.09*	*0.0400*	
DY 2, DS 1 vs 3	*29.8305*	*23.4238*	*1.27*	*0.2068*	
DY 2, DS 1 vs 4	*-1.6747*	*23.4241*	*-0.07*	*0.9432*	
DY 1, B 1, DS TREND	*106.92*	*109.32*	*0.98*	*0.3289*	
DY 1, B 1, DS 1 v 2	*35.4512*	*34.5638*	*1.03*	*0.3059*	
DY 1, B 1, DS 1 v 3	*18.2036*	*34.5754*	*0.53*	*0.5989*	
DY 1, B 1, DS 1 v 4	*41.3884*	*34.5638*	*1.20*	*0.2321*	
DY 1, B 2, DS TREND	*200.42*	*109.32*	*1.83*	*0.0678*	
DY 1, B 2, DS 1 v 2	*34.2012*	*34.5638*	*0.99*	*0.3232*	
DY 1, B 2, DS 1 v 3	*35.9536*	*34.5754*	*1.04*	*0.2993*	
DY 1, B 2, DS 1 v 4	*66.2217*	*34.5638*	*1.92*	*0.0564*	
DY 1, B 3, DS TREND	*164.42*	*109.32*	*1.50*	*0.1337*	
DY 1, B 3, DS 1 v 2	*55.7012*	*34.5638*	*1.61*	*0.1081*	
DY 1, B 3, DS 1 v 3	*57.9536*	*34.5754*	*1.68*	*0.0948*	
DY 1, B 3, DS 1 v 4	*54.0551*	*34.5638*	*1.56*	*0.1189*	
DY 1, B 4, DS TREND	*80.4176*	*109.32*	*0.74*	*0.4626*	
DY 1, B 4, DS 1 v 2	*46.7012*	*34.5638*	*1.35*	*0.1777*	
DY 1, B 4, DS 1 v 3	*15.4536*	*34.5754*	*0.45*	*0.6552*	
DY 1, B 4, DS 1 v 4	*37.2217*	*34.5638*	*1.08*	*0.2824*	
DY 1, B 5, DS TREND	*154.00*	*109.32*	*1.41*	*0.1600*	
DY 1, B 5, DS 1 v 2	*6.2012*	*34.5638*	*0.18*	*0.8577*	
DY 1, B 5, DS 1 v 3	*-2.7130*	*34.5754*	*-0.08*	*0.9375*	
DY 1, B 5, DS 1 v 4	*54.3051*	*34.5638*	*1.57*	*0.1172*	
DY 1, B 6, DS TREND	*61.3343*	*109.32*	*0.56*	*0.5752*	
DY 1, B 6, DS 1 v 2	*-5.1321*	*34.5638*	*-0.15*	*0.8821*	
DY 1, B 6, DS 1 v 3	*33.0370*	*34.5754*	*0.96*	*0.3401*	

Duration of Movement

Female (continued)

DY 1, B 6, DS 1 v 4	*7.7217*	*34.5638*	*0.22*	*0.8234*
DY 2, B 1, DS TREND	*135.13*	*109.36*	*1.24*	*0.2176*
DY 2, B 1, DS 1 v 2	*39.8186*	*34.5637*	*1.15*	*0.2503*
DY 2, B 1, DS 1 v 3	*25.2194*	*34.5753*	*0.73*	*0.4663*
DY 2, B 1, DS 1 v 4	*49.9086*	*34.5756*	*1.44*	*0.1500*
DY 2, B 2, DS TREND	*68.6266*	*109.36*	*0.63*	*0.5308*
DY 2, B 2, DS 1 v 2	*34.1519*	*34.5637*	*0.99*	*0.3239*
DY 2, B 2, DS 1 v 3	*39.0527*	*34.5753*	*1.13*	*0.2596*
DY 2, B 2, DS 1 v 4	*21.2419*	*34.5756*	*0.61*	*0.5395*
DY 2, B 3, DS TREND	*-50.4567*	*109.36*	*-0.46*	*0.6449*
DY 2, B 3, DS 1 v 2	*44.1519*	*34.5637*	*1.28*	*0.2025*
DY 2, B 3, DS 1 v 3	*35.4694*	*34.5753*	*1.03*	*0.3058*
DY 2, B 3, DS 1 v 4	*-13.9247*	*34.5756*	*-0.40*	*0.6874*
DY 2, B 4, DS TREND	*-200.54*	*109.36*	*-1.83*	*0.0677*
DY 2, B 4, DS 1 v 2	*18.8186*	*34.5637*	*0.54*	*0.5865*
DY 2, B 4, DS 1 v 3	*-8.4473*	*34.5753*	*-0.24*	*0.8072*
DY 2, B 4, DS 1 v 4	*-57.7581*	*34.5756*	*-1.67*	*0.0959*
DY 2, B 5, DS TREND	*-150.87*	*109.36*	*-1.38*	*0.1688*
DY 2, B 5, DS 1 v 2	*46.4019*	*34.5637*	*1.34*	*0.1805*
DY 2, B 5, DS 1 v 3	*35.5527*	*34.5753*	*1.03*	*0.3047*
DY 2, B 5, DS 1 v 4	*-46.6747*	*34.5756*	*-1.35*	*0.1781*
DY 2, B 6, DS TREND	*53.3766*	*109.36*	*0.49*	*0.6258*
DY 2, B 6, DS 1 v 2	*110.24*	*34.5637*	*3.19*	*0.0016*
DY 2, B 6, DS 1 v 3	*52.1360*	*34.5753*	*1.51*	*0.1327*
DY 2, B 6, DS 1 v 4	*37.1586*	*34.5756*	*1.07*	*0.2834*

If the DOSE*DAY and DOSE*BIN(DAY) interactions are not significant and the dose-trend on a given day or day-bin combination is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if the named interactions are not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Total Duration of Movement

Male

CovParm	Estimate
RAT(DOSE)	*10.1207*
Residual	*11.7164*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
DAY	*1*	*44*	*4.14*	*0.0478*	*DAY*	*
DOSE	*3*	*44*	*1.06*	*0.3759*	*DOSE*	
*DAY*DOSE*	*3*	*44*	*0.74*	*0.5343*	*DAY*DOSE*	

MALE sqrttime, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*-0.3991*	*5.1606*	*-0.08*	*0.9387*	
DY 1, DS TREND	*3.3092*	*6.0328*	*0.55*	*0.5850*	
DY 1, DS 1 vs 2	*-1.8885*	*1.9078*	*-0.99*	*0.3255*	
DY 1, DS 1 vs 3	*1.9082*	*1.9078*	*1.00*	*0.3205*	
DY 1, DS 1 vs 4	*-0.1625*	*1.9078*	*-0.09*	*0.9324*	
DY 2, DS TREND	*-4.1073*	*6.0328*	*-0.68*	*0.4981*	
DY 2, DS 1 vs 2	*-1.0608*	*1.9078*	*-0.56*	*0.5799*	
DY 2, DS 1 vs 3	*0.4867*	*1.9078*	*0.26*	*0.7994*	
DY 2, DS 1 vs 4	*-1.8849*	*1.9078*	*-0.99*	*0.3264*	

There was a normality problem in the residuals so an analysis was performed on SQRT(*response*).

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Total Duration of Movement

Female

CovParm	Estimate
RAT(DOSE)	*42929*
Residual	*68134*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
DAY	*1*	*44*	*4.29*	*0.0443*	*DAY*	*
DOSE	*3*	*44*	*1.53*	*0.2198*	*DOSE*	
*DAY*DOSE*	*3*	*44*	*2.47*	*0.0740*	*DAY*DOSE*	

FEMALE tot_time, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*316.00*	*358.23*	*0.88*	*0.3825*	
DY 1, DS TREND	*774.50*	*430.24*	*1.80*	*0.0758*	
DY 1, DS 1 vs 2	*173.92*	*136.05*	*1.28*	*0.2050*	
DY 1, DS 1 vs 3	*162.17*	*136.05*	*1.19*	*0.2370*	
DY 1, DS 1 vs 4	*262.08*	*136.05*	*1.93*	*0.0578*	
DY 2, DS TREND	*-142.50*	*430.24*	*-0.33*	*0.7414*	
DY 2, DS 1 vs 2	*294.67*	*136.05*	*2.17*	*0.0334*	
DY 2, DS 1 vs 3	*180.67*	*136.05*	*1.33*	*0.1882*	
DY 2, DS 1 vs 4	*-9.5000*	*136.05*	*-0.07*	*0.9445*	

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Number of Movements

Male

CovParm	Estimate
Variance	*1.1626*
AR(1)	*0.01911*
Residual	*5.5222*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
DAY	*1*	*95.1*	*8.40*	*0.0047*	*DAY*	*
BIN(DAY)	*10*	*439*	*121.68*	*<.0001*	*BIN(DAY)*	*
DOSE	*3*	*46.9*	*0.38*	*0.7651*	*DOSE*	
*DAY*DOSE*	*3*	*93.8*	*0.25*	*0.8582*	*DAY*DOSE*	
*DOSE*BIN(DAY)*	*30*	*439*	*0.96*	*0.5308*	*DOSE*BIN(DAY)*	

MALE, sqrtnum, reml, ar(1), FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*-0.05240*	*1.9440*	*-0.03*	*0.9786*	
DY 1, DS TREND	*0.7164*	*2.3549*	*0.30*	*0.7621*	
DY 1, DS 1 vs 2	*-0.5407*	*0.7446*	*-0.73*	*0.4707*	
DY 1, DS 1 vs 3	*0.3834*	*0.7448*	*0.51*	*0.6087*	
DY 1, DS 1 vs 4	*-0.06922*	*0.7446*	*-0.09*	*0.9263*	
DY 2, DS TREND	*-0.8212*	*2.3556*	*-0.35*	*0.7287*	
DY 2, DS 1 vs 2	*-0.5006*	*0.7446*	*-0.67*	*0.5040*	
DY 2, DS 1 vs 3	*-0.2209*	*0.7448*	*-0.30*	*0.7678*	
DY 2, DS 1 vs 4	*-0.3670*	*0.7448*	*-0.49*	*0.6241*	
DY 1, B 1, DS TREND	*1.1877*	*3.6353*	*0.33*	*0.7441*	
DY 1, B 1, DS 1 v 2	*0.5864*	*1.1495*	*0.51*	*0.6104*	
DY 1, B 1, DS 1 v 3	*0.3625*	*1.1496*	*0.32*	*0.7528*	
DY 1, B 1, DS 1 v 4	*0.4705*	*1.1495*	*0.41*	*0.6826*	
DY 1, B 2, DS TREND	*-0.2261*	*3.6353*	*-0.06*	*0.9505*	
DY 1, B 2, DS 1 v 2	*-0.2326*	*1.1495*	*-0.20*	*0.8398*	
DY 1, B 2, DS 1 v 3	*-0.00618*	*1.1496*	*-0.01*	*0.9957*	
DY 1, B 2, DS 1 v 4	*-0.1508*	*1.1495*	*-0.13*	*0.8957*	
DY 1, B 3, DS TREND	*4.3586*	*3.6353*	*1.20*	*0.2316*	
DY 1, B 3, DS 1 v 2	*-0.2477*	*1.1495*	*-0.22*	*0.8296*	
DY 1, B 3, DS 1 v 3	*2.0117*	*1.1496*	*1.75*	*0.0813*	
DY 1, B 3, DS 1 v 4	*0.6998*	*1.1495*	*0.61*	*0.5432*	
DY 1, B 4, DS TREND	*0.6074*	*3.6353*	*0.17*	*0.8674*	
DY 1, B 4, DS 1 v 2	*-2.5224*	*1.1495*	*-2.19*	*0.0291*	
DY 1, B 4, DS 1 v 3	*0.2640*	*1.1496*	*0.23*	*0.8185*	
DY 1, B 4, DS 1 v 4	*-0.7263*	*1.1495*	*-0.63*	*0.5280*	
DY 1, B 5, DS TREND	*-1.2415*	*3.6353*	*-0.34*	*0.7330*	
DY 1, B 5, DS 1 v 2	*-1.2513*	*1.1495*	*-1.09*	*0.2773*	
DY 1, B 5, DS 1 v 3	*-0.6533*	*1.1496*	*-0.57*	*0.5703*	
DY 1, B 5, DS 1 v 4	*-0.6132*	*1.1495*	*-0.53*	*0.5942*	
DY 1, B 6, DS TREND	*-0.3877*	*3.6353*	*-0.11*	*0.9151*	
DY 1, B 6, DS 1 v 2	*0.4237*	*1.1495*	*0.37*	*0.7127*	

Number of Movements

Male (continued)

DY 1, B 6, DS 1 v 3	*0.3219*	*1.1496*	*0.28*	*0.7797*
DY 1, B 6, DS 1 v 4	*-0.09529*	*1.1495*	*-0.08*	*0.9340*
DY 2, B 1, DS TREND	*1.0960*	*3.6357*	*0.30*	*0.7633*
DY 2, B 1, DS 1 v 2	*0.5263*	*1.1495*	*0.46*	*0.6475*
DY 2, B 1, DS 1 v 3	*0.04549*	*1.1496*	*0.04*	*0.9685*
DY 2, B 1, DS 1 v 4	*0.5256*	*1.1496*	*0.46*	*0.6479*
DY 2, B 2, DS TREND	*1.6418*	*3.6357*	*0.45*	*0.6519*
DY 2, B 2, DS 1 v 2	*0.8673*	*1.1495*	*0.75*	*0.4512*
DY 2, B 2, DS 1 v 3	*0.4906*	*1.1496*	*0.43*	*0.6699*
DY 2, B 2, DS 1 v 4	*0.6728*	*1.1496*	*0.59*	*0.5589*
DY 2, B 3, DS TREND	*-3.7503*	*3.6357*	*-1.03*	*0.3032*
DY 2, B 3, DS 1 v 2	*-0.1590*	*1.1495*	*-0.14*	*0.8901*
DY 2, B 3, DS 1 v 3	*-0.8307*	*1.1496*	*-0.72*	*0.4705*
DY 2, B 3, DS 1 v 4	*-1.0262*	*1.1496*	*-0.89*	*0.3729*
DY 2, B 4, DS TREND	*-1.0306*	*3.6357*	*-0.28*	*0.7770*
DY 2, B 4, DS 1 v 2	*-1.7391*	*1.1495*	*-1.51*	*0.1315*
DY 2, B 4, DS 1 v 3	*-0.9798*	*1.1496*	*-0.85*	*0.3948*
DY 2, B 4, DS 1 v 4	*-0.5966*	*1.1496*	*-0.52*	*0.6042*
DY 2, B 5, DS TREND	*-0.1281*	*3.6357*	*-0.04*	*0.9719*
DY 2, B 5, DS 1 v 2	*-0.08796*	*1.1495*	*-0.08*	*0.9391*
DY 2, B 5, DS 1 v 3	*-0.09495*	*1.1496*	*-0.08*	*0.9342*
DY 2, B 5, DS 1 v 4	*-0.04037*	*1.1496*	*-0.04*	*0.9720*
DY 2, B 6, DS TREND	*-2.7562*	*3.6357*	*-0.76*	*0.4491*
DY 2, B 6, DS 1 v 2	*-2.4113*	*1.1495*	*-2.10*	*0.0369*
DY 2, B 6, DS 1 v 3	*0.04391*	*1.1496*	*0.04*	*0.9696*
DY 2, B 6, DS 1 v 4	*-1.7371*	*1.1496*	*-1.51*	*0.1320*

There was a normality problem in the residuals so an analysis was performed on SQRT(*response*).

If the DOSE*DAY and DOSE*BIN(DAY) interactions are not significant and the dose-trend on a given day or day-bin combination is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if the named interactions are not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Number of Movements

Female

CovParm	Estimate
Variance	*162.03*
AR(1)	*-0.03036*
Residual	*1146.83*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
DAY	*1*	*159*	*4.62*	*0.0332*	*DAY*	*
BIN(DAY)	*10*	*447*	*39.78*	*<.0001*	*BIN(DAY)*	*
DOSE	*3*	*65.5*	*0.62*	*0.6025*	*DOSE*	
*DAY*DOSE*	*3*	*160*	*2.27*	*0.0825*	*DAY*DOSE*	
*DOSE*BIN(DAY)*	*30*	*447*	*1.24*	*0.1805*	*DOSE*BIN(DAY)*	

FEMALE, mo_num, reml, ar(1), FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*-12.3790*	*23.2796*	*-0.53*	*0.5967*	
DY 1, DS TREND	*23.0033*	*28.8026*	*0.80*	*0.4267*	
DY 1, DS 1 vs 2	*3.1843*	*9.1102*	*0.35*	*0.7275*	
DY 1, DS 1 vs 3	*4.9935*	*9.1068*	*0.55*	*0.5849*	
DY 1, DS 1 vs 4	*7.0647*	*9.1102*	*0.78*	*0.4402*	
DY 2, DS TREND	*-47.7613*	*28.7929*	*-1.66*	*0.1008*	
DY 2, DS 1 vs 2	*9.9419*	*9.1102*	*1.09*	*0.2782*	
DY 2, DS 1 vs 3	*1.3283*	*9.1068*	*0.15*	*0.8844*	
DY 2, DS 1 vs 4	*-13.0492*	*9.1068*	*-1.43*	*0.1555*	
DY 1, B 1, DS TREND	*4.8366*	*49.2179*	*0.10*	*0.9218*	
DY 1, B 1, DS 1 v 2	*-1.9545*	*15.5653*	*-0.13*	*0.9001*	
DY 1, B 1, DS 1 v 3	*3.0213*	*15.5633*	*0.19*	*0.8462*	
DY 1, B 1, DS 1 v 4	*-0.04641*	*15.5653*	*-0.00*	*0.9976*	
DY 1, B 2, DS TREND	*-7.9967*	*49.2179*	*-0.16*	*0.8710*	
DY 1, B 2, DS 1 v 2	*-2.0379*	*15.5653*	*-0.13*	*0.8959*	
DY 1, B 2, DS 1 v 3	*2.6046*	*15.5633*	*0.17*	*0.8672*	
DY 1, B 2, DS 1 v 4	*-4.2131*	*15.5653*	*-0.27*	*0.7868*	
DY 1, B 3, DS TREND	*30.5866*	*49.2179*	*0.62*	*0.5346*	
DY 1, B 3, DS 1 v 2	*9.8788*	*15.5653*	*0.63*	*0.5260*	
DY 1, B 3, DS 1 v 3	*22.6046*	*15.5633*	*1.45*	*0.1471*	
DY 1, B 3, DS 1 v 4	*5.9536*	*15.5653*	*0.38*	*0.7023*	
DY 1, B 4, DS TREND	*41.7533*	*49.2179*	*0.85*	*0.3967*	
DY 1, B 4, DS 1 v 2	*20.5455*	*15.5653*	*1.32*	*0.1876*	
DY 1, B 4, DS 1 v 3	*9.6880*	*15.5633*	*0.62*	*0.5340*	
DY 1, B 4, DS 1 v 4	*17.5369*	*15.5653*	*1.13*	*0.2605*	
DY 1, B 5, DS TREND	*57.1700*	*49.2179*	*1.16*	*0.2461*	
DY 1, B 5, DS 1 v 2	*0.04546*	*15.5653*	*0.00*	*0.9977*	
DY 1, B 5, DS 1 v 3	*-12.8954*	*15.5633*	*-0.83*	*0.4078*	
DY 1, B 5, DS 1 v 4	*23.3703*	*15.5653*	*1.50*	*0.1340*	
DY 1, B 6, DS TREND	*11.6700*	*49.2179*	*0.24*	*0.8127*	
DY 1, B 6, DS 1 v 2	*-7.3712*	*15.5653*	*-0.47*	*0.6361*	
DY 1, B 6, DS 1 v 3	*4.9380*	*15.5633*	*0.32*	*0.7512*	

Number of Movements

Female (continued)

DY 1, B 6, DS 1 v 4	*-0.2131*	*15.5653*	*-0.01*	*0.9891*
DY 2, B 1, DS TREND	*-32.2196*	*49.2122*	*-0.65*	*0.5130*
DY 2, B 1, DS 1 v 2	*-12.2525*	*15.5653*	*-0.79*	*0.4316*
DY 2, B 1, DS 1 v 3	*-8.6995*	*15.5633*	*-0.56*	*0.5765*
DY 2, B 1, DS 1 v 4	*-11.9242*	*15.5633*	*-0.77*	*0.4440*
DY 2, B 2, DS TREND	*-5.8030*	*49.2122*	*-0.12*	*0.9062*
DY 2, B 2, DS 1 v 2	*-5.0858*	*15.5653*	*-0.33*	*0.7440*
DY 2, B 2, DS 1 v 3	*-2.3662*	*15.5633*	*-0.15*	*0.8792*
DY 2, B 2, DS 1 v 4	*-2.8409*	*15.5633*	*-0.18*	*0.8552*
DY 2, B 3, DS TREND	*-51.7196*	*49.2122*	*-1.05*	*0.2939*
DY 2, B 3, DS 1 v 2	*0.6642*	*15.5653*	*0.04*	*0.9660*
DY 2, B 3, DS 1 v 3	*-9.0328*	*15.5633*	*-0.58*	*0.5620*
DY 2, B 3, DS 1 v 4	*-14.0075*	*15.5633*	*-0.90*	*0.3686*
DY 2, B 4, DS TREND	*-95.2196*	*49.2122*	*-1.93*	*0.0537*
DY 2, B 4, DS 1 v 2	*-0.2525*	*15.5653*	*-0.02*	*0.9871*
DY 2, B 4, DS 1 v 3	*-13.6995*	*15.5633*	*-0.88*	*0.3792*
DY 2, B 4, DS 1 v 4	*-27.2575*	*15.5633*	*-1.75*	*0.0806*
DY 2, B 5, DS TREND	*-97.1363*	*49.2122*	*-1.97*	*0.0491*
DY 2, B 5, DS 1 v 2	*36.4975*	*15.5653*	*2.34*	*0.0195*
DY 2, B 5, DS 1 v 3	*20.3838*	*15.5633*	*1.31*	*0.1910*
DY 2, B 5, DS 1 v 4	*-27.0075*	*15.5633*	*-1.74*	*0.0834*
DY 2, B 6, DS TREND	*-4.4696*	*49.2122*	*-0.09*	*0.9277*
DY 2, B 6, DS 1 v 2	*40.0808*	*15.5653*	*2.58*	*0.0104*
DY 2, B 6, DS 1 v 3	*21.3838*	*15.5633*	*1.37*	*0.1702*
DY 2, B 6, DS 1 v 4	*4.7425*	*15.5633*	*0.30*	*0.7607*

If the DOSE*DAY and DOSE*BIN(DAY) interactions are not significant and the dose-trend on a given day or day-bin combination is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if the named interactions are not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Total Number of Movements

Male

CovParm	Estimate
RAT(DOSE)	*7012.15*
Residual	*13491*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
DAY	*1*	*44*	*6.14*	*0.0171*	*DAY*	*
DOSE	*3*	*44*	*0.43*	*0.7295*	*DOSE*	
*DAY*DOSE*	*3*	*44*	*0.46*	*0.7114*	*DAY*DOSE*	

MALE tot_num, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*23.5417*	*151.43*	*0.16*	*0.8772*	
DY 1, DS TREND	*106.17*	*184.86*	*0.57*	*0.5674*	
DY 1, DS 1 vs 2	*-48.8333*	*58.4575*	*-0.84*	*0.4060*	
DY 1, DS 1 vs 3	*40.5833*	*58.4575*	*0.69*	*0.4896*	
DY 1, DS 1 vs 4	*5.5833*	*58.4575*	*0.10*	*0.9242*	
DY 2, DS TREND	*-59.0833*	*184.86*	*-0.32*	*0.7501*	
DY 2, DS 1 vs 2	*-24.3333*	*58.4575*	*-0.42*	*0.6784*	
DY 2, DS 1 vs 3	*-7.1667*	*58.4575*	*-0.12*	*0.9027*	
DY 2, DS 1 vs 4	*-25.4167*	*58.4575*	*-0.43*	*0.6649*	

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Total Number of Movements

Female

CovParm	Estimate
RAT(DOSE)	*7841.07*
Residual	*10997*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
DAY	*1*	*44*	*5.21*	*0.0274*	*DAY*	*
DOSE	*3*	*44*	*0.55*	*0.6531*	*DOSE*	
*DAY*DOSE*	*3*	*44*	*2.54*	*0.0684*	*DAY*DOSE*	

FEMALE tot_num, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*-76.8750*	*149.11*	*-0.52*	*0.6087*	
DY 1, DS TREND	*134.00*	*177.19*	*0.76*	*0.4519*	
DY 1, DS 1 vs 2	*18.3333*	*56.0335*	*0.33*	*0.7444*	
DY 1, DS 1 vs 3	*28.8333*	*56.0335*	*0.51*	*0.6084*	
DY 1, DS 1 vs 4	*41.1667*	*56.0335*	*0.73*	*0.4648*	
DY 2, DS TREND	*-287.75*	*177.19*	*-1.62*	*0.1086*	
DY 2, DS 1 vs 2	*59.1667*	*56.0335*	*1.06*	*0.2944*	
DY 2, DS 1 vs 3	*7.6667*	*56.0335*	*0.14*	*0.8915*	
DY 2, DS 1 vs 4	*-78.7500*	*56.0335*	*-1.41*	*0.1640*	

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Forelimb Grip Strength

Male

CovParm	Estimate
RAT(dose)	*0.009617*
Residual	*0.01718*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
day	*1*	*44*	*421.89*	*<.0001*	*day*	*
dose	*3*	*44*	*0.60*	*0.6216*	*dose*	
*day*dose*	*3*	*44*	*0.57*	*0.6361*	*day*dose*	

MALE fgrip, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*0.1393*	*0.1742*	*0.80*	*0.4282*	
DY 1, DS TREND	*0.1197*	*0.2113*	*0.57*	*0.5727*	
DY 1, DS 1 vs 2	*0.04722*	*0.06683*	*0.71*	*0.4819*	
DY 1, DS 1 vs 3	*0.02611*	*0.06683*	*0.39*	*0.6971*	
DY 1, DS 1 vs 4	*0.04694*	*0.06683*	*0.70*	*0.4845*	
DY 2, DS TREND	*0.1589*	*0.2113*	*0.75*	*0.4544*	
DY 2, DS 1 vs 2	*0.07139*	*0.06683*	*1.07*	*0.2887*	
DY 2, DS 1 vs 3	*0.1086*	*0.06683*	*1.63*	*0.1081*	
DY 2, DS 1 vs 4	*0.04056*	*0.06683*	*0.61*	*0.5457*	

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Forelimb Grip Strength

Female

CovParm	Estimate
RAT(dose)	*0*
Residual	*0.02365*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
day	*1*	*88*	*216.25*	*<.0001*	*day*	*
dose	*3*	*88*	*0.55*	*0.6481*	*dose*	
*day*dose*	*3*	*88*	*0.39*	*0.7628*	*day*dose*	

FEMALE fgrip, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*-0.1312*	*0.1404*	*-0.93*	*0.3524*	
DY 1, DS TREND	*-0.1136*	*0.1985*	*-0.57*	*0.5686*	
DY 1, DS 1 vs 2	*0.03778*	*0.06278*	*0.60*	*0.5489*	
DY 1, DS 1 vs 3	*-0.01000*	*0.06278*	*-0.16*	*0.8738*	
DY 1, DS 1 vs 4	*-0.02194*	*0.06278*	*-0.35*	*0.7275*	
DY 2, DS TREND	*-0.1489*	*0.1985*	*-0.75*	*0.4553*	
DY 2, DS 1 vs 2	*-0.02139*	*0.06278*	*-0.34*	*0.7341*	
DY 2, DS 1 vs 3	*0.01722*	*0.06278*	*0.27*	*0.7845*	
DY 2, DS 1 vs 4	*-0.06250*	*0.06278*	*-1.00*	*0.3222*	

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Hindlimb Grip Strength

Male

CovParm	Estimate
RAT(dose)	*0.001767*
Residual	*0.003142*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
day	*1*	*44*	*373.16*	*<.0001*	*day*	*
dose	*3*	*44*	*0.38*	*0.7662*	*dose*	
*day*dose*	*3*	*44*	*0.24*	*0.8660*	*day*dose*	

MALE hgrip, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*0.04014*	*0.07459*	*0.54*	*0.5932*	
DY 1, DS TREND	*0.01611*	*0.09046*	*0.18*	*0.8591*	
DY 1, DS 1 vs 2	*-0.02139*	*0.02861*	*-0.75*	*0.4569*	
DY 1, DS 1 vs 3	*0.01139*	*0.02861*	*0.40*	*0.6916*	
DY 1, DS 1 vs 4	*-0.00556*	*0.02861*	*-0.19*	*0.8465*	
DY 2, DS TREND	*0.06417*	*0.09046*	*0.71*	*0.4802*	
DY 2, DS 1 vs 2	*-0.00389*	*0.02861*	*-0.14*	*0.8922*	
DY 2, DS 1 vs 3	*0.01194*	*0.02861*	*0.42*	*0.6774*	
DY 2, DS 1 vs 4	*0.01611*	*0.02861*	*0.56*	*0.5749*	

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Hindlimb Grip Strength

Female

CovParm	Estimate
RAT(dose)	*0.001331*
Residual	*0.003138*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
day	*1*	*44*	*216.72*	*<.0001*	*day*	*
dose	*3*	*44*	*1.41*	*0.2535*	*dose*	
*day*dose*	*3*	*44*	*0.19*	*0.9048*	*day*dose*	

FEMALE hgrip, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*-0.04056*	*0.06952*	*-0.58*	*0.5626*	
DY 1, DS TREND	*-0.00944*	*0.08630*	*-0.11*	*0.9131*	
DY 1, DS 1 vs 2	*0.005000*	*0.02729*	*0.18*	*0.8551*	
DY 1, DS 1 vs 3	*-0.02611*	*0.02729*	*-0.96*	*0.3416*	
DY 1, DS 1 vs 4	*0.007222*	*0.02729*	*0.26*	*0.7920*	
DY 2, DS TREND	*-0.07167*	*0.08630*	*-0.83*	*0.4088*	
DY 2, DS 1 vs 2	*-0.00778*	*0.02729*	*-0.28*	*0.7764*	
DY 2, DS 1 vs 3	*-0.04944*	*0.02729*	*-1.81*	*0.0737*	
DY 2, DS 1 vs 4	*-0.01000*	*0.02729*	*-0.37*	*0.7150*	

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Rearing

Male

CovParm	Estimate
RAT(dose)	*6.2159*
Residual	*3.2064*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
day	*1*	*44*	*16.84*	*0.0002*	*day*	*
dose	*3*	*44*	*0.70*	*0.5567*	*dose*	
*day*dose*	*3*	*44*	*0.41*	*0.7486*	*day*dose*	

MALE rearing, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*4.7500*	*3.6100*	*1.32*	*0.1951*	
DY 1, DS TREND	*4.4167*	*3.9628*	*1.11*	*0.2694*	
DY 1, DS 1 vs 2	*0.7500*	*1.2532*	*0.60*	*0.5517*	
DY 1, DS 1 vs 3	*0.6667*	*1.2532*	*0.53*	*0.5967*	
DY 1, DS 1 vs 4	*1.5000*	*1.2532*	*1.20*	*0.2359*	
DY 2, DS TREND	*5.0833*	*3.9628*	*1.28*	*0.2044*	
DY 2, DS 1 vs 2	*-0.1667*	*1.2532*	*-0.13*	*0.8946*	
DY 2, DS 1 vs 3	*0.1667*	*1.2532*	*0.13*	*0.8946*	
DY 2, DS 1 vs 4	*1.5833*	*1.2532*	*1.26*	*0.2112*	

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Rearing

Female

CovParm	Estimate
RAT(dose)	*2.2708*
Residual	*6.8703*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
day	*1*	*44*	*0.18*	*0.6705*	*day*	
dose	*3*	*44*	*0.10*	*0.9578*	*dose*	
*day*dose*	*3*	*44*	*0.73*	*0.5424*	*day*dose*	

FEMALE rearing, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*-0.6250*	*3.0838*	*-0.20*	*0.8403*	
DY 1, DS TREND	*1.5000*	*3.9032*	*0.38*	*0.7017*	
DY 1, DS 1 vs 2	*-0.08333*	*1.2343*	*-0.07*	*0.9463*	
DY 1, DS 1 vs 3	*1.1667*	*1.2343*	*0.95*	*0.3473*	
DY 1, DS 1 vs 4	*0.08333*	*1.2343*	*0.07*	*0.9463*	
DY 2, DS TREND	*-2.7500*	*3.9032*	*-0.70*	*0.4831*	
DY 2, DS 1 vs 2	*0.08333*	*1.2343*	*0.07*	*0.9463*	
DY 2, DS 1 vs 3	*-0.6667*	*1.2343*	*-0.54*	*0.5906*	
DY 2, DS 1 vs 4	*-0.6667*	*1.2343*	*-0.54*	*0.5906*	

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Hindlimb Splay

Male

CovParm	Estimate
RAT(dose)	*1.0718*
Residual	*1.8339*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
day	*1*	*44*	*26.96*	*<.0001*	*day*	*
dose	*3*	*44*	*0.65*	*0.5860*	*dose*	
*day*dose*	*3*	*44*	*1.41*	*0.2529*	*day*dose*	

MALE splay, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*2.4042*	*1.8206*	*1.32*	*0.1935*	
DAY 1, DOSE TREND	*4.4250*	*2.2007*	*2.01*	*0.0478*	
DAY 1, DOSE 1 vs 2	*0.2417*	*0.6959*	*0.35*	*0.7293*	
DAY 1, DOSE 1 vs 3	*0.7167*	*0.6959*	*1.03*	*0.3063*	
DAY 1, DOSE 1 vs 4	*1.3167*	*0.6959*	*1.89*	*0.0622*	
DAY 2, DOSE TREND	*0.3833*	*2.2007*	*0.17*	*0.8622*	
DAY 2, DOSE 1 vs 2	*0.3667*	*0.6959*	*0.53*	*0.5998*	
DAY 2, DOSE 1 vs 3	*0.6500*	*0.6959*	*0.93*	*0.3532*	
DAY 2, DOSE 1 vs 4	*0.03333*	*0.6959*	*0.05*	*0.9619*	

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Hindlimb Splay

Female

CovParm	Estimate
RAT(dose)	*1.1444*
Residual	*1.0044*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
day	*1*	*44*	*1.92*	*0.1730*	*day*	
dose	*3*	*44*	*1.76*	*0.1684*	*dose*	
*day*dose*	*3*	*44*	*0.30*	*0.8283*	*day*dose*	

FEMALE splay, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*0.7500*	*1.6566*	*0.45*	*0.6530*	
DAY 1, DOSE TREND	*-0.07500*	*1.8924*	*-0.04*	*0.9685*	
DAY 1, DOSE 1 vs 2	*-0.4667*	*0.5984*	*-0.78*	*0.4382*	
DAY 1, DOSE 1 vs 3	*-0.9667*	*0.5984*	*-1.62*	*0.1108*	
DAY 1, DOSE 1 vs 4	*0.1417*	*0.5984*	*0.24*	*0.8136*	
DAY 2, DOSE TREND	*1.5750*	*1.8924*	*0.83*	*0.4081*	
DAY 2, DOSE 1 vs 2	*-0.1583*	*0.5984*	*-0.26*	*0.7921*	
DAY 2, DOSE 1 vs 3	*-0.5583*	*0.5984*	*-0.93*	*0.3541*	
DAY 2, DOSE 1 vs 4	*0.6583*	*0.5984*	*1.10*	*0.2751*	

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

Body Temperature
Male

JONCKHEERE RESULTS MALE tempture, FULL DATA	JONC	ZCCF	P1UPCF	P1DNCF	SIGNIF
	.	.	.	.	
DAY 1, BIN 1, HIDOSE 4	*359.0*	*-1.34067*	*0.90999*	*0.08705*	
DAY 2, BIN 1, HIDOSE 4	*383.5*	*-0.88684*	*0.81242*	*0.18265*	

There was a variance heterogeneity problem for which no variance stabilizing transform could be found, so a non-parametric analysis was done.

Body Temperature
Female

CovParm	Estimate
RAT(dose)	*0.04934*
Residual	*0.3056*

Effect	NumDF	DenDF	FValue	ProbF	SOURCE	SIGNIF
day	*1*	*44*	*49.22*	*<.0001*	*day*	*
dose	*3*	*44*	*2.50*	*0.0715*	*dose*	
*day*dose*	*3*	*44*	*1.72*	*0.1777*	*day*dose*	

FEMALE tempture, reml, simple, FULL	Estimate	Standard Error	t Value	Pr > |t|	SIGNIF
LINEAR TREND:DOSE	*1.5833*	*0.5804*	*2.73*	*0.0091*	*
DAY 1, DOSE TREND	*1.0833*	*0.7691*	*1.41*	*0.1626*	
DAY 1, DOSE 1 vs 2	*0.3167*	*0.2432*	*1.30*	*0.1964*	
DAY 1, DOSE 1 vs 3	*0.4750*	*0.2432*	*1.95*	*0.0541*	
DAY 1, DOSE 1 vs 4	*0.3083*	*0.2432*	*1.27*	*0.2083*	
DAY 2, DOSE TREND	*2.0833*	*0.7691*	*2.71*	*0.0081*	*
DAY 2, DOSE 1 vs 2	*0.09167*	*0.2432*	*0.38*	*0.7072*	
DAY 2, DOSE 1 vs 3	*0.1750*	*0.2432*	*0.72*	*0.4738*	
DAY 2, DOSE 1 vs 4	*0.6667*	*0.2432*	*2.74*	*0.0074*	*

If the DOSE*DAY interaction is not significant and the dose-trend on a given day is also not significant, then comparisons of individual treatment groups to control are ignored. Furthermore, if this interaction is not significant, then tests for dose-trend are adjusted for the number of such combinations tested.

APPENDIX HH

Individual Animal Clinical Pathology Data

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES

ABBREVIATIONS:

General:

ADEQ - adequate
CLOT - sample clotted
DECR - decreased
INCR - increased
NT - not taken or not performed
OK - sample condition OK for testing
RNV - result not valid
UTD - unable to determine
< - less than

Individual Hematology Values:

COND - sample condition
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

Individual Red Blood Cell Morphology Values:

NORM - Normal
ANIS - anisocytosis
MIC - microcytes
MAC - macrocytes
POLY - polychromasia
HYPO - hypochromasia
ECHI - echinocytes
ACAN - acanthocytes
TARG - Target cells
RX - rouleaux
HJB - Howell-Jolly body
- - not observed or not examined; see whole blood sample condition

Individual White Blood Cell / Platelet Morphology Values:

NORM - Normal
SM - Smudge white blood cells
TOX - toxic neutrophils
DB - Döhle bodies
VC - vacuolated cytoplasm
BC - basophilic cytoplasm
PCE - platelet clumps / estimate
GP - giant platelets
BP - bizarre platelets
- - not observed or not examined; see whole blood sample condition

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES (Continued)

ABBREVIATIONS: (Continued)

Individual Coagulation Values:

PHEM - plasma hemolysis
PLIP - plasma lipemia
PICT - plasma icterus
PT - prothrombin time
APTT - activated partial thromboplastin time

Individual Clinical Chemistry Values:

SHEM - serum hemolysis
SLIP - serum lipemia
SICT - serum icterus
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

NOTES:

When individual animal data are not reported, it may be due to one of the following reasons or other reasons, all of which are explained in the study records:

the sample was clotted (CLOT)
there was insufficient sample for testing (QNS)
a valid result could not be obtained (RNV)
the sample was not suitable for testing
the animal died prior to sample collection
no sample was available for testing (NSR)

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 <0.10, 0.05 was used for any calculations performed with that data.

Individual Hematology Values

Animal Number	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$
Male, Group I - 0 mg/kg/day - Day 30												
1	OK	7.92	15.0	46.6	58.9	18.9	32.1	10.7	210.7	1183	10.09	1.59
8	OK	7.99	15.3	47.5	59.5	19.2	32.2	11.1	173.2	999	15.20	2.30
10	OK	8.59	16.7	50.9	59.3	19.5	32.8	11.1	222.7	1129	14.00	1.68
12	OK	7.93	15.6	48.0	60.5	19.7	32.5	11.0	192.9	1170	17.48	1.36
13	OK	8.12	15.8	48.3	59.5	19.5	32.7	11.3	182.6	1073	11.83	2.22
22	OK	7.88	15.0	46.4	58.9	19.0	32.3	10.6	162.7	1267	10.53	1.77
31	OK	8.19	15.5	47.6	58.0	18.9	32.6	11.2	221.0	1086	15.25	2.58
36	OK	7.85	16.0	50.8	64.8	20.3	31.4	13.2	237.6	998	10.87	1.38
41	OK	7.63	15.1	47.4	62.2	19.8	31.8	10.5	155.3	958	13.30	1.81
44	OK	8.06	16.1	49.7	61.7	19.9	32.3	10.9	195.2	1150	15.55	2.79
45	OK	8.38	15.4	48.3	57.7	18.4	31.9	10.7	164.8	RNV	14.25	2.06
54	OK	7.95	14.6	46.1	57.9	18.4	31.7	11.7	169.5	1351	16.37	1.92
Male, Group III - 35 mg/kg/day - Day 30												
3	OK	8.62	15.4	48.8	56.6	17.9	31.6	11.6	203.2	1252	15.50	2.72
5	OK	8.12	16.4	49.8	61.3	20.2	33.0	10.6	217.1	1233	9.42	1.55
14	OK	8.52	16.3	49.7	58.3	19.1	32.8	10.9	200.3	1126	13.31	1.29
18	OK	8.03	16.0	49.2	61.3	19.9	32.5	10.7	231.8	1101	16.38	2.54
20	OK	8.05	15.0	46.0	57.1	18.6	32.6	11.3	192.5	RNV	13.53	1.97
26	OK	7.68	15.6	48.3	62.9	20.2	32.2	11.1	205.9	949	11.66	2.43
35	OK	8.34	15.2	48.3	57.9	18.2	31.5	12.0	203.0	1403	11.84	1.90
46	OK	7.74	15.5	47.9	61.9	20.0	32.4	10.9	219.7	RNV	15.88	2.54
48	OK	8.05	15.5	48.1	59.8	19.2	32.2	10.8	198.8	1209	13.74	2.81
50	OK	8.18	15.8	48.7	59.5	19.3	32.3	11.6	220.9	1451	14.27	2.42
55	OK	8.09	15.2	47.5	58.8	18.8	31.9	11.4	170.4	1022	11.73	1.50
56	OK	7.52	15.0	46.3	61.5	20.0	32.4	11.2	237.4	1176	16.79	3.70

Individual Hematology Values

Animal Number	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$
Male, Group V - 125 mg/kg/day - Day 30												
4	OK	8.64	16.4	51.3	59.4	19.0	32.1	10.9	213.0	959	10.21	1.61
9	OK	8.03	15.7	47.7	59.4	19.6	33.0	10.8	303.0	1051	14.38	1.45
25	OK	9.13	16.4	51.8	56.7	18.0	31.7	11.1	206.6	1263	14.66	3.03
28	OK	8.14	15.8	48.5	59.6	19.4	32.5	11.4	232.0	1054	9.43	1.79
30	OK	8.08	15.0	47.3	58.5	18.6	31.8	11.6	248.9	1195	12.31	2.13
32	OK	8.76	15.7	48.8	55.8	17.9	32.2	11.7	229.3	1267	13.32	2.51
37	OK	7.88	15.4	48.0	60.9	19.5	32.1	10.5	260.4	RNV	7.99	1.37
38	OK	7.72	15.3	46.8	60.6	19.8	32.7	11.2	192.7	1137	18.57	2.88
43	OK	8.49	15.7	48.8	57.4	18.5	32.2	10.9	216.6	RNV	13.15	1.73
47	OK	8.08	15.9	48.6	60.2	19.7	32.8	11.7	213.9	RNV	15.21	2.53
49	OK	8.97	16.3	52.3	58.3	18.2	31.3	11.2	217.5	1006	12.52	1.70
51	OK	8.27	15.7	49.0	59.2	19.0	32.1	11.3	199.4	1083	16.39	2.69
Male, Group VII - 375 mg/kg/day - Day 30												
2	OK	8.37	15.3	47.4	56.7	18.3	32.3	11.0	147.2	896	16.49	1.60
6	OK	8.58	16.2	50.6	59.0	18.9	32.0	11.1	221.1	RNV	13.08	3.53
11	OK	7.93	15.7	49.0	61.9	19.8	32.0	11.4	206.8	1115	12.05	2.07
16	OK	8.16	15.6	48.5	59.4	19.1	32.1	11.3	207.2	1176	11.98	1.94
19	OK	8.37	15.0	47.4	56.7	18.0	31.7	11.5	166.5	1063	9.06	1.83
21	OK	8.24	16.3	51.5	62.6	19.8	31.6	10.7	220.3	982	11.59	1.57
27	OK	8.36	15.3	47.8	57.1	18.2	31.9	11.2	208.8	992	10.33	1.77
33	OK	8.58	16.1	49.9	58.1	18.8	32.3	11.3	205.7	1185	14.28	1.77
39	OK	8.33	16.1	50.5	60.6	19.3	31.9	11.3	269.8	1301	21.28	3.90
40	OK	8.56	16.1	50.6	59.2	18.9	31.9	10.7	170.1	RNV	14.30	3.42
52	OK	7.77	15.8	48.3	62.1	20.4	32.8	11.1	193.4	1051	12.61	1.96
53	OK	7.72	14.5	45.5	58.9	18.8	32.0	13.1	261.4	1102	16.76	2.21

Individual Hematology Values

Animal Number	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
Male, Group I - 0 mg/kg/day - Day 30					
1	8.16	0.19	0.08	0.04	0.04
8	12.16	0.40	0.10	0.15	0.09
10	11.65	0.36	0.13	0.10	0.09
12	15.24	0.41	0.22	0.10	0.14
13	8.99	0.35	0.13	0.07	0.07
22	8.28	0.31	0.07	0.03	0.07
31	12.13	0.32	0.13	0.04	0.05
36	9.11	0.19	0.06	0.03	0.09
41	10.90	0.29	0.14	0.09	0.07
44	12.14	0.42	0.08	0.07	0.06
45	11.72	0.27	0.06	0.06	0.08
54	13.64	0.31	0.19	0.11	0.20
Male, Group III - 35 mg/kg/day - Day 30					
3	12.18	0.21	0.21	0.11	0.07
5	7.39	0.31	0.07	0.05	0.05
14	11.47	0.24	0.15	0.09	0.07
18	13.17	0.41	0.08	0.07	0.11
20	11.01	0.30	0.09	0.05	0.11
26	8.68	0.34	0.08	0.04	0.09
35	9.37	0.34	0.15	0.04	0.05
46	12.62	0.41	0.12	0.06	0.13
48	10.36	0.25	0.14	0.09	0.09
50	11.19	0.34	0.13	0.07	0.12
55	9.85	0.16	0.11	0.06	0.05
56	12.26	0.39	0.29	0.07	0.07

Individual Hematology Values

Animal Number	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
Male, Group V - 125 mg/kg/day - Day 30					
4	8.10	0.25	0.11	0.09	0.05
9	12.33	0.30	0.09	0.09	0.12
25	11.08	0.28	0.13	0.07	0.08
28	7.21	0.21	0.10	0.07	0.06
30	9.51	0.33	0.23	0.06	0.05
32	10.10	0.30	0.26	0.07	0.08
37	6.31	0.19	0.06	0.03	0.04
38	14.85	0.42	0.14	0.08	0.20
43	10.92	0.23	0.10	0.08	0.07
47	12.08	0.32	0.09	0.07	0.12
49	10.40	0.21	0.09	0.04	0.08
51	13.09	0.37	0.10	0.07	0.08
Male, Group VII - 375 mg/kg/day - Day 30					
2	14.19	0.37	0.10	0.08	0.16
6	9.00	0.28	0.13	0.08	0.07
11	9.61	0.17	0.09	0.04	0.06
16	9.58	0.25	0.08	0.05	0.09
19	6.82	0.26	0.04	0.05	0.07
21	9.36	0.40	0.05	0.09	0.12
27	8.25	0.15	0.08	0.04	0.03
33	12.07	0.17	0.09	0.08	0.10
39	16.35	0.41	0.30	0.12	0.21
40	10.33	0.40	0.04	0.04	0.05
52	10.20	0.27	0.07	0.04	0.06
53	13.71	0.51	0.20	0.06	0.09

Individual Hematology Values

Animal Number	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$
Female, Group II - 0 mg/kg/day - Day 31												
69	OK	8.05	16.6	48.8	60.7	20.6	34.0	10.9	169.2	1104	9.55	0.66
89	OK	7.65	15.8	47.3	61.8	20.6	33.4	10.6	185.9	1169	12.31	0.89
101	OK	8.02	15.7	48.1	60.0	19.6	32.6	10.2	243.3	1414	13.34	0.69
112	OK	7.86	15.7	47.2	60.0	20.0	33.3	10.8	201.3	1109	8.45	1.68
113	OK	7.36	14.6	43.4	58.9	19.9	33.7	11.1	143.9	RNV	13.68	1.43
123	OK	7.87	15.3	45.7	58.1	19.4	33.4	10.5	155.6	RNV	8.66	1.00
126	CLOT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
144	OK	8.31	16.7	50.3	60.6	20.1	33.2	10.6	185.6	RNV	9.91	1.14
152	OK	8.50	16.2	48.7	57.3	19.1	33.2	10.6	135.1	RNV	13.51	1.09
155	OK	7.97	15.8	48.5	60.9	19.8	32.5	10.4	246.7	RNV	9.79	1.01
162	OK	7.11	15.0	43.1	60.6	21.0	34.7	10.7	157.0	1154	10.84	1.77
163	OK	7.96	15.3	46.6	58.6	19.3	32.9	10.6	163.2	1222	7.56	0.75
Female, Group IV - 35 mg/kg/day - Day 31												
71	OK	8.10	15.9	47.5	58.6	19.7	33.6	10.6	167.0	891	12.54	1.83
75	OK	7.70	16.1	48.5	62.9	20.9	33.2	10.8	245.9	RNV	10.64	1.56
83	OK	7.60	15.1	46.3	60.9	19.9	32.7	10.7	231.8	1258	9.89	2.16
107	OK	8.01	15.5	47.8	59.7	19.3	32.4	10.8	203.2	849	7.05	0.57
119	OK	8.03	16.0	48.2	60.0	19.9	33.1	10.3	142.9	1173	7.19	1.24
120	OK	8.10	15.3	46.4	57.2	18.9	33.0	10.5	195.3	RNV	11.07	1.27
128	OK	7.84	16.2	49.7	63.5	20.6	32.5	10.5	251.6	1256	6.37	1.01
138	OK	7.74	15.4	47.3	61.1	19.8	32.5	11.2	159.9	RNV	7.74	1.18
145	OK	7.93	16.0	47.5	59.9	20.2	33.7	10.7	136.0	1153	9.82	0.77
149	OK	7.58	15.1	44.9	59.3	20.0	33.7	10.4	137.8	1305	11.91	1.16
160	OK	7.21	15.2	45.8	63.6	21.1	33.3	11.0	163.8	1314	14.41	1.11
164	OK	7.92	16.0	48.1	60.7	20.2	33.2	10.5	177.0	957	9.07	0.97

Individual Hematology Values

Animal Number	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$
Female, Group VI - 125 mg/kg/day - Day 31												
62	OK	7.68	15.3	46.3	60.3	19.9	33.0	10.4	124.6	1144	10.51	0.71
79	OK	7.43	15.4	46.0	62.0	20.7	33.4	10.3	153.9	1167	11.17	0.73
99	OK	7.63	14.8	45.8	60.0	19.4	32.4	10.9	240.1	RNV	12.45	0.49
135	OK	8.35	15.7	48.2	57.7	18.8	32.7	10.8	233.2	966	9.08	1.04
142	OK	7.80	15.4	45.7	58.7	19.7	33.6	11.2	224.8	RNV	8.94	1.18
143	OK	8.10	16.4	50.0	61.8	20.2	32.7	10.4	226.5	1021	13.25	2.27
147	CLOT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
150	OK	8.02	15.6	49.1	61.2	19.4	31.7	11.9	248.2	RNV	7.02	1.12
153	CLOT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
154	OK	7.19	15.1	45.8	63.6	21.0	33.1	11.0	153.3	1411	11.58	1.95
156	OK	8.14	15.9	48.6	59.7	19.6	32.8	11.1	140.6	1268	8.52	1.20
161	OK	8.11	15.8	48.4	59.6	19.5	32.7	11.3	128.0	RNV	9.86	1.10
Female, Group VIII - 375 mg/kg/day - Day 31												
67	OK	7.44	15.0	45.1	60.5	20.1	33.2	11.0	243.4	RNV	7.78	1.14
68	OK	7.52	15.5	45.8	60.8	20.6	33.9	10.4	235.1	1108	10.14	1.04
70	OK	7.78	15.5	46.8	60.1	19.9	33.1	10.9	252.9	1144	14.58	1.60
76	OK	7.25	15.5	47.8	65.9	21.3	32.3	11.4	295.7	940	8.47	1.83
77	OK	7.47	14.7	45.0	60.3	19.7	32.6	11.6	260.4	1213	9.23	1.95
84	OK	7.71	15.4	46.3	60.1	20.0	33.2	11.7	165.1	RNV	9.28	1.75
88	OK	7.78	16.0	48.0	61.6	20.6	33.5	11.2	368.4	1163	10.08	1.75
114	OK	7.71	14.9	45.6	59.2	19.4	32.7	11.4	271.2	1265	5.89	0.65
129	OK	7.26	14.1	43.8	60.3	19.4	32.2	10.8	196.7	1537	13.85	0.92
146	OK	8.03	15.5	47.5	59.2	19.3	32.6	11.6	269.0	1105	12.45	1.24
151	OK	7.57	15.0	45.3	59.9	19.8	33.0	10.7	198.0	RNV	10.50	1.82
159	OK	7.46	15.3	46.0	61.6	20.5	33.4	10.3	139.0	969	10.35	0.89

Individual Hematology Values

Animal Number	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
Female, Group II - 0 mg/kg/day - Day 31					
69	8.48	0.17	0.11	0.05	0.08
89	10.88	0.30	0.10	0.07	0.06
101	12.14	0.18	0.09	0.08	0.15
112	6.40	0.14	0.10	0.07	0.05
113	11.26	0.31	0.38	0.14	0.17
123	7.16	0.30	0.11	0.05	0.04
126	NT	NT	NT	NT	NT
144	8.15	0.38	0.08	0.04	0.11
152	11.85	0.31	0.10	0.05	0.10
155	8.20	0.25	0.16	0.06	0.11
162	8.65	0.22	0.10	0.04	0.06
163	6.38	0.23	0.06	0.06	0.08
Female, Group IV - 35 mg/kg/day - Day 31					
71	10.21	0.17	0.06	0.16	0.11
75	8.64	0.20	0.14	0.04	0.06
83	7.38	0.16	0.10	0.03	0.06
107	6.18	0.07	0.13	0.05	0.05
119	5.64	0.17	0.10	0.02	0.03
120	9.16	0.21	0.23	0.08	0.12
128	5.11	0.09	0.10	0.03	0.03
138	6.21	0.18	0.10	0.03	0.05
145	8.79	0.13	0.06	0.03	0.05
149	10.40	0.15	0.09	0.05	0.08
160	12.55	0.41	0.06	0.06	0.21
164	7.75	0.15	0.10	0.04	0.06

Individual Hematology Values

Animal Number	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
Female, Group VI - 125 mg/kg/day - Day 31					
62	9.26	0.23	0.20	0.06	0.06
79	9.97	0.21	0.06	0.08	0.11
99	11.51	0.24	0.06	0.06	0.08
135	7.61	0.25	0.07	0.04	0.08
142	7.26	0.16	0.23	0.04	0.07
143	10.22	0.31	0.19	0.14	0.12
147	NT	NT	NT	NT	NT
150	5.58	0.19	0.07	0.02	0.05
153	NT	NT	NT	NT	NT
154	9.11	0.30	0.09	0.05	0.08
156	6.97	0.18	0.09	0.04	0.04
161	8.36	0.16	0.12	0.03	0.08
Female, Group VIII - 375 mg/kg/day - Day 31					
67	6.29	0.16	0.10	0.02	0.06
68	8.60	0.27	0.11	0.04	0.07
70	12.48	0.13	0.13	0.13	0.11
76	6.33	0.16	0.07	0.04	0.04
77	7.01	0.09	0.09	0.02	0.06
84	7.05	0.24	0.12	0.05	0.07
88	7.83	0.24	0.15	0.04	0.08
114	4.99	0.11	0.10	0.02	0.03
129	12.60	0.13	0.06	0.04	0.10
146	10.50	0.32	0.18	0.06	0.16
151	8.19	0.18	0.16	0.07	0.08
159	8.96	0.28	0.09	0.02	0.10

Individual Red Blood Cell Morphology Values

Animal Number	NORM	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
Male, Group I - 0 mg/kg/day - Day 30											
1	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
8	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
10	NO	-	-	-	TRACE	-	TRACE	FEW	-	-	-
12	NO	-	-	-	TRACE	-	-	TRACE	-	-	-
13	NO	-	-	-	TRACE	-	FEW	MODERATE	-	-	-
22	NO	-	-	-	TRACE	-	MODERATE	FEW	-	-	-
31	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	TRACE
36	NO	-	-	-	TRACE	-	-	-	-	-	-
41	NO	-	-	-	TRACE	-	-	TRACE	-	-	-
44	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
45	NO	-	-	-	TRACE	-	-	FEW	-	-	-
54	NO	-	-	-	TRACE	-	TRACE	FEW	-	-	-
Male, Group III - 35 mg/kg/day - Day 30											
3	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
5	NO	-	-	-	TRACE	-	TRACE	-	-	-	-
14	NO	-	-	-	TRACE	-	TRACE	FEW	-	-	-
18	NO	-	-	-	TRACE	-	TRACE	FEW	-	-	-
20	NO	-	-	-	TRACE	-	FEW	TRACE	-	-	-
26	NO	-	-	-	TRACE	-	FEW	TRACE	-	-	-
35	NO	-	-	-	TRACE	-	TRACE	MODERATE	-	-	-
46	NO	-	-	-	TRACE	-	-	TRACE	-	-	-
48	NO	-	-	-	TRACE	-	-	FEW	-	-	-
50	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
55	NO	-	-	-	TRACE	-	-	-	-	-	-
56	NO	-	-	-	TRACE	-	-	-	-	-	-

Individual Red Blood Cell Morphology Values

Animal Number	NORM	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
Male, Group V - 125 mg/kg/day - Day 30											
4	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
9	NO	-	-	-	TRACE	-	TRACE	-	-	-	-
25	NO	-	-	-	TRACE	-	TRACE	FEW	-	-	-
28	NO	-	-	-	TRACE	-	-	TRACE	-	-	-
30	NO	-	-	-	TRACE	-	TRACE	FEW	-	-	-
32	NO	-	-	-	TRACE	-	FEW	TRACE	-	-	-
37	NO	-	-	-	TRACE	-	-	-	-	-	-
38	NO	-	-	-	TRACE	-	-	TRACE	-	-	-
43	NO	-	-	-	TRACE	-	-	-	-	-	-
47	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
49	NO	-	-	-	TRACE	-	-	-	-	-	-
51	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
Male, Group VII - 375 mg/kg/day - Day 30											
2	NO	-	-	-	TRACE	-	-	TRACE	-	-	-
6	NO	-	-	-	TRACE	-	-	TRACE	-	-	-
11	NO	-	-	-	TRACE	-	TRACE	-	-	-	-
16	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
19	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
21	NO	-	-	-	TRACE	-	-	-	-	-	-
27	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
33	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
39	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
40	NO	-	-	-	TRACE	-	FEW	-	-	-	-
52	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
53	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-

Individual Red Blood Cell Morphology Values

Animal Number	NORM	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
Female, Group II - 0 mg/kg/day - Day 31											
69	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
89	NO	-	-	-	TRACE	-	MODERATE	FEW	-	-	-
101	NO	-	-	-	TRACE	-	MODERATE	FEW	-	-	-
112	NO	-	-	-	TRACE	-	MODERATE	FEW	-	-	-
113	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
123	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
126	CLOT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
144	NO	-	-	-	TRACE	-	-	-	-	-	-
152	NO	-	-	-	TRACE	-	MODERATE	-	-	-	-
155	NO	-	-	-	TRACE	-	-	-	-	-	-
162	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
163	NO	-	-	-	TRACE	-	-	-	-	-	-
Female, Group IV - 35 mg/kg/day - Day 31											
71	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
75	NO	-	-	-	TRACE	-	FEW	TRACE	-	-	-
83	NO	-	-	-	TRACE	-	TRACE	-	-	-	-
107	NO	-	-	-	TRACE	-	FEW	TRACE	-	-	-
119	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
120	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
128	NO	-	-	-	TRACE	-	-	-	-	-	-
138	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
145	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
149	NO	-	-	-	TRACE	-	FEW	TRACE	-	-	-
160	NO	-	-	-	TRACE	-	-	-	-	-	-
164	NO	-	-	-	TRACE	-	-	-	-	-	-

Individual Red Blood Cell Morphology Values

Animal Number	NORM	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
Female, Group VI - 125 mg/kg/day - Day 31											
62	NO	-	-	-	TRACE	-	MANY	FEW	-	-	-
79	NO	-	-	-	TRACE	-	FEW	TRACE	-	-	-
99	NO	-	-	-	TRACE	-	MODERATE	FEW	-	-	-
135	NO	-	-	-	TRACE	-	TRACE	-	-	-	-
142	NO	-	-	-	TRACE	-	FEW	-	-	-	-
143	NO	-	-	-	TRACE	-	-	-	-	-	-
147	CLOT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
150	NO	-	-	-	TRACE	-	MANY	MODERATE	-		TRACE
153	CLOT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
154	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
156	NO	-	-	-	TRACE	-	-	-	-	-	-
161	NO	-	-	-	TRACE	-	TRACE	-		-	-
Female, Group VIII - 375 mg/kg/day - Day 31											
67	NO	-	-	-	FEW	-	MODERATE	FEW	-	-	-
68	NO	-	-	-	TRACE	-	-	-	-		-
70	NO	-	-	-	TRACE	-	MANY	FEW	-	-	-
76	NO	-	-	-	FEW	-	TRACE	-	-	-	-
77	NO	-	-	-	TRACE	-	MANY	FEW	-	-	-
84	NO	-	-	-	TRACE	-	TRACE	FEW	-	-	-
88	NO	-	-	-	FEW	-	FEW	TRACE	-	-	-
114	NO	-	-	-	TRACE	-	TRACE	-	-	-	-
129	NO	-	-	-	TRACE	-	MODERATE	TRACE	-	-	-
146	NO	-	-	-	TRACE	-	MODERATE	FEW	-	-	TRACE
151	NO	-	-	-	FEW	-	TRACE	TRACE	-	-	-
159	NO	-	-	-	TRACE	-	-	-	-	-	-

Individual White Blood Cell / Platelet Morphology Values

Animal Number	NORM	SM	TOX	DB	VC	BC	PCE	GP	BP
Male, Group I - 0 mg/kg/day - Day 30									
1	YES	-	-	-	-	-	-	-	-
8	YES	-	-	-	-	-	-	-	-
10	YES	-	-	-	-	-	-	-	-
12	YES	-	-	-	-	-	-	-	-
13	YES	-	-	-	-	-	-	-	-
22	YES	-	-	-	-	-	-	-	-
31	YES	-	-	-	-	-	-	-	-
36	NO	-	-	-	-	-	-	TRACE	-
41	YES	-	-	-	-	-	-	-	-
44	NO	-	-	-	-	-	-	TRACE	-
45	NO	-	-	-	-	-	YES/ADEQ	-	-
54	YES	-	-	-	-	-	-	-	-
Male, Group III - 35 mg/kg/day - Day 30									
3	YES	-	-	-	-	-	-	-	-
5	YES	-	-	-	-	-	-	-	-
14	YES	-	-	-	-	-	-	-	-
18	NO	-	-	-	-	-	-	TRACE	-
20	NO	-	-	-	-	-	YES/ADEQ	TRACE	-
26	YES	-	-	-	-	-	-	-	-
35	YES	-	-	-	-	-	-	-	-
46	NO	-	-	-	-	-	YES/DECR	-	-
48	YES	-	-	-	-	-	-	-	-
50	YES	-	-	-	-	-	-	-	-
55	YES	-	-	-	-	-	-	-	-
56	YES	-	-	-	-	-	-	-	-

Individual White Blood Cell / Platelet Morphology Values

Animal Number	NORM	SM	TOX	DB	VC	BC	PCE	GP	BP
Male, Group V - 125 mg/kg/day - Day 30									
4	YES	-	-	-	-	-	-	-	-
9	YES	-	-	-	-	-	-	-	-
25	NO	-	-	-	-	-	-	TRACE	-
28	YES	-	-	-	-	-	-	-	-
30	NO	-	-	-	-	-	-	TRACE	-
32	YES	-	-	-	-	-	-	-	-
37	NO	-	-	-	-	-	YES/DECR	-	-
38	YES	-	-	-	-	-	-	-	-
43	NO	-	-	-	-	-	YES/ADEQ	-	-
47	NO	-	-	-	-	-	YES/DECR	-	-
49	YES	-	-	-	-	-	-	-	-
51	YES	-	-	-	-	-	-	-	-
Male, Group VII - 375 mg/kg/day - Day 30									
2	YES	-	-	-	-	-	-	-	-
6	NO	-	-	-	-	-	YES/ADEQ	TRACE	-
11	YES	-	-	-	-	-	-	-	-
16	YES	-	-	-	-	-	-	-	-
19	YES	-	-	-	-	-	-	-	-
21	YES	-	-	-	-	-	-	-	-
27	YES	-	-	-	-	-	-	-	-
33	NO	-	-	-	-	-	-	TRACE	-
39	YES	-	-	-	-	-	-	-	-
40	NO	-	-	-	-	-	YES/DECR	-	-
52	YES	-	-	-	-	-	-	-	-
53	YES	-	-	-	-	-	-	-	-

Individual White Blood Cell / Platelet Morphology Values

Animal Number	NORM	SM	TOX	DB	VC	BC	PCE	GP	BP
Female, Group II - 0 mg/kg/day - Day 31									
69	YES	-	-	-	-	-	-	-	-
89	YES	-	-	-	-	-	-	-	-
101	YES	-	-	-	-	-	-	-	-
112	YES	-	-	-	-	-	-	-	-
113	NO	-	-	-	-	-	YES/INCR	-	-
123	NO	-	-	-	-	-	YES/INCR	-	-
126	CLOT	NT	NT	NT	NT	NT	NT	NT	NT
144	NO	-	-	-	-	-	YES/ADEQ	-	-
152	NO	-	-	-	-	-	YES/UTD	-	-
155	NO	-	-	-	-	-	YES/ADEQ	-	-
162	YES	-	-	-	-	-	-	-	-
163	YES	-	-	-	-	-	-	-	-
Female, Group IV - 35 mg/kg/day - Day 31									
71	YES	-	-	-	-	-	-	-	-
75	NO	-	-	-	-	-	YES/UTD	-	
83	NO	-	-	-	-	-	-	TRACE	-
107	YES	-	-	-	-	-	-	-	-
119	YES	-	-	-	-	-	-	-	-
120	NO	-	-	-	-	-	YES/ADEQ	-	-
128	NO	-	-	-	-	-	-	TRACE	-
138	NO	-	-	-	-	-	YES/ADEQ	-	-
145	YES	-	-	-	-	-	-	-	-
149	YES	-	-	-	-	-	-	-	-
160	YES	-	-	-	-	-	-	-	-
164	YES	-	-	-	-	-	-	-	-

Individual White Blood Cell / Platelet Morphology Values

Animal Number	NORM	SM	TOX	DB	VC	BC	PCE	GP	BP
Female, Group VI - 125 mg/kg/day - Day 31									
62	YES	-	-	-	-	-	-	-	-
79	YES	-	-	-	-	-	-	-	-
99	NO	-	-	-	-	-	YES/UTD	-	-
135	YES	-	-	-	-	-	-	-	-
142	NO	-	-	-	-	-	YES/UTD	-	-
143	YES	-	-	-	-	-	-	-	-
147	CLOT	NT	NT	NT	NT	NT	NT	NT	NT
150	NO	-	-	-	-	-	YES/ADEQ	-	-
153	CLOT	NT	NT	NT	NT	NT	NT	NT	NT
154	YES	-	-	-	-	-	-	-	-
156	YES	-	-	-	-	-	-	-	-
161	NO	-	-	-	-	-	YES/ADEQ	-	-
Female, Group VIII - 375 mg/kg/day - Day 31									
67	NO	-	-	-	-	-	YES/DECR	-	-
68	YES	-	-	-	-	-	-	-	-
70	YES	-	-	-	-	-	-	-	-
76	YES	-	-	-	-	-	-	-	-
77	YES	-	-	-	-	-	-	-	-
84	NO	-	-	-	-		YES/ADEQ	-	-
88	YES	-	-	-	-	-	-	-	-
114	YES	-	-	-	-	-	-	-	-
129	YES	-	-	-	-	-	-	-	-
146	YES	-	-	-	-	-	-	-	-
151	YES	-	-	-	-	-	-	-	-
159	YES	-	-	-	-	-	-	-	-

Individual Coagulation Values

Animal Number	PHEM	PLIP	PICT	PT sec	APTT sec
Male, Group I - 0 mg/kg/day - Day 30					
1	NONE	NONE	NONE	15.0	15.6
8	NONE	NONE	NONE	15.6	17.2
10	NONE	NONE	NONE	15.2	18.0
12	NONE	NONE	NONE	15.6	20.8
13	NONE	NONE	NONE	14.7	18.1
22	NONE	NONE	NONE	15.6	17.3
31	NONE	NONE	NONE	15.4	18.0
36	NONE	NONE	NONE	15.1	20.6
41	NONE	NONE	NONE	14.6	17.4
44	NONE	NONE	NONE	16.7	17.8
45	NONE	NONE	NONE	14.3	16.1
54	NONE	NONE	NONE	14.4	13.6
Male, Group III - 35 mg/kg/day - Day 30					
3	NONE	NONE	NONE	15.5	17.4
5	NONE	NONE	NONE	17.2	19.5
14	NONE	NONE	NONE	15.3	20.3
18	NONE	NONE	NONE	18.0	19.9
20	NONE	NONE	NONE	15.2	17.8
26	NONE	NONE	NONE	14.2	12.3
35	NONE	NONE	NONE	14.6	16.4
46	NONE	NONE	NONE	14.2	14.7
48	NONE	NONE	NONE	15.1	19.8
50	NONE	NONE	NONE	15.5	17.4
55	NONE	NONE	NONE	14.9	16.7
56	NONE	NONE	NONE	16.4	17.5

Individual Coagulation Values

Animal Number	PHEM	PLIP	PICT	PT sec	APTT sec
Male, Group V - 125 mg/kg/day - Day 30					
4	NONE	NONE	NONE	17.5	18.0
9	NONE	NONE	NONE	16.6	16.2
25	NONE	NONE	NONE	17.5	18.6
28	NONE	NONE	NONE	13.9	14.4
30	NONE	NONE	NONE	15.1	14.7
32	NONE	NONE	NONE	15.1	15.7
37	NONE	NONE	NONE	16.4	20.3
38	NONE	NONE	NONE	22.3	19.4
43	NONE	NONE	NONE	15.8	18.1
47	NONE	NONE	NONE	15.8	16.9
49	NONE	NONE	NONE	15.8	18.2
51	NONE	NONE	NONE	15.5	16.7
Male, Group VII - 375 mg/kg/day - Day 30					
2	NONE	NONE	NONE	14.7	17.4
6	NONE	NONE	NONE	15.1	14.0
11	NONE	NONE	NONE	15.6	16.5
16	NONE	NONE	NONE	22.6	20.6
19	NONE	NONE	NONE	16.7	17.6
21	NONE	NONE	NONE	15.0	15.8
27	NONE	NONE	NONE	14.3	15.4
33	NONE	NONE	NONE	17.1	18.9
39	NONE	NONE	NONE	15.6	16.2
40	NONE	NONE	NONE	16.2	17.9
52	NONE	NONE	NONE	15.9	19.2
53	NONE	NONE	NONE	14.6	16.3

Individual Coagulation Values

Animal Number	PHEM	PLIP	PICT	PT sec	APTT sec
Female, Group II - 0 mg/kg/day - Day 31					
69	NONE	NONE	NONE	14.8	15.8
89	NONE	NONE	NONE	15.1	18.3
101	NONE	NONE	NONE	15.0	12.8
112	NONE	NONE	NONE	15.8	18.1
113	NONE	NONE	NONE	14.6	16.5
123	NONE	NONE	NONE	15.0	12.6
126	NONE	NONE	NONE	13.0	14.7
144	NONE	NONE	NONE	14.7	18.0
152	NONE	NONE	NONE	14.2	14.2
155	NONE	NONE	NONE	14.2	13.1
162	NONE	NONE	NONE	14.7	16.1
163	NONE	NONE	NONE	14.7	18.2
Female, Group IV - 35 mg/kg/day - Day 31					
71	NONE	NONE	NONE	14.7	13.2
75	NONE	NONE	NONE	12.8	14.3
83	NONE	NONE	NONE	14.9	18.5
107	NONE	NONE	NONE	14.0	16.9
119	NONE	NONE	NONE	14.3	15.7
120	NONE	NONE	NONE	15.1	14.2
128	NONE	NONE	NONE	14.3	17.6
138	NONE	NONE	NONE	14.0	13.3
145	TRACE	NONE	NONE	12.8	12.3
149	NONE	NONE	NONE	13.0	16.1
160	NONE	NONE	NONE	13.4	13.0
164	NONE	NONE	NONE	14.0	15.3

Individual Coagulation Values

Animal Number	PHEM	PLIP	PICT	PT sec	APTT sec
Female, Group VI - 125 mg/kg/day - Day 31					
62	NONE	NONE	NONE	13.9	16.9
79	NONE	NONE	NONE	15.1	15.8
99	NONE	NONE	NONE	15.6	19.2
135	NONE	NONE	NONE	14.4	14.9
142	NONE	NONE	NONE	10.3	12.9
143	NONE	NONE	NONE	15.5	15.8
147	NONE	NONE	NONE	15.4	16.2
150	NONE	NONE	NONE	13.4	14.5
153	NONE	NONE	NONE	14.1	16.0
154	NONE	NONE	NONE	14.5	13.5
156	NONE	NONE	NONE	15.0	17.3
161	NONE	NONE	NONE	16.0	15.7
Female, Group VIII - 375 mg/kg/day - Day 31					
67	NONE	NONE	NONE	15.0	19.1
68	NONE	NONE	NONE	14.4	15.4
70	NONE	NONE	NONE	15.9	19.6
76	NONE	NONE	NONE	15.1	15.4
77	NONE	NONE	NONE	14.9	16.5
84	NONE	NONE	NONE	15.2	14.5
88	NONE	NONE	NONE	15.9	17.0
114	NONE	NONE	NONE	13.9	14.3
129	NONE	NONE	NONE	14.1	13.2
146	NONE	NONE	NONE	13.7	16.2
151	NONE	NONE	NONE	14.6	16.3
159	NONE	NONE	NONE	15.1	15.6

Individual Clinical Chemistry Values

Animal Number	SHEM	SLIP	SICT	AST U/L	ALT U/L	SDH U/L	ALKP U/L	BILI mg/dL	BUN mg/dL	CREA mg/dL	CHOL mg/dL	TRIG mg/dL
Male, Group I - 0 mg/kg/day - Day 30												
1	NONE	NONE	NONE	92	38	17.9	205	0.11	13	0.28	37	43
8	TRACE	NONE	NONE	66	23	10.3	147	<0.10	12	0.24	56	68
10	TRACE	NONE	NONE	100	29	10.1	160	0.12	14	0.33	53	39
12	TRACE	NONE	NONE	89	31	15.7	167	0.14	13	0.28	50	61
13	NONE	NONE	NONE	87	33	12.6	154	0.12	13	0.31	64	88
22	NONE	NONE	NONE	84	30	10.5	142	0.11	9	0.33	55	68
31	NONE	NONE	NONE	95	26	13.8	170	0.12	10	0.24	42	87
36	TRACE	NONE	NONE	79	30	11.5	160	0.11	12	0.28	53	30
41	NONE	NONE	NONE	81	32	14.9	154	0.13	14	0.29	44	69
44	NONE	NONE	NONE	81	30	10.6	192	0.15	11	0.28	60	66
45	NONE	NONE	NONE	89	30	7.0	195	0.12	13	0.30	43	40
54	NONE	NONE	NONE	119	42	16.0	126	0.13	10	0.26	58	76
Male, Group III - 35 mg/kg/day - Day 30												
3	NONE	NONE	NONE	97	31	16.9	138	0.13	13	0.35	56	65
5	NONE	NONE	NONE	89	34	16.4	150	0.12	12	0.33	56	29
14	NONE	NONE	NONE	80	24	11.8	146	<0.10	13	0.29	39	34
18	NONE	NONE	NONE	125	40	20.7	156	0.14	9	0.34	50	75
20	NONE	NONE	NONE	142	33	8.5	169	0.13	11	0.29	50	29
26	NONE	NONE	NONE	68	22	13.6	238	0.10	11	0.29	49	71
35	TRACE	NONE	NONE	76	28	16.2	134	0.11	13	0.31	40	30
46	NONE	NONE	NONE	77	25	22.7	199	<0.10	10	0.33	47	80
48	NONE	NONE	NONE	76	25	15.2	114	<0.10	9	0.30	45	38
50	NONE	NONE	NONE	99	42	20.2	157	0.14	9	0.26	55	78
55	NONE	NONE	NONE	75	27	11.6	200	0.11	13	0.35	53	77
56	NONE	NONE	NONE	96	39	9.4	127	0.12	11	0.18	45	56

Individual Clinical Chemistry Values

Animal Number	SHEM	SLIP	SICT	AST U/L	ALT U/L	SDH U/L	ALKP U/L	BILI mg/dL	BUN mg/dL	CREA mg/dL	CHOL mg/dL	TRIG mg/dL
Male, Group V - 125 mg/kg/day - Day 30												
4	NONE	NONE	NONE	91	30	20.7	270	0.10	13	0.34	45	87
9	TRACE	NONE	NONE	105	32	12.4	141	0.12	12	0.26	39	32
25	NONE	NONE	NONE	87	36	20.3	203	0.11	12	0.45	43	54
28	NONE	NONE	NONE	83	27	16.3	163	0.13	9	0.30	45	107
30	NONE	NONE	NONE	97	26	20.6	152	0.13	14	0.44	73	91
32	NONE	NONE	NONE	90	31	16.8	216	0.14	13	0.37	62	78
37	TRACE	NONE	NONE	96	29	11.8	147	0.12	11	0.30	59	30
38	NONE	NONE	NONE	89	28	17.2	174	0.13	11	0.27	60	31
43	NONE	NONE	NONE	99	34	15.1	236	0.15	12	0.34	51	38
47	TRACE	NONE	NONE	73	22	10.4	134	<0.10	12	0.27	50	50
49	NONE	NONE	NONE	87	26	11.8	213	0.13	12	0.34	45	46
51	TRACE	NONE	NONE	80	29	14.8	126	0.12	12	0.35	63	107
Male, Group VII - 375 mg/kg/day - Day 30												
2	NONE	NONE	NONE	77	26	12.3	196	0.12	13	0.34	50	56
6	NONE	NONE	NONE	71	24	17.4	233	0.11	12	0.39	62	50
11	NONE	NONE	NONE	80	29	12.5	197	0.15	14	0.35	46	26
16	NONE	NONE	NONE	67	29	14.0	136	0.12	12	0.31	57	73
19	NONE	NONE	NONE	90	36	13.8	135	<0.10	10	0.35	40	29
21	NONE	NONE	NONE	110	35	16.6	163	0.12	13	0.33	89	62
27	NONE	NONE	NONE	70	30	12.0	169	0.11	12	0.34	45	44
33	NONE	NONE	NONE	82	36	18.7	136	<0.10	11	0.33	54	141
39	NONE	NONE	TRACE	98	39	11.8	143	0.18	11	0.40	50	62
40	NONE	NONE	NONE	89	26	10.9	124	0.13	11	0.32	61	50
52	NONE	NONE	NONE	79	27	14.2	117	0.12	13	0.34	56	50
53	NONE	NONE	NONE	82	44	12.2	137	0.13	13	0.30	57	91

Individual Clinical Chemistry Values

Animal Number	GLUC mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	CALC mg/dL	IPHS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
Male, Group I - 0 mg/kg/day - Day 30									
1	112	6.1	4.3	1.8	10.5	8.7	148.0	5.58	103.0
8	113	6.6	4.3	2.3	10.6	8.6	149.1	5.79	102.6
10	97	6.8	4.7	2.1	11.0	9.1	148.3	6.40	100.5
12	112	6.7	4.6	2.1	10.7	9.2	148.4	6.42	103.2
13	99	6.6	4.3	2.3	11.1	9.6	149.0	6.09	102.7
22	100	6.7	4.4	2.3	11.0	8.3	151.9	5.95	104.8
31	94	6.6	4.5	2.1	10.9	9.2	148.5	6.17	104.7
36	98	5.9	4.2	1.7	11.0	10.6	151.0	5.52	103.7
41	112	6.5	4.6	1.9	11.2	8.1	149.4	5.87	102.4
44	108	6.9	4.7	2.2	11.3	8.9	151.1	6.01	104.2
45	113	6.5	4.4	2.1	10.8	8.5	149.4	5.95	103.4
54	127	6.5	4.7	1.8	11.0	9.1	153.4	5.17	104.4
Male, Group III - 35 mg/kg/day - Day 30									
3	113	6.5	4.5	2.0	10.9	8.8	148.9	5.49	98.5
5	85	6.7	4.7	2.0	10.8	8.8	150.1	5.89	100.6
14	99	6.4	4.4	2.0	10.3	8.7	147.3	6.13	104.0
18	99	6.5	4.6	1.9	10.9	8.4	151.6	6.04	103.7
20	99	6.3	4.4	1.9	10.1	8.2	149.1	6.11	107.4
26	105	6.7	4.4	2.3	10.9	9.7	153.9	6.35	105.6
35	98	6.3	4.4	1.9	10.8	10.2	148.9	6.44	103.4
46	99	6.2	4.3	1.9	10.6	9.2	150.8	5.45	103.8
48	99	7.1	4.6	2.5	11.0	8.5	148.6	6.51	102.5
50	104	6.7	4.6	2.1	10.8	8.3	151.4	5.98	101.7
55	105	6.7	4.4	2.3	11.3	8.0	151.7	5.58	104.2
56	104	6.1	4.3	1.8	11.1	9.4	152.5	5.65	105.6

Individual Clinical Chemistry Values

Animal Number	GLUC mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	CALC mg/dL	IPHS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
Male, Group V - 125 mg/kg/day - Day 30									
4	96	6.6	4.7	1.9	10.9	8.4	149.1	6.60	101.3
9	96	6.6	4.5	2.1	10.7	9.4	148.5	6.40	101.3
25	95	7.1	4.9	2.2	10.9	9.1	151.4	6.10	100.8
28	94	6.3	4.3	2.0	10.3	8.8	150.6	5.82	105.1
30	105	7.2	4.8	2.4	11.2	10.5	152.3	5.75	102.4
32	99	6.9	4.9	2.0	11.1	9.3	154.0	5.58	102.4
37	96	6.2	4.4	1.8	10.6	9.2	149.3	6.19	105.1
38	91	6.5	4.6	1.9	11.3	8.6	149.8	5.82	101.5
43	104	6.7	4.6	2.1	11.1	8.1	150.6	5.65	101.8
47	101	6.3	4.4	1.9	10.6	9.2	150.4	5.95	103.8
49	102	6.5	4.8	1.7	11.2	8.7	151.4	6.47	103.3
51	107	7.0	4.6	2.4	11.2	9.3	155.0	4.94	103.0
Male, Group VII - 375 mg/kg/day - Day 30									
2	95	6.4	4.5	1.9	10.7	8.7	148.1	6.05	102.6
6	94	6.8	4.6	2.2	10.7	8.7	151.3	6.20	103.1
11	87	6.7	4.7	2.0	10.9	7.9	151.9	5.87	102.6
16	101	6.3	4.3	2.0	10.6	9.4	150.5	5.96	104.0
19	74	6.3	4.7	1.6	10.8	8.4	152.0	6.50	103.7
21	98	6.8	4.9	1.9	10.9	9.0	153.1	5.95	105.5
27	93	7.0	4.7	2.3	11.5	8.2	150.1	5.67	102.1
33	103	7.2	4.8	2.4	11.2	8.7	150.1	6.43	101.2
39	102	7.1	4.9	2.2	11.5	8.2	151.4	5.36	101.0
40	85	6.7	4.6	2.1	11.0	10.4	150.6	6.92	105.2
52	93	7.0	4.8	2.2	11.3	8.3	153.3	6.33	103.5
53	98	6.9	4.7	2.2	10.9	9.7	151.8	5.96	103.3

Individual Clinical Chemistry Values

Animal Number	SHEM	SLIP	SICT	AST U/L	ALT U/L	SDH U/L	ALKP U/L	BILI mg/dL	BUN mg/dL	CREA mg/dL	CHOL mg/dL	TRIG mg/dL
Female, Group II - 0 mg/kg/day - Day 31												
69	TRACE	NONE	NONE	106	31	18.7	117	0.16	16	0.33	59	20
89	NONE	NONE	NONE	84	29	19.9	72	0.20	13	0.34	65	49
101	NONE	NONE	NONE	76	27	16.1	124	0.19	19	0.41	84	47
112	TRACE	NONE	NONE	94	27	14.5	89	0.19	11	0.33	60	43
113	NONE	NONE	NONE	108	27	13.5	89	0.14	15	0.29	93	53
123	SMALL	NONE	NONE	91	25	9.2	104	0.16	17	0.36	55	27
126	TRACE	NONE	NONE	87	23	8.6	71	0.15	13	0.32	71	37
144	NONE	NONE	NONE	75	24	15.6	66	0.15	14	0.37	80	38
152	NONE	NONE	NONE	79	20	9.3	82	0.17	15	0.37	53	28
155	NONE	NONE	NONE	84	23	9.4	62	0.14	14	0.33	67	33
162	TRACE	NONE	NONE	95	32	14.1	62	0.18	13	0.34	56	32
163	NONE	NONE	NONE	73	31	14.4	101	0.17	15	0.46	68	29
Female, Group IV - 35 mg/kg/day - Day 31												
71	TRACE	NONE	NONE	85	23	14.6	82	0.20	10	0.33	71	27
75	NONE	NONE	NONE	92	30	17.9	98	0.15	10	0.36	84	35
83	TRACE	NONE	NONE	95	22	6.3	77	0.17	13	0.39	70	34
107	NONE	NONE	NONE	106	22	8.6	94	0.18	11	0.35	63	26
119	TRACE	NONE	NONE	88	28	15.5	146	0.15	12	0.42	55	41
120	NONE	NONE	NONE	98	40	16.4	107	0.14	17	0.30	75	53
128	NONE	NONE	NONE	74	24	16.7	88	0.13	17	0.41	97	45
138	NONE	NONE	NONE	62	24	8.5	78	0.17	14	0.33	76	36
145	NONE	NONE	NONE	89	25	14.3	95	0.12	13	0.27	61	31
149	NONE	NONE	NONE	80	17	10.4	64	0.13	13	0.31	73	23
160	NONE	NONE	NONE	68	24	9.6	93	0.12	14	0.32	76	38
164	NONE	NONE	NONE	76	30	12.9	110	0.17	10	0.32	63	29

Individual Clinical Chemistry Values

Animal Number	SHEM	SLIP	SICT	AST U/L	ALT U/L	SDH U/L	ALKP U/L	BILI mg/dL	BUN mg/dL	CREA mg/dL	CHOL mg/dL	TRIG mg/dL
Female, Group VI - 125 mg/kg/day - Day 31												
62	NONE	NONE	NONE	85	20	14.8	53	0.15	15	0.37	57	25
79	SMALL	NONE	NONE	93	26	13.0	80	0.14	12	0.41	58	25
99	NONE	NONE	NONE	67	25	10.9	104	0.12	15	0.36	107	40
135	TRACE	NONE	NONE	82	21	16.0	70	0.14	14	0.42	67	26
142	SMALL	NONE	NONE	83	21	13.5	102	0.17	15	0.46	46	21
143	NONE	NONE	NONE	77	23	16.1	66	0.18	11	0.43	98	25
147	NONE	NONE	NONE	97	34	18.0	112	0.14	14	0.38	84	27
150	TRACE	NONE	NONE	85	21	14.2	93	0.14	15	0.42	121	28
153	NONE	NONE	NONE	115	43	19.8	110	0.17	19	0.48	79	43
154	NONE	NONE	NONE	80	24	10.3	123	0.14	11	0.33	62	21
156	NONE	NONE	NONE	74	19	6.0	116	0.13	12	0.30	55	23
161	NONE	NONE	NONE	70	18	9.3	72	0.10	13	0.36	34	25
Female, Group VIII - 375 mg/kg/day - Day 31												
67	SMALL	NONE	NONE	121	34	7.4	132	<0.10	14	0.59	78	32
68	NONE	NONE	NONE	112	25	8.5	63	0.12	13	0.43	79	24
70	NONE	NONE	NONE	90	33	19.5	93	0.14	15	0.44	51	24
76	TRACE	NONE	NONE	88	23	13.3	97	0.17	13	0.30	63	20
77	TRACE	NONE	NONE	102	26	8.7	111	0.13	15	0.38	91	43
84	NONE	NONE	NONE	86	24	11.7	95	0.13	15	0.49	63	24
88	NONE	NONE	NONE	84	26	21.1	73	0.17	13	0.48	83	17
114	NONE	NONE	NONE	73	22	16.2	128	0.16	14	0.47	74	28
129	NONE	NONE	NONE	54	29	8.6	69	0.19	11	0.41	101	32
146	NONE	NONE	NONE	66	17	11.3	120	0.15	15	0.49	95	35
151	NONE	NONE	NONE	70	35	6.6	81	0.14	14	0.45	89	34
159	NONE	NONE	NONE	71	25	9.3	123	0.13	13	0.35	98	53

Individual Clinical Chemistry Values

Animal Number	GLUC mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	CALC mg/dL	IPHS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
Female, Group II - 0 mg/kg/day - Day 31									
69	90	6.6	4.6	2.0	10.1	7.7	147.7	5.70	102.4
89	100	7.5	5.2	2.3	11.1	6.9	146.9	5.45	101.8
101	103	7.3	5.1	2.2	11.3	6.7	147.2	6.01	102.5
112	105	8.0	5.4	2.6	11.0	6.1	147.2	5.73	104.8
113	100	6.4	4.4	2.0	10.5	6.5	146.4	5.61	103.2
123	97	7.3	5.1	2.2	11.1	8.1	147.4	5.97	103.5
126	110	6.9	4.5	2.4	10.6	7.4	143.5	6.26	104.0
144	103	7.3	5.1	2.2	11.4	8.4	145.3	6.04	101.1
152	85	7.0	4.8	2.2	10.9	8.2	147.9	5.82	103.3
155	109	7.2	4.9	2.3	10.8	7.3	148.1	6.44	104.9
162	156	7.0	4.8	2.2	11.3	8.1	145.8	5.44	102.7
163	109	7.6	5.4	2.2	11.0	7.2	147.7	5.58	102.2
Female, Group IV - 35 mg/kg/day - Day 31									
71	98	7.1	4.9	2.2	10.7	7.1	146.9	5.43	103.1
75	105	7.7	5.2	2.5	11.0	7.1	145.9	5.51	103.1
83	107	7.5	5.1	2.4	10.9	7.6	146.3	5.99	103.5
107	116	7.5	5.4	2.1	10.5	6.4	147.6	5.89	103.4
119	113	7.1	5.0	2.1	10.9	7.5	147.6	6.60	103.9
120	98	6.9	4.6	2.3	10.9	5.3	146.0	5.29	103.7
128	106	7.7	5.3	2.4	10.9	6.1	148.7	5.84	104.5
138	98	7.2	5.2	2.0	11.4	8.3	148.5	5.67	102.7
145	95	6.8	4.8	2.0	10.8	7.9	148.8	6.39	105.7
149	104	7.2	4.8	2.4	10.8	8.2	145.2	5.94	102.4
160	108	7.2	5.0	2.2	11.3	8.3	146.0	6.26	101.8
164	115	7.0	5.1	1.9	11.0	6.8	148.6	5.64	102.7

Individual Clinical Chemistry Values

Animal Number	GLUC mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	CALC mg/dL	IPHS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
Female, Group VI - 125 mg/kg/day - Day 31									
62	88	7.0	4.9	2.1	10.7	8.1	146.0	6.20	100.7
79	114	7.3	4.9	2.4	10.4	5.7	148.4	5.41	105.9
99	105	6.8	4.5	2.3	11.2	6.6	148.3	5.92	102.2
135	95	7.0	4.7	2.3	10.5	7.2	147.2	5.90	100.9
142	145	7.2	4.9	2.3	10.9	8.6	146.1	5.53	103.1
143	114	7.8	5.5	2.3	11.3	6.3	146.2	5.94	105.9
147	103	7.4	5.0	2.4	11.7	8.9	149.3	6.52	105.5
150	103	7.5	5.3	2.2	11.5	9.6	148.0	7.04	105.4
153	104	7.2	4.9	2.3	11.6	9.6	146.4	6.41	104.7
154	106	7.1	4.8	2.3	10.8	7.9	146.9	5.69	103.1
156	95	6.7	4.6	2.1	10.8	7.2	146.5	5.97	100.8
161	129	6.5	4.6	1.9	11.2	9.0	148.0	6.81	104.4
Female, Group VIII - 375 mg/kg/day - Day 31									
67	88	7.1	5.0	2.1	10.6	6.7	146.2	5.80	102.7
68	88	7.1	5.1	2.0	10.3	7.0	145.2	5.73	103.4
70	103	7.5	5.2	2.3	11.4	6.8	149.4	5.69	104.4
76	99	6.5	4.7	1.8	10.8	8.1	148.4	6.37	104.6
77	99	7.1	4.9	2.2	10.6	6.9	146.2	5.98	104.9
84	93	7.2	4.7	2.5	10.7	7.5	148.4	5.98	102.9
88	104	7.7	5.4	2.3	11.4	8.8	146.3	6.96	103.3
114	101	7.6	5.3	2.3	11.1	6.8	147.9	6.13	103.6
129	107	7.7	5.4	2.3	11.6	8.0	147.7	5.97	104.1
146	111	7.0	5.0	2.0	10.7	6.8	144.4	5.52	104.3
151	120	7.2	5.0	2.2	10.7	6.7	145.0	5.32	102.5
159	103	6.6	4.7	1.9	11.1	9.2	146.7	5.42	103.1

APPENDIX II

Individual Animal Final Body and Organ Weights in Subchronic Adult Males and Females

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

KEY OF ABBREVIATIONS

EPIDID – EPIDIDYMIDES

WE = WEIGHING ERROR

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams) FROM MALE RATS

GROUP : I - 0 mg/kg/day

ANIMAL NUMBER	FINAL BODY	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	TESTES
1	354.9	11.506	2.980	1.671	1.502	0.727	0.504	WE	3.248
8	384.1	12.343	2.981	1.775	1.423	0.654	0.574	0.045	2.972
10	394.3	10.880	3.384	1.750	1.555	0.758	0.543	0.066	3.562
12	397.3	12.237	3.285	1.665	1.515	0.833	0.617	0.050	3.001
13	386.9	12.195	2.965	1.752	1.402	0.501	0.527	0.064	3.138
22	377.3	11.256	3.115	1.672	1.255	0.734	0.523	0.060	3.275
31	387.1	12.340	3.176	1.836	1.505	0.757	0.498	0.070	3.427
36	360.4	10.496	3.264	1.738	1.445	0.675	0.404	0.064	3.424
41	397.6	13.038	3.870	1.811	1.448	0.793	0.451	0.068	3.069
44	414.6	11.767	2.947	1.649	1.416	0.702	0.336	0.059	3.077
45	369.4	11.374	2.905	1.864	1.332	0.731	0.578	0.057	3.216
54	429.3	14.486	3.530	1.895	1.750	0.819	0.486	0.062	3.576

ANIMAL NUMBER	FINAL BODY	EPIDID	BRAIN
1	354.9	1.085	2.134
8	384.1	0.947	1.969
10	394.3	1.176	2.045
12	397.3	1.055	1.956
13	386.9	1.134	1.897
22	377.3	1.058	1.897
31	387.1	1.125	2.033
36	360.4	1.072	2.019
41	397.6	0.953	2.043
44	414.6	1.082	2.083
45	369.4	0.998	2.138
54	429.3	1.342	2.019

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams) FROM MALE RATS

GROUP : III - 35 mg/kg/day

ANIMAL NUMBER	FINAL BODY	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	TESTES
3	385.3	13.043	3.283	1.504	1.321	0.715	0.442	0.060	3.232
5	366.9	11.009	3.068	1.678	1.131	0.677	0.558	0.069	3.223
14	381.0	10.762	3.389	1.860	1.592	0.621	0.525	0.044	3.604
18	370.5	11.772	3.012	1.695	1.230	0.721	0.401	0.058	3.288
20	364.1	10.611	3.072	1.588	1.253	0.695	0.381	0.047	3.143
26	397.0	13.338	3.235	2.020	1.447	0.601	0.523	0.071	3.168
35	369.6	11.593	3.054	1.638	1.520	0.683	0.494	0.072	3.313
46	406.6	13.643	3.418	1.907	1.572	0.762	0.545	0.064	3.012
48	357.6	11.579	3.252	1.587	1.393	0.581	0.496	0.062	2.907
50	381.7	10.949	3.258	1.903	1.324	0.755	0.472	0.055	3.491
55	386.9	12.328	2.712	1.705	1.332	0.598	0.500	0.060	3.016
56	384.2	12.471	3.286	1.857	1.456	0.918	0.495	0.068	3.129

ANIMAL NUMBER	FINAL BODY	EPIDID	BRAIN
3	385.3	1.140	1.997
5	366.9	1.101	1.991
14	381.0	1.132	1.918
18	370.5	1.140	1.896
20	364.1	1.052	2.003
26	397.0	1.239	2.003
35	369.6	1.144	1.916
46	406.6	1.187	2.050
48	357.6	0.977	1.945
50	381.7	1.149	2.113
55	386.9	1.190	2.010
56	384.2	1.085	2.118

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams) FROM MALE RATS

GROUP : V - 125 mg/kg/day

ANIMAL NUMBER	FINAL BODY	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	TESTES
4	324.5	10.408	2.621	1.429	1.201	0.543	0.354	0.044	2.855
9	337.4	10.491	3.274	1.644	1.396	0.869	0.431	0.062	3.148
25	365.2	11.589	3.467	1.890	1.319	0.578	0.491	0.059	3.215
28	390.9	12.584	3.504	1.787	1.373	0.574	0.426	0.065	3.177
30	368.4	13.061	3.048	1.710	1.407	0.648	0.418	0.061	2.944
32	368.2	11.719	3.159	2.104	1.367	0.617	0.398	0.057	3.303
37	344.5	10.621	3.206	1.693	1.253	0.612	0.392	0.051	3.304
38	363.2	11.062	3.323	1.677	1.308	0.622	0.460	0.050	3.069
43	357.4	11.136	3.089	1.685	1.301	0.695	0.458	0.068	3.117
47	378.9	11.922	3.051	1.890	1.402	0.710	0.367	0.069	3.095
49	344.8	10.195	2.934	1.681	1.501	0.661	0.413	0.046	2.953
51	361.6	11.628	3.087	1.558	1.263	0.614	0.395	0.052	3.357

ANIMAL NUMBER	FINAL BODY	EPIDID	BRAIN
4	324.5	1.047	2.011
9	337.4	1.072	1.974
25	365.2	1.081	2.051
28	390.9	1.034	2.078
30	368.4	1.119	1.911
32	368.2	1.108	1.932
37	344.5	1.010	2.050
38	363.2	1.053	2.051
43	357.4	1.101	2.066
47	378.9	1.162	2.001
49	344.8	1.090	2.140
51	361.6	1.153	2.052

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams) FROM MALE RATS

GROUP : VII - 375 mg/kg/day

ANIMAL NUMBER	FINAL BODY	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	TESTES
2	356.6	11.976	3.484	1.413	1.234	0.642	0.322	0.052	2.839
6	355.8	13.614	3.332	1.641	1.235	0.599	0.424	0.063	2.992
11	333.5	11.791	3.157	1.615	1.287	0.703	0.363	0.072	3.351
16	355.2	13.754	3.380	1.601	1.278	0.591	0.402	0.053	3.033
19	321.9	10.331	3.297	1.695	1.369	0.577	0.304	0.040	3.220
21	349.5	11.727	3.514	1.553	1.256	0.579	0.343	0.051	3.223
27	355.1	13.378	3.263	1.599	1.225	0.522	0.428	0.053	2.942
33	346.4	11.628	3.086	1.619	1.170	0.658	0.422	0.055	3.242
39	346.9	12.061	3.179	1.739	1.326	0.678	0.461	0.050	3.298
40	333.7	11.881	3.213	1.867	1.184	0.577	0.337	0.048	3.189
52	336.7	11.458	2.794	1.558	1.197	0.624	0.338	0.058	3.013
53	384.5	13.904	3.875	1.995	1.642	0.665	0.410	0.064	3.490

ANIMAL NUMBER	FINAL BODY	EPIDID	BRAIN
2	356.6	1.171	2.038
6	355.8	1.165	1.981
11	333.5	1.174	1.947
16	355.2	1.056	2.049
19	321.9	0.954	1.887
21	349.5	1.009	2.012
27	355.1	1.061	1.903
33	346.4	0.957	1.962
39	346.9	1.044	1.996
40	333.7	0.993	2.050
52	336.7	1.058	1.983
53	384.5	1.090	1.959

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (% of body weight) FROM MALE RATS

GROUP : I - 0 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	TESTES	EPIDID
1	3.242	0.840	0.471	0.423	0.205	0.142	WE	0.915	0.306
8	3.213	0.776	0.462	0.370	0.170	0.149	0.012	0.774	0.247
10	2.759	0.858	0.444	0.394	0.192	0.138	0.017	0.903	0.298
12	3.080	0.827	0.419	0.381	0.210	0.155	0.013	0.755	0.266
13	3.152	0.766	0.453	0.362	0.129	0.136	0.017	0.811	0.293
22	2.983	0.826	0.443	0.333	0.195	0.139	0.016	0.868	0.280
31	3.188	0.820	0.474	0.389	0.196	0.129	0.018	0.885	0.291
36	2.912	0.906	0.482	0.401	0.187	0.112	0.018	0.950	0.297
41	3.279	0.973	0.455	0.364	0.199	0.113	0.017	0.772	0.240
44	2.838	0.711	0.398	0.342	0.169	0.081	0.014	0.742	0.261
45	3.079	0.786	0.505	0.361	0.198	0.156	0.015	0.871	0.270
54	3.374	0.822	0.441	0.408	0.191	0.113	0.014	0.833	0.313

ANIMAL NUMBER	BRAIN
1	0.601
8	0.513
10	0.519
12	0.492
13	0.490
22	0.503
31	0.525
36	0.560
41	0.514
44	0.502
45	0.579
54	0.470

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (% of body weight) FROM MALE RATS

GROUP : III - 35 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	TESTES	EPIDID
3	3.385	0.852	0.390	0.343	0.186	0.115	0.016	0.839	0.296
5	3.001	0.836	0.457	0.308	0.185	0.152	0.019	0.878	0.300
14	2.825	0.890	0.488	0.418	0.163	0.138	0.012	0.946	0.297
18	3.177	0.813	0.457	0.332	0.195	0.108	0.016	0.887	0.308
20	2.914	0.844	0.436	0.344	0.191	0.105	0.013	0.863	0.289
26	3.360	0.815	0.509	0.364	0.151	0.132	0.018	0.798	0.312
35	3.137	0.826	0.443	0.411	0.185	0.134	0.019	0.896	0.310
46	3.355	0.841	0.469	0.387	0.187	0.134	0.016	0.741	0.292
48	3.238	0.909	0.444	0.390	0.162	0.139	0.017	0.813	0.273
50	2.868	0.854	0.499	0.347	0.198	0.124	0.014	0.915	0.301
55	3.186	0.701	0.441	0.344	0.155	0.129	0.016	0.780	0.308
56	3.246	0.855	0.483	0.379	0.239	0.129	0.018	0.814	0.282

ANIMAL NUMBER	BRAIN
3	0.518
5	0.543
14	0.503
18	0.512
20	0.550
26	0.505
35	0.518
46	0.504
48	0.544
50	0.554
55	0.520
56	0.551

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (% of body weight) FROM MALE RATS

GROUP : V - 125 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	TESTES	EPIDID
4	3.207	0.808	0.440	0.370	0.167	0.109	0.014	0.880	0.323
9	3.109	0.970	0.487	0.414	0.258	0.128	0.018	0.933	0.318
25	3.173	0.949	0.518	0.361	0.158	0.134	0.016	0.880	0.296
28	3.219	0.896	0.457	0.351	0.147	0.109	0.017	0.813	0.265
30	3.545	0.827	0.464	0.382	0.176	0.113	0.017	0.799	0.304
32	3.183	0.858	0.571	0.371	0.168	0.108	0.015	0.897	0.301
37	3.083	0.931	0.491	0.364	0.178	0.114	0.015	0.959	0.293
38	3.046	0.915	0.462	0.360	0.171	0.127	0.014	0.845	0.290
43	3.116	0.864	0.471	0.364	0.194	0.128	0.019	0.872	0.308
47	3.146	0.805	0.499	0.370	0.187	0.097	0.018	0.817	0.307
49	2.957	0.851	0.488	0.435	0.192	0.120	0.013	0.856	0.316
51	3.216	0.854	0.431	0.349	0.170	0.109	0.014	0.928	0.319

ANIMAL NUMBER	BRAIN
4	0.620
9	0.585
25	0.562
28	0.532
30	0.519
32	0.525
37	0.595
38	0.565
43	0.578
47	0.528
49	0.621
51	0.567

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (% of body weight) FROM MALE RATS

GROUP : VII - 375 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	TESTES	EPIDID
2	3.358	0.977	0.396	0.346	0.180	0.090	0.015	0.796	0.328
6	3.826	0.936	0.461	0.347	0.168	0.119	0.018	0.841	0.327
11	3.536	0.947	0.484	0.386	0.211	0.109	0.022	1.005	0.352
16	3.872	0.952	0.451	0.360	0.166	0.113	0.015	0.854	0.297
19	3.209	1.024	0.527	0.425	0.179	0.094	0.012	1.000	0.296
21	3.355	1.005	0.444	0.359	0.166	0.098	0.015	0.922	0.289
27	3.767	0.919	0.450	0.345	0.147	0.121	0.015	0.828	0.299
33	3.357	0.891	0.467	0.338	0.190	0.122	0.016	0.936	0.276
39	3.477	0.916	0.501	0.382	0.195	0.133	0.014	0.951	0.301
40	3.560	0.963	0.559	0.355	0.173	0.101	0.014	0.956	0.298
52	3.403	0.830	0.463	0.356	0.185	0.100	0.017	0.895	0.314
53	3.616	1.008	0.519	0.427	0.173	0.107	0.017	0.908	0.283

ANIMAL NUMBER	BRAIN
2	0.572
6	0.557
11	0.584
16	0.577
19	0.586
21	0.576
27	0.536
33	0.566
39	0.575
40	0.614
52	0.589
53	0.509

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (organ to brain weight ratio) FROM MALE RATS

GROUP : I - 0 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	TESTES	EPIDID
1	5.392	1.396	0.783	0.704	0.341	0.236	WE	1.522	0.508
8	6.269	1.514	0.901	0.723	0.332	0.292	0.023	1.509	0.481
10	5.320	1.655	0.856	0.760	0.371	0.266	0.032	1.742	0.575
12	6.256	1.679	0.851	0.775	0.426	0.315	0.026	1.534	0.539
13	6.429	1.563	0.924	0.739	0.264	0.278	0.034	1.654	0.598
22	5.934	1.642	0.881	0.662	0.387	0.276	0.032	1.726	0.558
31	6.070	1.562	0.903	0.740	0.372	0.245	0.034	1.686	0.553
36	5.199	1.617	0.861	0.716	0.334	0.200	0.032	1.696	0.531
41	6.382	1.894	0.886	0.709	0.388	0.221	0.033	1.502	0.466
44	5.649	1.415	0.792	0.680	0.337	0.161	0.028	1.477	0.519
45	5.320	1.359	0.872	0.623	0.342	0.270	0.027	1.504	0.467
54	7.175	1.748	0.939	0.867	0.406	0.241	0.031	1.771	0.665

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (organ to brain weight ratio) FROM MALE RATS

GROUP : III - 35 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	TESTES	EPIDID
3	6.531	1.644	0.753	0.661	0.358	0.221	0.030	1.618	0.571
5	5.529	1.541	0.843	0.568	0.340	0.280	0.035	1.619	0.553
14	5.611	1.767	0.970	0.830	0.324	0.274	0.023	1.879	0.590
18	6.209	1.589	0.894	0.649	0.380	0.211	0.031	1.734	0.601
20	5.298	1.534	0.793	0.626	0.347	0.190	0.023	1.569	0.525
26	6.659	1.615	1.008	0.722	0.300	0.261	0.035	1.582	0.619
35	6.051	1.594	0.855	0.793	0.356	0.258	0.038	1.729	0.597
46	6.655	1.667	0.930	0.767	0.372	0.266	0.031	1.469	0.579
48	5.953	1.672	0.816	0.716	0.299	0.255	0.032	1.495	0.502
50	5.182	1.542	0.901	0.627	0.357	0.223	0.026	1.652	0.544
55	6.133	1.349	0.848	0.663	0.298	0.249	0.030	1.500	0.592
56	5.888	1.551	0.877	0.687	0.433	0.234	0.032	1.477	0.512

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (organ to brain weight ratio) FROM MALE RATS

GROUP : V - 125 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	TESTES	EPIDID
4	5.176	1.303	0.711	0.597	0.270	0.176	0.022	1.420	0.521
9	5.315	1.659	0.833	0.707	0.440	0.218	0.031	1.595	0.543
25	5.650	1.690	0.922	0.643	0.282	0.239	0.029	1.568	0.527
28	6.056	1.686	0.860	0.661	0.276	0.205	0.031	1.529	0.498
30	6.835	1.595	0.895	0.736	0.339	0.219	0.032	1.541	0.586
32	6.066	1.635	1.089	0.708	0.319	0.206	0.030	1.710	0.573
37	5.181	1.564	0.826	0.611	0.299	0.191	0.025	1.612	0.493
38	5.393	1.620	0.818	0.638	0.303	0.224	0.024	1.496	0.513
43	5.390	1.495	0.816	0.630	0.336	0.222	0.033	1.509	0.533
47	5.958	1.525	0.945	0.701	0.355	0.183	0.034	1.547	0.581
49	4.764	1.371	0.786	0.701	0.309	0.193	0.021	1.380	0.509
51	5.667	1.504	0.759	0.615	0.299	0.192	0.025	1.636	0.562

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (organ to brain weight ratio) FROM MALE RATS

GROUP : VII - 375 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	TESTES	EPIDID
2	5.876	1.710	0.693	0.605	0.315	0.158	0.026	1.393	0.575
6	6.872	1.682	0.828	0.623	0.302	0.214	0.032	1.510	0.588
11	6.056	1.621	0.829	0.661	0.361	0.186	0.037	1.721	0.603
16	6.713	1.650	0.781	0.624	0.288	0.196	0.026	1.480	0.515
19	5.475	1.747	0.898	0.725	0.306	0.161	0.021	1.706	0.506
21	5.829	1.747	0.772	0.624	0.288	0.170	0.025	1.602	0.501
27	7.030	1.715	0.840	0.644	0.274	0.225	0.028	1.546	0.558
33	5.927	1.573	0.825	0.596	0.335	0.215	0.028	1.652	0.488
39	6.043	1.593	0.871	0.664	0.340	0.231	0.025	1.652	0.523
40	5.796	1.567	0.911	0.578	0.281	0.164	0.023	1.556	0.484
52	5.778	1.409	0.786	0.604	0.315	0.170	0.029	1.519	0.534
53	7.097	1.978	1.018	0.838	0.339	0.209	0.033	1.782	0.556

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams) FROM FEMALE RATS

GROUP : II - 0 mg/kg/day

ANIMAL NUMBER	FINAL BODY	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	OVARIES
69	248.2	7.052	1.828	1.484	0.869	0.449	0.396	0.072	0.126
89	270.8	8.305	2.075	1.583	1.155	0.499	0.619	0.084	0.125
101	246.4	7.298	1.822	1.577	1.029	0.593	0.344	0.061	0.123
112	232.0	7.646	1.792	1.129	0.950	0.520	0.431	0.064	0.104
113	232.4	6.157	1.681	1.241	0.822	0.471	0.488	0.048	0.118
123	250.7	8.281	1.927	1.400	0.876	0.485	0.302	0.070	0.121
126	234.5	7.104	1.841	1.514	0.997	0.528	0.640	0.068	0.130
144	261.6	7.819	1.946	1.580	1.088	0.510	0.510	0.058	0.128
152	193.7	5.169	1.436	1.366	0.700	0.390	0.239	0.053	0.106
155	235.1	7.614	1.893	1.388	0.959	0.495	0.426	0.063	0.121
162	257.5	7.751	2.061	1.386	0.924	0.575	0.434	0.083	0.140
163	256.6	7.978	2.150	1.457	0.941	0.412	0.440	0.091	0.108

ANIMAL NUMBER	FINAL BODY	UTERUS	BRAIN
69	248.2	0.430	1.865
89	270.8	0.896	1.967
101	246.4	0.412	1.855
112	232.0	0.451	1.747
113	232.4	0.648	1.852
123	250.7	0.559	1.898
126	234.5	0.634	1.877
144	261.6	0.402	1.789
152	193.7	0.336	1.780
155	235.1	0.324	1.903
162	257.5	0.732	1.933
163	256.6	0.744	1.884

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams) FROM FEMALE RATS

GROUP : IV - 35 mg/kg/day

ANIMAL NUMBER	FINAL BODY	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	OVARIES
71	232.6	7.363	2.084	1.315	0.931	0.552	0.374	0.066	0.104
75	265.5	9.572	2.166	1.636	1.118	0.497	0.488	0.070	0.161
83	251.8	8.837	1.988	1.278	0.930	0.574	0.414	0.061	0.122
107	237.0	6.895	2.120	1.434	0.912	0.469	0.393	0.053	0.116
119	234.6	7.673	1.745	1.359	0.828	0.406	0.398	0.064	0.150
120	233.5	6.883	1.728	1.287	0.755	0.495	0.426	0.058	0.121
128	232.7	8.122	1.949	1.302	1.065	0.539	0.451	0.065	0.142
138	249.0	7.965	1.874	1.365	1.099	0.452	0.424	0.074	0.131
145	228.6	6.725	1.740	1.292	0.856	0.429	0.306	0.058	0.124
149	233.6	6.996	1.932	1.384	0.908	0.618	0.431	0.070	0.121
160	243.8	7.756	1.998	1.342	0.970	0.598	0.348	0.074	0.117
164	228.7	7.080	1.975	1.388	0.884	0.444	0.513	0.075	0.114

ANIMAL NUMBER	FINAL BODY	UTERUS	BRAIN
71	232.6	0.392	1.885
75	265.5	0.586	1.918
83	251.8	0.555	1.853
107	237.0	1.208	1.712
119	234.6	0.581	1.876
120	233.5	0.912	1.850
128	232.7	0.706	1.877
138	249.0	0.417	1.746
145	228.6	0.640	1.805
149	233.6	0.481	2.089
160	243.8	0.559	1.810
164	228.7	0.613	1.866

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams) FROM FEMALE RATS

GROUP : VI - 125 mg/kg/day

ANIMAL NUMBER	FINAL BODY	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	OVARIES
62	240.5	8.140	1.999	1.440	0.912	0.480	0.371	0.077	0.141
79	259.0	8.597	2.235	1.331	0.931	0.570	0.590	0.082	0.162
99	228.1	7.640	1.880	1.323	0.999	0.529	0.496	0.075	0.106
135	225.9	7.205	1.926	1.440	1.114	0.512	0.304	0.074	0.153
142	250.1	8.385	2.095	1.458	1.041	0.550	0.386	0.074	0.151
143	227.2	7.752	1.848	1.299	0.915	0.514	0.369	0.059	0.113
147	211.0	6.475	1.743	1.535	0.845	0.370	0.418	0.070	0.086
150	202.5	6.776	1.589	1.110	0.773	0.361	0.280	0.068	0.113
153	229.7	7.644	1.939	1.331	0.840	0.508	0.352	0.077	0.114
154	252.7	7.773	1.950	1.342	0.876	0.472	0.445	0.063	0.124
156	250.0	8.628	2.144	1.409	0.831	0.480	0.598	0.089	0.143
161	233.8	7.375	1.903	1.471	0.857	0.443	0.412	0.072	0.154

ANIMAL NUMBER	FINAL BODY	UTERUS	BRAIN
62	240.5	0.487	1.939
79	259.0	0.670	1.822
99	228.1	0.658	1.812
135	225.9	0.687	1.875
142	250.1	0.762	1.761
143	227.2	0.460	1.694
147	211.0	0.437	1.798
150	202.5	0.548	1.631
153	229.7	0.449	1.835
154	252.7	0.581	1.865
156	250.0	0.424	1.940
161	233.8	0.725	1.893

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams) FROM FEMALE RATS

GROUP : VIII - 375 mg/kg/day

ANIMAL NUMBER	FINAL BODY	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	OVARIES
67	222.8	7.160	1.493	1.213	0.711	0.371	0.300	0.061	0.124
68	239.0	8.988	2.106	1.384	0.976	0.537	0.614	0.086	0.157
70	237.6	8.319	1.985	1.370	0.877	0.510	0.362	0.080	0.160
76	238.3	7.395	1.974	1.266	0.908	0.656	0.425	0.081	0.144
77	210.0	7.756	1.940	1.379	0.807	0.450	0.269	0.061	0.113
84	240.5	7.564	1.930	1.361	0.806	0.416	0.323	0.074	0.119
88	218.1	7.534	1.992	1.368	0.985	0.449	0.359	0.065	0.103
114	204.2	6.838	1.606	1.827	0.909	0.486	0.290	0.067	0.103
129	255.9	9.352	2.268	1.462	1.086	0.519	0.534	0.072	0.131
146	214.8	7.973	1.696	1.378	0.788	0.422	0.403	0.060	0.136
151	222.9	7.826	1.625	1.282	0.847	0.471	0.375	0.081	0.093
159	236.1	8.186	1.820	1.324	0.783	0.437	0.265	0.071	0.119

ANIMAL NUMBER	FINAL BODY	UTERUS	BRAIN
67	222.8	0.448	1.832
68	239.0	0.479	1.928
70	237.6	0.569	1.903
76	238.3	0.816	1.719
77	210.0	0.559	1.815
84	240.5	0.420	1.979
88	218.1	0.481	1.840
114	204.2	1.351	1.879
129	255.9	0.923	1.903
146	214.8	0.508	1.753
151	222.9	0.676	1.864
159	236.1	0.654	1.850

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (% of body weight) FROM FEMALE RATS

GROUP : II - 0 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	OVARIES	UTERUS
69	2.841	0.737	0.598	0.350	0.181	0.160	0.029	0.051	0.173
89	3.067	0.766	0.585	0.427	0.184	0.229	0.031	0.046	0.331
101	2.962	0.739	0.640	0.418	0.241	0.140	0.025	0.050	0.167
112	3.296	0.772	0.487	0.409	0.224	0.186	0.028	0.045	0.194
113	2.649	0.723	0.534	0.354	0.203	0.210	0.021	0.051	0.279
123	3.303	0.769	0.558	0.349	0.193	0.120	0.028	0.048	0.223
126	3.029	0.785	0.646	0.425	0.225	0.273	0.029	0.055	0.270
144	2.989	0.744	0.604	0.416	0.195	0.195	0.022	0.049	0.154
152	2.669	0.741	0.705	0.361	0.201	0.123	0.027	0.055	0.173
155	3.239	0.805	0.590	0.408	0.211	0.181	0.027	0.051	0.138
162	3.010	0.800	0.538	0.359	0.223	0.169	0.032	0.054	0.284
163	3.109	0.838	0.568	0.367	0.161	0.171	0.035	0.042	0.290

ANIMAL NUMBER	BRAIN
69	0.751
89	0.726
101	0.753
112	0.753
113	0.797
123	0.757
126	0.800
144	0.684
152	0.919
155	0.809
162	0.751
163	0.734

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (% of body weight) FROM FEMALE RATS

GROUP : IV - 35 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	OVARIES	UTERUS
71	3.166	0.896	0.565	0.400	0.237	0.161	0.028	0.045	0.169
75	3.605	0.816	0.616	0.421	0.187	0.184	0.026	0.061	0.221
83	3.510	0.790	0.508	0.369	0.228	0.164	0.024	0.048	0.220
107	2.909	0.895	0.605	0.385	0.198	0.166	0.022	0.049	0.510
119	3.271	0.744	0.579	0.353	0.173	0.170	0.027	0.064	0.248
120	2.948	0.740	0.551	0.323	0.212	0.182	0.025	0.052	0.391
128	3.490	0.838	0.560	0.458	0.232	0.194	0.028	0.061	0.303
138	3.199	0.753	0.548	0.441	0.182	0.170	0.030	0.053	0.167
145	2.942	0.761	0.565	0.374	0.188	0.134	0.025	0.054	0.280
149	2.995	0.827	0.592	0.389	0.265	0.185	0.030	0.052	0.206
160	3.181	0.820	0.550	0.398	0.245	0.143	0.030	0.048	0.229
164	3.096	0.864	0.607	0.387	0.194	0.224	0.033	0.050	0.268

ANIMAL NUMBER	BRAIN
71	0.810
75	0.722
83	0.736
107	0.722
119	0.800
120	0.792
128	0.807
138	0.701
145	0.790
149	0.894
160	0.742
164	0.816

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (% of body weight) FROM FEMALE RATS

GROUP : VI - 125 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	OVARIES	UTERUS
62	3.385	0.831	0.599	0.379	0.200	0.154	0.032	0.059	0.202
79	3.319	0.863	0.514	0.359	0.220	0.228	0.032	0.063	0.259
99	3.349	0.824	0.580	0.438	0.232	0.217	0.033	0.046	0.288
135	3.189	0.853	0.637	0.493	0.227	0.135	0.033	0.068	0.304
142	3.353	0.838	0.583	0.416	0.220	0.154	0.030	0.060	0.305
143	3.412	0.813	0.572	0.403	0.226	0.162	0.026	0.050	0.202
147	3.069	0.826	0.727	0.400	0.175	0.198	0.033	0.041	0.207
150	3.346	0.785	0.548	0.382	0.178	0.138	0.034	0.056	0.271
153	3.328	0.844	0.579	0.366	0.221	0.153	0.034	0.050	0.195
154	3.076	0.772	0.531	0.347	0.187	0.176	0.025	0.049	0.230
156	3.451	0.858	0.564	0.332	0.192	0.239	0.036	0.057	0.170
161	3.154	0.814	0.629	0.367	0.189	0.176	0.031	0.066	0.310

ANIMAL NUMBER	BRAIN
62	0.806
79	0.703
99	0.794
135	0.830
142	0.704
143	0.746
147	0.852
150	0.805
153	0.799
154	0.738
156	0.776
161	0.810

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (% of body weight) FROM FEMALE RATS

GROUP : VIII - 375 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	OVARIES	UTERUS
67	3.214	0.670	0.544	0.319	0.167	0.135	0.027	0.056	0.201
68	3.761	0.881	0.579	0.408	0.225	0.257	0.036	0.066	0.200
70	3.501	0.835	0.577	0.369	0.215	0.152	0.034	0.067	0.239
76	3.103	0.828	0.531	0.381	0.275	0.178	0.034	0.060	0.342
77	3.693	0.924	0.657	0.384	0.214	0.128	0.029	0.054	0.266
84	3.145	0.802	0.566	0.335	0.173	0.134	0.031	0.049	0.175
88	3.454	0.913	0.627	0.452	0.206	0.165	0.030	0.047	0.221
114	3.349	0.786	0.895	0.445	0.238	0.142	0.033	0.050	0.662
129	3.655	0.886	0.571	0.424	0.203	0.209	0.028	0.051	0.361
146	3.712	0.790	0.642	0.367	0.196	0.188	0.028	0.063	0.236
151	3.511	0.729	0.575	0.380	0.211	0.168	0.036	0.042	0.303
159	3.467	0.771	0.561	0.332	0.185	0.112	0.030	0.050	0.277

ANIMAL NUMBER	BRAIN
67	0.822
68	0.807
70	0.801
76	0.721
77	0.864
84	0.823
88	0.844
114	0.920
129	0.744
146	0.816
151	0.836
159	0.784

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (organ to brain weight ratio) FROM FEMALE RATS

GROUP : II - 0 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	OVARIES	UTERUS
69	3.781	0.980	0.796	0.466	0.241	0.212	0.039	0.068	0.231
89	4.222	1.055	0.805	0.587	0.254	0.315	0.043	0.064	0.456
101	3.934	0.982	0.850	0.555	0.320	0.185	0.033	0.066	0.222
112	4.377	1.026	0.646	0.544	0.298	0.247	0.037	0.060	0.258
113	3.325	0.908	0.670	0.444	0.254	0.263	0.026	0.064	0.350
123	4.363	1.015	0.738	0.462	0.256	0.159	0.037	0.064	0.295
126	3.785	0.981	0.807	0.531	0.281	0.341	0.036	0.069	0.338
144	4.371	1.088	0.883	0.608	0.285	0.285	0.032	0.072	0.225
152	2.904	0.807	0.767	0.393	0.219	0.134	0.030	0.060	0.189
155	4.001	0.995	0.729	0.504	0.260	0.224	0.033	0.064	0.170
162	4.010	1.066	0.717	0.478	0.297	0.225	0.043	0.072	0.379
163	4.235	1.141	0.773	0.499	0.219	0.234	0.048	0.057	0.395

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (organ to brain weight ratio) FROM FEMALE RATS

GROUP : IV - 35 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	OVARIES	UTERUS
71	3.906	1.106	0.698	0.494	0.293	0.198	0.035	0.055	0.208
75	4.991	1.129	0.853	0.583	0.259	0.254	0.036	0.084	0.306
83	4.769	1.073	0.690	0.502	0.310	0.223	0.033	0.066	0.300
107	4.027	1.238	0.838	0.533	0.274	0.230	0.031	0.068	0.706
119	4.090	0.930	0.724	0.441	0.216	0.212	0.034	0.080	0.310
120	3.721	0.934	0.696	0.408	0.268	0.230	0.031	0.065	0.493
128	4.327	1.038	0.694	0.567	0.287	0.240	0.035	0.076	0.376
138	4.562	1.073	0.782	0.629	0.259	0.243	0.042	0.075	0.239
145	3.726	0.964	0.716	0.474	0.238	0.170	0.032	0.069	0.355
149	3.349	0.925	0.663	0.435	0.296	0.206	0.034	0.058	0.230
160	4.285	1.104	0.741	0.536	0.330	0.192	0.041	0.065	0.309
164	3.794	1.058	0.744	0.474	0.238	0.275	0.040	0.061	0.329

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (organ to brain weight ratio) FROM FEMALE RATS

GROUP : VI - 125 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	OVARIES	UTERUS
62	4.198	1.031	0.743	0.470	0.248	0.191	0.040	0.073	0.251
79	4.718	1.227	0.731	0.511	0.313	0.324	0.045	0.089	0.368
99	4.216	1.038	0.730	0.551	0.292	0.274	0.041	0.058	0.363
135	3.843	1.027	0.768	0.594	0.273	0.162	0.039	0.082	0.366
142	4.761	1.190	0.828	0.591	0.312	0.219	0.042	0.086	0.433
143	4.576	1.091	0.767	0.540	0.303	0.218	0.035	0.067	0.272
147	3.601	0.969	0.854	0.470	0.206	0.232	0.039	0.048	0.243
150	4.155	0.974	0.681	0.474	0.221	0.172	0.042	0.069	0.336
153	4.166	1.057	0.725	0.458	0.277	0.192	0.042	0.062	0.245
154	4.168	1.046	0.720	0.470	0.253	0.239	0.034	0.066	0.312
156	4.447	1.105	0.726	0.428	0.247	0.308	0.046	0.074	0.219
161	3.896	1.005	0.777	0.453	0.234	0.218	0.038	0.081	0.383

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SUBCHRONIC ADULT MALES AND FEMALES

RELATIVE ORGAN WEIGHTS (organ to brain weight ratio) FROM FEMALE RATS

GROUP : VIII - 375 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	HEART	SPLEEN	THYMUS	ADRENAL GLANDS	OVARIES	UTERUS
67	3.908	0.815	0.662	0.388	0.203	0.164	0.033	0.068	0.245
68	4.662	1.092	0.718	0.506	0.279	0.318	0.045	0.081	0.248
70	4.372	1.043	0.720	0.461	0.268	0.190	0.042	0.084	0.299
76	4.302	1.148	0.736	0.528	0.382	0.247	0.047	0.084	0.475
77	4.273	1.069	0.760	0.445	0.248	0.148	0.034	0.062	0.308
84	3.822	0.975	0.688	0.407	0.210	0.163	0.037	0.060	0.212
88	4.095	1.083	0.743	0.535	0.244	0.195	0.035	0.056	0.261
114	3.639	0.855	0.972	0.484	0.259	0.154	0.036	0.055	0.719
129	4.914	1.192	0.768	0.571	0.273	0.281	0.038	0.069	0.485
146	4.548	0.967	0.786	0.450	0.241	0.230	0.034	0.078	0.290
151	4.198	0.872	0.688	0.454	0.253	0.201	0.043	0.050	0.363
159	4.425	0.984	0.716	0.423	0.236	0.143	0.038	0.064	0.354

APPENDIX JJ

Individual Animal Gross and Microscopic Pathology Data in Subchronic Adult Males and Females

KEY TO APPENDIX

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MODE OF DEATH

SD: SACRIFICED BY DESIGN
SE: SACRIFICED IN EXTREMIS
FD: FOUND DEAD
AK: ACCIDENTLY KILLED (INCLUDES ANIMALS PRESENTED DEAD OR MORIBUND THAT HAVE INJURED THEMSELVES OR WERE INADVERTENTLY INJURED WHEN BEING HANDLED. IN-LIFE AND NECROPSY FINDINGS MAY BE USED TO MAKE THIS DETERMINATION.)

LESION GRADING

HISTOPATHOLOGICAL CHANGES ARE DESCRIBED ACCORDING TO THEIR MORPHOLOGIC CHARACTER, DISTRIBUTION AND SEVERITY. THE DISTRIBUTION (EXTENT OF TISSUE INVOLVEMENT) IS INDICATED, WHERE APPROPRIATE, BY MODIFIERS SUCH AS FOCAL, MULTIFOCAL, DIFFUSE, UNILATERAL, BILATERAL, ETC.; A SEVERITY SCORE, IF APPROPRIATE, IS ALSO ASSIGNED AS FOLLOWS:

PRESENT: LESION PRESENT, SEVERITY NOT GRADED.
MINIMAL: THE AMOUNT OF CHANGE PRESENT BARELY EXCEEDS THAT WHICH IS CONSIDERED TO BE WITHIN NORMAL LIMITS.
MILD: IN GENERAL, THE LESION IS EASILY IDENTIFIED BUT OF LIMITED SEVERITY. THE LESION PROBABLY DOES NOT PRODUCE ANY FUNCTIONAL IMPAIRMENT.
MODERATE: THE LESION IS PROMINENT BUT THERE IS SIGNIFICANT POTENTIAL FOR INCREASED SEVERITY. LIMITED TISSUE OR ORGAN DYSFUNCTION IS POSSIBLE.
SEVERE: THE DEGREE OF CHANGE IS EITHER AS COMPLETE AS CONSIDERED POSSIBLE OR GREAT ENOUGH IN INTENSITY OR EXTENT TO EXPECT SIGNIFICANT TISSUE OR ORGAN DYSFUNCTION.

COMMENT:

GRADES MINIMAL THROUGH SEVERE REPRESENT PROGRESSIVE INVOLVEMENT/SEVERITY ALONG A CONTINUUM WITH MINIMAL LESIONS BEING THE LEAST SEVERE AND SEVERE LESIONS BEING THE MOST SEVERE. WHILE THE GRADES REFER TO THE MORPHOLOGICAL CHARACTERISTICS OF LESIONS, THEY ALSO INDICATE THEIR RELATIVE BIOLOGICAL SIGNIFICANCE.

GROSS OBSERVATIONS LISTING MULTIPLE MASSES FOR A TISSUE ARE DISTINGUISHED WITH LETTERS (i.e., A, B, C, D, etc.)

MICROSCOPIC CORRELATE (selected lesions)

THE MICROSCOPIC CORRELATE FOR SELECTED GROSS OBSERVATIONS, PRIMARILY MASSES, IS PROVIDED TO THE RIGHT OF THE RESPECTIVE GROSS OBSERVATION.

NEOPLASM DESIGNATIONS

*B: BENIGN NEOPLASM, PRIMARY SITE
*M: MALIGNANT NEOPLASM, PRIMARY SITE
*X: MALIGNANT NEOPLASM, METASTATIC OR SECONDARY SITE

ABBREVIATIONS
NPT = NONPROTOCOL TISSUE
NOS = NOT OTHERWISE SPECIFIED

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: I DOSE: 0 mg/kg/day

ANIMAL NUMBER: 1 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- FOLD/ROSETTE, RETINAL, MINIMAL
	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- CYST, MILD
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
PHARYNX/LARYNX	- DEGENERATION, MYOFIBER, FOCAL, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, LUNGS, MESENTERIC LYMPH NODE, PANCREAS, PITUITARY GLAND, PROSTATE, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER, PARATHYROID GLAND

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: I DOSE: 0 mg/kg/day

ANIMAL NUMBER: 8 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EPIDIDYMIDES	- AGGREGATES, LYMPHOID, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- AGGREGATES, LYMPHOID, MINIMAL
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- HEMATOPOIESIS, INCREASED EXTRAMEDULLARY, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, PROSTATE, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: I DOSE: 0 mg/kg/day

ANIMAL NUMBER: 10 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT
KIDNEYS	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MINIMAL
PROSTATE	- AGGREGATES, LYMPHOID, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, LUNGS, MANDIBULAR LYMPH NODE, MEDIASTINAL LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: I DOSE: 0 mg/kg/day

ANIMAL NUMBER: 12 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
	- NECROSIS, COAGULATIVE, FOCAL, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
	- HYPERTROPHY, VASCULAR MEDIAL, MILD
MEDIASTINAL LYMPH NODE	- INFLAMMATION, SUBACUTE/CHRONIC, MEDIASTINAL, MINIMAL
MESENTERIC LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
PROSTATE	- AGGREGATES, LYMPHOID, MILD
THYMUS	- HEMORRHAGE, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, MANDIBULAR LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: I DOSE: 0 mg/kg/day

ANIMAL NUMBER: 13 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

CECUM	- CELLULARITY INCREASED, LAMINA PROPRIA, MILD
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
	- OPTIC NERVE NOT PRESENT, UNILATERAL
ILEUM	- PEYER'S PATCH NOT PRESENT
KIDNEYS	- HYDRONEPHROSIS, UNILATERAL, MILD
LIVER	- FATTY CHANGE, MEDIAN CLEFT, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
PROSTATE	- AGGREGATES, LYMPHOID, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, COAGULATING GLANDS,
COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, LUNGS, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: I DOSE: 0 mg/kg/day

ANIMAL NUMBER: 22 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

CECUM	- CELLULARITY INCREASED, LAMINA PROPRIA, MILD
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
	- HISTIOCYTOSIS, ALVEOLAR, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
STOMACH	- EROSION/ULCER, GLANDULAR, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, COAGULATING GLANDS,
COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, EYES, FEMUR/KNEE JOINT, HEART, JEJUNUM, KIDNEYS,
MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, PROSTATE,
RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM,
TESTES, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: I DOSE: 0 mg/kg/day

ANIMAL NUMBER: 31 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EPIDIDYMIDES	- AGGREGATES, LYMPHOID, MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
LIVER	- FATTY CHANGE, MEDIAN CLEFT, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
	- HISTIOCYTOSIS, ALVEOLAR, MINIMAL
	- INFLAMMATION, ALVEOLAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, PERIVASCULAR, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
SALIVARY GLANDS	- DEGENERATION/NECROSIS, FOCAL (PAROTID GLAND), MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL
THYROID GLAND	- HYPERTROPHY, FOLLICULAR CELL, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, EYES, FEMUR/KNEE JOINT, HEART, JEJUNUM, KIDNEYS, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, PROSTATE, RECTUM, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: MEDIASTINAL LYMPH NODE, OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: I DOSE: 0 mg/kg/day

ANIMAL NUMBER: 36 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EXORBITAL LACRIMAL GLANDS	- AGGREGATES, LYMPHOID, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
HEART	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- HYDRONEPHROSIS, UNILATERAL, MILD
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
PROSTATE	- AGGREGATES, LYMPHOID, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL
THYROID GLAND	- ECTOPIC THYMUS TISSUE

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, FEMUR/KNEE JOINT, JEJUNUM, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: I DOSE: 0 mg/kg/day

ANIMAL NUMBER: 41 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EXORBITAL LACRIMAL GLANDS	- AGGREGATES, LYMPHOID, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
	- HISTIOCYTOSIS, ALVEOLAR, MINIMAL
	- INFLAMMATION, ALVEOLAR, MINIMAL
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
PROSTATE	- AGGREGATES, LYMPHOID, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL
THYROID GLAND	- HYPERTROPHY, FOLLICULAR CELL, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, FEMUR/KNEE JOINT, HEART, JEJUNUM, KIDNEYS, MEDIASTINAL LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: I DOSE: 0 mg/kg/day

ANIMAL NUMBER: 44 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EPIDIDYMIDES	- AGGREGATES, LYMPHOID, MINIMAL
HEART	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MILD
LUNGS	- HEMORRHAGE, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
THYMUS	- HEMORRHAGE, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, EYES, FEMUR/KNEE JOINT, JEJUNUM, KIDNEYS, MANDIBULAR LYMPH NODE, MEDIASTINAL LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, PROSTATE, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: I DOSE: 0 mg/kg/day

ANIMAL NUMBER: 45 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EPIDIDYMIDES	- AGGREGATES, LYMPHOID, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
	- OPTIC NERVE NOT PRESENT, UNILATERAL
HEART	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
LIVER	- HEMATOPOIESIS, INCREASED EXTRAMEDULLARY, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- INFLAMMATION, ALVEOLAR, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
PROSTATE	- AGGREGATES, LYMPHOID, MINIMAL
SALIVARY GLANDS	- DEGENERATION/NECROSIS, FOCAL (PAROTID GLAND), MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, JEJUNUM, KIDNEYS, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: I DOSE: 0 mg/kg/day

ANIMAL NUMBER: 54 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MILD
HEART	- INFLAMMATION, SUBACUTE/CHRONIC, MILD
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
LIVER	- FATTY CHANGE, MEDIAN CLEFT, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
	- NECROSIS, COAGULATIVE, FOCAL, MILD
LUNGS	- INFLAMMATION, ALVEOLAR, MILD
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MINIMAL
PROSTATE	- AGGREGATES, LYMPHOID, MODERATE
THYMUS	- HEMORRHAGE, MINIMAL
THYROID GLAND	- ECTOPIC THYMUS TISSUE
URINARY BLADDER	- AGGREGATES, LYMPHOID, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, JEJUNUM, KIDNEYS, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, TONGUE, TRACHEA

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: III DOSE: 35 mg/kg/day

ANIMAL NUMBER: 3 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MINIMAL
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: III DOSE: 35 mg/kg/day

ANIMAL NUMBER: 5 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- AGGREGATES, LYMPHOID, MINIMAL
	- HYALINE DROPLETS, INCREASED, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: III DOSE: 35 mg/kg/day

ANIMAL NUMBER: 14 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MINIMAL
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: III DOSE: 35 mg/kg/day

ANIMAL NUMBER: 18 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MINIMAL
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: III DOSE: 35 mg/kg/day

ANIMAL NUMBER: 20 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MINIMAL
LIVER	- FATTY CHANGE, MEDIAN CLEFT, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: III DOSE: 35 mg/kg/day

ANIMAL NUMBER: 26 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
THYROID GLAND	- HYPERTROPHY, FOLLICULAR CELL, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: III DOSE: 35 mg/kg/day

ANIMAL NUMBER: 35 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
KIDNEYS - HYALINE DROPLETS, INCREASED, MINIMAL
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: III DOSE: 35 mg/kg/day

ANIMAL NUMBER: 46 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MINIMAL
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
THYROID GLAND	- HYPERTROPHY, FOLLICULAR CELL, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: III DOSE: 35 mg/kg/day

ANIMAL NUMBER: 48 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
KIDNEYS - DILATATION, RIGHT, PELVIS

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
KIDNEYS - AGGREGATES, LYMPHOID, MINIMAL
- HYALINE DROPLETS, INCREASED, MINIMAL
- HYDRONEPHROSIS, UNILATERAL, MILD
LIVER - FATTY CHANGE, MEDIAN CLEFT, MINIMAL
- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: III DOSE: 35 mg/kg/day

ANIMAL NUMBER: 50 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
KIDNEYS - HYALINE DROPLETS, INCREASED, MINIMAL
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: III DOSE: 35 mg/kg/day

ANIMAL NUMBER: 55 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MINIMAL
	- HYDRONEPHROSIS, BILATERAL, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: III DOSE: 35 mg/kg/day

ANIMAL NUMBER: 56 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MINIMAL
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
THYROID GLAND	- HYPERTROPHY, FOLLICULAR CELL, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: V DOSE: 125 mg/kg/day

ANIMAL NUMBER: 4 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
KIDNEYS - HYALINE DROPLETS, INCREASED, MILD
LIVER - HEMATOPOIESIS, INCREASED EXTRAMEDULLARY, MINIMAL
- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: V DOSE: 125 mg/kg/day

ANIMAL NUMBER: 9 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EPIDIDYMIDES	- AGGREGATES, LYMPHOID, MINIMAL
KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: COAGULATING GLANDS, PROSTATE, SEMINAL VESICLES, TESTES, THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: V DOSE: 125 mg/kg/day

ANIMAL NUMBER: 25 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
	- HYDRONEPHROSIS, UNILATERAL, MINIMAL
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: V DOSE: 125 mg/kg/day

ANIMAL NUMBER: 28 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
THYROID GLAND	- ECTOPIC THYMUS TISSUE

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: V DOSE: 125 mg/kg/day

ANIMAL NUMBER: 30 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: V DOSE: 125 mg/kg/day

ANIMAL NUMBER: 32 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
KIDNEYS - HYALINE DROPLETS, INCREASED, MILD

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: LIVER, THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: V DOSE: 125 mg/kg/day

ANIMAL NUMBER: 37 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- AGGREGATES, LYMPHOID, MINIMAL
	- HYALINE DROPLETS, INCREASED, MINIMAL
	- INFARCT, MINIMAL
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: V DOSE: 125 mg/kg/day

ANIMAL NUMBER: 38 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
KIDNEYS - HYALINE DROPLETS, INCREASED, MILD
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: V DOSE: 125 mg/kg/day

ANIMAL NUMBER: 43 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
KIDNEYS - HYALINE DROPLETS, INCREASED, MINIMAL
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: V DOSE: 125 mg/kg/day

ANIMAL NUMBER: 47 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
THYROID GLAND	- HYPERTROPHY, FOLLICULAR CELL, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: V DOSE: 125 mg/kg/day

ANIMAL NUMBER: 49 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
THYROID GLAND	- HYPERTROPHY, FOLLICULAR CELL, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: V DOSE: 125 mg/kg/day

ANIMAL NUMBER: 51 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: THYROID GLAND

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 2 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EPIDIDYMIDES	- AGGREGATES, LYMPHOID, MINIMAL
ESOPHAGUS	- DEGENERATION, MYOFIBER, FOCAL, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
LIVER	- HEMATOPOIESIS, INCREASED EXTRAMEDULLARY, MINIMAL
	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
PROSTATE	- AGGREGATES, LYMPHOID, MILD
THYMUS	- HEMORRHAGE, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, MANDIBULAR LYMPH NODE, MEDIASTINAL LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 6 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EPIDIDYMIDES	- AGGREGATES, LYMPHOID, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- HYALINE DROPLETS, INCREASED, MODERATE
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- HEMATOPOIESIS, INCREASED EXTRAMEDULLARY, MINIMAL
	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL
THYROID GLAND	- HYPERTROPHY, FOLLICULAR CELL, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, LUNGS, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, PROSTATE, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 11 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- AGGREGATES, LYMPHOID, MINIMAL
	- HYALINE DROPLETS, INCREASED, MILD
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
	- HISTIOCYTOSIS, ALVEOLAR, MINIMAL
	- INFLAMMATION, ALVEOLAR, MILD
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MINIMAL
PROSTATE	- AGGREGATES, LYMPHOID, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 16 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EPIDIDYMIDES	- AGGREGATES, LYMPHOID, MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MILD
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
MESENTERIC LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
THYROID GLAND	- HYPERTROPHY, FOLLICULAR CELL, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, EYES, FEMUR/KNEE JOINT, HEART, JEJUNUM, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, PROSTATE, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYMUS, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 19 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

CECUM	- CELLULARITY INCREASED, LAMINA PROPRIA, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- FATTY CHANGE, MEDIAN CLEFT, MINIMAL
	- HEMATOPOIESIS, INCREASED EXTRAMEDULLARY, MINIMAL
	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MODERATE
THYMUS	- HEMORRHAGE, MINIMAL
THYROID GLAND	- ECTOPIC THYMUS TISSUE

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, COAGULATING GLANDS,
COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, MESENTERIC LYMPH NODE, PANCREAS, PHARYNX/LARYNX, PITUITARY GLAND, PROSTATE, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER, PARATHYROID GLAND

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 21 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- OPTIC NERVE NOT PRESENT, UNILATERAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HISTIOCYTOSIS, ALVEOLAR, MILD
	- INFLAMMATION, ALVEOLAR, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
PROSTATE	- AGGREGATES, LYMPHOID, MILD
THYMUS	- HEMORRHAGE, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 27 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:

		MICROSCOPIC CORRELATE (selected lesions):
KIDNEYS	- DILATATION, UNILATERAL, PELVIS	

MICROSCOPIC OBSERVATIONS:

KIDNEYS	- CYST, MILD
	- HYALINE DROPLETS, INCREASED, MILD
	- HYDRONEPHROSIS, UNILATERAL, MILD
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- INFLAMMATION, ALVEOLAR, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
THYMUS	- HEMORRHAGE, MILD

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, EYES, FEMUR/KNEE JOINT, HEART, ILEUM, JEJUNUM, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, PROSTATE, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 33 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EPIDIDYMIDES	- AGGREGATES, LYMPHOID, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT
KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- INFLAMMATION, ALVEOLAR, MINIMAL
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
THYMUS	- HEMORRHAGE, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, PROSTATE, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 39 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EPIDIDYMIDES	- AGGREGATES, LYMPHOID, MINIMAL
ESOPHAGUS	- INFLAMMATION, MUSCULAR, FOCAL, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MILD
KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- INFLAMMATION, ALVEOLAR, MINIMAL
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
MESENTERIC LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
THYROID GLAND	- HYPERTROPHY, FOLLICULAR CELL, MINIMAL
URINARY BLADDER	- AGGREGATES, LYMPHOID, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, ILEUM, JEJUNUM, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, PROSTATE, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYMUS, TONGUE, TRACHEA

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 40 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS: MICROSCOPIC CORRELATE (selected lesions):

KIDNEYS	- DILATATION, BILATERAL, PELVIS

MICROSCOPIC OBSERVATIONS:

CECUM	- CELLULARITY INCREASED, LAMINA PROPRIA, MILD
EPIDIDYMIDES	- AGGREGATES, LYMPHOID, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
	- OPTIC NERVE NOT PRESENT, UNILATERAL
HEART	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
	- HYDRONEPHROSIS, BILATERAL, MILD
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- HEMATOPOIESIS, INCREASED EXTRAMEDULLARY, MINIMAL
	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
	- HISTIOCYTOSIS, ALVEOLAR, MINIMAL
	- INFLAMMATION, ALVEOLAR, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MINIMAL
PITUITARY GLAND	- CYST, MILD
	- HYPERPLASIA, CRANIOPHARYNGEAL, MILD
PROSTATE	- AGGREGATES, LYMPHOID, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MILD
THYMUS	- HEMORRHAGE, MINIMAL
THYROID GLAND	- HYPERTROPHY, FOLLICULAR CELL, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, COAGULATING GLANDS,
COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, JEJUNUM, MANDIBULAR LYMPH NODE, MEDIASTINAL LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, TONGUE, TRACHEA, URINARY BLADDER

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 40 (Continued)

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 52 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

CECUM	- CELLULARITY INCREASED, LAMINA PROPRIA, MILD
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MILD
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HISTIOCYTOSIS, ALVEOLAR, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MINIMAL
PROSTATE	- AGGREGATES, LYMPHOID, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, COAGULATING GLANDS,
COLON, DUODENUM, EPIDIDYMIDES, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

MALE RATS GROUP: VII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 53 DAYS ON TEST: 30 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EPIDIDYMIDES	- AGGREGATES, LYMPHOID, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MILD
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- HYALINE DROPLETS, INCREASED, MILD
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
NOSE	- INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE), MILD
SPLEEN	- HEMATOPOIESIS, INCREASED EXTRAMEDULLARY, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, COAGULATING GLANDS, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, MESENTERIC LYMPH NODE, PANCREAS, PHARYNX/LARYNX, PITUITARY GLAND, PROSTATE, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SEMINAL VESICLES, SKELETAL MUSCLE, SKIN, SPINAL CORD, STERNUM, STOMACH, TESTES, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER, PARATHYROID GLAND

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: II DOSE: 0 mg/kg/day

ANIMAL NUMBER: 69 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
KIDNEYS	- MINERALIZATION, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL
VAGINA	- ESTRUS STAGE: METESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, ILEUM, JEJUNUM, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MEDIASTINAL LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: II DOSE: 0 mg/kg/day

ANIMAL NUMBER: 89 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- AGGREGATES, LYMPHOID, MINIMAL
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL
VAGINA	- ESTRUS STAGE: PROESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, EYES, FEMUR/KNEE JOINT, HEART, JEJUNUM, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: II DOSE: 0 mg/kg/day

ANIMAL NUMBER: 101 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EXORBITAL LACRIMAL GLANDS	- AGGREGATES, LYMPHOID, MINIMAL
EYES	- FOLD/ROSETTE, RETINAL, MINIMAL
	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
HEART	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- AGGREGATES, LYMPHOID, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
THYMUS	- HEMORRHAGE, MINIMAL
VAGINA	- ESTRUS STAGE: METESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, FEMUR/KNEE JOINT, JEJUNUM, LIVER, MAMMARY GLAND, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: II DOSE: 0 mg/kg/day

ANIMAL NUMBER: 112 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

HEART	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT
KIDNEYS	- AGGREGATES, LYMPHOID, MINIMAL
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
	- HISTIOCYTOSIS, ALVEOLAR, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
VAGINA	- ESTRUS STAGE: ESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, EYES, FEMUR/KNEE JOINT, JEJUNUM, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: II DOSE: 0 mg/kg/day

ANIMAL NUMBER: 113 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- INFLAMMATION, SUBACUTE/CHRONIC, PERIVASCULAR, MINIMAL
VAGINA	- ESTRUS STAGE: PROESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, KIDNEYS, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MEDIASTINAL LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: II DOSE: 0 mg/kg/day

ANIMAL NUMBER: 123 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

ESOPHAGUS	- DEGENERATION, MYOFIBER, FOCAL, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
	- OPTIC NERVE NOT PRESENT, UNILATERAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- AGGREGATES, LYMPHOID, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
THYROID GLAND	- ECTOPIC THYMUS TISSUE
TRACHEA	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
VAGINA	- ESTRUS STAGE: METESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, LUNGS, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, TONGUE, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: II DOSE: 0 mg/kg/day

ANIMAL NUMBER: 126 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
KIDNEYS	- AGGREGATES, LYMPHOID, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HISTIOCYTOSIS, ALVEOLAR, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
URINARY BLADDER	- AGGREGATES, LYMPHOID, MINIMAL
VAGINA	- ESTRUS STAGE: PROESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, ILEUM, JEJUNUM, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, THYROID GLAND, TONGUE, TRACHEA, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: II DOSE: 0 mg/kg/day

ANIMAL NUMBER: 144 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

ESOPHAGUS	- DEGENERATION, MYOFIBER, FOCAL, MINIMAL
EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MILD
LUNGS	- HEMORRHAGE, MILD
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
VAGINA	- ESTRUS STAGE: METESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, ILEUM, JEJUNUM, KIDNEYS, LIVER, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: II DOSE: 0 mg/kg/day

ANIMAL NUMBER: 152 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- AGGREGATES, LYMPHOID, MINIMAL
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- HEMATOPOIESIS, INCREASED EXTRAMEDULLARY, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HISTIOCYTOSIS, ALVEOLAR, MINIMAL
	- INFLAMMATION, SUBACUTE/CHRONIC, PERIVASCULAR, MINIMAL
VAGINA	- ESTRUS STAGE: METESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MEDIASTINAL LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: II DOSE: 0 mg/kg/day

ANIMAL NUMBER: 155 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
SPLEEN	- HEMATOPOIESIS, INCREASED EXTRAMEDULLARY, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL
VAGINA	- ESTRUS STAGE: METESTRUS
	- INFLAMMATION, SUBACUTE/CHRONIC, MODERATE

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, KIDNEYS, LUNGS, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, STERNUM, STOMACH, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: II DOSE: 0 mg/kg/day

ANIMAL NUMBER: 162 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MILD
	- OPTIC NERVE NOT PRESENT, UNILATERAL
KIDNEYS	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
THYMUS	- HEMORRHAGE, MINIMAL
VAGINA	- ESTRUS STAGE: ESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, ILEUM, JEJUNUM, MAMMARY GLAND, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: II DOSE: 0 mg/kg/day

ANIMAL NUMBER: 163 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
VAGINA	- ESTRUS STAGE: PROESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, EYES, FEMUR/KNEE JOINT, HEART, JEJUNUM, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: IV DOSE: 35 mg/kg/day

ANIMAL NUMBER: 71 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: IV DOSE: 35 mg/kg/day

ANIMAL NUMBER: 75 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: IV DOSE: 35 mg/kg/day

ANIMAL NUMBER: 83 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - FATTY CHANGE, MEDIAN CLEFT, MINIMAL
- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: IV DOSE: 35 mg/kg/day

ANIMAL NUMBER: 107 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER
- FATTY CHANGE, MEDIAN CLEFT, MINIMAL
- HEMATOPOIESIS, INCREASED EXTRAMEDULLARY, MINIMAL
- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: IV DOSE: 35 mg/kg/day

ANIMAL NUMBER: 119 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: IV DOSE: 35 mg/kg/day

ANIMAL NUMBER: 120 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: IV DOSE: 35 mg/kg/day

ANIMAL NUMBER: 128 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: IV DOSE: 35 mg/kg/day

ANIMAL NUMBER: 138 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: IV DOSE: 35 mg/kg/day

ANIMAL NUMBER: 145 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: IV DOSE: 35 mg/kg/day

ANIMAL NUMBER: 149 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - FATTY CHANGE, MEDIAN CLEFT, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: IV DOSE: 35 mg/kg/day

ANIMAL NUMBER: 160 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: IV DOSE: 35 mg/kg/day

ANIMAL NUMBER: 164 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER
- FATTY CHANGE, MEDIAN CLEFT, MINIMAL
- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
- NECROSIS, COAGULATIVE, FOCAL, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VI DOSE: 125 mg/kg/day

ANIMAL NUMBER: 62 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VI DOSE: 125 mg/kg/day

ANIMAL NUMBER: 79 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER
- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VI DOSE: 125 mg/kg/day

ANIMAL NUMBER: 99 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VI DOSE: 125 mg/kg/day

ANIMAL NUMBER: 135 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VI DOSE: 125 mg/kg/day

ANIMAL NUMBER: 142 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VI DOSE: 125 mg/kg/day

ANIMAL NUMBER: 143 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER
- HEMATOPOIESIS, INCREASED EXTRAMEDULLARY, MINIMAL
- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MINIMAL
- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VI DOSE: 125 mg/kg/day

ANIMAL NUMBER: 147 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VI DOSE: 125 mg/kg/day

ANIMAL NUMBER: 150 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VI DOSE: 125 mg/kg/day

ANIMAL NUMBER: 153 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VI DOSE: 125 mg/kg/day

ANIMAL NUMBER: 154 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VI DOSE: 125 mg/kg/day

ANIMAL NUMBER: 156 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VI DOSE: 125 mg/kg/day

ANIMAL NUMBER: 161 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
LIVER - INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: NONE

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VIII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 67 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL
VAGINA	- ESTRUS STAGE: ESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, EYES, FEMUR/KNEE JOINT, HEART, JEJUNUM, LUNGS, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: MEDIASTINAL LYMPH NODE, OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VIII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 68 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- FOLD/ROSETTE, RETINAL, MINIMAL
	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL
VAGINA	- ESTRUS STAGE: METESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, KIDNEYS, LUNGS, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VIII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 70 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS: MICROSCOPIC CORRELATE (selected lesions):

SKIN	- ALOPECIA, PERINEUM

MICROSCOPIC OBSERVATIONS:

ILEUM	- PEYER'S PATCH NOT PRESENT
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
OTHER	- SKIN: NO ABNORMALITIES DETECTED
THYROID GLAND	- HYPERTROPHY, FOLLICULAR CELL, MINIMAL
VAGINA	- ESTRUS STAGE: ESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, EYES, FEMUR/KNEE JOINT, HEART, JEJUNUM, KIDNEYS, LUNGS, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: MEDIASTINAL LYMPH NODE

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VIII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 76 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HISTIOCYTOSIS, ALVEOLAR, MINIMAL
SALIVARY GLANDS	- FOCUS OF CELLULAR ALTERATION, BASOPHILIC (PAROTID GLAND), MINIMAL
VAGINA	- ESTRUS STAGE: PROESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, KIDNEYS, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MEDIASTINAL LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VIII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 77 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MILD
	- OPTIC NERVE NOT PRESENT, UNILATERAL
ILEUM	- PEYER'S PATCH NOT PRESENT
KIDNEYS	- AGGREGATES, LYMPHOID, MINIMAL
	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
VAGINA	- ESTRUS STAGE: ESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, LUNGS, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VIII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 84 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

CECUM	- CELLULARITY INCREASED, LAMINA PROPRIA, MINIMAL
ESOPHAGUS	- DEGENERATION, MYOFIBER, FOCAL, MILD
EYES	- FOLD/ROSETTE, RETINAL, MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
VAGINA	- ESTRUS STAGE: METESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CERVIX, COLON, DUODENUM, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, KIDNEYS, LUNGS, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VIII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 88 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- FOLD/ROSETTE, RETINAL, MINIMAL
	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MILD
	- NEOVASCULARIZATION, CORNEAL, MINIMAL
	- OPTIC NERVE NOT PRESENT, UNILATERAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL
VAGINA	- ESTRUS STAGE: ESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, KIDNEYS, LUNGS, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VIII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 114 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:

		MICROSCOPIC CORRELATE (selected lesions):
UTERUS	- DILATATION	

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MINIMAL
	- OPTIC NERVE NOT PRESENT, UNILATERAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
KIDNEYS	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL
THYROID GLAND	- ECTOPIC THYMUS TISSUE
URINARY BLADDER	- AGGREGATES, LYMPHOID, MINIMAL
VAGINA	- ESTRUS STAGE: ESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, LUNGS, MAMMARY GLAND, MEDIASTINAL LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, TONGUE, TRACHEA, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VIII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 129 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MILD
ILEUM	- PEYER'S PATCH NOT PRESENT
KIDNEYS	- AGGREGATES, LYMPHOID, MINIMAL
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- INFLAMMATION, ALVEOLAR, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MILD
PANCREAS	- AGGREGATES, LYMPHOID, MINIMAL
VAGINA	- ESTRUS STAGE: PROESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, JEJUNUM, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES: NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VIII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 146 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

ESOPHAGUS	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
ILEUM	- PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
VAGINA	- ESTRUS STAGE: ESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, EXORBITAL LACRIMAL GLANDS, EYES, FEMUR/KNEE JOINT, HEART, JEJUNUM, KIDNEYS, LUNGS, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MEDIASTINAL LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VIII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 151 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

ILEUM	- PEYER'S PATCH NOT PRESENT
KIDNEYS	- NEPHROPATHY, CHRONIC PROGRESSIVE, MINIMAL
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
LUNGS	- HEMORRHAGE, MINIMAL
THYMUS	- HEMORRHAGE, MINIMAL
TRACHEA	- AGGREGATES, LYMPHOID, MINIMAL
VAGINA	- ESTRUS STAGE: PROESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, EYES, FEMUR/KNEE JOINT, HEART, JEJUNUM, MAMMARY GLAND, MANDIBULAR LYMPH NODE, MEDIASTINAL LYMPH NODE, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYROID GLAND, TONGUE, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC PATHOLOGY DATA IN SUBCHRONIC ADULT MALES AND FEMALES

FEMALE RATS GROUP: VIII DOSE: 375 mg/kg/day

ANIMAL NUMBER: 159 DAYS ON TEST: 31 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:

EYES	- FOLD/ROSETTE, RETINAL, MINIMAL
	- INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE), MILD
	- LENS NOT PRESENT, UNILATERAL
LIVER	- HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR, MILD
	- INFLAMMATION, SUBACUTE/CHRONIC, MINIMAL
MANDIBULAR LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
MEDIASTINAL LYMPH NODE	- ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, MINIMAL
VAGINA	- ESTRUS STAGE: PROESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: ADRENAL GLANDS, AORTA, BONE MARROW, BRAIN, CECUM, CERVIX, COLON, DUODENUM, ESOPHAGUS, EXORBITAL LACRIMAL GLANDS, FEMUR/KNEE JOINT, HEART, ILEUM, JEJUNUM, KIDNEYS, LUNGS, MAMMARY GLAND, MESENTERIC LYMPH NODE, NOSE, OVARIES, PANCREAS, PARATHYROID GLAND, PHARYNX/LARYNX, PITUITARY GLAND, RECTUM, SALIVARY GLANDS, SCIATIC NERVE, SKELETAL MUSCLE, SKIN, SPINAL CORD, SPLEEN, STERNUM, STOMACH, THYMUS, THYROID GLAND, TONGUE, TRACHEA, URINARY BLADDER, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

APPENDIX KK

Individual Animal Final Body and Organ Weights in Satellite Adult Female Rats

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SATELLITE ADULT FEMALE RATS

FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams) FROM FEMALE RATS

GROUP : II-0 - 0 mg/kg/day

ANIMAL NUMBER	FINAL BODY	LIVER	KIDNEYS	LUNGS	OVARIES	UTERUS
57	323.8	13.522	2.258	1.285	0.117	0.796
59	318.6	12.459	2.268	1.422	0.119	0.688
72	365.8	15.154	2.591	1.644	0.165	0.845
82	358.9	15.833	2.274	1.633	0.152	0.663
87	336.6	14.014	2.448	1.652	0.120	0.764
90	303.3	12.167	2.227	1.393	0.145	0.578
91	310.5	13.990	2.178	1.525	0.128	0.702
94	311.0	10.809	2.151	1.461	0.170	1.064
109	306.5	14.720	1.971	1.541	0.122	0.592
118	320.1	11.600	2.296	1.591	0.170	1.809
121	333.9	16.476	2.661	1.560	0.134	0.745
132	331.4	13.691	2.265	1.474	0.100	0.700

FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams) FROM FEMALE RATS

GROUP : IV-0 - 35 mg/kg/day

ANIMAL NUMBER	FINAL BODY	LIVER	KIDNEYS	LUNGS	OVARIES	UTERUS
60	305.6	13.115	2.009	1.421	0.121	0.664
64	339.3	12.330	2.164	1.640	0.136	0.722
100	319.7	14.028	2.217	1.468	0.125	0.823
102	312.1	12.916	2.155	1.366	0.105	0.706
103	333.2	14.449	2.091	1.630	0.103	0.608
105	324.1	13.899	2.340	1.566	0.157	0.787
106	249.5	8.209	2.106	1.992	0.142	0.629
115	298.8	12.537	2.149	1.407	0.115	0.713
116	327.6	14.612	2.393	1.504	0.148	0.667
117	337.8	14.778	2.316	1.595	0.151	0.884
140	340.2	13.405	2.485	1.397	0.140	0.730
165	326.7	13.480	2.549	1.527	0.136	0.590

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SATELLITE ADULT FEMALE RATS

FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams) FROM FEMALE RATS

GROUP : VI-0 - 125 mg/kg/day

ANIMAL NUMBER	FINAL BODY	LIVER	KIDNEYS	LUNGS	OVARIES	UTERUS
61	319.6	13.755	1.974	1.427	0.138	0.612
78	279.5	11.910	2.316	1.555	0.136	0.421
85	298.6	12.681	2.067	1.304	0.123	0.776
86	306.2	13.437	2.133	1.567	0.119	0.531
97	274.2	11.528	1.832	1.284	0.086	0.746
104	289.6	11.714	1.971	1.271	0.115	0.697
110	280.0	13.022	2.291	1.359	0.120	0.727
122	303.5	13.136	2.116	1.375	0.132	0.606
130	309.3	13.486	2.411	1.489	0.125	0.942
131	323.3	18.365	2.701	1.522	0.178	0.797
137	342.1	15.614	2.587	1.507	0.111	0.782
157	297.2	11.623	1.961	1.509	0.119	0.590

FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams) FROM FEMALE RATS

GROUP : VIII-0 - 375 mg/kg/day

ANIMAL NUMBER	FINAL BODY	LIVER	KIDNEYS	LUNGS	OVARIES	UTERUS
63	325.1	14.784	2.620	1.565	0.148	0.666
65	311.3	16.389	2.378	1.443	0.128	0.762
66	305.7	15.549	2.311	1.400	0.130	0.769
73	296.0	13.110	2.205	1.418	0.156	0.588
81	307.7	13.884	2.202	1.678	0.143	0.640
92	306.6	14.434	2.396	1.380	0.111	0.638
95	287.5	14.581	2.068	1.555	0.172	0.702
96	273.6	12.765	1.912	1.477	0.099	0.591
125	311.2	16.137	2.552	1.551	0.127	0.797
127	293.6	12.372	2.568	1.564	0.138	0.391
133	304.8	12.682	2.124	1.449	0.115	0.654
166	327.8	15.575	2.515	1.547	0.130	0.802

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SATELLITE ADULT FEMALE RATS

RELATIVE ORGAN WEIGHTS (% of body weight) FROM FEMALE RATS

GROUP : II-0 - 0 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	OVARIES	UTERUS
57	4.176	0.697	0.397	0.036	0.246
59	3.911	0.712	0.446	0.037	0.216
72	4.143	0.708	0.449	0.045	0.231
82	4.412	0.634	0.455	0.042	0.185
87	4.163	0.727	0.491	0.036	0.227
90	4.012	0.734	0.459	0.048	0.191
91	4.506	0.701	0.491	0.041	0.226
94	3.476	0.692	0.470	0.055	0.342
109	4.803	0.643	0.503	0.040	0.193
118	3.624	0.717	0.497	0.053	0.565
121	4.934	0.797	0.467	0.040	0.223
132	4.131	0.683	0.445	0.030	0.211

RELATIVE ORGAN WEIGHTS (% of body weight) FROM FEMALE RATS

GROUP : IV-0 - 35 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	OVARIES	UTERUS
60	4.292	0.657	0.465	0.040	0.217
64	3.634	0.638	0.483	0.040	0.213
100	4.388	0.693	0.459	0.039	0.257
102	4.138	0.690	0.438	0.034	0.226
103	4.336	0.628	0.489	0.031	0.182
105	4.288	0.722	0.483	0.048	0.243
106	3.290	0.844	0.798	0.057	0.252
115	4.196	0.719	0.471	0.038	0.239
116	4.460	0.730	0.459	0.045	0.204
117	4.375	0.686	0.472	0.045	0.262
140	3.940	0.730	0.411	0.041	0.215
165	4.126	0.780	0.467	0.042	0.181

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS IN SATELLITE ADULT FEMALE RATS

RELATIVE ORGAN WEIGHTS (% of body weight) FROM FEMALE RATS

GROUP : VI-0 - 125 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	OVARIES	UTERUS
61	4.304	0.618	0.446	0.043	0.191
78	4.261	0.829	0.556	0.049	0.151
85	4.247	0.692	0.437	0.041	0.260
86	4.388	0.697	0.512	0.039	0.173
97	4.204	0.668	0.468	0.031	0.272
104	4.045	0.681	0.439	0.040	0.241
110	4.651	0.818	0.485	0.043	0.260
122	4.328	0.697	0.453	0.043	0.200
130	4.360	0.780	0.481	0.040	0.305
131	5.680	0.835	0.471	0.055	0.247
137	4.564	0.756	0.441	0.032	0.229
157	3.911	0.660	0.508	0.040	0.199

RELATIVE ORGAN WEIGHTS (% of body weight) FROM FEMALE RATS

GROUP : VIII-0 - 375 mg/kg/day

ANIMAL NUMBER	LIVER	KIDNEYS	LUNGS	OVARIES	UTERUS
63	4.548	0.806	0.481	0.046	0.205
65	5.265	0.764	0.464	0.041	0.245
66	5.086	0.756	0.458	0.043	0.252
73	4.429	0.745	0.479	0.053	0.199
81	4.512	0.716	0.545	0.046	0.208
92	4.708	0.781	0.450	0.036	0.208
95	5.072	0.719	0.541	0.060	0.244
96	4.666	0.699	0.540	0.036	0.216
125	5.185	0.820	0.498	0.041	0.256
127	4.214	0.875	0.533	0.047	0.133
133	4.161	0.697	0.475	0.038	0.215
166	4.751	0.767	0.472	0.040	0.245

APPENDIX LL

Individual Gross Observation in Satellite Adult Female Rats

INDIVIDUAL GROSS OBSERVATION IN SATELLITE ADULT FEMALE RATS

FEMALE RATA GROUP: II-0 DOSE: 0 mg/kg/day

ANIMAL NUMBER	DAYS ON TEST	MODE OF DEATH	OBSERVATIONS
57	45	SD	13 CORPORA LUTEA 13 IMPLANT SITES NO ABNORMALITIES DETECTED
59	43	SD	16 IMPLANT SITES 17 CORPORA LUTEA NO ABNORMALITIES DETECTED
72	45	SD	17 IMPLANT SITES 19 CORPORA LUTEA NO ABNORMALITIES DETECTED
82	48	SD	14 CORPORA LUTEA 14 IMPLANT SITES NO ABNORMALITIES DETECTED
87	42	SD	15 CORPORA LUTEA 15 IMPLANT SITES NO ABNORMALITIES DETECTED
90	44	SD	10 IMPLANT SITES 11 CORPORA LUTEA NO ABNORMALITIES DETECTED
91	49	SD	16 IMPLANT SITES 19 CORPORA LUTEA NO ABNORMALITIES DETECTED
94	48	SD	0 CORPORA LUTEA 0 IMPLANT SITES UTERUS - FLUID, CLEAR, VISCOUS, BODY

INDIVIDUAL GROSS OBSERVATION IN SATELLITE ADULT FEMALE RATS

FEMALE RATA GROUP: II-0 DOSE: 0 mg/kg/day

ANIMAL NUMBER	DAYS ON TEST	MODE OF DEATH	OBSERVATIONS
109	42	SD	15 corpora lutea 15 implant sites NO ABNORMALITIES DETECTED
118	48	SD	0 CORPORA LUTEA 0 IMPLANT SITES UTERUS - FLUID, CLEAR, VISCOUS, BODY, HORNS
121	49	SD	16 CORPORA LUTEA 16 IMPLANT SITES NO ABNORMALITIES DETECTED
132	43	SD	16 CORPORA LUTEA 16 IMPLANT SITES KIDNEYS - DILATATION, RIGHT, PELVIS

INDIVIDUAL GROSS OBSERVATION IN SATELLITE ADULT FEMALE RATS

FEMALE RATA GROUP: IV-0 DOSE: 35 mg/kg/day

ANIMAL NUMBER	DAYS ON TEST	MODE OF DEATH	OBSERVATIONS
60	44	SD	13 IMPLANT SITES 15 CORPORA LUTEA NO ABNORMALITIES DETECTED
64	42	SD	16 CORPORA LUTEA 16 IMPLANT SITES NO ABNORMALITIES DETECTED
100	45	SD	15 CORPORA LUTEA 15 IMPLANT SITES NO ABNORMALITIES DETECTED
102	43	SD	15 IMPLANT SITES 18 CORPORA LUTEA NO ABNORMALITIES DETECTED
103	43	SD	17 CORPORA LUTEA 17 IMPLANT SITES NO ABNORMALITIES DETECTED
105	43	SD	17 CORPORA LUTEA 17 IMPLANT SITES NO ABNORMALITIES DETECTED
106	44	SD	16 CORPORA LUTEA 16 IMPLANT SITES NO ABNORMALITIES DETECTED
115	42	SD	15 CORPORA LUTEA 15 IMPLANT SITES NO ABNORMALITIES DETECTED

INDIVIDUAL GROSS OBSERVATION IN SATELLITE ADULT FEMALE RATS

FEMALE RATA GROUP: IV-0 DOSE: 35 mg/kg/day

ANIMAL NUMBER	DAYS ON TEST	MODE OF DEATH	OBSERVATIONS
116	47	SD	16 CORPORA LUTEA 16 IMPLANT SITES NO ABNORMALITIES DETECTED
117	47	SD	16 IMPLANT SITES 19 CORPORA LUTEA NO ABNORMALITIES DETECTED
140	43	SD	16 CORPORA LUTEA 16 IMPLANT SITES NO ABNORMALITIES DETECTED
165	45	SD	16 IMPLANT SITES 18 CORPORA LUTEA NO ABNORMALITIES DETECTED

INDIVIDUAL GROSS OBSERVATION IN SATELLITE ADULT FEMALE RATS

FEMALE RATA GROUP: VI-0 DOSE: 125 mg/kg/day

ANIMAL NUMBER	DAYS ON TEST	MODE OF DEATH	OBSERVATIONS
61	45	SD	15 IMPLANT SITES 19 CORPORA LUTEA NO ABNORMALITIES DETECTED
78	48	SD	0 CORPORA LUTEA 0 IMPLANT SITES NO ABNORMALITIES DETECTED
85	45	SD	13 IMPLANT SITES 14 CORPORA LUTEA NO ABNORMALITIES DETECTED
86	45	SD	13 IMPLANT SITES 16 CORPORA LUTEA NO ABNORMALITIES DETECTED
97	45	SD	13 IMPLANT SITES 14 CORPORA LUTEA NO ABNORMALITIES DETECTED
104	43	SD	15 CORPORA LUTEA 15 IMPLANT SITES NO ABNORMALITIES DETECTED
110	43	SD	17 IMPLANT SITES 18 CORPORA LUTEA NO ABNORMALITIES DETECTED
122	44	SD	15 IMPLANT SITES 16 CORPORA LUTEA NO ABNORMALITIES DETECTED

INDIVIDUAL GROSS OBSERVATION IN SATELLITE ADULT FEMALE RATS

FEMALE RATA GROUP: VI-0 DOSE: 125 mg/kg/day

ANIMAL NUMBER	DAYS ON TEST	MODE OF DEATH	OBSERVATIONS
130	45	SD	17 CORPORA LUTEA 17 IMPLANT SITES NO ABNORMALITIES DETECTED
131	46	SD	18 IMPLANT SITES 22 CORPORA LUTEA NO ABNORMALITIES DETECTED
137	43	SD	17 CORPORA LUTEA 17 IMPLANT SITES NO ABNORMALITIES DETECTED
157	44	SD	14 IMPLANT SITES 15 CORPORA LUTEA NO ABNORMALITIES DETECTED

INDIVIDUAL GROSS OBSERVATION IN SATELLITE ADULT FEMALE RATS

FEMALE RATA GROUP: VIII-0 DOSE: 375 mg/kg/day

ANIMAL NUMBER	DAYS ON TEST	MODE OF DEATH	OBSERVATIONS
63	44	SD	17 CORPORA LUTEA 17 IMPLANT SITES NO ABNORMALITIES DETECTED
65	46	SD	16 IMPLANT SITES 17 CORPORA LUTEA NO ABNORMALITIES DETECTED
66	45	SD	16 IMPLANT SITES 17 CORPORA LUTEA NO ABNORMALITIES DETECTED
73	43	SD	15 CORPORA LUTEA 15 IMPLANT SITES NO ABNORMALITIES DETECTED
81	44	SD	14 CORPORA LUTEA 14 IMPLANT SITES NO ABNORMALITIES DETECTED
92	43	SD	14 IMPLANT SITES 17 CORPORA LUTEA NO ABNORMALITIES DETECTED
95	42	SD	20 IMPLANT SITES 22 CORPORA LUTEA NO ABNORMALITIES DETECTED
96	43	SD	14 IMPLANT SITES 16 CORPORA LUTEA NO ABNORMALITIES DETECTED

INDIVIDUAL GROSS OBSERVATION IN SATELLITE ADULT FEMALE RATS

FEMALE RATA GROUP: VIII-0 DOSE: 375 mg/kg/day

ANIMAL NUMBER	DAYS ON TEST	MODE OF DEATH	OBSERVATIONS
125	45	SD	17 IMPLANT SITES 18 CORPORA LUTEA NO ABNORMALITIES DETECTED
127	48	SD	0 CORPORA LUTEA 0 IMPLANT SITES NO ABNORMALITIES DETECTED
133	45	SD	13 CORPORA LUTEA 13 IMPLANT SITES NO ABNORMALITIES DETECTED
166	45	SD	16 IMPLANT SITES 18 CORPORA LUTEA NO ABNORMALITIES DETECTED

APPENDIX MM

Individual Animal Pathology Data in Satellite Female Rats

KEY TO APPENDIX
INDIVIDUAL ANIMAL PATHOLOGY DATA IN SATELLITE FEMALE RATS

MODE OF DEATH

SD: SACRIFICED BY DESIGN
SE: SACRIFICED IN EXTREMIS
FD: FOUND DEAD
AK: ACCIDENTLY KILLED (INCLUDES ANIMALS PRESENTED DEAD OR MORIBUND THAT HAVE INJURED THEMSELVES OR WERE INADVERTENTLY INJURED WHEN BEING HANDLED. IN-LIFE AND NECROPSY FINDINGS MAY BE USED TO MAKE THIS DETERMINATION.)

LESION GRADING

HISTOPATHOLOGICAL CHANGES ARE DESCRIBED ACCORDING TO THEIR MORPHOLOGIC CHARACTER, DISTRIBUTION AND SEVERITY. THE DISTRIBUTION (EXTENT OF TISSUE INVOLVEMENT) IS INDICATED, WHERE APPROPRIATE, BY MODIFIERS SUCH AS FOCAL, MULTIFOCAL, DIFFUSE, UNILATERAL, BILATERAL, ETC.; A SEVERITY SCORE, IF APPROPRIATE, IS ALSO ASSIGNED AS FOLLOWS:

PRESENT: LESION PRESENT, SEVERITY NOT GRADED.
MINIMAL: THE AMOUNT OF CHANGE PRESENT BARELY EXCEEDS THAT WHICH IS CONSIDERED TO BE WITHIN NORMAL LIMITS.
MILD: IN GENERAL, THE LESION IS EASILY IDENTIFIED BUT OF LIMITED SEVERITY. THE LESION PROBABLY DOES NOT PRODUCE ANY FUNCTIONAL IMPAIRMENT.
MODERATE: THE LESION IS PROMINENT BUT THERE IS SIGNIFICANT POTENTIAL FOR INCREASED SEVERITY. LIMITED TISSUE OR ORGAN DYSFUNCTION IS POSSIBLE.
SEVERE: THE DEGREE OF CHANGE IS EITHER AS COMPLETE AS CONSIDERED POSSIBLE OR GREAT ENOUGH IN INTENSITY OR EXTENT TO EXPECT SIGNIFICANT TISSUE OR ORGAN DYSFUNCTION.

COMMENT:

GRADES MINIMAL THROUGH SEVERE REPRESENT PROGRESSIVE INVOLVEMENT/SEVERITY ALONG A CONTINUUM WITH MINIMAL LESIONS BEING THE LEAST SEVERE AND SEVERE LESIONS BEING THE MOST SEVERE. WHILE THE GRADES REFER TO THE MORPHOLOGICAL CHARACTERISTICS OF LESIONS, THEY ALSO INDICATE THEIR RELATIVE BIOLOGICAL SIGNIFICANCE.

GROSS OBSERVATIONS LISTING MULTIPLE MASSES FOR A TISSUE ARE DISTINGUISHED WITH LETTERS (i.e., A, B, C, D, etc.)

MICROSCOPIC CORRELATE (selected lesions)

THE MICROSCOPIC CORRELATE FOR SELECTED GROSS OBSERVATIONS, PRIMARILY MASSES, IS PROVIDED TO THE RIGHT OF THE RESPECTIVE GROSS OBSERVATION.

NEOPLASM DESIGNATIONS

*B: BENIGN NEOPLASM, PRIMARY SITE
*M: MALIGNANT NEOPLASM, PRIMARY SITE
*X: MALIGNANT NEOPLASM, METASTATIC OR SECONDARY SITE

ABBREVIATIONS
NPT = NONPROTOCOL TISSUE
NOS = NOT OTHERWISE SPECIFIED

INDIVIDUAL ANIMAL PATHOLOGY DATA IN SATELLITE FEMALE RATS

FEMALE RATS GROUP: II-0 DOSE: 0 mg/kg/day

ANIMAL NUMBER: 94 DAYS ON TEST: 48 MODE OF DEATH: SD

GROSS OBSERVATIONS: MICROSCOPIC CORRELATE (selected lesions):
UTERUS - FLUID, CLEAR, VISCOUS, BODY

MICROSCOPIC OBSERVATIONS:
VAGINA - ESTRUS STAGE: ESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: CERVIX, OVARIES, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL PATHOLOGY DATA IN SATELLITE FEMALE RATS

FEMALE RATS GROUP: II-0 DOSE: 0 mg/kg/day

ANIMAL NUMBER: 118 DAYS ON TEST: 48 MODE OF DEATH: SD

GROSS OBSERVATIONS:
UTERUS - FLUID, CLEAR, VISCOUS, BODY, HORNS

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
VAGINA - ESTRUS STAGE: ESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: CERVIX, OVARIES, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL PATHOLOGY DATA IN SATELLITE FEMALE RATS

FEMALE RATS GROUP: VI-0 DOSE: 125 mg/kg/day

ANIMAL NUMBER: 78 DAYS ON TEST: 48 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
VAGINA - ESTRUS STAGE: METESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: CERVIX, OVARIES, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

INDIVIDUAL ANIMAL PATHOLOGY DATA IN SATELLITE FEMALE RATS

FEMALE RATS GROUP: VIII-0 DOSE: 375 mg/kg/day

ANIMAL NUMBER: 127 DAYS ON TEST: 48 MODE OF DEATH: SD

GROSS OBSERVATIONS:
NO ABNORMALITIES DETECTED

MICROSCOPIC CORRELATE (selected lesions):

MICROSCOPIC OBSERVATIONS:
VAGINA - ESTRUS STAGE: DIESTRUS

THE FOLLOWING TISSUES WERE UNREMARKABLE MICROSCOPICALLY: CERVIX, OVARIES, UTERUS

THE FOLLOWING TISSUES WERE AUTOLYZED; DEGREE OF AUTOLYSIS DID NOT PRECLUDE MICROSCOPIC EXAMINATION: NONE

THE FOLLOWING TISSUES WERE SEVERELY AUTOLYZED; MICROSCOPIC DIAGNOSES NOT MADE, ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

SECTIONS OF THE FOLLOWING TISSUES WERE NOT PRESENT FOR MICROSCOPIC EXAMINATION: OTHER

SECTIONS OF THE FOLLOWING TISSUES WERE INSUFFICIENT FOR MICROSCOPIC EXAMINATION; ORGAN NOT COUNTED IN INCIDENCE TABLES:
NONE

CAUSE OF DEATH/MORIBUND CONDITION: SACRIFICED BY DESIGN

APPENDIX NN

Robust Summary

Low Dicylopentadiene Resin Oil : Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats

Repeated Dose Toxicity

Test Substance	
Remarks	Low DCPD Resin Oil is a C8 to C10 distillate obtained from a pyrolysis gasoline stream produced by an ethylene production process (steam cracking process). The sample tested consisted of vinyltoluenes (17%), trimethylbenzenes (9%), styrene and methylstyrenes (3%), indene (14%), methylindene (8%), and naphthalene (1%). The balance of the composition is expected to consist of other hydrocarbons with carbon range primarily 8 to 10, mainly aromatics and olefins, with some paraffins.
Method	
Method/guideline followed	OECD 422
Test type	Combined repeated dose toxicity study with the reproduction / developmental screening test
GLP	Yes.
Year	2003
Species	Rat
Strain	Crl:CD® (Sprague-Dawley) IGS BR
Route of administration	Gavage
Duration of test	4 Weeks
Doses/concentration levels	0, 35, 125, 375 mg/kg/day
Sex	12 male, 12 female per group.
Exposure period	Not applicable
Frequency of treatment	7 days/week
Control group and treatment	12 male, 12 female, corn oil vehicle.
Post exposure observation period	Not applicable.
Statistical methods	Group means and standard deviations were calculated for all measured parameters. Body weight, weight gain, food consumption, and organ weights were analyzed by Jonckheere-Terpstra trend test. Food efficiency and clinical pathology parameters were analyzed by one-way analysis of variance followed with Dunnett's test. Clinical observations and FOB parameters were analyzed by Cochran-Armitage trend test. Grip strength, foot splay, rearing, body temperature, and motor activity were analyzed by repeated measures analysis of variance with linear contrasts or Jonckheere's trend test.
Test conditions	Groups of 12 young, adult, male or nulliparous, female rats were administered an oral, daily dose of 0, 35, 125, or 375 mg/kg/day

Low DCPD Resin Oil for approximately 30 days. The study also contained reproductive and developmental toxicity satellite groups (summarized separately).

After approximately 30 days, blood samples were collected from all male rats and all subchronic female rats for measurement of hematology and clinical chemistry parameters. A neurobehavioral test battery, consisting of motor activity and functional observational battery assessments, was conducted on all male rats and subchronic female rats prior to test substance administration in order to obtain baseline measurements. This neurobehavioral test battery was conducted again following approximately 4 weeks of test substance administration. On test days 30 and 31, respectively, all subchronic male and female rats underwent gross necropsy. Selected tissues from the control and 375 mg/kg/day groups, and target tissues from all groups were processed for histopathology and examined.

Results

NOAEL (NOEL)

Parameters	NOEL (mg/kg/d)	NOAEL (mg/kg/d)	LOEL (mg/kg/d)
Systemic	35 M 35 F	35 M 35 F	125 M 125 F
Neurobehavioral	375 M 375 F	375 M 375 F	- -
Pathology	- 35 F	125 M 375 F	35 M 125 F
Reproductive	375 M 375 F	375 M 375 F	- -
Developmental (Pups)	125	125	125

LOAEL (LOEL) See table above

Remarks

Clinical Signs of Toxicity and Mortality in Subchronic Males and Females: Test substance-related increases in the incidences of stained fur, and/or wet fur were observed in males and subchronic females following administration of 375 mg/kg/day Low DCPD Resin Oil. Stained and/or wet fur were also occasionally observed in males and subchronic females administered 125 mg/kg/day. These clinical signs were not present during either the detailed clinical observations in an open field arena, or during the FOB evaluation. Test substance-related mortality did not occur.

Body Weight and Body Weight Gain in Subchronic Males and Females: Test substance-related decreases in body weight and/or

	weight gain were observed in males, and subchronic females administered 375 mg/kg/day of the test substance. In addition, instances of decreased body weight and/or weight gain were also observed in males administered 125 mg/kg/day of the test substance. *Food Consumption and Food Efficiency in Subchronic Males and Females*: Food consumption and/or food efficiency were reduced in 125 mg/kg/day and above males, and in 375 mg/kg/day females. *Clinical Pathology Parameters*: There were no effects on hematological or clinical chemistry parameters in male or subchronic female rats. *Neurobehavioral Parameters*: No test substance-related effects were observed in motor activity, any neurobehavioral parameters in the FOB, or in grip strength, foot splay, rearing, or body temperature, in males or subchronic females. *Pathology*: Administration of 35, 125, or 375 mg/kg/day of the test substance for approximately 30 days produced a dose-related increase in renal tubular hyaline droplets in male rats, however, hyaline droplet nephropathy was not observed. Increased hyaline droplets were not observed in females. The hyaline droplet accumulation in male rats was not considered to be an adverse effect of the test substance, since it is species and sex specific, and is not predictive of an effect on other species. Minimal to mild hepatocellular hypertrophy, and associated increases in liver weight parameters were observed in 375 mg/kg/day males, and in 125 and 375 mg/kg/day females; however, this change is considered to be secondary to enzyme induction as a pharmacological response to a xenobiotic, and was not considered to be adverse. Minimal thyroid follicular cell hypertrophy was observed in 375 mg/kg/day males, which was considered to be test substance-related and potentially adverse. Thymus weight was decreased in 125 and 375 mg/kg/day males, and in 375 mg/kg/day females. However, there was no corresponding microscopic effect on the thymus.
Conclusions	Repeated administration of Low Dicyclopentadiene Resin Oil in male and female Sprague Dawley rats at dosages of 375 mg/kg/day produced effects on clinical signs, of toxicity, body weight, food consumption, and histopathological changes. In

	addition, effects on body weight, clinical signs and food consumption were observed at 125 mg/kg/day. Based on these data, the no-observable-effect level (NOAEL) for systemic toxicity was 35 mg/kg/day in males and 125 mg/kg/day in females.
Data Quality	
Reliabilities	Klimish value = 1 (Reliable without restrictions).
References	Malley, L. A. Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats. DuPont-13041. Report of E. I. du Pont de Nemours and Company conducted for the American Chemistry Council Olefins Panel.
Other	
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Toxicity to Reproduction

Test Substance	
Remarks	Low DCPD Resin Oil is a C8 to C10 distillate obtained from a pyrolysis gasoline stream produced by an ethylene production process (steam cracking process). The sample tested consisted of vinyltoluenes (17%), trimethylbenzenes (9%), styrene and methylstyrenes (3%), indene (14%), methylindene (8%), and naphthalene (1%). The balance of the composition is expected to consist of other hydrocarbons with carbon range primarily 8 to 10, mainly aromatics and olefins, with some paraffins.
Method	
Method/guideline followed	OECD 422
Test type	Combined repeated dose toxicity study with the reproduction / developmental screening test
GLP	Yes.
Year	2003
Species	Rat
Strain	Crl:CD® (Sprague-Dawley) IGS BR
Route of administration	Gavage.
Duration of test	Satellite groups of 12 young, nulliparous, female rats were administered an oral, daily dose of the test substance during a premating period of approximately 2 weeks, a cohabitation period of approximately 2 weeks, a gestation period of approximately 3 weeks, and a lactation period of approximately 4 days. The males were exposed for 30 days.
Doses/concentration levels	0, 35, 125 or 375 mg/kg/day.
Sex	12 males, 12 females per group.
Exposure period	Not applicable
Frequency of treatment	7 days/week
Control group and treatment	12 male, 12 female, corn oil vehicle.
Post exposure observation period	Not applicable.
Statistical methods	Group means and standard deviations were calculated for all measured parameters. Body weight, weight gain, food consumption, and organ weights were analyzed by Jonckheere-Terpstra trend test. Food efficiency was analyzed by one-way analysis of variance followed with Dunnett's test. Clinical observations, mating index, fertility index, and gestation index were analyzed by Cochran-Armitage trend test. Gestation length, implantation site numbers, implantation efficiency, mean number of pups per litter, percent of pups born alive, day 0-4 viability of pups, viability index, number of *corpora lutea*, sex ratio, pre-implantation loss, and post-implantation loss were analyzed by Jonckheere-Terpstra trend test. Mean pup weights were analyzed by linear contrast of the least

	square means.
Test Conditions	Satellite groups of 12 young, nulliparous, female rats were administered an oral, daily dose of 0, 35, 125, or 375 mg/kg/day during a premating period of approximately 2 weeks, a cohabitation period of approximately 2 weeks, a gestation period of approximately 3 weeks, and a lactation period of approximately 4 days. Following the 2-week premating period, each satellite female was paired with a male of the same respective dosage group during a 2 week cohabitation period. Measurements of body weight, food consumption, and clinical signs of toxicity in females were conducted throughout premating, cohabitation, gestation, and lactation. After postpartum day 4, lactating females, and nonpregnant females were sacrificed, selected organs were weighed, and selected tissues were evaluated microscopically. Offspring were evaluated for external abnormalities, and sacrificed on postnatal day 4. The study design included a main study for repeated dose toxicity end points (summarized separately). The males were exposed for a total of 30 days, and were then necropsied. In addition to the repeated dose toxicity end points assessed (discussed separately), reproductive assessment of the males included mating, conception and fertility indices, reproductive organ weights and gross/histopathology of the reproductive tract.
Results NOAEL (NOEL)	375 mg/kg/day for paternal animals 125 mg/kg/day for pups.
LOAEL (LOEL)	Not applicable.
Remarks	*Clinical signs and mortality*: Test substance-related increases in the incidences of stained fur, and/or wet fur were observed in males, and satellite females following administration of 375 mg/kg/day Low DCPD Resin Oil. Stained and/or wet fur were also occasionally observed in males and satellite females administered 125 mg/kg/day. *Body weight and weight gain*: Test substance-related decreases in body weight and/or weight gain were observed in males and satellite females administered 375 mg/kg/day of the test substance. In addition, instances of decreased body weight and/or weight gain were also observed in males administered 125 mg/kg/day of the test substance. *Food Consumption and Food Efficiency*: Decreased food

	consumption and food efficiency occurred in 125 mg/kg/day and above males. *Reproductive Indices*: No test substance-related effects or statistically significant differences in mating index, fertility index, gestation length, number of implantation sites, implantation efficiency, pre-implantation loss, post-implantation loss, or number of *corpora lutea* were observed for any dosage of the test substance in satellite females. *Offspring Parameters*: Decreased mean pup weight was observed in offspring from the 375 mg/kg/day group. No effects were observed at any dosage for the number of pups born, number of pups born alive, sex ratio, gestation index, external abnormalities, or litter survival for postnatal days 0-4 in the offspring from any dosage group. *Reproductive Pathology*: There were no test substance-related effects on morphology of the reproductive tract in either males or females.
Conclusions	Repeated administration of Low Dicyclopentadiene Resin Oil to male and female Sprague Dawley rats at dosages of 0, 35, 125, or 375 mg/kg/day produced no evidence of adverse effects on any measures of reproductive function. Pups from the 375 mg/kg/day group had decreased body weight. Based on these data, the no-observable-effect level (NOEL) for reproductive toxicity was 375 mg/kg/day in parental animals and 125 mg/kg/day in pups.
Data Quality Reliabilities	Klimish value = 1 (Reliable without restrictions).
References	Malley, L. A. Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats. DuPont-13041. Report of E. I. du Pont de Nemours and Company conducted for the American Chemistry Council Olefins Panel.
Other Last changed	05-Feb-04 Robust summary prepared by contractor to Olefins Panel

Developmental Toxicity/Teratogenicity

Test Substance	
Remarks	Low DCPD Resin Oil is a C8 to C10 distillate obtained from a pyrolysis gasoline stream produced by an ethylene production process (steam cracking process). The sample tested consisted of vinyltoluenes (17%), trimethylbenzenes (9%), styrene and methylstyrenes (3%), indene (14%), methylindene (8%), and naphthalene (1%). The balance of the composition is expected to consist of other hydrocarbons with carbon range primarily 8 to 10, mainly aromatics and olefins, with some paraffins.
Method	
Method/guideline followed	OECD 422
Test type	Combined repeated dose toxicity study with the reproduction/developmental screening test
GLP	Yes.
Year	2003
Species	Rat
Strain	Crl:CD® (Sprague-Dawley) IGS BR
Route of administration	Oral gavage.
Duration of test	Satellite groups of 12 young, nulliparous, nonpregnant female rats were administered an oral, daily dose of the test substance during a premating period of approximately 2 weeks, a cohabitation period of approximately 2 weeks, a gestation period of approximately 3 weeks, and a lactation period of approximately 4 days. The males were exposed for 30 days.
Doses/concentration levels	0, 35 125, or 375 mg/kg/day
Sex	12 male, 12 female per group.
Exposure period	Not applicable
Frequency of treatment	7 days/week
Control group and treatment	12 male, 12 female, corn oil vehicle.
Post exposure observation period	Not applicable.
Statistical methods	Group means and standard deviations were calculated for all measured parameters. Body weight, weight gain, food consumption, and organ weights were analyzed by Jonckheere-Terpstra trend test. Food efficiency was analyzed by one-way analysis of variance followed with Dunnett's test. Clinical observations, mating index, fertility index, and gestation index were analyzed by Cochran-Armitage trend test. Gestation length, implantation site numbers, implantation efficiency, mean number of pups per litter, percent of pups born alive, day 0-4 viability of pups, viability index, number of corpora lutea, sex ratio, pre-implantation loss, and post-implantation loss were analyzed by Jonckheere-Terpstra trend test. Mean pup weights were analyzed by linear contrast of the least square means.

Test Conditions	Satellite groups of 12 young, nulliparous, female rats were administered an oral, daily dose of 0, 35, 125, or 375 mg/kg/day during a premating period of approximately 2 weeks, a cohabitation period of approximately 2 weeks, a gestation period of approximately 3 weeks, and a lactation period of approximately 4 days. Following the 2-week premating period, each satellite female was paired with a male of the same respective dosage group during a 2-week cohabitation period. Measurements of body weight, food consumption, and clinical signs of toxicity in females were conducted throughout premating, cohabitation, gestation, and lactation. After postpartum day 4, lactating females and nonpregnant females were sacrificed, selected organs were weighed, and selected tissues were evaluated microscopically. Offspring were evaluated for external abnormalities, and sacrificed on postnatal day 4. The study design included a main study for repeated dose toxicity end points (summarized separately).
Results	
NOAEL (NOEL)	375 mg/kg/day for paternal animals, and 125 mg/kg/day for pups
LOAEL (LOEL)	Not applicable.
Remarks	*Clinical signs and mortality*: Test substance-related increases in the incidences of stained fur, and/or wet fur were observed in satellite females following administration of 375 mg/kg/day Low DCPD Resin Oil. *Maternal Body Weight and Weight Gain*: Test substance-related decreases in body weight and/or weight gain were observed in satellite females administered 375 mg/kg/day of the test substance. *Food Consumption and Food Efficiency*: There were no effects on maternal food consumption or food efficiency. *Reproductive Indices*: No test substance-related effects or statistically significant differences in gestation length, number of implantation sites, implantation efficiency, pre-implantation loss, post-implantation loss, or number of *corpora lutea* were observed for any dosage of the test substance in satellite maternal females. *Offspring Parameters*: Decreased mean pup weight was observed in offspring from the 375 mg/kg/day group. No effects were observed at any dosage for the number of pups

	born, number of pups born alive, sex ratio, gestation index, external abnormalities, or litter survival for postnatal days 0-4 in the offspring from any dosage group.
Conclusions	Repeated administration of Low Dicyclopentadiene Resin Oil to male and female Sprague Dawley rats at dosages of 0, 35, 125, or 375 mg/kg/day produced no evidence of teratogenicity, however, pups from the 375 mg/kg/day group had decreased body weight. Based on these data, the no-observable-effect level (NOEL) for developmental toxicity was 125 mg/kg/day.
Data Quality	
Reliabilities	Klimish value = 1 (Reliable without restrictions).
References	Malley, L. A. Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats. DuPont-13041. Report of E. I. du Pont de Nemours and Company conducted for the American Chemistry Council Olefins Panel.
Other	
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