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DOCUMENT DESCRIPTION	DOCUMENT CONTROL NUMBER	DATE RECEIVED
8EHQ-09-17450	89100000124	2/17/10

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SEHSC®
SILICONES ENVIRONMENTAL, HEALTH AND SAFETY COUNCIL NORTH AMERICA

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2325 Dulles Corner Boulevard
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Herndon, VA 20171

Via Certified Mail

8EHQ-09-17450

February 3, 2010

TSCA Confidential Business Information Center (7407M)
EPA East - Room 6428 Attn: Section 8(e)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

89100000124

Re: Supplemental TSCA Section 8(e) Submission 8EHQ-09-17450: Final Report - Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Dimethyldimethoxysilane in Sprague-Dawley Rats via Oral Gavage

Dear TSCA Section 8(e) Coordinator:

In accordance with the provisions of Section 8(e) of the Toxic Substances and Control Act (TSCA), as interpreted in the TSCA Section 8(e) Policy Statement and Guidance, Fed. Reg. 33129 (June 3, 2003) and other Agency guidance, the Silicones Environmental, Health and Safety Council (SEHSC)[1] submits, on behalf of its member companies, a final study report as a supplemental submission to our March 12, 2009 and May 7, 2009 TSCA Section 8(e) notifications.

Chemical Substance
Dimethyldimethoxysilane (CAS No. 1112-39-6)

Completed Study
Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Dimethyldimethoxysilane in Sprague-Dawley Rats via Oral Gavage.

Summary
Preliminary results from a repeated-dose toxicity study with reproductive/developmental screening endpoints conducted with dimethyldimethoxysilane in Sprague-Dawley rats were reported to EPA by SEHSC on March 12, 2009 and May 7, 2009. The enclosed final report for the Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Dimethyldimethoxysilane in Sprague-Dawley Rats via Oral Gavage is provided for the Agency's

[1] SEHSC is a not-for-profit trade association whose mission is to promote the safe use of silicones through product stewardship and environmental, health, and safety research. The Council is comprised of North American silicone chemical producers and importers.

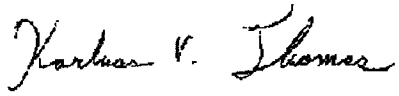
CONTAINS NO CB

324724

reference. Neither SEHSC, nor any member company, has made a determination at this time that any significant risk of injury to human health or the environment is presented by these findings.

If you have any questions concerning this submission, please contact me at (703) 788-6570, kthomas@sehsc.com, or at the address provided herein.

Sincerely,



Karluss Thomas
Executive Director

Enclosure

DOW CORNING CORPORATION
HEALTH & ENVIRONMENTAL SCIENCES (HES)
TECHNICAL REPORT

RECEIVED
10 FEB 17 AM 6:04

Study Title:	Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Dimethyldimethoxysilane in Sprague-Dawley Rats via Oral Gavage
Study Number:	10705-102
Test Article:	Dimethyldimethoxysilane
Study Director:	Jeanne Y. Domoradzki, Ph.D., D.A.B.T.
Sponsor:	Silicones Environmental, Health and Safety Council 2325 Dulles Corner Blvd., Suite 500 Herndon, VA 20171
Sponsor Representative:	Wendy H. Koch, Ph.D. Epona Associates, LLC
HES Management:	Paul A. Jean, Ph.D. Team Leader, Toxicology Health and Environmental Sciences
Testing Facility:	Dow Corning Corporation Health and Environmental Sciences 2200 W. Salzburg Road Auburn, MI 48611
Study Completion Date:	January 11, 2010

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1 ABSTRACT

The objective of this study was to evaluate the potential toxicity of dimethyldimethoxysilane in a 28-day combined repeated dose toxicity study with the reproductive/developmental toxicity screening test in Sprague-Dawley rats by oral gavage administration based on OECD Test Guideline 422, (1996). Male and female Sprague-Dawley rats were administered by oral gavage doses of 0, 50, 250 or 1000 mg/kg bw/day for 28 to 51 consecutive days. The study animals were divided into three groups. There were 10 male rats per exposure concentration in Group 1 (male group). Rats in this group, used both to assess toxicity of the test material and for mating, were administered the test article for 29 consecutive days and then euthanized the next day. There were 10 female rats per dose group in Group 2 (toxicity group females). Rats in this group were administered the test article for 28 consecutive days and then euthanized the next day for assessment of toxicity. Group 3 (reproductive group females) was comprised of 10 female rats per dose group. Rats in this group were exposed for a two-week pre-mating phase, a 1 – 14-day mating phase, and through day 3 post-partum, up to 51 days in total.

Animals were observed twice daily on weekdays and once daily on weekends and holidays for mortality or morbidity. Clinical observations were performed daily immediately following exposure. Body weight measurements were performed weekly. All animals received a detailed physical examination once before the first dose (to allow for within-subject comparisons), and weekly thereafter. Additional body weights on reproductive group females were obtained on gestational days (GD) 0, 7, 14, and 20, within 24 hours of parturition, and on post-partum day four. Individual food consumption was recorded at least weekly, except during the cohabitation period. Functional observational battery (FOB) and motor activity evaluations were performed on males and toxicity group females once prior to initiation of exposures and during the 4th week of exposure. Blood samples for hematology and serum chemistry evaluations were collected at the scheduled necropsy from males and toxicity group females. Complete necropsies were performed on the males and the toxicity group females and selected organs were weighed. Microscopic examination was performed on protocol-specified tissues on all males and toxicity group females from the control and 1000 mg/kg bw/day dose groups. Target tissues were examined from the 50 and 250 mg/kg bw/day groups.

Mating was initiated after the first two weeks of exposure by pairing reproductive group females with males of the same treatment group until positive evidence of mating was obtained. Reproductive and developmental parameters evaluated included evidence of mating, pregnancy, duration of gestation, mean litter size, mean live litter size, mean litter weight, and mean ratio of live births/litter size. Dams and pups were euthanized on post-partum day 4 and examined for external gross lesions. The number of corpora lutea, and the number of uterine implantation sites were determined for all reproductive group females.

Oral gavage administration of dimethyldimethoxysilane in a corn oil vehicle to male and female Sprague-Dawley rats at concentrations of up to 1000 mg/kg bw/day was generally well tolerated. For the males at 1000 mg/kg bw/day, significant abnormal observations were noted and included soiling of the chin and urogenital area. Soiling of the chin, muzzle and urogenital areas were significant abnormal observations in the toxicity group females at 1000 mg/kg bw/day. Abdominal, chin, muzzle and urogenital soiling were significant abnormal observations in the reproductive group females at 1000 mg/kg bw/day.

There were no statistically significant differences between controls and treatment groups in the mean body weights on any day for any of the three groups: males, toxicity group females, and reproductive group females. There were no statistically significant differences between controls and treatment groups in mean body weight gains for any interval for males and toxicity group females. There was a statistically significant decrease in body weight gain compared to control values for the reproductive group females during gestational week 3 and for the interval from day 1 of study to post-partum day 4 in the 1000 mg/kg bw/day group.

There were no differences in the average daily food consumption between controls and treatment groups for the male and toxicity group females for any of the measured time periods. In the 1000 mg/kg bw/day reproductive group females, there was a significant decrease (35%) in food consumption during the interval post-partum days 0-4.

No statistically significant differences were found between the control and treatment groups in either sex for all the FOB ranked tests. There were no statistically significant differences between either males or toxicity group females and their respective controls for the FOB continuous test and motor activity. There were no treatment-related changes associated with dimethyldimethoxysilane administration on rat neurobiological function as evaluated with FOB and motor activity parameters.

Statistically significant changes noted in hematological parameters and prothrombin times and clinical chemistry parameters for males and toxicity group females were within or slightly above/below historical control values and these findings did not correlate with a pathological outcome, therefore, no toxicological significance is given to any of these statistically identified differences.

There were statistically significant differences compared to controls noted for the following organ weights in males: adrenal glands (decrease at 1000 mg/kg bw/day), liver (increase at 250 and 1000 mg/kg bw/day), testes (decrease at 1000 mg/kg bw/day), thymus (decrease at 1000 mg/kg bw/day), epididymides (decrease at 1000 mg/kg bw/day), prostate gland (decrease at 1000 mg/kg bw/day) and seminal vesicles (decrease at 1000 mg/kg bw/day). There were statistically significant differences for the mean percentage of organ weights relative to body weights for adrenal glands (decrease at 1000 mg/kg bw/day), liver (increase at 250 and 1000 mg/kg bw/day), thymus (decrease at 1000 mg/kg bw/day) and testes (decrease at 1000 mg/kg bw/day) for the males.

There were statistically significant differences noted for organ weights in toxicity group females compared to controls; liver (increase at 250 and 1000 mg/kg bw/day) and spleen (decrease at 1000 mg/kg bw/day). There were statistically significant differences for the mean percentage of organ weights relative to body weights for liver (increase at 250 and 1000 mg/kg bw/day) and spleen (decrease at 1000 mg/kg bw/day) for the toxicity group females.

A standard set of protocol-defined tissues was examined for control and high-dose groups. Identified target tissues were examined for low- and mid-dose groups. Effects attributable to test article administration in males occurred in the liver, thyroid gland, adrenal glands, kidneys, testes, and epididymides. In females test material effects were observed in the liver and thyroid glands. There were questionable effects in the spleen of males and the lungs of both sexes. Target tissues examined at 50 and 250 mg/kg bw/day in males were liver, lungs, thyroid glands, adrenal glands, kidneys, testes, epididymides and spleen. In females, the target tissues examined were liver, lungs and thyroid glands.

In the liver, there were three primary effects of the test article observed, including panlobular hepatocellular hypertrophy in both sexes at 1000 mg/kg bw/day and centrilobular hypertrophy in females at 250 mg/kg bw/day, increased periportal hepatocellular vacuolation (microvesicular lipidosis, females administered 1000 mg/kg bw/day), and protoporphyrin accumulation (males only). The latter was usually accompanied by chronic inflammation and bile duct hyperplasia. Hepatocellular hypertrophy (panlobular or centrilobular) is considered an adaptive change. Hepatic vacuolation, unless severe, is generally considered non-adverse. Hepatic protoporphyrin accumulation is considered an adverse effect.

Thyroid follicular cell hypertrophy was observed in the thyroid gland of high-dose rats of both sexes. This is considered an adaptive secondary effect and adverse for the rat, but the mechanism is generally not applicable to species with significant levels of thyroid binding globulin (Capen *et al.*, 2002).

There was minimal adrenal cortical atrophy in half of the male rats dosed at 1000 mg/kg bw/day. The pathogenesis and significance of this finding is not clear.

In the testes there was moderate to marked seminiferous tubule degeneration observed in all 1000 mg/kg bw/day male rats that was characterized by degeneration of spermatocytes. A downstream effect was observed in the epididymides of the same rats. This is an adverse finding.

Kidney findings tabulated as protein droplet nephropathy and consistent with minimal alpha-2-U-nephropathy (Hard *et al.*, 1999) were observed in all male rats administered 1000 mg/kg bw/day. The finding was not detected in lower dose males, and, characteristically, was not observed in female rats. This is a male-rat-specific finding.

Based on initial examination of lung and spleen from control and high-dose animals, these tissues were considered possible targets; however, further examination and inclusion of animals from the mid- and low-dose groups did not support this interpretation.

The increased liver weights in males and toxicity group females at 1000 mg/kg bw/day correlated with the histopathologic finding of panlobular hypertrophy and centrilobular hypertrophy in females at 250 mg/kg bw/day. In males, adrenal cortical atrophy was accompanied by a decrease in absolute and relative adrenal weights at 1000 mg/kg bw/day, seminiferous tubule degeneration was accompanied by a decrease in absolute and relative testes weights at 1000 mg/kg bw/day, epididymal effects were accompanied by a decrease in absolute and relative decreases in epididymal weights, and kidney nephropathy findings were accompanied by a increase in relative kidney weights.

In the reproductive group females, there were no statistically significant differences across treatment groups for corpora lutea counts and total implants. However, there were statistically significant differences at 1000 mg/kg bw/day for post-implantation losses, days of gestation, total pups and total live pups with the 1000 mg/kg bw/day group having significantly more post-implantation losses, a longer gestation period, fewer pups in the litter and fewer live pups in the litter than were seen in the control group.

There were no statistically significant differences across treatment groups for the number of male pups, the number of female pups and the male/female ratio although there was a significant litter size effect for both the number male and number female pups with a fewer number of male pups than female pups appearing in smaller litter sizes.

The number of day 4 viable pups and the ratio of the number of viable pups to the total litter size was significantly different, with the 1000 mg/kg bw/day group having fewer viable pups by day 4 and a smaller viable/total ratio than did the control group. The percentage of post-natal loss was significantly different, with the 1000 mg/kg bw/day having a significantly higher loss than did the control group.

The initial litter weight and average pup weights (defined using the live pup litter weight divided by the total number of live pups on day 0) were significantly different only for the 250 mg/kg bw/day group having a significantly increased litter weight and average pup weight compared to that in the control group after adjusting for litter size. The litter size was also a significant variable for these two endpoints with larger litters having larger litter weights but smaller average pup weights. For the final litter weight and average pup weights, there was also a significant difference, but it was the 1000 mg/kg bw/day group that was significantly different from the control group with both smaller overall litter weights and smaller average pup weight than in control group. There were no grossly visible external abnormalities observed in the pups.

Based on results observed at 1000 mg/kg bw/day in male (hepatic protoporphyrin accumulation, adrenal cortical atrophy, kidney protein droplet nephropathy, testicular seminiferous tubule degeneration with epididymides involvement) and in female rats (periportal vacuolation), the NOAEL (No-Observed-Adverse-Effect-Level) for systemic toxicity of dimethyldimethoxysilane is 250 mg/kg bw/day. Based on observations at 1000 mg/kg bw/day (an increase in post-implantation loss, an increase in days of gestation, a decrease in live pups, a decrease in the total viable pups/total, a decrease in final litter weight, a decrease in final average pup weight and an increase in the % of post-natal loss), the NOAEL mg/kg bw/day for reproductive and developmental toxicity is 250 mg/kg bw/day.

2 GLP COMPLIANCE STATEMENT

The study was conducted in compliance with the USEPA (TSCA) Good Laboratory Practice Standards 40 CFR Part 792.

Protocol deviations are located in Table 36.

Wendy H. Koch, Ph.D. — Date: January 8, 2010
Epona Associates, LLC

Paul A. Jean, Ph.D. — Date: 11 Jan 10
Team Leader, Toxicology
Dow Corning Corporation

Jeanne Y. Domoradzki, Ph.D., D.A.B.T. — Date: January 11, 2010
Study Director, Toxicology
Dow Corning Corporation

3 QUALITY ASSURANCE STATEMENT

Title: Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Dimethyldimethoxysilane in Sprague-Dawley Rats via Oral Gavage

Study Number: 10705-102

This study has been audited by the Dow Corning Corporation Health and Environmental Sciences Quality Assurance Unit according to approved Standard Operating Procedures to assure that the raw data are accurately reflected within this final report. The following are the inspection dates and the dates inspection findings were reported.

Dates of Inspection	Phase Inspected	Findings Reported to Study Director	Findings Reported to Management
11 Sept 2008	Draft Protocol	12 Sept 2008	19 Sept 2008
10 Nov 2008	Functional Observation Battery	10 Nov 2008	12 Nov 2008
17 Nov 2008	Hematology	17 Nov 2008	23 Nov 2008
04 Dec 2008	Detailed Physical Examinations	05 Dec 2008	11Dec 2008
19-23 Mar 2009	Contributing Scientist Report and Associated Raw Data	24 Mar 2009	27 Mar 2009
12-14 Aug 2009	Appendices A, B, C and Tables 1, 2, 3	14 Aug 2009	28 Aug 2009
17, 18 Aug 2009	Appendices D, E, F and Tables 4, 5, 6	18 Aug 2009	27 Aug 2009
05, 18 Aug 2009	Contributing Scientist Report, Main Report, Tables and All Associated Raw Data	19 Aug 2009	21 Sept 2009
21 Aug 2009	Draft Final Report and Raw Data: Table 36	21 Aug 2009	28 Aug 2009
19-24 Aug 2009	Contributing Scientist Report (Appendix S), Main Report, Tables and All Associated Raw Data	24 Aug 2009	28 Sept 2009

20, 21, 24 Aug 2009	Appendices G, H, I and Tables 7, 8, 9, 10, 11	24 Aug 2009	27 Aug 2009
26 Aug 2009	Appendix M and Table 30	27 Aug 2009	01 Sept 2009
28 Aug 2009	Appendix N and Table 31	28 Aug 2009	08 Sept 2009
26-31 Aug 2009	Contributing Scientist Report (Appendix U), Main Report, Tables (32, 33 and 34) and All Associate Raw Data	31 Aug 2009	22 Sept 2009
31 Aug & 1-2 Sept 2009	Appendix R Contributing Scientist Report and Associated Raw Data	02 Sept 2009	29 Sept 2009
10 Aug- 04 Sept 2009	Draft Final Report and Associated Raw Data	04 Sept 2009	12 Oct 2009
31 Aug -03 Sept 2009	Draft Final Report and Raw Data-Dosing	03 Sept 2009	28 Sept 2009
04 Sept 2009	Draft Final Report and Raw Data Appendix J, K, L Tables 12, 13, 14	04 Sept 2009	16 Sept 2009
22 Sept 2009	Wet Specimen Verifaction	22 Sept 2009	28 Sept 2009

Linda Stilgenbauer, B.S.
Quality Assurance Auditor
Dow Corning Corporation
Health & Environmental Sciences

11-13-09
Date

4 APPROVAL SIGNATURES

The report consists of pages 1 through 480, including Tables 1 to 36 and Appendices A through U. The undersigned have read and approved this report:

Wendy H. Koch, Ph.D. — January 8, 2010
Epona Associates, LLC — Date

Paul A. Jean, Ph.D. — 11 Jan 10
Team Leader, Toxicology — Date
Dow Corning Corporation

Jeanne Y. Domoradzki, Ph.D., D.A.B.T. — January 11, 2010
Study Director, Toxicology — Date
Dow Corning Corporation

5 STUDY INFORMATION

Study Initiation Date:	September 29, 2008
Experimental Start Date:	October 20, 2008
Experimental Termination Date:	July 30, 2009
Study Completion Date:	January 11, 2010
HES Study Number:	10705-102
Manager, Toxicology	Paul A. Jean, Ph.D.
Study Director:	Jeanne Y. Domoradzki, Ph.D., D.A.B.T.
Study Coordinator:	Becki Uhlenhake D.M.R.A.L.A.T.
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6 STUDY PURPOSE

The objective of this study is to evaluate the potential toxic effects of dimethyldimethoxysilane following daily oral administration to male and female Sprague-Dawley rats from before mating, through mating, gestation and beginning of lactation.

7 GUIDELINES

The study design was based on the requirements of the following guidelines:

Organization for Economic Cooperation and Development. OECD Guideline for Testing of Chemicals. Section 4, No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, (1996).

U.S. Environmental Protection Agency, Health Effects Test Guidelines, OPPTS 870.3650. Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test. (2000).

8 TEST ARTICLE / SUBSTANCE / ITEM

The Study Director reviewed results of test article characterization and that review was documented in the study file. The test article characterization report is included in Appendix P.

Identification:	Dimethyldimethoxysilane Supplied as Dow Corning® Z-6329 Silane
Lot/Batch/Reference Number:	0004979431
Expiration Date:	27 February 2010
Source:	Dow Corning Corporation Auburn, MI 48611
CAS Number:	1112-39-6
Physical Description:	Colorless liquid
Stability:	Stable in absence of water, moisture or humid air
Purity:	99.82 +/- 0.002% (HES Study 10702-102)
Solubility:	Soluble in acetone, ethanol
Storage Conditions:	Room temperature
Chemical Characterization:	HES Study 10702-102
Archive:	A reserved sample was retained

9 CARRIER

Identification:	Corn Oil; Dried and deacidified at Dow Corning Corporation
Batch Number:	058K0070
Source:	Sigma-Aldrich, Inc. 3050 Spruce Street Saint Louis, MO 63103
Storage Conditions:	Room temperature

10 TEST SYSTEM

Species:	Albino Rat
Strain:	Crl: CD® (SD) IGS BR VAF/Plus®
Source:	Charles River Laboratories, Inc. 401 S New Hope Road Raleigh, NC 27610
Age:	9 weeks at experimental start
Body weight:	Females: 192 to 239 g at experimental start Males: 283 to 341 g at experimental start
Sex and number used on study:	80 nulliparous and nongravid females 40 males
Number of animals ordered:	90 nulliparous and nongravid females 45 males
Number of groups:	4
Identification method:	IMI Transponders (BioMedic Data Systems, Seaford, DE)

11 JUSTIFICATION FOR SELECTION OF TEST SYSTEM

The rat is recognized as appropriate for toxicity studies and is recommended in the OECD and OPPTS test guidelines. Sprague-Dawley rats (Crl: CD® (SD) IGS BR VAF/Plus®) have previously been used in repeated-dose toxicology studies of various silicones and were considered an appropriate strain for use in reproductive hazard assessment studies.

12 METHOD OF RANDOMIZATION

Animals including extras were ordered and acclimated to ensure adequate numbers for randomization into test groups. After release from quarantine/acclimation, rats were assigned to test groups based on a weight-stratified randomization process in Provantis™ v8.2 (Instem LSS,

Conshohocken, PA). Extra animals were returned to animal resources. At randomization the sex-specific weight variation of animals in each group did not exceed ± 20% of the mean weight for that group.

13 HOUSING AND MAINTENANCE

13.1 Animal Receipt and Quarantine/Acclimation

Animal resource personnel inspected each animal upon receipt and at least once daily during the quarantine period. Animals were quarantined/acclimated for five days. The attending veterinarian examined all animals before release from quarantine/acclimation. Animals judged to be in good health and suitable as test animals were released for study use.

13.2 Animal Housing

Animals were individually housed in suspended wire-mesh cages elevated above fecal pans containing Bed-O'Cobs® litter, during quarantine/acclimation and during the in-life phase of the study except during mating, gestation and lactation periods. During cohabitation (mating) the females were paired 1:1 with a male from the same treatment group. The animals were paired in the home cage of the male. After demonstrating positive evidence of mating, females were moved into shoebox cages containing Bed-O' Cobs® combination bedding. During the lactation period, dams were housed together with their litters. The Study Director reviewed the analysis of the Bed-O' Cobs® Combination bedding and found it free of contaminants that would have an impact on the outcome of the study. The cages, litter/fecal pans were routinely cleaned, consistent with good husbandry practices.

13.3 Enrichment

Animals were given Nylabones® and Cozee Pads™ for environmental enrichment while in standard housing and Nylabones® only while in shoebox caging.

Exception: Environmental enrichment was removed from the toxicity group male and female animals the afternoon/evening prior to necropsy.

13.4 Environmental Conditions

Animals were housed in an environmentally controlled animal room (12-hour fluorescent-light/dark cycle, 20.5-21.7°C, 53-59% humidity, 14.3 air changes per hour) throughout the study. Temperature and humidity was monitored continuously, recorded every 15 minutes using a HOBO® Data Logger (Onset Computer, Bourne, MA; software: BoxCar® Pro 4.3.1.1), and manually recorded twice daily on weekdays and at least once per day during weekends and holidays. The Study Director reviewed the last verification of air changes.

13.5 Basal Diet

Lab Diet 5002, Certified Rodent Diet (PMI Nutrition International), was provided *ad libitum* during the quarantine/acclimation period and throughout the study. Manufacturer's periodic analyses of the certified feed for the presence of heavy metals and pesticides maintained on file at the testing facility was reviewed by the Study Director to ensure that none were present in concentrations that would be expected to affect the outcome of the study.

Exceptions: Food was not provided during functional observation battery or motor activity assessment periods. Additionally, food was removed the afternoon/evening prior to necropsy of the toxicology animals.

13.6 Drinking Water

Municipal water, further purified by reverse osmosis was available *ad libitum* via automatic watering system. Water is monitored routinely and also analyzed on a semi-annual basis. To ensure that no contaminants were present at a concentration expected to interfere with the integrity of the study, the Study Director reviewed the most recent analysis results maintained on file at the testing facility.

Exceptions: Water was not provided during functional observation battery or motor activity assessment periods.

14 ANIMAL WELFARE ACT COMPLIANCE

This study complied with all applicable sections of the final rules of the Animal Welfare Act regulations (9 CFR, Part 1, 2, and 3) and was approved by the Laboratory Animal Care and Use Committee (LACUC) before animals were ordered.

15 EXPERIMENTAL DESIGN

15.1 Timeline of Study Events

Endpoints	Toxicity Group Females	Males	Reproductive Group Females
Acclimation	5 days (minimum)	5 days (minimum)	5 days (minimum)
Baseline FOB/ Motor Activity	2-8 days prior to dosing	2-8 days prior to dosing	_____
Detailed Physical Examinations	Prior to dosing and weekly throughout	Prior to dosing and weekly throughout	Prior to dosing and weekly throughout
Dosing begins	Study Day 1	Study Day 1	Study Day 1
Clinical Observations	Daily except when on day of detailed physical exam	Daily except when on day of detailed physical exam	Daily except when on day of detailed physical exam
Individual Body Weight	Randomization Study Day 1 At least weekly Termination	Randomization Study Day 1 At least weekly Termination	Randomization Study Day 1 At least weekly At a minimum; GD 0, 7, 14, and 20 within 24 hours after parturition Day 4 post-partum
Individual Food Consumption	Days 1, 8, 15, 22 and day prior to necropsy	Two weeks pre-mating only; Days 1, 8 and 15	Day 1, 8 and 15 GD 0, 7, 14 and 20 Day 0 and 4 post-partum
Hematology/Clinical Chemistry	Termination	Termination	_____
Mating (animals paired)	_____	Study Day 15 up to Study Day 28	Study Day 15 up to Study Day 28
Treated FOB/Motor Activity	Week 4	Week 4	_____
Gestation	_____	_____	Approximately 21 days
Parturition	_____	_____	Normally on day 21 or 22 post-coitum Beginning on GD 20, animals checked 3 times daily; twice on weekends
Lactation	_____	_____	Until day 4 post-partum
Dosing ends	One day prior to the actual day of necropsy	One day prior to the actual day of necropsy	Day 3 post-partum
Termination	After a minimum of 28 days on study	After a minimum of 28 days on study	Day 4 post-partum

15.2 Data Acquisition System

Test system observations, body weights, food consumption, FOB, and morphologic pathology data, at a minimum, will be collected using Provantis® v8.2 (Instem LSS, Conshohocken, PA). There may be occasions, however, when manual collection of data is necessary.

15.3 Route and Rationale of Test Article Administration

Route

Test article was administered by oral gavage in dried, deacidified corn oil.

Rationale

Oral gavage is an accepted method of administration of the test article and is recommended by the OECD and OPPTS Test Guidelines.

Based upon the physical and chemical properties of the test article, dried and deacidified corn oil was considered to be the most appropriate vehicle for oral administration.

Administration of doses

Dosing solutions were administered by oral gavage with a 100 mm, 15 gauge (1.8 mm), plastic feeding tube and syringe. The test article was administered at a dose volume of 4 mL/kg body weight and was calculated from the most recent body weight.

15.4 Dosing Solution Preparation, Analysis and Storage

Preparation

Each dosing solution was prepared individually. Calculations and preparation methods were documented in the raw data. Frequency of preparation of dosing solutions was every 28 days based on the results of stability testing. Dosing solutions were prepared by adding the appropriate amount of the test article to a tared container and adding the appropriate amount of corn oil to yield the desired dose level.

Analysis

Dosing solution analyses were performed by a GC/FID method to verify concentration, stability, and homogeneity of the test article in carrier. All details of the analytical method are documented in the study records.

Concentration verification was conducted for the initial and third dose preparations. Homogeneity and stability determinations were performed on the high and low dose preparations from the first set of dose preparations.

Storage conditions

The dosing solution preparations were stored at room temperature in a desiccator.

15.5 Organization of Test Groups and Dose Levels

The following table summarizes the organization of the test groups and test article dose levels. Ten female animals per dose group were placed on study for the purpose of toxicological evaluation only (toxicity group). Ten female animals per dose group were placed on study for the purpose of evaluating reproductive endpoints only (reproductive group). Ten male rats per dose group were placed on study for the purpose of evaluating both reproductive and toxicological endpoints.

The dose levels were selected based on results from a previous range finding study (HES Study number 10704-102) and to provide dose-response data for the test article.

Group/ Sex	Number of Animals		Dose Level (mg/kg bw/day)	Animal ID Numbers	
	Toxicity Group	Reproductive Group		Toxicity Group	Reproductive Group
1m	10 males	*	0	D5634-D5643	
1f	10 females	10 females		D5624-D5633	D5644-D5653
2m	10 males	*	50	D5634-D5643	
2f	10 females	10 females		D5654-D5663	D5674-D5683
3m	10 males	*	250	D5694-D5703	
3f	10 females	10 females		D5684-D5693	D5704-D5713
4m	10 males	*	1000	D5724-D5733	
4f	10 females	10 females		D5714-D5717** &D5719-D5723	D5734-D5743

* - Ten male rats per dose group were placed on study for the purpose of evaluating both reproductive and toxicological endpoints. **D5718 took the identity of D5743, n=9 for the toxicity group females (the test group and the animal ID of the two rats were switched).

15.6 Treatment Regimen

Test substance was administered once daily by oral gavage, seven days per week, at approximately the same time each day with the exception of the week of FOB and MA testing, in which dosing was conducted following testing. Treatment of both sexes began two weeks prior to initiating mating and continued through the mating period. Male animals were treated for 29 days and euthanized the day after the last treatment. The toxicity group females were treated for 28 days and euthanized the day after the last treatment. Reproductive group females were treated through post-partum day 3 or until euthanized in extremis.

15.7 Mating Procedure

A 1:1 mating ratio was used. On study day 15, the animals were paired by placing the lowest identification number (ID) numbered female of each group with the lowest ID numbered male of that group, then the next lowest ID numbered female with the next lowest numbered male, etc., until all animals were paired. The female animals were housed continuously with the same male until evidence of mating occurred or two weeks had elapsed. Reproductive group females were evaluated daily for evidence of copulation, by confirming the presence of either a vaginal copulatory plug or sperm in the vaginal smear. Day 0 of gestation was defined as the day evidence of copulation was observed, at which time the female was individually caged.

15.8 Method of Disposition

Scheduled Animal Euthanasia

All males and toxicity group females were euthanized by exsanguination. While under Isoflurane® anesthesia, blood was collected from the caudal vena cava followed by the cutting of major abdominal vessels.

The reproductive group females were euthanized by CO_2 inhalation on post-partum day 4. Three nongravid female demonstrating no evidence of copulation (D5683, D5736, D5738) were euthanized 25 days after the last day of the mating period. One reproductive group female with evidence of copulation that did not deliver (D5678) was euthanized on gestation day 27.

Day four rat pups were euthanized by intraperitoneal injection with Socumb®.

Unscheduled
One animal, D5718, was euthanized on day 12 of study due to repeated difficulty in gavaging this animal with the test article solution.

15.9 Test System Observations

Mortality/Morbidity/Moribundity
All animals were observed at least twice daily (once daily on weekends and holidays) in their cages for mortality, morbidity, and moribundity by study personnel throughout the completion of the in-life phase of the study.

Clinical Observations
General clinical observations were conducted at least once a day, beginning on the first day of treatment, at approximately the same time(s) each day. The health condition of the animals was recorded. Findings noted at the clinical examination were recorded for individual animals. Daily observations were also performed on all animals on the day of, but prior to, their scheduled necropsy.

General clinical observations were not performed on the same day that detailed physical examinations were performed.

Detailed Physical Examinations
All animals received a detailed physical examination once before the first dose (to allow for within-subject comparisons), and weekly thereafter. The observations were made outside the home cage in a standard arena at approximately the same time each day. Observations were detailed and carefully recorded. Signs noted included, but were not limited to, changes in skin, fur, eyes, mucous membranes, occurrence of secretions and excretions, and autonomic activity (e.g., lacrimation, piloerection, pupil size, and unusual respiratory pattern). Changes in gait, posture and response to handling, as well as the presence of clonic or tonic movements, stereotypies (e.g., excessive grooming, repetitive circling), difficult or prolonged parturition or bizarre behavior were recorded. The presence or absence of findings was recorded for individual animals.

Reproductive Female Observations
The duration of gestation was calculated from day 0 gestation for each female. Beginning on gestation day 20, pregnant animals were checked at least three times daily (twice daily on weekends and holidays) for evidence of parturition. If difficulties were observed, progress of the parturition process was monitored.

16 PARAMETERS MEASURED

16.1 Individual Body Weights

Individual body weights were determined beginning with randomization into test groups, on the first day of dosing, at least weekly thereafter, and on the day of euthanasia. During gestation, the

reproductive group females were weighed (at a minimum) on gestation days 0, 7, 14 and 20, within 24 hours after parturition, and on day 4 post-partum. Litter weights were taken within 24 hours of parturition and on day 4 post-partum.

16.2 Individual Food Consumption

Individual animal food consumption was recorded at least weekly for the periods listed below.

Male rats:	Two week pre-mating period only Feeder weights were taken on days 1, 8, and 15.
Female rats:	
Toxicity group:	Day 1 of dosing to necropsy Feeder weights were taken on day 1, 8, 15, 22 and the day prior to necropsy.
Reproductive group:	Two week pre-mating period, gestation and post-partum. Feeder weights were taken on days 1, 8, 15, and on gestation days 0, 7, 14, 20, and on day 0 and 4 post-partum.

16.3 Functional Observational Battery and Motor Activity

Functional Observational Battery (FOB) evaluations were performed on all adult males and all toxicity group females prior to the start of dosing (baseline evaluations). Testing performed during the fourth week of dosing took place prior to daily dosing. FOB and Motor Activity examinations were performed on all animals since no signs of toxicity to an extent that would significantly interfere with the evaluation were noted.

Baseline evaluations were also performed on the "extra" or "reserve" animals in the event that a replacement was needed for an animal already on study. Data were not reported as no replacements were made.

Animals were observed as described below:

Cage Side Observations
Abnormal muscle movements (e.g., tremors, convulsions), abnormal behavior (e.g., circling, stereotypy), posture and resistance to removal from the cage

Hand-held Observations
Palpebral closure, lacrimation, pupil size, pupil reactivity, salivation, muscle tone, extensor thrust response, and reactivity to handling

Open Field Observations
A one-minute evaluation of level of activity (ambulatory and rearing), responsiveness to sharp noise, touch, and tail pinch, gait evaluation, quantity of urine voided and fecal pellets eliminated

Categorical Observations
Behavior, skin/fur/mucous membrane, respiration, muscle, eyes, urine or feces, soiling, posture and other abnormalities (can be made any time during the FOB)

Measurements/Counts
Rectal temperature, hind-limb/forelimb grip strength, landing foot splay

Motor Activity
Locomotor activity was determined using a Cage Rack Activity System (CRAS) purchased from San Diego Instruments (San Diego, CA) and PAS v2.03 software. Each test session was 80 minutes in length (10 X 8 minute intervals).

16.4 Clinical Pathology

Clinical pathology assessments were made on all surviving adult males and toxicity group females from which adequate samples were collected. Food was removed on the evening prior to scheduled necropsy.

Blood samples were collected for hematological and clinical chemistry evaluations from all males and toxicity group females on the day of scheduled euthanasia as a terminal procedure. While the animals were under Isoflurane® anesthesia a syringe and needle were used to collect blood samples from the abdominal vena cava and distributed to three sample collection tubes containing either sodium citrate, EDTA, or no anticoagulant. Samples that clotted or were inadequate in volume were not analyzed for every parameter.

Hematology
Blood samples were collected into test tubes containing EDTA and were assayed on the same day as collection for the following hematology parameters using a Cell Dyn 3700 Hematology Analyzer (Abbott Diagnostics, Dallas, TX):

- Erythrocyte count (RBC)
- Erythrocyte Indices (MCV, MCH, MCHC)
- Leukocyte counts (WBC, total and differential)
- Hemoglobin (Hgb)
- Hematocrit (Hct)
- Platelet count (PLT)

Coagulation
Blood samples were collected for coagulation assessment (prothrombin times) into test tubes containing sodium citrate, centrifuged within two hours of collection and the plasma separated for testing. Plasma samples were analyzed by nephelometry using the ACL 100 (Instrumentation Laboratory Company, Lexington, MA).

Serum Chemistry
Blood samples were placed into test tubes not containing anticoagulant, allowed to clot and then centrifuged within two hours of collection and the serum was separated for testing. The following serum chemistries were determined on the Cobas Integra 400 plus® (Roche Diagnostics, Indianapolis, IN).

- Alanine aminotransferase
- Albumin
- Alkaline phosphatase
- Aspartate aminotransferase
- Calcium
- Cholesterol
- Chloride
- Creatinine
- Glucose
- Phosphorus
- Potassium
- Sodium
- Total bilirubin
- Total protein
- Urea nitrogen

16.5 Morphologic Pathology

Macroscopic Examination

Males and Toxicity Group Females: All adult males and all toxicity group females were subjected to a complete gross necropsy that included examination of the external surface and all orifices of the body, the cranial, thoracic and abdominal cavities and their contents.

Reproductive Group Females: For reproductive group females, the number of corpora lutea and the number of implantation sites were recorded. Dead pups and pups euthanized on day 4 post-partum were examined for external gross abnormalities only. No pup tissues were collected and the carcasses were discarded. For females with positive evidence of mating, but which failed to produce a litter, the uteri were stained to enable counting of possible reabsorbed implantation sites. The uteri were stained with an equal mixture of 20% Potassium Ferricyanide and 1% Hydrochloric Acid. A uterus from a pregnant animal was stained and used as a positive control.

Organ Weights

At necropsy, the following organs from males and toxicity group females were trimmed and weighed: adrenal glands, brain, heart, kidneys, liver, spleen and thymus. Testes, epididymides, seminal vesicles and prostate weights were recorded for all male adult animals. Ovary and uterine weights were recorded for toxicity group females.

Microscopic Examination

Tissues and organs required for histopathological examination from the males and toxicity group females were taken and preserved in fixative.

Organ Weights*	Organs Collected
	Macroscopic lesions
X	Adrenals
X	Brain (including cerebrum, cerebellum and pons)
	Cecum
	Colon
	Duodenum
X	Epididymides
X	Heart
	Ileum
	Jejunum
X	Kidneys
X	Liver
	Lungs (preserved by inflation with fixative and then immersion)
	Lymph nodes (mediastinal and mesenteric)
X	Ovaries
X	Prostate
	Sciatic nerve
X	Seminal vesicles
	Spinal cord (cervical, thoracic and lumbar)
X	Spleen
	Sternum with bone marrow
	Stomach

Organ Weights*	Organs Collected
X	Testes
X	Thymus
	Thyroid
	Trachea
	Urinary bladder
X	Uterus (horns and cervix)

*Paired organs were weighed together; adrenals, epididymides, kidneys, ovaries, testes, and seminal vesicles.

The testes and epididymides were preserved in Bouin's solution. All other tissues were placed in 10% Neutral Buffered Formalin for preservation. A histopathological examination was conducted on the collected tissues from the adult animals in the control and high dose groups (males and toxicity group females). All gross lesions were examined. The liver, lungs, thyroid glands, adrenal glands, kidneys, testes, epididymides and spleen were examined for 50 and 250 mg/kg bw/day males. The liver, lungs, and thyroid glands, were examined for 50 and 250 mg/kg bw/day toxicity group females.

16.6 Reproductive Parameters

The duration of gestation was calculated for each female. Each litter was examined as soon as possible after delivery to determine the number and sex of the pups, the number of pups alive, number of pups dead, runts, and the presence of any gross abnormalities. Live pups were counted, sexed and the sex ratio calculated. Litter weights were taken within 24 hours of parturition and on day 4 post-partum. The day parturition was observed as complete, was considered day 0 post-partum.

16.7 Sample Identification

Samples collected were identified by study number, test system or specimen number, identity/name of sample, date of collection and storage conditions, if appropriate.

17 DATA ANALYSIS

17.1 Parameters to be evaluated

Mean body weight values and body weight changes, mean food consumption values, mean hematology and serum chemistry values, mean terminal organ weights and organ/bodyweight ratios, mean gestation length, mean litter size, mean live litter size, mean litter weight, mean ratio live births/litter size, litter sex ratio, mean number of implantation sites, mean number of corpora lutea, mean mating and fertility indices, and mean neurotoxicological parameters were evaluated, as appropriate.

17.2 Statistical methods

Statistical analysis of reproductive female body weights and changes in body weights, female reproductive group food consumption, reproductive parameters, clinical signs, functional observational battery (FOB) and motor activity, and histological microscopic data were conducted using SAS v9.1.3 (SAS Institute, 2006) and are presented as a contributing scientist

report provided in Appendix R. All other statistical analyses reported were conducted using Provantis™ v8.2 with SAS v9.1.3 (Instem LSS, Conshohocken, PA).

Body weight, changes in body weight, organ weight, organ to body weight ratios, food consumption data, hematology data, serum chemistry and prothrombin times were analyzed using a one-way Analysis of Variance (ANOVA) if the data satisfied the requirements of normality of the residuals and homogeneity of variance as determined using a statistical test for normality and homogeneity of variance (Wilks-Shapiro and Bartlett's. respectively; Gad and Chengelis, 1998). If the data did not satisfy the parametric requirements, a Kruskal-Wallis test was used (Kruskal and Wallis, 1952; Kruskal, 1952). In the case of clinical pathology data a log or rank transformation was performed. If the ANOVA or Kruskal-Wallis test was significant ($p < 0.05$), pair-wise comparisons of the exposed groups to control were made using the Dunnett's test (Dunnett, 1955, 1964) or a Wilcoxon test, respectively.

For variables with multiple measurements across time (motor activity, body weight and food consumption), a repeated measurements ANOVA was performed to determine if a significant time by treatment group interaction exists. Repeated measurements ANOVAs were done using the time (baseline and post-treatment), interval, sex and treatment to look for interactions between the treatment, the time and sex to determine if analysis could be done with the sexes combined.

For those reproductive endpoints that involve occurrences up to birth (corpora lutea counts, total implants, post-implantation losses, days gestation) and for the total number of pups in the litter and total live pups in the litter, an ANOVA was done. If a statistically significant difference across treatment groups was seen, pair-wise comparisons are made between the control group and the treated groups using Dunnett's test. For the remaining endpoints an ANCOVA with the treatment and total litter size as independent variables was done. For all these analyses total litter size is defined as the total number of pups, both alive and dead. If the treatment was a significant variable in the analysis, then pair-wise comparisons are made between the control and each treated group using Dunnett's test and adjusting for the litter sizes.

Measured continuous FOB data were analyzed using a combination of ANCOVA with baseline evaluations used as the covariate and repeated measures ANOVA. Categorical FOB data were analyzed using the Jonckheere-Terpstra test (Jonckheere-Terpstra, 1954).

Microscopic findings were also analyzed using a Cochran-Armitage trend test to indicate an increasing incidence trend regardless of grade with a Fisher's Exact test used to indicate increased incidence (non-grade specific) over the control. In addition, for those microscopic findings with one or more incidences in the control group, the graded animals only were compared using a Kruskal-Wallis test to determine if there was an increase in severity grade between the control group and the treated groups. Pair-wise comparisons of the graded-only animals were done using a Wilcoxon test if the overall Kruskal-Wallis test was significant.

The clinical signs data were analyzed using Mixed Modeling repeated measures. Mixed models represent the fixed effect of treatments and the random effect of variability from animal to animal and observation to observation (within animal). Mixed models are generalizations of standard linear models (e.g., analysis of variance) and the SAS procedure PROC MIXED was used in instances where every animal was not examined at every time point without loss of observations as would occur when using PROC GLM to do a repeated measurement ANOVA. The repeated measures aspect of the analysis recognizes that the variability in the responses is

the result of animal-to-animal variability and of variability among the individual observations within each animal over the course of the study. Using the SAS procedure PROC MIXED, the model was defined as

Response = treatmentgrp,

where, treatmentgrp indicates the class variable associated with each treatment level, with animal within treatment group as the "subject" (where the "subject" is the unit for which there are repeated observations), and the response was a binomial variable indicating that the animal had or did not have a specific abnormal response at each time point for which examination data were available. Such a mixed model represents the mean responses as a function of the treatment group with variation (standard errors) that account for animal-to-animal and within-animal variability. As in an analysis of variance, the treatment groups were examined to determine if there was an overall "treatment effect" and, if there was, then pair-wise comparisons of the individual exposed groups to the control group were completed.

18 PROTOCOL DEVIATIONS

Protocol deviations are presented in Table 36.

19 RESULTS AND DISCUSSION

19.1 Homogeneity, Concentration Verification and Stability for Dosing Solutions

Dose solutions were prepared twice during the study and verification of each dose solution concentration was conducted. For the low concentration dosing solutions (50 mg/kg bw/day group), the mean measured concentrations for the two preparations were 104.2 and 100% of the target concentration. For the mid dose concentration dosing solutions (250 mg/kg group), the mean measured concentrations for the two preparations were 102.5 and 97.9% of the target concentration. The mean measured concentrations for the two preparations of the high dose concentration dosing solutions (1000 mg/kg bw/day group), were 104.0 and 96.0% of the target concentration. Homogeneity was determined for the low (50 mg/kg bw/day group) and high (1000 mg/kg bw/day) dosing solutions and these solutions were found to be homogeneous. Stability of dimethyldimethoxysilane in dried, de-acidified corn oil was determined to be at least 29 days.

19.2 Mortality and Morbidity

All but one animal survived to their scheduled necropsy. Difficulty in gavage administration of the test article solution occurred repeatedly with one animal (D5743) assigned to group 4 (1000 mg/kg bw/day group) of the reproductive group females. Animal D5743 was switched with an animal in the group 4 (1000 mg/kg bw/day) of the toxicity group females (animal D5718). After the switch animal D5718 in the toxicity group females (formerly animal D5743 in the reproductive group females before the switch) was euthanized which reduced the number of animals in the 1000 mg/kg bw/day toxicity group females to nine.

19.3 Clinical Observations

The incidence of clinical observations is summarized in Tables 1-3. Individual clinical examination data are presented in Appendices A-C. Observations recorded during the weekly detailed physical examinations were not different from those recorded during the daily clinical

examinations. Therefore, the findings were combined and are presented in total. For the males at 1000 mg/kg bw/day, significant abnormal observations ($p<0.01$) were noted and included soiling of the chin and urogenital area. Soiling of the chin, muzzle and urogenital areas were significant abnormal observation ($p<0.01$) in the toxicity group females at 1000 mg/kg bw/day. Abdominal, chin, muzzle and urogenital soiling were significant abnormal observations ($p<0.01$) in the reproductive group females at 1000 mg/kg bw/day.

19.4 Body Weight

Summaries of weekly mean body weights are shown in Tables 4-6. Mean body weight gain summaries are shown in Tables 7-11. Individual animal body weight data and body weight gain data are given in Appendices D-F and Appendices G-I, respectively.

There were no statistically significant differences between controls and treatment groups in the mean body weights on any day for any of the three groups: males, toxicity group females, and reproductive group females. There were no statistically significant differences between controls and treatment groups in mean body weight gains for any interval for males and toxicity group females. There was a statistically significant decrease (19%) in body weight gain compared to control values for the reproductive group females during gestational week 3 in the 1000 mg/kg bw/day group. Weight gain for the reproductive group females in the 1000 mg/kg bw/day group was statistically decreased from controls for the interval from day 1 of study to post-partum day 4.

19.5 Food Consumption

Weekly mean food consumption data are presented in Tables 12-14. Individual animal food consumption values are given in Appendices J-L. There were no differences in the average daily food consumption between controls and treatment groups for the males and toxicity group females for any of the measured time periods. In the reproductive group females, at 1000 mg/kg bw/day, there was a significant decrease (35%) in food consumption from controls during the interval post-partum days 0-4.

19.6 Functional Observation Battery and Motor Activity

Functional Observation Battery (FOB) and Motor Activity data are presented in Tables 15-21 and individual animal values presented in a contributing scientist report, Appendix S. No statistically significant differences were observed between the control and treatment groups in either sex at the treated time point for all the FOB ranked tests. There were no statistically significant differences between either males or toxicity group females and their respective controls for the FOB continuous test and motor activity.

19.7 Clinical Pathology

Clinical Chemistry

Group mean summaries of serum chemistry data are presented in Tables 22 and 23 and individual values are given in Appendix T.

Statistically significant differences were observed in the male rats (Table 24) for alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, BUN, glucose, calcium, total protein and sodium. Alkaline phosphatase (group 4, 93.2 U/L), aspartate aminotransferase (group 4, 55.5 U/L), total bilirubin (group 4, 0.081 mg/dL), and sodium (group

4, 139.7) were statistically decreased (p<0.01) in male rats at 1000 mg/kg bw/day; -34, -35, -23.6, and -1.4%, respectively. A significant increase (*p*<0.01) for alanine aminotransferase (43.7 U/L), total protein (6.10 g/dL), BUN (15.5 mg/dL), glucose (143.7 mg/dL), and calcium (10.27 mg/dL) was seen in males at 1000 mg/kg bw/day; 96.0, 8.5, 33.6, 19.4 and 4.4%, respectively. These parameters were within historical control ranges of this laboratory for male Sprague-Dawley rats: alkaline phosphatase (80-227 U/L), aspartate aminotransferase (55.0-129.0 U/L), total bilirubin (0.07-0.31 mg/dL, calcium (9.2-11.2 mg/dL), glucose (97.0-249.0 mg/dL), total protein (5.2-6.7 g/dL), BUN (9.0-17.0 mg/dL) and sodium (139.0-146.0 mmol/L). The group mean value for alanine aminotransferase was above the historical control of 13.0-36.0 U/L.

Statistically significant differences were observed in toxicity group females at 1000 mg/kg bw/day rats (Table 25) for alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin, BUN, creatinine and cholesterol. Alkaline phosphatase (41.9U/L), bilirubin (0.088 mg/dL), albumin (3.84 mmol/L), and creatinine (0.30 mg/dL) were statistically decreased (p <0.01); -42.8, -37.1, -11.3, and -18.9%, respectively. A significant increase (*p*<0.01) for alanine aminotransferase (35.4 U/L), BUN (19.3 mg/dL) and cholesterol (109.9 mg/dL) was seen in group 4; 96.7, 34.0, and 108.1%, respectively. Most group means values were within historical control ranges of this laboratory for female Sprague-Dawley rats: alkaline phosphatase (36-125 U/L), alanine aminotransferase (11.0-56.0 U/L), albumin (2.9-5.2 g/dL), BUN (9-20 mg/dL), and creatinine (0.3-0.6 mg/dL). The group mean value for total bilirubin was slightly below the historical control range of 0.09-0.34 mg/dL and the group mean value for cholesterol was above the historical control range of 31-99 mg/dL

Hematology

Group mean summaries of hematology parameters are given in Tables 24-27 and Appendix T.

Male rats (Table 19) in group 4 compared to control had statistically significant decreases for hemoglobin and hematocrit (p<0.01), and red blood cell count (p<0.05); -9.5, -8.7, and -6.5%, respectively. The group mean values for hemoglobin (13.76 g/dL), red blood cell count (7.128x106/uL) and hematocrit (38.72%) were within or slightly below historical control ranges (13.6-16.1 g/dL, 7.2-8.9x106/uL and 40.0-45.9%, respectively).

Statistically significant decreases for hemoglobin (p<0.01), mean cell volume (p<0.05) and mean cell hemoglobin (p<0.01) were observed between control and group 4, toxicity group females (Table 20); -5.1, -3.2, and -5.2%, respectively. The group mean values for hemoglobin (14.24 g/dL), mean cell volume (55.78 fL) and mean cell hemoglobin (19.24 pg). These were within historical control ranges of hemoglobin, mean cell volume and mean cell hemoglobin; 13.8-15.8 g/dL, 52.8-64.2fL, and 17.7-21.4 pg, respectively.

Male rats in group 4 had a statistically significant increase in monocytes (p<0.05) and statistically significant decreases in relative and absolute eosinophils (p<0.05) compared to controls. The group mean values were monocytes (8.24%), eosinophils (1.07%) and absolute eosin ($0.0935x10^3$/uL). Group mean values for monocytes and eosinophils were within historical control ranges for male rats, 0.1-10.7% and 0.7-3.6%, respectively. The group mean value for absolute eosinophils was slightly below the historical control range of $0.1-0.3x10^3$/uL.

Toxicity group female rats in group 4 had a statistically significant increase in monocytes (8.33% at p<0.01) although the value fell within the historical control range of 0.2-12.0%.

Coagulation (Prothrombin Times)

Prothrombin times are summarized in Table 28-29 and Appendix T.

No statistically significant differences between control and treatment groups were noted for prothrombin times in male rats (Table 23). Toxicity group females in group 4 had a statistically significant decrease, -5.8%, in prothrombin times. Statistically significant prothrombin times were within historical control ranges, however, there was a dose-related decrease. Changes in prothrombin times were considered treatment-related and of no toxicological significance.

19.8 Organ Weights

Organ weight and organ to body weight ratios are summarized in Tables 30-31 and individual animal data are presented in Appendices M-N.

There were statistically significant differences compared to controls noted for the following organ weights in males: adrenal glands (24% decrease at 1000 mg/kg bw/day at $p < 0.01$), liver (18% increase at 250 and 60% increase at 1000 mg/kg bw/day at $p < 0.05$ and $p < 0.01$, respectively), testes (31% decrease at 1000 mg/kg bw/day at $p < 0.01$), thymus (47% decrease at 1000 mg/kg bw/day at $p < 0.01$), epididymides (16% decrease at 1000 mg/kg bw/day at $p < 0.01$), prostate gland (26% decrease at 1000 mg/kg bw/day at $p < 0.05$) and seminal vesicles (24% decrease at 1000 mg/kg bw/day at $p < 0.05$). There were statistically significant differences for the mean percentage of organ weights relative to body weights for adrenal glands (decrease at $p < 0.05$), liver (increase at 250 and 1000 mg/kg bw/day at $p < 0.01$), thymus (decrease at $p < 0.01$) and testes (decrease at $p < 0.01$) for males.

There were statistically significant differences noted liver weights in toxicity group females compared to controls: liver (17% increase at 250 and 92% increase at 1000 mg/kg bw/day at $p < 0.01$) and spleen (21% decrease at 1000 mg/kg bw/day at $p < 0.01$). There were statistically significant differences for the mean percentage of organ weights relative to body weights for liver (increase at 250 and 1000 mg/kg bw/day at $p < 0.01$) and spleen (decrease at 1000 mg/kg bw/day at $p < 0.01$) for the toxicity group females.

The increased liver weights in males and toxicity group females correlated with the histopathologic finding of panlobular and/or centrilobular hypertrophy.

19.9 Morphological Pathology

Morphologic pathology data are presented in a contributing scientist report in Appendix U.

Macroscopic Examination:

Macroscopic pathology data are presented in Table 32 and a contributing scientist report in Appendix U.

In the liver, the finding of discoloration (unspecified, dark or mottled) was observed in 9/10 rats of both sexes administered 1000 mg/kg bw/day and 1-2 animals of each sex at 250 mg/kg bw/day. The adrenal glands appeared enlarged in 1-2 females/group administered ≥250 mg/kg bw/day. The adrenal glands appeared decreased in size in 2 males administered 1000 mg/kg bw/day. The ovaries appeared enlarged in one female/group administered ≥50 mg/kg bw/day. The seminal vesicles appeared small in 4 males administered 1000 mg/kg bw/day, and in one animal each at the 50 and 250 mg/kg bw/day dosage levels. Splenic discoloration, dark or white, was observed in 4 males administered 1000 mg/kg bw/day and one dosed at 50 mg/kg bw/day. The thymus appeared small in 4 males administered 1000 mg/kg bw/day and one dosed at 250 mg/kg bw/day. Other findings generally occurred singly and were probably not attributable to test article administration.

Microscopic Pathology
The incidence and severity of microscopic findings are summarized in Tables 33-34 and individual animal data are presented in a contributing scientist report in Appendix U.

Males
Liver

There were two primary liver findings in male rats. In the liver of male rats, the incidence of panlobular hypertrophy was significantly increased ($p<0.01$) in the 1000 mg/kg bw/day groups (10/10 animals) over control. The increased incidence of panlobular hypertrophy identified correlates with the statistically significant increase in relative liver weight observed for these groups. This is a common effect of xenobiotic administration and is considered an adaptive change (Cattley and Popp, 2002).

Additionally, in males, there was minimal to moderate, statistically significant at $p<0.02$, brown pigment accumulation in 5/10 male rats given 1000 mg/kg bw/day and minimal accumulation of the pigment in 1/10 male rats given 250 mg/kg bw/day (not statistically significant at this level). The pigment accumulation was almost always associated with bile duct hyperplasia and chronic inflammation. The pigment was birefringent under polarized light, appearing bright red with Maltese cross patterns, characteristic of protophorphyrin (Greaves 2000; DeMatteis *et al.*, 1987). The finding was divided into three components 1) protoporphyrin accumulation, 2) periportal chronic inflammation associated with protoporphyrin accumulation, and 3) bile duct hyperplasia associated with protoporphyrin accumulation. The severity of the inflammatory and bile duct hyperplasia components generally closely matched the pigment accumulation. The brown pigment was not observed in control animals, males administered 50 mg/kg bw/day, or in any toxicity group female rats. Periportal chronic inflammation (4/10 animals, $p<0.05$), hyperplasia in the bile ducts associated with protoporphyrin accumulation (4/10 animals, $p<0.05$), and protoporphyrin accumulation (5/10 animals) showed significant increase in incidence ($p<0.02$) over control only in the 1000 mg/kg bw/day group. For these microscopic findings in the liver, there were no significant shifts in severity across treatment groups.

Adrenal Glands

There was minimal adrenal cortical atrophy in 5/10 male rats administered 1000 mg/kg bw/day; this result was statistically significant at $p<0.02$. The finding was not observed in control rats, at lower dosage levels, or in any toxicity group female rats.

Testes

There was moderate to marked seminiferous tubule degeneration observed in all 1000 mg/kg bw/day male rats, significant at $p<0.01$. Minimal seminiferous tubule degeneration was recorded for one male rat dosed at 250 mg/kg bw/day (not statistically significant). The finding was not observed in control rats or those administered 50 mg/kg bw/day. The finding was characterized by degeneration of spermatocytes that appeared to be arrested and dying while in meiotic division (to become spermatids) or degenerating at earlier spermatocyte stages. Because of cell death at the meiotic spermatocyte stage, meiotic spindles were observed much more commonly in the high-dose males than in controls.

Epididymides

The beginning of the downstream effect of the spermatocyte degeneration in the testes was observed in the epididymides of all 1000 mg/kg bw/day male rats. A mild increase in immature

spermatids was observed throughout the epididymides in 10/10 animals, significant at $p<0.01$, however they were especially common in the head portion. A minimal number of immature spermatids were observed in one 250 mg/kg bw/day male rat. Mild to moderate hypospermia, statistically significant at $p<0.01$, in 9/10 animals was also observed at the highest dosage, but it should be noted that this was largely confined to the head of the epididymides. Sperm numbers appeared to be near normal in the remainder of the epididymides. The transit time of maturing sperm and storage in the epididymides is approximately 8 days in the rat. It is possible that with exposure to the test article for a longer duration, hypospermia may be observed throughout the epididymides.

Kidneys

Findings consistent with minimal alpha-2-U-nephropathy (Hard *et al.*, 1999) were observed in all male rats administered 1000 mg/kg bw/day at a significance of $p<0.01$. The finding was characterized by a subtle increase in eosinophilic rhomboidal or needle-shaped crystalline cytoplasmic inclusions in renal proximal tubule epithelial lining cells, and a small increase in degenerating and sloughing cells in this same cell population. The finding was not detected in lower dose level males.

Lung

There was minimal to mild, focal and multifocal, pulmonary histiocytosis (aggregates of foamy macrophages) in males. A trend was observed across dose levels for focal histiocytosis. When the incidences of histiocytosis, multifocal and focal, were combined and statistically analyzed, statistical significance was achieved in the 1000 mg/kg bw/day dose level at $p<0.05$. Among males, 4/10 controls and 9/10 high dose rats were affected. This is a very common spontaneous finding (Renne *et al.*, 2003) and there was no clear increase in severity associated with dosage. This finding may be attributable to test article administration.

Spleen

Mild to moderate chronic inflammation of the splenic serosa (outside surface of capsule) was observed to be more common in males administered 1000 mg/kg bw/day. In the minimal degree it also occurred in control and low-dose male rats, and in a single control toxicity group female. In the more severe degrees (mild to moderate), the finding was characterized by fibrotic plaques with lymphocyte aggregates on the surface of the spleen. This finding correlates with the gross finding of surface discolorations on the spleen and is not attributable to a direct toxic effect of the test article.

Thyroid Gland

There was minimal to moderate thyroid follicular cell hypertrophy in all rats administered 1000 mg/kg bw/day and a statistically significant increase in the incidence ($p<0.01$) of thyroid gland follicular hypertrophy compared to the control group; comparison of the graded male animals showed a significant increase in severity grade across treatment groups. Hypertrophy of the thyroid follicular epithelium is a common secondary response to increased thyroid hormone catabolism due to up-regulation of hepatic microsomal enzymes in response to xenobiotic administration (Capen *et al.*, 2002). The rat is particularly sensitive to this effect due to the species' lack of a protective carrier protein, thyroid binding globulin.

Females

Liver

In the liver, the incidence of panlobular hypertrophy was significantly increased ($p<0.01$) at 1000 mg/kg bw/day in the toxicity group females (in 9/9 animals). When panlobular hypertrophy was combined with centrilobular hypertrophy (8/10 animals), the incidence was a statistically significant increased ($p<0.01$) compared to controls at 250 mg/kg bw/day The increased incidence of panlobular and centrilobular hypertrophy identified correlates with the statistically significant increase in absolute and relative liver weight observed for these groups. This is a common effect of xenobiotic administration and is considered an adaptive change (Cattley and Popp, 2002).

For liver periportal vacuolation, only the 1000 mg/kg bw/day toxicity group females (8/9 animals) was significantly ($p<0.02$) increased in incidence over the control group. It is generally but not universally held that this finding in and of itself is not considered adverse unless severe (Cattley and Popp, 2002).

Lung

There was minimal to mild, multifocal, pulmonary histiocytosis (aggregates of foamy macrophages) in toxicity group females at $p<0.05$. Among females, 0/9 controls and 4/9 high dose rats were affected. This is a very common spontaneous finding (Renne *et al.*, 2003) and there was no clear increase in severity associated with dosage. When the incidences of histiocytosis, multifocal and focal, were combined and statistically analyzed, no statistical significance was achieved. This finding is not considered to be attributable to test article administration.

Thyroid Gland

There was minimal to moderate thyroid follicular cell hypertrophy in all rats administered 1000 mg/kg bw/day that was statistically significantly increased in incidence ($p<0.01$) compared to the control group (0/10 animals). Hypertrophy of the thyroid follicular epithelium is a common secondary response to increased thyroid hormone catabolism due to up-regulation of hepatic microsomal enzymes in response to xenobiotic administration (Capen *et al.*, 2002). The rat is particularly sensitive to this effect due to the species' lack of a protective carrier protein, thyroid binding globulin.

19.10 Reproductive Parameters

The mean values for reproductive parameters are presented in Table 35 and individual animal data are given in Appendix O. Three reproductive females, D5683 (Group 2, 50 mg/kg bw/day group), D5736 (group 4, 1000 mg/kg bw/day group), and D5738 (group 4, 1000 mg/kg bw/day group), did not show positive evidence of mating and were found to be non-pregnant. Reproductive group female, D5678, (Group 2, 50 mg/kg bw/day group) did show positive evidence of mating, but was also not pregnant.

There were no statistically significant differences across treatment groups for corpora lutea counts and total implants. However, there were statistically significant differences across treatment groups for post-implantation losses, days of gestation, total pups and total live pups with the 1000 mg/kg bw/day group having significantly more post-implantation losses, a longer

gestation period, fewer pups in the litter and fewer live pups in the litter than were seen in the control group.

There were no statistically significant differences across treatment groups for the number of male pups, the number of female pups and the male/female ratio although there was a significant litter size effect for both the number of male and number of female pups with a fewer number of male pups than female pups appearing in smaller litter sizes (see individual animal data).

The day 4 viable number of pups and the ratio of the number of viable pups to the total litter size was significantly different across doses with the 1000 mg/kg bw/day group having fewer viable pups by day 4 and a smaller viable/total ratio than did the control group. The litter size was also a significant variable for the number of viable pups at day 4 as larger litters had more viable pups by day 4 but, when expressed as a ratio of the viable pups to total litter size, the litter size was no longer significant.

The initial litter weight and average pup weights (defined using the live pup litter weight divided by the total number of live pups on day 0) were significantly different across treatments with only the 250 mg/kg bw/day group having a significantly different litter weight and average pup weight compared to the control group after adjusting for litter size. The litter size was also a significant variable for these two endpoints with larger litters having larger litter weights but smaller average pup weights.

For the final litter weight and average pup weights, there was also a significant difference across groups but it was the 1000 mg/kg bw/day group that was significantly different with both smaller overall litter weights and smaller average pup weight compared to the control group. Again the litter size was a significant variable with smaller litters having an overall smaller litter weight but the larger litters having a smaller average pup weight.

The percentage of post-natal loss was significantly different across treatment groups with the 1000 mg/kg bw/day having a significantly higher loss than did the control group and the litter size was also significant with the largest percentage of loss appearing in the largest litter of the 1000 mg/kg bw/day group (100% loss in a litter of 13).

20 CONCLUSIONS

Based on results observed at 1000 mg/kg bw/day in male rats (hepatic protoporphyrin accumulation, adrenal cortical atrophy, kidney hyaline droplets, testicular seminiferous tubule degeneration with epididymides involvement) and in female rats (periportal vacuolation), the NOAEL (No-Observed-Adverse-Effect-Level) for systemic toxicity of dimethyldimethoxysilane is 250 mg/kg bw/day. Based on observations at 1000 mg/kg bw/day (an increase in post-implantation loss, an increase in days of gestation, a decrease in live pups, a decrease in the total viable pups/total, a decrease in final litter weight, a decrease in final average pup weight and an increase in the % of post-natal loss), the NOAEL for reproductive and developmental toxicity is 250 mg/kg bw/day.

21 ARCHIVE

All work product including the protocol, amendments and deviations, study authorization form, raw data, correspondence, samples/specimens, and final report (at a minimum) were retained for up to five years at the HES Archives, Dow Corning Corporation, 2200 W. Salzburg Road, Auburn, MI 48611. Thereafter, the Sponsor will be contacted for the disposition of the

archived material. The Sponsor will then assume responsibility for the archived materials and any expense for further archiving, disposal, and/or shipment.

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Table 1 - Combined Clinical Observations and Detailed Physical Examination Summary: Male Rats

Clinical Signs
(number of occurrences/number of animals)

	Control (0 mg/kg/day)		50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day	
Toxicity Males						
No Significant Clinical observations	298/10		296/10	296/10	177/10	
Soiling: Abdomen, General (unspecified, clear, red, or yellow)	1/1		0/0	2/1	9/3	
Soiling: Chin (clear or red)	0/0	***	0/0	1/1	17/7	***
Soiling: Muzzle, General (clear, red or yellow)	2/2		4/3	0/0	13/4	
Soiling, Perineal (clear or unspecified)	0/0		0/0	0/0	8/3	
Soiling: Urogenital, General (yellow)	0/0	***	0/0	3/2	101/9	***

Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

Unspecified equals urine.

Table 2 - Combined Clinical Observations and Detailed Physical Examination Summary: Toxicity Group Female Rats

Clinical Signs
(number of occurrences/number of animals)

	Control (0 mg/kg/day)		50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day	
No Significant Clinical observations	274/10		289/10	288/10	203/10	
Skin, Scab: Muzzle, Left or Right (focal)	2/1		0/0	0/0	0/0	
Soiling: Abdomen, General (unspecified, clear, red, or yellow)	0/0		0/0	0/0	4/1	
Soiling: Chin (clear or red)	0/0	***	0/0	0/0	16/5	***
Soiling: Eye, Left (red)	7/1		0/0	0/0	0/0	
Soiling: Head, General (red)	0/0		0/0	0/0	4/1	
Soiling: Muzzle, General (clear, red or yellow)	2/1	***	0/0	0/0	36/6	***
Soiling: Nose (red)	4/2		1/1	2/1	1/1	
Soiling: Urogenital, General (yellow)	1/1	**	0/0	0/0	22/4	***

Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

Table 3 - Combined Clinical Observations and Detailed Physical Examination Summary: Reproductive Group Female Rats

	Clinical Signs (number of occurrences/number of animals)					
	Control (0 mg/kg/day)		50 mg/kg/day	250 mg/kg/day	1000 mg/kg/day	
Reproductive Females						
No Significant Clinical observations	388/9 [a]		424/10	427/10	380/10	
Skin Abcess(es): Muzzle, Right	4/1		0/0	0/0	0/0	
Skin, Excessive Hair Loss (minimal 10-30%)	42/1		10/1	0/0	0/0	
Skin, Scab: Forepaw, Bilateral (multifocal)	0/0		0/0	0/0	4/1	
Skin, Scab: Muzzle, Left or Right (focal)	3/1		0/0	0/0	9/2	
Skin, Scab: Neck, Right (focal)	5/1		0/0	0/0	0/0	
Soiling: Abdomen, General (unspecified, clear, red, or yellow)	0/0	***	0/0	0/0	19/6	***
Soiling: Chin (clear or red)	0/0	***	0/0	11/3	26/7	***
Soiling: Eye, Left (red)	0/0		0/0	1/1	0/0	
Soiling: Head, General (red)	1/1		9/4	4/2	4/2	
Soiling: Muzzle, General (clear, red or yellow)	0/0	***	3/1	5/4	20/7	***
Soiling: Nose (red)	2/1		3/1	2/2	0/0	
Soiling: Urogenital, General (yellow)	0/0	***	0/0	2/1	31/6	***

Asterisks indicate a significant difference across treatment groups (in the control column) or between control and a treatment group with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

[a]N=9 since ane animal in control group always had significant clinical observations

Table 4 - Summary of Weekly Mean Body Weights (grams): Male Rats

		Day(s) Relative to Start Date				
		1	8	15	22	29 *
0 mg/kg	Mean	309.19	339.37	370.37	401.10	429.02
	SD	9.60	15.66	16.49	19.94	22.13
	N	10	10	10	10	10
50 mg/kg	Mean	314.61	346.51	382.40	409.02	437.23
	SD	15.00	24.45	32.73	37.01	42.24
	N	10	10	10	10	10
250 mg/kg	Mean	314.41	349.67	385.84	412.99	438.99
	SD	16.26	26.84	33.26	36.86	42.39
	N	10	10	10	10	10
1000 mg/kg	Mean	310.38	341.71	364.88	379.99	397.10
	SD	13.17	21.26	24.98	30.21	34.27
	N	10	10	10	10	10

* $p < 0.05$ significance level

Asterisks indicate a significant difference across treatment groups (in day row) or between control and a treatment group.

Table 5 - Summary of Weekly Mean Body Weights (grams): Toxicity Group Female Rats

		Day(s) Relative to Start Date				
		1	8	15	22	28
0 mg/kg	Mean	219.38	227.27	237.13	247.32	254.51
	SD	13.49	15.60	18.74	22.73	23.37
	N	10	10	10	10	10
50 mg/kg	Mean	219.14	233.05	245.75	257.25	264.69
	SD	14.74	17.23	21.23	22.97	24.86
	N	10	10	10	10	10
250 mg/kg	Mean	217.19	229.14	242.03	254.22	257.90
	SD	10.06	14.93	18.63	18.73	22.20
	N	10	10	10	10	10
1000 mg/kg	Mean	216.30	225.34	242.56	246.78	250.49
	SD	10.83	12.49	17.52	19.73	19.81
	N	9	9	9	9	9

Table 6 - Summary of Weekly Mean Body Weights (grams): Reproductive Group Female Rats

		BW 1 (g)	BW 8 (g)	BW 15 (g)	BW 22 (g)	Gest BW 0 (g)	Gest BW 7 (g)	Gest BW 14 (g)
0 mg/kg	Mean	214.84	221.46	230.98	.	243.73	274.37	308.74
	SD	12.71	17.99	22.78	.	24.11	23.89	24.67
	N	10	10	10	.	10	10	10
50 mg/kg	Mean	214.73	227.54	238.77	.	252.06	283.05	322.01
	SD	11.40	16.44	19.35	.	8.16	8.44	11.93
	N	10	10	10	.	8	8	8
250 mg/kg	Mean	215.55	223.50	236.48	287.00	245.38	275.62	309.93
	SD	5.94	12.04	13.29	.	20.98	20.23	19.23
	N	10	10	10	1	10	10	10
1000 mg/kg	Mean	222.81	235.26	249.67	.	251.06	278.64	308.11
	SD	15.34	17.79	20.53	.	26.28	25.03	26.66
	N	10	10	10		8	8	8

BW = Body Weight
Gest = Gestational Day

Table 6 - Summary of Weekly Mean Body Weights (grams): Reproductive Group Female Rats (continued)

		Gest BW 20* (g)	P-Partum BW 0 (g)	P-Partum BW 4* (g)
0 mg/kg	Mean	387.31	301.78	318.54
	SD	24.44	27.12	28.93
	N	10	10	10
50 mg/kg	Mean	410.44	308.58	334.11
	SD	18.49	13.60	11.09
	N	8	8	8
250 mg/kg	Mean	392.61	302.79	313.87
	SD	23.40	21.41	25.54
	N	10	10	10
1000 mg/kg	Mean	371.65	287.01	292.69
	SD	33.66	31.04	34.13
	N	8	8	8

BW = Body Weight
Gest = Gestational Day
P-Partum = Post-Partum Day
* = $p < 0.05$ significance level
Asterisks indicate a significant difference across treatment groups (in day row) or between control and a treatment group.

Table 7 - Summary of Weekly Mean Body Weight Gain (grams): Male Rats

		Day(s) Relative to Start Date			
		1 → 8	8 → 15 **	15 → 22 **	22 → 29 *
0 mg/kg	Mean	30.18	31.00	30.73	27.92
	SD	7.94	5.49	9.91	10.33
	N	10	10	10	10
50 mg/kg	Mean	31.90	35.89	26.62	28.21
	SD	12.22	10.68	9.62	7.10
	N	10	10	10	10
250 mg/kg	Mean	35.26	36.17	27.15	26.00
	SD	12.27	8.58	6.09	8.17
	N	10	10	10	10
1000 mg/kg	Mean	31.33	23.17	15.11 **	17.11 *
	SD	10.38	8.33	9.18	7.93
	N	10	10	10	10

** = $p < 0.01$ significance level

* = $p < 0.05$ significance level

Asterisks indicate a significant difference across treatment groups (in day row) or between control and a treatment group.

Table 8 - Summary of Total Body Weight Gain (grams): Male Rats

		Day(s) Relative to Start Date
		1 → 29
0 mg/kg	Mean	119.83
	SD	18.07
	N	10
50 mg/kg	Mean	122.62
	SD	29.37
	N	10
250 mg/kg	Mean	124.58
	SD	28.23
	N	10
1000 mg/kg	Mean	86.72 *
	SD	23.33
	N	10

* = $p < 0.05$ significance level

Table 9 - Summary of Weekly Mean Body Weight Gain (grams): Toxicity Group Female Rats

		Day(s) Relative to Start Date			
		1 → 8	8 → 15	15 → 22	22 → 28
0 mg/kg	Mean	7.89	9.86	10.19	7.19
	SD	4.72	8.12	7.91	7.58
	N	10	10	10	10
50 mg/kg	Mean	13.91	12.70	11.50	7.44
	SD	5.09	7.49	7.74	5.22
	N	10	10	10	10
250 mg/kg	Mean	11.95	12.89	12.19	3.68
	SD	7.86	7.50	5.66	6.51
	N	10	10	10	10
1000 mg/kg	Mean	9.04	17.21	4.22	3.71
	SD	6.26	7.66	7.44	5.09
	N	9	9	9	9

Table 10 - Summary of Total Body Weight Gain (grams): Toxicity Group Female Rats

		Day(s) Relative to Start Date
		1 → 28
0 mg/kg	Mean	35.13
	SD	14.67
	N	10
50 mg/kg	Mean	45.55
	SD	13.90
	N	10
250 mg/kg	Mean	40.71
	SD	16.36
	N	10
1000 mg/kg	Mean	34.19
	SD	13.65
	N	9

Table 11 - Summary of Weekly Mean Body Weight Gain (grams): Reproductive Group Female Rats

		Repro 1-8 (g)	Repro 8-15 (g)	Gest 0-7 (g)	Gest 7-14 (g)	Gest 14-20** (g)	P-Partum 0-4*** (g)	Total BW Change*** (g)
0 mg/kg	Mean	6.62	9.52	30.64	34.37	78.57	16.76	103.70
	SD	9.68	6.83	7.49	5.10	6.76	9.90	23.01
	N	10	10	10	10	10	10	10
50 mg/kg	Mean	12.81	11.23	30.99	38.96	88.43	25.54	116.90
	SD	7.27	5.21	7.02	8.49	9.39	8.08	14.88
	N	10	10	8	8	8	8	8
250 mg/kg	Mean	7.95	12.98	30.24	34.31	82.68	11.08	98.32
	SD	9.00	4.37	6.75	5.32	11.75	10.42	23.81
	N	10	10	10	10	10	10	10
1000 mg/kg	Mean	12.45	14.41	27.58	29.48	63.54 **	5.68	69.24 **
	SD	5.69	5.98	5.57	3.56	14.51	12.77	28.74
	N	10	10	8	8	8	8	8

* = p < 0.05 significance level
** = p < 0.02 significance level
*** = p < 0.01 significance level
Asterisks indicate a significant difference across treatment groups (in day row) or between control and a treatment group.
Repro = Pre-mating Body Weight Days
Gest = Gestational Days
P-Partum = Post-Partum Days

Table 12 - Summary of Weekly Mean Food Consumption (grams/animal/day): Male Rats

		Day(s) Relative to Start Date		
		Mean Food Consumption (g/day)	Mean Food Consumption (g/day)	Total Food Consumption (g/day)
		1 → 8	8 → 15	1 → 15
0 mg/kg	Mean	23.02	23.68	326.90
	SD	2.05	1.70	22.76
	N	10	10	10
50 mg/kg	Mean	24.06	25.00	343.45
	SD	3.51	3.39	47.21
	N	10	10	10
250 mg/kg	Mean	26.48	24.94	359.98
	SD	3.58	3.08	45.56
	N	10	10	10
1000 mg/kg	Mean	24.68	21.94	326.33
	SD	2.18	2.44	30.08
	N	10	10	10

Table 13 - Summary of Weekly Mean Food Consumption (grams/animal/day): Toxicity Group Female Rats

		Day(s) Relative to Start Date				
		Mean Food Consumption (g/day)	Mean Food Consumption (g/day)	Mean Food Consumption (g/day)	Mean Food Consumption (g/day)	Total Food Consumption (g)
		1 → 8	8 → 15	15 → 22	22 → 28	1 → 28
0 mg/kg	Mean	15.92	17.13	17.63	16.03	450.95
	SD	1.72	2.10	2.10	2.71	54.71
	N	10	10	10	10	10
50 mg/kg	Mean	17.32	18.02	18.48	15.99	472.64
	SD	1.74	1.68	2.82	1.56	49.90
	N	10	10	10	10	10
250 mg/kg	Mean	18.27	16.93	18.02	15.70	466.71
	SD	2.79	2.83	2.35	2.37	65.26
	N	10	10	10	10	10
1000 mg/kg	Mean	16.27	16.62	17.98	17.10	458.68
	SD	1.28	1.80	1.76	2.83	39.38
	N	9	9	9	9	9

Table 14 - Summary of Weekly Mean Food Consumption (grams/animal/day): Reproductive Group Female Rats

		1-8 (grams/day)	8-15 (grams/day)	Pre-Mating Total (g)	Gest 0-7 (grams/day)	Gest 7-14 (grams/day)	Gest 14-20 (grams/day)	Gestational Total (g)
0mg/kg	Mean	15.58	16.83	226.84	18.16	18.88	22.09	391.82
	SD	2.19	2.18	30.00	2.10	2.78	2.13	44.96
	N	10	10	10	10	10	10	10
50mg/kg	Mean	16.67	17.49	239.11	18.93	19.94	21.99	404.05
	SD	1.28	1.79	20.54	0.95	1.43	1.66	17.61
	N	10	10	10	8	8	8	8
250mg/kg	Mean	17.07	15.96	231.24	17.25	18.71	23.16	390.60
	SD	2.28	2.15	29.57	1.20	1.67	2.04	29.45
	N	10	10	10	10	10	10	10
1000 mg/kg	Mean	17.59	17.81	247.82	18.59	20.44	22.78	409.93
	SD	2.08	1.97	27.52	1.61	3.08	2.03	40.32
	N	10	10	10	8	8	8	8

Table 14 - Summary of Weekly Mean Food Consumption (grams/animal/day): Reproductive Group Female Rats (continued)

		PP FC 0-term** (grams/day)	P-Partum Total (g)	Total Food Consumed (g)
0mg/kg	Mean	32.17	128.69	747.35
	SD	7.34	29.37	89.82
	N	10	10	10
50mg/kg	Mean	37.35	149.41	727.49
	SD	3.27	13.09	197.55
	N	8	8	9
250mg/kg	Mean	30.46	121.82	743.66
	SD	5.73	22.92	69.73
	N	10	10	10
1000 mg/kg	Mean	20.76 **	83.05	642.20
	SD	5.71	22.84	223.76
	N	8	8	10

** = p < 0.01 significance level

Asterisks indicate a significant difference across treatment groups (in day row) or between control and a treatment group.

Table 15 - Summary of FOB Ranked Observations: Male Rats

Endpoint	Time	#Examined / Response	Control (0 mg/kg bw/day)	50 mg/kg bw/day	250 mg/kg bw/day	1000 mg/kg bw/day
Resistance to Removal	Baseline	# Examined	10	10	10	10
		Moderate; actively avoids capture but is not aggressive	10	10	10	8
		Pronounced; actively avoids capture and/or is mildly aggressive	0	0	0	2
	Treated	# Examined	10	10	10	10
		Moderate; actively avoids capture but is not aggressive	10	10	10	10
Palpebral Closure	Baseline	# Examined	10	10	10	10
		Open	10	10	10	10
	Treated	# Examined	10	10	10	10
		Open	10	10	10	10
Pupil Reactivity	Baseline	# Examined	10	10	10	10
		Dilated, briskly reactive pupil	10	10	10	10
	Treated	# Examined	10	10	10	10
		Dilated, briskly reactive pupil	10	10	10	10
Pupil Size	Baseline	# Examined	10	10	10	10
		Normal pupil size	10	10	10	10
	Treated	# Examined	10	10	10	10
		Normal pupil size	10	10	10	10
Lacrimation	Baseline	# Examined	10	10	10	10
		Glistening cornea	10	10	10	10
	Treated	# Examined	10	10	10	10
		Glistening cornea	10	10	10	10
Salivation	Baseline	# Examined	10	10	10	10
		Glistening oral cavity/lips, no wetness	10	10	10	10
	Treated	# Examined	10	10	10	10
		Glistening oral cavity/lips, no wetness	10	10	10	10

Table 15 - Summary of FOB Ranked Observations: Male Rats (continued)

Endpoint	Time	#Examined / Response	Control (0 mg/kg bw/day)	50 mg/kg bw/day	250 mg/kg bw/day	1000 mg/kg bw/day
Muscle Tone	Baseline	# Examined	10	10	10	10
		Moderate; animal is neither very relaxed nor tense	10	10	10	10
	Treated	# Examined	10	10	10	10
		Moderate; animal is neither very relaxed nor tense	10	10	10	10
Extensor Thrust	Baseline	# Examined	10	10	10	10
		Moderate; clearly detectable	10	9	10	10
		Pronounced; pushes vigorously	0	1	0	0
	Treated	# Examined	10	10	10	10
		Moderate; clearly detectable	7	8	8	9
		Pronounced; pushes vigorously	3	2	2	1
Reactivity to Handling	Baseline	# Examined	10	10	10	10
		Moderate struggling with little or no vocalization	10	10	10	8
		Pronounced struggling, animal may vocalize	0	0	0	2
	Treated	# Examined	10	10	10	10
		Moderate struggling with little or no vocalization	10	8	10	10
		Pronounced struggling, animal may vocalize	0	2	0	0
Level of Activity	Baseline	# Examined	10	10	10	10
		Moderate; inactive less than 50% of the time	10	10	10	10
	Treated	# Examined	10	10	10	10
		Minimal; inactive more than 50% of the time	6	1	4	5
		Moderate; inactive less than 50% of the time	4	9	6	5

Table 15 - Summary of FOB Ranked Observations: Male Rats (continued)

Endpoint	Time	#Examined / Response	Control (0 mg/kg bw/day)	50 mg/kg bw/day	250 mg/kg bw/day	1000 mg/kg bw/day
Response to Sharp Noise	Baseline	# Examined	10	10	10	10
		Minimal; only the ears and/or head moves	0	0	2	2
		Moderate; clear movement of the head, neck, ears and possibly shoulders/upper body	10	9	8	5
		Pronounced; clear movement of head, neck and ears, plus clear movement of whole body.	0	1	0	3
	Treated	# Examined	10	10	10	10
		Minimal; only the ears and/or head moves	0	1	1	0
		Moderate; clear movement of the head, neck, ears and possibly shoulders/upper body	10	7	7	8
		Pronounced; clear movement of head, neck and ears, plus clear movement of whole body.	0	2	2	2
Response to Touch	Baseline	# Examined	10	10	10	10
		Moderate; spontaneously lifts tail when touched	10	9	10	10
		Pronounced; spontaneously lifts tail and acts startled	0	1	0	0
	Treated	# Examined	10	10	10	10
		Moderate; spontaneously lifts tail when touched	10	10	10	10
Response to Tail Pinch	Baseline	# Examined	10	10	10	10
		Minimal; animal flinches and may vocalize slightly	0	0	1	0
		Moderate; animal flinches, moves rapidly and/or vocalizes	10	10	9	10
	Treated	# Examined	10	10	10	10
		Minimal; animal flinches and may vocalize slightly	1	1	1	0
		Moderate; animal flinches, moves rapidly and/or vocalizes	9	9	9	10

Table 15 - Summary of FOB Ranked Observations: Male Rats (continued)

Endpoint	Time	#Examined / Response	Control 0 mg/kg bw/day	50 mg/kg bw/day	250 mg/kg bw/day	1000 mg/kg bw/day
Gait Evaluation	Baseline	# Examined	10	10	10	10
		Smooth and coordinated gait	10	10	10	10
	Treated	# Examined	10	10	10	10
		Smooth and coordinated gait	10	10	10	10
Urination	Baseline	# Examined	10	10	10	10
		No drops of urine	5	3	2	3
		Minimal; a few (1-4) small drops or a small pool (~1 cm)	3	4	1	2
		Moderate; a few (1-4) small pools or a moderate pool (2-3 cm)	0	2	2	1
		Pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)	0	1	2	1
		Exaggerated; >4 moderate pools or a single pool >5 cm	2	0	3	3
	Treated	# Examined	10	10	10	10
		No drops of urine	1	0	0	0
		Minimal; a few (1-4) small drops or a small pool (~1 cm)	2	0	2	2
		Moderate; a few (1-4) small pools or a moderate pool (2-3 cm)	1	5	1	4
		Pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)	2	0	2	2
		Exaggerated; >4 moderate pools or a single pool >5 cm	4	5	5	2
Defecation	Baseline	# Examined	10	10	10	10
		No pellets voided	6	5	5	4
		Minimal; 1 or 2 pellets voided	3	4	3	5
		Moderate; 3 pellets voided	1	0	2	1
		Pronounced; 4 pellets voided	0	1	0	0
	Treated	# Examined	10	10	10	10
		No pellets voided	4	3	1	1
		Minimal; 1 or 2 pellets voided	2	3	5	4
		Moderate; 3 pellets voided	0	2	2	3
		Pronounced; 4 pellets voided	2	1	1	2
		Exaggerated; 5 or more pellets voided	2	1	1	0

Table 16 - Summary of FOB Ranked Observations: Toxicity Group Female Rats

Endpoint	Time	#Examined / Response	Control (0 mg/kg bw/day)	100 mg/kg bw/day	250 mg/kg bw/day	1000 mg/kg bw/day
Resistance to Removal	Baseline	# Examined	10	10	10	9
		Moderate; actively avoids capture but is not aggressive	10	10	8	8
		Pronounced; actively avoids capture and/or is mildly aggressive	0	0	2	1
	Treated	# Examined	10	10	10	9
		Moderate; actively avoids capture but is not aggressive	10	10	10	9
Palpebral Closure	Baseline	# Examined	10	10	10	9
		Open	10	10	10	9
	Treated	# Examined	10	10	10	9
		Open	10	10	10	9
Pupil Reactivity	Baseline	# Examined	10	10	10	9
		Dilated, briskly reactive pupil	10	10	10	9
	Treated	# Examined	10	10	10	9
		Dilated, briskly reactive pupil	10	10	10	9
Pupil Size	Baseline	# Examined	10	10	10	9
		Normal pupil size	10	10	10	9
	Treated	# Examined	10	10	10	9
		Normal pupil size	10	10	10	9
Lacrimation	Baseline	# Examined	10	10	10	9
		Glistening cornea	10	10	10	9
	Treated	# Examined	10	10	10	9
		Glistening cornea	10	10	10	9
Salivation	Baseline	# Examined	10	10	10	9
		Glistening oral cavity/lips, no wetness	10	10	10	9
	Treated	# Examined	10	10	10	9
		Glistening oral cavity/lips, no wetness	10	10	10	9
Muscle Tone	Baseline	# Examined	10	10	10	9
		Moderate; animal is neither very relaxed nor tense	10	10	10	9
	Treated	# Examined	10	10	10	9
		Moderate; animal is neither very relaxed nor tense	10	10	10	9

Table 16 - Summary of FOB Ranked Observations: Toxicity Group Female Rats(continued)

Endpoint	Time	#Examined / Response	Control (0 mg/kg bw/day)	50 mg/kg bw/day	250 mg/kg bw/day	1000 mg/kg bw/day
Extensor Thrust	Baseline	# Examined	10	10	10	9
		Moderate; clearly detectable	9	10	10	9
		Pronounced; pushes vigorously	1	0	0	0
	Treated	# Examined	10	10	10	9
		Moderate; clearly detectable	10	9	10	9
		Pronounced; pushes vigorously	0	1	0	0
Reactivity to Handling	Baseline	# Examined	10	10	10	9
		Moderate struggling with little or no vocalization	10	10	9	9
		Pronounced struggling, animal may vocalize	0	0	1	0
	Treated	# Examined	10	10	10	9
		Moderate struggling with little or no vocalization	10	9	10	9
		Pronounced struggling, animal may vocalize	0	1	0	0
Level of Activity	Baseline	# Examined	10	10	10	9
		Moderate; inactive less than 50% of the time	10	10	10	8
		Pronounced; leaves circle, occasional inactivity.	0	0	0	1
	Treated	# Examined	10	10	10	9
		Minimal; inactive more than 50% of the time	0	0	1	0
		Moderate; inactive less than 50% of the time	10	9	9	9
		Pronounced; leaves circle, occasional inactivity.	0	1	0	0
Response to Sharp Noise	Baseline	# Examined	10	10	10	9
		Minimal; only the ears and/or head moves	1	0	2	0
		Moderate; clear movement of the head, neck, ears and possibly shoulders/upper body	8	9	6	9
		Pronounced; clear movement of head, neck and ears, plus clear movement of whole body.	1	0	2	0
		Exaggerated; whole body response to stimulus more intense than "pronounced"; includes whole body going airborne	0	1	0	0

Table 16 - Summary of FOB Ranked Observations: Toxicity Group Female Rats(continued)

Endpoint	Time	#Examined / Response	Control (0 mg/kg bw/day)	50 mg/kg bw/day	250 mg/kg bw/day	1000 mg/kg bw/day
Response to Sharp Noise (continued)	Treated	# Examined	10	10	10	9
		Minimal; only the ears and/or head moves	0	1	0	1
		Moderate; clear movement of the head, neck, ears and possibly shoulders/upper body	10	9	8	6
		Pronounced; clear movement of head, neck and ears, plus clear movemcnt of whole body.	0	0	2	2
Response to Touch	Baseline	# Examined	10	10	10	9
		Moderate; spontaneously lifts tail when touched	9	10	10	9
		Pronounced; spontaneously lifts tail and acts startled	1	0	0	0
	Treated	# Examined	10	10	10	9
		Moderate; spontaneously lifts tail when touched	10	10	10	9
Response to Tail Pinch	Baseline	# Examined	10	10	10	9
		Minimal; animal flinches and may vocalize slightly	0	0	1	0
		Moderate; animal flinches, moves rapidly and/or vocalizes	10	10	9	9
	Treated	# Examined	10	10	10	9
		Minimal; animal flinches and may vocalize slightly	0	0	1	0
		Moderate; animal flinches, moves rapidly and/or vocalizes	10	10	9	9
Gait Evaluation	Baseline	# Examined	10	10	10	9
		Smooth and coordinated gait	10	10	10	9
	Treated	# Examined	10	10	10	9
		Smooth and coordinated gait	10	10	10	9
Urination	Baseline	# Examined	10	10	10	9
		No drops of urine	5	2	2	6
		Minimal; a few (1-4) small drops or a small pool (~1 cm)	3	6	6	3
		Moderate; a few (1-4) small pools or a moderate pool (2-3 cm)	1	1	2	0
		Pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)	1	0	0	0
		Exaggerated; >4 moderate pools or a single pool >5 cm	0	1	0	0

Table 16 - Summary of FOB Ranked Observations: Toxicity Group Female Rats(continued)

Endpoint	Time	#Examined / Response	Control (0 mg/kg bw/day)		50 mg/kg bw/day		250 mg/kg bw/day		1000 mg/kg bw/day	
Urination (continued)	Treated	# Examined	10		10		10		9	
		No drops of urine	3		1		2		4	
		Minimal; a few (1-4) small drops or a small pool (~1 cm)	3		4		4		2	
		Moderate; a few (1-4) small pools or a moderate pool (2-3 cm)	1		5		0		2	
		Pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)	3		0		1		0	
		Exaggerated; >4 moderate pools or a single pool >5 cm	0		0		3		1	
Defecation	Baseline	# Examined	10		10		10		9	
		No pellets voided	8		8		9		9	
		Minimal; 1 or 2 pellets voided	2		1		1		0	
		Moderate; 3 pellets voided	0		1		0		0	
	Treated	# Examined	10		10		10		9	
		No pellets voided	9		7		8		7	
		Minimal; 1 or 2 pellets voided	0		1		2		2	
		Moderate; 3 pellets voided	1		1		0		0	
		Exaggerated; 5 or more pellets voided	0		1		0		0	

Table 17 – FOB Categorical Incidence: Male and Toxicity Group Female Rats

	Time	# Examined / Response	Group 1 (0 mg/kg/day)	Group 2 (50 mg/kg/day)	Group 3 (250 mg/kg/day)	Group 4 (1000 mg/kg/day)
Males	Baseline	# Examined	10	10	10	10
		Normal	10	10	10	10
	Treated	# Examined	10	10	10	10
		Normal	10	9	10	7
		Soiling, Perioral; Red	0	1	0	0
		Soiling, Perineal; Urine	0	0	0	3
Females	Baseline	# Examined	10	10	10	9
		Normal	10	10	10	8
		Skin, Ulceration; focal	0	0	0	1*
	Treated	# Examined	10	10	10	9
		Normal	10	10	10	8
		Soiling, Perineal; Urine	0	0	0	1

* Sore on back of neck due to transponder protruding.

Table 18 – FOB Continuous Data Summary: Male Rats

Endpoint	Time		Control (0 mg/kg bw/day)	100 mg/kg bw/day	300 mg/kg bw/day	1000 mg/kg bw/day
Forelimb Grip Strength (g)	Baseline	Mean	925.5	851.2	897.5	863.7
		Std	185.2	127.6	140.2	122.6
		N	10	10	10	10
	Treated	Mean	1412.2	1436.9	1378.9	1174.7
		Std	197.8	210.6	200.1	188.9
		N	10	10	10	10
Hindlimb Grip Strength (g)	Baseline	Mean	746.8	766.0	725.7	860.2
		Std	158.9	154.8	146.0	132.7
		N	10	10	10	10
	Treated	Mean	1412.7	1346.0	1339.2	1271.7
		Std	102.4	142.1	205.8	173.1
		N	10	10	10	10
Landing Foot Splay (cm)	Baseline	Mean	13.0	12.9	12.7	12.3
		Std	1.4	1.2	1.7	2.5
		N	10	10	10	10
	Treated	Mean	13.3	13.5	13.1	13.7
		Std	2.5	1.4	2.3	1.9
		N	10	10	10	10
Rectal Temperature (oCelsius)	Baseline	Mean	37.8	37.9	37.8	37.8
		Std	0.3	0.4	0.4	0.5
		N	10	10	10	10
	Treated	Mean	38.5	38.5	38.3	38.1
		Std	0.3	0.4	0.6	0.5
		N	10	10	10	10

Table 19 – FOB Continuous Data Summary: Toxicity Group Female Rats

Endpoint	Time		Control (0 mg/kg bw/day)	50 mg/kg bw/day	250 mg/kg bw/day	1000 mg/kg bw/day
Forelimb Grip Strength (g)	Baseline	Mean	810.2	859.7	850.7	804.3
		Std	124.1	173.2	259.5	131.1
		N	10	10	10	9
	Treated	Mean	1001.7	1064.0	1028.2	973.9
		Std	151.5	154.7	206.9	173.5
		N	10	10	10	9
Hindlimb Grip Strength (g)	Baseline	Mean	760.5	754.8	704.0	792.8
		Std	113.0	128.0	119.7	160.1
		N	10	10	10	9
	Treated	Mean	1005.7	1107.2	1037.2	999.4
		Std	142.0	277.9	129.5	145.8
		N	10	10	10	9
Landing Foot Splay (cm)	Baseline	Mean	10.0	10.9	10.0	10.2
		Std	2.1	2.3	1.8	2.0
		N	10	10	10	9
	Treated	Mean	9.9	11.0	10.2	11.4
		Std	1.5	1.5	1.3	1.7
		N	10	10	10	9
Rectal Temperature (oCelsius)	Baseline	Mean	38.2	38.3	38.2	38.0
		Std	0.5	0.4	0.6	0.4
		N	10	10	10	9
	Treated	Mean	38.6	38.6	38.3	38.6
		Std	0.3	0.5	0.7	0.5
		N	10	10	10	9

Table 20 – Motor Activity Summary: Male Rats

Endpoint	Time		Control (0 mg/kg bw/day)	50 mg/kg bw/day	250 mg/kg bw/day	1000 mg/kg bw/day
Interval 1	Baseline	Mean	207	249	223	218
		Std	49	56	31	64
		N	10	10	10	10
	Treated	Mean	195	210	203	228
		Std	31	24	42	61
		N	10	10	10	10
Interval 2	Baseline	Mean	173	164	167	148
		Std	21	47	41	73
		N	10	10	10	10
	Treated	Mean	146	159	147	171
		Std	34	36	46	60
		N	10	10	10	10
Interval 3	Baseline	Mean	129	107	95	123
		Std	55	64	41	52
		N	10	10	10	10
	Treated	Mean	105	97	108	131
		Std	53	26	40	32
		N	10	10	10	10
Interval 4	Baseline	Mean	84	52	69	105
		Std	52	48	56	72
		N	10	10	10	10
	Treated	Mean	96	56	77	99
		Std	42	42	45	29
		N	10	10	10	10
Interval 5	Baseline	Mean	59	24	41	39
		Std	42	35	46	56
		N	10	10	10	10
	Treated	Mean	76	76	45	77
		Std	37	47	44	46
		N	10	10	10	10

Table 20 – Motor Activity Summary: Male Rats (continued)

Endpoint	Time		Control (0 mg/kg bw/day)	50 mg/kg bw/day	250 mg/kg bw/day	1000 mg/kg bw/day
Interval 6	Baseline	Mean	50	41	24	19
		Std	56	58	35	34
		N	10	10	10	10
	Treated	Mean	52	46	54	54
		Std	33	67	52	40
		N	10	10	10	10
Interval 7	Baseline	Mean	32	25	24	13
		Std	47	49	37	32
		N	10	10	10	10
	Treated	Mean	49	44	50	53
		Std	42	39	38	45
		N	10	10	10	10
Interval 8	Baseline	Mean	36	30	23	22
		Std	71	61	40	53
		N	10	10	10	10
	Treated	Mean	42	61	25	61
		Std	29	40	34	57
		N	10	10	10	10
Interval 9	Baseline	Mean	10	20	8	22
		Std	28	51	21	47
		N	10	10	10	10
	Treated	Mean	40	57	10	56
		Std	28	39	19	45
		N	10	10	10	10
Interval 10	Baseline	Mean	0	9	13	4
		Std	0	25	22	9
		N	10	10	10	10
	Treated	Mean	34	41	27	53
		Std	35	38	34	50
		N	10	10	10	10
Total	Baseline	Mean	779	719	686	713
		Std	264	370	293	313
		N	10	10	10	10
	Treated	Mean	834	846	744	983
		Std	229	258	270	322
		N	10	10	10	10

Table 21 – Motor Activity Summary: Toxicity Group Female Rats

Endpoint	Time		Control (0 mg/kg bw/day)	50 mg/kg bw/day	250 mg/kg bw/day	1000 mg/kg bw/day
Interval 1	Baseline	Mean	229	247	229	230
		Std	58	30	37	20
		N	10	10	10	9
	Treated	Mean	232	226	224	179
		Std	62	36	45	19
		N	10	10	10	9
Interval 2	Baseline	Mean	162	186	181	149
		Std	68	42	42	30
		N	10	10	10	9
	Treated	Mean	193	172	169	150
		Std	34	39	43	25
		N	10	10	10	9
Interval 3	Baseline	Mean	132	136	152	96
		Std	71	55	102	66
		N	10	10	10	9
	Treated	Mean	165	129	127	105
		Std	52	26	57	44
		N	10	10	10	9
Interval 4	Baseline	Mean	107	101	103	76
		Std	59	73	76	74
		N	10	10	10	9
	Treated	Mean	141	118	93	95
		Std	37	35	81	31
		N	10	10	10	9
Interval 5	Baseline	Mean	82	83	92	65
		Std	65	62	77	62
		N	10	10	10	9
	Treated	Mean	101	105	78	66
		Std	68	43	71	19
		N	10	10	10	9

Table 21 – Motor Activity Summary: Toxicity Group Female Rats (continued)

Endpoint	Time		Control (0 mg/kg bw/day)	50 mg/kg bw/day	250 mg/kg bw/day	1000 mg/kg bw/day
Interval 6	Baseline	Mean	76	92	72	49
		Std	73	55	85	52
		N	10	10	10	9
	Treated	Mean	75	100	37	61
		Std	60	35	35	33
		N	10	10	10	9
Interval 7	Baseline	Mean	75	78	84	37
		Std	59	49	91	55
		N	10	10	10	9
	Treated	Mean	92	75	65	68
		Std	79	48	60	48
		N	10	10	10	9
Interval 8	Baseline	Mean	58	56	44	17
		Std	59	54	61	35
		N	10	10	10	9
	Treated	Mean	75	62	61	54
		Std	61	39	57	32
		N	10	10	10	9
Interval 9	Baseline	Mean	43	33	37	3
		Std	43	56	49	7
		N	10	10	10	9
	Treated	Mean	103	73	79	45
		Std	31	50	58	57
		N	10	10	10	9
Interval 10	Baseline	Mean	31	37	31	1
		Std	44	58	46	3
		N	10	10	10	9
	Treated	Mean	68	65	54	37
		Std	75	49	48	52
		N	10	10	10	9
Total	Baseline	Mean	993	1049	1024	723
		Std	478	388	544	312
		N	10	10	10	9
	Treated	Mean	1245	1125	987	860
		Std	459	250	301	190
		N	10	10	10	9

Table 22 - Summary of Mean Clinical Chemistry Data: Male Rats

		0 mg/kg	50 mg/kg	250 mg/kg	1000 mg/kg
ALP** (U/L)	Mean	141.3	124.6	115.2	93.2 **
	SD	23.2	23.3	28.5	21.4
	N	10	10	10	10
ALT** (U/L)	Mean	22.3	23.0	25.4	43.7 **
	SD	2.9	2.3	6.1	17.5
	N	10	10	10	10
AST** (U/L)	Mean	85.4	90.1	68.8	55.5 **
	SD	17.8	18.7	15.4	11.1
	N	10	10	10	10
TBILI** (mg/dL)	Mean	0.106	0.113	0.089	0.081 **
	SD	0.025	0.012	0.007	0.014
	N	10	10	10	10
ALB (mmol/L)	Mean	3.73	3.83	3.74	3.72
	SD	0.13	0.13	0.17	0.18
	N	10	10	10	10
TP** (g/dL)	Mean	5.62	5.79	5.71	6.10 **
	SD	0.15	0.29	0.24	0.29
	N	10	10	10	10
BUN** (mg/dL)	Mean	11.6	11.7	10.9	15.5 **
	SD	1.8	1.1	1.7	2.2
	N	10	10	10	10
CREAT (mg/dL)	Mean	0.31	0.30	0.28	0.29
	SD	0.03	0.05	0.04	0.06
	N	10	10	10	10
GLUC * (mg/dL)	Mean	120.4	138.0 *	133.9	143.7 **
	SD	17.7	11.9	19.5	11.5
	N	10	10	10	10
CHOL (mg/dL)	Mean	46.8	51.9	45.5	60.8
	SD	10.3	11.8	10.9	25.6
	N	10	10	10	10

** = $p < 0.01$ significance level

* = $p < 0.05$ significance level

Asterisks indicate a significant difference across treatment groups (with parameter – 1-way ANOVA)) or between control and a treatment group (Dunnett's Test).

Table 22 - Summary of Mean Clinical Chemistry Data: Male Rats (continued)

		0 mg/kg	50 mg/kg	250 mg/kg	1000 mg/kg
CA * (mg/dL)	Mean	9.84	9.93	10.15	10.27 **
	SD	0.28	0.33	0.20	0.38
	N	10	10	10	10
PHOS (mg/dL)	Mean	7.78	7.58	7.81	7.17
	SD	0.81	0.84	0.70	0.61
	N	10	10	10	10
NA ** (mmol/L)	Mean	141.7	141.0	141.7	139.7 **
	SD	1.6	0.9	1.3	0.9
	N	10	10	10	10
K (mmol/L)	Mean	4.54	4.52	4.43	4.58
	SD	0.27	0.19	0.25	0.23
	N	10	10	10	10
CL* (mmol/L)	Mean	103.5	103.0	104.4	103.1
	SD	1.3	1.4	0.7	1.0
	N	10	10	10	10

* = $p < 0.05$ significance level

** = $p < 0.01$ significance level

Asterisks indicate a significant difference across treatment groups (with parameter - 1-way ANOVA)) or between control and a treatment group (Dunnett's Test).

Table 23 - Summary of Mean Clinical Chemistry Data: Toxicity Group Female Rats

		0 mg/kg	50 mg/kg	250 mg/kg	1000 mg/kg
ALP ** (U/L)	Mean	73.3	72.4	62.4	41.9 **
	SD	18.8	22.9	10.5	11.6
	N	10	10	10	9
ALT ** (U/L)	Mean	18.0	20.7	21.2	35.4 **
	SD	4.0	5.0	3.0	5.8
	N	10	10	10	9
AST * (U/L)	Mean	71.0	74.8	67.0	55.6
	SD	14.8	18.5	12.4	7.3
	N	10	10	10	9
TBILI ** (mg/dL)	Mean	0.140	0.109 *	0.121	0.088 **
	SD	0.026	0.019	0.033	0.016
	N	10	10	10	9
ALB** (mmol/L)	Mean	4.33	4.27	4.24	3.84 **
	SD	0.16	0.15	0.24	0.38
	N	10	10	10	9
TP (g/dL)	Mean	6.20	6.10	6.04	6.26
	SD	0.25	0.26	0.37	0.40
	N	10	10	10	9
BUN** (mg/dL)	Mean	14.4	14.3	14.4	19.3 **
	SD	2.9	1.8	2.5	3.9
	N	10	10	10	9
CREAT** (mg/dL)	Mean	0.37	0.37	0.35	0.30 **
	SD	0.05	0.05	0.05	0.00
	N	10	10	10	9
GLUC (mg/dL)	Mean	120.2	125.0	120.6	126.2
	SD	15.9	15.3	16.9	11.5
	N	10	10	10	9
CHOL** (mg/dL)	Mean	52.8	50.8	63.1	109.9 **
	SD	10.3	13.6	7.9	23.2
	N	10	10	10	9

** = $p < 0.01$ significance level

* = $p < 0.05$ significance level

Asterisks indicate a significant difference across treatment groups (with peremeter – 1-way ANOVA)) or between control and a treatment group (Dunnett's Test).

Table 23 - Summary of Mean Clinical Chemistry Data: Toxicity Group Female Rats (continued)

		0 mg/kg	50 mg/kg	250 mg/kg	1000 mg/kg
CA (mg/dL)	Mean	10.18	10.26	10.34	10.61
	SD	0.29	0.27	0.44	0.36
	N	10	10	10	9
PHOS (mg/dL)	Mean	6.55	7.14	6.91	6.39
	SD	0.84	0.85	0.68	0.84
	N	10	10	10	9
NA* (mmol/L)	Mean	142.2	142.5	142.8	141.3
	SD	0.9	1.1	0.9	1.2
	N	10	10	10	9
K (mmol/L)	Mean	4.17	4.16	4.13	4.11
	SD	0.25	0.28	0.31	0.32
	N	10	10	10	9
CL (mmol/L)	Mean	103.3	103.5	103.8	102.9
	SD	1.3	1.3	1.4	3.3
	N	10	10	10	9

Table 24 - Summary of Mean Hematology Data: Male Rats

		0 mg/kg	50 mg/kg	250 mg/kg	1000 mg/kg
WBC (10^3/uL)	Mean	9.21	9.81	10.37	8.74
	SD	2.75	2.43	3.24	1.79
	N	10	10	10	10
RBC** (10^6/uL)	Mean	7.621	7.820	7.473	7.128 *
	SD	0.339	0.492	0.342	0.279
	N	10	10	10	10
HGB** (g/dL)	Mean	15.20	15.29	14.83	13.76 **
	SD	0.42	0.82	0.54	0.49
	N	10	10	10	10
HCT** (%)	Mean	42.39	42.29	41.40	38.72 **
	SD	1.15	1.74	1.34	1.44
	N	10	10	10	10
MCV (fL)	Mean	55.67	54.15	55.47	54.33
	SD	1.73	1.70	2.10	1.51
	N	10	10	10	10
MCH (pg)	Mean	19.95	19.55	19.89	19.30
	SD	0.61	0.46	0.76	0.67
	N	10	10	10	10
MCHC (g/dL)	Mean	35.84	36.14	35.85	35.54
	SD	0.53	0.69	0.56	0.69
	N	10	10	10	10
PLT (10^3/uL)	Mean	915.75	912.00	876.50	904.75
	SD	114.86	97.02	105.17	131.36
	N	10	10	10	10

** = $p < 0.01$ significance level

* = $p < 0.05$ significance level

Asterisks indicate a significant difference across treatment groups (with perameter - 1-way ANOVA)) or between control and a treatment group (Dunnett's Test).

Table 25 - Summary of Mean Hematology Data: Toxicity Group Female Rats

		0 mg/kg	50 mg/kg	250 mg/kg	1000 mg/kg
WBC (10^3/uL)	Mean	7.94	7.46	8.73	8.18
	SD	2.54	2.21	1.44	2.56
	N	10	10	10	9
RBC (10^6/uL)	Mean	7.402	7.252	7.251	7.400
	SD	0.269	0.175	0.405	0.270
	N	10	9	10	9
HGB* (g/dL)	Mean	15.01	14.71	15.02	14.24 **
	SD	0.55	0.43	0.57	0.57
	N	10	10	10	9
HCT (%)	Mean	42.63	41.48	42.68	41.27
	SD	2.12	0.69	1.58	1.50
	N	10	10	10	9
MCV** (fL)	Mean	57.60	56.96	58.97	55.78 *
	SD	1.92	1.17	2.56	0.92
	N	10	10	10	9
MCH** (pg)	Mean	20.30	20.19	20.73	19.24 **
	SD	0.59	0.63	0.62	0.51
	N	10	10	10	9
MCHC* (g/dL)	Mean	35.24	35.45	35.19	34.52
	SD	0.70	0.78	0.57	0.62
	N	10	10	10	9
PLT (10^3/uL)	Mean	946.25	938.50	900.00	865.83
	SD	152.69	161.79	115.84	90.55
	N	10	10	10	9

* = $p < 0.05$ significance level

** = $p < 0.01$ significance level

Asterisks indicate a significant difference across treatment groups (with parameter – 1-way ANOVA)) or between control and a treatment group (Dunnett's Test).

Table 26 - Summary of Mean Hematology Differential Data: Male Rats

		0 mg/kg	50 mg/kg	250 mg/kg	1000 mg/kg
Neutro (%)	Mean	13.47	20.18	15.91	20.31
	SD	7.31	8.95	7.04	8.72
	N	10	10	10	10
Abs Neut (10^3/uL)	Mean	1.2505	1.9794	1.7337	1.7751
	SD	0.7639	1.1023	1.1418	0.8554
	N	10	10	10	10
Lymph (%)	Mean	75.68	68.23	73.79	67.58
	SD	7.93	7.75	7.30	7.26
	N	10	10	10	10
Abs Lymph (10^3/uL)	Mean	6.9730	6.7050	7.6190	5.9250
	SD	2.1220	1.8698	2.3920	1.4532
	N	10	10	10	10
Mono* (%)	Mean	6.05	6.23	5.82	8.24 *
	SD	1.54	1.72	1.87	2.02
	N	10	10	10	10
Abs Mono (10^3/uL)	Mean	0.5631	0.5958	0.5592	0.7077
	SD	0.2338	0.1721	0.1074	0.1735
	N	10	10	10	10
Eosin** (%)	Mean	1.82	2.03	1.72	1.07 *
	SD	0.54	0.78	0.55	0.40
	N	10	10	10	10
Abs** Eosin (10^3/uL)	Mean	0.1670	0.1883	0.1851	0.0935 *
	SD	0.0606	0.0732	0.1020	0.0436
	N	10	10	10	10
Baso (%)	Mean	2.99	3.36	2.80	2.82
	SD	0.58	1.42	0.79	0.53
	N	10	10	10	10
Abs Baso (10^3/uL)	Mean	0.2657	0.3329	0.2849	0.2466
	SD	0.0662	0.1628	0.1146	0.0719
	N	10	10	10	10

* = $p < 0.05$ significance level

** = $p < 0.01$ significance level

Asterisks indicate a significant difference across treatment groups (with parameter - 1-way ANOVA)) or between control and a treatment group (Dunnett's Test).

Table 27 - Summary of Mean Hematology Differential Data: Toxicity Group Female Rats

		0 mg/kg	50 mg/kg	250 mg/kg	1000 mg/kg
Neutro (%)	Mean	13.98	14.67	14.58	10.00
	SD	7.71	6.63	8.70	3.64
	N	10	10	10	9
Abs Neut (10^3/uL)	Mean	1.1731	1.1663	1.3286	0.8098
	SD	0.9824	0.8218	0.8700	0.4349
	N	10	10	10	9
Lymph (%)	Mean	76.42	76.18	75.51	78.21
	SD	8.76	7.49	9.82	5.17
	N	10	10	10	9
Abs Lymph (10^3/uL)	Mean	6.0440	5.5960	6.5020	6.4211
	SD	1.7316	1.4202	0.9378	2.1152
	N	10	10	10	9
Mono** (%)	Mean	5.68	5.52	6.25	8.33 **
	SD	1.41	1.22	2.20	2.23
	N	10	10	10	9
Abs Mono (10^3/uL)	Mean	0.4320	0.4243	0.5610	0.6629
	SD	0.1173	0.1900	0.2692	0.2479
	N	10	10	10	9
Eosin (%)	Mean	1.76	1.39	1.52	1.24
	SD	0.80	0.28	0.33	0.54
	N	10	10	10	9
Abs Eosin (10^3/uL)	Mean	0.1370	0.1023	0.1292	0.0971
	SD	0.0607	0.0344	0.0285	0.0379
	N	10	10	10	9
Baso (%)	Mean	2.19	2.29	2.15	2.23
	SD	0.84	0.86	0.95	0.79
	N	10	10	10	9
Abs Baso (10^3/uL)	Mean	0.1695	0.1737	0.1947	0.1931
	SD	0.0614	0.0935	0.1117	0.1024
	N	10	10	10	9

** = $p < 0.01$ significance level
Asterisks indicate a significant difference across treatment groups (with parameter - 1-way ANOVA)) or between control and a treatment group (Dunnett's

Table 28 - Summary of Mean Prothrombin Times in Rats: Male Rats

		0 mg/kg	50 mg/kg	250 mg/kg	1000 mg/kg
Prothrombin* Time (Seconds)	Mean	15.31	14.30	15.48	15.49
	SD	1.76	0.81	1.13	0.98
	N	10	10	10	10

*= $p < 0.05$ significance level

Asterisks indicate a significant difference across treatment groups (with parameter – 1-way ANOVA)) or between control and a treatment group (Dunnett's Test).

Table 29 - Summary of Mean Prothrombin Times in Rats: Toxicity Group Female Rats

		0 mg/kg	50 mg/kg	250 mg/kg	1000 mg/kg
Prothrombin** Time (Seconds)	Mean	14.58	14.42	14.12	13.74 **
	SD	0.46	0.43	0.50	0.70
	N	10	10	10	9

**= p < 0.01 significance level

Asterisks indicate a significant difference across treatment groupa (with parameter - 1-way ANOVA)) or between control and a treatment group (Dunnalt's Test).

Table 30 - Summary of Mean Organ Weights (grams) and Organ-to-Body Weight (% Ratio): Male Rats

		Terminal BW* (g)	Adrenal** (g)	Adrenal /BW* (%Ratio)	Brain* (g)	Brain / BW (%Ratio)	Epidid-Ymides** (g)	Epididy - mides/BW (%Ratio)
0 mg/kg	Mean	407.42	0.05766	0.01421	2.1042	0.51814	1.2234	0.30092
	SD	21.19	0.00928	0.00251	0.1143	0.04458	0.0946	0.02641
	N	10	10	10	10	10	10	10
50 mg/kg	Mean	413.35	0.05713	0.01388	2.0452	0.49910	1.2024	0.29241
	SD	40.78	0.00659	0.00153	0.0517	0.05035	0.1111	0.02894
	N	10	10	10	10	10	10	10
250 mg/kg	Mean	417.45	0.05135	0.01235	2.0075	0.48473	1.1835	0.28481
	SD	41.56	0.00602	0.00134	0.0956	0.04729	0.1052	0.02504
	N	10	10	10	10	10	10	10
1000 mg/kg	Mean	371.05	0.04400 **	0.01192 *	1.9863 *	0.53995	1.0330 **	0.28023
	SD	33.11	0.00720	0.00212	0.0889	0.06197	0.0846	0.03240
	N	10	10	10	10	10	10	10

Asterisks indicate a significant difference across treatment groups (in parameter heading row) or between control and a treatment group.

** = $p < 0.01$ significance level

* = $p < 0.05$ significance level

Table 30 - Summary of Mean Organ Weights (grams) and Organ-to-Body Weight (% Ratio): Male Rats (continued)

		Heart (g)	Heart /BW (%Ratio)	Kidney (g)	Kidney /BW** (%Ratio)	Liver** (g)	Liver / BW** (%Ratio)	Prostate* (g)
0 mg/kg	Mean	1.3229	0.32461	2.8207	0.69271	10.8983	2.67340	0.8395
	SD	0.1455	0.02969	0.2386	0.05030	1.0156	0.17948	0.1096
	N	10	10	10	10	10	10	10
50 mg/kg	Mean	1.3192	0.32179	2.8035	0.68309	11.5918	2.79384	0.8100
	SD	0.0913	0.03707	0.5011	0.12772	1.6751	0.15126	0.2169
	N	10	10	10	10	10	10	10
250 mg/kg	Mean	1.2881	0.30871	2.9436	0.70586	12.8622 *	3.07258 **	0.8027
	SD	0.1624	0.02541	0.3295	0.04940	1.7918	0.17545	0.1930
	N	10	10	10	10	10	10	10
1000 mg/kg	Mean	1.1708	0.31521	2.8896	0.78046 **	17.4436 **	4.70938 **	0.6220 *
	SD	0.1422	0.02163	0.2346	0.04545	1.9059	0.42064	0.1402
	N	10	10	10	10	10	10	10

Asterisks indicate a significant difference across treatment groups (in parameter heading row) or between control and a treatment group.
** = p > 0.01significance level
* = p > 0.05significance level

Table 30 - Summary of Mean Organ Weights (grams) and Organ-to-Body Weight (% Ratio): Male Rats (continued)

		Prostate / BW (%Ratio)	Seminal Vessicle* (g)	Seminal Vess /BW (%Ratio)	Spleen (g)	Spleen / BW (%Ratio)	Testes** (g)	Testes / BW** (%Ratio)
0 mg/kg	Mean	0.20712	1.9692	0.48393	0.7186	0.17589	3.3492	0.82372
	SD	0.03264	0.1764	0.04440	0.1138	0.02266	0.2045	0.06040
	N	10	10	10	10	10	10	10
50 mg/kg	Mean	0.19564	1.9210	0.46596	0.7217	0.17525	3.2803	0.80125
	SD	0.05006	0.3398	0.08160	0.0756	0.01746	0.1837	0.09672
	N	10	10	10	10	10	10	10
250 mg/kg	Mean	0.19114	1.9247	0.45744	0.7712	0.18550	3.4070	0.82215
	SD	0.03522	0.4545	0.07794	0.1283	0.03010	0.2141	0.08412
	N	10	10	10	10	10	10	10
1000 mg/kg	Mean	0.16584	1.4961 *	0.40035	0.6992	0.18778	2.2972 **	0.62646 **
	SD	0.02571	0.4126	0.09206	0.1352	0.02920	0.2931	0.11544
	N	10	10	10	10	10	10	10

Asterisks indicate a significant difference across treatment groups (in parameter heading row) or between control and a treatment group.

* = $p < 0.05$ significance level

** = $p < 0.01$ significance level

Table 30 - Summary of Mean Organ Weights (grams) and Organ-to-Body Weight (% Ratio): Male Rats (continued)

		Thymus** (g)	Thymus /BW** (%Ratio)
0 mg/kg	Mean	0.3943	0.09664
	SD	0.1060	0.02393
	N	10	10
50 mg/kg	Mean	0.4170	0.10112
	SD	0.1101	0.02502
	N	10	10
250 mg/kg	Mean	0.3626	0.08741
	SD	0.0822	0.02072
	N	10	10
1000 mg/kg	Mean	0.2075 **	0.05642 **
	SD	0.0388	0.01194
	N	10	10

Asterisks indicate a significant difference across treatment groups (in parameter heading row) or between control and a treatment group.
** = $p < 0.01$ significance level

Table 31 - Summary of Mean Organ Weights (grams) and Organ-to-Body Weight (% Ratio): Toxicity Group Female Rats

		Terminal BW (g)	Adrenal (g)	Adrenal /BW (%Ratio)	Brain (g)	Brain / BW (%Ratio)	Heart (g)	Heart /BW (%Ratio)
0 mg/kg	Mean	239.89	0.06655	0.02784	1.9319	0.81067	0.8434	0.35293
	SD	21.78	0.01077	0.00467	0.0670	0.07025	0.0908	0.03877
	N	10	10	10	10	10	10	10
50 mg/kg	Mean	249.39	0.06985	0.02818	1.9000	0.76765	0.8483	0.34118
	SD	23.08	0.00734	0.00351	0.0608	0.07545	0.0575	0.01759
	N	10	10	10	10	10	10	10
250 mg/kg	Mean	245.41	0.07375	0.03016	1.8701	0.76750	0.8441	0.34474
	SD	20.15	0.01836	0.00767	0.0953	0.08324	0.0914	0.03320
	N	10	10	10	10	10	10	10
1000 mg/kg	Mean	235.87	0.07164	0.03050	1.8608	0.79302	0.8218	0.34912
	SD	19.68	0.00979	0.00431	0.0944	0.06768	0.0724	0.02450
	N	9	9	9	9	9	9	9

Table 31 - Summary of Mean Organ Weights (grams) and Organ-to-Body Weight (% Ratio): Toxicity Group Female Rats (continued)

		Kidney (g)	Kidney /BW (%Ratio)	Liver** (g)	Liver / BW** (%Ratio)	Ovaries (g)	Ovaries /BW (%Ratio)	Spleen** (g)
0 mg/kg	Mean	1.6097	0.67205	6.5394	2.72437	0.13792	0.057222	0.5340
	SD	0.1455	0.04054	0.7114	0.13835	0.02468	0.006522	0.0784
	N	10	10	10	10	10	10	10
50 mg/kg	Mean	1.6674	0.67039	6.9706	2.79539	0.14314	0.057759	0.5657
	SD	0.1512	0.05123	0.8284	0.21961	0.02922	0.012523	0.0841
	N	10	10	10	10	10	10	10
250 mg/kg	Mean	1.6904	0.68859	7.6811 *	3.12320 **	0.13716	0.055581	0.5566
	SD	0.1911	0.05318	1.0616	0.25878	0.02843	0.008680	0.0790
	N	10	10	10	10	10	10	10
1000 mg/kg	Mean	1.6963	0.72137	12.5687 **	5.33827 **	0.11948	0.050903	0.4222 **
	SD	0.1574	0.06411	1.0097	0.32961	0.01255	0.006405	0.0464
	N	9	9	9	9	9	9	9

Asterisks indicate a significant difference across treatment groups (in parameter heading row) or between control and a treatment group.

* = $p < 0.05$ significance level

** = $p < 0.01$ significance level

Table 31 - Summary of Mean Organ Weights (grams) and Organ-to-Body Weight (% Ratio): Toxicity Group Female Rats (continued)

		Spleen / BW** (%Ratio)	Thymus (g)	Thymus /BW (%Ratio)	Uterus (g)	Uterus /BW (%Ratio)
0 mg/kg	Mean	0.22292	0.3448	0.14137	0.4932	0.205854
	SD	0.03000	0.1141	0.03494	0.0909	0.035880
	N	10	10	10	10	10
50 mg/kg	Mean	0.22654	0.3910	0.15827	0.5916	0.238079
	SD	0.02410	0.1299	0.05909	0.1792	0.066994
	N	10	10	10	10	10
250 mg/kg	Mean	0.22721	0.3383	0.13778	0.6046	0.244920
	SD	0.02916	0.0657	0.02296	0.2754	0.101242
	N	10	10	10	10	10
1000 mg/kg	Mean	0.17900 **	0.2759	0.11663	0.5241	0.222671
	SD	0.01133	0.0504	0.01618	0.1628	0.071839
	N	9	9	9	9	9

Asterisks indicate a significant difference across treatment groups (in parameter heading row) or between control and a treatment group.
** = $p < 0.01$ significance level

Table 32 - Summary of Macroscopic Findings: Male and Toxicity Group Female Rats

Removal Reasons: All of those SELECTED	MALES				FEMALES			
	0mg/kg	50mg/kg	250mg/kg	1000 mg/kg	0mg/kg	50mg/kg	250mg/kg	1000 mg/kg
Number of Animals on Study :	10	10	10	10	10	10	10	9
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
ADRENAL GLANDS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	8	10	10	7	8
Enlarged; bilateral	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(1)
mild	0	0	0	0	0	0	0	1
moderate	0	0	0	0	0	0	2	0
Deformity; unilateral; single	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
marked	0	0	0	0	0	0	1	0
Decreased Size; bilateral	0	0	0	1	0	0	0	0
Decreased Size; unilateral	0	0	0	1	0	0	0	0
BONE MARROW, STERNUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9
BRAIN;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9
EPIDIDYMIDES;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	10	10	10	10	-	-	-	-
HEART;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9
INTESTINE, CECUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9
INTESTINE, COLON;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9

Table 32 - Summary of Macroscopic Findings: Male and Toxicity Group Female Rats (continued)

Removal Reasons: All of those SELECTED	MALES				FEMALES			
	0mg/kg	50mg/kg	250mg/kg	1000 mg/kg	0mg/kg	50mg/kg	250mg/kg	1000 mg/kg
Number of Animals on Study :	10	10	10	10	10	10	10	9
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
INTESTINE, DUODENUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	9	9
Deformity	0	0	0	0	0	0	1	0
INTESTINE, ILEUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9
INTESTINE, JEJUNUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9
KIDNEYS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	9	9
Deformity; irregular; cortex	0	0	0	0	0	0	1	0
LIVER;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	9	1	10	10	8	0
Discoloration	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
marked	0	0	0	0	0	0	0	1
Discoloration; dark	0	0	0	3	0	0	0	0
Discoloration; mottled	(0)	(0)	(1)	(6)	(0)	(0)	(2)	(8)
mild	0	0	1	0	0	0	2	0
moderate	0	0	0	2	0	0	0	0
marked	0	0	0	4	0	0	0	5
LUNGS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9

Table 32 - Summary of Macroscopic Findings: Male and Toxicity Group Female Rats (continued)

Removal Reasons: All of those SELECTED	MALES				FEMALES			
	0mg/kg	50mg/kg	250mg/kg	1000 mg/kg	0mg/kg	50mg/kg	250mg/kg	1000 mg/kg
Number of Animals on Study :	10	10	10	10	10	10	10	9
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
LYMPH NODE, MEDIASTINAL;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9
LYMPH NODE, MESENTERIC;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9
NERVE, SCIATIC;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9
OVARIES;								
Submitted	(-)	(-)	(-)	(-)	(10)	(10)	(10)	(9)
No Visible Lesions	-	-	-	-	10	9	9	8
Enlarged	(-)	(-)	(-)	(-)	(0)	(1)	(1)	(0)
mild	-	-	-	-	0	1	1	0
Enlarged; pale	-	-	-	-	0	0	0	1
PROSTATE GLAND;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	10	10	10	10	-	-	-	-
SEMINAL VESICLES;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	10	9	9	6	-	-	-	-
Small	0	0	1	3	-	-	-	-
Small; unilateral	0	1	0	1	-	-	-	-
SPINAL CORD;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9

Table 32 - Summary of Macroscopic Findings: Male and Toxicity Group Female Rats (continued)

Removal Reasons: All of those SELECTED	MALES				FEMALES			
	0mg/kg	50mg/kg	250mg/kg	1000 mg/kg	0mg/kg	50mg/kg	250mg/kg	1000 mg/kg
Number of Animals on Study :	10	10	10	10	10	10	10	9
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
SPLEEN;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	9	9	6	10	10	10	9
Discoloration; dark; multifocal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
moderate	0	0	0	1	0	0	0	0
Discoloration; white; widespread	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)
marked	0	0	0	2	0	0	0	0
Discoloration; white; multifocal	(0)	(1)	(0)	(1)	(0)	(0)	(0)	(0)
mild	0	1	0	1	0	0	0	0
Malformation; roughened	0	0	1	0	0	0	0	0
STOMACH;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9
TESTES;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	10	10	10	10	-	-	-	-
THYMUS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	9	6	10	9	9	9
Discoloration; hemorrhagic; unilateral; focal	0	0	0	0	0	0	1	0
Discoloration; red; multifocal	0	0	0	0	0	1	0	0
Small	0	0	1	4	0	0	0	0
THYROID GLANDS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9
TRACHEA;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions	10	10	10	10	10	10	10	9

Table 32 - Summary of Macroscopic Findings: Male and Toxicity Group Female Rats (continued)

Removal Reasons: All of those SELECTED	MALES				FEMALES			
	0mg/kg	50mg/kg	250mg/kg	1000 mg/kg	0mg/kg	50mg/kg	250mg/kg	1000 mg/kg
Number of Animals on Study :	10	10	10	10	10	10	10	9
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
URINARY BLADDER;								
Submitted.....	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(9)
No Visible Lesions.....	10	10	10	10	10	10	10	9
UTERUS;								
Submitted.....	(-)	(-)	(-)	(-)	(10)	(10)	(10)	(9)
No Visible Lesions.....	-	-	-	-	10	10	10	9

Table 33 - Summary of Microscopic Findings: Toxicity Group Female Rats

Organ	Finding	Examined/Grade	Control (0 mg/kg bw/day)		50 mg/kg bw/day		250 mg/kg bw/day		1000 mg/kg bw/day	
KIDNEYS	Inflammation; chronic; focal	# Examined	10		0		0		9	
		All Grades	2		0		0		0	
		Minimal	2		0		0		0	
	Inflammation; chronic; multifocal	# Examined	10		0		0		9	
		All Grades	1		0		0		0	
		Minimal	1		0		0		0	
	Inflammation; chronic; focal or multifocal	# Examined	10		0		0		9	
		All Grades	3		0		0		0	
		Minimal	3		0		0		0	
	pelvis; Inflammation; chronic; bilateral	# Examined	10		0		0		9	
		All Grades	0		0		0		1	
		Moderate	0		0		0		1	
	tubule; Mineralization	# Examined	10		0		0		9	
		All Grades	1		0		0		0	
		Mild	1		0		0		0	
	cortex; Cyst	# Examined	10		0		0		9	
		Present	0		0		0		1	
LIVER	Inflammation; chronic	# Examined	10		10		10		9	
		All Grades	9		8		8		9	
		Minimal	7		8		8		9	
		Mild	2		0		0		0	
	centrilobular; Hypertrophy	# Examined	10		10		10		9	
		All Grades	0		0		8		0	
		Minimal	0		0		8		0	
	panlobular; Hypertrophy	# Examined	10		10		10		9	
		All Grades	0	+++	0		0		9	+++
		Mild	0		0		0		2	
		Moderate	0		0		0		7	
	centrilobular and panlobular; Hypertrophy	# Examined	10		10		10		9	
		All Grades	0	+++	0		8	+++	9	+++
		Minimal	0		0		8		0	
		Mild	0		0		0		2	
		Moderate	0		0		0		7	

Table 33 - Summary of Microscopic Findings: Toxicity Group Female Rats (continued)

Organ	Finding	Examined/Grade	Control (0 mg/kg bw/day)		50 mg/kg bw/day		250 mg/kg bw/day		1000 mg/kg bw/day	
LIVER (continued)	periportal; Vacuolation	# Examined	10		10		10		9	
		All Grades	3	+++	2		4		8	++
		Minimal	2		1		2		1	
		Mild	1		0		2		7	
		Moderate	0		1		0		0	
LUNGS	Fibrosis; focal	# Examined	10		10		10		9	
		All Grades	0		0		0		1	
		Mild	0		0		0		1	
	Hemorrhage; chronic; focal	# Examined	10		10		10		9	
		All Grades	1		0		2		2	
		Minimal	1		0		1		2	
		Mild	0		0		1		0	
	Inflammation; chronic; focal	# Examined	10		10		10		9	
		All Grades	0		0		1		0	
		Minimal	0		0		1		0	
	Histiocytosis; focal	# Examined	10		10		10		9	
		All Grades	1		3		1		0	
		Minimal	1		3		1		0	
	Histiocytosis; multifocal	# Examined	10		10		10		9	
		All Grades	0	+++	0		0		4	+
		Minimal	0		0		0		2	
		Mild	0		0		0		2	
	Histiocytosis; focal and multifocal	# Examined	10		10		10		9	
		All Grades	1		3		1		4	
		Minimal	1		3		1		2	
		Mild	0		0		0		2	
LYMPH NODE, MEDIASTINAL	Pigmentation, Hemosiderin	# Examined	10		0		0		9	
		All Grades	1		0		0		0	
		Moderate	1		0		0		0	
SPLEEN	serosa; Inflammation; chronic	# Examined	10		0		0		9	
		All Grades	1		0		0		0	
		Minimal	1		0		0		0	
THYMUS	Atrophy	# Examined	10		0		0		9	
		All Grades	0		0		0		1	
		Minimal	0		0		0		1	

Table 33 - Summary of Microscopic Findings: Toxicity Group Female Rats (continued)

Organ	Finding	Examined/Grade	Control (0 mg/kg bw/day)		50 mg/kg bw/day		250 mg/kg bw/day		1000 mg/kg bw/day	
THYROID GLANDS	Cyst; ultimobranchial	# Examined	10		10		10		9	
		Present	1		0		0		1	
	Hypertrophy; diffuse	# Examined	10		10		10		9	
		All Grades	0	+++	0		0		9	+++
		Minimal	0		0		0		3	
		Mild	0		0		0		5	
		Moderate	0		0		0		1	
URINARY BLADDER	Hyperplasia; epithelial; diffuse	# Examined	10		0		0		9	
		All Grades	0		0		0		2	
		Minimal	0		0		0		2	

Plus Signs indicate a significant trend in incidence by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

Table 34 - Summary of Microscopic Findings: Male Rats

Organ	Finding	Examined/ Grade	Control (0 mg/kg bw/day)		50 mg/kg bw/day		250 mg/kg bw/day		1000 mg/kg bw/day	
ADRENAL GLANDS	cortex; Atrophy	# Examined	10		10		10		10	
		All Grades	0	+++	0		0		5	++
		Minimal	0		0		0		5	
EPIDIDYMIDES	Hypospermia	# Examined	10		10		10		10	
		All Grades	0	+++	0		0		9	+++
		Mild	0		0		0		8	
		Moderate	0		0		0		1	
	spermatid; Immature	# Examined	10		10		10		10	
		All Grades	0	+++	0		1		10	+++
		Minimal	0		0		1		0	
		Mild	0		0		0		10	
HEART	Inflammation; chronic	# Examined	10		0		0		10	
		All Grades	1		0		0		2	
		Minimal	1		0		0		2	
	Inflammation; chronic-active	# Examined	10		0		0		10	
		All Grades	1		0		0		0	
		Minimal	1		0		0		0	
KIDNEYS	Cast; eosinophilic	# Examined	10		10		10		10	
		All Grades	1		0		0		0	
		Minimal	1		0		0		0	
	Chronic Progressive Nephropathy; active	# Examined	10		10		10		10	
		All Grades	1		0		0		0	
		Mild	1		0		0		0	
	Inflammation; chronic; focal	# Examined	10		10		10		10	
		All Grades	0		1		0		1	
		Minimal	0		1		0		1	
	Inflammation; chronic; multifocal	# Examined	10		10		10		10	
		All Grades	1		1		1		0	
		Minimal	0		1		1		0	
		Mild	1		0		0		0	
	Inflammation; chronic; focal or multifocal	# Examined	10		10		10		10	
		All Grades	1		2		1		1	
		Minimal	0		2		1		1	
		Mild	1		0		0		0	
	Nephropathy; protein droplet,	# Examined	10		10		10		10	
		All Grades	0	+++	0		0		10	+++
		Minimal	0		0		0		10	

Table 34 - Summary of Microscopic Findings: Male Rats (continued)

Organ	Finding	Examined/ Grade	Control (0 mg/kg bw/day)		50 mg/kg bw/day		250 mg/kg bw/day		1000 mg/kg bw/day	
KIDNEYS (continued)	tubule; Basophilia	# Examined	10		10		10		10	
		All Grades	1		4		3		0	
		Minimal	1		4		3		0	
	cortex; Cyst	# Examined	10		10		10		10	
		Present	0		1		0		0	
LIVER	Inflammation; chronic	# Examined	10		10		10		10	
		All Grades	8		9		8		6	
		Minimal	7		7		8		5	
		Mild	1		2		0		1	
	Necrosis; focal	# Examined	10		10		10		10	
		All Grades	0		0		0		1	
		Mild	0		0		0		1	
	Inflammation, Chronic, Associated with Protoporphyrin Accumulation	# Examined	10		10		10		10	
		All Grades	0	+++	0		0		4	+
		Minimal	0		0		0		1	
		Mild	0		0		0		2	
		Moderate	0		0		0		1	
	Hyperplasia, Bile Duct, Associated with Protoporphyrin Accumulation	# Examined	10		10		10		10	
		All Grades	0	+++	0		0		4	+
		Minimal	0		0		0		2	
		Mild	0		0		0		1	
		Moderate	0		0		0		1	
	Protoporphyrin Accumulation	# Examined	10		10		10		10	
		All Grades	0	+++	0		1		5	++
		Minimal	0		0		1		3	
		Mild	0		0		0		1	
		Moderate	0		0		0		1	
	panlobular; Hypertrophy	# Examined	10		10		10		10	
		All Grades	0	+++	0		0		10	+++
		Mild	0		0		0		2	
		Moderate	0		0		0		8	
	periportal; Vacuolation	# Examined	10		10		10		10	
		All Grades	1		0		0		2	
		Minimal	1		0		0		1	
		Mild	0		0		0		1	

Table 34 - Summary of Microscopic Findings: Male Rats (continued)

Organ	Finding	Examined/ Grade	Control (0 mg/kg bw/day)		50 mg/kg bw/day		250 mg/kg bw/day		1000 mg/kg bw/day	
LUNGS	Hemorrhage; chronic; focal	# Examined	10		10		10		10	
		All Grades	1		2		1		1	
		Minimal	1		2		0		1	
		Mild	0		0		1		0	
	Inflammation; chronic; focal	# Examined	10		10		10		10	
		All Grades	2		1		0		1	
		Minimal	2		1		0		1	
	Inflammation; chronic; multifocal	# Examined	10		10		10		10	
		All Grades	1		4		0		1	
		Minimal	1		2		0		1	
		Mild	0		2		0		0	
	Inflammation; chronic;focal or multifocal	# Examined	10		10		10		10	
		All Grades	3		5		0		2	
		Minimal	3		3		0		2	
		Mild	0		2		0		0	
	Histiocytosis; focal	# Examined	10		10		10		10	
		All Grades	2	+	3		3		6	
		Minimal	2		3		3		6	
	Histiocytosis; multifocal	# Examined	10		10		10		10	
		All Grades	2		1		1		3	
		Minimal	0		1		1		0	
		Mild	2		0		0		3	
	Histiocytosis; focal and multifocal	# Examined	10		10		10		10	
		All Grades	4	++	4		4		9	+
		Minimal	2		4		4		6	
		Mild	2		0		0		3	
PROSTATE GLAND	Inflammation; chronic	# Examined	10		0		0		10	
		All Grades	7		0		0		3	
		Minimal	1		0		0		1	
		Mild	6		0		0		2	
SPLEEN	serosa; Inflammation; chronic	# Examined	10		10		10		10	
		All Grades	1	+	2		0		5	
		Minimal	1		2		0		1	
		Mild	0		0		0		2	
		Moderate	0		0		0		2	
STOMACH	Hyperkeratosis	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Minimal	0		0		0		1	

Table 34 - Summary of Microscopic Findings: Male Rats (continued)

Organ	Finding	Examined/ Grade	Control (0 mg/kg bw/day)		50 mg/kg bw/day		250 mg/kg bw/day		1000 mg/kg bw/day	
TESTES	seminiferous tubule; Degeneration	# Examined	10		10		10		10	
		All Grades	0	+++	0		1		10	+++
		Minimal	0		0		1		0	
		Moderate	0		0		0		8	
		Marked	0		0		0		2	
THYROID GLANDS	Hypertrophy; diffuse	# Examined	10		10		10		10	
		All Grades	1	+++**	2		3		10	+++
		Minimal	1		2		2		0	
		Mild	0		0		1		8	
		Moderate	0		0		0		2	
URINARY BLADDER	Inflammation; chronic	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Minimal	0		0		0		1	

Plus Signs indicate a significant trend in incidence by the Cochran-Armitage Test across treatment groups (in the control column) or between control and a treatment group by Fisher's Exact Test with p-values of + < 0.05, ++ < 0.02 or +++ < 0.01. Asterisks indicate a significant shift in grade across treatment groups (in the control column) with p-values of * < 0.05, ** < 0.02 or *** < 0.01.

Table 35 - Summary of Mean Reproductive Parameters for Reproductive Group Female Rats

		Control (0 mg/kg bw/day)		50 mg/kg bw/day		300 mg/kg bw/day		1000 mg/kg bw/day		Litter Size
Corpora Lutea Counts	Mean	21		18		17		22		N/A
	Std	5		5		3		5		
	N	10		8		10		8		
Total Implants	Mean	15		16		14		13		N/A
	Std	1.2		2.0		2.0		3.7		
	N	10		8		10		8		
Post-Implantation Loss (%)	Mean	9.8	***	4.3		8.6		23.5	**	N/A
	Std	5.9		7.7		10.2		14.3		
	N	10		8		10		8		
Days Gestation	Mean	22	***	22		22		23	***	N/A
	Std	1		1		1		1		
	N	10		8		10		8		
Total Pups	Mean	13.7	***	16.0		13.0		10.3	***	N/A
	Std	0.8		2.3		1.8		2.8		
	N	10		8		10		8		
Total Live Pups Day 0	Mean	13.4	***	15.6		12.7		9.8	***	N/A
	Std	0.8		2.8		1.7		2.7		
	N	10		8		10		8		
Male Pups	Mean	7		8		6		5		***
	Std	2		3		2		3		
	N	10		8		10		8		
Female Pups	Mean	6		8		6		5		*
	Std	1		2		2		2		
	N	10		8		10		8		
Males/Females	Mean	1.4		1.1		1.2		1.2		
	Std	0.8		0.7		0.7		0.9		
	N	10		8		10		8		
Day 4 Viable Pups	Mean	13	***	15		13		7	***	***
	Std	1		3		2		4		
	N	10		8		10		8		
Viable/Total	Mean	0.97	***	0.96		0.97		0.74	***	
	Std	0.04		0.04		0.05		0.31		
	N	10		8		10		8		

Note: Asterisks next to the control indicate a significant treatment effect in the ANCOVA, asterisks in the litter column indicate a significant litter effect in the ANCOVA with p-values of * < 0.05, ** < 0.02 or *** <0.01 in the control columns and significance in the litter sizes with p-values of * < 0.05, ** < 0.02 or *** < 0.01 in the litter significance column. N/A is the litter column indicates that the litter was not used as a covariate in the analysis of that endpoint.

% Post-Implantation Loss = ((# Implantations - # Live at First Litter Check) / # Implantations) *100

% Post-Natal Loss = ((# live pups Day 0 - # live pups Day 4) / # live pups Day 0) *100

Table 35 - Summary of Reproductive Performance for Reproductive Group Female Rats (continued)

		Control (0 mg/kg bw/day)		50 mg/kg bw/day		250 mg/kg bw/day		1000 mg/kg bw/day		Litter Size
Initial Litter Weight (g) [Live Pups only]	Mean	88.0	***	100.0		93.1	*	65.4		***
	Std	7.4		13.8		11.8		14.1		
	N	10		8		10		8		
Initial Average Pup Weight (g) [Live Pups only]	Mean	6.6	***	6.5		7.4	***	6.8		***
	Std	0.5		0.6		0.4		0.7		
	N	10		8		10		8		
Final Litter Weight (g)	Mean	145.5	***	160.6		142.0		72.9	***	***
	Std	12.6		18.8		16.0		15.5		
	N	10		8		10		7		
Final Average Pup Weight (g)	Mean	11.0	***	10.5		11.3		8.9	***	***
	Std	0.9		1.0		1.0		1.3		
	N	10		8		10		7		
Post-Natal Loss (%)	Mean	0.7	***	1.3		0.7		24.0	***	*
	Std	2.3		3.7		2.3		32.6		
	N	10		8		10		8		

Note: Asterisks next to the control indicate a significant treatment effect in the ANCOVA, asterisks in the litter column indicate a significant litter effect in the ANCOVA with p-values of * < 0.05, ** < 0.02 or *** <0.01 in the control columns and significance in the litter sizes with p-values of * < 0.05, ** < 0.02 or *** < 0.01 in the litter significance column. N/A is the litter column indicates that the litter was not used as a covariate in the analysis of that endpoint.

Table 36 - Protocol Deviations

Protocol Section	Protocol Requirement	Deviation	Impact
13.9	All animals will be observed at least twice daily (once daily on weekend and holidays) in their cages for mortality, morbidity and moribundity.	Mortality/morbidity check was inadvertently missed on 10/16/08 and 12/4/08.	None
11	Animals will be in individually housed in suspended wire-mesh cages.	Animal D5708 was found out of her cage on 10/27/08.	None
11	Animals will be housed in an environmentally controlled animal room (12-hour fluorescent-light/dark cycle).	Animals received an extra hour of light on 11/2/08 and ~0.5 hour less light on 11/5/08..	None
11	Animals will be housed in an environmentally controlled animal room (30-70% relative humidity).	Humidity in room 217 was out of range for approximately 4 hours.	None
13.5	Individual body weights will be determined beginning with randomization into test groups, on the first day of dosing, at least weekly thereafter, and the day of euthanasia or when found dead.	Terminal body weights for animals D5736, D5738 and D5683 were not collected. These animals did not show positive evidence of mating and were not pregnant.	None
13.5	Analysis will be conducted with the Cell Dyn 3700 Hematology Analyzer.	The platelet counts were evaluated manually due to technical difficulties with the instrumentation.	None