

*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)

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**STUDY COMPLETED ON:** November 19, 2004

**PERFORMING LABORATORY:** E.I. du Pont de Nemours and Company  
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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

### 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.

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**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

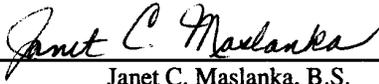
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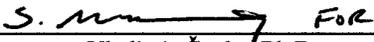
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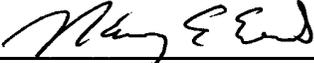
19-Nov-2004  
Date

### CERTIFICATION

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

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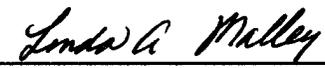
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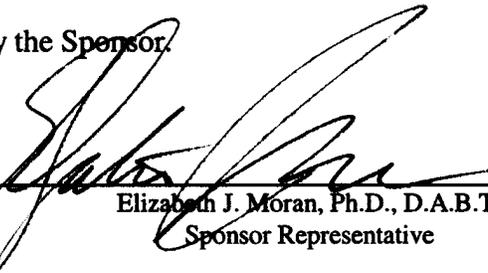
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This report was accepted by the Sponsor.

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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: 0.0005 wt % Benzene  
(provided by the sponsor) 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.

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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 CrI:CD<sup>®</sup>(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 pre-mating 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 (FOB) 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 pre-mating 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 pre-mating, 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, decreased body weight and/or weight gain were also observed in males and satellite females administered 125 mg/kg/day of the test substance. Body weight and weight gain of 375 mg/kg/day males was 10% and 24% lower than control values for test days 29 and 1-29, respectively. Body weight and weight gain of 125 mg/kg/day males was 7% and 16% lower than the control values for test days 29 and 1-29, respectively. Body weight and weight gain of 375 mg/kg/day subchronic females was 5% and 14% lower than the control values for test days 29 and 1-29, respectively. During the pre-mating period, body weight and weight gain of

375 mg/kg/day satellite females was 3% and 14% lower than the control values for test days 15 and 1-15, respectively. During the gestation period, body weight and weight gain of 375 mg/kg/day satellite females was 6% and 9% lower than the control values for gestation days 21 and 0-21, respectively. During lactation, body weights of 125 and 375 mg/kg/day satellite females were 8% and 7% lower than the control values on lactation day 4, respectively. Test substance-related decreases in food consumption and food efficiency occurred in 125 mg/kg/day and above males, and food consumption was decreased in 375 mg/kg/day subchronic females. These effects 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 (15% lower than the control value on lactation day 4) 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.

A slight increase in the incidence of 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, decreased body weight, weight gain, food consumption, and food efficiency 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 hepatocellular 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.<sup>(1)</sup> 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 <sup>a</sup>				Satellite <sup>b</sup>		Dosage	
Group Male	Number of Males	Group Female	Number of Females	Group Female	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
<p>Clinical Observations</p> <ul style="list-style-type: none"> <li>• Predosing Observations (Subchronic and Satellite)<sup>a</sup></li> <li>• Mortality/Moribundity Checks (Subchronic and Satellite)<sup>b</sup></li> <li>• Detailed Clinical Observations (Subchronic)<sup>c</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Daily prior to dosing</li> </ul> <p>Twice daily (a.m. and p.m.)</p> <ul style="list-style-type: none"> <li>• Pretest, and Days 8, 15, 22, and 29 (1-2 hour post-dosing)</li> </ul>
<p>Body Weights</p>	<ul style="list-style-type: none"> <li>• Study Days 1, 8, 15, 22, and 29 and at scheduled sacrifice (Subchronic)</li> <li>• Days 1, 8, and 15 – Premating (Satellite)</li> <li>• Weekly – Mating (Satellite)</li> <li>• Daily - Gestation (Satellite)</li> <li>• Days 0 and 4 - Lactation (Satellite)</li> </ul>
<p>Food Consumption</p>	<p>Study Days 1, 8, 15, 22, and 29 (Subchronic)</p> <p>Food consumption was discontinued for males upon cohabitation</p> <p>Days 1, 8, and 15 – Premating (Satellite)</p> <p>Days 0, 7, 14, and 21 - Gestation (Satellite)</p> <p>Days 0 and 4 - Lactation (Satellite)</p>
<p>Functional Observational Battery (Subchronic)</p>	<p>Pretest and Study Day 29-30</p>
<p>Motor Activity (Subchronic)</p>	<p>Pretest and Study Day 29-30</p>
<p>Clinical Pathology (Subchronic)</p>	<p>Study Day 30-31</p>
<p>Necropsy</p> <ul style="list-style-type: none"> <li>• Subchronic Males</li> <li>• Subchronic Females</li> <li>• Pregnant Satellite Rats</li> <li>• Satellite Rats that did not deliver a litter</li> <li>• Pups</li> <li>• Satellite Rats with no Evidence of Mating</li> </ul>	<p>Sacrifice Schedule</p> <ul style="list-style-type: none"> <li>• Study Day 30</li> <li>• Study Day 31</li> <li>• Lactation Day 4</li> <li>• Gestation Day 27 (approximately)</li> <li>• Lactation Day 4</li> <li>• Study Day 43 (approximately)</li> </ul>

- 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<sup>®</sup>

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.<sup>(2,3)</sup>

## **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<sup>®</sup> 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<sup>®</sup> 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) CrI:CD<sup>®</sup>(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 CrI:CD<sup>®</sup>(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<sup>®</sup>) 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  $22^{\circ} \pm 3^{\circ}\text{C}$  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<sup>®</sup> Nutrition International, LLC Certified Rodent LabDiet<sup>®</sup> 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  $\pm 20\%$  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.<sup>(1)</sup> 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 pre-mating 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 pre-mating 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.

### **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 Functional 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<sup>®</sup> -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<sup>™</sup> 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<sup>®</sup>). 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.<sup>(4,5,6,7,8)</sup> 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	platelet count
hemoglobin	white blood cell count
hematocrit	differential white blood cell count
mean corpuscular volume	microscopic blood smear examination
mean corpuscular hemoglobin	
mean corpuscular hemoglobin concentration	
red cell distribution width	
absolute reticulocyte count	
prothrombin time	
activated partial thromboplastin time	

## 2. Clinical Chemistry

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

The following parameters were determined:

aspartate aminotransferase	glucose
alanine aminotransferase	total protein
sorbitol dehydrogenase	albumin
alkaline phosphatase	globulin
total bilirubin	calcium
urea nitrogen	inorganic phosphorus
creatinine	sodium
cholesterol	potassium
triglycerides	chloride

## 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<sub>1</sub> 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:

<u>Digestive System<sup>a</sup></u>	<u>Hematopoietic System</u>	<u>Reproductive System</u>
liver	spleen	<u>Male</u>
esophagus	thymus	testes
stomach	mediastinal lymph node	epididymides
duodenum	mandibular lymph node	prostate
jejunum	mesenteric lymph node	seminal vesicles
ileum <sup>a</sup>	bone marrow <sup>b</sup>	coagulating glands
cecum		
colon	<u>Endocrine System</u>	<u>Female</u>
rectum	pituitary gland	ovaries (with oviducts) <sup>c</sup>
tongue	parathyroid gland	cervix
pancreas	thyroid gland	uterus <sup>c</sup>
	adrenal glands	vagina
<u>Urinary System</u>	<u>Nervous System</u>	<u>Integumentary System</u>
kidneys	brain (three sections)	skin
urinary bladder	spinal cord (three levels)	salivary glands
<u>Respiratory System</u>	eyes (with optic nerve)	lacrimal glands
lungs	sciatic nerve	mammary gland <sup>d</sup>
trachea		
nose	<u>Musculoskeletal System</u>	<u>Miscellaneous</u>
pharynx/larynx	femur/knee joint	gross observations <sup>e</sup>
	sternum	
<u>Cardiovascular System</u>	skeletal muscle	
heart		
aorta		

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<sub>1</sub> Adults

P<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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 (%) <sup>c</sup>	=	$\frac{\text{Number of Pups Born}}{\text{Number of Implantation Sites}}$	x 100
Pups Born Alive (%) <sup>c</sup>	=	$\frac{\text{Number of Pups Born Alive}}{\text{Number of Pups Born}}$	x 100
Viability Index (%) <sup>c,d</sup>	=	$\frac{\text{Number of Pups Alive Day 4 Preculling}}{\text{Number of pups born alive}}$	x 100
Preimplantation Loss <sup>e</sup>	=	$\frac{\text{Number of corpora lutea} - \text{Number of implantation sites}}{\text{Number of corpora lutea}}$	
Postimplantation Loss <sup>e</sup>	=	$\frac{\text{Number of implantation sites} - \text{Number of pups}}{\text{Number of implantation sites}}$	

- 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 pre mating (satellite females), test days 0-21 of gestation (satellite females), and test days 0-4 of lactation (satellite females).

### 3. Statistical Methods

Parameter	Preliminary Test	Method of Statistical Analysis	
		If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Gestation Length Implantation Site Numbers Implantation Efficiency	Test for lack of trend <sup>(9)</sup>	Sequential application <sup>(10)</sup> of the Jonckheere-Terpstra trend test <sup>(11)</sup>	Preliminary tests for pairwise comparison
Mean Number of Pups per Litter Percent Born Alive 0-4 Day Viability Viability Index Number of <i>Corpora Lutea</i> Sex Ratio Preimplantation Loss Postimplantation Loss Organ Weights			
Food Efficiency	None	One-way analysis of variance <sup>(14)</sup> followed with Dunnett's test <sup>(15, 16, 17)</sup>	
Incidence of Clinical Observations Incidence of FOB Descriptive Parameters Mating Index Fertility Index Gestation Index	None	Cochran-Armitage test for trend <sup>(14)c</sup>	
Clinical Pathology <sup>d</sup>	Levene's test for homogeneity <sup>(12)</sup> and Shapiro-Wilk test <sup>(13)</sup> for normality <sup>b</sup>	One-way analysis of variance <sup>(14)</sup> followed with Dunnett's test <sup>(15, 16, 17)</sup>	Kruskal-Wallis test <sup>(18)</sup> followed with Dunn's test <sup>(19)</sup>
Mean Pup Weights (Covariates: litter size, sex ratio)	None	Linear contrast of the least square means <sup>(20)</sup>	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<sup>(21)</sup> 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<sup>(22)</sup> 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,<sup>(20)</sup> auto-regressive,<sup>(23)</sup> heterogeneous auto-regressive,<sup>(23)</sup> or heterogeneous compound symmetry<sup>(20)</sup>) 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<sup>(24)</sup> for sphericity, through inspection of the sample variance-covariance matrix, or through the use of variance-covariance diagnostics described in Hocking *et al.*,<sup>(25)</sup> Green and Hocking,<sup>(23)</sup> Grynovicki and Green,<sup>(26)</sup> and Searle *et al.*<sup>(27)</sup>

The responses were assessed for normality using the Shapiro-Wilk<sup>(13)</sup> 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<sup>(12)</sup> 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<sup>(28)</sup> 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<sup>(29)</sup> 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.<sup>(10)</sup>

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.<sup>(30)</sup>

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<sup>(11)</sup> was not applicable, exact p values were calculated using permutation methodology.<sup>(31)</sup>

## 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 <sup>a</sup> mg/mL	Mean (T,M,B) % Nominal	C.V. (%)	Stability <sup>b</sup> % Nominal
10-Sept-03 Homogeneity	0	ND <sup>c</sup>	---	---	---
	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 <sup>a</sup> mg/mL	Average % Nominal	CV %
1-Oct-2003	0	ND <sup>b</sup>	---	---
	17.5	17.9, 19.2	106.3	5
	62.5	61.3, 66.0 <sup>c</sup>	101.9	5
	187.5	214 <sup>c</sup> , 182	105.6	11
15-Oct-2003	0	ND <sup>b</sup>	---	---
	17.5	20.3, 19.1	112.6	4
	62.5	55.1, 56.7	89.4	2
	187.5	170 <sup>d</sup> , 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 ( $\pm 6.3\%$  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 ( $\pm 12.6\%$  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  $95.2\% \pm 2.6$  and  $100.3\% \pm 3.6$  for samples analyzed on July 1, 2003 and October 20, 2003. This work was reported in analytical reports Dupont-13355<sup>(2)</sup> and Dupont-13877,<sup>(3)</sup> (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. Episodes 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 375 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 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. Wet chin in the 3 affected dams lasted 5-12 days. Stained chin was observed 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. Wet chin was observed for 3-19 days in the affected rats. In addition, wet chin was observed in 1 rat in the 125 mg/kg/day group which lasted only 1 day.

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

Stained perineum was observed in 1 female rat administered 375 mg/kg/day Low DCPD Resin Oil during lactation days 0-4, observed prior to the daily administration of the test substance.

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 pre-mating 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 pre-mating 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 pre-mating.

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, 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<sup>(1)</sup> 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, Appendices CC-DD)

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 375 mg/kg/day 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). Mean red cell distribution width for this group was within the historical range of control group means, and individual values were within the historical control range. Mean reticulocyte count was greater than the historical range of control group means, and individual animal values were also greater than the historical control range. 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.

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

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

4. 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). Mean creatinine concentrations for males dosed with 125 or 375 mg/kg/day were within the historical range of control group means, and individual values, with the exception of 2 of 12 males dosed with 125 mg/kg/day, were within the historical control range. Mean creatinine concentration for females dosed with 375 mg/kg/day was greater than the historical range of control group means, and 3 of 12 individual animal values were also greater than the historical control range. These changes in creatinine are 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,<sup>(32,33)</sup> 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). Mean glucose concentrations in males dosed with 125 or 375 mg/kg/day were within the historical range of control group means, and individual values, with the exception of 1 of 12 males dosed with 375 mg/kg/day, were within the historical control range. These changes were possibly due to treatment at 375 mg/kg/day.

However, with a few exceptions, the range of individual animal data was generally 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). Mean bilirubin concentration for this group was within the historical range of control group means, and individual values, with the exception of 1 of 12 females, were within the historical control range. 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.<sup>(34,35)</sup> Therefore, these changes were considered to be nonadverse.

## 5. 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**

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

# 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 (see Microscopic Findings), 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).

a. 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.

b. 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**

Dose (mg/kg/day):	<u>Male</u>				<u>Female</u>			
	0	35	125	375	0	35	125	375
Final Body Weight (grams)	387.8	379.3	<u>358.8#</u>	<u>348.0#</u>	243.3	239.3	234.2	<u>228.4#</u>
<u>Kidney</u>								
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
<u>Adrenal</u>								
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**

	Dose (mg/kg/day):	Male				Female			
		0	35	125	375	0	35	125	375
Number of Rats:	12	12	12	12	12	12	12	12	12
<u>Kidney</u>									
Hyaline droplets, increased	0	<u>12</u>	<u>12</u>	<u>12</u>	0	-	-	0	
<u>Liver</u>									
Hypertrophy, hepatocyte, centrilobular	0	0	0	<u>10</u>	0	0	<u>3</u>	<u>12</u>	
<u>Thyroid Gland</u>									
Hypertrophy, follicular cell	2	3	2	<u>4</u>	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.<sup>(36)</sup>

## 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.<sup>(37)</sup> 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.<sup>(37)</sup>

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<sub>1</sub> 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<sub>1</sub> males is presented with the subchronic toxicity study since those males were cohabited with the P<sub>1</sub> female satellite groups for production of the F<sub>1</sub> offspring.

In the satellite P<sub>1</sub> 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<sub>1</sub> Female Rats (Satellite Groups)**

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

# 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<sub>1</sub> males is presented with the subchronic toxicity study.

No test substance-related gross observations were observed in the P<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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, decreased body weight and/or weight gain were also observed in males and satellite females administered 125 mg/kg/day of the test substance. Body weight and weight gain of 375 mg/kg/day males was 10% and 24% lower than control values for test day 29 and 1-29, respectively. Body weight and weight gain of 125 mg/kg/day males was 7 % and 16% lower than the control values for test days 29 and 1-29, respectively. Body weight and weight gain for 375 mg/kg/day subchronic females was 5% and 14% lower than the control value for test days 29 and 1-29, respectively. During the pre-mating period, body weight and weight gain for 375 mg/kg/day satellite females was 3% and 14% lower than the control value for test days 15 and 1-15, respectively. During the gestation period, body weight and weight gain of 375 mg/kg/day satellite females was 6% and 9% lower than the control value for gestation days 21 and 0-21, respectively. During lactation, body weights were 8% and 7% lower than the control value for 125 and 375 mg/kg/day satellite females on lactation day 4, respectively. Test substance-related decreases in food consumption and food efficiency occurred in 125 mg/kg/day and above males, and food consumption was decreased in 375 mg/kg/day subchronic females. These effects 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 (15% lower than the control value on lactation day 4) 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.

A slight increase in the incidences of 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**

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TABLES

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**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

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TABLES

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**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

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

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
<u>OBSERVATION</u>					
	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			
		-----			
CONCENTRATION	GROUP:	I	III	V	VII
	(MG/KG/DAY):	0	35	125	375
	N:	12	12	12	12
<u>OBSERVATION</u>					
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
<u>PRETEST OBSERVATIONS</u>					
	RATS WITH CLINICAL SIGNS	0	0	0	0
<u>DOSING PERIOD OBSERVATIONS</u>					
	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
<u>OBSERVATION</u>					
	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
<u>OBSERVATION</u>					
	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
<u>PRETEST OBSERVATIONS</u>					
	RATS WITH CLINICAL SIGNS	0	0	0	0
<u>DOSING PERIOD OBSERVATIONS</u>					
	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)			
		I	III	V	VII
CONCENTRATION (MG/KG/DAY) :	Group:	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 <sup>a</sup>		92.4 (10.0)	87.3 (8.2)	68.6 (12.2) *	70.5 (7.8) *
15-29 <sup>b</sup>		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)			
		II	IV	VI	VIII
CONCENTRATION (MG/KG/DAY) :	Group:	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)			
		I	III	V	VII
CONCENTRATION (MG/KG/DAY) :	Group:	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
<u>OBSERVATION</u>					
	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			
		II-0	IV-0	VI-0	VIII-0
CONCENTRATION	GROUP:	0	35	125	375
	(MG/KG/DAY):				
	N:	12	12	12	12
<u>OBSERVATION</u>					
	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			
		-----			
CONCENTRATION	GROUP:	II-0	IV-0	VI-0	VIII-0
	(MG/KG/DAY):	0	35	125	375
	N:	11	12	12	11
<u>OBSERVATION</u>					
	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	3

---

\*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			
		-----			
CONCENTRATION	GROUP:	II-0	IV-0	VI-0	VIII-0
	(MG/KG/DAY):	0	35	125	375
	N:	11	12	12	11
<u>OBSERVATION</u>					
	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
<u>OBSERVATION</u>					
	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
<u>OBSERVATION</u>					
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)			
		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)			
		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)			
		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)			
		II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	GROUP:	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)			
		II-0	IV-0	VI-0	VIII-0
CONCENTRATION	GROUP:	0	35	125	375
	(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)			
		II-0	IV-0	VI-0	VIII-0
CONCENTRATION (MG/KG/DAY):	GROUP:	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)			
		II-0	IV-0	VI-0	VIII-0
CONCENTRATION	GROUP:	II-0	IV-0	VI-0	VIII-0
	(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)			
		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)			
		II-0	IV-0	VI-0	VIII-0
CONCENTRATION	GROUP: (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)			
		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)			
		II-0	IV-0	VI-0	VIII-0
CONCENTRATION	GROUP:	II-0	IV-0	VI-0	VIII-0
	(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)			
		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<sub>1</sub> GENERATION

MATERNAL GROUP: CONCENTRATION (MG/KG/DAY):	II-0 0	IV-0 35	VI-0 125	VIII-0 375
MATING INDEX (%) (# copulated/cohoused)	100.0 (12/12)	100.0 (12/12)	100.0 (12/12)	91.7 (11/12)
FERTILITY INDEX (%) (# pregnant/copulated)	83.3 (10/12)	100.0 (12/12)	91.7 (11/12)	100.0 (11/11)
GESTATION LENGTH (days) <sup>a</sup>	22.3	22.3	22.3	22.2
NUMBER OF IMPLANTATION SITES per pregnant female Standard deviation (# in group)	15 2(10)	16 1(12)	15 2(11)	16 2(11)
IMPLANTATION EFFICIENCY (%) Standard deviation (# in group)	90.5 15.0(10)	92.6 7.8(12)	91.7 8.0(11)	95.3 5.2(11)
NUMBER OF CORPORA LUTEA per pregnant female Standard deviation (# in group)	16 3(10)	17 1(12)	17 2(11)	17 2(11)
PRE-IMPLANTATION LOSS Standard deviation (# in group)	0.1 0.1(10)	0.1 0.1(12)	0.1 0.1(11)	0.1 0.1(11)
POST-IMPLANTATION LOSS Standard deviation (# in group)	0.1 0.1(10)	0.1 0.1(12)	0.1 0.1(11)	0.1 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;  $p < 0.05$ .

<sup>a</sup> 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<sub>1</sub> GENERATION

MATERNAL GROUP: CONCENTRATION (MG/KG/DAY) : N:	II-0 0 10	IV-0 35 12	VI-0 125 11	VIII-0 375 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

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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<sub>1</sub> GENERATION

MATERNAL GROUP: CONCENTRATION (MG/KG/DAY): N:	II-0 0 10	IV-0 35 12	VI-0 125 11	VIII-0 375 11
<u>MEAN NUMBER OF PUPS/LITTER</u>				
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
<u>MEAN NUMBER OF MALE PUPS/LITTER</u>				
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
<u>MEAN NUMBER OF FEMALE PUPS/LITTER</u>				
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 <sup>a</sup>	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<sub>1</sub> GENERATION

<b>Maternal Group:</b>	II-0	IV-0	VI-0	VIII-0
<b>Concentration (mg/kg/day) :</b>	0	35	125	375
<b>N:</b>	10	12	11	11
	<u>MEAN PUP WEIGHTS</u>			
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) *
	<u>MEAN MALE PUP WEIGHTS</u>			
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)
	<u>MEAN FEMALE PUP WEIGHTS</u>			
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)

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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)
<b>Baseline</b>								
	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)
<b>Week 4</b>								
	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)
<b><u>Baseline</u></b>								
	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)
<b><u>Week 4</u></b>								
	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

GROUP	BASELINE				WEEK 4			
	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

GROUP	BASELINE				WEEK 4			
	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
<b>EASE OF HANDLING:</b>								
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
<b>MUSCLE TONE:</b>								
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
<b>VOCALIZATIONS:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>PILOERECTION:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>BITE MARKS ON TAIL/PAWS:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>PALPEBRAL CLOSURE:</b>								
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
<b>FUR APPEARANCE:</b>								
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
<b>LACRIMATION:</b>								
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
<b>SALIVATION:</b>								
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

GROUP	BASELINE				WEEK 4			
	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
<b>EXOPHTHALAMUS:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>OPEN FIELD:</b>								
<b>RIGHTING REFLEX:</b>								
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
<b>RESPIRATION EASE:</b>								
normal	12	12	12	12	12	12	12	12
labored breathing	0	0	0	0	0	0	0	0
<b>RATE OF RESPIRATION:</b>								
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
<b>POSTURE:</b>								
normal	12	12	12	12	12	12	12	12
abnormal	0	0	0	0	0	0	0	0
<b>CONVULSIONS:</b>								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
<b>TREMORS:</b>								
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
<b>MUSCLE SPASMS:</b>								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
<b>MUSCLE FASCICULATION:</b>								
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

GROUP	BASELINE				WEEK 4			
	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
<b>GROOMING:</b>								
normal or none	12	12	12	12	12	12	12	12
repetitive, stereotypy	0	0	0	0	0	0	0	0
<b>GAIT/COORDINATION:</b>								
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
<b>AROUSAL:</b>								
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
<b>VOCALIZATIONS:</b>								
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
<b>PALPEBRAL CLOSURE:</b>								
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
<b>DIARRHEA:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>POLYURIA:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>MANIPULATIONS:</b>								
<b>APPROACH &amp; TOUCH:</b>								
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

GROUP	BASELINE				WEEK 4			
	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
<b>AUDITORY STIMULUS:</b>								
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
<b>TAIL PINCH:</b>								
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
<b><u>IN MOTOR ACTIVITY MONITOR:</u></b>								
<b>PUPILLARY RESPONSE:</b>								
present	12	12	12	12	12	12	12	12
absent	0	0	0	0	0	0	0	0
<b>DIARRHEA:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>POLYURIA:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b><u>ADDITIONAL FINDINGS:</u></b>								
<b>HEAD SHAKE</b>								
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

GROUP CONCENTRATION (mg/kg/day) NUMBER EXAMINED	BASELINE				WEEK 4			
	II	IV	VI	VIII	II	IV	VI	VIII
	0	35	125	375	0	35	125	375
	12	12	12	12	12	12	12	12
<b><u>HOME CAGE:</u></b>								
<b>POSTURE:</b>								
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
<b>PALPEBRAL CLOSURE:</b>								
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
<b>WRITHING:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>CIRCLING:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>BITING:</b>								
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
<b>GAIT/COORDINATION:</b>								
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
<b><u>REMOVAL FROM CAGE:</u></b>								
<b>EASE OF REMOVAL:</b>								
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

GROUP	BASELINE				WEEK 4			
	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
<b>EASE OF HANDLING:</b>								
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
<b>MUSCLE TONE:</b>								
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
<b>VOCALIZATIONS:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>PILOERECTION:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>BITE MARKS ON TAIL/PAWS:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>PALPEBRAL CLOSURE:</b>								
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
<b>FUR APPEARANCE:</b>								
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
<b>LACRIMATION:</b>								
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
<b>SALIVATION:</b>								
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

GROUP	BASELINE				WEEK 4			
	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
<b>EXOPHTHALAMUS:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>OPEN FIELD:</b>								
<b>RIGHTING REFLEX:</b>								
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
<b>RESPIRATION EASE:</b>								
normal	12	12	12	12	12	12	12	12
labored breathing	0	0	0	0	0	0	0	0
<b>RATE OF RESPIRATION:</b>								
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
<b>POSTURE:</b>								
normal	12	12	12	12	12	12	12	12
abnormal	0	0	0	0	0	0	0	0
<b>CONVULSIONS:</b>								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
<b>TREMORS:</b>								
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
<b>MUSCLE SPASMS:</b>								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
<b>MUSCLE FASCICULATION:</b>								
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

GROUP	BASELINE				WEEK 4			
	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
<b>GROOMING:</b>								
normal or none	12	12	12	12	12	12	12	12
repetitive, stereotypy	0	0	0	0	0	0	0	0
<b>GAIT/COORDINATION:</b>								
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
<b>AROUSAL:</b>								
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
<b>VOCALIZATIONS:</b>								
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
<b>PALPEBRAL CLOSURE:</b>								
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
<b>DIARRHEA:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>POLYURIA:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>MANIPULATIONS:</b>								
<b>APPROACH &amp; TOUCH:</b>								
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

GROUP	BASELINE				WEEK 4			
	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
<b>AUDITORY STIMULUS:</b>								
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
<b>TAIL PINCH:</b>								
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
<b><u>IN MOTOR ACTIVITY MONITOR:</u></b>								
<b>PUPILLARY RESPONSE:</b>								
normal	12	12	12	12	12	12	12	12
abnormal	0	0	0	0	0	0	0	0
<b>DIARRHEA:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b>POLYURIA:</b>								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
<b><u>ADDITIONAL FINDINGS:</u></b>								
<b>HEAD SHAKE</b>								
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						TOTAL
			<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	
<b><u>BASELINE</u></b>									
	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)
<b><u>WEEK 4</u></b>									
	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						TOTAL
			<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	
<b><u>BASELINE</u></b>									
	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)
<b><u>WEEK 4</u></b>									
	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	CONCENTRATION GROUP (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						TOTAL
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	
<b><u>BASELINE</u></b>								
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)
<b><u>WEEK 4</u></b>								
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	CONCENTRATION GROUP (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						TOTAL	
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>		
<b><u>BASELINE</u></b>									
	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)
<b><u>WEEK 4</u></b>									
	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 <sup>6</sup> /μL)				
DAY 30	8.04 0.25(12)	8.08 0.32(12)	8.35 0.45(12)	8.25 0.30(12)
HGB (g/dL)				
DAY 30	15.5 0.6(12)	15.6 0.5(12)	15.8 0.4(12)	15.7 0.6(12)
HCT (%)				
DAY 30	48.1 1.6(12)	48.2 1.2(12)	49.1 1.8(12)	48.9 1.8(12)
MCV (fl)				
DAY 30	59.9 2.1(12)	59.7 2.0(12)	58.8 1.6(12)	59.4 2.1(12)
MCH (pg)				
DAY 30	19.3 0.6(12)	19.3 0.8(12)	18.9 0.7(12)	19.0 0.7(12)
MCHC (g/dL)				
DAY 30	32.2 0.4(12)	32.3 0.4(12)	32.2 0.5(12)	32.0 0.3(12)
RDW (%)				
DAY 30	11.2 0.7(12)	11.2 0.4(12)	11.2 0.4(12)	11.3 0.6(12)
ARET (x10 <sup>3</sup> /μL)				
DAY 30	190.7 27.1(12)	208.4 18.3(12)	227.8* 30.6(12)	206.5 35.7(12)
PLT (x10 <sup>3</sup> /μL)				
DAY 30	1124 119(11)	1192 156(10)	1113 110(9)	1086 117(10)
WBC (x10 <sup>3</sup> /μL)				
DAY 30	13.73 2.42(12)	13.67 2.24(12)	13.18 2.99(12)	13.65 3.30(12)
ANEU (x10 <sup>3</sup> /μL)				
DAY 30	1.95 0.45(12)	2.28 0.68(12)	2.12 0.58(12)	2.30 0.82(12)
ALYM (x10 <sup>3</sup> /μL)				
DAY 30	11.18 2.19(12)	10.80 1.73(12)	10.50 2.47(12)	10.79 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 <sup>3</sup> /μL)				
DAY 30	0.32 0.08(12)	0.31 0.08(12)	0.28 0.07(12)	0.30 0.11(12)
AEOS (x10 <sup>3</sup> /μL)				
DAY 30	0.12 0.05(12)	0.14 0.06(12)	0.13 0.06(12)	0.11 0.08(12)
ABAS (x10 <sup>3</sup> /μL)				
DAY 30	0.07 0.04(12)	0.07 0.02(12)	0.07 0.02(12)	0.06 0.03(12)
ALUC (x10 <sup>3</sup> /μL)				
DAY 30	0.09 0.04(12)	0.08 0.03(12)	0.09 0.04(12)	0.09 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 <sup>6</sup> /μL)				
DAY 31	7.88 0.39(11)	7.81 0.26(12)	7.85 0.36(10)	7.58 0.23(12)
HGB (g/dL)				
DAY 31	15.7 0.6(11)	15.7 0.4(12)	15.5 0.4(10)	15.2 0.5(12)
HCT (%)				
DAY 31	47.1 2.2(11)	47.3 1.3(12)	47.4 1.6(10)	46.1 1.3(12)
MCV (fl)				
DAY 31	59.8 1.4(11)	60.6 2.0(12)	60.5 1.7(10)	60.8 1.8(12)
MCH (pg)				
DAY 31	19.9 0.6(11)	20.0 0.6(12)	19.8 0.7(10)	20.1 0.6(12)
MCHC (g/dL)				
DAY 31	33.4 0.6(11)	33.1 0.5(12)	32.8 0.5(10)	33.0 0.5(12)
RDW (%)				
DAY 31	10.6 0.2(11)	10.7 0.3(12)	10.9 0.5(10)	11.1* 0.5(12)
ARET (x10 <sup>3</sup> /μL)				
DAY 31	180.6 37.2(11)	184.4 41.2(12)	187.3 51.0(10)	241.2* 61.4(12)
PLT (x10 <sup>3</sup> /μL)				
DAY 31	1195 116(6)	1128 182(9)	1163 162(6)	1160 176(9)
WBC (x10 <sup>3</sup> /μL)				
DAY 31	10.69 2.20(11)	9.81 2.46(12)	10.24 1.92(10)	10.22 2.47(12)
ANEU (x10 <sup>3</sup> /μL)				
DAY 31	1.10 0.38(11)	1.24 0.44(12)	1.18 0.55(10)	1.38 0.45(12)
ALYM (x10 <sup>3</sup> /μL)				
DAY 31	9.05 2.13(11)	8.17 2.22(12)	8.59 1.77(10)	8.40 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 <sup>3</sup> /μL)				
DAY 31	0.25 0.07(11)	0.17* 0.08(12)	0.22 0.05(10)	0.19 0.07(12)
AEOS (x10 <sup>3</sup> /μL)				
DAY 31	0.13 0.09(11)	0.11 0.05(12)	0.12 0.06(10)	0.11 0.04(12)
ABAS (x10 <sup>3</sup> /μL)				
DAY 31	0.06 0.03(11)	0.05 0.04(12)	0.06 0.03(10)	0.05 0.03(12)
ALUC (x10 <sup>3</sup> /μL)				
DAY 31	0.09 0.04(11)	0.08 0.05(12)	0.08 0.02(10)	0.08 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 13(12)	92 22(12)	90 9(12)	83 12(12)
ALT (U/L)				
DAY 30	31 5(12)	31 7(12)	29 4(12)	32 6(12)
SDH (U/L)				
DAY 30	12.6 3.1(12)	15.3 4.5(12)	15.7 3.6(12)	13.9 2.5(12)
ALKP (U/L)				
DAY 30	164 23(12)	161 36(12)	181 46(12)	157 35(12)
BILI (mg/dL)				
DAY 30	0.12 0.02(12)	0.10 0.03(12)	0.12 0.03(12)	0.12 0.04(12)
BUN (mg/dL)				
DAY 30	12 2(12)	11 2(12)	12 1(12)	12 1(12)
CREA (mg/dL)				
DAY 30	0.29 0.03(12)	0.30 0.05(12)	0.34* 0.06(12)	0.34* 0.03(12)
CHOL (mg/dL)				
DAY 30	51 8(12)	49 6(12)	53 10(12)	56 12(12)
TRIG (mg/dL)				
DAY 30	61 19(12)	55 22(12)	63 30(12)	61 31(12)
GLUC (mg/dL)				
DAY 30	107 10(12)	101 7(12)	99* 5(12)	94* 8(12)
TP (g/dL)				
DAY 30	6.5 0.3(12)	6.5 0.3(12)	6.7 0.3(12)	6.8 0.3(12)
ALB (g/dL)				
DAY 30	4.5 0.2(12)	4.5 0.1(12)	4.6 0.2(12)	4.7* 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 12(12)	84 13(12)	84 13(12)	85 20(12)
ALT (U/L)				
DAY 31	27 4(12)	26 6(12)	25 7(12)	27 5(12)
SDH (U/L)				
DAY 31	13.6 3.8(12)	12.6 3.8(12)	13.5 3.9(12)	11.9 4.8(12)
ALKP (U/L)				
DAY 31	87 21(12)	94 21(12)	92 23(12)	99 24(12)
BILI (mg/dL)				
DAY 31	0.17 0.02(12)	0.15 0.03(12)	0.14 0.02(12)	0.14* 0.04(12)
BUN (mg/dL)				
DAY 31	15 2(12)	13 2(12)	14 2(12)	14 1(12)
CREA (mg/dL)				
DAY 31	0.35 0.05(12)	0.34 0.05(12)	0.39 0.05(12)	0.44* 0.08(12)
CHOL (mg/dL)				
DAY 31	68 13(12)	72 11(12)	72 26(12)	80 16(12)
TRIG (mg/dL)				
DAY 31	36 10(12)	35 9(12)	27 7(12)	31 10(12)
GLUC (mg/dL)				
DAY 31	106 18(12)	105 7(12)	108 16(12)	101 9(12)
TP (g/dL)				
DAY 31	7.2 0.4(12)	7.2 0.3(12)	7.1 0.4(12)	7.2 0.4(12)
ALB (g/dL)				
DAY 31	4.9 0.3(12)	5.0 0.2(12)	4.9 0.3(12)	5.0 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 0.2(12)	2.2 0.2(12)	2.2 0.1(12)	2.2 0.2(12)
CALC (mg/dL)				
DAY 31	10.9 0.4(12)	10.9 0.2(12)	11.1 0.4(12)	10.9 0.4(12)
IPHS (mg/dL)				
DAY 31	7.4 0.7(12)	7.2 0.9(12)	7.9 1.3(12)	7.4 0.9(12)
NA (mmol/L)				
DAY 31	146.8 1.3(12)	147.2 1.3(12)	147.3 1.1(12)	146.8 1.6(12)
K (mmol/L)				
DAY 31	5.84 0.31(12)	5.87 0.40(12)	6.11 0.50(12)	5.91 0.45(12)
CL (mmol/L)				
DAY 31	103.0 1.2(12)	103.4 1.0(12)	103.6 2.0(12)	103.7 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: Dosage (mg/kg/day)	I 0	III 35	V 125	VII 375
Final Body Weight	387.8 21.2 (12)	379.3 14.2 (12)	358.8# 18.4 (12)	348.0# 16.0 (12)
Liver	11.993 1.059 (12)	11.925 1.035 (12)	11.368 0.887 (12)	12.292 1.109 (12)
Kidneys	3.200 0.288 (12)	3.170 0.196 (12)	3.147 0.239 (12)	3.298 0.263 (12)
Lungs	1.757 0.083 (12)	1.745 0.160 (12)	1.729 0.173 (12)	1.658 0.153 (12)
Heart	1.462 0.123 (12)	1.381 0.142 (12)	1.341# 0.083 (12)	1.284# 0.127 (12)
Spleen	0.724 0.088 (12)	0.694 0.093 (12)	0.645# 0.086 (12)	0.618# 0.053 (12)
Thymus	0.503 0.078 (12)	0.486 0.054 (12)	0.417# 0.040 (12)	0.380# 0.051 (12)
Adrenal Glands	0.060 0.008 (11)	0.061 0.009 (12)	0.057 0.008 (12)	0.055 0.008 (12)
Testes	3.249 0.209 (12)	3.211 0.198 (12)	3.128 0.156 (12)	3.153 0.190 (12)

TABLE 52 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT MALE

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

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

TABLE 52 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT MALE

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

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

TABLE 52 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT MALE

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

Group: Dosage (mg/kg/day)	I 0	III 35	V 125	VII 375
Epididymides/Final Body * 100	0.280 0.023 (12)	0.297 0.012 (12)	0.303# 0.016 (12)	0.305# 0.022 (12)
Brain/Final Body * 100	0.522 0.039 (12)	0.527 0.020 (12)	0.566# 0.035 (12)	0.570# 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: Dosage (mg/kg/day)	I 0	III 35	V 125	VII 375
Liver/Brain * 100	594.942 59.436 (12)	597.494 50.024 (12)	562.083 54.787 (12)	620.757 55.912 (12)
Kidneys/Brain * 100	158.706 15.436 (12)	158.876 10.220 (12)	155.400 12.167 (12)	166.591 13.720 (12)
Lungs/Brain * 100	87.074 4.710 (12)	87.398 7.268 (12)	85.476 9.907 (12)	83.784 8.210 (12)
Heart/Brain * 100	72.470 6.143 (12)	69.245 7.637 (12)	66.236# 4.632 (12)	64.893# 7.121 (12)
Spleen/Brain * 100	35.832 4.268 (12)	34.702 3.940 (12)	31.899# 4.618 (12)	31.212# 2.717 (12)
Thymus/Brain * 100	25.003 4.222 (12)	24.356 2.746 (12)	20.580# 1.904 (12)	19.178# 2.657 (12)
Adrenal Glands/Brain * 100	3.011 0.374 (11)	3.048 0.451 (12)	2.819 0.443 (12)	2.775 0.438 (12)
Testes/Brain * 100	161.037 11.119 (12)	161.035 12.399 (12)	154.503 9.032 (12)	159.335 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	56.547	53.653	53.590
	5.747 (12)	3.777 (12)	3.230 (12)	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: Dosage (mg/kg/day)	II 0	IV 35	VI 125	VIII 375
Final Body Weight	243.3 20.0 (12)	239.3 11.1 (12)	234.2 17.1 (12)	228.4# 15.2 (12)
Liver	7.348 0.907 (12)	7.656 0.868 (12)	7.699 0.677 (12)	7.908 0.723 (12)
Kidneys	1.871 0.191 (12)	1.942 0.147 (12)	1.938 0.174 (12)	1.870 0.227 (12)
Lungs	1.425 0.139 (12)	1.365 0.098 (12)	1.374 0.111 (12)	1.385 0.154 (12)
Heart	0.943 0.121 (12)	0.938 0.110 (12)	0.911 0.098 (12)	0.874 0.105 (12)
Spleen	0.494 0.059 (12)	0.506 0.069 (12)	0.482 0.065 (12)	0.477 0.074 (12)
Thymus	0.439 0.117 (12)	0.414 0.057 (12)	0.418 0.100 (12)	0.377# 0.107 (12)
Adrenal Glands	0.068 0.013 (12)	0.066 0.007 (12)	0.073 0.008 (12)	0.072 0.009 (12)
Ovaries	0.121 0.011 (12)	0.127 0.016 (12)	0.130 0.024 (12)	0.125 0.021 (12)

TABLE 53 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT FEMALE

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

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

TABLE 53 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT FEMALE

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

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

TABLE 53 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SUBCHRONIC ADULT FEMALE

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

Group: Dosage (mg/kg/day)	II 0	IV 35	VI 125	VIII 375
Uterus/Final Body * 100	0.223 0.065 (12)	0.268 0.098 (12)	0.245 0.050 (12)	0.290 0.130 (12)
Brain/Final Body * 100	0.770 0.058 (12)	0.778 0.055 (12)	0.780 0.048 (12)	0.815# 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: Dosage (mg/kg/day)	II 0	IV 35	VI 125	VIII 375
Liver/Brain * 100	394.222 45.041 (12)	412.890 47.811 (12)	422.881 35.163 (12)	426.322 36.258 (12)
Kidneys/Brain * 100	100.362 8.674 (12)	104.775 9.526 (12)	106.327 7.900 (12)	100.792 11.821 (12)
Lungs/Brain * 100	76.513 6.940 (12)	73.642 5.968 (12)	75.405 4.836 (12)	74.645 7.967 (12)
Heart/Brain * 100	50.592 6.212 (12)	50.635 6.577 (12)	50.088 5.564 (12)	47.102 5.519 (12)
Spleen/Brain * 100	26.528 3.158 (12)	27.229 3.283 (12)	26.497 3.576 (12)	25.782 4.521 (12)
Thymus/Brain * 100	23.534 6.041 (12)	22.287 2.904 (12)	22.904 5.071 (12)	20.296 5.586 (12)
Adrenal Glands/Brain * 100	3.637 0.619 (12)	3.538 0.384 (12)	4.023 0.360 (12)	3.858 0.465 (12)
Ovaries/Brain * 100	6.484 0.477 (12)	6.843 0.874 (12)	7.125 1.199 (12)	6.757 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 9.051 (12)	34.653 13.573 (12)	31.579 6.879 (12)	35.486 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: Dosage (mg/kg/day)	II-0 0	IV-0 35	VI-0 125	VIII-0 375
Final Body Weight	326.7 19.8 (12)	317.9 25.3 (12)	301.9# 20.0 (12)	304.2# 15.1 (12)
Liver	13.703 1.713 (12)	13.147 1.745 (12)	13.356 1.957 (12)	14.355 1.398 (12)
Kidneys	2.299 0.189 (12)	2.248 0.168 (12)	2.197 0.268 (12)	2.321 0.223 (12)
Lungs	1.515 0.112 (12)	1.543 0.169 (12)	1.431 0.108 (12)	1.502 0.088 (12)
Ovaries	0.137 0.023 (12)	0.132 0.018 (12)	0.125 0.021 (12)	0.133 0.020 (12)
Uterus	0.829 0.334 (12)	0.710 0.088 (12)	0.686 0.140 (12)	0.667 0.115 (12)

TABLE 54 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS - SATELLITE ADULT FEMALE

MEAN RELATIVE ORGAN WEIGHTS (% of body weight)

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

Note:

# Trend test (Jonckheere-Terpstra) significant

TABLE 55

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS - SUBCHRONIC ADULTS

	GROUP DESIGNATION:	I	III	V	VII
	DOSE (mg/kg/day):	0	35	125	375
SITE/LESION:	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

	GROUP DESIGNATION:	II	IV	VI	VIII
	DOSE (mg/kg/day):	0	35	125	375
SITE/LESION:	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:			
		DOSE (mg/kg/day): NUMBER IN GROUP:	I 0 12	III 35 12	V 125 12
=====					
<u>DIGESTIVE SYSTEM</u>					
LIVER		<u>12</u>	<u>12</u>	<u>12</u>	<u>12</u>
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		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
TONGUE		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
ESOPHAGUS		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
DEGENERATION, MYOFIBER, FOCAL		-	-	-	1 (-, 1, -, -, -)
INFLAMMATION, MUSCULAR, FOCAL		-	-	-	1 (-, 1, -, -, -)
STOMACH		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
EROSION/ULCER, GLANDULAR		1 (-, 1, -, -, -)	-	-	-
DUODENUM		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
JEJUNUM		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
ILEUM		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
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:			
		DOSE (mg/kg/day): NUMBER IN GROUP:	I 0 12	III 35 12	V 125 12
<u>DIGESTIVE SYSTEM</u> (Cont'd)					
CECUM		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
CELLULARITY INCREASED, LAMINA PROPRIA		2 (-, -, 2, -, -)	-	-	3 (-, 1, 2, -, -)
COLON		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
RECTUM		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
<u>URINARY SYSTEM</u>					
KIDNEYS		<u>12</u>	<u>12</u>	<u>12</u>	<u>12</u>
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		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
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:				
		DOSE (mg/kg/day): NUMBER IN GROUP:	I 0 12	III 35 12	V 125 12	VII 375 12
<u>RESPIRATORY SYSTEM</u>						
NOSE			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
INFLAMMATION/HEMORRHAGE (BLEEDING PROCEDURE)			11 (-, 3, 8, -, -)	-	-	11 (-, 3, 7, 1, -)
PHARYNX/LARYNX			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
DEGENERATION, MYOFIBER, FOCAL			1 (-, 1, -, -, -)	-	-	-
TRACHEA			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
LUNGS			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
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, -, -, -)	-	-	-
<u>CARDIOVASCULAR SYSTEM</u>						
HEART			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
INFLAMMATION, SUBACUTE/CHRONIC			4 (-, 3, 1, -, -)	-	-	1 (-, 1, -, -, -)
AORTA			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
<u>HEMATOPOIETIC SYSTEM</u>						
BONE MARROW			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>

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

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:				
		DOSE (mg/kg/day): NUMBER IN GROUP:	I 0 12	III 35 12	V 125 12	VII 375 12
<u>NERVOUS SYSTEM</u>						
BRAIN			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
SPINAL CORD			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
SCIATIC NERVE			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
EYES			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
FOLD/ROSETTE, RETINAL			1 (-, 1, -, -, -)	-	-	-
INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE)			9 (-, 8, 1, -, -)	-	-	9 (-, 6, 3, -, -)
OPTIC NERVE NOT PRESENT, UNILATERAL			2 (2, -, -, -, -)	-	-	2 (2, -, -, -, -)
<u>MUSCULOSKELETAL SYSTEM</u>						
FEMUR/KNEE JOINT			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
STERNUM			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
SKELETAL MUSCLE			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
<u>REPRODUCTIVE SYSTEM</u>						
TESTES			<u>12</u>	<u>0</u>	<u>1</u>	<u>12</u>
EPIDIDYMIDES			<u>12</u>	<u>0</u>	<u>1</u>	<u>12</u>
AGGREGATES, LYMPHOID			4 (-, 4, -, -, -)	-	1 (-, 1, -, -, -)	7 (-, 7, -, -, -)
PROSTATE			<u>12</u>	<u>0</u>	<u>1</u>	<u>12</u>
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 DOSE (mg/kg/day): NUMBER IN GROUP:	III 35 12	V 125 12	VII 375 12
<hr/>					
<u>REPRODUCTIVE SYSTEM</u> (Cont'd)					
SEMINAL VESICLES		<u>12</u>	<u>0</u>	<u>1</u>	<u>12</u>
COAGULATING GLANDS		<u>12</u>	<u>0</u>	<u>1</u>	<u>12</u>
<u>INTEGUMENTARY SYSTEM</u>					
SKIN		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
SALIVARY GLANDS DEGENERATION/NECROSIS, FOCAL (PAROTID GLAND)		<u>12</u> 2 (-, 2, -, -, -)	<u>0</u> -	<u>0</u> -	<u>12</u> -
EXORBITAL LACRIMAL GLANDS AGGREGATES, LYMPHOID		<u>12</u> 2 (-, 2, -, -, -)	<u>0</u> -	<u>0</u> -	<u>12</u> -
<u>MISCELLANEOUS</u>					
OTHER		<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
CAUSE OF DEATH SACRIFICED BY DESIGN		<u>12</u> 12 (1, , , , ) (2, -, -, -, -)	<u>0</u> -	<u>0</u> -	<u>12</u> 12 (1, , , , ) (2, -, -, -, -)
<hr/>					
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 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 DOSE (mg/kg/day): NUMBER IN GROUP:	IV 35 12	VI 125 12	VIII 375 12
<u>DIGESTIVE SYSTEM</u>					
LIVER		<u>12</u>	<u>12</u>	<u>12</u>	<u>12</u>
FATTY CHANGE, MEDIAN CLEFT		-	4 (-, 4, -, -, -)	-	-
HEMATOPOIESIS, INCREASED EXTRAMEDULLARY		1 (-, 1, -, -, -)	1 (-, 1, -, -, -)	1 (-, 1, -, -, -)	-
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR		-	-	3 (, , , , , )	12 (, , , 1, , , )
				(-, 3, -, -, -)	(-, -, 2, -, -)
INFLAMMATION, SUBACUTE/CHRONIC		10 (, 1, , , , )	11 (, 1, , , , )	12 (, 1, , , , )	12 (, 1, , , , )
		(-, 0, -, -, -)	(-, 1, -, -, -)	(-, 2, -, -, -)	(-, 2, -, -, -)
NECROSIS, COAGULATIVE, FOCAL		-	1 (-, 1, -, -, -)	-	-
PANCREAS		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
AGGREGATES, LYMPHOID		-	-	-	1 (-, 1, -, -, -)
TONGUE		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
ESOPHAGUS		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
DEGENERATION, MYOFIBER, FOCAL		2 (-, 2, -, -, -)	-	-	1 (-, -, 1, -, -)
INFLAMMATION, SUBACUTE/CHRONIC		-	-	-	1 (-, 1, -, -, -)
STOMACH		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
DUODENUM		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
JEJUNUM		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
ILEUM		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
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:			
		II DOSE (mg/kg/day): NUMBER IN GROUP:	IV 35 12	VI 125 12	VIII 375 12
=====					
<u>DIGESTIVE SYSTEM</u> ((Cont'd)					
CECUM		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
CELLULARITY INCREASED, LAMINA PROPRIA		-	-	-	1 (-, 1, -, -, -)
COLON		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
RECTUM		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
<u>URINARY SYSTEM</u>					
KIDNEYS		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
AGGREGATES, LYMPHOID MINERALIZATION		6 (-, 6, -, -, -)	-	-	2 (-, 2, -, -, -)
NEPHROPATHY, CHRONIC PROGRESSIVE		1 (-, 1, -, -, -)	-	-	-
		5 (-, 5, -, -, -)	-	-	4 (-, 4, -, -, -)
URINARY BLADDER		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
AGGREGATES, LYMPHOID		1 (-, 1, -, -, -)	-	-	1 (-, 1, -, -, -)
<u>RESPIRATORY SYSTEM</u>					
NOSE		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
PHARYNX/LARYNX		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
TRACHEA		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
AGGREGATES, LYMPHOID INFLAMMATION, SUBACUTE/CHRONIC		-	-	-	1 (-, 1, -, -, -)
		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:				
		DOSE (mg/kg/day): NUMBER IN GROUP:	II 0 12	IV 35 12	VI 125 12	VIII 375 12
<b>RESPIRATORY SYSTEM (Cont'd)</b>						
LUNGS			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
HEMORRHAGE			<u>7</u> (-, 6, 1, -, -)	-	-	<u>1</u> (-, 1, -, -, -)
HISTIOCYTOSIS, ALVEOLAR			<u>3</u> (-, 3, -, -, -)	-	-	<u>1</u> (-, 1, -, -, -)
INFLAMMATION, ALVEOLAR			-	-	-	<u>1</u> (-, 1, -, -, -)
INFLAMMATION, SUBACUTE/CHRONIC, PERIVASCULAR			<u>2</u> (-, 2, -, -, -)	-	-	-
<b>CARDIOVASCULAR SYSTEM</b>						
HEART			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
INFLAMMATION, SUBACUTE/CHRONIC			<u>2</u> (-, 2, -, -, -)	-	-	-
AORTA			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
<b>HEMATOPOIETIC SYSTEM</b>						
BONE MARROW			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
THYMUS			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
HEMORRHAGE			<u>5</u> (-, 5, -, -, -)	-	-	<u>5</u> (-, 5, -, -, -)
SPLEEN			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
HEMATOPOIESIS, INCREASED EXTRAMEDULLARY			<u>1</u> (-, 1, -, -, -)	-	-	-
MANDIBULAR LYMPH NODE			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS			<u>2</u> (-, 2, -, -, -)	-	-	<u>2</u> (-, 2, -, -, -)
MEDIASTINAL LYMPH NODE			<u>12</u>	<u>0</u>	<u>0</u>	<u>10</u>
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS			<u>9</u> (-, 4, 5, -, -)	-	-	<u>6</u> (-, 3, 3, -, -)
MESENTERIC LYMPH NODE			<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>

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
<u>ENDOCRINE SYSTEM</u>					
PITUITARY GLAND			<u>0</u>	<u>0</u>	<u>12</u>
ADRENAL GLANDS			<u>0</u>	<u>0</u>	<u>12</u>
THYROID GLAND		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
ECTOPIC THYMUS TISSUE		<u>1</u> (1, -, -, -, -)	-	-	<u>1</u> (1, -, -, -, -)
HYPERTROPHY, FOLLICULAR CELL		-	-	-	<u>1</u> (-, 1, -, -, -)
PARATHYROID GLAND		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
<u>NERVOUS SYSTEM</u>					
BRAIN		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
SPINAL CORD		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
SCIATIC NERVE		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
EYES		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
FOLD/ROSETTE, RETINAL		<u>1</u> (-, 1, -, -, -)	-	-	<u>4</u> (-, 4, -, -, -)
INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE)		<u>9</u> (-, 7, 2, -, -)	-	-	<u>7</u> (-, 3, 4, -, -)
LENS NOT PRESENT, UNILATERAL		-	-	-	<u>1</u> (1, -, -, -, -)
NEOVASCULARIZATION, CORNEAL		-	-	-	<u>1</u> (-, 1, -, -, -)
OPTIC NERVE NOT PRESENT, UNILATERAL		<u>2</u> (2, -, -, -, -)	-	-	<u>3</u> (3, -, -, -, -)
<u>MUSCULOSKELETAL SYSTEM</u>					
FEMUR/KNEE JOINT		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>

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 DOSE (mg/kg/day): NUMBER IN GROUP:	IV 35 12	VI 125 12	VIII 375 12
=====					
<u>MUSCULOSKELETAL SYSTEM</u> (Cont'd)					
STERNUM		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
SKELETAL MUSCLE		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
<u>REPRODUCTIVE SYSTEM</u>					
OVARIES		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
UTERUS		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
CERVIX		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
VAGINA		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
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, -)	-	-	-
<u>INTEGUMENTARY SYSTEM</u>					
SKIN		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
SALIVARY GLANDS		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
FOCUS OF CELLULAR ALTERATION, BASOPHILIC (PAROTID GLAND)		-	-	-	1 (-, 1, -, -, -)
EXORBITAL LACRIMAL GLANDS		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>
AGGREGATES, LYMPHOID		1 (-, 1, -, -, -)	-	-	-
MAMMARY GLAND		<u>12</u>	<u>0</u>	<u>0</u>	<u>12</u>

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
=====						
<u>MISCELLANEOUS</u>						
OTHER			0	0	0	1
SKIN: NO ABNORMALITIES DETECTED			-	-	-	1 (1, -, -, -, -)
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

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): NUMBER IN GROUP:	0 12	35 12	125 12	375 12
<u>REPRODUCTIVE SYSTEM</u>						
OVARIES			<u>2</u>	<u>0</u>	<u>1</u>	<u>1</u>
UTERUS			<u>2</u>	<u>0</u>	<u>1</u>	<u>1</u>
CERVIX			<u>2</u>	<u>0</u>	<u>1</u>	<u>1</u>
VAGINA			<u>2</u>	<u>0</u>	<u>1</u>	<u>1</u>
ESTRUS STAGE: DIESTRUS			-	-	-	1 (1, -, -, -, -)
ESTRUS STAGE: ESTRUS			2 (2, -, -, -, -)	-	-	-
ESTRUS STAGE: METESTRUS			-	-	1 (1, -, -, -, -)	-
<u>MISCELLANEOUS</u>						
CAUSE OF DEATH			<u>2</u>	<u>0</u>	<u>1</u>	<u>1</u>
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

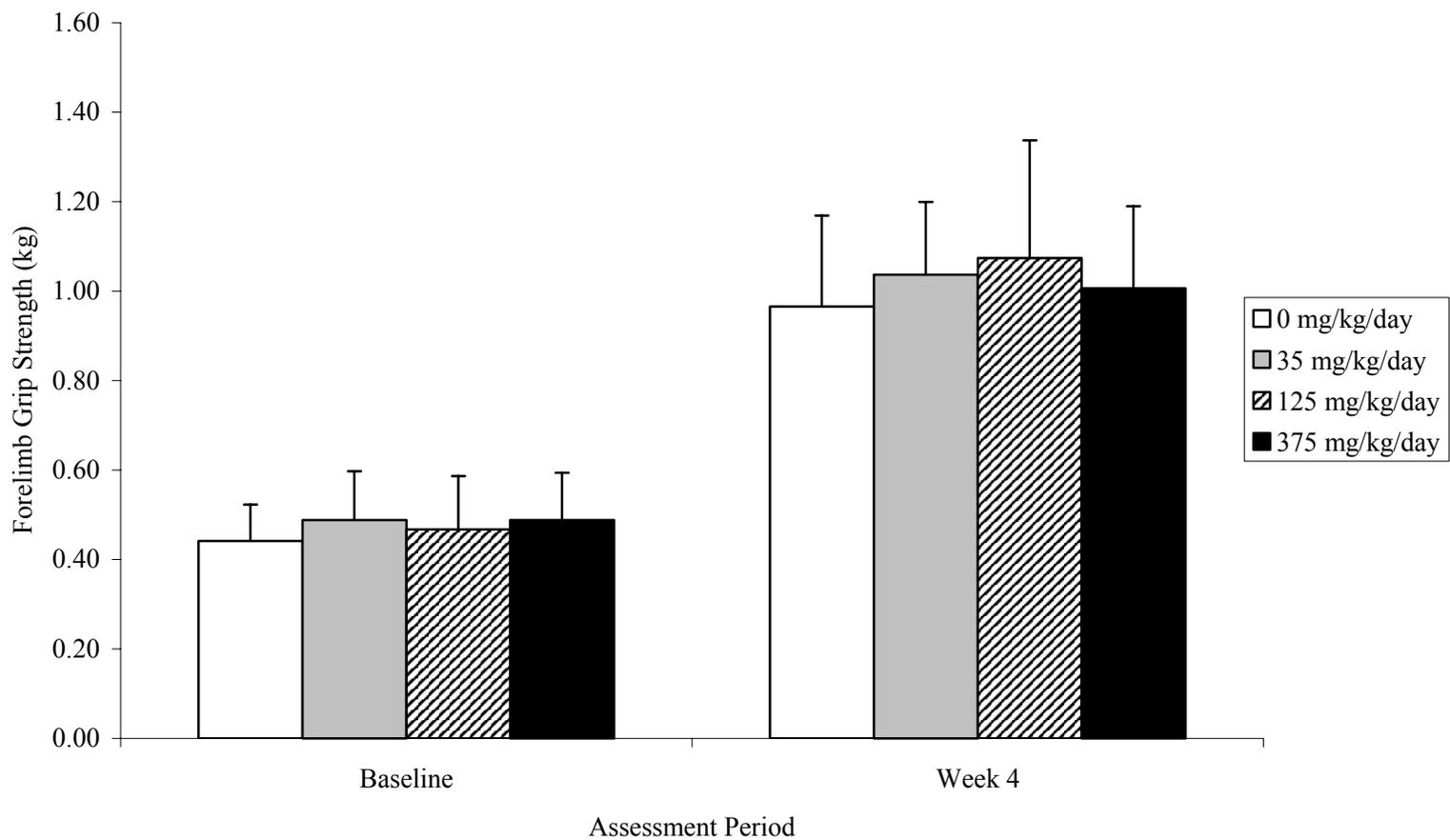


FIGURE 2

MEAN FORELIMB GRIP STRENGTH FOR FEMALE RATS

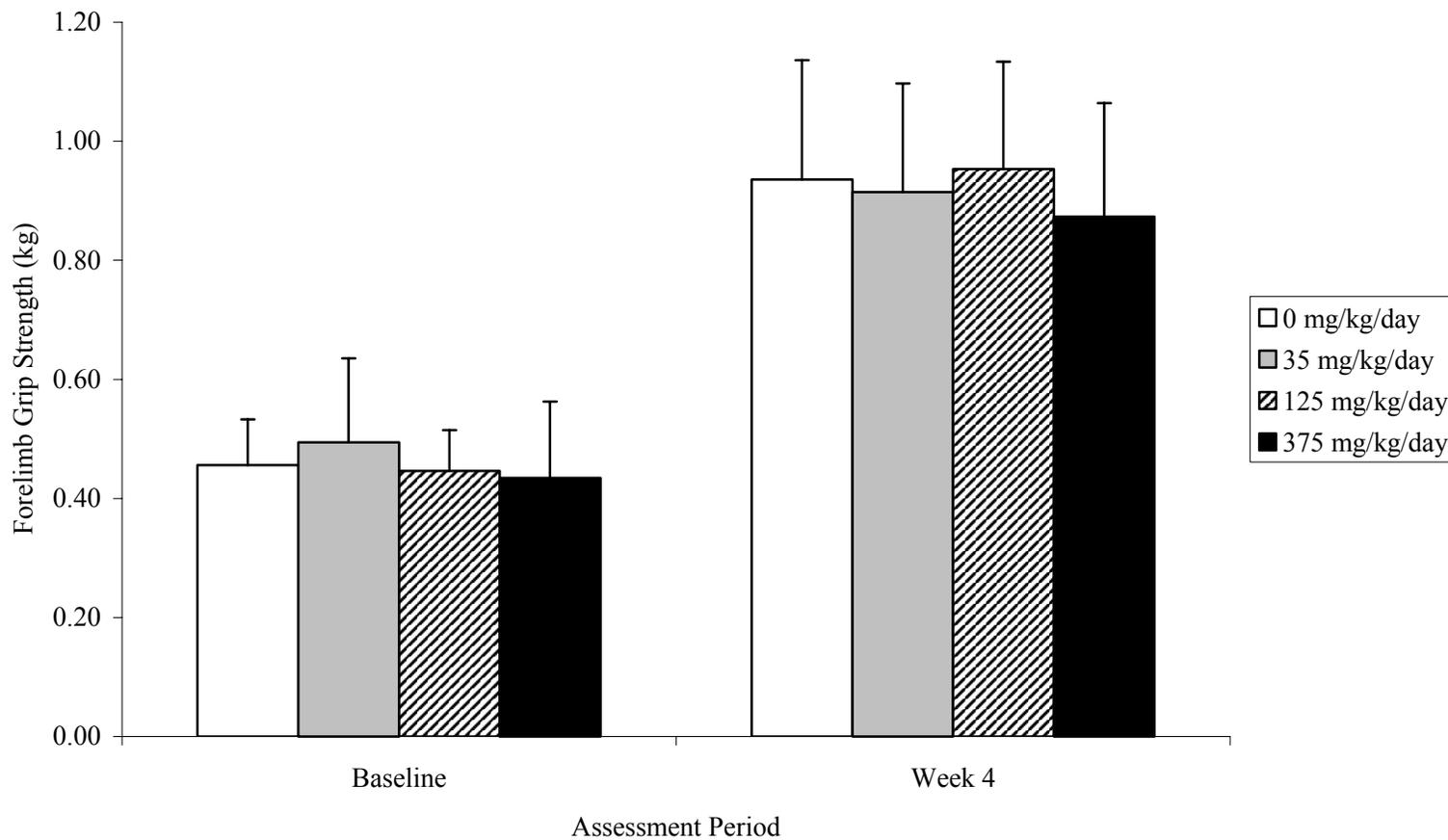


FIGURE 3

MEAN HINDLIMB GRIP STRENGTH FOR MALE RATS

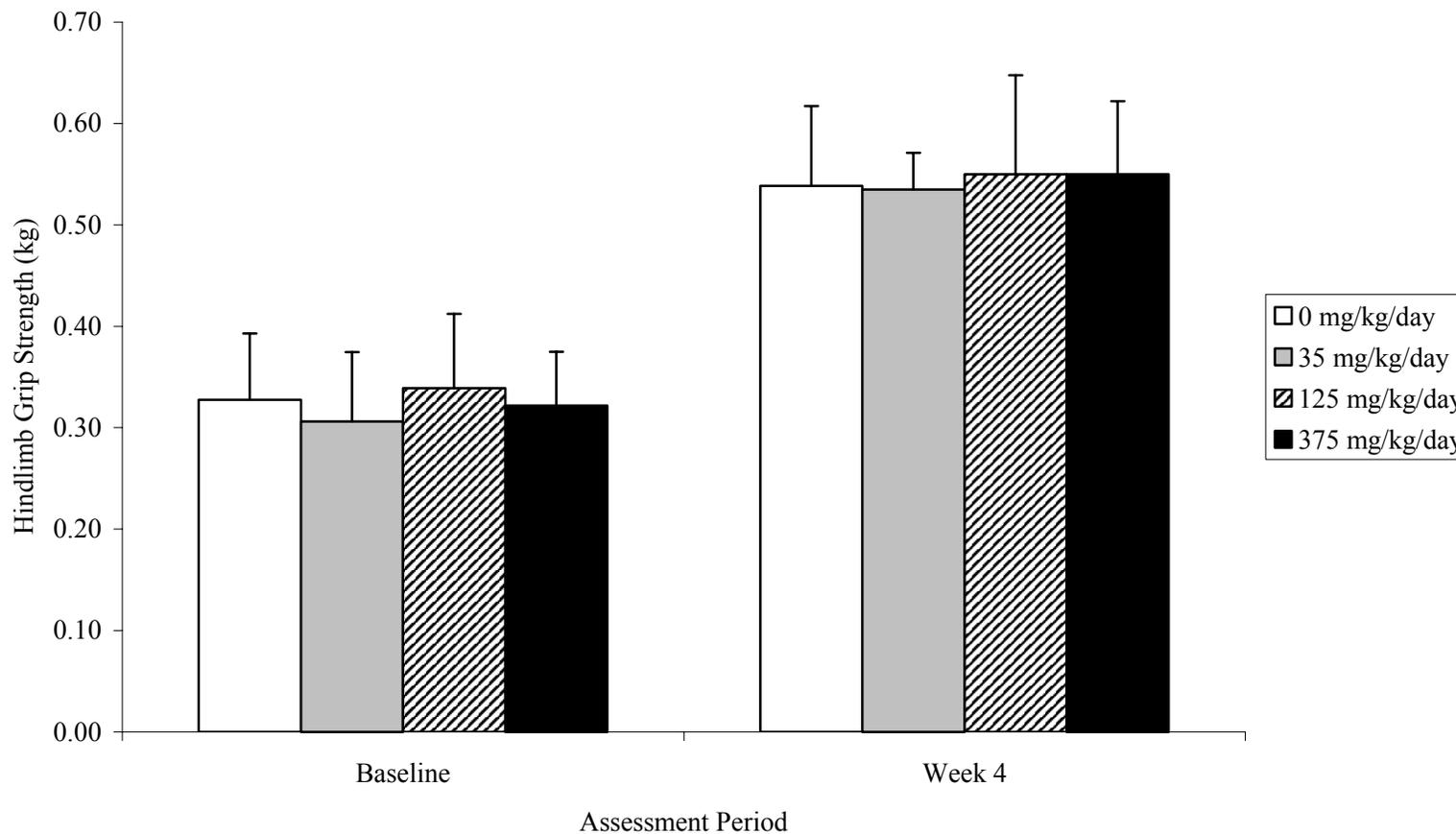


FIGURE 4

MEAN HINDLIMB GRIP STRENGTH FOR FEMALE RATS

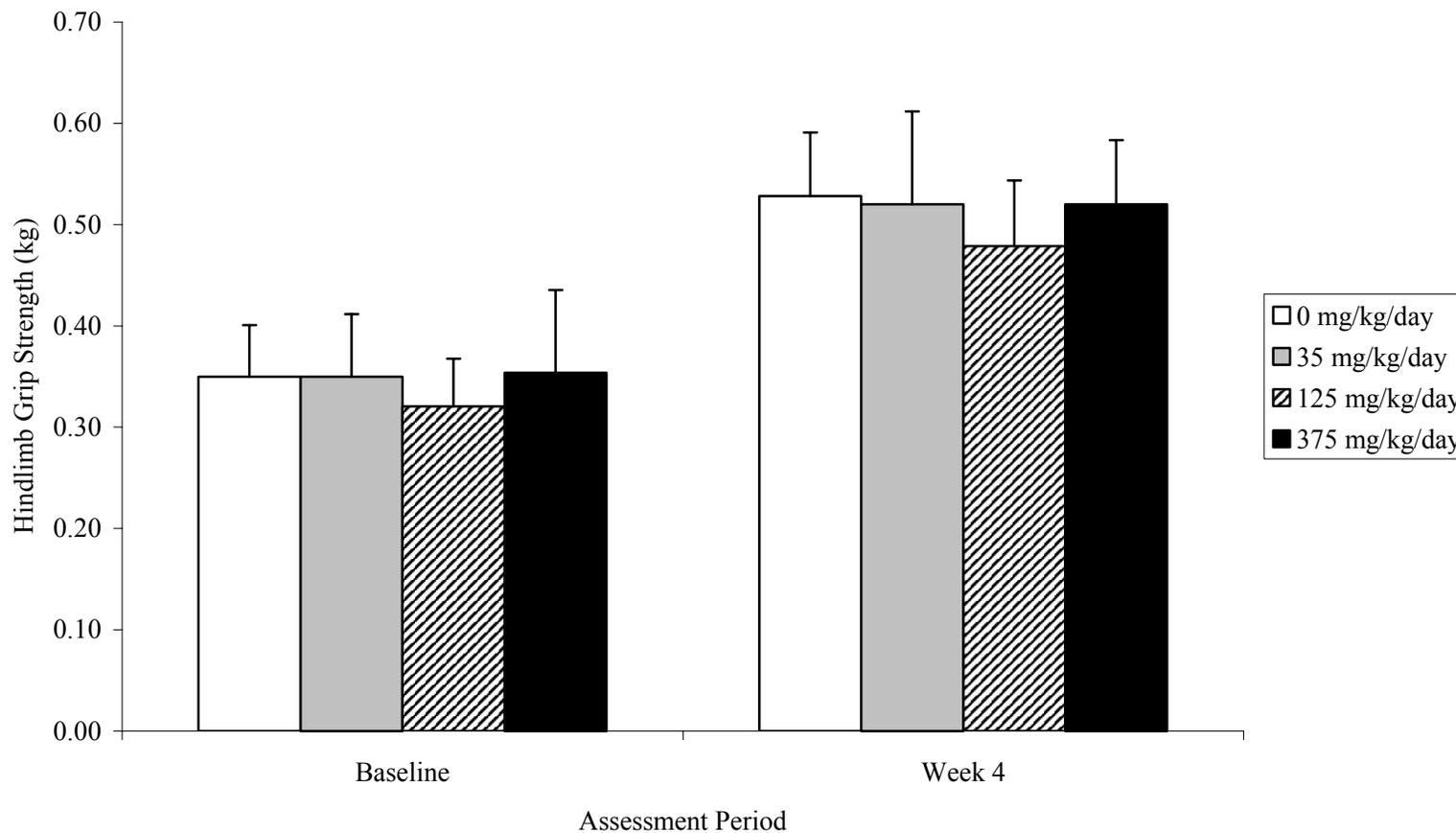


FIGURE 5

MEAN HINDLIMB FOOT SPLAY FOR MALE RATS

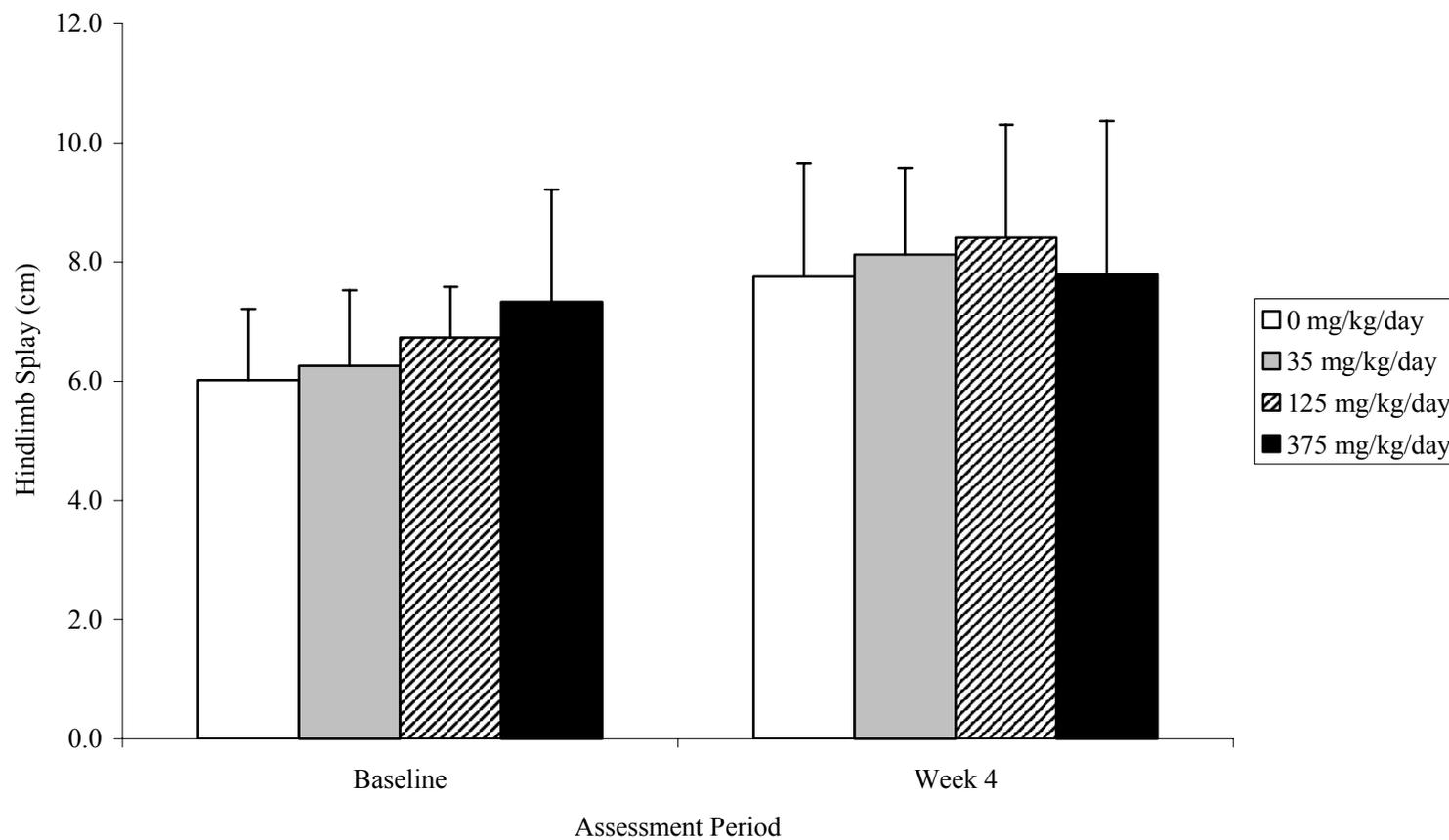


FIGURE 6

MEAN HINDLIMB FOOT SPLAY FOR FEMALE RATS

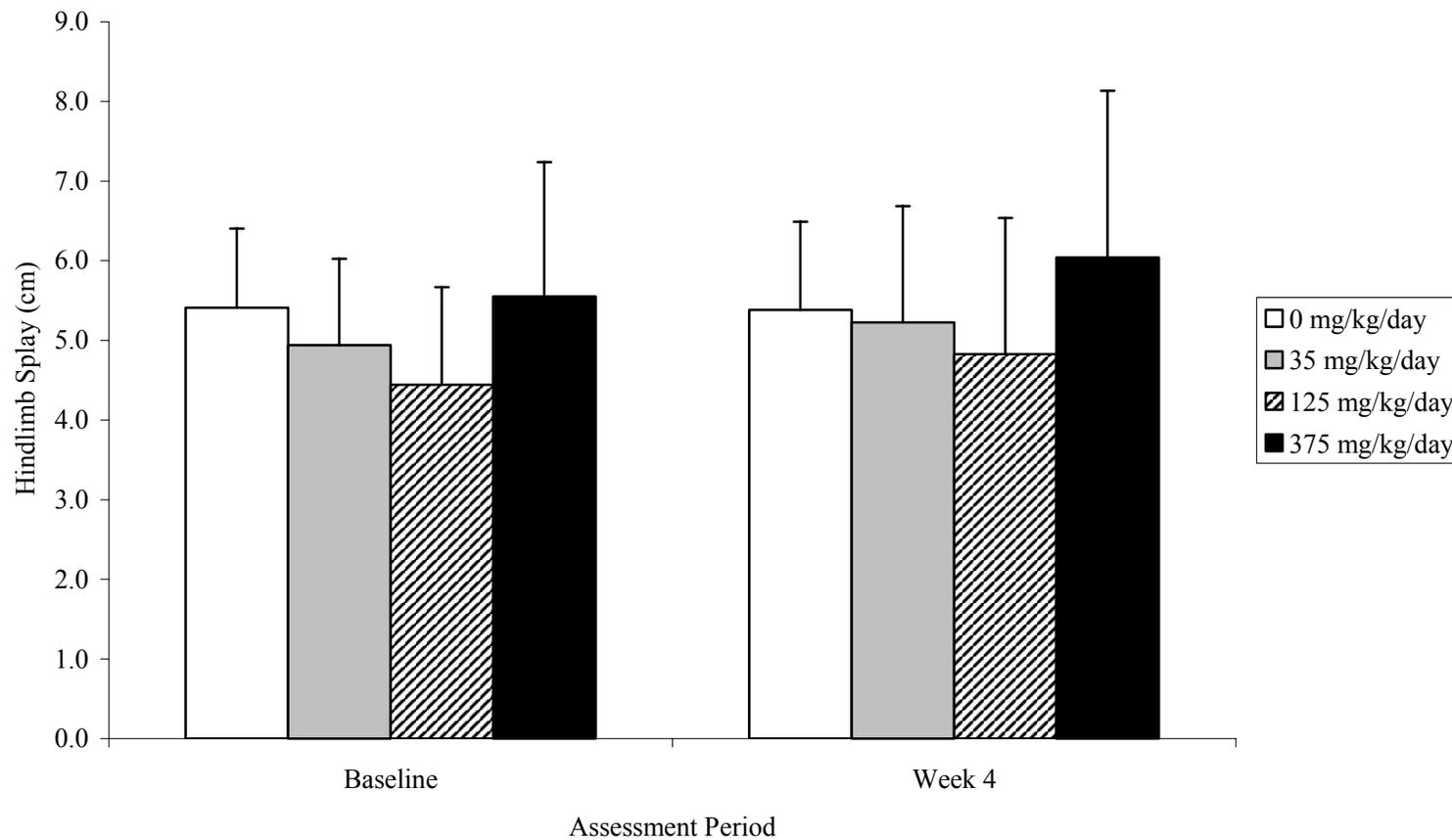


FIGURE 7

MEAN TOTAL DURATION OF MOVEMENT FOR MALE RATS

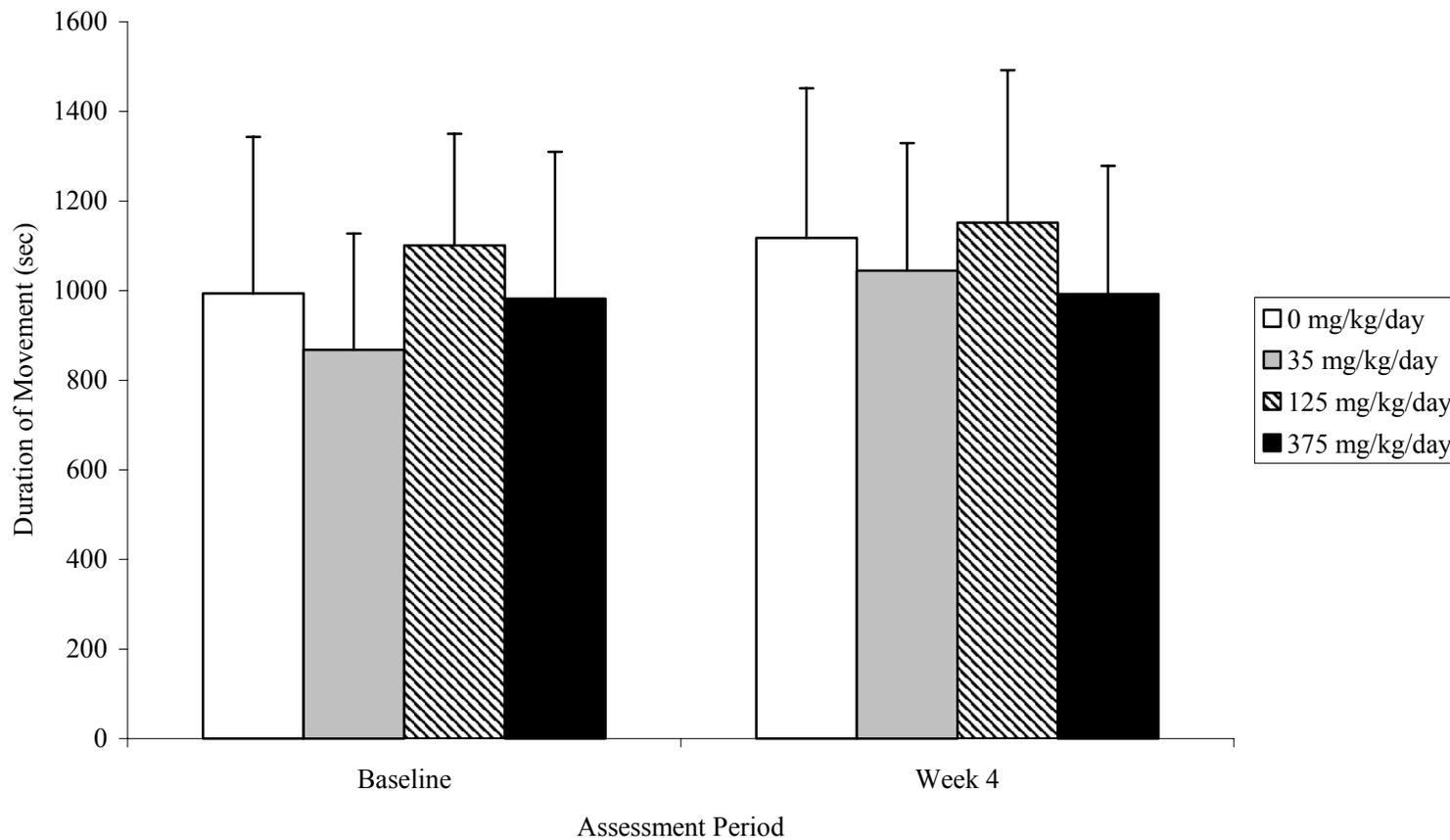


FIGURE 8

MEAN TOTAL DURATION OF MOVEMENT FOR FEMALE RATS

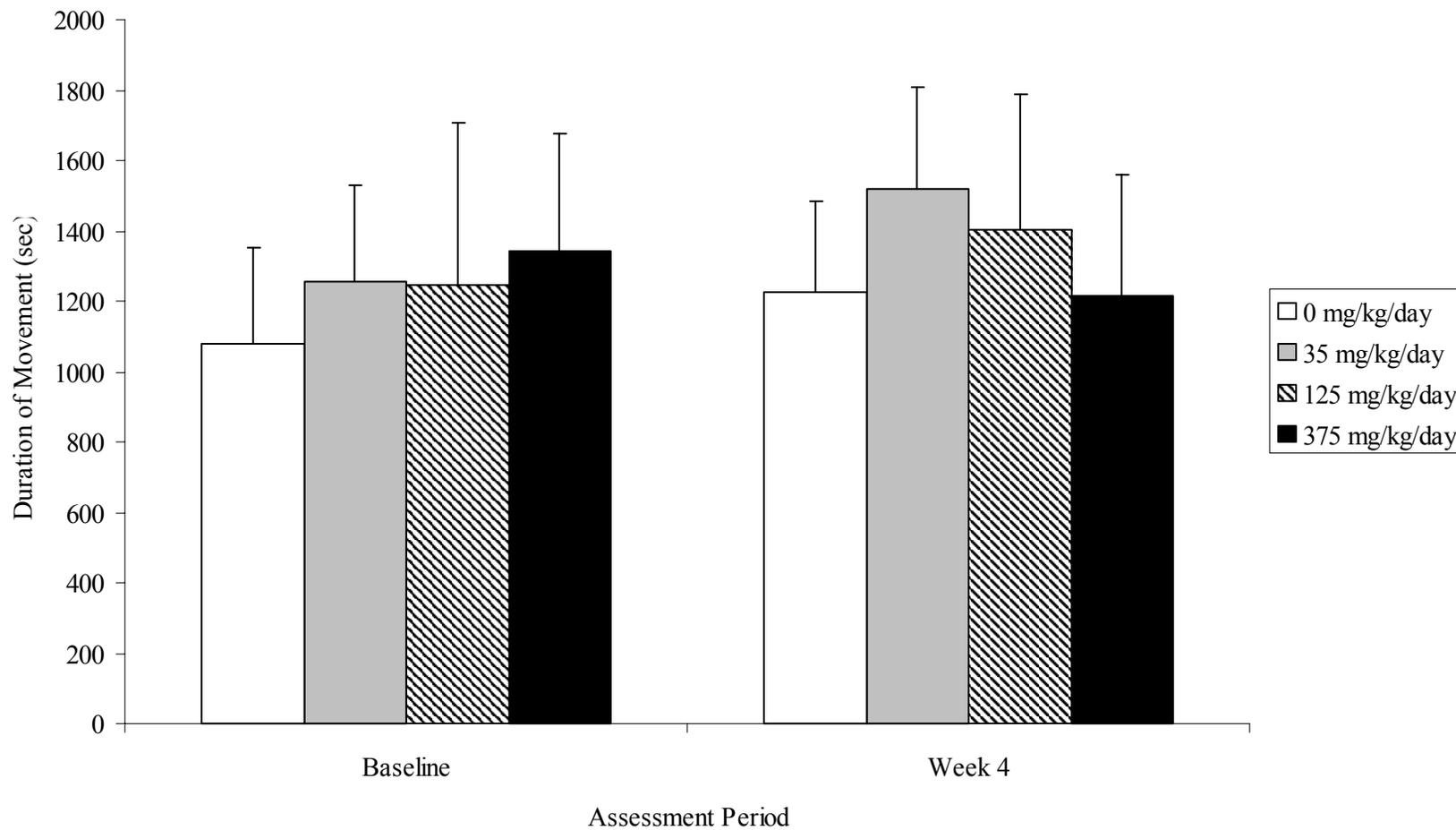


FIGURE 9

MEAN TOTAL NUMBER OF MOVEMENTS FOR MALE RATS

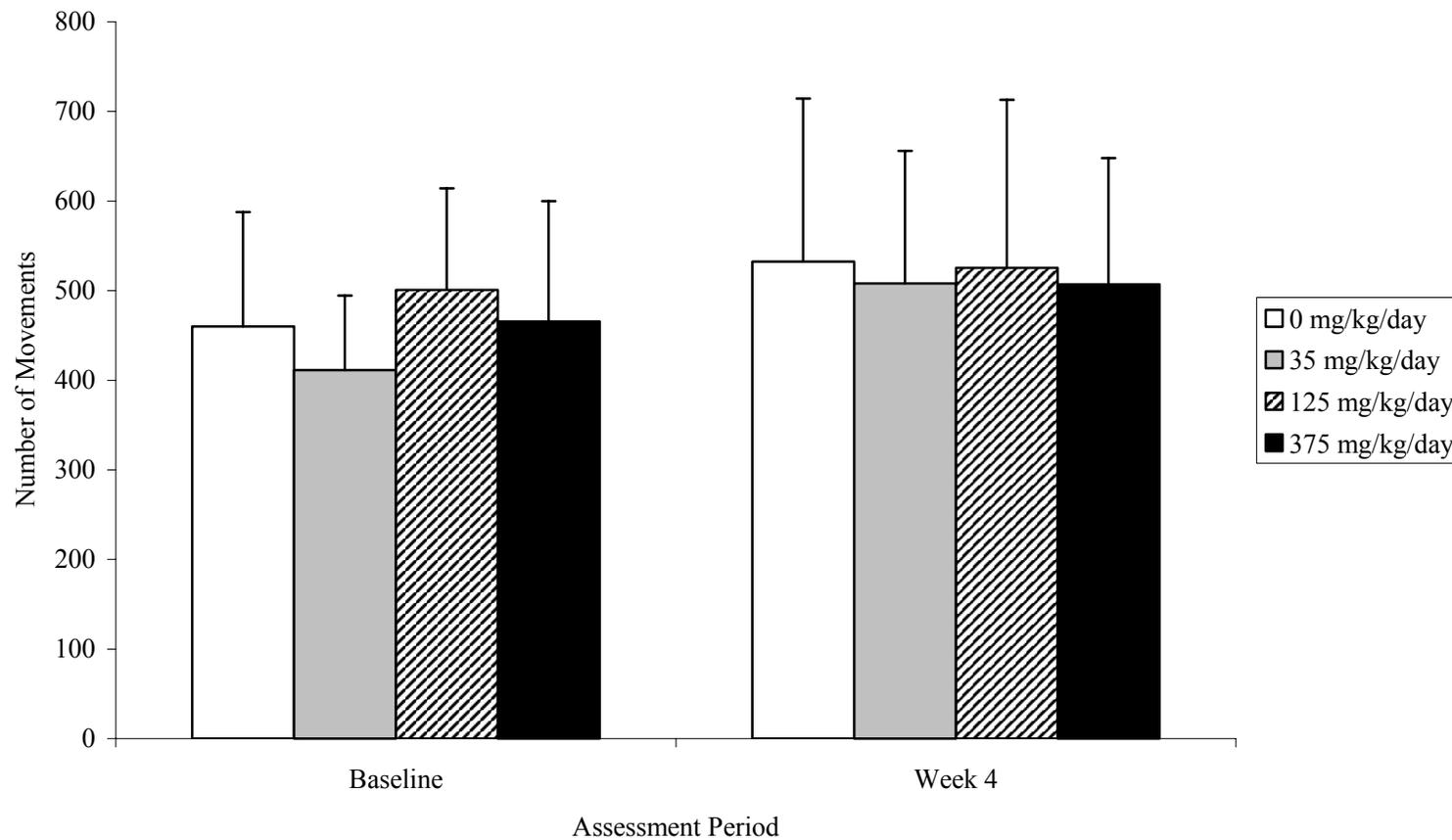
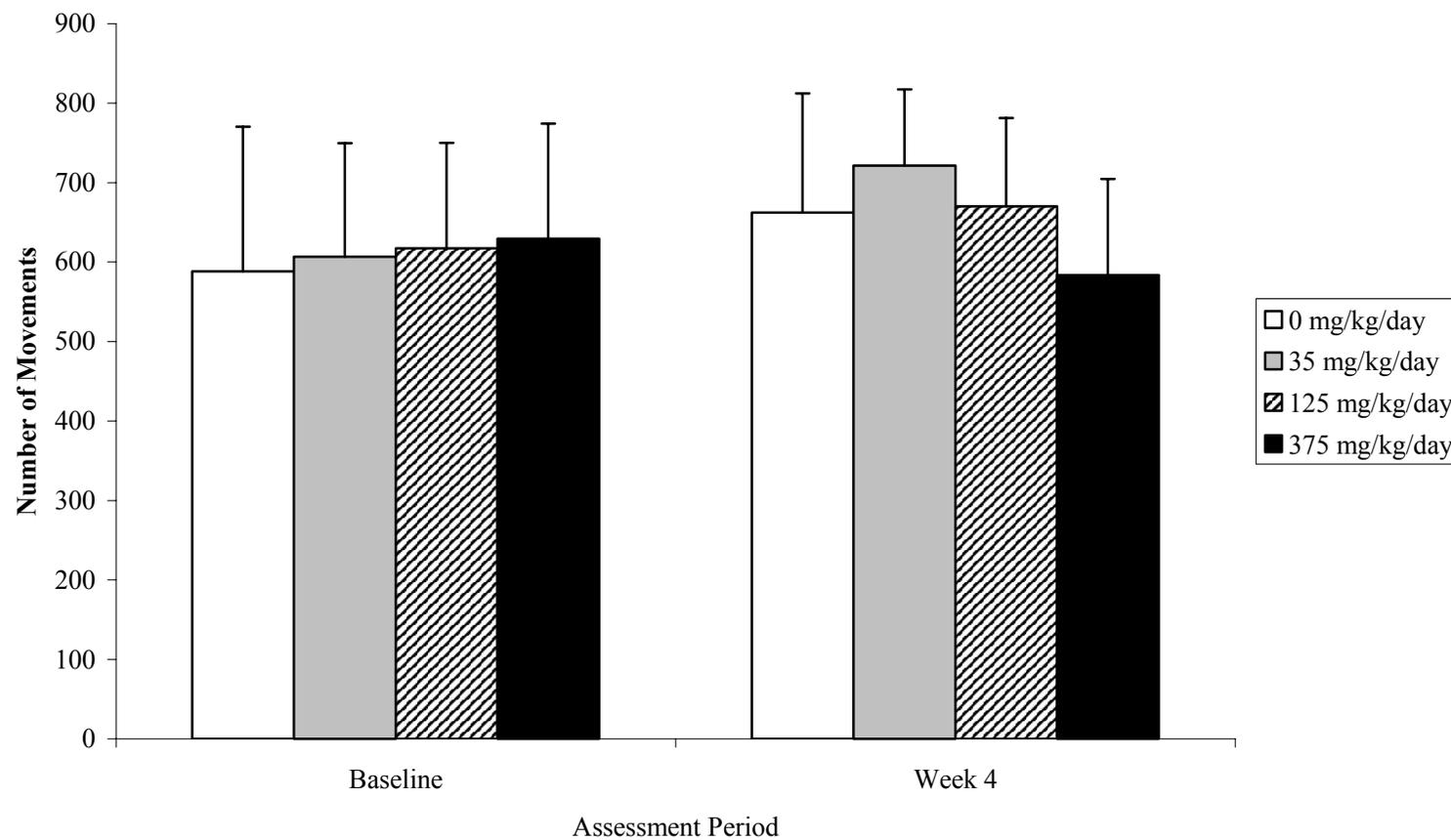


FIGURE 10

MEAN TOTAL NUMBER OF MOVEMENTS FOR FEMALE RATS



**APPENDICES**

**APPENDIX A**  
**Protocol and Protocol Amendments**

DuPont-13041

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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

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## 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 pre-mating (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.<sup>(1,2)</sup> 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)<sup>(3)</sup> and the EPA Health Effects Guideline OPPTS 870.3650 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test.<sup>(4)</sup> 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

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STUDY DESIGN

Treatment Groups and Dose Levels

Main Subchronic <sup>a</sup>				Satellite <sup>b</sup>		Dosage
Group Male <sup>a</sup>	Number of Males	Group Female <sup>a</sup>	Number of Females	Group Females <sup>b</sup>	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
<b>Clinical Observations</b> <ul style="list-style-type: none"> <li>• Predosing Observations (Main and Satellite)<sup>a</sup></li> <li>• Mortality/Moribundity Checks (Main and Satellite)<sup>b</sup></li> <li>• Detailed Clinical Observations (Main)<sup>c</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Daily prior to dosing</li> <li>• Twice daily (a.m. and p.m.)</li> <li>• Pretest, and Days 8, 15, 22, and 29</li> </ul>
<b>Body Weights</b>	<ul style="list-style-type: none"> <li>• Study Days 1, 8, 15, 22, and 29 and at scheduled sacrifice (Main)</li> <li>• Days 1, 8, and 15 – Premating (Satellite)</li> <li>• Weekly – Mating (Satellite)</li> <li>• Daily - Gestation (Satellite)</li> <li>• Days 0 and 4 - Lactation (Satellite)</li> </ul>
<b>Food Consumption</b>	<ul style="list-style-type: none"> <li>• Study Days 1, 8, 15, 22 and 29 (Main) Food consumption will be discontinued for males upon cohabitation</li> <li>• Days 1, 8, and 15 – Premating (Satellite)</li> <li>• Days 0, 7, 14, and 21 - Gestation (Satellite)</li> <li>• Days 0 and 4 - Lactation (Satellite)</li> </ul>
<b>Functional Observational Battery (Main)</b>	Pretest and Study Day 29-30
<b>Motor Activity (Main)</b>	Pretest and Study Day 29-30
<b>Clinical Pathology (Main)</b>	Study Day 30-31
<b>Necropsy</b> <ul style="list-style-type: none"> <li>• Main Males</li> <li>• Main Females</li> <li>• Pregnant Satellite Rats</li> <li>• Satellite Rats that did not deliver a litter</li> <li>• Pups</li> <li>• Satellite Rats with no Evidence of Mating</li> </ul>	<b>Sacrifice Schedule</b> <ul style="list-style-type: none"> <li>• Study Day 30</li> <li>• Study Day 31</li> <li>• Lactation Day 4</li> <li>• Gestation Day 27 (approximately)</li> <li>• Lactation Day 4</li> <li>• Study Day 43 (approximately)</li> </ul>

- 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.

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.

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.

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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) CrI:CD<sup>®</sup>(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 CrI:CD<sup>®</sup>(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<sup>®</sup>) 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  $22^{\circ} \pm 3^{\circ}\text{C}$  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.

3. Feed and Water

All rats will be provided tap water (United Water Delaware) ad libitum. They will be fed PMI<sup>®</sup> Nutrition International, LLC Certified Rodent LabDiet<sup>®</sup> 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.

- 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  $\pm 20\%$  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 pre-mating 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 pre-mating period (approximately 2 weeks), during the mating period until evidence of copulation is observed, and

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

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

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

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

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

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.

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 euthanized 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.

<u>Digestive System<sup>a</sup></u>	<u>Hematopoietic System</u>	<u>Reproductive System</u>
liver	spleen	Male
esophagus	thymus	testes
stomach	mediastinal lymph node	epididymides
duodenum	mandibular lymph node	prostate
jejunum	mesenteric lymph node	seminal vesicles
ileum	bone marrow <sup>b</sup>	coagulating glands
cecum		Female <sup>c</sup>
colon	<u>Endocrine System</u>	ovaries (with oviducts)
rectum	pituitary gland	cervix
tongue	parathyroid gland	uterus
pancreas	thyroid gland	vagina
	adrenal glands	
<u>Urinary System</u>	<u>Nervous System</u>	<u>Integumentary System</u>
kidneys	brain (3 sections)	skin
urinary bladder	spinal cord (3 levels)	salivary glands
	eyes (with optic nerve)	lacrimal glands
<u>Respiratory System</u>	sciatic nerve	mammary gland (females only)
lungs		
trachea	<u>Musculoskeletal System</u>	<u>Miscellaneous</u>
nose	femur/knee joint	gross observations <sup>d</sup>
pharynx/larynx	stemum	
<u>Cardiovascular System</u>	skeletal muscle	
heart		
aorta		

a Peyer's patches will be collected from sections of the digestive tract.

b Bone marrow will be collected with the femur and stemum.

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<sub>1</sub> adults.

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

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.

Statistical Methods

Parameter	Method of Statistical Analysis								
	Preliminary Test	If preliminary test is not significant	If preliminary test is significant						
Body Weight	Test for lack of trend <sup>(5)</sup>	Sequential application <sup>(6)</sup> of the Jonckheere-Terpstra trend test <sup>(7)</sup>	Preliminary tests for pairwise comparison						
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	Levene's test for homogeneity <sup>(8)</sup> and Shapiro-Wilk test <sup>(9)</sup> for normality <sup>b</sup>	One-way analysis of variance <sup>(10)</sup> and Dunnett's test <sup>(11,12,13)</sup>	Kruskal-Wallis test <sup>(14)</sup> and Dunn's test <sup>(15)</sup>						
Sex Ratio									
0-4 Day Viability									
Number of <i>Corpora Lutea</i>									
Organ Weight									
Incidence of Clinical Observations									
Incidence of Descriptive Functional Observational Battery Parameters									
Mating Index									
Fertility Index									
Gestation Index									
Grip Strength	None	Cochran-Armitage test for trend <sup>(16)</sup>							
Foot Splay									
Body Temperature									
Rearing									
Motor Activity <sup>d</sup>				Bartlett's test <sup>(16)</sup> for homogeneity of variances	One-way analysis of variance <sup>(10)</sup> and Dunnett's test <sup>(11,12,13)</sup>	Kruskal-Wallis test <sup>(14)</sup> and Dunn's test <sup>(15)</sup>			
Clinical Pathology <sup>e</sup>									
Mean Pup Weights (Covariates: litter size, sex ratio)									
Incidence of Microscopic Lesions									
							Levene's test for homogeneity <sup>(8)</sup> and Shapiro-Wilk test <sup>(9)</sup> for normality <sup>b</sup>	Repeated measures analysis of variance followed by contrasts <sup>(17)</sup>	Sequential application <sup>(6)</sup> of the Jonckheere-Terpstra trend test <sup>(7)</sup>
	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<sup>(19)</sup> 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.

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.<sup>(6)</sup> For litter parameters, the proportion of affected fetuses per litter or the litter mean will be used as the experimental unit for statistical evaluation.<sup>(20)</sup> 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<sup>(7)</sup> is not applicable, exact  $p$  values will be calculated using permutation methodology.<sup>(21)</sup>

#### SPECIAL SAFETY AND HANDLING PROCEDURES

The test substance will be dispensed, mixed, and sampled in a chemical fume hood. Laboratory personnel will wear Rascal 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

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LACRIMATION:	0 = none 1 = slight 2 = severe
SALIVATION:	0 = none 1 = slight (wet chin) 2 = severe (active salivation, drooling)
EXOPHTHALMUS:	1 = present 0 = absent
<b><u>OPEN FIELD ARENA (IN FREE ROAMING SPACE)</u></b>	
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- nipping 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 (light 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

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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)

PROTOCOL APPENDIX B

STUDY FUNCTIONS AND STUDY PERSONNEL

<u>Study Function</u>	<u>Study Personnel</u>
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

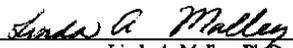
Study Dates

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

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SIGNATURES

Approved by:  02-Sept-03  
Linda A. Malley, Ph.D., D.A.B.T. Date  
Study Director  
Developmental, Reproductive, and Neurobehavioral Toxicology  
DuPont Haskell Laboratory

 11-Sept-03  
Elizabeth Moran, Ph.D. Date  
Sponsor Representative

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. Mukeji L.J. Lewis R.L. Poore  
J.C. Maslanka S.R. Frame S.C. Craven  
D.A. Vick

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Low Dicyclopentadiene Resin Oil: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats  
 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<sub>1</sub> 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 (%) <sup>c</sup>	=	$\frac{\text{Number of Pups Born}}{\text{Number of Implantation Sites}}$	x 100
Pups Born Alive (%) <sup>e</sup>	=	$\frac{\text{Number of Pups Born Alive}}{\text{Number of Pups Born}}$	x 100
Viability Index (%) <sup>c,d</sup>	=	$\frac{\text{Number of Pups Alive Day 4 Preculling}}{\text{Number of pups born alive}}$	x 100
Preimplantation Loss <sup>o</sup>	=	$\frac{\text{Number of corpora lutea} - \text{Number of implantation sites}}{\text{Number of corpora lutea}}$	
Postimplantation Loss <sup>o</sup>	=	$\frac{\text{Number of implantation sites} - \text{Number of pups}}{\text{Number of implantation sites}}$	

- 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.

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

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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 pre-mating (satellite females), test days 0-21 of gestation (satellite females), and test days 0-4 of lactation (satellite females).

3. Statistical Methods

Parameter	Preliminary Test	Method of Statistical Analysis	
		If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Gestation Length Implantation Site Numbers Implantation Efficiency Mean Number of Pups per Litter Percent Born Alive	Test for lack of trend	Sequential application of the Jonckheere-Terpstra trend test	Preliminary tests for pairwise comparison
0-4 Day Viability Viability Index Number of <i>Corpora Lutea</i> Sex Ratio Pre-implantation Loss Post-implantation Loss Organ Weights	Levene's test for homogeneity and Shapiro-Wilk test for normality <sup>b</sup>	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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Parameter	Preliminary Test	Method of Statistical Analysis	
		If preliminary test is not significant	If preliminary test is significant
Clinical Pathology <sup>d</sup>	Levene's test for homogeneity and Shapiro-Wilk test for normality <sup>b</sup>	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
<p>a Pairwise comparisons and associated preliminary tests were only conducted if the test for lack of trend was significant.</p> <p>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.</p> <p>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.</p> <p>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 &lt;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 &gt;1.083, 1.083 was used for any calculations performed with that data.</p>			

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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PROTOCOL AMENDMENT 1 (Continued)

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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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 19-Feb-04  
Linda A. Malley, Ph.D. Date  
Study Director  
Developmental, Reproductive, and Neurobehavioral Toxicology  
DuPont Haskell Laboratory

Elizabeth Moran 3-Mar-04  
Elizabeth Moran, Ph.D. Date  
Sponsor Representative

**APPENDIX B**  
**Test Substance Characterization**

## APPENDIX B

### Supplemental information for the Test Substance characterization.

Analytical method provided by the sponsor. Inserted as received from the sponsor (17 pages).

Table 1. Composition of Low DCPD Resin Oil Test Substance (H# 25429, inserted as received from the sponsor).

Figure 1. Chromatogram of Low DCPD Resin Oil Test Substance (H# 25429, inserted as received from the sponsor, 3 pages).

Analytical method developed at Haskell Laboratory.

Figure 2. Representative chromatogram of Low DCPD Resin Oil Test Substance (H# 25429) analyzed at Haskell Laboratory.

Table 2. Composition of selected components of Low DCPD Resin Oil test substance.

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

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### 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

#### APPARATUS

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 - 1.0 $\mu$ L size.
3. Nelson Analytical Interface and Associated software.

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**TYPICAL INSTRUMENT PARAMETERS**

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<sup>-11</sup>

b. attenuation 16

c. sample size 0.3µL (2,000,000 area counts)

**REAGENTS**

1. Chromatographic Grade Helium (ALPHAGAZ)

2. Chromatographic Grade Hydrogen (ALPHAGAZ)

3. Chromatographic Grade Air

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**CALIBRATION**

See CHO-LAB-0604 for calibration procedure.

**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.

**CALCULATIONS**

All calculations are handled by Nelson Analytical Software.

**REPORTING**

Log reactives and 2,6 ditertiary butyl 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-indene <sup>4</sup> ) 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**



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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)
RUN TIME (minutes) 1
END TIME FOR PLOTS (default=RUN TIME) 107.00
SOLVENT DELAY TIME (minutes) 107.00
PEAK DETECTION THRESHOLD (microv/sec) 0.00
Area Threshold 0.01
MINIMUM PEAK WIDTH (seconds) 5.00
TIME FOR ONE SAMPLE (seconds) 5.00
NUMBER OF REAL TIME CRT PAGES TO PLOT (0 TO 99) 0.30
REAL TIME PLOT FULL SCALE FOR CH.0 (millivolts) 0.00
REAL TIME FULL SCALE FOR CH.1 (millivolts) 1.00
HARD COPY REAL TIME PLOT 200.00
AUTO ZERO REAL TIME PLOT NO
Pre Version 4 method YE
=====
RECORD AREA TABLES ON DISK NO
RECORD RAW DATA NO
NUMBER OF CRT PAGES FOR REPLOT (1 TO 99) YE
VERTICAL SCALE FACTOR FOR REPLOT (units of largest peak) 0
OFFSET FOR THE REPLOT (millivolts) 1.00
PUT NAMES ON REPLOT? 0.00
=====
AREA PERCENT REPORT YE
EXTERNAL STANDARD REPORT NO
INTERNAL STANDARD REPORT NO
FINAL REPORT AREA REJECT (microvolt-sec) NO
LINK TO USER PROGRAM 0.00
FORCE DROP LINE INTEGRATION YE
FORCE COMMON BASE LINE NO
FULL SCALE RANGE FOR A.D.C. (3=1VOLT, 1=2VOLT, 0=10VOLT) NO
=====
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 1.00
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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Method:Q:AY010

```

=====
No.      Component      Ret      Tol      Fit      Resp      RF
      Name      Time      Type      Fact      #
=====
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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Method: Q:AY010

Event#	Time	Event	Event Explanations
1	24.50	EPD-	1 to 8 (C/O) relay (Close/Open)
2	25.05	EPD+	AT (D/H) Area Threshold (Double/Halve)
3	57.28	EPD-	FBA Force Baseline at All peak starts
4	58.79	EPD+	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 (on/off)
			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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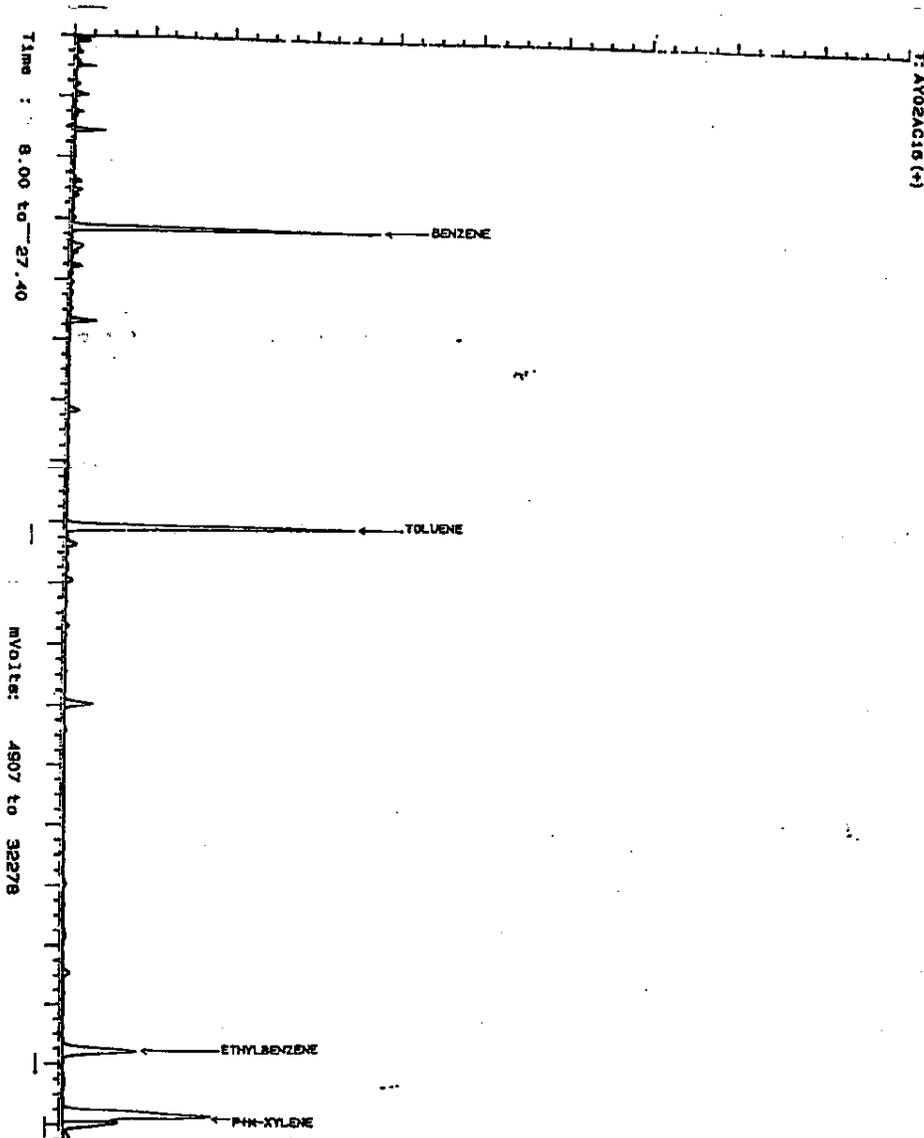
DOCUMENT NUMBER <b>CHO-LYON-5852</b>	REVISION NUMBER <b>4</b>
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**ATTACHMENT II  
GC CHROMATOGRAM**

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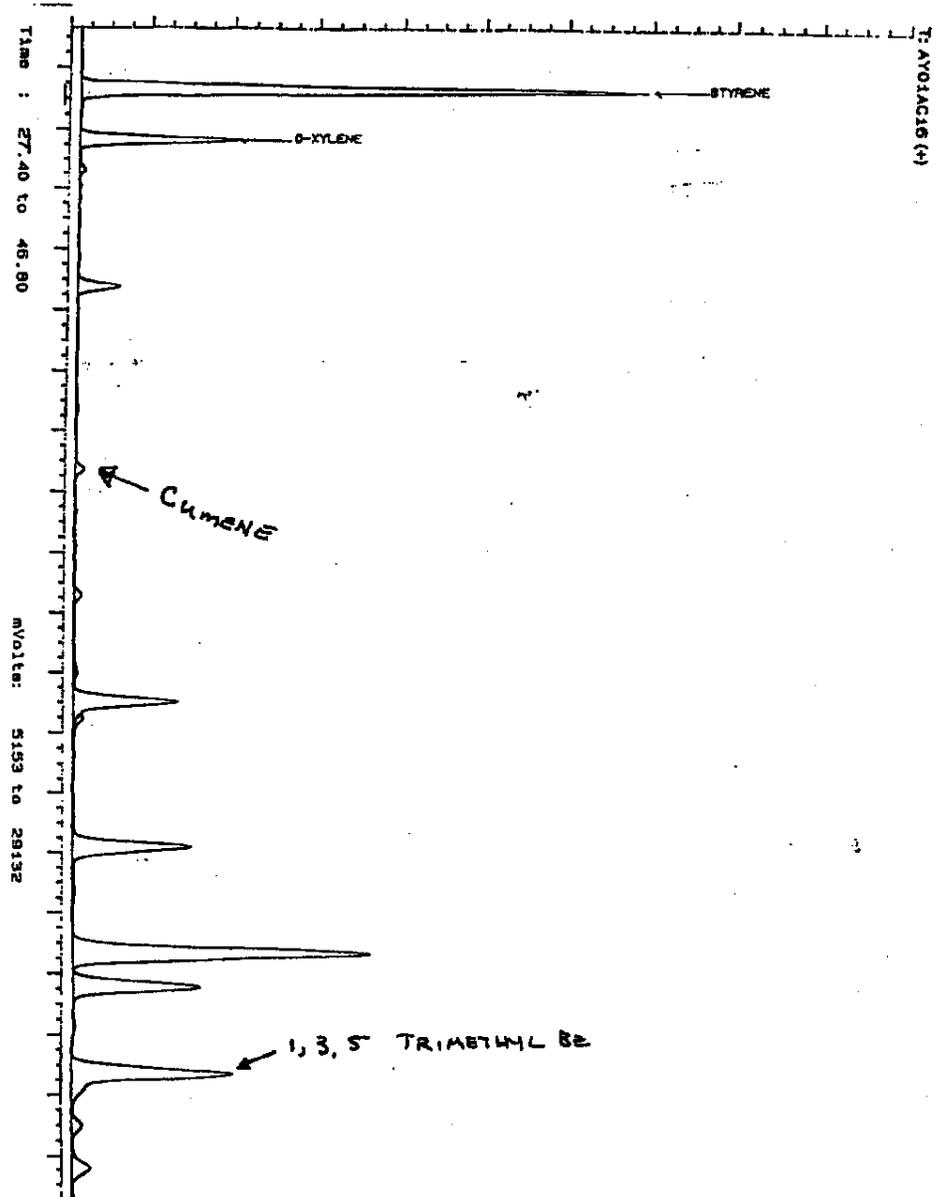
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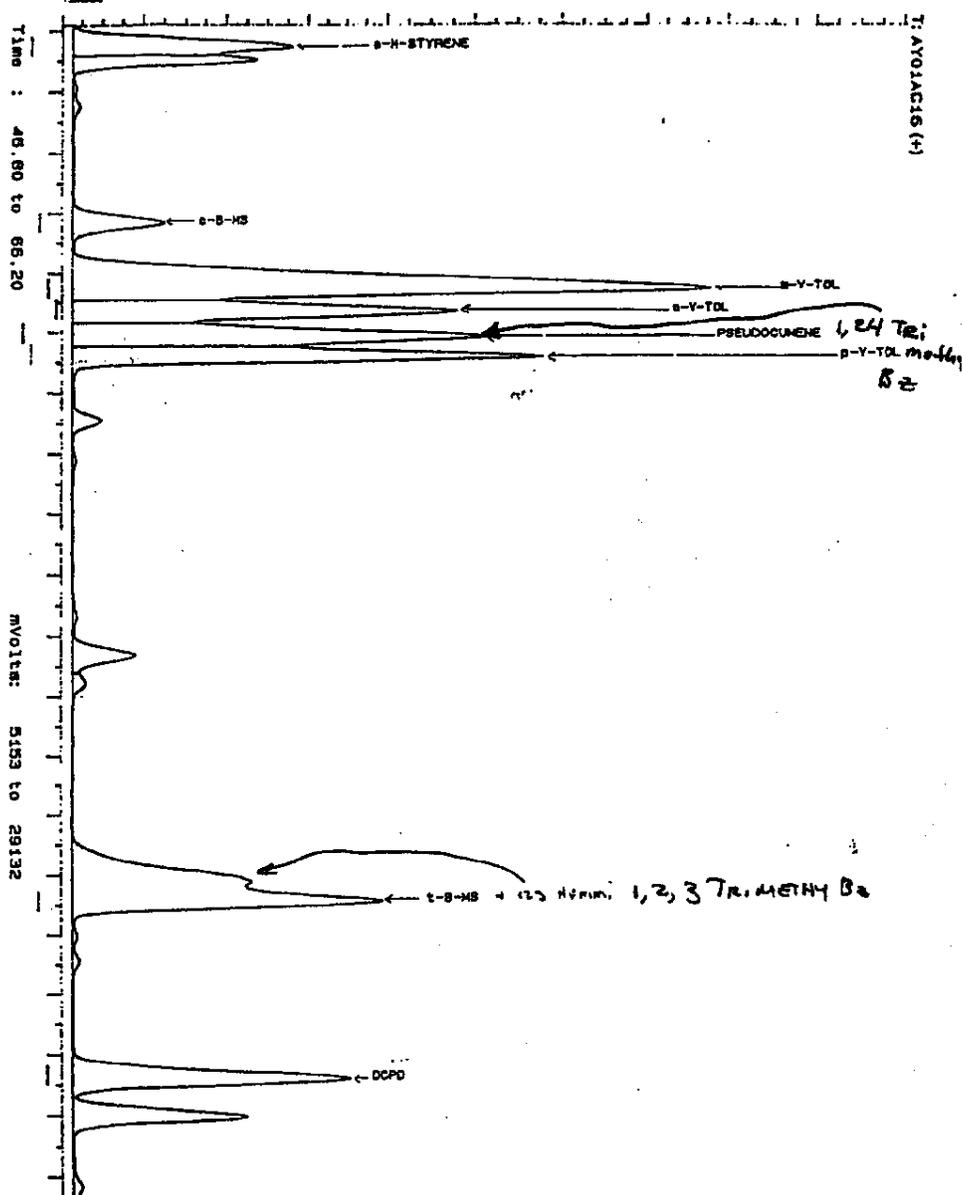
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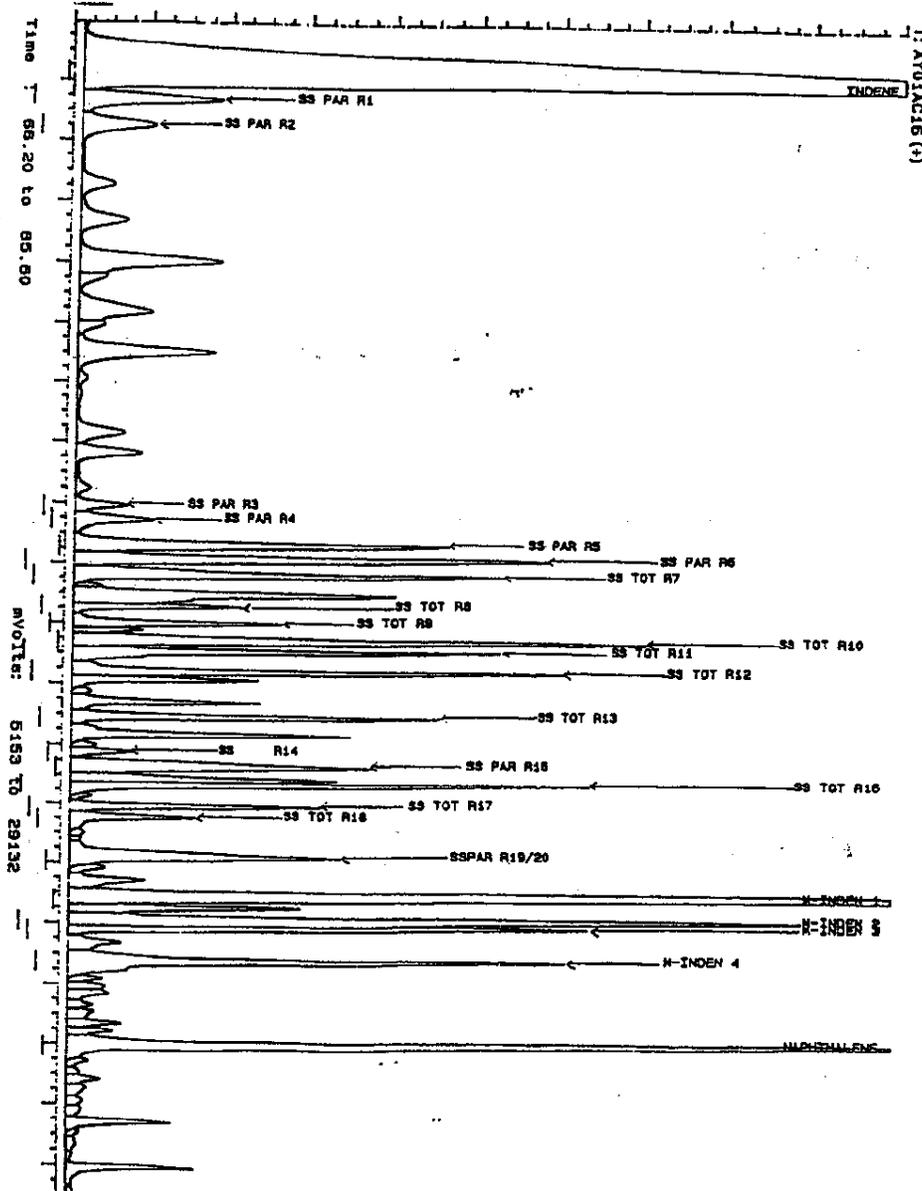
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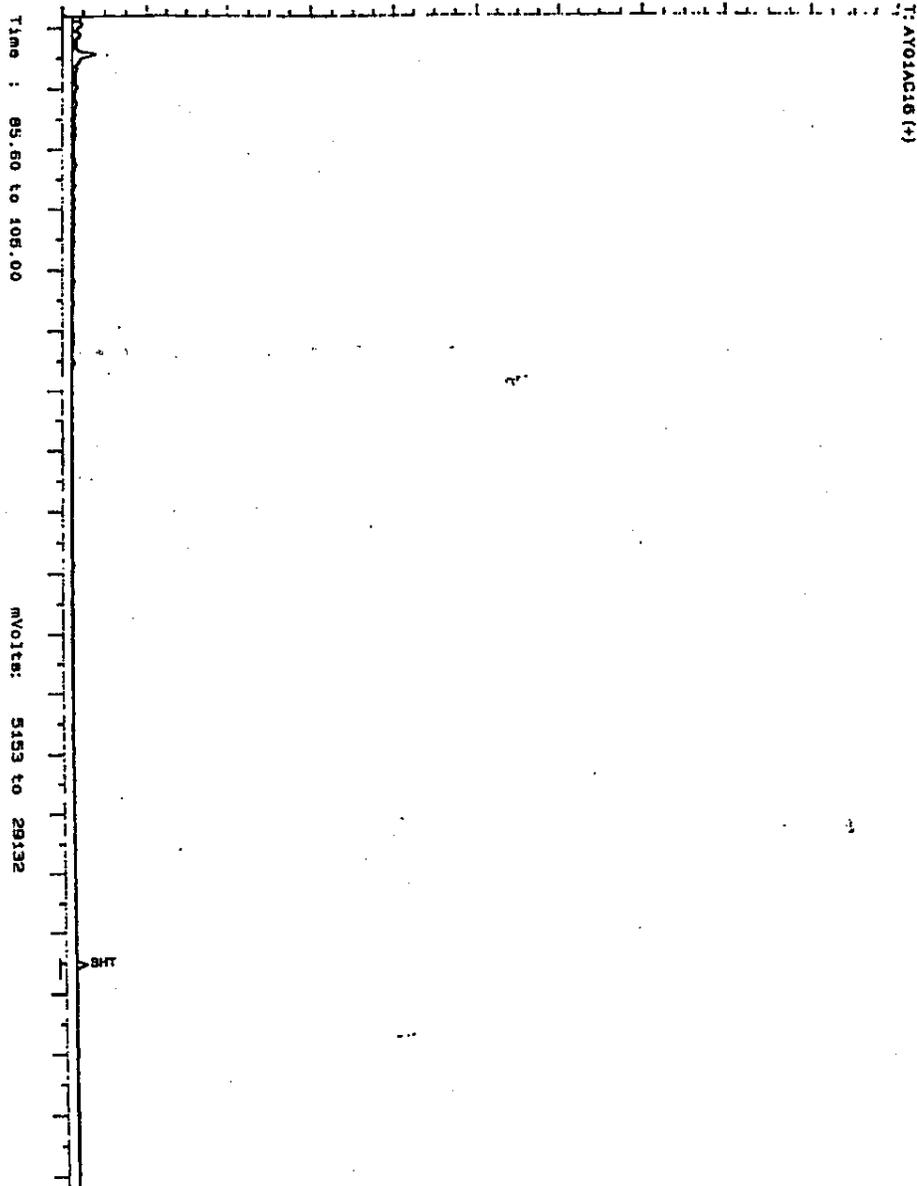
DOCUMENT NUMBER <b>CHO-LYON-5852</b>	REVISION NUMBER <b>4</b>
PAGE 15 OF 17	REVISION DATE <b>JUNE 1993</b>

**ATTACHMENT III  
PRECISION DATA**

**IF LOGO IS NOT IN COLOR, THIS IS NOT A CONTROLLED DOCUMENT.**



DOCUMENT NUMBER <b>CHO-LYON-5852</b>	REVISION NUMBER <b>4</b>
PAGE 18 OF 17	REVISION DATE <b>JUNE 1993</b>



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DOCUMENT NUMBER <b>CHO-LYON-5852</b>	REVISION NUMBER <b>4</b>
PAGE 17 OF 17	REVISION DATE <b>JUNE 1993</b>

Component	Styrene	Indene	Naphthalene	Total Reactives
	3.98	13.29	4.74	66.43
	3.93	13.11	4.71	66.41
	4.26	13.08	4.87	66.32
	3.98	13.16	4.71	66.31
	3.98	13.11	4.68	66.35
	4.06	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
	3.99	13.19	4.72	66.49
	3.94	13.10	4.79	66.47
	3.94	13.14	4.79	66.43
	3.77	12.93	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

IF LOGO IS NOT IN COLOR, THIS IS NOT A CONTROLLED DOCUMENT.

**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).

<b>Low DCPD Resin Oil HPV SAMPLE</b>	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 Cyclo diene Dimer Concentrates Category. The test substance was sent on about February 10, 2003, to the EMBSI and Haskell Labs (received on February 27, 2003).

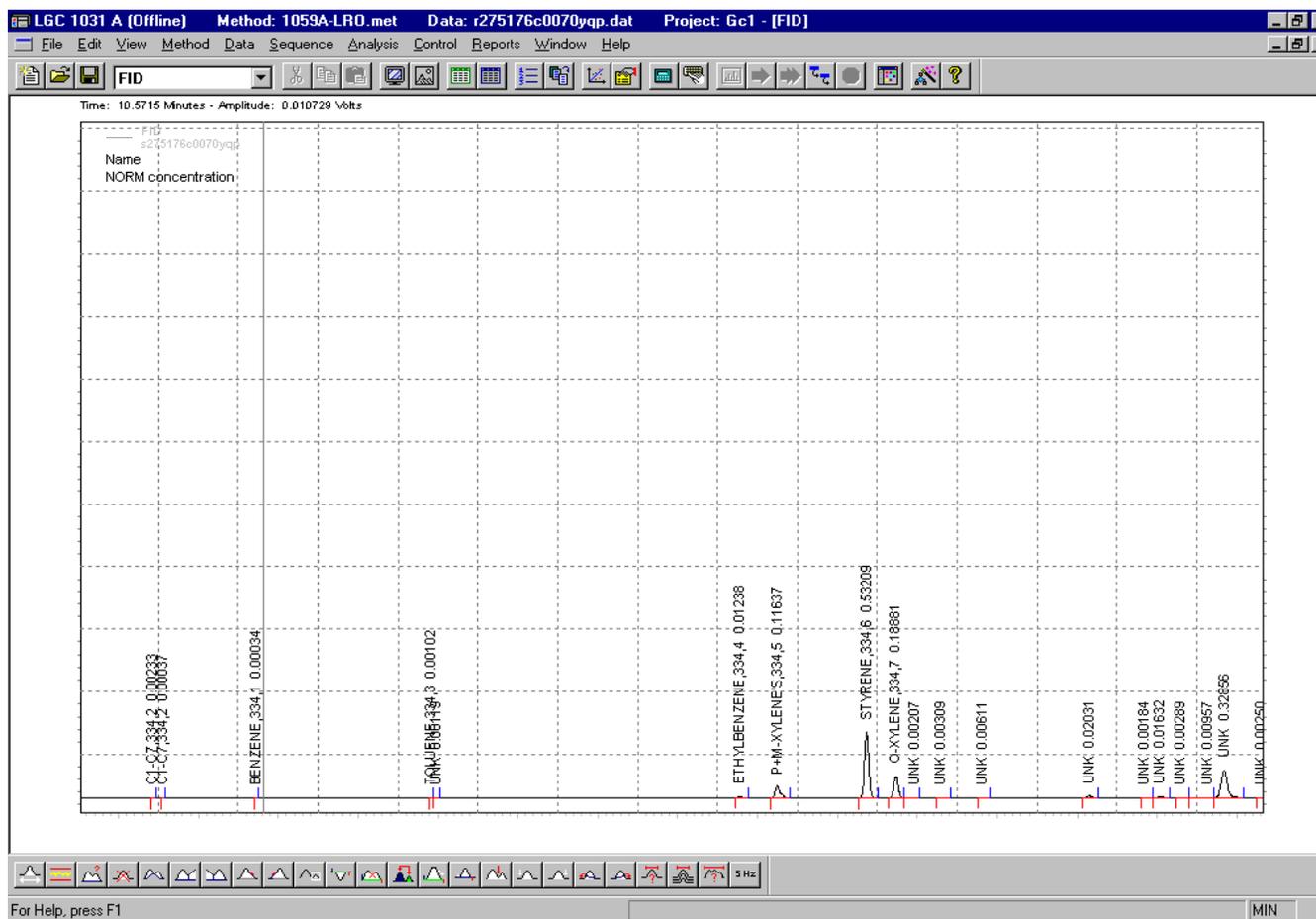
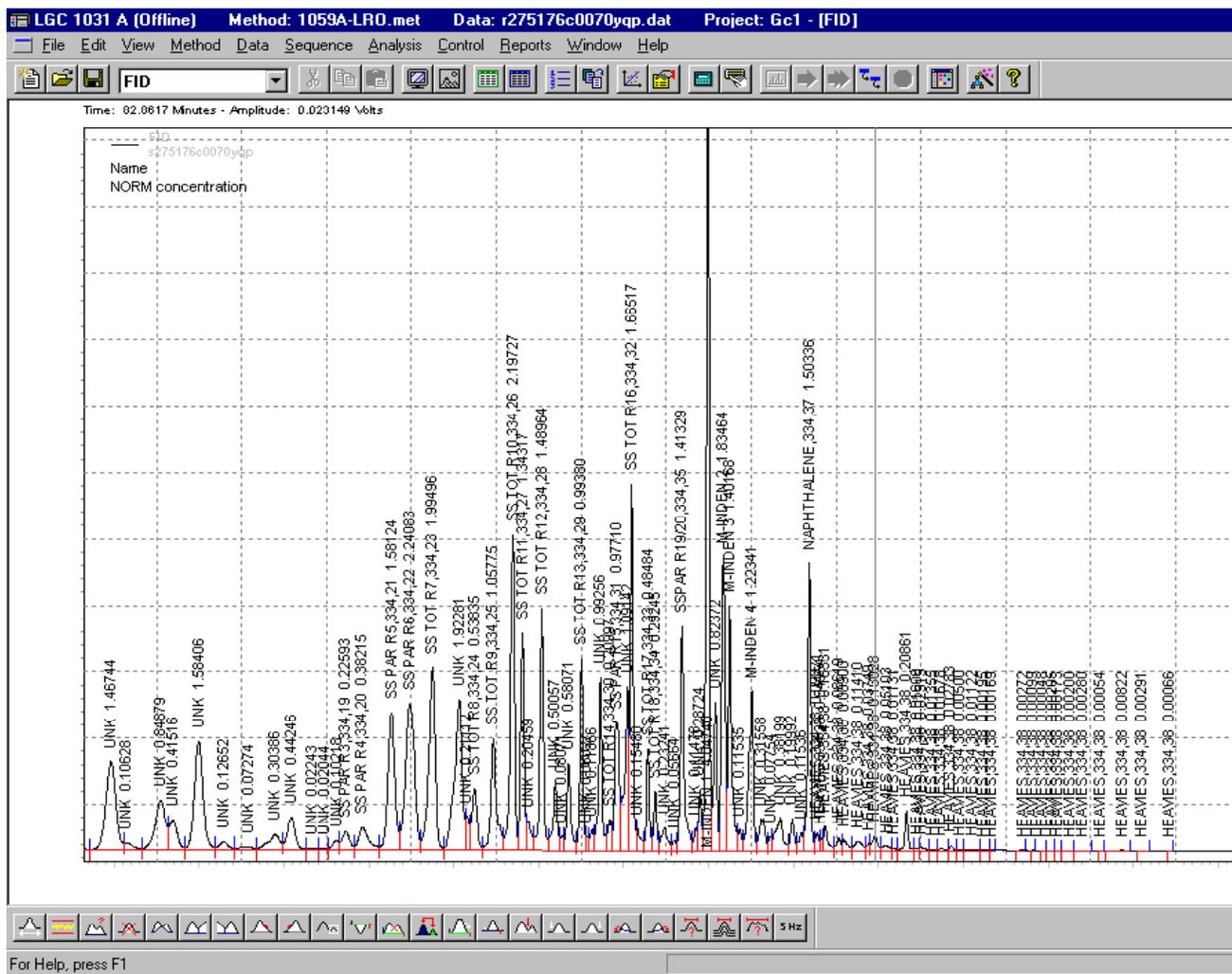




Figure 1 (continued)



**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 $\mu$ m 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 $\mu$ L
Injection Volume:	0.1 $\mu$ L
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).

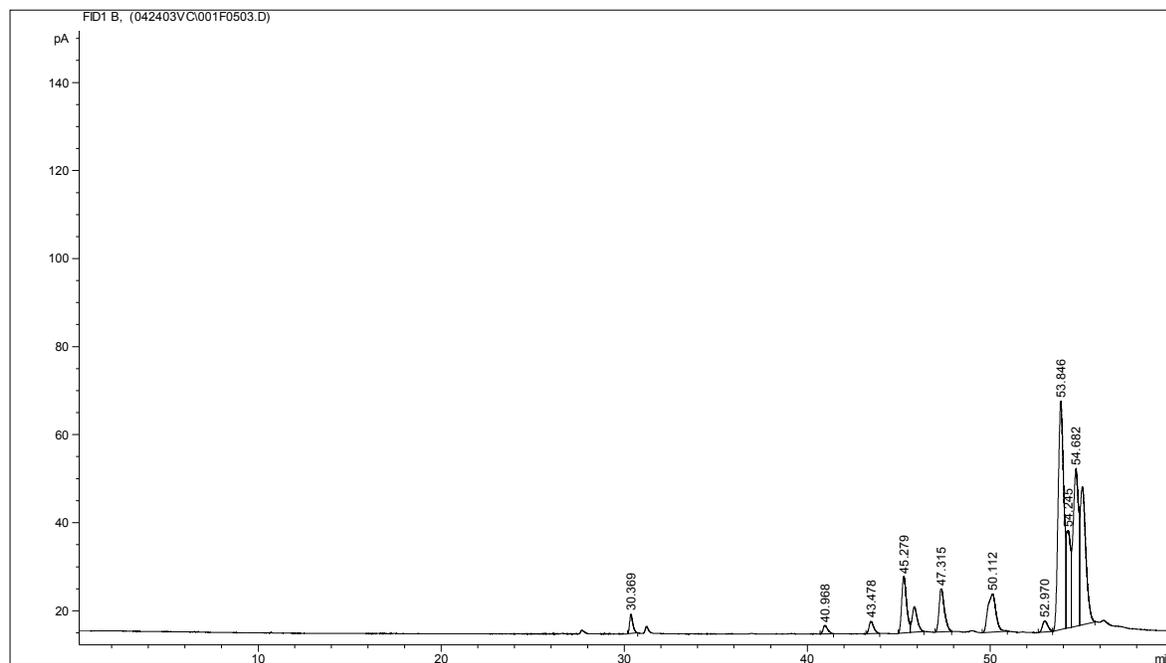
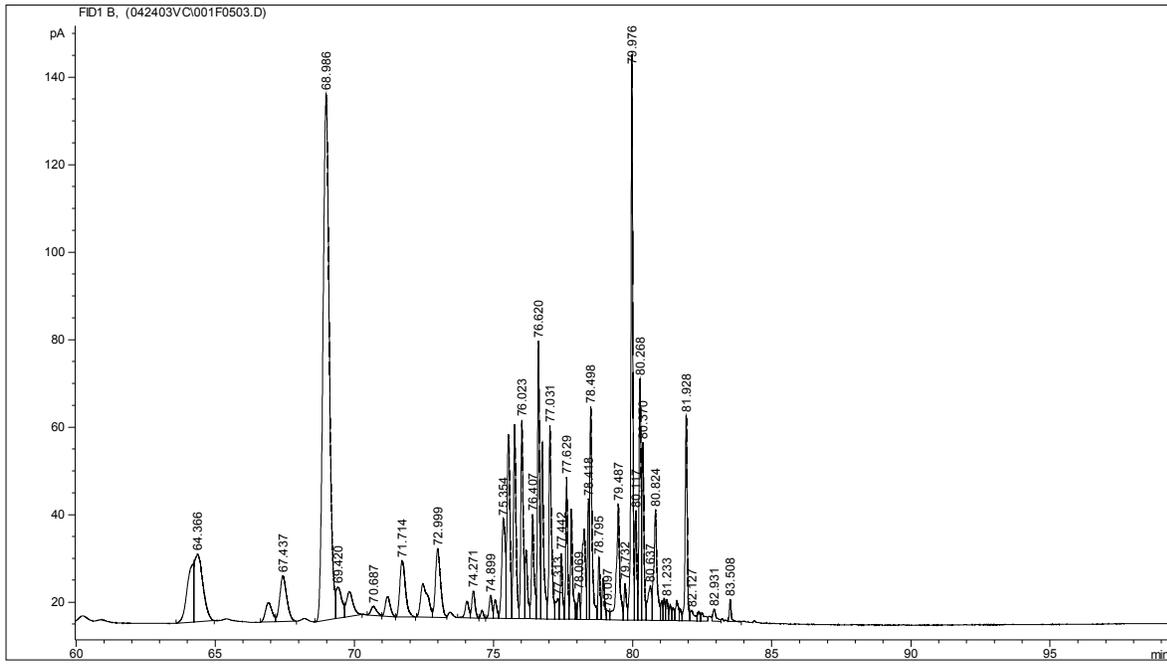


Figure 2 (continued)



**Table 2**

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

Retention Time (min)	Component Name <sup>a</sup>	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

<sup>a</sup> 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
	Nominal	Measured	
RECOVERY <sup>(A)</sup>	14.4	15.3	106.3
RECOVERY <sup>(B)</sup>	14.5	16.0	110.3
RECOVERY <sup>(D)</sup>	14.5	14.4 <sup>(C)</sup>	99.3
		<b>Mean</b>	<b>105.3 ± 5.6,</b> <b>C.V. 5%</b>
RECOVERY <sup>(A)</sup>	52.2	56.6	108.4
RECOVERY <sup>(B)</sup>	52.8	54.4 <sup>(C)</sup>	103.0
RECOVERY <sup>(D)</sup>	54.4	51.3 <sup>(C)</sup>	94.3
		<b>Mean</b>	<b>101.9 ± 7.1,</b> <b>C.V. 7%</b>
RECOVERY <sup>(A)</sup>	188.9	203	107.5
RECOVERY <sup>(B)</sup>	189.6	172	90.7
RECOVERY <sup>(D)</sup>	188.5	175 <sup>(E)</sup>	92.8
		<b>Mean</b>	<b>97.0 ± 9.2,</b> <b>C.V. 9%</b>

- (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			
<b>Homogeneity</b>			
CONTROL	0.00	ND(A)	----
TOP	17.5	18.1	103.4
MIDDLE	17.5	17.6	100.6
BOTTOM	17.5	<u>18.8</u>	107.4
		<b>Mean(B): 18.2 ± 0.60</b>	<b>(104.0%)</b>
		<b>C.V. 3%</b>	
TOP	62.5	68.6	109.8
MIDDLE	62.5	68.9	110.2
BOTTOM	62.5	<u>65.8</u>	105.3
		<b>Mean(B): 67.8 ± 1.7</b>	<b>(108.5%)</b>
		<b>C.V. 3%</b>	
TOP	187.5	215	114.7
MIDDLE	187.5	203	108.3
BOTTOM	187.5	<u>210</u>	112.0
		<b>Mean(B): 209 ± 6.0</b>	<b>(111.5%)</b>
		<b>C.V. 3%</b>	
<b>Stability(C)</b>			
	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		Percent
	Nominal	Measured	Nominal
<u>1-Oct-2003</u>			
<u>Concentration Verification</u>			
CONTROL	0.00	ND(A)	----
#1	17.5	17.9	102.3
#2	17.5	<u>19.2</u>	109.7
		<b>Mean(B): 18.6 ± 0.92</b>	<b>(106.3%)</b>
		<b>C.V. 5%</b>	
#1	62.5	61.3	98.1
#2	62.5	<u>66.0(C)</u>	105.6
		<b>Mean(D): 63.7 ± 3.3</b>	<b>(101.9%)</b>
		<b>C.V. 5%</b>	
#1	187.5	214(C)	114.1
#2	187.5	<u>182</u>	97.1
		<b>Mean(D): 198 ± 23</b>	<b>(105.6%)</b>
		<b>C.V. 11%</b>	
<u>15-Oct-2003</u>			
<u>Concentration Verification</u>			
CONTROL	0.00	ND(A)	----
#1	17.5	20.3	116.0
#2	17.5	<u>19.1</u>	109.1
		<b>Mean(B): 19.7 ± 0.84</b>	<b>(112.6%)</b>
		<b>C.V. 4%</b>	
#1	62.5	55.1	88.2
#2	62.5	<u>56.7</u>	90.7
		<b>Mean(B): 55.9 ± 1.1</b>	<b>(89.4%)</b>
		<b>C.V. 2%</b>	
#1	187.5	170(E)	90.7
#2	187.5	<u>162</u>	86.4
		<b>Mean(D): 166 ± 5.7</b>	<b>(88.5%)</b>
		<b>C.V. 3%</b>	

(A) Denotes not detected.

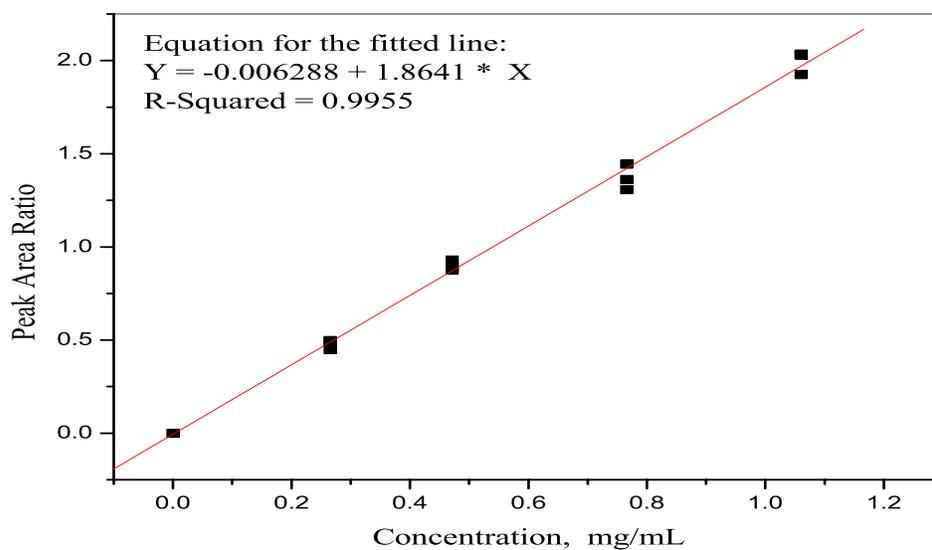
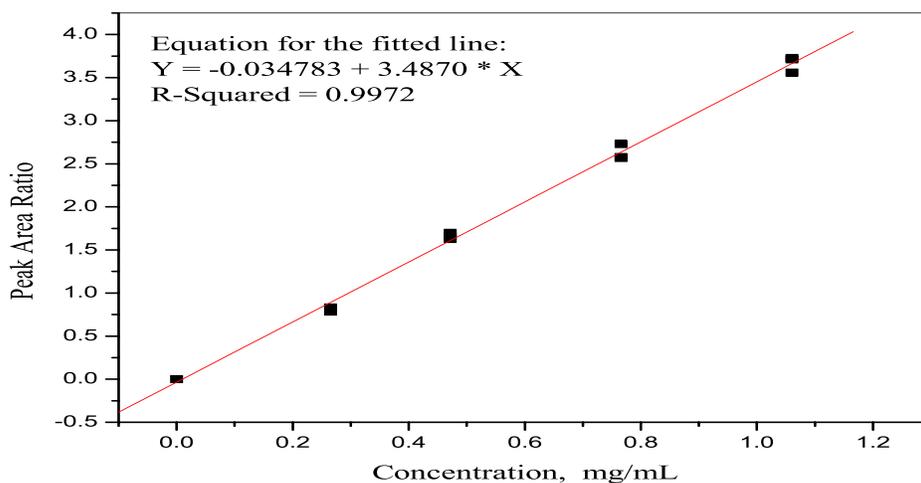
(B) The average measured concentration, average percent of nominal (in parentheses and based on averaged measured), standard deviation, and coefficient of variation of duplicate samples.

(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.

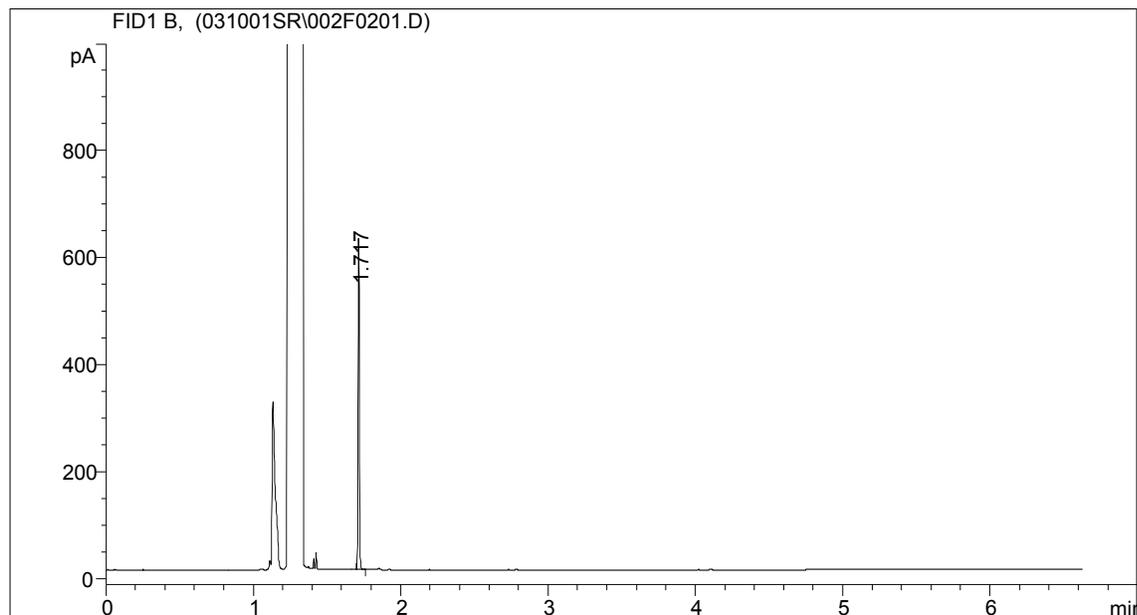
(E) The average measured concentration, average percent of nominal of the original analysis and duplicate reanalysis of the original sample.

**Figure 1**  
**Representative Analytical Calibration Curve**

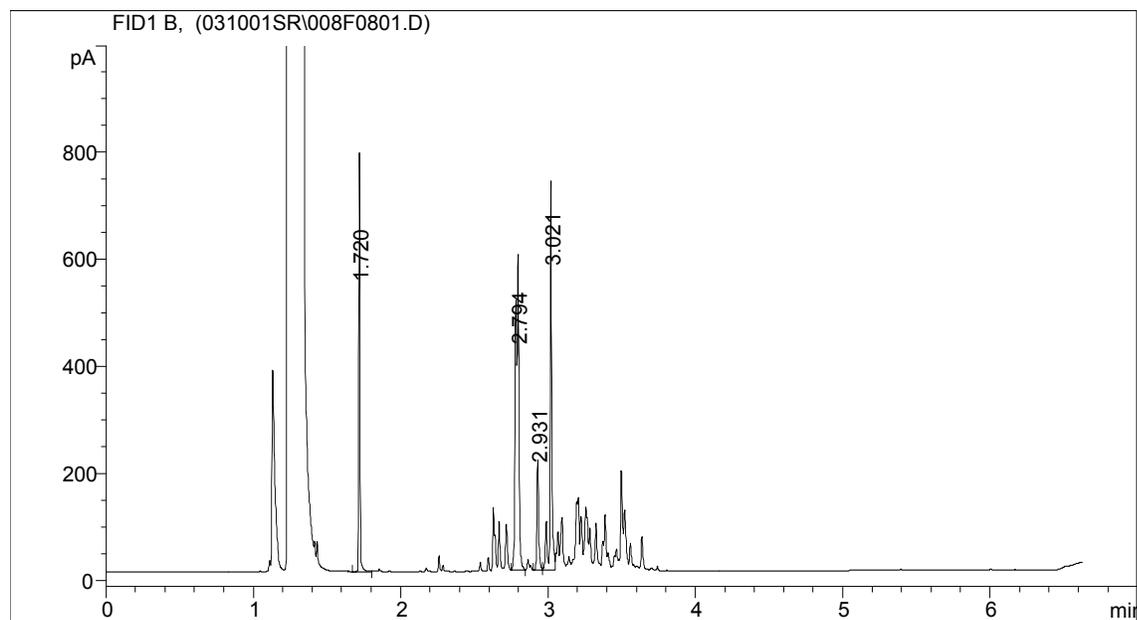


**Figure 1:** Calibration curve showing linear fit (line) to replicate peak height ratio (squares) for calibration solutions of Low DCPD Resin Oil diluted over a concentration range of 0.2651 to 1.0602 mg/mL based on peak areas ratio at (a) 1<sup>st</sup> peak (2.5 or 2.7 minutes) and (b) 2<sup>nd</sup> peak. (2.7 or 3.0 minutes).

**Figure 2**  
**Representative Gas Chromatography Chromatograms**

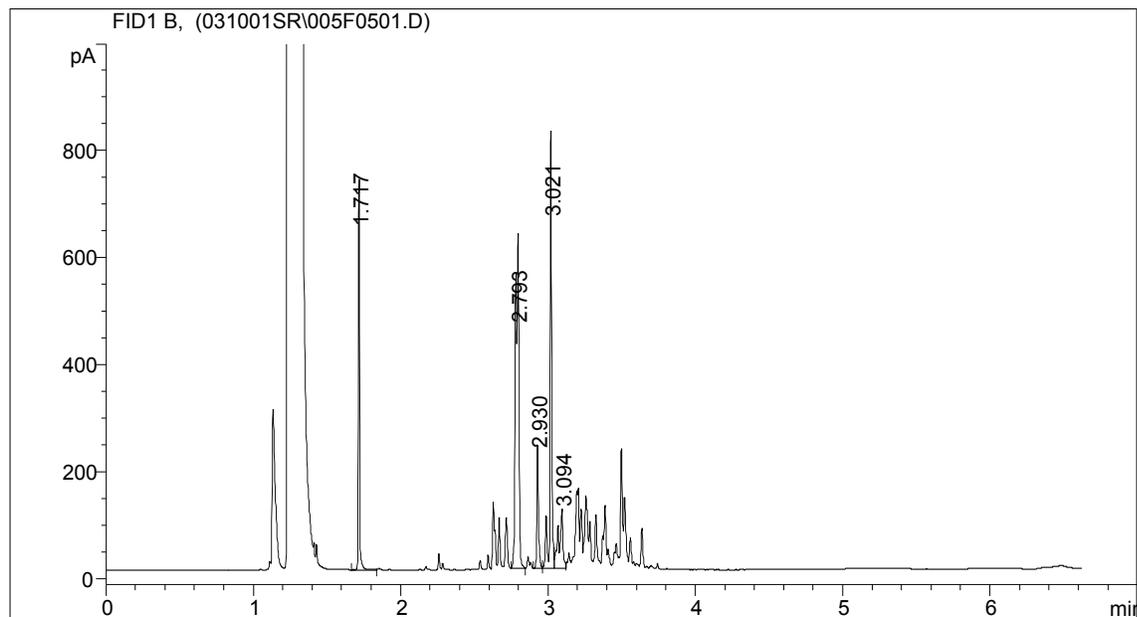


**Figure 2a:** Representative GC chromatogram of the 0 mg/mL (control) sample. Retention time for the 2 peaks used for the Low DCPD Resin Oil are approximately 2.7 minutes and 3.0 minutes. The internal standard peak retention time is approximately 1.7 minutes.

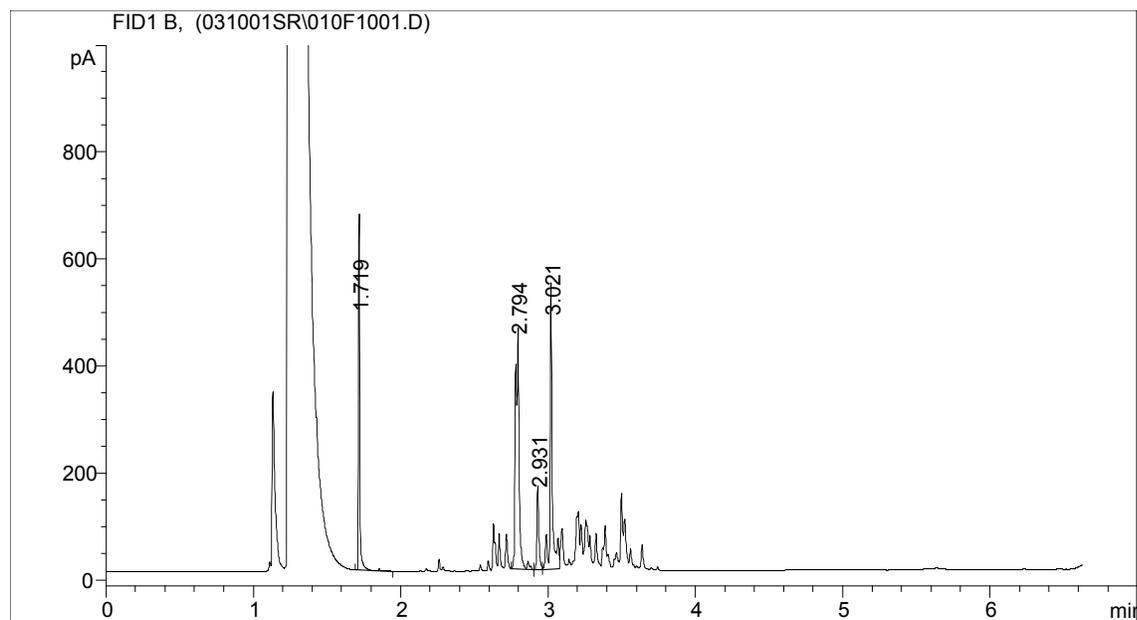


**Figure 2b:** Representative GC chromatogram of 17.5 mg/mL Low DCPD Resin Oil dosing formulation diluted to a nominal concentration of 0.735 mg/mL. The mean measured concentration of the representative solution is 19.7 mg/mL.

**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  $95.2\% \pm 2.6$  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 Date  
Chemistry Associate

Report by: Janet C. Maslanka 3-Nov-2003  
Janet C. Maslanka Date  
Analytical Staff Chemist

Date issued: 3-Nov-2003

Dupont-13355 page 2 of 3

## 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 $\mu$ m 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.

Dupont-13355 page 3 of 3

**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.**

Aliquot	ppm Low DCPD Resin Oil		Percent Nominal
	Targeted	Measured	
1	1090	1070	98.2
2	1120	1055	94.2
3	1110	1035	93.2
<b>Average Percent Nominal</b>			<b>95.2</b>
<b>Standard Deviation</b>			<b>± 2.6</b>
<b>Coefficient of Variation</b>			<b>3%</b>

**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 October 14, 2003, and analyzed October 20, 2003. The percentage of Low DCPD Resin Oil was measured to be  $100.3\% \pm 3.6$  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 Date  
Chemistry Associate

Report by: Janet C. Maslanka 18 Feb 2004  
Janet C. Maslanka Date  
Senior Staff Chemist

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 $\mu$ m 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.

Dupont-13877 page 3 of 3

**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.**

Aliquot	ppm Low DCPD Resin Oil		Percent Nominal
	Targeted	Measured	
1	689	712	103.3
2	700	674	96.3
3	638	646	101.2
<b>Average Percent Nominal</b>			<b>100.3</b>
<b>Standard Deviation</b>			<b>± 3.6</b>
<b>Coefficient of Variation</b>			<b>4%</b>

## **APPENDIX F**

### **Individual Clinical Observations and Mortality Data in Subchronic Male Rats**

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INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA  
IN SUBCHRONIC MALE RATS

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**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) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 30	22 28	30 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 WET CHIN	1 28	1 28
16	-		
19	WET CHIN	17	19
21	STAINED CHIN BROWN	1	1
27	WET CHIN STAINED CHIN BROWN	13 22	20 23
33	WET CHIN	24	24
39	-		
40	WET CHIN	9	9
52	WET CHIN STAINED CHIN BROWN	1 16	13 16
53	STAINED CHIN BROWN WET CHIN	1 29	1 29

## **APPENDIX G**

### **Individual Detailed Clinical Observations in Subchronic Male Rats**

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INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

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**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) ALOPECIA BOTH FRONT LEG(S)	22 29	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**

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INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA  
IN SUBCHRONIC FEMALE RATS

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**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) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 31	28 28	31 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) SACRIFICED BY DESIGN TEST DAY 31	5	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) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 31	8 8	31 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) ALOPECIA RIGHT FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 31	10 29	28 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 WET CHIN	1 20	1 26
88	STAINED CHIN BROWN WET CHIN	1 24	1 24
114	-		
129	-		
146	STAINED CHIN BROWN	1	1
151	-		
159	STAINED CHIN BROWN WET CHIN	1 13	1 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) ALOPECIA BOTH FRONT LEG(S)	29 29	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) ALOPECIA BOTH FRONT LEG(S)	8 8	29 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) ALOPECIA RIGHT FRONT PAW(S)	15 29	22 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**

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INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS  
OF SUBCHRONIC MALE RATS

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**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

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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

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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

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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**

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INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS  
OF SUBCHRONIC FEMALE RATS

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**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

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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

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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

ANIMAL #	MEAN BODY WEIGHT (grams)					
	DAYS ON TEST: 1	8	15	22	29	31
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

ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
	DAYS ON TEST: 1-8	8-15	15-22	22-29	1-29
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

ANIMAL #	MEAN BODY WEIGHT (grams)					
	DAYS ON TEST: 1	8	15	22	29	31
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

ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
	DAYS ON TEST: 1-8	8-15	15-22	22-29	1-29
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

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ANIMAL #	MEAN BODY WEIGHT (grams)					
	DAYS ON TEST: 1	8	15	22	29	31
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

---

ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
	DAYS ON TEST: 1-8	8-15	15-22	22-29	1-29
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

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## **APPENDIX L**

### **Individual Food Consumption by Subchronic Male Rats During Premating**

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INDIVIDUAL FOOD CONSUMPTION BY SUBCHRONIC MALE RATS DURING  
PREMATING

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**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

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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

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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

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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**

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INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS  
DURING PREMATING AND COHABITATION

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**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) ALOPECIA BOTH FRONT LEG(S)	1 1	15 15
81	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S)	2 7	15 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**

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INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING  
GESTATION

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**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 SPERM POSITIVE	0 0	0 0
72	VAGINAL PLUG	0	0
82	CAGEBOARD PLUGS SPERM POSITIVE	0 0	0 0
87	CAGEBOARD PLUGS SPERM POSITIVE	0 0	0 0
90	ALOPECIA BOTH FRONT LEG(S) CAGEBOARD PLUGS SPERM POSITIVE	0 0 0	18 0 0
94	VAGINAL PLUG	0	0
109	CAGEBOARD PLUGS SPERM POSITIVE	0 0	0 0
118	CAGEBOARD PLUGS SPERM POSITIVE	0 0	0 0
121	CAGEBOARD PLUGS SPERM POSITIVE ALOPECIA RIGHT FRONT LEG(S)	0 0 12	0 0 18
132	CAGEBOARD PLUGS SPERM POSITIVE	0 0	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 SPERM POSITIVE	0 0	0 0
85	VAGINAL PLUG	0	0
86	VAGINAL PLUG	0	0
97	VAGINAL PLUG ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S)	0 16 18	0 21 21
104	SPERM POSITIVE	0	0
110	SPERM POSITIVE	0	0
122	CAGEBOARD PLUGS SPERM POSITIVE	0 0	0 0
130	VAGINAL PLUG	0	0
131	ALOPECIA BOTH FRONT LEG(S) VAGINAL PLUG ALOPECIA BOTH FRONT PAW(S)	0 0 1	22 0 22
137	CAGEBOARD PLUGS SPERM POSITIVE	0 0	0 0
157	CAGEBOARD PLUGS SPERM POSITIVE	0 0	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**

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INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN SATELLITE  
FEMALE RATS DURING LACTATION

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**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) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 43	0 0	4 4
106	ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 44	0	4
115	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 42		
116	ALOPECIA BOTH FRONT LEG(S) ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 47	0 3	4 4
117	ALOPECIA BOTH FRONT LEG(S) ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 47	0 0	4 4
140	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		
165	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 45	0 0	4 4

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) SACRIFICED BY DESIGN TEST DAY 45	1	4
86	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
97	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 45	0 0	4 4
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) ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 46	0 0	4 4
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 ALOPECIA LEFT SIDE(S) SACRIFICED BY DESIGN TEST DAY 46	0 0	4 4
66	STAINED PERINEUM YELLOW SACRIFICED BY DESIGN TEST DAY 45	0	4
73	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 43	0 0	4 4
81	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 44	0 0	4 4
92	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		
95	ALOPECIA BOTH FRONT LEG(S) ALOPECIA UNDERBODY SACRIFICED BY DESIGN TEST DAY 42	0 0	4 4
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	-		
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**

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INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF SATELLITE FEMALE  
RATS DURING PREMATING

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**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 #			
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

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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 #	<u>MEAN BODY WEIGHT (grams)</u>		
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

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DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #	<u>MEAN BODY WEIGHT GAINS (grams)</u>		
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 #	<u>MEAN BODY WEIGHT (grams)</u>		
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 #	<u>MEAN BODY WEIGHT GAINS (grams)</u>		
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

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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 #	<u>MEAN BODY WEIGHT (grams)</u>		
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 #	<u>MEAN BODY WEIGHT GAINS (grams)</u>		
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