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SILICONES ENVIRONMENTAL, HEALTH AND SAFETY COUNCIL
NORTH AMERICA

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8EHQ-08-17187

Via Certified Mail
March 22, 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

89100000170

Re: Supplemental TSCA Section 8(e) Notification (8EHQ-1208-17187B): Final Report - Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Triethoxyoctylsilane 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 June 19, 2008 and December 14, 2008 TSCA Section 8(e) notifications.

Chemical Substance
2943-75-1 Triethoxyoctylsilane

Completed Study
Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Triethoxyoctylsilane in Sprague-Dawley Rats via Oral Gavage, HES Study Number: 10709-102.

Summary
Preliminary results from a repeated-dose toxicity study with reproductive/developmental screening endpoints conducted with triethoxyoctylsilane in Sprague-Dawley rats were reported to EPA by SEHSC on June 19, 2008 and December 14, 2008. The enclosed final study report for the Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Triethoxyoctylsilane in Sprague-Dawley Rats via Oral Gavage is provided for the Agency's 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.

[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.

MR 325796

CONTAINS NO CBI

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

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DOW CORNING CORPORATION
HEALTH & ENVIRONMENTAL SCIENCES
TECHNICAL REPORT

Study Title:	Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Triethoxyoctylsilane in Sprague-Dawley Rats via Oral Gavage
HES Study Number:	10709-102
Test Article:	Triethoxyoctylsilane
Study Director:	Tami S. McMullin, Ph.D.
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
Testing Facility:	Dow Corning Corporation Health and Environmental Sciences 2200 W. Salzburg Road Auburn, MI 48611
Study Completion Date:	02 March 2010

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1 ABSTRACT

The objective of this study was to evaluate the potential toxicity of triethoxyoctylsilane in a combined repeated oral gavage toxicity study that included reproductive/developmental toxicity screening in Sprague-Dawley rats. The test article was administered in dried, deacidified peanut oil daily, seven days a week by oral gavage to 10 rats/sex/group at 0, 100, 300 or 1000 mg/kg bw/day for up to 45 consecutive days. Females were divided into a toxicity group and a reproductive group. The same males were used for both the toxicity and reproductive phases of the study. Males and toxicity group females were treated for 28 and 29 days, respectively. Reproductive group females were treated for 14 days prior to mating, during mating, gestation, and up to and including post-partum day 3. Mating was initiated after two weeks of dosing. Reproductive group females cohabitated with males of the same treatment group until positive evidence of mating occurred. A maximum of 14 days were allowed for mating.

Animals were observed twice daily for mortality, morbidity, and moribundity. Clinical examinations were performed daily following dosing. Functional Observational Battery (FOB) and Motor Activity (MA) evaluations were performed on males and toxicity group females once prior to the first dose and again during the fourth-week of dosing. Detailed physical examinations and body weight measurements were performed weekly for all groups. Additional body weights for reproductive group females were obtained on gestational days 0, 7, 14, and 20, again within 24 hours after parturition, and on post-partum day 4. Individual food consumption was recorded weekly for all groups, except during the cohabitation period for the toxicity group males and reproductive group females. 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 from the control and high dose males, toxicity group females and reproductive group females. Based on clinical and histopathology findings in all high dose groups, various target tissues for the males, toxicity and reproductive group females were also examined at the mid and low dose groups. Reproductive and developmental parameters evaluated included evidence of mating, pregnancy, duration of gestation, mean litter size, mean live litter size, mean litter weight, mean ratio of live births/litter size, sex ratio, pup body weight gain, and evaluation of loss of offspring. 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.

There was a dose-related increase in soiling around the nose and chin and generalized soiling around the muzzle in the 300 and 1000 mg/kg bw/day dose toxicity group males and females and 1000 mg/kg bw/day reproductive group females. Clinical observations consistent with neurological toxicity occurred in the 1000 mg/kg bw/day reproductive group females, but were not observed in the toxicity group females or males. A total of 9/10 reproductive group females exhibited an increased incidence of decreased activity, dragging of the hindlimbs and/or incoordinated gait; three of these animals also exhibited rapid respiration. Due to the severity of these clinical signs, these three 1000 mg/kg bw/day reproductive group females were euthanized prior to scheduled necropsy.

Treatment-related decreases in group mean body weights and/or body weights gains occurred in all 1000 mg/kg bw/day dose groups with associated decreases in food consumption in the toxicity group females and reproductive group females.

There were no statistically significant differences across dose groups in either the baseline or treated FOB categorical and motor activity data for both the males and toxicity group females.

All clinical pathology changes were within the range of historical control values for this laboratory, not in the direction of a pathological change and thus were not considered toxicologically significant.

A slight but statistically significant increase in absolute adrenal gland weights occurred in the 100 and 300 mg/kg bw/day group males compared to controls, and a slight decrease in relative prostate weights occurred only in the 300 mg/kg bw/day group males. These changes were not dose-related and were not associated with any pathological changes and therefore, were not considered to be related to test-article exposure. A dose-related increase in mean absolute and relative liver weights occurred in the 300 and 1000 mg /kg bw/day group males, resulting in an 11.7% and 17.3% increase in relative liver weights at these dose levels compared to controls.

A 14.6% increase in mean relative kidney weights occurred in 100 mg/kg bw/day toxicity group females compared to controls. A dose-related increase in mean absolute liver weights also occurred in 300 and 1000 mg/kg bw/day toxicity group females that attained statistical significance only in the 1000 mg/kg bw/day toxicity group females compared to controls. These increases in absolute liver weights were associated with an increase in mean relative liver weights. Mean relative liver weights were increased by 4.7% and 27.8% in the 300 and 1000 mg/kg bw/day toxicity group females, respectively. Absolute, but not relative, ovarian weights were also statistically decreased in the 300 and 1000 mg /kg bw/day toxicity group females.

There were no macroscopic findings attributable to test article in male or female toxicity group animals. The 1000 mg/kg bw/day reproductive group females exhibited various gross findings that included a generalized thinness of the body, decreased thymus and spleen size, decreases in hind leg skeletal muscle mass and decreased ingesta in all or parts of the intestinal tract. Notable litter observations included milk not present in the stomach of several pups from most of the 1000 mg/kg bw/day dams and several very thin pups from litters from two of the dams.

Histopathological findings were identified in the liver, urinary tract (bladder and kidneys), the lymphoreticular system (adrenal and spleen) and neuromuscular system (brain, spinal cord, peripheral nerves and skeletal muscles). A dose-related statistically significant increase in centrilobular hypertrophy of the liver occurred in males and females (toxicity and reproductive groups) at the 300 mg/kg bw/day and 1000 mg/kg bw/day dose levels. These microscopic findings were associated with a statistically significant increase in mean absolute and relative liver weights in the males and toxicity group females at the 1000 mg/kg bw/day dose level only. Diffuse epithelial hyperplasia of the urinary bladder occurred in all groups (males, toxicity and reproductive group females) of animals treated with 1000 mg/kg bw/day. The 1000 mg/kg bw/day dose group reproductive females but not males or toxicity group females also exhibited atrophy of the spleen and thymus with correlated gross findings of decreased spleen and small thymus.

Several treatment-related histopathological changes occurred in the neuromuscular system of the 1000 mg/kg bw/day toxicity and reproductive female dose groups. Central nervous system degeneration of white matter was observed in the toxicity group and reproductive group females. In the brain, predominantly the cerebellum and medulla, 40% and 80% of the 1000 mg/kg bw/day toxicity and reproductive group females exhibited various degrees of white matter degeneration while degeneration of the spinal cord occurred in 50% and 90% of the toxicity and reproductive group females, respectively. The peripheral nerves examined, the sciatic and tibial nerves, also demonstrated evidence of minimal to severe degeneration and demyelination in the 1000 mg/kg bw/day toxicity and reproductive group females, with less incidence and severity occurring in the toxicity group females compared to the reproductive group females. Consistent with demyelination and degeneration of these peripheral nerves, many of these animals exhibited pathological findings associated with skeletal muscle denervation such as adductor and gastrocnemius muscle degeneration. Animals affected with neurological findings also showed gross muscle atrophy, diffuse decreased muscle fiber size, fiber fragmentation, increased density of myofiber nuclei, and focal areas of inflammation around necrotic fibers.

Changes in reproductive and developmental parameters were limited to the 1000 mg/kg bw/day dose level. Mating and fertility were unaffected by treatment. The mean duration of gestation was increased compared to controls. Of the seven dams that successfully initiated parturition, four of these dams exhibited dystocia (difficult/prolonged labor). The total litter sizes in the 1000 mg/kg bw/day dose group were unaffected by treatment but the number of viable pups on post-natal day (PND) 0 was statistically decreased by 39.3% compared to controls. PND 0 mean litter weights, average pup body weights and body weight gains were similar to controls. By PND 4, several dams in Group 4 had been euthanized due to the severity of various clinical signs and/or difficulty during labor. Only four dams continued through PND 4. Of these litters, the total viable pups on PND 4 was decreased compared to controls, resulting in a 25.2% decrease in percent viability of pups/dam on PND 4 compared to controls. This significant decrease was due to a single dam that had a 14.3% post-natal loss of offspring. The remaining dams had no post-natal loss of pups between Day 0-4. PND 4 mean litter weights, average pup body weights and body weight gains in the 1000 mg/kg bw/day group were also decreased compared to control weights.

Based on the bladder epithelial hyperplasia in males and the neuromuscular findings in the toxicity and reproductive group females at 1000 mg/kg bw/day, a NOAEL (No-Observable-Adverse-Effect-Level) of 300 mg triethoxyoctylsilane/kg bw/day is assigned for systemic toxicity. Because the reproductive/developmental effects in the litters only occurred at levels that were also toxic to parent animals and therefore, considered secondary to the parental systemic findings, a NOAEL of 1000 mg triethoxyoctylsilane/kg bw/day is assigned for reproductive /developmental toxicity.

2 GLP COMPLIANCE STATEMENT

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

Wendy H. Koch, Ph.D.
Epona Associates, LLC

February 11, 2010
Date

Paul A. Jean, Ph.D.
Team Leader, Toxicology
Dow Corning Corporation

28 FEB 2010
Date

Tami S. McMullin, Ph.D.
Study Director, Toxicology
Dow Corning Corporation

02 March 2010
Date

3 QUALITY ASSURANCE STATEMENT

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

Study Number: 10709-102

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 that the inspection findings were reported.

Dates of Inspection	Phase Inspected	Findings Reported to Study Director	Findings Reported to Management
28 Dec 2007	Draft Protocol Review	28 Dec 2007	21 Jan 2008
14 Feb 2008	Dosing	14 Feb 2008	19 Feb 2008
23 Apr 2008	Clinical Observations	23 Apr 2008	02 May 2008
12 May 2008	Necropsy	12 May 2008	27 May 2008
13 May 2008	Clinical Pathology	14 May 2008	27 May 2008
07, 08 May 2009	Appendix A, Table 2	11 May 2009	10 Jun 2009
11 May 2009	Appendix B, Table 3	11 May 2009	10 Jun 2009
14, 15, 17 May 2009	Appendix C, Table 4	17 May 2009	10 Jun 2009
17 May 2009	Appendix D, Tables 5, 8	17 May 2009	10 Jun 2009
18 May 2009	Appendix E, Tables 6, 9	18 May 2009	10 Jun 2009
19, 20 May 2009	Appendix F, Tables 7, 10	21 May 2009	22 Jun 2009
22 May 2009	Appendix G	22 May 2009	22 Jun 2009

26 May 2009	Appendices H, I	26 May 2009	10 Jun 2009
25 May- 03 Jun 2009	Appendices J-L, Tables 11-13	04 Jun 2009	19 Jun 2009
26, 27 May 2009	Appendix M, Table 26	27 May 2009	10 Jun 2009
27, 28 May 2009	Appendix N, Table 27	28 May 2009	22 Jun 2009
29 May, 01 Jun 2009	Appendix O, Tables 33, 34	01 Jun 2009	22 Jun 2009
14, 15 Apr 2009	Appendix Q	06 May 2009	06 May 2009
01-03 Jun 2009	Appendix R	08 Jul 2009	25 Aug 2009
28-30 May 2009	Appendix S	25 Jun 2009	16 Jul 2009
13-15, 18 May 2009	Appendix T	18 May 2009	19 Jun 2009
20-27 May 2009	Appendix U	13 Jul 2009	25 Aug 2009
06 May- 04 Jun 2009	Draft Final Report and Associated Raw Data Review	04 Jun 2009	08 Jul 2009
23 Jun 2009	Wet Specimen Verification	23 Jun 2009	08 Jul 2009

Tom Brasseur

Tom Brasseur, B.S.
Quality Assurance Auditor
Dow Corning Corporation
Health & Environmental Sciences

22 Dec 2009
Date

4 APPROVAL SIGNATURES

The undersigned have read and approved this report:

Wendy H. Koch, Ph.D.
Epona Associates, LLC

February 23, 2010
Date

Paul A. Jean, Ph.D.
Team Leader, Toxicology
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28 FEB 2010
Date

Tami S. McMullin, Ph.D.
Study Director, Toxicology
Dow Corning Corporation

02 March 2010
Date

5 STUDY INFORMATION

Study Initiation Date:	January 24, 2008
Experimental Start Date:	January 28, 2008
Repeated Study Experimental Start Date:	April 14, 2008
Experimental Termination Date:	June 07, 2008
Study Completion Date:	March 02, 2010
HES Study Number:	10709-102
Study Title:	Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Triethoxyoctylsilane in Sprague-Dawley Rats
Testing Facility:	Health and Environmental Sciences (HES) Dow Corning Corporation 2200 West Salzburg Road Auburn, MI 48611
Sponsor:	Silicones Environmental, Health and Safety Council 2325 Dulles Corner Blvd. Suite 500 Herndon, VA 20171
Study Director:	Tami S. McMullin, Ph.D.
HES Group Manager/Team Leader:	Paul A. Jean, Ph.D. Team Leader, Toxicology Health and Environmental Sciences
Study Coordinator:	Becki Uhlenhake D.M.R.A.L.A.T.
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Health and Environmental Sciences

6 STUDY PURPOSE

The objective of this study was to evaluate the potential toxic effects of Triethoxyoctylsilane in a combined repeated oral gavage toxicity study that included reproductive/developmental toxicity screening testing Sprague-Dawley rats.

7 BACKGROUND

The experimental phase of the original study was started on January 28, 2008. This study was terminated on February 27, 2008 due to an error that occurred in the preparation of the dosing solutions. All data for this original study are located in the study file. The experimental phase of the second trial of this study was started on April 14, 2008. The data reported in this report are the data from the second trial of this study with the exception of the data on the stability of the test article, which was collected during the first trial of this study.

8 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).

9 TEST ARTICLE / SUBSTANCE / ITEM

The study director reviewed results of test article characterization. The test article characterization report is included in Appendix P.

Identification:	Triethoxyoctylsilane (Supplied as Dow Corning ® Z-6341 Silane) Synonym: n-octyltriethoxysilane
Lot Number:	0005021818
Expiration Date:	August 6, 2010
Source:	Dow Corning Corporation Auburn, MI 48611
CAS Number:	2943-75-1
Physical Description:	Colorless liquid
Stability:	Stable, will react to moisture

Purity	97.7 ± 0.06 % pure (HES Study Number 10900-102)
Solubility:	Soluble in methanol and ethanol
Storage Conditions:	Room temperature
Chemical Characterization:	HES Study Number 10900-102
Archive:	A reserved sample was retained

10 CARRIER

Identification:	Dried, deacidified peanut oil
Lot Number:	080408 and 090408
Source:	Health and Environmental Sciences Dow Corning Corporation Auburn, MI 48611
Storage Conditions:	Room temperature in desiccator

11 TEST SYSTEM

Species:	Albino Rat
Strain:	Crl: CD® (SD) IGS BR VAF/Plus®
Source:	*Charles River Laboratories, Inc.* P.O Box 176 Portage MI 49081
Age:	9 weeks minimum at experimental start
Body weight:	Females: 159.6 to 201.7 g at randomization Males: 210.1 to 254.6 g at randomization
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:	Transponders (BioMedic Data Systems, Inc. Seaford, DE)

12 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.

13 METHOD OF RANDOMIZATION

Extra animals were ordered and acclimated for randomization. After release from quarantine/acclimation, rats were assigned to test groups based on a weight-stratified randomization process in Provantis™ v.6.5. At randomization, the sex specific weight variation of animals in each group did not exceed ± 20% of the mean weight for that group.

14 HOUSING AND MAINTENANCE

14.1 Animal Receipt and Quarantine/Acclimation

Animal resource personnel inspected each animal upon receipt and at least once daily during the quarantine period. Following examination by the attending veterinarian, all animals judged to be in good health and suitable as test animals were released from quarantine/acclimation five days after receipt.

14.2 Animal Housing

Animals were individually housed in suspended wire-mesh cages elevated over Bed-O'Cobs® bedding, during quarantine and throughout the course of the study, with the following exceptions. During cohabitation the reproductive group 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, the reproductive group female was individually caged. Pregnant females were moved into shoebox cages containing Bed-O' Cobs® Combination bedding on day 0 of gestation and remained there throughout the remainder of the study. 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, bedding/fecal pans were routinely cleaned, consistent with good husbandry practices.

14.3 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 toxicology animals the afternoon/evening prior to necropsy.

14.4 Environmental Conditions

Animals were housed in an environmentally controlled animal room (12-hour fluorescent-light/dark cycle, 20.1 – 21.3 °C, 39 - 60% humidity, 13.5 air changes per hour). Temperature and humidity were recorded continuously and monitored twice a day on weekdays and once a day during weekends and holidays. The study director reviewed the last verification of air changes.

14.5 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 may affect the outcome of the study.

Exceptions: Food was not provided during functional observation battery (FOB) or motor activity (MA) assessment periods. Additionally, food was removed the day prior to necropsy of the toxicology animals.

14.6 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 (FOB) or motor activity (MA) assessment periods.

15 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 Institutional Laboratory Animal Care and Use Committee (LACUC) before animals were ordered.

16 EXPERIMENTAL DESIGN

16.1 Data Acquisition System

Dosing, clinical observations and detailed physical observations, body weights, food consumption, select reproductive parameters, FOB, and morphologic pathology data were collected using Provantis™ v6.5 and Provantis ™ v8.2 (Instem LSS, Conshohocken, PA).

16.2 Route and Rationale of Test Article and Vehicle Administration

Route

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

Rationale
Oral ingestion 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 peanut oil was considered to be the most appropriate vehicle for oral administration.

16.3 Administration of doses

Dosing solutions were administered by oral gavage. The test article or carrier was administered to each dose group at an equal dose volume (2 mL/kg bw) and was calculated from the most recent body weight.

16.4 Dosing Solution Preparation and Analysis

Preparation
Dosing solutions were individually prepared. Stability data indicated that triethoxyoctylsilane was stable for 32 days (Appendix Q). Based on these data, the dosing solutions were prepared two times during the study. Calculations and preparation methods are documented in the raw data.

In order to enhance the stability of the test substance in the vehicle, the peanut oil carrier was dried and de-acidified. The following methodology was used in the preparation of the peanut oil. Approximately a 50/50 mixture of activated silica and aluminum oxide were dried in an oven at approximately 250^{0}C overnight. After drying, the mixture was transferred to a desiccator and allowed to cool to room temperature. For the oil drying procedure, the alumina/silica mixture was mixed with peanut oil at a ratio of approximately 80 grams per liter of oil. The mixture was mixed on a stir plate for approximately two hours under a nitrogen purge. Upon settling, the mixture was filtered under vacuum to remove the alumina and silica. The filtered peanut oil container was purged with nitrogen, the lid was sealed with parafilm and the container was stored at room temperature in a desiccator.

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 GC method are documented in the study records.

Dosing solutions were analyzed prior to study initiation to ensure stability and homogeneity. Stability was determined on study days 0, 4, 15, 21 and 32.

Dosing solutions were also analyzed for concentration verifications following each dose solution preparation.

Storage conditions
The filtered peanut oil and dose solution preparations were stored at room temperature in a desiccator.

16.5 Test Groups and Dose Levels

See Text Table 1 for organization of test groups and test article dose levels. A total of 30 animals were assigned to each dose group. 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 place on study for the purpose of evaluating both reproductive and toxicological endpoints. No animals needed to be replaced at any time during the study.

Text Table 1. Organization of Test Groups and Dose Levels

Group	Number of Animals		Dose Level (mg/kg bw/day)
	Reproductive	Toxicity	
1	10 males 10 females	10 females	0
2	10 males 10 females	10 females	100
3	10 males 10 females	10 females	300
4	10 males 10 females	10 females	1000

The control group received carrier only. The treatment groups received test article at three dose levels. These dose levels were selected based on results from a previous range finding study (HES Study Number 10708-102) and provided dose-response data for the test article.

16.6 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 28 days and euthanized the day after the last treatment. The toxicity group females were treated for 29 days and euthanized the day after the last treatment. Reproductive group females were treated through post-partum day 3 or until euthanized in extremis (up to post-partum day 2).

16.7 Mating Procedure

A 1:1 mating ratio was used. On study day 15, the animals were paired by placing the lowest numbered reproductive group female of each group with the lowest numbered male of that group, then the next lowest numbered reproductive group female with the next lowest numbered male, etc., until all animals were paired. The reproductive group female animals were housed continuously with the same male until evidence of mating occurred. 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 gestation was defined as the day evidence of copulation was observed, at which time the reproductive group female was individually caged.

16.8 Method of Euthanasia/Terminal Procedure

Scheduled

All males and toxicity group females were euthanized by exsanguination. While under Isoflurane® anesthesia, blood was collected from the abdominal 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. One nongravid female demonstrating no evidence of copulation (D5305) was euthanized 25 days after the last day of the mating period. Three reproductive group females with evidence of copulation and positive evidence of pregnancy that did not deliver (D5223, D5277, D5310) were euthanized on gestation days 25-26.

Pups were euthanized by intraperitoneal injection of pentobarbitol.

Unscheduled

Three reproductive group females (D5306, D5309, D5311) displayed signs of distress during or after delivery that warranted euthanasia prior to scheduled termination via the same method of euthanasia as the scheduled dams.

16.9 Test System Observations

See Text Table 2 for Timeline of Study Events.

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. No adult animals were found dead. Pups found dead were examined for external gross abnormalities only. The study director and veterinarian were notified when animals were found sick, moribund, or dead.

Clinical Observations

General clinical observations were made at least once a day, beginning on the first day of treatment, at approximately the same time(s) each day, with the exception of the week of FOB and MA testing, in which dosing was conducted following testing. The health conditions of the individual animals were recorded. Daily observations were also performed on all animals on the day of, but prior to, their scheduled necropsy. Clinical observations were not performed on the day of the detailed clinical observations.

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. Examinations included, but were not limited to, changes in skin, fur, eyes, mucous membranes, occurrence of secretions and excretions, and autonomic activity. Changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypies, difficult or prolonged parturition or bizarre behavior were recorded. The presence or absence of findings was recorded for individual animals.

Reproductive Group Female Observations

The duration of gestation was calculated from day 0 gestation for each reproductive group female. From day 20 after evidence of mating, pregnant animals were checked at least three times daily (twice daily on weekends and holidays) for evidence of parturition.

17 PARAMETERS MEASURED

17.1 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 the day of necropsy. During gestation, the pregnant reproductive group females were weighed (at a minimum) on gestation days 0, 7, 14 and 20, within 24 hours after parturition, and day 4 post-partum or upon terminal euthanasia of the dam. Litter weights were taken within 24 hours of parturition and on day 4 post-partum or upon terminal euthanasia of the dams.

17.2 Individual Food Consumption

Individual animal food consumption was recorded at least weekly on an individual animal basis 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:	Day 1 of dosing to necropsy Feeder weights were taken on day 1, 8, 15, 22 and the day prior to necropsy.
Reproductive:	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.

17.3 Functional Observational Battery

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.

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 and fecal pellets voided

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 v.2.03 software. Each test session was 80 minutes in length (10 X 8- minute intervals).

17.4 Clinical Pathology

Clinical Pathology assessments were made on all surviving fasted adult males and toxicity group females from which adequate samples were collected. Blood samples were collected for hematological and serum chemistry evaluations from all males and all toxicity group females on the day of scheduled euthanasia as a terminal procedure. While under Isoflurane® anesthesia, blood samples were collected from the abdominal vena cava using a syringe and needle and distributed to three sample collection tubes containing either sodium citrate, EDTA, or no anticoagulant.

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

Coagulation (Prothrombin Time)

Blood samples were collected into test tubes containing sodium citrate, centrifuged within two hours of collection. The plasma was separated for testing and 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 Intergra 400 plus® (Roche Diagnostics, Indianapolis, IN).

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

17.5 Morphologic Pathology

Macroscopic Examination

Males and Toxicity Group Females: All males and 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 Females: Based on clinical findings during the study, all reproductive females were also 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. In addition, the number of corpora lutea and the number of implantation sites were recorded. The uteri of reproductive group females with positive evidence of mating that failed to produce a litter (D5223 – Group 1, D5277 – Group 3, D5310 – Group 4) were stained with an equal mixture of 20% Potassium Ferricyanide and 1% Hydrochloric Acid to enable counting of possible reabsorbed implant sites. A uterus from a control group dam was also stained and used as a positive control.

Pups: Dead pups and pups euthanized on day 4 post-partum or *in extremis* were examined for external gross abnormalities. Pup tissues were not collected and the carcasses were discarded.

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 males. 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 collected from all animals in all treatment groups. Based on various clinical signs in the reproductive group females, the tissues and organs from all treatment groups of animals were also collected. The following organs/tissues were taken for male, toxicity and reproductive groups and preserved in fixative with the exception of the hindlimb and mammary tissue, which were collected on the reproductive group females only due to notable clinical signs and gross findings (lack of milk in pups' bellies) in the high dose group that warranted collection of these tissues for this group (Text Table 3).

Text Table 3. Organs/Tissue Collected and Selected Organs Weighed

Organ Weights [1,2]	Organs Collected[@]
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
X	Testes

Organ Weights [1,2]	Organs Collected[@]
X	Thymus
	Thyroid
	Trachea
	Urinary bladder
X	Uterus (horns and cervix)
	Hind limb[3]
	Mammary Tissue (including mammary skin)[3]

[1]Paired organs were weighed together.
[2]Organ weights were only conducted on the males and toxicity group females.
[3]Reproductive group females only.
[@]The testes and epididymides were preserved in Bouin's solution. All other tissues collected were placed in 10% neutral buffered formalin for preservation.

The testes and epididymides were preserved in Bouin's solution. All other tissues were placed in 10% Neutral Buffered Formalin for preservation.

A thorough histopathological examination was conducted on the collected tissues from the males, toxicity group females and reproductive group females in the control and high dose groups. All gross lesions were examined histopathologically with the exception of the mammary tissue from the reproductive group females. Based on histopathology findings in the high dose group, selected tissues for the males, toxicity and reproductive group females were examined at the mid and low dose groups (Text Table 4).

Text Table 4. Selected Tissues Examined for Mid and Low Dose Groups

Toxicity Groups		Reproductive Group Females
Males	Females	
liver, kidneys, urinary bladder	brain, spinal cord, sciatic nerve, liver, urinary bladder	brain, spinal cord, sciatic nerve, hindlimb (tibial nerve, adductor muscle, gastrocnemius muscle) liver, urinary bladder, spleen, thymus

17.6 Reproductive Parameters

The duration of gestation was calculated for each reproductive group 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. The day parturition was observed as complete was considered day 0 post-partum. Reproductive-type parameters evaluated were evidence of mating, pregnancy, and duration of gestation. In particular, the number of corpora lutea and the number of uterine implantation sites were determined for all females.

17.7 Developmental Parameters

Pups were examined daily for survival, external abnormalities and clinical signs during the lactation period. Each litter was examined as soon as possible after delivery (within 24 hours) 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. All pups were counted, weighed, sexed and the sex ratio calculated. Litter weights were taken within 24 hours of completion of parturition and on post-partum day 4 or earlier if the dam was euthanized prior to post-partum day 4. Developmental parameters evaluated included mean litter size, offspring survival, sex ratio and offspring body weight gain. Pups were euthanized on post partum day 4 and examined for external gross lesions. No tissues were collected from the pups for microscopic examination.

17.8 Sample Identification

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

18 DATA ANALYSIS

18.1 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.

18.2 Statistical methods

Statistical analysis of reproductive female body weights and changes in body weights, males and females (toxicity and reproductive groups) 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 (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). 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, 1962) 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.

Reproductive parameters with the exception of litter size were analyzed using an ANCOVA (Analysis of Covariance) with litter size as the covariate. Litter size was analyzed using an ANOVA.

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 was analyzed using the Jonckheere-Terpstra test (Jonkheere-Terpstra, 1956).

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.

19 PROTOCOL DEVIATIONS

Animal D5251 (Group 1) inadvertently did not have the gross necropsy examination documented in the study file. This protocol deviation did not adversely affect the quality or integrity of the study data, as tissues were collected and histopathology evaluation was completed on this animal.

20 RESULTS AND DISCUSSION

20.1 Homogeneity, Concentration Verification and Stability for Dosing Solutions

All homogeneity, concentration verification and stability data for the dosing solutions are presented in a contributing scientist report (Appendix Q).

Verification of the concentrations of triethoxyoctylsilane in the dosing solutions was conducted each time the dosing solution was made. The results from the concentration verification for the solutions mixed April 10, 2008 were 95.4%, 96.2% and 98.9% of target for the low, middle and high doses, respectively. The results from the concentration verification for the solutions mixed May 8, 2008 were 94.4%, 96.0% and 97.7% of target for the low, middle and high doses, respectively.

Homogeneity was determined for the low, middle, and high dose solutions from the initial trial of the study prepared on February 04, 2008 by sampling from the top, bottom and middle of the respective solutions. Results from the analysis gave a percent relative standard deviation (% RSD) for the solutions of 0.8%, 0.4% and 0.5%, respectively. All dosing solutions were found to be homogeneous.

Stability of the test article in dried, deacidified peanut oil was determined on the day of mixing and at intervals extending to Day 32. Triethoxyoctylsilane was stable in dried, deacidified peanut oil for at least 32 days.

20.2 Mortality and Morbidity

A summary of euthanasia data is provided in Table 1. All toxicity group males and females and reproductive group females in Groups 1-3 survived until scheduled necropsy. One nongravid female demonstrating no evidence of copulation (D5305) was euthanized 25 days after the last day of the mating period. Three females (D5223, D5310, and D5277) with evidence of copulation and positive evidence of pregnancy failed to deliver and were euthanized on gestation day 26, 25, and 25, respectively.

Due to the severity of clinical signs, the following Group 4 reproductive group females were euthanized prior to scheduled necropsy: animal D5309 was euthanized on study day 38, D5306 and D5311 were euthanized on study day 40, animal D5308 that had failed to initiate parturition by gestation day 24 and also exhibited clinical signs and was euthanized on study day 43.

20.3 Clinical Observations

Observations recorded during the weekly detailed physical examinations and those recorded during the daily clinical examinations are combined and are summarized in Tables 2-4. Individual data are provided in Appendices A-C.

There was a dose-related increase in soiling around the nose and chin and generalized soiling around the muzzle in the Group 3 and 4 males and toxicity group females. These clinical observations were statistically significant ($p<0.01$) in group 4 males and females. All ten reproductive group females also exhibited various degrees of soiling around the muzzle, nose and chin areas ($p<0.01$).

There were statistically significant changes in the incidence of neurological clinical signs only in Group 4 reproductive group females compared to controls. Hind limb dragging (5/10) and incoordinated gait (5/10) occurred in Group 4 reproductive group females. None of these neurological signs were noted until study day 32, with the exception of one animal that exhibited incoordinated gait on day 21 and dragging hindlimbs by day 25. These effects were also associated with a generalized decrease in overall activity ($p<0.01$) in 5/9 affected females. Rapid respiration occurred in 3/10 animals ($p<0.05$) beginning on the day prior to and/or on the day these animals were euthanized *in extremis*.

20.4 Body Weight

A summary of weekly mean body weights is presented in Tables 5-7 and mean body weight gains are presented in Tables 8-10. Individual body weight and body weight gain data are provided in Appendices D-F and Appendices G-I, respectively.

There were no significant differences in weekly mean body weights and body weight gains in all male groups compared to controls but there was a 6.8% decrease in mean overall body weight gain in the Group 4 males compared to controls ($p<0.05$).

Weekly mean body weights but not body weight gains were decreased on day 22 (8.9%) and 28 (9.3%) for the Group 4 toxicity group females compared to controls ($p<0.05$). Mean overall weight gains in Group 4 were also decreased (26.9%) compared to controls ($p<0.05$). There were no effects on body weights in the other treatment groups.

Mean body weights (data exclude all non-pregnant animals) and body weight gains across all reproductive group female dose levels were comparable to control throughout the pre-mating period. A 19.7% decrease in gestation week 2 mean body weight gains occurred in Group 3 reproductive group females compared to controls ($p<0.05$) but were similar to control values throughout the remainder of the study. Mean body weights of Group 4 reproductive group females were statistically decreased compared to controls throughout gestation ($p<0.01$). Associated body weight gains in this group were also decreased by 45.9% ($p<0.01$) by the end of gestation week 1 and 29.1% ($p<0.01$) by the end of the gestation period. There was also a significant decrease in Group 4 reproductive group female mean body weights throughout the post-partum period compared to controls ($p<0.01$). Although Group 4 reproductive group females exhibited a 73.9% decrease in mean body weight gains between post-partum day 0 to 4, this did not attain significance.

20.5 Food Consumption

Mean food consumption data are presented in Tables 11-13. Individual food consumption data are provided in Appendices J-L.

There were no significant differences in average daily food consumption of all male groups compared to controls.

Average daily food consumption during week 3 in Group 2 ($p<0.05$) and 4 ($p<0.02$) toxicity group females were statistically decreased compared to controls, respectively.

No changes in average daily food consumption of the reproductive group females occurred during the two week pre-mating period. A statistically significant decrease in average daily food

consumption of the Group 4 reproductive group females occurred throughout gestation (17.8%) and the post-partum period until terminal sacrifice (48.9%) ($p < 0.01$) compared to controls.

20.6 Functional Observation Battery and Motor Activity

FOB and MA data are presented in a contributing scientist report provided in Appendix S. A summary of FOB and motor activity data are presented in Tables 14-19. There were no statistically significant differences across dose groups in either the baseline or treated FOB categorical and motor activity data for both the males and toxicity group females.

20.7 Clinical Pathology

Individual and summary clinical pathology data are presented in a report provided in Appendix T.

Serum Chemistry

A summary of serum chemistry data is presented in Tables 20 and 21. In male rats, alkaline phosphatase and aspartate aminotransferase were decreased with increasing dose in Groups 2-4 compared to controls. Total bilirubin was statically different ($p<0.05$) only in Group 2 compared to controls. All these values were within range of historical control values for this laboratory (Appendix T), not in the direction of a pathological change and therefore, were not considered toxicologically significant.

In the toxicity group females, aspartate aminotransferase, albumin, creatinine and sodium were decreased with increasing dose in Groups 2-4 compared to controls, but only attained statistical significance in Group 4. There was a dose-related increase in cholesterol that was statistically significant in Group 4 toxicity group females. All these serum chemistry values were within range of historical control values for this laboratory (Appendix T) and not in the direction of a pathological change and therefore, were not considered toxicologically significant.

Hematology

A summary of hematology parameters is presented in Tables 22-23. There were no changes in hematology parameters noted in the male rats. A slight dose-related decrease in platelets occurred in the Group 4 toxicity group females compared to controls ($p<0.05$) but this value was within historical control range of the laboratory and did not correlate with any other effects and therefore, were not considered toxicologically significant (Appendix T).

Coagulation (Prothrombin Times)

A summary of prothrombin times is presented in Table 24-25. There were no effects on prothrombin times.

20.8 Organ Weights

Summary organ weight and organ-to-body weight ratio data are presented in Tables 26-27. Individual data are provided in Appendices M-N.

A slight but statistically significant increase ($p<0.05$) in absolute adrenal gland weights occurred in the Group 2 and 3 males compared to controls, and a slight decrease in relative prostate weights occurred only in the Group 2 males ($p<0.05$). These changes were not dose-related and

were not associated with any pathological changes and therefore, were not considered to be related to test-article exposure. A dose-related increase in mean absolute ($p<0.05$) and relative ($p<0.01$) liver weights occurred in Group 3 and Group 4 males, resulting in an 11.7% and 17.3% increase in relative liver weights at these dose levels compared to controls.

A 14.6% increase ($p<0.01$) in mean relative kidney weights occurred in Group 4 toxicity group females compared to controls. A dose-related increase in mean absolute liver weights also occurred in Group 3 and 4 toxicity group females that attained statistical significance only in the Group 4 toxicity group females compared to controls ($p<0.01$). These increases in absolute liver weights were associated with an increase in mean relative liver weights. Mean relative liver weights were increased by 4.7% ($p<0.05$) and 27.8% ($p<0.01$) in the Group 3 and 4 toxicity group females, respectively. Absolute, but not relative, ovarian weights were also statistically decreased ($p<0.05$) in the Group 3 and 4 toxicity group females.

There were no other differences in organ weight or organ-to-body weight ratios attributed to the test article.

20.9 Morphological Pathology

Macroscopic Examination

Gross pathology data are presented as a contributing scientist report in Appendix U. Summaries of the macroscopic findings are presented in Tables 28-29.

Males and Toxicity Group Females

There were no gross findings attributable to test article in male or female toxicity group animals.

Reproductive Group Females

The Group 4 reproductive group females exhibited various gross findings that included a generalized thinness of the body in 8/10 animals, decreased thymus size in 6/10 animals and spleen size in 7/10 animals. Five of these animals also had notable decreases in hind leg skeletal muscle mass. These macroscopic findings are consistent with the clinical observations of incoordinated gait and/or hindlimb dragging and microscopic neurological findings that occurred in all of these animals. In addition to the other gross findings, two animals had decreased ingesta in all or parts of the intestinal tract. No gross findings occurred at the lower dosage levels.

The uteri of reproductive group females with positive evidence of mating that failed to produce a litter (D5223, D5277, D5310) were stained with an equal mixture of 20% potassium ferricyanide and 1% hydrochloric acid to enable counting of possible reabsorbed implant sites. No implantation sites were found in these animals. A uterus from a control group dam was also stained and used as a positive control.

Other findings occurred only once or were considered typical of rats of this age and stock and unrelated to test article dosage.

Pups

Litter observations indicated that there was one runt in Group 3. Gross observations in Group 4 litters included milk not present in the stomach of several pups in 6/7 litters of dams and two dams that had several pups that were very thin compared to controls. There were no gross findings at any lower dose levels.

Microscopic Pathology

Summaries of the microscopic findings are presented in Tables 30-32. The incidence of microscopic findings and a detailed report of these findings are presented as a contributing scientist report in Appendix U.

Liver

There was a dose-related statistically significant increase in the incidence of centrilobular hypertrophy of the liver in Groups 3 and 4 males and females (toxicity and reproductive groups). In group 3, 8/10 males ($p<0.01$), 4/10 toxicity group females ($p<0.05$) and 10/10 ($p<0.01$) reproductive group females had minimal to mild centrilobular hypertrophy while all males and females (toxicity and reproductive) in Group 4 exhibited this finding ($p<0.01$). This finding was not observed in controls. These histopathological findings in the liver were associated with an increase in mean absolute and relative liver weights in both the Group 4 male and female toxicity groups and are consistent with common adaptive changes that occur in the liver upon xenobiotic administration.

Urinary Tract

There was a statistically significant increase in the incidence (7/10) of minimal to mild diffuse epithelial hyperplasia of the urinary bladder of Group 4 males compared to controls ($p<0.01$). One male was affected in Group 2; no males had these findings in Group 3. There was no significant effect in toxicity group females. Epithelial hyperplasia of the urinary bladder was observed, however, in 7/10 Group 4 reproductive group females and not in the controls ($p<0.01$). Although two reproductive group females in Group 2 had this finding in the urinary bladder, there was no dose-related effect as this finding did not occur in reproductive group females in Group 3.

Lymphoreticular System

A statistically significant increase in the incidence of mild to moderate atrophy of the spleen ($p<0.02$) and thymus ($p<0.02$) was identified in 5/10 Group 4 reproductive group females and not in the controls. These findings are consistent with the gross findings of decreased spleen and small thymus in several of the reproductive group females.

Neuromuscular System

The main finding in the central nervous system was white matter degeneration of the brain and spinal cord in Group 4 toxicity group females and reproductive group females, with an increased incidence in the reproductive group females compared to the toxicity group females. The cerebellum and medulla appeared to be the most prominently affected areas of the brain. There was an increase in the incidence of minimal white

matter degeneration (vacuolation) of the brain in 4/10 Group 4 toxicity group females and one control. In the Group 4 reproductive group females, this effect attained statistical significance, with 8/10 Group 4 animals exhibiting mild to marked vacuolation in the brain and no effects in the controls ($p<0.01$). The spinal cord of the toxicity group females also exhibited diffuse white matter vacuolation in both the sensory and motor nerve roots in 5/10 Group 4 and no control toxicity group females ($p<0.01$). Minimal to marked demyelination of the spinal cord also occurred in 9/10 Group 4 reproductive group females and no controls ($p<0.01$). Although the incidence of the effects in the brain were less prominant and did not attain statistical significance in the toxicity group females, there was evidence of minimal white matter vacuolation of the brain in 4/10 Group 4, 1/10 Group 3 and 1/10 control females. There were no effects on the central nervous system in males.

In the peripheral nerves examined, the sciatic and tibial nerves, there was a statistically significant increase in the incidence of minimal to severe demyelination /degeneration in 8/10 (sciatic) ($p<0.01$) and 9/9 (tibial) ($p<0.01$) Group 4 reproductive group animals and not in the controls. Affected animals tended to show the change in multiple sites unless only the spinal cord was involved. Minimal to mild nerve degeneration also occurred in 3/10 Group 4 toxicity group females and no controls but did not attain statistical significance. The only neurological effect in the males was minimal sciatic nerve degeneration in 2/10 Group 4 males, which also occurred in 1/10 controls.

Based on clinical signs in the Group 4 reproductive group females, two skeletal muscle sections of the hindlimb were evaluated (the adductor muscles of the inner thigh and the gastrocnemious (calf) muscle) in the reproductive group females. There was a statistically significant increase in Group 4 reproductive group female adductor muscle degeneration (10/10) compared to controls (4/10) ($p<0.01$). There was a trend toward significance in the incidence of degeneration of the gastrocnemius muscle in Group 4 reproductive group females (9/10) compared to controls (5/10) and a statistically significant increase in the severity of degeneration compared to controls. Animals affected with neurological findings also showed gross muscle atrophy, diffuse decreased muscle fiber size, fiber fragmentation, increased density of myofiber nuclei, and focal areas of inflammation around necrotic fibers. The animals with these skeletal muscle findings also had notable decreases in hind leg skeletal muscle mass. These findings are consistent with denervation atrophy and considered secondary to the nerve changes. Although the Group 4 reproductive group animals that demonstrated clinical signs also exhibited microscopic evidence of neuronal degeneration, the severity of the neurological lesions in the nerves did not necessarily correlate with the severity of neurological clinical signs observed in these animals.

These data indicate that the severity of the clinical and microscopic tissue neuromuscular effects is a likely reflection of duration of exposure rather than an effect specific to the reproductive status of the animal as the toxicity group females were only dosed for 29 days compared up to 45 days for the reproductive females.

These neurological findings did not occur at any lower dose levels or in males. Other histopathological findings of the neuromuscular system were of a type and severity

common to rats of this age and strain, and were not attributed to the effects of exposure to test article.

20.10 Reproductive Parameters

Summaries of the reproductive parameters are presented in Tables 33. Individual data are provided in Appendix O.

Mating and Fertility Data

A summary of mating and fertility data are presented in Table 33. All reproductive group females in Groups 1-3 demonstrated evidence of copulation. One animal in Group 1 and one in Group 3 were not pregnant. There were two reproductive group animals in Group 4 that were not pregnant; one female that had no evidence of copulation and was not pregnant and one that demonstrated evidence of copulation, but was not pregnant

Mating and fertility were unaffected by treatment as the mean number of implantations/dam and corpora lutea/dam and % pre-implantation loss were similar to control values. The mean duration of gestation, however, was statistically increased (5.6%) in Group 4 reproductive females compared to controls ($p<0.01$). The mean duration of gestation was 21.4, 21.7, 21.7 and 22.6 days, in order of ascending dose level. All pregnant dams in Groups 1-3 and seven dams in Group 4 successfully initiated parturition. One pregnant reproductive group female from Group 4 that exhibited severe clinical signs also failed to initiate parturition by gestation day 24 and was subsequently euthanized on that day. Of the seven dams in Group 4 that initiated parturition, four of these dams had dystocia (difficult/prolonged labor). All these dams also had clinical neurological signs of hindlimb weakness/dragging that likely contributed to the dystocia. Of these, one animal was euthanized prior to completion of parturition due to severity of clinical signs; necropsy indicated there was a dead fetus in the birth canal.

Loss of offspring

Summary of loss of offspring data is presented in Table 33. Mean percent pre-implantation and post-natal loss were unaffected by treatment. Mean percent post-implantation loss, however, was statistically increased in Group 4 (39.9%) compared to controls (5.7%) ($p<0.01$). Post-implantation loss values include loss of fetuses and/or pups that occurred between implantation and first litter check (within the first 24 hours of completion of parturition).

20.11 Developmental Parameters

Summaries of the developmental parameters are presented in Tables 34. Individual data are provided in Appendix O.

Litter Data

Summary litter data are presented in Table 34. There was a statistically significant increase in the mean ratio of male to female pups/litter on post-natal day (PND) 0 in Group 2 and in the number of live male pups/litter on PND 4 after adjusting for the mean litter size. These effects did not occur at any other dose levels and are likely not attributable to test article exposure.

Total litter size was unaffected by treatment. The number of live male and female pups/dam at first litter check (PND 0) in Group 4 were statistically decreased compared to controls ($p<0.01$), resulting in a 39.3% decrease ($p<0.01$) in percent viability pups/dam at first litter check compared to controls. Pup viability was unaffected at all lower dosages.

By PND 4, several dams in Group 4 had been euthanized due to the severity of various clinical signs and/or difficulty during labor. Only four dams continued through PND 4. Of these litters, the total viable pups on PND 4 was decreased compared to controls, resulting in a 25.2% decrease in percent viability of pups/dam on PND 4 compared to controls ($p<0.01$). This significant decrease was due to a single dam that had a 14.3% post-natal loss of offspring. The remaining dams had no post-natal loss of pups between PND 0-4.

On PND 0, mean litter weights and average pup body weights were similar to controls. By PND 4, weights in Group 4 were decreased compared to control weights ($p<0.02$). Average pup weights on PND 4 of the surviving pups were decreased by 25.2% and average pup weight gains of the surviving pups were decreased by 60% compared to controls ($p<0.01$). The loss of pup body weights in the Group 4 surviving pups resulted in a 50.1% decrease in mean live litter weights compared to controls.

21 CONCLUSIONS

Treatment-related effects were primarily limited to the Group 4 animals. These effects included clinical findings, decreased body weights, body weight gains and food consumption, changes in select organ weights, various changes in reproductive parameters and histopathological findings in the liver, urinary tract, lymphoreticular system and neuromuscular system.

Treatment-related decreases in mean body weights and/or body weights gains occurred in all Group 4 animals. Decreased body weights and body weight gains were most pronounced in the reproductive group females throughout gestation and the post-partum period. Mean body weights and overall weight gains for the toxicity group females were decreased only toward the end of the study. These changes in body weights were associated with decreases in average daily food consumption during the same periods in the Group 4 toxicity group females and reproductive group females. Males were minimally affected, only demonstrating a decrease in overall body weight gains throughout the study.

Clinical signs were observed predominantly in the Group 4 reproductive group females that included soiling around the nose and chin and generalized soiling around the muzzle and clinical signs of neurological dysfunction (incoordinated gait and hindlimb dragging). An increased incidence of decreased activity, dragging of the hindlimbs and/or incoordinated gait occurred in 9/10 Group 4 reproductive group females. Two of the reproductive group females in Group 4 that exhibited incoordinated gait were not pregnant. Three of these animals also exhibited rapid respiration as the clinical signs progressed. Due to the severity of these clinical signs, these three Group 4 reproductive group females were euthanized prior to schedule necropsy on post-partum day 4 along with one additional dam that also exhibited neurological clinical signs and had not initiated partruition by gestation day 24. The only clinical signs observed in the toxicity group animals were a dose-related increase in soiling around the nose and chin and generalized soiling around the muzzle in the Group 3 and 4 toxicity group males and females. This effect was statistically significant in both Group 4 males and females groups.

All changes in hematology and clinical pathology parameters were within the range of historical control values for this laboratory.

There were no macroscopic findings attributable to test article in male or female toxicity group animals. The Group 4 reproductive group females exhibited various gross findings that included a generalized thinness of the body, decreased thymus and spleen size, decreases in hind leg skeletal muscle mass and decreased ingesta in all or parts of the intestinal tract. Notable litter findings included milk not present in the stomach of several pups from most of the Group 4 dams and several very thin pups from two of the dams.

Histopathological findings were identified in the liver, urinary tract (bladder and kidneys), the lymphoreticular system (adrenal and spleen) and neuromuscular system (brain, spinal cord, peripheral nerves and skeletal muscles). A dose-related increase in centrilobular hypertrophy of the liver occurred in all Group 3 and Group 4 animals (males, toxicity group females and reproductive group females). These microscopic findings were associated with an increase in mean absolute and relative liver weights in the Group 4 toxicity males and toxicity group females and are considered to be adaptive changes that occur frequently in the liver upon xenobiotic administration. Diffuse epithelial hyperplasia of the urinary bladder occurred in all Group 4 animals. The Group 4 reproductive females also exhibited atrophy of the spleen and thymus with correlated gross findings of decreased spleen and small thymus.

There were several neurological findings that occurred in the Group 4 female rats, predominantly in the reproductive group females. There were no observed neuromuscular effects clearly attributable to the test article among male rats. The prominent histopathological findings observed in the females occurred in the brain, spinal cord, peripheral nerves, and skeletal muscle and appear to represent a primary effect on the myelin sheaths surrounding the axons of the nerves. These findings did not occur at any of the lower dose levels.

Degeneration of white matter within the central nervous system occurred in a large percentage of toxicity group and reproductive group females. In the brain, predominantly the cerebellum and medulla, 40% and 80% of the Group 4 toxicity and reproductive group females exhibited white matter degeneration. Degeneration of the spinal cord occurred in 50% and 90% of the Group 4 toxicity and reproductive group females, respectively. Minimal to severe degeneration of the peripheral nerves of the hindlimb (sciatic and tibial) also occurred in the Group 4 toxicity and reproductive group females, with less incidence and severity occurring in the toxicity group females compared to the reproductive group females. Consistent with secondary effects of degeneration of these peripheral nerves, many of these animals exhibited pathological findings associated with skeletal muscle denervation. These findings included gross muscle atrophy, decreased muscle fiber size and fiber fragmentation and an increased density of myofiber nuclei with focal areas of inflammation around the necrotic fibers. These neurological histopathology findings are consistent with the neurological clinical findings that occurred in the reproductive group females. Although the Group 4 reproductive group animals that demonstrated clinical signs also exhibited microscopic evidence of neuronal degeneration, the severity of the neurological lesions in the nerves did not necessarily correlate with the severity of neurological clinical signs observed in these animals.

Although the neurological clinical signs only occurred in the reproductive group females, these effects are clearly not attributable to reproductive status; two of the females that exhibited

moderate to severe neurological clinical and histopathological findings were not pregnant and histopathological findings also occurred, but to less severity, in the toxicity group females. These data indicate that the severity of the clinical and microscopic tissue neuromuscular effects is a likely reflection of duration of exposure rather than an effect specific to the reproductive status of the animal as the toxicity group females were only dosed for 29 days compared up to 45 days for the reproductive females.

No statistically significant changes in functional observation battery and motor activity were noted in males or toxicity group females; dosing in these groups was for 28 and 29 day, respectively.

Changes in reproductive parameters were limited to the Group 4 reproductive group females. Mating and fertility were unaffected by treatment. The mean duration of gestation was statistically significantly increased by 5.6% in the Group 4 reproductive group females compared to controls. All pregnant dams in Groups 1-3 and seven dams in group 4 successfully initiated parturition. One female from Group 4 exhibiting severe clinical signs also failed to initiate parturition by gestation day 24 and was subsequently euthanized. Of the seven dams that initiated parturition, four of these dams had dystocia (difficult/prolonged labor) and one of these dams was euthanized prior to completion of parturition due to the severity of clinical signs.

Changes in developmental parameters were limited to the Group 4 reproductive group females. The mean number of live male and female pups/dam at first litter check (PND 0) in Group 4 was statistically decreased compared to controls, resulting in a 39.3% decrease in mean total number of live pups/dam on PND 0 compared to controls. Of the four litters that remained through PND 4, there was a 3.6% post–natal loss of pups compared to controls. Mean litter weights and average pup body weights on PND 4 were also statistically decreased in Group 4. By PND 4, several dams in Group 4 had been euthanized due to the severity of various clinical signs and/or difficulty during labor. Only four dams continued through PND 4. All of the dams with complications during parturition and/or changes in litter parameters exhibited various degrees of hindlimb weakness that likely contributed to the difficulty in delivering the pups and consequent decreases in average pup weights and pup body weight gains and pup viability on PND 0 through PND 4. Because these reproductive/developmental effects occurred only in affected dams, these effects are considered a consequence of maternal neuromuscular toxicity. Pup viability was unaffected at all lower dosages.

Based on the bladder epithelial hyperplasia in males and the neuromuscular findings in the toxicity and reproductive group females at 1000 mg/kg bw/day, a NOAEL (No-Observable-Adverse-Effect-Level) of 300 mg triethoxyoctylsilane/kg bw/day is assigned for systemic toxicity. Because the reproductive/developmental effects in the litters only occurred at levels that were also toxic to parent animals, a NOAEL of 1000 mg/kg bw/day is assigned for reproductive /developmental toxicity.

22 ARCHIVE

All work product including the protocol, amendments and deviations, study authorization documentation, 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. Summary of Animal Euthanasia

Group	Sex	Terminal Sacrifice	Euthanized	Found Dead
1	M-tox.	10/10	0/10	0/10
	F-tox.	10/10	0/10	0/10
	F-repro.	10/10	0/10	0/10
2	M-tox.	10/10	0/10	0/10
	F-tox.	10/10	0/10	0/10
	F-repro.	10/10	0/10	0/10
3	M-tox.	10/10	0/10	0/10
	F-tox.	10/10	0/10	0/10
	F-repro.	10/10	0/10	0/10
4	M-tox.	10/10	0/10	0/10
	F-tox.	10/10	0/10	0/10
	F-repro.	6/10	4/10[a]	0/10

[a] Animals 5306 and 5311 were euthanized on study day 40, 5309 was euthanized on study day 38, animal 5308 was euthanized on study day 43.

Table 2. Summary Combined Clinical Observations and Detailed Physical Exams – Male Toxicity Groups

	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	
No abnormalities detected	299/10	296/10	259/10	204/10	
Skin: scab lower forelimb, right, focal	0/0	3/1	0/0	0/0	
Skin: scab shoulder, left, focal	0/0	0/0	7/1	0/0	
Skin: scab upper back, thoracic, right, focal	0/0	0/0	9/1	0/0	
Soiling: abdomen, general (yellow)	0/0	0/0	1/1	3/2	
Soiling: nose, chin, (red, clear, or yellow)	1/1	1/1	5/4	54/8	***
Soiling: muzzle, general (red or clear)	0/0	0/0	13/5	40/8	***
Soiling: urogenital, general (red or yellow)	0/0	0/0	11/4	11/4	

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

Values in the table represent the total number of clinical observations over the number of animals in which those observations occurred.

Table 3. Summary Combined Clinical Observations and Detailed Physical Exams – Female Toxicity Groups

	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	
No abnormalities detected	282/10	282/10	275/10	224/10	
Behavior activity: decreased	0/0	0/0	0/0	1/1	
Eye: increased lacrimation, bilateral	0/0	0/0	0/0	1/1	
Skin: scab head, top, focal	7/1	8/1	0/0	0/0	
Skin: scab muzzle, right, focal	1/1	0/0	0/0	0/0	
Skin: scab neck, right, focal	7/1	0/0	0/0	0/0	
Skin: scab shoulder, left, focal	0/0	0/0	8/1	7/1	
Soiling: nose, chin, (red, clear, or yellow)	0/0	0/0	5/1	20/7	***
Soiling: muzzle, general (red or clear)	0/0	0/0	3/2	41/7	***
Soiling: urogenital, general (red or yellow)	0/0	0/0	0/0	1/1	

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

Values in the table represent the total number of clinical observations over the number of animals in which those observations occurred.

Table 4. Summary Combined Clinical Observations and Detailed Physical Exams – Female Reproductive Groups

	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	
No abnormalities detected	391/10	434/10	438/10	274/10	
Behavior activity: decreased	0/0	0/0	0/0	37/5	***
Excessive hair loss: hindlimb, bilateral	17/1	0/0	0/0	0/0	
Gait: dragging hindquarters, limbs flacid	0/0	0/0	0/0	43/5	***
Gait: incoordinated	0/0	0/0	0/0	28/5	***
Misc.: thin	0/0	0/0	0/0	1/1	
Respiration: rapid	0/0	0/0	0/0	5/3	**
Skin: scab lower hindlimb, right, focal	18/1	0/0	0/0	0/0	
Skin: ungroomed appearance	0/0	0/0	0/0	1/1	
Soiling: abdomen, general (yellow)	1/1	0/0	0/0	4/1	
Soiling: nose, chin, (red, clear, or yellow)	0/0	0/0	2/1	77/10	***
Soiling: muzzle, general (red or clear)	0/0	0/0	0/0	50/9	***
Soiling: eye, bilateral red	0/0	0/0	0/0	4/2	
Soiling: urogenital, general (red or yellow)	2/2	0/0	0/0	1/1	

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

Values in the table represent the total number of clinical observations over the number of animals in which those observations occurred.

Table 5. Summary of Mean Body Weight – Male Toxicity Groups

		Day(s) Relative to Start Date (grams)				
		1	8	15	22	29
0 mg/kg/day	Mean	301.38	334.85	366.07	392.09	419.47
	SD	7.70	8.89	13.01	19.24	23.63
	N	10	10	10	10	10
100 mg/kg/day	Mean	304.60	341.88	378.23	402.15	429.89
	SD	10.65	14.82	16.86	25.35	25.65
	N	10	10	10	10	10
300 mg/kg/day	Mean	305.67	341.49	372.40	398.51	426.45
	SD	10.26	14.80	20.11	22.39	22.94
	N	10	10	10	10	10
1000 mg/kg/day	Mean	304.17	336.33	365.12	389.02	414.19
	SD	12.45	20.97	26.75	28.73	31.46
	N	10	10	10	10	10

Table 6. Summary of Mean Body Weight – Female Toxicity Groups

		Day(s) Relative to Start Date (grams)				
		1	8	15	22	28
0 mg/kg/day	Mean	207.17	220.99	235.02	252.08	261.20
	SD	9.77	15.83	16.74	19.02	18.72
	N	10	10	10	10	10
100 mg/kg/day	Mean	198.78	215.32	228.27	246.21	255.04
	SD	10.38	13.53	16.44	15.10	16.82
	N	10	10	10	10	10
300 mg/kg/day	Mean	207.41	218.68	234.08	249.71	258.48
	SD	13.80	12.76	16.46	15.74	15.82
	N	10	10	10	10	10
1000 mg/kg/day	Mean	197.35	208.05	218.03	229.77 *	236.87 *
	SD	10.52	14.12	15.95	16.02	20.36
	N	10	10	10	10	10

* = p-values < 0.05 significance level

Table 7. Summary of Mean Body Weight – Female Reproductive Groups

Study Day		1 (g)	8 (g)	15 (g)	Gest 0 (g)	Gest 7 (g)	Gest 14 (g)	Gest 20 (g)
0 mg/kg/day	Mean	206.52	225.04	242.33	254.42	287.66	332.82	421.97
	SD	13.09	20.71	21.20	21.16	21.11	22.03	22.22
	N	10	10	10	9[a]	9	9	9
100 mg/kg/day	Mean	203.47	218.74	232.76	242.30	272.05	313.83	400.78
	SD	13.80	14.51	19.28	18.50	19.29	21.10	26.34
	N	10	10	10	10	10	10	10
300 mg/kg/day	Mean	204.71	218.77	231.90	246.74	279.77	316.03	403.87
	SD	9.65	16.23	16.68	21.05	20.82	23.19	17.22
	N	10	10	10	9[b]	9	9	9
1000 mg/kg/day	Mean	206.39	215.99	230.62	237.60	255.58 ***	280.16 ***	343.35 ***
	SD	12.80	12.87	15.37	13.98	22.21	36.92	36.13
	N	10	10	10	8[c]	8	8	8

Gest = Gestational Day
[a]5223 had evidence of mating, but was not pregnant.
[b]5277 had evidence of mating, but was not pregnant.
[c]5305 had no evidence of mating and did not deliver; 5310 evidence of mating but was not pregnant.
*** = p-values < 0.01 significance level

Table 7. Summary of Mean Body Weight – Female Reproductive Groups (continued)

Study Day		P-Partum 0 (g)	P-Partum 4 (g)
0 mg/kg/day	Mean	329.44	340.72
	SD	21.40	26.21
	N	9[a]	9
100 mg/kg/day	Mean	312.74	317.71
	SD	24.78	26.72
	N	10	10
300 mg/kg/day	Mean	318.38	327.82
	SD	22.16	23.74
	N	9[b]	9
1000 mg/kg/day	Mean	259.44 ***	243.03 ***
	SD	35.17	53.01
	N	7[c]	4[d]

P-Partum = Postpartum Day
*** = p-values < 0.01 significance level
[a]5223 had evidence of mating, but was not pregnant.
[b]5277 had evidence of mating, but was not pregnant.
[c]5305 had no evidence of mating and did not deliver; 5308 was euthanized on Gestation Day 24; 5310 evidence of mating but was not pregnant.
[d]5306 was euthanized on P-Partum Day 2; 5309 was euthanized on P-Partum Day 0; 5311 was euthanized on P-Partum day 0; .

Table 8. Summary of Mean Body Weight Gains – Male Toxicity Groups

		Day(s) Relative to Start Date (grams)				
		1 → 8	8 → 15	15 → 22	22 → 29	1 → 29
0 mg/kg/day	Mean	33.47	31.22	26.02	27.38	118.09
	SD	8.59	7.76	8.46	7.72	21.17
	N	10	10	10	10	10
100 mg/kg/day	Mean	37.28	36.35	23.92	27.74	125.29
	SD	8.78	5.71	11.92	4.07	22.50
	N	10	10	10	10	10
300 mg/kg/day	Mean	35.82	30.91	26.11	27.94	120.78
	SD	6.63	10.47	9.09	4.69	19.25
	N	10	10	10	10	10
1000 mg/kg/day	Mean	32.16	28.79	23.90	25.17	110.02 *
	SD	10.86	8.57	6.18	9.11	23.63
	N	10	10	10	10	10

* = p-values < 0.05 significance level

Table 9. Summary of Mean Body Weight Gains – Female Toxicity Groups

		Day(s) Relative to Start Date (grams)				
		1 → 8	8 → 15	15 → 22	22 → 28	1 → 28
0 mg/kg/day	Mean	13.82	14.03	17.06	9.12	54.03
	SD	7.64	4.65	6.72	4.57	10.90
	N	10	10	10	10	10
100 mg/kg/day	Mean	16.54	12.95	17.94	8.83	56.26
	SD	6.84	5.54	8.61	6.13	10.94
	N	10	10	10	10	10
300 mg/kg/day	Mean	11.27	15.40	15.63	8.77	51.07
	SD	2.90	4.97	6.45	7.23	8.59
	N	10	10	10	10	10
1000 mg/kg/day	Mean	10.70	9.98	11.74	7.10	39.52 *
	SD	5.50	5.93	4.46	10.99	14.01
	N	10	10	10	10	10

* = p-values < 0.05 significance level

Table 10. Summary of Mean Body Weight Gains – Female Reproductive Groups

Study Day		1-8 (g)	8-15 (g)	Gest 0-7 (g)	Gest 7-14 (g)	Gest 14-20 (g)	P-Partum 0-4 (g)	Total Change (Day 1 – P-Partum 4) (g)
0 mg/kg/day	Mean	18.52	17.29	33.23	45.17	89.14	11.28	132.86
	SD	10.03	4.37	9.08	5.06	10.80	10.59	19.84
	N	10	10	9[a]	9	9	9	9
100 mg/kg/day	Mean	15.27	14.02	29.75	41.78	86.95	4.97	114.24
	SD	5.12	8.28	7.92	3.72	10.76	25.46	26.27
	N	10	10	10	10	10	10	10
300 mg/kg/day	Mean	14.06	13.13	33.02	36.27	87.83	9.44	121.43
	SD	8.61	6.97	6.88	10.82	13.13	5.26	21.74
	N	10	10	9[b]	9	9	9	9
1000 mg/kg/day	Mean	9.60	14.63	17.98 ***	24.59 ***	63.19 ***	-16.08	34.68 ***
	SD	3.40	4.66	12.85	17.74	19.27	32.82	55.87
	N	10	10	8[c]	8	8	4[d]	4

Gest = Gestational Days; P-Partum = Post-partum Days
*** = p-values < 0.01 significance level
[a]5223 had evidence of mating, but was not pregnant.
[b]5277 had evidence of mating, but was not pregnant.
[c]5305 had no evidence of mating and did not deliver; 5310 evidence of mating but was not pregnant.
[d]5306 was euthanized on P-Partum Day 2; 5308 was euthanized on Gestation Day 24; 5309 was euthanized on P-Partum Day 0; 5311 was euthanized on P-Partum day 0; .

Table 11. Summary of Mean Food Consumption – Male Toxicity Groups

		Mean Food Consumption (g/day)	Mean Food Consumption (g/day)	Total Food Consumption (g)
		1 → 8	8 → 15	1 → 15
0 mg/kg/day	Mean	26.35	26.88	372.66
	SD	2.23	2.39	30.24
	N	10	10	10
100 mg/kg/day	Mean	26.94	28.00	384.61
	SD	2.20	3.06	35.41
	N	10	10	10
300 mg/kg/day	Mean	26.83	27.49	380.27
	SD	0.83	1.81	16.81
	N	10	10	10
1000 mg/kg/day	Mean	26.79	27.60	380.72
	SD	3.12	3.72	45.87
	N	10	10	10

Table 12. Summary of Mean Food Consumption – Female Toxicity Groups

		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/day	Mean	19.77	22.20	22.52	20.38	573.69
	SD	2.01	1.68	1.72	1.89	44.61
	N	10	10	10	10	10
100 mg/kg/day	Mean	18.73	21.03	20.41 *	19.86	540.31
	SD	1.96	1.94	2.16	1.63	49.64
	N	10	10	10	10	10
300 mg/kg/day	Mean	18.83	21.44	21.00	19.60	546.52
	SD	1.34	1.03	1.29	1.20	28.27
	N	10	10	10	10	10
1000 mg/kg/day	Mean	17.64	20.61	20.23 **	19.77	528.04
	SD	1.39	1.80	1.65	2.26	39.67
	N	10	10	10	10	10

* = p-values <0.05 significance level
** = p-values <0.02 significance level

Table 13. Summary of Mean Food Consumption – Female Reproductive Groups

		1-8 (g/day)	8-15 (g/day)	Pre-Mating Total (g)	Gest 0-7 (g/day)	Gest 7-14 (g/day)	Gest 14-20 (g/day)	Gestational Total (g)
0 mg/kg/day	Mean	19.85	21.54	289.75	21.93	24.49	27.99	492.87
	SD	2.37	2.10	30.11	1.68	1.55	2.10	33.42
	N	10	10	10	9	9	9	9
100 mg/kg/day	Mean	18.64	20.88	276.65	20.87	22.77 *	25.55	458.77
	SD	1.74	1.77	23.17	2.06	1.91	2.61	38.76
	N	10	10	10	10	10	10	10
300 mg/kg/day	Mean	19.43	21.93	289.55	21.01	23.52	26.56	471.01
	SD	2.24	2.13	27.08	1.80	2.29	2.25	41.12
	N	10	10	10	9	9	9	9
1000 mg/kg/day	Mean	18.12	20.58	270.90	19.21 **	19.66 **	22.19 ***	405.23 ***
	SD	1.37	2.84	27.77	2.02	3.90	3.05	50.37
	N	10	10	10	8[a]	8	8	8

* = p-values <0.05 significance level
** = p-values <0.02 significance level
*** = p-values <0.01 significance level
Gest = Gestational Days
[a]5305 and 5311 had no evidence of mating and were not pregnant.

Table 13. Summary of Mean Food Consumption – Female Reproductive Groups

		P-Partum 0-4 (g/day)	P-Partum Total (g)
0 mg/kg/day	Mean	35.54	142.14
	SD	6.48	25.93
	N	9[a]	9
100 mg/kg/day	Mean	30.94	123.77
	SD	5.74	22.95
	N	10	10
300 mg/kg/day	Mean	32.48	129.91
	SD	4.07	16.29
	N	9[b]	9
1000 mg/kg/day	Mean	18.17 ***	72.68 ***
	SD	11.38	45.50
	N	4[c]	4

P-Partum = Post-Partum Days
*** = p-values <0.01 significance level
[a]5223 had evidence of mating, but was not pregnant.
[b]5277 had evidence of mating, but was not pregnant.
[c]5305 had no evidence of mating and did not deliver; 5306 euthanized on PP2; 5308 euthanized on GD24 without delivering; 5309 euthanized on PP0; 5310 evidence of mating but was not pregnant; 5311 euthanized on PP0.

Table 14. Summary of FOB Ranked/Categorical Incidence – Male Toxicity Groups

	Baseline				Treated			
Dose Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Number of Animals Examined	10	10	10	10	10	10	10	10
Resistance to Removal								
(3) Moderate; actively avoids capture but is not aggressive	10	10	10	10	10	10	10	10
Palpebral Closure								
(3) Open	10	10	10	10	10	10	10	10
Pupil Reactivity								
(3) dilated, briskly reactive pupil	10	10	10	10	10	10	10	10
Pupil Size								
(3) Normal pupil size	10	10	10	10	10	10	10	10
Lacrimation								
(3) Glistening cornea	10	10	10	10	10	10	10	10
Salivation								
(3) glistening oral cavity/lips, no wetness	10	10	10	10	10	10	10	10
Muscle Tone								
(3) moderate; animal is neither very relaxed nor tense	10	10	10	10	10	10	10	10

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Table is replicated from Appendix S.

Table 14. Summary of FOB Ranked/Categorical Incidence – Male Toxicity Groups (continued)

	Baseline				Treated			
Dose Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Number of Animals Examined	10	10	10	10	10	10	10	10
Extensor Thrust								
(3) moderate; clearly detectable	10	10	10	10	10	10	8	10
(4) Pronounced; pushes vigorously	0	0	0	0	0	0	2	0
Reactivity to Handling								
(3) moderate struggling with little or no vocalization	10	10	10	10	10	10	10	10
Level of Activity								
(1) None, animal doesn't leave the center circle (20 cm dia.)	0	0	0	0	0	0	0	1
(2) minimal, inactive more than 50% of the time	0	0	0	0	6	3	5	5
(3) moderate, inactive less than 50% of the time	10	10	10	10	4	7	5	4
Response to Noise								
(3) moderate; clear movement of the head, neck, ears and possibly front shoulders/upper body	7	9	9	9	8	7	9	10
(4) pronounced; clear movement of head, neck and ears, plus clear movement of whole body	2	1	1	1	2	3	1	0
(5) exaggerated; whole body response to stimulus, more intense than "pronounced"; includes whole body	1	0	0	0	0	0	0	0
Response to Touch								
(3) moderate; spontaneously lifts tail when touched	10	10	10	10	10	10	10	10

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Table is replicated from Appendix S.

Table 14. Summary of FOB Ranked/Categorical Incidence – Male Toxicity Groups (continued)

	Baseline				Treated			
Dose Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Number of Animals Examined	10	10	10	10	10	10	10	10
Response to Tail Pinch								
(2) minimal; animal flinches and may vocalize	0	0	0	0	1	0	1	0
(3) moderate; animal flinches, moves rapidly and/or vocalizes	10	10	10	10	9	10	9	10
Gait Evaluation								
(1) smooth and coordinated gait	10	10	10	10	10	10	10	10
Urination								
(1) no drops of urine	1	4	1	1	0	0	0	1
(2) minimal; a few (1-4) small drops or a small pool (~1 cm)	3	2	1	0	1	1	0	1
(3) moderate; a few (1-4) small pools or a moderate pool (2-3 cm)	3	1	2	3	2	1	3	2
(4) pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)	1	0	3	2	2	3	3	4
(5) Exaggerated; >4 moderate pools or single pool >5 cm.	2	3	3	4	5	5	4	2

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Table is replicated from Appendix S.

Table 14. Summary of FOB Ranked/Categorical Incidence – Male Toxicity Groups (continued)

	Baseline				Treated			
Dose Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Number of Animals Examined	10	10	10	10	10	10	10	10
Defecation								
(1) no pellets voided	4	5	4	6	3	2	6	2
(2) minimal; 1 or 2 pellets voided	4	3	1	4	2	2	0	1
(3) moderate ; 3 pellets voided	2	2	4	0	1	2	1	3
(4) pronounced; 4 pellets voided	0	0	1	0	1	3	2	4
(5) Exaggerated; 5 or more pellets voided	0	0	0	0	3	1	1	0
Categorical Observations								
Behavior Repetitive (Head Sway)	0	0	0	0	0	1	0	0
No Abnormalities Detected	10	10	10	10	10	9	10	10

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Table is replicated from Appendix S.

Table 15. Summary of FOB Ranked/Categorical Incidence – Female Toxicity Groups

	Baseline				Treated			
Dose Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Number of Animals Examined	10	10	10	10	10	10	10	10
Resistance to Removal								
(3) Moderate; actively avoids capture but is not aggressive	10	8	10	10	10	10	10	10
(4) Pronounced; actively avoids capture and/or is mildly aggressive	0	2	0	0	0	0	0	0
Palpebral Closure								
(3) Open	10	10	10	10	10	10	10	10
Pupil Reactivity								
(3) dilated, briskly reactive pupil	10	10	10	10	10	10	10	10
Pupil Size								
(3) Normal pupil size	10	10	10	10	10	10	10	10
Lacrimation								
(3) Glistening cornea	10	10	10	10	10	10	10	10
Salivation								
(3) glistening oral cavity/lips, no wetness	10	10	10	10	10	10	10	10
Muscle Tone								
(3) moderate; animal is neither very relaxed nor tense	10	10	10	10	10	10	10	10

Nominal Dose. Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Table is replicated from Appendix S.

Table 15. Summary of FOB Ranked/Categorical Incidence – Female Toxicity Groups (continued)

	Baseline				Treated			
Dose Group	1	2	3	4	1	2	3	4
Number of Animals Examined	10	10	10	10	10	10	10	10
Extensor Thrust								
(3) moderate; clearly detectable	10	10	10	10	10	10	10	10
Reactivity to Handling								
(3) moderate struggling with little or no vocalization	9	9	10	10	10	10	10	10
(4) pronounced struggling, animal may vocalize	1	1	0	0	0	0	0	0
Level of Activity								
(2) minimal, inactive more than 50% of the time	0	0	0	0	1	1	2	0
(3) moderate, inactive less than 50% of the time	10	10	9	9	8	9	8	10
(4) pronounced; leaves circle, occasional inactivity	0	0	1	1	1	0	0	0
Response to Noise								
(3) moderate; clear movement of the head, neck, ears and possibly front shoulders/upper body	8	10	8	9	10	10	8	10
(4) pronounced; clear movement of head, neck and ears, plus clear movement of whole body	2	0	1	1	0	0	2	0
(5) exaggerated; whole body response to stimulus, more intense than "pronounced"; includes whole body	0	0	1	0	0	0	0	0

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Table is replicated from Appendix S.

Table 15. Summary of FOB Ranked/Categorical Incidence – Female Toxicity Groups (continued)

	Baseline				Treated			
Dose Group	1	2	3	4	1	2	3	4
Number of Animals Examined	10	10	10	10	10	10	10	10
Response to Touch								
(3) moderate; spontaneously lifts tail when touched	10	10	10	10	10	9	10	9
(4) Pronounced; spontaneously lifts tail and acts startled	0	0	0	0	0	1	0	1
Response to Tail Pinch								
(3) moderate; animal flinches, moves rapidly and/or vocalizes	10	10	10	10	9	10	10	10
(4) Pronounced; animal moves vigorously in opposite direction of source of stimulation and vocalized	0	0	0	0	1	0	0	0
Gait Evaluation								
(1) smooth and coordinated gait	10	10	10	10	10	10	10	10
Urinatiou								
(1) no drops of urine	4	3	5	2	3	2	6	0
(2) minimal; a few (1-4) small drops or a small pool (~1 cm)	3	5	2	2	5	4	2	3
(3) moderate; a few (1-4) small pools or a moderate pool (2-3 cm)	1	2	3	5	2	3	0	5
(4) pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)	1	0	0	0	0	0	2	1
(5) Exaggerated; >4 moderate pools or single pool >5 cm.	1	0	0	1	0	1	0	1

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Table is replicated from Appendix S.

Table I5. Summary of FOB Ranked/Categorical Incidence – Female Toxicity Groups (continued)

	Baseline				Treated			
Dose Group	1	2	3	4	1	2	3	4
Number of Animals Examined	10	10	10	10	10	10	10	10
Defecation								
(1) no pellets voided	8	10	9	7	9	9	7	7
(2) minimal; 1 or 2 pellets voided	2	0	1	3	1	1	1	1
(3) moderate ; 3 pellets voided	0	0	0	0	0	0	0	2
(4) pronounced; 4 pellets voided	0	0	0	0	0	0	2	0
Categorical Observations								
Soiling Chin (Red)	0	0	0	0	0	0	0	1
No Abnormalities Detected	10	10	10	10	10	10	10	9

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Table is replicated from Appendix S.

Table 16. FOB Continuous Data Summary – Male Toxicity Groups

Group Sex		Baseline Rectal Temperature (°C)	Baseline Hindlimb Grip Strength (g)	Baseline Forelimb Grip Strength (g)	Baseline Landing Foot Splay (cm)	Treated Rectal Temperature (°C)	Treated Hindlimb Grip Strength (g)	Treated Forelimb Grip Strength (g)	Treated Landing Foot Splay (cm)
1m	Mean	37.8	690.0	790.3	12.2	38.0	1272.5	1197.8	11.2
	S.D.	0.4	74.8	147.9	2.2	0.4	128.9	202.7	1.7
	N	10	10	10	10	10	10	10	10
2m	Mean	38.0	752.8	856.3	12.4	38.2	1196.2	1329.8	12.2
	S.D.	0.3	68.5	110.8	2.2	0.4	161.0	222.7	1.8
	N	10	10	10	10	10	10	10	10
3m	Mean	38.0	692.3	776.7	11.4	37.9	1140.5	1088.7	11.2
	S.D.	0.5	134.9	126.7	1.6	0.4	178.1	238.2	1.5
	N	10	10	10	10	10	10	10	10
4m	Mean	38.1	733.0	783.8	12.9	37.9	1116.5	1036.2	12.2
	S.D.	0.3	116.4	139.8	2.1	0.4	170.3	232.4	2.0
	N	10	10	10	10	10	10	10	10

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Table is replicated from Appendix S.

Table 17. FOB Continuous Data Summary – Female Toxicity Groups

Group Sex		Baseline				Treated			
		Rectal Temperature (°C)	Hindlimb Grip Strength (g)	Forelimb Grip Strength (g)	Landing Foot Splay (cm)	Rectal Temperature (°C)	Hindlimb Grip Strength (g)	Forelimb Grip Strength (g)	Landing Foot Splay (cm)
1f	Mean	38.4	608.3	700.0	11.1	38.6	987.0	966.8	10.5
	S.D.	0.4	89.4	73.2	1.8	0.5	101.5	150.4	2.0
	N	10	10	10	10	10	10	10	10
2f	Mean	38.2	653.0	714.3	10.6	38.4	959.5	1009.0	9.1
	S.D.	0.4	112.2	148.3	2.0	0.4	125.7	276.1	1.6
	N	10	10	10	10	10	10	10	10
3f	Mean	38.4	665.8	749.2	10.6	38.3	985.3	1025.0	10.0
	S.D.	0.4	123.2	93.3	1.9	0.6	153.7	159.9	1.4
	N	10	10	10	10	10	10	10	10
4f	Mean	38.0	624.7	782.5	9.4	38.4	868.2	887.3	8.8
	S.D.	0.4	116.7	118.1	1.5	0.3	157.1	154.2	2.1
	N	10	10	10	10	10	10	10	10

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Table is replicated from Appendix S.

Table 18. Motor Activity Summary – Male Toxicity Groups

Interval	Group/Sex	Baseline 1m	Baseline 2m	Baseline 3m	Baseline 4m	Treated 1m	Treated 2m	Treated 3m	Treated 4m
(8 minutes)	N	10	10	10	10	10	10	10	10
1	Mean	234.8	215.3	228.5	233.9	220.6	216.5	219.6	191 5
	S.D.	34.5	39.8	48.8	55.2	56.2	41.7	35.5	38.5
2	Mean	152.8	151 3	137.5	145 1	154.1	160.5	125.7	142.5
	S.D.	46.2	34.1	40.5	64.3	39.1	38.3	25.3	33.6
3	Mean	120.4	118.5	95.9	121.8	105.5	74.1	78.9	91.0
	S.D.	48.5	49.1	24.5	65.1	29.8	26 9	51.3	40.0
4	Mean	87.6	68.0	54.3	77.1	61.1	42.2	49.6	59.9
	S.D.	62.5	58.1	47.4	62.7	54.3	29 3	37.2	37 1
5	Mean	59.8	30 6	28.0	55.8	53.7	35.8	44.7	23.0
	S.D.	46.8	29.1	45.5	54.2	47.6	47.0	46.4	29.1
6	Mean	31.3	26.8	18.0	28.4	41.0	22.3	40.5	55 3
	S.D.	53.5	65.8	33.6	54.2	38.3	27.3	37.2	55.9
7	Mean	13.4	12.9	15.8	22.0	24.3	22.7	31.7	31.8
	S.D.	17.0	40.8	37.6	52.8	35.6	26.2	24.5	48.2
8	Mean	6.2	2.3	5.1	6.5	18.0	22.8	17.6	27.1
	S.D.	10.9	5.7	14.1	17.2	41.0	39.5	21.5	48.2
9	Mean	0.8	1.8	4.2	9.0	16.0	20.2	12.1	16.9
	S.D.	2.2	5 0	13.3	27 8	34.6	37.4	19.9	17.7
10	Mean	0.9	8.9	11.6	10.9	17.8	15.6	17.7	24.2
	S.D.	2.2	27.8	36.3	19.9	36.9	25.3	34.2	33.5
Total	Mean	708.0	636.4	598.9	710.5	712.1	632.7	638.1	663.2
	S.D.	239.1	213.5	182.9	380.0	304.5	189.0	149.8	260.9

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Means and Standard Deviations were calculated using Microsoft Excel 2003(v.11.8169.8172)SP3
Table is replicated from Appendix S.

Table 19. Motor Activity Summary – Female Toxicity Groups

		Baseline				Treated			
Interval	Group/Sex	1f	2f	3f	4f	1f	2f	3f	4f
(8 minutes)	N	10	10	10	10	10	10	10	10
1	Mean	256.1	246.1	247.0	241.7	230.3	215.3	232.6	218.9
	S.D.	35.3	34.4	48.9	30.2	36.3	38.6	50.2	44.1
2	Mean	199.8	171.8	177.6	185.9	162.9	168.1	186.2	171.0
	S.D.	35.4	31.2	44.7	43.5	59.8	37.6	50.8	42.4
3	Mean	141.9	119.2	136.5	141.4	149.2	108.9	146.4	118.2
	S.D.	60.5	47.6	65.9	55.5	57.3	53.9	51.6	82.2
4	Mean	111.7	83.9	109.1	94.6	110.0	85.2	101.9	67.8
	S.D.	67.8	53.1	60.4	64.9	75.0	55.0	60.3	74.5
5	Mean	79.7	67.5	82.0	53.6	87.5	85.7	59.7	72.2
	S.D.	68.4	50.1	59.4	46.3	64.0	48.2	73.0	71.4
6	Mean	93.5	60.1	65.5	43.7	90.0	65.1	69.2	52.8
	S.D.	58.6	73.1	51.8	57.1	67.8	40.9	51.7	51.4
7	Mean	113.8	68.6	36.6	47.1	75.2	54.1	97.4	70.8
	S.D.	65.3	74.8	40.6	64.3	48.2	45.9	53.7	58.6
8	Mean	87.2	51.6	16.4	23.9	75.7	43.1	70.7	56.9
	S.D.	57.5	66.5	46.3	39.1	59.2	42.9	36.5	58.4
9	Mean	43.0	46.4	31.6	16.3	68.1	34.8	48.8	31.2
	S.D.	52.2	53.4	67.2	28.3	53.8	43.7	37.9	35.1
10	Mean	35.6	43.1	26.7	11.9	47.5	47.3	48.5	29.3
	S.D.	51.0	64.1	45.7	29.7	48.6	45.7	38.1	30.4
Total	Mean	1162.3	958.3	929.0	860.1	1096.4	907.6	1061.4	889.1
	S.D.	380.7	356.8	316.3	254.6	427.8	276.3	286.4	397.7

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Means and Standard Deviations were calculated using Microsoft Excel 2003(v.11.8169.8172)SP3
Table is replicated from Appendix S.

Table 20. Summary of Serum Chemistry – Male Toxicity Groups

		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
ALP (U/L)	Mean	156.3	125.0 **	120.0 **	106.6 **
	SD	14.7	22.7	24.9	20.5
	N	10	10	10	10
ALT (U/L)	Mean	22.3	20.9	22.6	19.4
	SD	2.9	3.3	5.4	3.9
	N	10	10	10	10
AST (U/L)	Mean	91.0	66.9 **	73.2 *	63.1 **
	SD	20.5	9.0	23.2	8.1
	N	10	10	10	10
TBILI (mg/dL)	Mean	0.128	0.101 *	0.109	0.109
	SD	0.024	0.013	0.025	0.019
	N	10	10	10	10
ALB (g/dL)	Mean	3.77	3.75	3.74	3.67
	SD	0.14	0.12	0.18	0.21
	N	10	10	10	10
TP (g/dL)	Mean	5.70	5.70	5.68	5.60
	SD	0.17	0.19	0.18	0.34
	N	10	10	10	10
BUN (mg/dL)	Mean	12.4	12.8	12.9	13.0
	SD	1.3	1.8	1.9	1.5
	N	10	10	10	10
CREAT (mg/dL)	Mean	0.28	0.29	0.28	0.26
	SD	0.04	0.03	0.06	0.05
	N	10	10	10	10
GLUC (mg/dL)	Mean	119.9	132.3	127.5	116.8
	SD	12.8	13.6	16.1	10.3
	N	10	10	10	10
CHOL (mg/dL)	Mean	41.0	47.7	49.4	49.8
	SD	6.8	8.9	11.4	16.5
	N	10	10	10	10

* = p-values < 0.05 significance level
** = p-values < 0.01 significance level
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; TBILI = Total bilirubin; ALB = Albumin; TP = Total protein; BUN = Blood Urea Nitrogen; CREAT = Creatinine; GLUC = Glucose; CHOL = Cholesterol

Table is replicated from Appendix T.

Table 20. Summary of Serum Chemistry – Male Toxicity Groups (continued)

		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
CA (mg/dL)	Mean	9.57	9.63	9.71	9.81
	SD	0.23	0.16	0.22	0.34
	N	10	10	10	10
PHOS (mg/dL)	Mean	7.59	7.30	7.41	7.55
	SD	0.23	0.53	0.52	0.58
	N	10	10	10	10
NA (mmol/L)	Mean	142.8	143.0	142.3	142.7
	SD	1.2	2.1	0.5	1.5
	N	10	10	10	10
K (mmol/L)	Mean	4.44	4.34	4.40	4.28
	SD	0.16	0.25	0.18	0.32
	N	10	10	10	10
CL (mmol/L)	Mean	104.4	105.2	104.3	104.7
	SD	1.6	1.7	1.2	1.1
	N	10	10	10	10

CA = Calcium; PHOS = Phosphate (phosphorus); NA = Sodium; K = Potassium; CL = Chloride

Table is replicated from Appendix T.

Table 21. Summary of Serum Chemistry – Female Toxicity Groups

		mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
ALP (U/L)	Mean	80.7	76.8	81.1	72.3
	SD	20.8	8.4	21.3	22.3
	N	10	10	10	10
ALT (U/L)	Mean	21.6	19.8	18.3	18.6
	SD	4.2	4.1	5.3	2.4
	N	10	10	10	10
AST (U/L)	Mean	89.5	87.2	73.9	61.4 **
	SD	13.3	18.4	15.0	14.8
	N	10	10	10	10
TBILI (mg/dL)	Mean	0.121	0.124	0.123	0.115
	SD	0.017	0.029	0.027	0.050
	N	10	10	10	10
ALB (g/dL)	Mean	4.22	4.16	4.14	3.91 *
	SD	0.25	0.29	0.26	0.14
	N	10	10	10	10
TP (g/dL)	Mean	5.97	5.96	5.85	5.66
	SD	0.36	0.34	0.48	0.26
	N	10	10	10	10
BUN (mg/dL)	Mean	14.6	15.5	15.7	12.9
	SD	2.2	2.1	3.0	2.6
	N	10	10	10	10
CREAT (mg/dL)	Mean	0.34	0.33	0.30	0.26 **
	SD	0.05	0.05	0.00	0.05
	N	10	10	10	10
GLUC (mg/dL)	Mean	125.4	125.0	122.8	136.0
	SD	12.8	10.4	11.6	22.6
	N	10	10	10	10
CHOL (mg/dL)	Mean	55.2	61.9	70.7	90.9 **
	SD	16.6	14.9	11.4	14.7
	N	10	10	10	10

* = p-values < 0.05 significance level
** = p-values < 0.01 significance level
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; TBILI = Total bilirubin; ALB = Albumin; TP = Total protein; BUN = Blood Urea Nitrogen; CREAT = Creatinine; GLUC = Glucose; CHOL = Cholesterol

Table is replicated from Appendix T.

Table 21. Summary of Serum Chemistry – Female Toxicity Groups (continued)

		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
CA (mg/dL)	Mean	9.86	9.79	10.03	10.04
	SD	0.25	0.30	0.28	0.28
	N	10	10	10	10
PHOS (mg/dL)	Mean	7.30	7.11	7.55	7.41
	SD	0.51	0.78	0.46	0.76
	N	10	10	10	10
NA (mmol/L)	Mean	140.9	140.8	140.1	139.4
	SD	1.3	1.1	0.9	1.1
	N	10	10	10	10
K (mmol/L)	Mean	4.09	4.00	4.16	4.01
	SD	0.21	0.22	0.37	0.28
	N	10	10	10	10
CL (mmol/L)	Mean	104.6	104.8	103.8	103.7
	SD	1.6	1.8	1.2	1.3
	N	10	10	10	10

* = p-values < 0.05 significance level
CA = Calcium; PHOS = Phosphate (phosphorus); NA = Sodium; K = Potassium; CL = Chloride

Table is replicated from Appendix T.

Table 22. Summary of Hematology Data – Male Toxicity Groups

		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
WBC (10^3/uL)	Mean	5.77	5.45	5.89	4.96
	SD	1.09	0.99	1.20	1.32
	N	10	10	10	10
RBC (10^6/uL)	Mean	8.111	7.803	7.943	7.776
	SD	0.417	0.342	0.391	0.395
	N	10	10	10	10
HGB (g/dL)	Mean	15.14	14.78	14.96	14.62
	SD	0.74	0.34	0.77	0.74
	N	10	10	10	10
HCT (%)	Mean	43.37	42.47	43.04	41.93
	SD	2.02	0.90	2.34	2.20
	N	10	10	10	10
MCV (fL)	Mean	53.46	54.50	54.19	53.92
	SD	1.12	2.56	1.41	0.67
	N	10	10	10	10
MCH (pg)	Mean	18.69	18.96	18.85	18.81
	SD	0.40	0.82	0.52	0.28
	N	10	10	10	10
MCHC (g/dL)	Mean	34.93	34.81	34.79	34.88
	SD	0.21	0.30	0.43	0.39
	N	10	10	10	10
PLT (10^3/uL)	Mean	960.80	876.80	933.50	903.70
	SD	97.97	266.96	111.21	86.77
	N	10	10	10	10

WBC = White blood cell; RBC = Red blood cell; HGB = Hemoglobin; HCT = Hematocrit; MCV = Mean Cell Volume; MCH = Mean Cell Hemoglobin; MCHC = Mean Cell Hemoglobin Concentration; PLT = Platelet

Table is replicated from Appendix T.

Table 22. Summary of Hematology Data – Male Toxicity Groups (continued)

		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Neutro (%)	Mean	20.84	17.79	20.20	18.59
	SD	5.99	7.28	8.98	5.06
	N	10	10	10	10
Abs Neut (10^3/uL)	Mean	1.2246	0.9712	1.1495	0.9132
	SD	0.5496	0.4857	0.4765	0.3875
	N	10	10	10	10
Lymph (%)	Mean	75.70	79.12	76.62	77.70
	SD	6.07	7.63	9.40	5.64
	N	10	10	10	10
Abs Lymph (10^3/uL)	Mean	4.3350	4.3100	4.5510	3.8710
	SD	0.7769	0.9051	1.1593	1.0977
	N	10	10	10	10
Mono (%)	Mean	0.90	1.02	1.01	1.04
	SD	0.74	1.04	1.53	1.21
	N	10	10	10	10
Abs Mono (10^3/uL)	Mean	0.0504	0.0532	0.0618	0.0490
	SD	0.0382	0.0517	0.0990	0.0521
	N	10	10	10	10
Eosin (%)	Mean	2.40	1.81	1.97	2.51
	SD	0.58	0.74	0.52	0.92
	N	10	10	10	10
Abs Eosin (10^3/uL)	Mean	0.1334	0.0995	0.1162	0.1185
	SD	0.0235	0.0460	0.0423	0.0336
	N	10	10	10	10
Baso (%)	Mean	0.15	0.28	0.19	0.19
	SD	0.18	0.20	0.19	0.17
	N	10	10	10	10
Abs Baso (10^3/uL)	Mean	0.0079	0.0143	0.0116	0.0090
	SD	0.0083	0.0090	0.0105	0.0058
	N	10	10	10	10

Abs = Absolute; Neutro = Neutrophil; Neut = Neutrophil; Lymph = Lymphocyte; Mono = Monocyte; Eosin = Eosinophil; Baso = Basophil

Table is replicated from Appendix T.

Table 23. Summary of Hematology Data – Female Toxicity Groups

		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
WBC (10^3/uL)	Mean	5.39	5.01	5.21	5.26
	SD	2.11	1.69	1.41	2.14
	N	10	10	10	10
RBC (10^6/uL)	Mean	7.585	7.618	7.704	7.761
	SD	0.117	0.336	0.375	0.224
	N	10	10	10	10
HGB (g/dL)	Mean	14.75	14.66	14.80	14.69
	SD	0.36	0.45	0.66	0.54
	N	10	10	10	10
HCT (%)	Mean	42.14	41.87	42.36	42.54
	SD	0.99	1.17	1.70	1.34
	N	10	10	10	10
MCV (fL)	Mean	55.56	55.02	55.02	54.83
	SD	1.87	2.20	1.99	1.55
	N	10	10	10	10
MCH (pg)	Mean	19.46	19.27	19.21	18.94
	SD	0.62	0.45	0.60	0.49
	N	10	10	10	10
MCHC (g/dL)	Mean	35.01	35.07	34.95	34.54
	SD	0.59	0.63	0.60	0.61
	N	10	10	10	10
PLT (10^3/uL)	Mean	995.70	976.00	971.70	869.50 *
	SD	92.31	47.59	105.20	117.05
	N	10	10	10	10

* = p-values < 0.05 significance level
WBC = White blood cell; RBC = Red blood cell; HGB = Hemoglobin; HCT = Hematocrit; MCV = Mean Cell Volume; MCH = Mean Cell Hemoglobin; MCHC = Mean Cell Hemoglobin Concentration; PLT = Platelet

Table is replicated from Appendix T.

Table 23. Summary of Hematology Data – Female Toxicity Groups (continued)

		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Neutro (%)	Mean	15.80	17.06	15.97	18.66
	SD	8.44	9.67	11.41	15.07
	N	10	10	10	10
Abs Neut (10^3/uL)	Mean	0.8849	0.8496	0.9372	1.1269
	SD	0.5555	0.5097	0.7930	1.1661
	N	10	10	10	10
Lymph (%)	Mean	80.74	80.01	80.31	77.15
	SD	8.42	9.57	11.06	13.25
	N	10	10	10	10
Abs Lymph (10^3/uL)	Mean	4.3310	4.0050	4.0660	3.9320
	SD	1.6762	1.4340	0.8094	1.3785
	N	10	10	10	10
Mono (%)	Mean	0.64	0.70	1.07	1.33
	SD	0.34	0.50	1.17	1.80
	N	10	10	10	10
Abs Mono (10^3/uL)	Mean	0.0393	0.0309	0.0628	0.0581
	SD	0.0386	0.0170	0.0771	0.0672
	N	10	10	10	10
Eosin (%)	Mean	2.29	2.08	2.01	2.02
	SD	0.90	1.02	0.68	1.01
	N	10	10	10	10
Abs Eosin (10^3/uL)	Mean	0.1224	0.1001	0.1070	0.1044
	SD	0.0549	0.0528	0.0485	0.0568
	N	10	10	10	10
Baso (%)	Mean	0.55	0.16	0.62	0.84
	SD	1.08	0.14	0.96	1.70
	N	10	10	10	10
Abs Beso (10^3/uL)	Mean	0.0219	0.0088	0.0254	0.0306
	SD	0.0336	0.0106	0.0281	0.0553
	N	10	10	10	10

Abs = Absolute; Neutro = Neutrophil; Neut = Neutrophil; Lymph = Lymphocyte; Mono = Monocyte; Eosin = Eosinophil; Baso = Basophil

Table is replicated from Appendix T.

Table 24. Summary of Prothrombin Times – Male Toxicity Groups

		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Prothrombin Time (Seconds)	Mean	14.04	14.81	14.34	14.70
	SD	0.49	1.02	0.98	1.02
	N	10	10	10	10

Table is replicated from Appendix T.

Table 25. Summary of Prothrombin Times – Female Toxicity Groups

		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Prothrombin Time (Seconds)	Mean	13.84	13.83	13.96	13.90
	SD	0.47	0.54	0.38	0.63
	N	10	10	10	10

Table is replicated from Appendix T.

Table 26. Summary of Mean Organ and Organ / Body Weight Ratios – Male Toxicity Groups

		Terminal BW (g)	Adrenal (g)	Adrenal /BW (%Ratio)	Brain (g)	Brain / BW (%Ratio)	Epidid-ymides (g)	Epididy-mides/BW (%Ratio)
0 mg/kg/day	Mean	393.17	0.04262	0.01089	2.0150	0.51343	1.2573	0.32106
	SD	22.18	0.00722	0.00198	0.0851	0.02609	0.0948	0.03456
	N	10	10	10	10	10	10	10
100 mg/kg/day	Mean	405.15	0.05126 *	0.01268	2.0283	0.50135	1.2493	0.30953
	SD	26.81	0.00982	0.00239	0.1073	0.02028	0.1246	0.03631
	N	10	10	10	10	10	10	10
300 mg/kg/day	Mean	399.53	0.05230 *	0.01312	2.0481	0.51365	1.1985	0.30033
	SD	22.39	0.00678	0.00173	0.1666	0.04463	0.0950	0.02255
	N	10	10	10	10	10	10	10
1000 mg/kg/day	Mean	387.54	0.04994	0.01297	1.9779	0.51360	1.1903	0.30728
	SD	31.31	0.00513	0.00170	0.0568	0.04607	0.1053	0.01452
	N	10	10	10	10	10	10	10

* = $p < 0.05$ significance level

Table 26. Summary of Mean Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

		Heart (g)	Heart /BW (%Ratio)	Kidney (g)	Kidney /BW (%Ratio)	Liver (g)	Liver / BW (%Ratio)	Prostate (g)
0 mg/kg/day	Mean	1.2867	0.32766	2.6894	0.68426	10.0351	2.55112	0.8580
	SD	0.1048	0.02666	0.1542	0.01985	0.9171	0.15127	0.1812
	N	10	10	10	10	10	10	10
100 mg/kg/day	Mean	1.2804	0.31644	2.8278	0.69861	11.1105	2.73770	0.7314
	SD	0.0848	0.01695	0.2597	0.05243	1.2311	0.17782	0.1222
	N	10	10	10	10	10	10	10
300 mg/kg/day	Mean	1.2872	0.32278	2.7123	0.67901	11.3885 *	2.85065 **	0.7281
	SD	0.0802	0.02314	0.2316	0.04580	0.8084	0.13177	0.0965
	N	10	10	10	10	10	10	10
1000 mg/kg/day	Mean	1.2996	0.33573	2.6728	0.69252	11.6231 *	2.99195 **	0.7243
	SD	0.1602	0.03537	0.1462	0.05125	1.6375	0.25562	0.0988
	N	10	10	10	10	10	10	10

* = p < 0.05 significance level

** < p 0.01 significance level

Table 26. Summary of Mean Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

		Prostate / BW (%Ratio)	Seminal Vessicle (g)	Seminal Vess /BW (%Ratio)	Spleen (g)	Spleen / BW (%Ratio)	Testes (g)	Testes / BW (%Ratio)
0 mg/kg/day	Mean	0.21918	1.6879	0.43102	0 6919	0.17655	3.5589	0.90618
	SD	0.04832	0.1906	0.05882	0.0676	0.02073	0.2449	0.05603
	N	10	10	10	10	10	10	10
100 mg/kg/day	Mean	0.18034 *	1.7280	0.42780	0.6949	0.17209	3.5476	0.87761
	SD	0.02703	0.1948	0.05061	0.0757	0.02039	0.2528	0.06830
	N	10	10	10	10	10	10	10
300 mg/kg/day	Mean	0.18291	1.5667	0.39375	0.6700	0.16786	3.4866	0.87473
	SD	0.02735	0.2459	0.06948	0.0819	0.01950	0.2632	0.07757
	N	10	10	10	10	10	10	10
1000 mg/kg/day	Mean	0.18730	1.7937	0.46412	0.6834	0.17662	3.4719	0.89993
	SD	0.02495	0.2429	0.06294	0.0697	0.01562	0.1397	0.06408
	N	10	10	10	10	10	10	10

* = $p < 0.05$ significance level

Table 26. Summary of Mean Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

		Thymus (g)	Thymus /BW (%Ratio)
0 mg/kg/day	Mean	0.3935	0.09962
	SD	0.1110	0.02588
	N	10	10
100 mg/kg/day	Mean	0.4351	0.10740
	SD	0.0999	0.02331
	N	10	10
300 mg/kg/day	Mean	0.4405	0.11137
	SD	0.1126	0.03194
	N	10	10
1000 mg/kg/day	Mean	0.3639	0.09334
	SD	0.0929	0.02020
	N	10	10

Table 27. Summary of Mean Organ and Organ / Body Weight Ratios – Female Toxicity Groups

		Terminal BW (g)	Adrenal (g)	Adrenal /BW (%Ratio)	Brain (g)	Brain / BW (%Ratio)	Heart (g)	Heart /BW (%Ratio)
0 mg/kg/day	Mean	247.01	0.06730	0.02725	1.9134	0.77777	0.8674	0.35138
	SD	16.66	0.00876	0.00290	0.1276	0.07201	0.0722	0.02030
	N	10	10	10	10	10	10	10
100 mg/kg/day	Mean	241.49	0.06259	0.02596	1.9040	0.79259	0.8666	0.35931
	SD	18.02	0.00804	0.00308	0.1021	0.07532	0.0718	0.02394
	N	10	10	10	10	10	10	10
300 mg/kg/day	Mean	243.74	0.05931	0.02443	1.8813	0.77537	0.8279	0.33940
	SD	16.02	0.01037	0.00429	0.0705	0.06451	0.0703	0.01113
	N	10	10	10	10	10	10	10
1000 mg/kg/day	Mean	220.95 **	0.06002	0.02738	1.8442	0.83802	0.8144	0.36978
	SD	18.22	0.00725	0.00417	0.0829	0.05277	0.0647	0.02984
	N	10	10	10	10	10	10	10

** = p 0.01 significance level

Table 27. Summary of Mean Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

		Kidney (g)	Kidney /BW (%Ratio)	Liver (g)	Liver / BW (%Ratio)	Ovaries (g)	Ovaries /BW (%Ratio)	Spleen (g)
0 mg/kg/day	Mean	1.7393	0.70450	6.9822	2.82522	0.14939	0.060612	0.5815
	SD	0.1480	0.04167	0.6195	0.12528	0.01523	0.006127	0.1043
	N	10	10	10	10	10	10	10
100 mg/kg/day	Mean	1.6977	0.70501	6.8378	2.82702	0.16252	0.065895	0.5837
	SD	0.1570	0.06663	0.7230	0.11414	0.10275	0.035361	0.2810
	N	10	10	10	10	10	10	10
300 mg/kg/day	Mean	1.6875	0.69290	7.2168	2.95786 *	0.12952 *	0.053223	0.5419
	SD	0.1524	0.05321	0.6802	0.14183	0.01914	0.007910	0.0982
	N	10	10	10	10	10	10	10
1000 mg/kg/day	Mean	1.7728	0.80632 **	7.9460 **	3.60905 **	0.12381 *	0.055909	0.4929
	SD	0.1401	0.08145	0.5639	0.28788	0.02100	0.007426	0.0738
	N	10	10	10	10	10	10	10

** - p 0.01 significance level
* - p 0.05 significance level

Table 27. Summary of Mean Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

		Spleen / BW (%Ratio)	Thymus (g)	Thymus /BW (%Ratio)	Uterus (g)	Uterus /BW (%Ratio)
0 mg/kg/day	Mean	0.23517	0.3615	0.14578	0.5616	0.224884
	SD	0.03650	0.0823	0.02875	0.2575	0.090484
	N	10	10	10	10	10
100 mg/kg/day	Mean	0.23720	0.3909	0.16133	0.6261	0.261396
	SD	0.09311	0.1039	0.03966	0.3009	0.124096
	N	10	10	10	10	10
300 mg/kg/day	Mean	0.22188	0.4208	0.17189	0.4693	0.193628
	SD	0.03389	0.1160	0.04079	0.0686	0.032733
	N	10	10	10	10	10
1000 mg/kg/day	Mean	0.22244	0.3030	0.13701	0.4543	0.206598
	SD	0.02150	0.0444	0.01644	0.0641	0.030578
	N	10	10	10	10	10

Table 28. Summary of Macroscopic Findings – Male and Female Toxicity Groups

Removal Reasons: All of those SELECTED	MALES				FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
ANIMAL IDENTIFICATION;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
ADRENAL GLANDS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
BONE MARROW, STERNUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
BRAIN;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
EPIDIDYMIDES;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	10	10	10	10	-	-	-	-
HEART;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
INTESTINE, CECUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
INTESTINE, COLON;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
INTESTINE, DUODENUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
INTESTINE, ILEUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)

Table 28. Summary of Macroscopic Findings – Male and Female Toxicity Groups (continued)

Removal Reasons: All of those SELECTED	MALES				FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
INTESTINE, ILEUM; (continued)								
No Visible Lesions	10	10	10	10	10	10	10	10
INTESTINE, JEJUNUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
KIDNEYS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
LIVER;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
LUNGS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
LYMPH NODE, MEDIASTINAL;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
LYMPH NODE, MESENTERIC;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
NERVE, SCIATIC;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
OVARIES;								
Submitted	(-)	(-)	(-)	(-)	(10)	(10)	(10)	(10)
No Visible Lesions	-	-	-	-	10	10	10	10
PROSTATE GLAND;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	10	10	10	10	-	-	-	-

Table 28. Summary of Macroscopic Findings – Male and Female Toxicity Groups (continued)

Removal Reasons: All of those SELECTED	MALES				FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
SEMINAL VESICLES;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	10	10	10	10	-	-	-	-
SPINAL CORD;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
SPLEEN;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	9	10	10
Enlarged	0	0	0	0	0	1	0	0
STOMACH;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
TESTES;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	10	10	10	10	-	-	-	-
THYMUS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	9	10
Discoloration; red; focal	0	0	0	0	0	0	1	0
THYROID GLANDS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
TRACHEA;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
URINARY BLADDER;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10

Table 28. Summary of Macroscopic Findings – Male and Female Toxicity Groups (continued)

Removal Reasons: All of those SELECTED	MALES				FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
UTERUS;								
Submitted	(-)	(-)	(-)	(-)	(10)	(10)	(10)	(10)
No Visible Lesions	-	-	-	-	10	10	10	10

Table 29. Summary of Macroscopic Findings – Female Reproductive Groups

Removal Reasons: All of those SELECTED	FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
ADRENAL GLANDS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
BONE MARROW, STERNUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
BRAIN;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
HEART;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
INTESTINE, CECUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	9
Not Examined: NOT COLLECTED	0	1	0	0
Decreased Ingesta	0	0	0	1
INTESTINE, COLON;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	9
Not Examined: NOT COLLECTED	0	1	0	0
Decreased Ingesta	0	0	0	1
INTESTINE, DUODENUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	8
Not Examined: NOT COLLECTED	0	1	0	0
Decreased Ingesta	0	0	0	2
INTESTINE, ILEUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	7
Not Examined: NOT COLLECTED	0	1	0	0
Contents Abnormal	0	0	0	1

Table 29. Summary of Macroscopic Findings – Female Reproductive Groups (continued)

Removal Reasons: All of those SELECTED	FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
INTESTINE, ILEUM; (continued)				
Decreased Ingesta	0	0	0	2
INTESTINE, JEJUNUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	8
Not Examined: NOT COLLECTED	0	1	0	0
Decreased Ingesta	0	0	0	2
KIDNEYS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	9
Not Examined: NOT COLLECTED	0	1	0	0
Discoloration	0	0	0	1
LIVER;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	9
Not Examined: NOT COLLECTED	0	1	0	0
Accentuated Lobular Pattern	0	0	0	1
LUNGS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
LYMPH NODE, MEDIASTINAL;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
LYMPH NODE, MESENTERIC;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
SKELETAL MUSCLE;				
Submitted	(0)	(0)	(0)	(5)
No Visible Lesions	0	0	0	0
Decreased Size	0	0	0	5
NERVE, SCIATIC;				
Submitted	(10)	(9)	(10)	(10)

Table 29. Summary of Macroscopic Findings – Female Reproductive Groups (continued)

Removal Reasons: All of those SELECTED

	FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
NERVE, SCIATIC; (continued)				
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
OVARIES;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
SPINAL CORD;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
SPLEEN;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	3
Not Examined: NOT COLLECTED	0	1	0	0
Decreased Size	0	0	0	7
STOMACH;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	8
Not Examined: NOT COLLECTED	0	1	0	0
Ulcer	0	0	0	1
Decreased Ingesta	0	0	0	1
THYMUS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	4
Not Examined: NOT COLLECTED	0	1	0	0
Small	0	0	0	6
THYROID GLANDS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
TRACHEA;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0

Table 29. Summary of Macroscopic Findings – Female Reproductive Groups (continued)

Removal Reasons: All of those SELECTEO	FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
URINARY BLADDER;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	8	10	10
Not Examined: NOT COLLECTEO	0	1	0	0
UTERUS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	9
Not Examined: NOT COLLECTEO	0	1	0	0
Pregnant	0	0	0	1
WHOLE BOOY;				
Submitted	(0)	(0)	(0)	(8)
No Visible Lesions	0	0	0	0
Not Examined: NOT COLLECTEO	0	1*	0	0
Thin	0	0	0	8
Soiling	0	0	0	1
RIGHT HINDLIMB;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTEO	0	1	0	0

*Gross necropsy data for animal 5251 was inadvertently not documented. Tissues were collected and animal is included in histopathology data.

Table 30. Summary of Microscopic Findings – Male Toxicity Groups

Toxicity Males Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
ADRENAL GLANDS	cortex Hypertrophy focal	# Examined	10	0	0	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
BRAIN	meninges Inflammation chronic	# Examined	10	0	0	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
HEART	Inflammation chronic	# Examined	10	0	0	10
		All Grades	2	0	0	2
		Minimal	2	0	0	2
KIDNEYS	Chronic Progressive Nephropathy	# Examined	10	10	10	10
		All Grades	1	0	3	1
		Minimal	1	0	3	1
	Inflammation chronic	# Examined	10	10	10	10
		All Grades	2	1	0	0
		Minimal	1	1	0	0
		Mild	1	0	0	0
	Inflammation chronic-active	# Examined	10	10	10	10
		All Grades	1	0	0	0
		Mild	1	0	0	0
	pelvis Hyperplasia bilateral diffuse	# Examined	10	10	10	10
		All Grades	0	1	0	2
		Minimal	0	0	0	1
		Moderate	0	1	0	1
	pelvis Inflammation chronic-active	# Examined	10	10	10	10
		All Grades	0	1	0	1
		Moderate	0	1	0	1
	cortex Necrosis focal	# Examined	10	10	10	10
		All Grades	0	0	1	0
		Mild	0	0	1	0
	cortex Cyst	# Examined	10	10	10	10
		Present	1	0	0	0
	tubule Basophilia	# Examined	10	10	10	10
		All Grades	5	1	1	2
		Minimal	5	1	1	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 is replicated from Appendix U.

Table 30. Summary of Microscopic Findings – Male Toxicity Groups (continued)

Toxicity Males Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
LIVER	Inflammation chronic multifocal	# Examined	10	10	10	10
		All Grades	8	7	4	8
		Minimal	8	7	4	8
	Necrosis focal	# Examined	10	10	10	10
		All Grades	0	0	0	1
		Minimal	0	0	0	1
	centrilobular Hypertrophy	# Examined	10	10	10	10
		All Grades	0 +++	2	8 +++	10 +++
		Minimal	0	2	8	7
		Mild	0	0	0	3
	midzonal Vacuolation	# Examined	10	10	10	10
		All Grades	0	1	0	0
		Mild	0	1	0	0
	periportal Vacuolation	# Examined	10	10	10	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
LUNGS	Inflammation chronic	# Examined	10	0	0	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
	Inflammation subacute	# Examined	10	0	0	10
		All Grades	1	0	0	1
		Minimal	1	0	0	0
		Mild	0	0	0	1
	Histocytosis	# Examined	10	0	0	10
		All Grades	4	0	0	5
		Minimal	4	0	0	4
		Mild	0	0	0	1
	Hypertrophy vascular	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Minimal	0	0	0	1
NERVE, SCIATIC	Degeneration	# Examined	10	0	0	10
		All Grades	1	0	0	2
		Minimal	1	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 is replicated from Appendix U.

Table 30. Summary of Microscopic Findings – Male Toxicity Groups (continued)

Toxicity Males Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
PROSTATE GLAND	Hyperplasia focal	# Examined	10	0	0	10
		All Grades	0	0	0	2
		Mild	0	0	0	2
	Inflammation chronic	# Examined	10	0	0	10
		All Grades	2	0	0	1
		Minimal	1	0	0	1
		Mild	1	0	0	0
	Inflammation chronic-active	# Examined	10	0	0	10
		All Grades	1	0	0	2
		Mild	1	0	0	2
STOMACH	non-glandular Cyst	# Examined	10	0	0	10
		Present	0	0	0	1
THYROID GLANDS	Cyst ultimobranchial	# Examined	10	0	0	10
		Present	0	0	0	2
URINARY BLADDER	Hyperplasia epithelial diffuse	# Examined	9	10	10	10
		All Grades	0 +++	1	0	7 +++
		Minimal	0	0	0	4
		Mild	0	1	0	3
	Inflammation chronic	# Examined	9	10	10	10
		All Grades	0	2	0	1
		Minimal	0	2	0	1
	Inflammation chronic-active	# Examined	9	10	10	10
		All Grades	0	0	0	1
		Mild	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 is replicated from Appendix U.

Table 31. Summary of Microscopic Findings – Female Toxicity Groups

Toxicity Females Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
BRAIN	Nematodiasis	# Examined	10	10	10	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
	white matter Degeneration	# Examined	10	10	10	10
		All Grades	1 +	0	1	4
		Minimal	1	0	1	4
HEART	Degeneration	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Minimal	0	0	0	1
KIDNEYS	Chronic Progressive Nephropathy	# Examined	10	0	0	10
		All Grades	2	0	0	2
		Minimal	2	0	0	1
		Mild	0	0	0	1
	Inflammation chronic	# Examined	10	0	0	10
		All Grades	3	0	0	0
		Minimal	3	0	0	0
	pelvis Hyperplasia bilateral diffuse	# Examined	10	0	0	10
		All Grades	0	0	0	0
	cortex Cyst	# Examined	10	0	0	10
		Present	0	0	0	2
	tubule Basophilia	# Examined	10	0	0	10
		All Grades	0	0	0	2
		Minimal	0	0	0	2
LIVER	Inflammation chronic multifocal	# Examined	10	10	10	10
		All Grades	7	10	5	9
		Minimal	7	10	5	9
	centrilobular Hypertrophy	# Examined	10	10	10	10
		All Grades	0 +++	0	4 +	10 +++
		Minimal	0	0	4	1
		Mild	0	0	0	9
	periportal Vacuolation	# Examined	10	10	10	10
		All Grades	3	1	3	2
		Minimal	1	1	3	1
		Mild	1	0	0	1
		Moderate	1	0	0	0

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 is replicated from Appendix U.

Table 31. Summary of Microscopic Findings – Female Toxicity Groups (continued)

Toxicity Females Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
LUNGS	Inflammation chronic	# Examined	10	0	0	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
	Histocytosis	# Examined	10	0	0	10
		All Grades	3	0	0	4
		Minimal	3	0	0	4
NERVE, SCIATIC	Degeneration	# Examined	10	10	10	10
		All Grades	0 +	1	0	3
		Minimal	0	1	0	1
		Mild	0	0	0	2
SPINAL CORD	white matter Degeneration	# Examined	10	10	10	10
		All Grades	0 +++	0	0	5 ++
		Minimal	0	0	0	4
		Mild	0	0	0	1
STOMACH	Hyperkeratosis	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Mild	0	0	0	1
	Edema	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Minimal	0	0	0	1
	mucosa non-glandular Vacuolation	# Examined	10	0	0	10
		All Grades	1	0	0	0
		Mild	1	0	0	0
THYMUS	Atrophy	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Minimal	0	0	0	1
	Cyst ultimobranchial	# Examined	10	0	0	10
		Present	2	0	0	1
THYROID GLANDS	Ectopic Thymus	# Examined	10	0	0	10
		Present	1	0	0	0
	colloid Vacuolation	# Examined	10	0	0	10
		All Grades	1	0	0	1
		Minimal	1	0	0	1
URINARY BLADDER	Hyperplasia epithelial diffuse	# Examined	10	10	10	10
		All Grades	2	0	0	2
		Minimal	2	0	0	2

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Table is replicated from Appendix U.

Table 32. Summary of Microscopic Findings – Female Reproductive Groups

Reproductive Females Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
BONE MARROW, STERNUM	Atrophy	# Examined	10	0	0	9
		All Grades	0	0	0	1
		Moderate	0	0	0	1
BRAIN	white matter Degeneration	# Examined	10	10	10	10
		All Grades	0 +++	0	0	8 +++
		Minimal	0	0	0	4
		Mild	0	0	0	1
		Moderate	0	0	0	2
		Marked	0	0	0	1
KIDNEYS	Inflammation chronic	# Examined	10	0	0	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
	pelvis Hyperplasia bilateral diffuse	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Mild	0	0	0	1
	pelvis Inflammation chronic	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Mild	0	0	0	1
	cortex Infarction chronic focal	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Mild	0	0	0	1
	tubule Basophilia	# Examined	10	0	0	10
		All Grades	3	0	0	0
		Minimal	3	0	0	0
LIVER	Inflammation chronic multifocal	# Examined	10	10	10	10
		All Grades	0	1	0	2
		Minimal	0	1	0	2
	Extramedullary Hematopoiesis	# Examined	10	10	10	10
		All Grades	0	1	0	0
		Minimal	0	1	0	0
	centrilobular Hypertrophy	# Examined	10	10	10	10
		All Grades	0 +++	0	10 +++	10 +++
		Minimal	0	0	10	3
		Mild	0	0	0	6
		Moderate	0	0	0	1
	centrilobular Vacuolation	# Examined	10	10	10	10
		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 is replicated from Appendix U.

Table 32. Summary of Microscopic Findings – Female Reproductive Groups (continued)

Reproductive Females Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
LUNGS	Congestion	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Mild	0	0	0	1
	Histocytosis	# Examined	10	0	0	10
		All Grades	5	0	0	2
		Minimal	5	0	0	2
LYMPH NODE, MEDIASTINAL	Atrophy	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Mild	0	0	0	1
NERVE, SCIATIC	Degeneration	# Examined	10	10	10	10
		All Grades	0 +++	0	0	8 +++
		Minimal	0	0	0	1
		Moderate	0	0	0	3
		Marked	0	0	0	4
NERVE, TIBIAL	Degeneration	# Examined	10	10	10	9
		All Grades	0 +++	0	0	9 +++
		Minimal	0	0	0	2
		Mild	0	0	0	3
		Moderate	0	0	0	3
		Marked	0	0	0	1
SKELETAL MUSCLE, ADDUCTOR	Degeneration	# Examined	10	10	10	10
		All Grades	4 +++	1	2	10 +++
		Minimal	3	0	1	4
		Mild	1	1	1	3
		Moderate	0	0	0	2
		Marked	0	0	0	1
	Inflammation, Chronic	# Examined	10	10	10	10
		All Grades	2	0	0	0
		Mild	2	0	0	0
SKELETAL MUSCLE, GASTROCNEMIUS	Degeneration	# Examined	10	10	10	10
		All Grades	5 ++*	0	3	9
		Minimal	5	0	3	3
		Mild	0	0	0	3
		Moderate	0	0	0	1
		Marked	0	0	0	2
	Inflammation, Chronic	# Examined	10	10	10	10
		All Grades	0	2	1	0
		Minimal	0	0	1	0
		Mild	0	2	0	0

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Table is replicated from Appendix U.

Table 32. Summary of Microscopic Findings – Female Reproductive Groups (continued)

Reproductive Females Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
SPINAL CORD	white matter Degeneration	# Examined	10	9	9	10
		All Grades	0 +++	1	1	9 +++
		Minimal	0	1	1	2
		Mild	0	0	0	2
		Moderate	0	0	0	2
		Marked	0	0	0	3
SPLEEN	Atrophy	# Examined	10	10	10	10
		All Grades	0 +++	0	0	5 ++
		Mild	0	0	0	3
		Moderate	0	0	0	2
STOMACH	glandular Ulceration focal	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Mild	0	0	0	1
THYMUS	Atrophy	# Examined	10	10	10	9
		All Grades	0 +++	0	0	5 ++
		Moderate	0	0	0	5
THYROID GLANDS	Cyst ultimobranchial	# Examined	10	0	0	10
		Present	1	0	0	2
URINARY BLADDER	Hyperplasia epithelial diffuse	# Examined	10	10	10	10
		All Grades	0 +++	2	0	7 +++
		Minimal	0	1	0	3
		Mild	0	1	0	4
	Inflammation chronic	# Examined	10	10	10	10
		All Grades	0	1	0	0
		Minimal	0	1	0	0
UTERUS	Pregnant	# Examined	10	0	0	10
		Present	0	0	0	2

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Table is replicated from Appendix U.

Table 33. Summary of Mating and Fertility Data – Female Reproductive Groups

	Group 1 0 mkd	Group 2 100 mkd	Group 3 300 mkd	Group 4 1000 mkd
Pairs Mated	10	10	10	10
Females that died during study	0	0	0	0
Females euthanized in extremis	0	0	0	4[a]
Females with Evidence of Copulation	10	10	10	9
Gravid	9	10	9	8
Non-Gravid	1[b]	0	1[b]	1[b]
Females with No Evidence of Copulation	0	0	0	1
Gravid	0	0	0	0
Non-Gravid	0	0	0	1[c]
Length of Gestation				
Mean	21.4	21.7	21.7	22.6***
SD	0.5	0.5	0.5	0.7
N	9	10	9	8
Females with Difficulty during Partruition	0	0	0	4[d]
Number of Corpora Lutea /Dam				
Mean	19.0	17.6	18.4	17.3
SD	2.7	3.1	2.8	3.4
N	9	10	9	8
Number of Implant Sites/Dam				
Mean	17.4	15.4	15.8	15.3
SD	1.9	1.3	1.8	2.4
N	9	10	9	8
% Pre-Implantation Loss[f]				
Mean	7.3	11.0	13.4	10.3
SD	10.4	11.8	12.0	12.1
N	9	10	9	8
% Post-Implantation Loss[g]				
Mean	5.7	5.3	7.6	39.9***
SD	4.8	5.5	10.9	29.5
N	9	10	9	6[e]

*** = $p<0.01$

[a] 5306 was euthanized on PP2 due to severity of clinical signs; 5308 was cuthanized on GD24 due to severity of clinical signs; 5309 was euthanized on PPO due to difficulty during labor; 5311 was euthanized on PP0 due to severity of clinical signs

[b] animals 5223, 5277 and 5310

[c] animal 5305

[d] animals 5306, 5309, 5311, and 5312

[e] animal 5305 and 5310 were not pregnant; 5308 was euthanized on GD 24; 5309 was euthanized euthanized on PP0 due to difficulty during labor

[f] % Preimplantation Loss = ((# Corpora Lutea -# Implantations) / # Corpora Lutea) * 100

[g] % Post-Implantation Loss = ((# Implantations - # Live Pups Day 0) / # Implantations) *100

Table 34. Summary of Litter Data

	Day 0										
	Live Male Pups	Live Female Pups	Dead Male Pups	Dead Female Pups	Dead Undetermined Sex	Total Male/Female Ratio	Total Live Pups	Total Litter Size	% Live Pups[a]	Live Litter Weight (g)	Live Average Pup weight (g)
Group 1 - 0mkd											
MEAN	8.1	8.3	0.0	0.0	0.0	1.0	16.4	16.4	100.0	103.0	6.3
SD	1.6	1.4	0.0	0.0	0.0	0.3	1.7	1.7	0.0	13.0	0.4
N	9[b]	9	9	9	9	9	9	9	9	9	9
Group 2 - 100 mkd											
MEAN	8.4	6.2	0.0	0.0	0.0	1.5*	14.6	14.6	100.0	93.8	6.5
SD	2.3	1.8	0.0	0.0	0.0	0.7	1.6	1.6	0.0	8.9	0.5
N	10	10	10	10	10	10	10	10	10	10	10
Group 3 - 300 mkd											
MEAN	7.8	6.8	0.0	0.0	0.0	1.1	14.6	14.6	100.0	93.7	6.5
SD	1.9	0.7	0.0	0.0	0.0	0.3	2.4	2.4	0.0	14.4	0.6
N	9[c]	9	9	9	9	9	9	9	9	9	9
Group 4 - 1000 mkd											
MEAN	4.7**	4.3***	2.5***	3.2***	0.3***	1.0	9.0***	15.0	60.7***	90.1	6.0
SD	1.8	3.4	1.9	2.9	0.5	0.3	4.4	1.7	29.5	7.4	0.5
N	6[d]	6	6	6	6	6	6	6	6	6	6

*p<0.05, **<0.02, ***p<0.01

[a] % Live Pups = (Total Live Pups/Total Litter Size)*100

[b] No data available for animal 5223 that demonstrated positive evidence of mating but did not deliver.

[c] No data available for animal 5277 that demonstrated positive evidence of mating but did not deliver.

[d] No data available for the following animals: 5305 -no evidence of mating and did not deliver; 5308 -euthanized on GD24 due to severity of clinical signs; 5309 - ethuhanized on PP0 due to difficulty during labor; 5310-evidence of mating but did not deliver.

Table 34. Summary of Litter Data (continued)

	Day 4								
	Live Male Pups	Live Female Pups	Total Male/Female Ratio	Total Live Pups	% Live Pups[a]	% Post-Natal Loss[c]	Live Litter Weight (g)	Live Average Pup weight (g)	Average Pup Weight Change (g)
Group 1 - 0mkd									
MEAN	8.1	8.3	1.0	16.4	100.0	0.0	169.4	10.3	4.0
SD	1.6	1.4	0.3	1.7	0.0	0.0	23.6	1.0	0.6
N	9	9	9	9	9	9	9	9	9
Group 2 - 100 mkd									
MEAN	8.4*	6.1	1.5	14.5	99.4	0.6	148.5	10.3	3.8
SD	2.3	1.6	0.7	1.6	2.0	2	14.2	0.9	0.5
N	10	10	10	10	10	10	10	10	10
Group 3 - 300 mkd									
MEAN	7.8	6.4	1.2	14.2	97.6	2.5	143.7	10.3	3.8
SD	1.9	1.0	0.3	2.5	3.7	3.8	16.4	1.4	1.1
N	9	9	9	9	9	9	9	9	9
Group 4 - 1000 mkd									
MEAN	5.5	5.5	1.3	11.0***	74.8***	3.6	84.6***	7.7***	1.6***
SD	1.3	3.4	0.6	3.9	22.7	7.1	31.2	0.7	1.0
N	4[b]	4	4	4	4	4	4	4	4

*p<0.05, **<0.02, ***p<0.01

[a] % Live Pups = (Total Live Pups/Total Litter Size)*100

[b] No data available for the following animals: 5306 - euthanized on PP2 due to severity of clinical signs; 5311 - euthanized on PP0 due to severity of clinical signs

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

Appendix A. Individual Combined Clinical Observations and Detailed Clinical Observations – Male Toxicity Groups

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1	m	5204	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5205	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5206	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5207	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5208	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5209	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5210	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5211	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5212	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5213	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix A. Individual Combined Clinical Observations and Detailed Clinical Observations – Male Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	23	24	25	26	27	28	29	30
1	m	5204	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5205	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5206	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5207	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5208	No Abnormalities Detected		X	X	X	X	X	.	X	X
			Soiling	Chin	.	.	.	.	.	C	.	.
		5209	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5210	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5211	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5212	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5213	No Abnormalities Detected		X	X	X	X	X	X	X	X

Severity Codes: X = Present; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix A. Individual Combined Clinical Observations and Detailed Clinical Observations – Male Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
2	m	5234	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5235	No Abnormalities Detected		X	X	X	.	.	.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Skin, Scab	Lower Forelimb, Right	.	.	.	F	F	F	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5236	No Abnormalities Detected		X	X	X	X	X	X	.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Soiling	Nose	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5237	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5238	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5239	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5240	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5241	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5242	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5243	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix A. Individual Combined Clinical Observations and Detailed Clinical Observations – Male Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	23	24	25	26	27	28	29	30
2	m	5234	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5235	No Abnormalities Detected		X	X	X	X	X	X	X	X
			Skin, Scab	Lower Forelimb, Right	.	.	.	.	.	.	.	.
		5236	No Abnormalities Detected		X	X	X	X	X	X	X	X
			Soiling	Nose	.	.	.	.	.	.	.	.
		5237	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5236	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5239	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5240	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5241	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5242	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5243	No Abnormalities Detected		X	X	X	X	X	X	X	X

Severity Codes: X = Present; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix A. Individual Combined Clinical Observations and Detailed Clinical Observations – Male Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	6	9	10	11	12	13	14	15	16	17	18	19	20	21	22
3	M	5264	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.
		5265	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	.	.	.	.	.	.	X	X	X	.	X	X	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	C
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	Y	Y	Y	Y	Y	Y	.	.	.	.	.	.	.
		5266	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	X	X	X	X	X	X	X	X	X	X	X	X	X
			Skin, Scab	Upper Back (Thoracic)	F	F	F	F	F	F	F	F	F	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5267	No Abnormalities Detected		.	.	.	.	.	.	.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Skin, Scab	Shoulder, Left	F	F	F	F	F	F	F	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5288	No Abnormalities Detected		X	X	X	X	X	X	X	.	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Soiling	Chin	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5269	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.	.	X	X	X	X	X	X	.	X	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	Y	Y	.	.	.	.	.	.	.	.	.	.
		5270	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5271	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5272	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5273	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	X	X	X	X	.	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	R	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.
			Soiling	Abdomen, General	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix A. Individual Combined Clinical Observations and Detailed Clinical Observations – Male Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	23	24	25	26	27	28	29	30
3	m	5264	No Abnormalities Detected		X	X	X	X	X	X	X	X
			Soiling	Chin	.	.	.	.	.	.	.	.
		5265	No Abnormalities Detected		.	.	.	.	.	X	X	X
			Soiling	Muzzle, General	C	C	C	C	C	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	Y	.	.	.	.	.
		5266	No Abnormalities Detected		.	X	X	X	X	X	X	X
			Skin, Scab	Upper Back (Thoracic)	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	R	.	.	.	.	.	.	.
		5267	No Abnormalities Detected		X	X	X	X	X	X	X	X
			Skin, Scab	Shoulder, Left	.	.	.	.	.	.	.	.
		5268	No Abnormalities Detected		X	X	X	X	X	X	X	X
			Soiling	Chin	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.
		5269	No Abnormalities Detected		X	X	X	X	X	X	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.
		5270	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5271	No Abnormalities Detected		X	X	X	X	X	X	X	X
		5272	No Abnormalities Detected		X	X	X	X	X	.	X	X
			Soiling	Muzzle, General	.	.	.	.	.	C	.	.
		5273	No Abnormalities Detected		.	.	.	X	X	X	X	X
			Soiling	Muzzle, General	R	R	R	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.
			Soiling	Abdomen, General	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.

Severity Codes: X = Present; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix A. Individual Combined Clinical Observations and Detailed Clinical Observations – Male Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
4	m	5294	No Abnormalities Detected		X	X	X	X	X	X	X	.	X	X	X	X	X	X	X	X	X	.	X	.	.	X
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	Y	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	Y	Y	.
		5295	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	.	.	X	X	X	X	X	X	X	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	C	C	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5296	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	.	.	.	.	X	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	C	C	C	C	.	C	C	C	.	R	C
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	R	.	.
		5297	No Abnormalities Detected		X	X	X	X	X	X	.	X	.	X	X	.	X	X	X	.	X	X	X	X	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	R	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	C	C
			Soiling	Abdomen, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	.	.
		5298	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.	.	.	X	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	C
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	Y	Y	Y	.	.	.
		5299	No Abnormalities Detected		X	X	X	X	X	X	X	.	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5300	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.	.	X	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	C	.	.	R	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	R	R
			Soiling	Abdomen, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	Y	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	Y	.	.	.	.	.
		5301	No Abnormalities Detected		X	X	X	X	X	X	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	R	R	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	R	R	.	R	R	R	R	.	C	C	C	C	C	C	C	C
		5302	No Abnormalities Detected		X	X	X	X	X	X	.	X	.	.	.	.	X	X	.	X	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	C	R	C	.	C	.
			Soiling	Chin	.	.	.	.	.	.	R	.	R	R	R	R	.	.	.	.	.	.	.	R	.	C
		5303	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix A. Individual Combined Clinical Observations and Detailed Clinical Observations – Male Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	23	24	25	26	27	28	29	30
4	m	5294	No Abnormalities Detected		X	X	X	X	X	X	X	X
			Soiling	Nose	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.
		5295	No Abnormalities Detected		X	.	X	X	X	X	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.
			Soiling	Chin	.	C	.	.	.	.	.	.
		5296	No Abnormalities Detected		.	.	X	.	.	.	.	X
			Soiling	Muzzle, General	C	C	.	C	C	C	C	.
			Soiling	Chin	.	.	.	.	.	.	.	.
		5297	No Abnormalities Detected		.	.	.	.	.	.	.	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.
			Soiling	Chin	C	C	C	C	C	C	C	.
			Soiling	Abdomen, General	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.
		5298	No Abnormalities Detected		X	X	X	X	.	.	.	X
			Soiling	Muzzle, General	.	.	.	.	C	C	.	.
			Soiling	Chin	.	.	.	.	.	.	R	.
			Soiling	Urogenital, General	.	.	.	.	Y	.	.	.
		5299	No Abnormalities Detected		X	X	X	X	X	X	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.
		5300	No Abnormalities Detected		.	.	.	X	.	.	X	X
			Soiling	Muzzle, General	.	.	R	.	C	R	.	.
			Soiling	Chin	R	R	.	.	.	.	.	.
			Soiling	Abdomen, General	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.
		5301	No Abnormalities Detected		.	.	.	.	X	.	.	X
			Soiling	Nose	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	C	.	.
			Soiling	Chin	C	C	C	C	.	.	C	.
		5302	No Abnormalities Detected		.	.	.	.	.	.	.	X
			Soiling	Muzzle, General	.	C	R	R	C	C	C	.
			Soiling	Chin	C	C	.	.	.	.	.	.
		5303	No Abnormalities Detected		X	X	X	X	X	X	X	X

Severity Codes: X = Present; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix B. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Toxicity Groups

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1	f	5194	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5195	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5196	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5197	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5198	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5199	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		52D0	No Abnormalities Detected		X	X	X	X	X	X	X	.	X	X	X	X	X	X	X	X	X	X	.	.	.	.	.
			Skin, Scab	Muzzle, Right	.	.	.	.	.	.	.	F	.	.	.	.	.	.	.	.	-	.	.	.	.	.	.
			Skin, Scab	Head, Top	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	-	.	F	F	F	F	F
			Skin, Scab	Neck, Right	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	F	F	F	F
		52D1	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		52D2	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		52D3	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; D = Decreased; I = Increased; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix B. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	24	25	26	27	28	29
1	f	5194	No Abnormalities Detected		X	X	X	X	X	X
		5195	No Abnormalities Detected		X	X	X	X	X	X
		5196	No Abnormalities Detected		X	X	X	X	X	X
		5197	No Abnormalities Detected		X	X	X	X	X	X
		5198	No Abnormalities Detected		X	X	X	X	X	X
		5199	No Abnormalities Detected		X	X	X	X	X	X
		5200	No Abnormalities Detected		.	.	X	X	X	X
			Skin, Scab	Muzzle, Right	.	.	.	.	.	.
			Skin, Scab	Head, Top	F	F	.	.	.	.
			Skin, Scab	Neck, Right	F	F	.	.	.	.
		5201	No Abnormalities Detected		X	X	X	X	X	X
		5202	No Abnormalities Detected		X	X	X	X	X	X
		5203	No Abnormalities Detected		X	X	X	X	X	X

Severity Codes: X = Present; D = Decreased; I = Increased; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix B. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
2	f	5224	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5225	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5226	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5227	No Abnormalities Detected		.	.	.	.	.	.	.	.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Skin, Scab	Head, Top	F	F	F	F	F	F	F	F	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5228	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5229	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5230	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5231	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5232	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5233	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; D = Decreased; I = Increased; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix B. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	24	25	26	27	28	29
2	f	5224	No Abnormalities Detected		X	X	X	X	X	X
		5225	No Abnormalities Detected		X	X	X	X	X	X
		5226	No Abnormalities Detected		X	X	X	X	X	X
		5227	No Abnormalities Detected		X	X	X	X	X	X
			Skin, Scab	Head, Top	.	.	.	.	.	.
		5228	No Abnormalities Detected		X	X	X	X	X	X
		5229	No Abnormalities Detected		X	X	X	X	X	X
		5230	No Abnormalities Detected		X	X	X	X	X	X
		5231	No Abnormalities Detected		X	X	X	X	X	X
		5232	No Abnormalities Detected		X	X	X	X	X	X
		5233	No Abnormalities Detected		X	X	X	X	X	X

Severity Codes: X = Present; D = Decreased; I = Increased; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix B. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	8	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3	f	5254	No Abnormalities Detected		.	X	.	.	.	.	.	.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Skin, Scab	Shoulder, Left	F	F	F	F	F	F	F	F	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5255	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5256	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5257	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	C
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5256	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5259	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5260	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5261	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5262	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5263	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; D = Decreased; I = Increased; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix B. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	24	25	26	27	28	29
3	f	5254	No Abnormalities Detected		X	X	X	X	X	X
			Skin, Scab	Shoulder, Left	.	.	.	.	.	.
		5255	No Abnormalities Detected		X	X	X	X	X	X
		5256	No Abnormalities Detected		X	X	X	X	X	X
		5257	No Abnormalities Detected		.	.	.	.	.	X
			Soiling	Muzzle, General	.	.	.	.	.	.
			Soiling	Chin	C	C	C	R	C	.
		5258	No Abnormalities Detected		X	X	X	X	X	X
		5259	No Abnormalities Detected		X	X	X	.	X	X
			Soiling	Muzzle, General	.	.	.	R	.	.
		5260	No Abnormalities Detected		X	X	X	X	X	X
		5261	No Abnormalities Detected		X	X	X	X	X	X
		5262	No Abnormalities Detected		X	X	X	X	X	X
		5263	No Abnormalities Detected		X	X	X	X	X	X

Severity Codes: X = Present; D = Decreased; I = Increased; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix B. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
4	f	5284	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.	.	.	.	.	.	X	X
			Skin, Scab	Shoulder, Left	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	F	F	F	F	F	F	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	R	.	.	.	.
		5285	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	.	.	X	.	X	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	C	C	.	C	.	C	R	C	.	R	.	C
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	R	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.
		5286	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	.	.	X	X	X	X	X	X	X	X	X	.	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	R	R	.	.	.	.	.	.	.	.	.	.	.	.
		5287	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.	.	X	X	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	R	R	.	.	C
		5288	No Abnormalities Detected		X	X	X	.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Soiling	Muzzle, General	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5289	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	.	X	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	R	.	C	C	C
		5290	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	.	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	C	.
		5291	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	X
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.
		5292	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	.	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	R	.	.
		5293	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	.	.	.	.	.	.
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	.	.	.
			Eye, Lacrimation	Bilateral	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	R	R	R	.	.	R
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	R	.

Severity Codes: X = Present; D = Decreased; I = Increased; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix B. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Toxicity Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	24	25	26	27	28	29
4	f	5284	No Abnormalities Detected		X	X	X	X	X	X
			Skin, Scab	Shoulder, Left	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.
		5285	No Abnormalities Detected		.	.	.	.	.	X
			Soiling	Muzzle, General	C	C	C	C	C	.
			Soiling	Chin	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.
		5286	No Abnormalities Detected		.	X	.	.	X	X
			Soiling	Muzzle, General	C	.	C	C	.	.
			Soiling	Chin	.	.	.	.	.	.
		5287	No Abnormalities Detected		X	X	X	X	X	X
			Soiling	Chin	.	.	.	.	.	.
		5288	No Abnormalities Detected		X	X	X	X	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.
		5289	No Abnormalities Detected		.	.	.	.	.	.
			Soiling	Muzzle, General	.	C	C	C	C	.
			Soiling	Chin	C	.	.	.	.	R
		5290	No Abnormalities Detected		.	.	.	.	.	X
			Soiling	Muzzle, General	C	C	C	C	C	.
		5291	No Abnormalities Detected		X	X	X	X	X	X
			Soiling	Chin	.	.	.	.	.	.
		5292	No Abnormalities Detected		X	X	X	X	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.
		5293	No Abnormalities Detected		.	.	.	.	.	X
			Behavior, Activity		.	.	.	.	.	.
			Eye, Lacrimation	Bilateral	.	.	.	.	.	.
			Soiling	Muzzle, General	R	R	C	C	C	.
			Soiling	Chin	.	.	.	.	.	.

Severity Codes: X = Present; D = Decreased; I = Increased; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1	f	5214	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5215	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.
			Skin, Scab	Lower Hindlimb, Right	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F
		5216	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5217	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	X	X
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	.	.
		5218	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5219	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5220	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5221	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5222	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.	X	X	X	X	X
			Excessive Hair Loss, Limbs	Hindlimb, Bilateral	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Abdomen, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	.	.
		5223	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	23	24	25	26	27	28	29	3D	31	32	33	34	35	36	37	38	39	4D	41	42	43	44
1	f	5214	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.
		5215	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	X	X	X	.
			Skin, Scab	Lower Hindlimb, Right	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	.	.	.	.	.
		5216	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.
		5217	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5218	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.	.
		5219	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.
		5220	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.
		5221	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5222	No Abnormalities Detected		X	X	X	X	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Excessive Hair Loss, Limbs	Hindlimb, Bilateral	.	.	.	.	.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Soiling	Abdomen, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5223	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.	.

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	45	46	47	48	49	50	51	52	53	54	55
1	f	5214	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5215	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Skin, Scab	Lower Hindlimb, Right	.	.	.	.	.	.	.	.	.	.	.
		5216	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5217	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.
		5218	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5219	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5220	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5221	No Abnormalities Detected		X	.	.	.	.	.	.	.	.	.	.
		5222	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Excessive Hair Loss, Limbs	Hindlimb, Bilateral	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Abdomen, General	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.
		5223	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
2	f	5244	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5245	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5246	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5247	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5248	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5249	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5250	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5251	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5252	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5253	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
2	f	5244	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.
		5245	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5246	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5247	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.
		5246	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5249	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.	.
		5250	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5251	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5252	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.
		5253	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	45	46	47	48	49	5D	51	52	53	54	55
2	f	5244	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5245	No Abnormalities Detected		X	.	.	.	.	.	.	.	.	.	.
		5246	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5247	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5248	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5249	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5250	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5251	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5252	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5253	No Abnormalities Detected		X	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
3	f	5274	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5275	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5276	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5277	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5278	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5279	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5280	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5281	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5282	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5283	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
3	f	5274	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5275	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.
		5276	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5277	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.
		5278	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	.	.	X	X	X	X	X	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	C	C	.	.	.	.	.	.	.	.
		5279	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5280	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.	.
		5281	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		5282	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.
		5283	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	45	46	47	48	49	50	51	52	53	54	55
3	f	5274	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5275	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5276	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X
		5277	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5278	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.
		5279	No Abnormalities Detected		X	.	.	.	.	.	.	.	.	.	.
		5280	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5281	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5282	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
		5283	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
4	f	5304	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	.	.	.	X	.	.	.	.	X	X	X
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Gait, Dragging Hindquarters		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	R	R	R	.	C	.	R	R	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Abdomen, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Y	Y	Y	Y	.	.	.
		5305	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	.	.	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	R	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	C	C
		5306	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	X	X	X	X	X	X
			Gait, Dragging Hindquarters		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Respiration, Rapid		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.
		5307	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	X	X
			Gait, Dragging Hindquarters		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Skin, Ungroomed Appearance		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.
		5308	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.	.	X	X	X	X	X	X	.	X	X	X
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Respiration, Rapid		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	R	R	.	.	.	.	.	.	.	.	.	.
			Soiling	Eye, Bilateral	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
4	f	5304	No Abnormalities Detected		.	.	X	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Behavior, Activity		.	.	.	.	.	.	.	.	.	D	D	D	D	D	D	D	D	D	D	D	D	D
			Gait, Dragging Hindquarters		.	.	.	.	.	.	.	.	.	L	L	L	L	L	L	L	L	L	L	L	L	L
			Soiling	Nose	.	R	.	.	.	.	.	R	R	R	.	.	.	.	.	.	.	R	R	R	R	R
			Soiling	Muzzle, General	.	.	.	C	.	C	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	C	.	.	.	.	.	.	.	C	.	.	.	R	.	.	C	C	C	C	C	C	C
			Soiling	Abdomen, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5305	No Abnormalities Detected		.	.	.	.	.	X	X	X	X	X	X	X	X	X.	X	X	.	.	.	.	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	X	X	X	X	X
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	C	C	C	C	C	.	.	.	.	.	.	.	.	.	.	.	.	C	C	C	C	C
		5306	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.	.	.	.	.
			Gait, Dragging Hindquarters		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	L	.	.	.	.
			Respiration, Rapid		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	R	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5307	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	X	.	.
			Gait, Dragging Hindquarters		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	L
			Skin, Ungroomed Appearance		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5308	No Abnormalities Detected		X	X	X	X	X	X	.	.	.	X	X	X	X	X	.	.	.	.	.	.	.	.
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	D	D	D	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	X	X	X	.
			Respiration, Rapid		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	X	.
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	R	R	R	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	C	C	.	.	.	.	.	C	C	R	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Eye, Bilateral	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	R	R	.

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	45	46	47	48	49	50	51	52	53	54	55
4	f	5304	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Behavior, Activity		D	.	.	.	.	.	.	.	.	.	.
			Gait, Dragging Hindquarters		L	.	.	.	.	.	.	.	.	.	.
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Abdomen, General	.	.	.	.	.	.	.	.	.	.	.
		5305	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Gait, Incoordinated		X	X	X	X	X	X	X	X	X	X	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.
		5306	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Gait, Dragging Hindquarters		.	.	.	.	.	.	.	.	.	.	.
			Respiration, Rapid		.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.
		5307	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Gait, Dragging Hindquarters		L	L	.	.	.	.	.	.	.	.	.
			Skin, Ungroomed Appearance		.	.	.	.	.	.	.	.	.	.	.
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Urogenital, General	.	.	.	.	.	.	.	.	.	.	.
		5308	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.
			Respiration, Rapid		.	.	.	.	.	.	.	.	.	.	.
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Eye, Bilateral	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
4	f	5309	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	X
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Gait, Dragging Hindquarters		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Respiration, Rapid		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.
			Soiling	Eye, Bilateral	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		5310	No Abnormalities Detected		X	X	X	X	X	.	X	X	X	X	X	X	.	.	.	.	.	.	.	.	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	R	.	.	.	.	.	.	C	C	C	C	C	C	R	.	C	C
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.
		5311	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	.	X	X	X	X	X	X	X	X	X	X	X
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.
		5312	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	.	.	.	X	.	X	.	X	X	X	X	.	X
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	.
			Gait, Dragging Hindquarters		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.
			Misc. Thin		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	R	C	C	.	.	.	R	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.
		5313	No Abnormalities Detected		X	X	X	X	X	X	X	.	X	X	X	.	.	.	.	X	.	.	.	.	X	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	R	.	.	.	C	C	C	C	.	C	R	C	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	C

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	23	24	25	26	27	26	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
4	f	5309	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	.	.	.	.	.	.	.	.	.	.	.
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.	.	.	D	D	D	.	.	.	.	.	.
			Gait, Dragging Hindquarters		.	.	.	.	.	.	.	.	.	.	.	L	L	L	L	L	.	.	.	.	.	.
			Respiration, Rapid		.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	X	.	.	.	.	.	.
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	R	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Eye, Bilateral	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.
		5310	No Abnormalities Detected		.	.	X	X	.	.	.	.	X	X	X	.	.	.	X	X	.	.	.	.	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	X	X	X	X	.
			Soiling	Muzzle, General	C	C	.	.	C	R	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	C	.	.	.	R	R	R	.	.	C	C	C	C	.	.
		5311	No Abnormalities Detected		.	.	.	X	.	X	X	X	.	X	X	X	X	X	X	X	.	.	.	.	.	.
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	.	.	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	X	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	C	C	R	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.
		5312	No Abnormalities Detected		X	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Behavior, Activity		.	.	.	.	.	.	D	D	D	D	D	D	D	D	D	D	D	D	D	D	.	.
			Gait, Dragging Hindquarters		.	.	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Misc. Thin		.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	R	R	R	.	.
		5313	No Abnormalities Detected		X	.	.	.	X	.	X	.	.	.	X	X	X	.	X	X	X	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	C	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	.
			Soiling	Chin	.	C	C	C	.	.	.	C	C	C	.	.	.	.	.	.	.	C	C	C	C	C

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Group 1 - 0 mg/kg/day Group 2 - 100 mg/kg/day Group 3 - 300 mg/kg/day Group 4 - 1000 mg/kg/day

Appendix C. Individual Combined Clinical Observations and Detailed Clinical Observations – Female Reproductive Groups (continued)

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	45	46	47	48	49	50	51	52	53	54	55
4	f	5309	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.
			Gait, Dragging Hindquarters		.	.	.	.	.	.	.	.	.	.	.
			Respiration, Rapid		.	.	.	.	.	.	.	.	.	.	.
			Soiling	Nose	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Eye, Bilateral	.	.	.	.	.	.	.	.	.	.	.
		5310	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.
		5311	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.
		5312	No Abnormalities Detected		.	.	.	.	.	.	.	.	.	.	.
			Behavior, Activity		.	.	.	.	.	.	.	.	.	.	.
			Gait, Dragging Hindquarters		.	.	.	.	.	.	.	.	.	.	.
			Gait, Incoordinated		.	.	.	.	.	.	.	.	.	.	.
			Misc. Thin		.	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.
		5313	No Abnormalities Detected		X	.	.	.	.	.	.	.	.	.	.
			Soiling	Muzzle, General	.	.	.	.	.	.	.	.	.	.	.
			Soiling	Chin	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present; D = Decreased; L = Limbs Flaccid; F = Focal; C = Clear; R = Red; Y = Yellow

Appendix D. Individual Body Weights – Male Toxicity Groups

0 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1	8	15	22	29
5204	306.0	350.8	387.2	425.8	460.6
5205	287.5	320.3	346.7	366.9	394.8
5206	307.5	331.2	355.3	373.9	399.4
5207	307.0	348.4	375.5	399.6	430.3
5208	308.5	333.4	360.4	399.3	437.5
5209	290.6	336.0	367.7	386.0	401.7
5210	302.3	331.4	373.7	407.7	444.2
5211	304.5	334.4	379.9	407.3	424.9
5212	294.1	333.2	362.3	386.3	411.0
5213	305.8	329.4	352.0	368.1	390.3
Mean	301.38	334.85	366.07	392.09	419.47
SD	7.70	8.89	13.01	19.24	23.63
N	10	10	10	10	10

Appendix D. Individual Body Weights – Male Toxicity Groups (continued)

100 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1	8	15	22	29
5234	293.7	324.6	354.1	350.1	374.9
5235	314.5	345.2	385.1	408.0	436.5
5236	315.2	353.7	386.9	406.6	434.3
5237	299.2	343.6	380.8	421.7	452.6
5238	320.1	348.3	378.9	408.6	430.9
5239	287.2	313.9	357.4	378.9	409.3
5240	305.6	348.5	383.6	406.0	427.6
5241	310.5	366.0	413.4	446.8	473.2
5242	304.5	341.8	375.7	397.1	427.2
5243	295.5	333.2	366.4	397.7	432.4
Mean	304.60	341.88	378.23	402.15	429.89
SD	10.65	14.82	16.86	25.35	25.65
N	10	10	10	10	10

Appendix D. Individual Body Weights – Male Toxicity Groups (continued)

300 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1	8	15	22	29
5264	307.4	339.1	366.6	386.6	417.0
5265	302.0	333.4	365.4	375.2	399.7
5266	324.3	370.1	405.5	429.4	455.8
5267	312.0	352.9	387.9	414.1	443.0
5268	303.0	340.9	375.7	405.2	432.4
5269	312.5	337.6	341.4	375.4	399.3
5270	307.7	348.3	379.8	422.1	443.7
5271	304.3	346.0	388.4	410.3	439.4
5272	298.7	333.5	371.5	404.6	443.4
5273	284.8	313.1	341.8	362.2	390.8
Mean	305.67	341.49	372.40	398.51	426.45
SD	10.26	14.80	20.11	22.39	22.94
N	10	10	10	10	10

Appendix D. Individual Body Weights – Male Toxicity Groups (continued)

1000 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1	8	15	22	29
5294	301.0	334.8	375.0	391.1	413.8
5295	302.1	335.5	356.7	380.1	420.6
5296	308.1	328.0	346.4	359.4	385.0
5297	281.6	301.4	330.9	350.4	376.9
5298	295.0	332.3	358.9	390.8	411.7
5299	291.8	313.9	329.8	359.8	379.9
5300	324.1	372.8	406.9	432.0	462.6
5301	314.3	364.3	405.8	435.5	469.1
5302	311.8	341.8	372.5	399.3	405.5
5303	311.9	338.5	368.3	391.8	416.8
Mean	304.17	336.33	365.12	389.02	414.19
SD	12.45	20.97	26.75	28.73	31.46
N	10	10	10	10	10

Appendix E. Individual Body Weight – Female Toxicity Groups

0 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1	8	15	22	28
5194	206.6	217.7	233.6	254.7	263.6
5195	186.2	185.8	198.9	210.6	219.6
5196	205.6	222.9	229.7	242.0	251.7
5197	203.8	214.7	228.2	245.1	254.6
5198	212.4	227.1	245.1	273.8	276.4
5199	217.3	231.5	241.6	263.8	266.6
5200	199.1	212.5	225.9	237.2	249.1
5201	206.1	220.8	243.7	266.2	271.9
5202	215.8	246.6	263.5	269.9	286.7
5203	218.8	230.3	240.0	257.5	271.8
Mean	207.17	220.99	235.02	252.08	261.20
SD	9.77	15.83	16.74	19.02	18.72
N	10	10	10	10	10

Appendix E. Individual Body Weight – Female Toxicity Groups (continued)

100 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1	8	15	22	28
5224	196.4	226.7	243.4	250.1	270 6
5225	204.1	215.6	235.7	254.6	258.4
5226	190.7	208.1	214.5	252.1	258.6
5227	193.7	201.7	220.9	235.2	242.2
5228	206.9	218.8	230.8	251.4	250.8
5229	202.6	220.6	232.1	246.3	252.5
5230	220.4	240.8	260.3	271.2	288.1
5231	199.7	222.7	229.8	255.2	262.5
5232	185.8	201.3	207.6	223.5	234.3
5233	187.5	196.9	207.6	222.5	232.4
Mean	198.78	215.32	228.27	246.21	255.04
SD	10.38	13.53	16.44	15.10	16.82
N	10	10	10	10	10

Appendix E. Individual Body Weight – Female Toxicity Groups (continued)

300 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1	8	15	22	28
5254	217.9	228.9	247.1	272.7	281.1
5255	215.1	227.4	247.5	253.5	278.5
5256	194.8	209.1	215.0	239.8	252.9
5257	221.7	233.3	254.2	271.5	271.5
5258	214.0	225.7	238.7	251.1	259.8
5259	187.6	198.2	207.2	227.0	234.1
5260	202.9	217.5	234.2	251.3	254.3
5261	186.3	198.2	214.5	227.3	235.6
5262	224.0	228.0	247.9	258.0	259.2
5263	209.8	220.5	234.5	244.9	257.8
Mean	207.41	218.68	234.08	249.71	258.48
SD	13.80	12.76	16.46	15.74	15.82
N	10	10	10	10	10

Appendix E. Individual Body Weight – Female Toxicity Groups (continued)

1000 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1	8	15	22	28
5284	203.9	224.6	235.2	245.8	258.8
5285	179.9	191.3	196.4	205.6	216.8
5286	191.7	198.8	202.5	213.3	225.4
5287	200.9	213.8	225.1	242.0	252.7
5288	182.3	185.4	200.5	215.4	212.9
5289	198.8	202.1	221.5	231.6	212.7
5290	209.9	226.7	244.6	256.9	264.8
5291	192.3	203.1	209.0	229.1	237.8
5292	209.2	221.1	229.2	236.1	258.2
5293	204.6	213.6	216.3	221.9	228.6
Mean	197.35	208.05	218.03	229.77	236.87
SD	10.52	14.12	15.95	16.02	20.36
N	10	10	10	10	10

Appendix F. Individual Body Weight – Female Reproductive Groups

0 mg/kg/day	1 (g)	8 (g)	15 (g)	22 (g)	Gest 0 (g)	Gest 7 (g)	Gest 14 (g)
5214	210.9	244.7	262.7	.	267.8	299.5	346.5
5215	227.2	245.7	263.8	.	270.8	308.8	357.3
5216	185.4	185.6	203.7	.	212.0	255.1	308.5
5217	217.0	249.0	270.1	.	281.3	325.6	371.4
5218	213.2	228.2	245.0	.	253.9	280.1	326.8
5219	211.1	233.9	241.6	.	249.3	276.1	314.9
5220	204.9	224.5	243.1	.	249.2	287.4	334.1
5221	211.8	228.6	249.6	.	269.4	285.4	328.3
5222	189.3	208.2	220.1	.	236.1	270.9	307.6
5223	194.4	202.0	223.6	.	227.7 E	262.8 E	284.8 E
Mean	206.52	225.04	242.33	.	254.42	287.66	332.82
SD	13.09	20.71	21.20	.	21.16	21.11	22.03
N	10	10	10	.	9	9	9

E = Excluded; 5223 was not pregnant.
Gest. = Gestational Day
. = No value present

Appendix F. Individual Body Weight – Female Reproductive Groups (continued)

0 mg/kg/day	Gest 20 (g)	P-Partum 0 (g)	P-Partum 4 (g)
5214	435.3	348.9	372.3
5215	450.6	352.4	373.3
5216	394.1	313.3	317.6
5217	442.7	351.1	367.3
5218	420.7	338.8	336.4
5219	395.6	309.4	307.4
5220	444.7	343.5	349.4
5221	413.5	307.4	332.5
5222	400.5	300.2	310.3
5223	274.7 E	271.3 E	.
Mean	421.97	329.44	340.72
SD	22.22	21.40	26.21
N	9	9	9

E = Excluded; 5223 was not pregnant.

Gest. = Gestational Day; P-Partum = PostPartum Day

Appendix F. Individual Body Weight – Female Reproductive Groups (continued)

100 mg/kg/day	1 (g)	8 (g)	15 (g)	22 (g)	Gest 0 (g)	Gest 7 (g)	Gest 14 (g)
5244	186.2	203.4	220.9	.	222.3	249.6	285.2
5245	198.7	204.1	209.9	.	229.1	255.9	298.9
5246	213.0	221.4	235.2	.	257.0	274.9	316.4
5247	206.5	224.7	254.5	.	253.6	278.0	317.9
5248	183.4	200.2	203.8	.	219.6	256.7	301.0
5249	219.7	232.7	258.1	.	259.0	301.0	343.4
5250	221.6	244.2	254.9	.	272.4	298.5	344.8
5251	188.5	207.1	218.3	.	223.4	246.8	285.8
5252	205.2	223.0	237.0	.	236.1	276.7	324.3
5253	211.9	226.6	235.0	.	250.5	282.4	320.6
Mean	203.47	218.74	232.76	.	242.30	272.05	313.83
SD	13.80	14.51	19.28	.	18.50	19.29	21.10
N	10	10	10	.	10	10	10

Gest. = Gestational Day
. = No value present

Appendix F. Individual Body Weight – Female Reproductive Groups (continued)

100 mg/kg/day	Gest 20 (g)	P-Partum 0 (g)	P-Partum 4 (g)
5244	372.8	280.3	307.1
5245	392.8	289.7	306.6
5246	408.5	319.6	315.2
5247	413.3	307.8	337.0
5248	385.0	310.4	316.7
5249	427.5	347.8	336.8
5250	448.6	355.5	345.7
5251	358.7	284.9	299.4
5252	391.4	318.6	351.4
5253	409.2	312.8	261.2
Mean	400.78	312.74	317.71
SD	26.34	24.78	26.72
N	10	10	10

Gest. = Gestational Day; P-Partum = PostPartum Day

Appendix F. Individual Body Weight – Female Reproductive Groups (continued)

300 mg/kg/day	1 (g)	8 (g)	15 (g)	22 (g)	Gest 0 (g)	Gest 7 (g)	Gest 14 (g)
5274	211.0	215.9	233.8	.	248.3	274.7	316.0
5275	206.5	228.7	248.4	.	252.6	273.0	314.6
5276	201.0	215.3	228.6	274.7	283.0	322.3	354.6
5277	199.3	211.3	211.5	.	230.9 E	236.7 E	254.7 E
5278	202.5	208.8	231.6	.	233.3	269.4	280.2
5279	209.7	220.0	225.1	.	241.7	275.4	308.5
5280	187.1	189.6	203.1	.	207.6	250.4	297.2
5281	195.2	212.0	230.3	.	235.4	265.4	299.8
5282	218.0	239.9	251.3	.	260.9	292.1	336.3
5283	216.8	246.2	255.3	.	257.9	295.2	337.1
Mean	204.71	218.77	231.90	274.70	246.74	279.77	316.03
SD	9.65	16.23	16.68	.	21.05	20.82	23.19
N	10	10	10	1	9	9	9

E = Excluded, 5277 was not pregnant.
Gest. = Gestational Day
. = No value present

Appendix F. Individual Body Weight – Female Reproductive Groups (continued)

300 mg/kg/day	Gest 20 (g)	P-Partum 0 (g)	P-Partum 4 (g)
5274	404.8	305.8	308.0
5275	399.6	300.8	315.9
5276	426 2	372.4	382.1
5277	256.2	262.6	.
5278	392.8	300.6	302.9
5279	389.0	313.6	330.1
5280	401.8	309.6	317.3
5281	375.5	312.7	318.9
5282	421.0	327.2	340.8
5283	424.1	322.7	334.4
Mean	403.87	318.38	327.82
SD	17.22	22.16	23.74
N	9	9	9

E = Excluded; 5277 was not pregnant.
Gest. = Gestational Day, P-Partum = PostPartum Day
. = No value present

Appendix F. Individual Body Weight – Female Reproductive Groups (continued)

1000 mg/kg/day	1 (g)	8 (g)	15 (g)	22 (g)	Gest 0 (g)	Gest 7 (g)	Gest 14 (g)
5304	204.0	215.4	234.9	.	245.1	247.8	248.9
5305	200.5	213.7	224.7	218.2	*	.	.
5306	189.9	196.6	209.4	.	217.1	234.1	270.2
5307	214.6	231.1	244.0	.	257.2	285.1	323.6
5308	191.8	202.4	208.1	.	223.4	233.2	234.5
5309	217.3	223.8	244.3	.	254.2	285.1	329.1
5310	232.3	238.6	256.4	.	260.5 E	273.8 E	281.7 E
5311	198.7	207.8	227.3	.	235.1	259.9	293.9
5312	211.3	220.5	234.2	.	233.3	232.4	241.2
5313	203.5	210.0	222.9	.	235.4	267.0	299.9
Mean	206.39	215.99	230.62	218.20	237.60	255.58	280.16
SD	12.80	12.87	15.37	.	13.98	22.21	36.92
N	10	10	10	1	8	8	8

*5305 was not pregnant.
E =Excluded; 5310 was not pregnant.
Gest. = Gestational Day
. = No value present

Appendix F. Individual Body Weight – Female Reproductive Groups (continued)

1000 mg/kg/day	Gest 20 (g)	P-Partum 0 (g)	P-Partum 4 (g)
5304	312.3	238.2	214.6
5305	.	.	.
5306	348.4	240.5	214.4 E[3]
5307	403.4	284.3	234.5
5308	292.8	255.0 E[2]	.
5309	349.1	311.0	.
5310	264.8 E	248.8 E	.
5311	353.6	228.2	.
5312	313.2	222.7	202.9
5313	374.0	291.2	320.1
Mean	343.35	259.44	243.03
SD	36.13	35.17	53.01
N	8	7	4

[a]5309 and 5311 were euthanized on Post-Partum Day 0.

E = Excluded; 5310 was not pregnant.

E[2] = Excluded; 5308 was euthanized on Gestational Day 24.

E[3] = Excluded; 5306 was euthanized Post-Partum Day 2.

Gest. = Gestational Day; P-Partum = Post--partum Day

. = No value present

Appendix G. Individual Body Weight Gains – Male Toxicity Groups

0 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1 → 8	8 → 15	15 → 22	22 → 29	1 → 29
5204	44.8	36.4	38.6	34.8	154.6
5205	32.8	26.4	20.2	27.9	107.3
5206	23.7	24.1	18.6	25.5	91.9
5207	41.4	27.1	24.1	30.7	123.3
5208	24.9	27.0	38.9	38.2	129.0
5209	45.4	31.7	18.3	15.7	111.1
5210	29.1	42.3	34.0	36.5	141.9
5211	29.9	45.5	27.4	17.6	120.4
5212	39.1	29.1	24.0	24.7	116.9
5213	23.6	22.6	16.1	22.2	84.5
Mean	33.47	31.22	26.02	27.38	118.09
SD	8.59	7.75	8.46	7.72	21.17
N	10	10	10	10	10

Appendix G. Individual Body Weight Gains – Male Toxicity Groups (continued)

100 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1 → 8	8 → 15	15 → 22	22 → 29	1 → 29
5234	30.9	29.5	-4.0	24.8	81.2
5235	30.7	39.9	22.9	28.5	122.0
5236	38.5	33.2	19.7	27.7	119.1
5237	44.4	37.2	40.9	30.9	153.4
5238	28.2	30.6	29.7	22.3	110.8
5239	26.7	43.5	21.5	30.4	122.1
5240	42.9	35.1	22.4	21.6	122.0
5241	55.5	47.4	33.4	26.4	162.7
5242	37.3	33.9	21.4	30.1	122.7
5243	37.7	33.2	31.3	34.7	136.9
Mean	37.28	36.35	23.92	27.74	125.29
SD	8.78	5.71	11.92	4.07	22.50
N	10	10	10	10	10

Appendix G. Individual Body Weight Gains – Male Toxicity Groups (continued)

300 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1 → 8	8 → 15	15 → 22	22 → 29	1 → 29
5264	31.7	27.5	20.0	30.4	109.6
5265	31.4	32.0	9.8	24.5	97.7
5266	45.8	35.4	23.9	26.4	131.5
5267	40.9	35.0	26.2	28.9	131.0
5268	37.9	34.8	29.5	27.2	129.4
5269	25.1	3.8	34.0	23.9	86.8
5270	40.6	31.5	42.3	21.6	136.0
5271	41.7	42.4	21.9	29.1	135.1
5272	34.8	38.0	33.1	38.8	144.7
5273	28.3	28.7	20.4	28.6	106.0
Mean	35.82	30.91	26.11	27.94	120.78
SD	6.63	10.47	9.09	4.69	19.24
N	10	10	10	10	10

Appendix G. Individual Body Weight Gains – Male Toxicity Groups (continued)

1000 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1 → 8	8 → 15	15 → 22	22 → 29	1 → 29
5294	33.8	40.2	16.1	22.7	112.8
5295	33.4	21.2	23.4	40.5	118.5
5296	19.9	18.4	13.0	25.6	76.9
5297	19.8	29.5	19.5	26.5	95.3
5298	37.3	26.6	31.9	20.9	116.7
5299	22.1	15.9	30.0	20.1	88.1
5300	48.7	34.1	25.1	30.6	138.5
5301	50.0	41.5	29.7	33.6	154.8
5302	30.0	30.7	26.8	6.2	93.7
5303	26.6	29.8	23.5	25.0	104.9
Mean	32.16	28.79	23.90	25.17	110.02
SD	10.86	8.57	6.18	9.11	23.63
N	10	10	10	10	10

Appendix H. Individual Body Weight Gains – Female Toxicity Groups

0 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1 → 8	8 → 15	15 → 22	22 → 28	1 → 28
5194	11.1	15.9	21.1	8.9	57.0
5195	-0.4	13.1	11.7	9.0	33.4
5196	17.3	6.8	12.3	9.7	46.1
5197	10.9	13.5	16.9	9.5	50.8
5198	14.7	18.0	28.7	2.6	64.0
5199	14.2	10.1	22.2	2.8	49.3
5200	13.4	13.4	11.3	11.9	50.0
5201	14.7	22.9	22.5	5.7	65.8
5202	30.8	16.9	6.4	16.8	70.9
5203	11.5	9.7	17.5	14.3	53.0
Mean	13.82	14.03	17.06	9.12	54.03
SD	7.64	4.64	6.72	4.57	10.90
N	10	10	10	10	10

Appendix H. Individual Body Weight Gains – Female Toxicity Groups (continued)

100 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1 → 8	8 → 15	15 → 22	22 → 28	1 → 28
5224	30.3	16.7	6.7	20.5	74.2
5225	11.5	20.1	18.9	3.8	54.3
5226	17.4	6.4	37.6	6.5	67.9
5227	8.0	19.2	14.3	7.0	48.5
5228	11.9	12.0	20.6	-0.6	43.9
5229	18.0	11.5	14.2	6.2	49.9
5230	20.4	19.5	10.9	16.9	67.7
5231	23.0	7.1	25.4	7.3	62.8
5232	15.5	6.3	15.9	10.8	48.5
5233	9.4	10.7	14.9	9.9	44.9
Mean	16.54	12.95	17.94	8.83	56.26
SD	6.84	5.54	8.61	6.13	10.94
N	10	10	10	10	10

Appendix H. Individual Body Weight Gains – Female Toxicity Groups (continued)

300 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1 → 8	8 → 15	15 → 22	22 → 28	1 → 28
5254	11.0	18.2	25.6	8.4	63.2
5255	12.3	20.1	6.0	25.0	63.4
5256	14.3	5.9	24.8	13.1	58.1
5257	11.6	20.9	17.3	0.0	49.8
5258	11.7	13.0	12.4	8.7	45.8
5259	10.6	9.0	19.8	7.1	46.5
5260	14.6	16.7	17.1	3.0	51.4
5261	11.9	16.3	12.8	8.3	49.3
5262	4.0	19.9	10.1	1.2	35.2
5263	10.7	14.0	10.4	12.9	48.0
Mean	11.27	15.40	15.63	8.77	51.07
SD	2.90	4.96	6.45	7.23	8.59
N	10	10	10	10	10

Appendix H. Individual Body Weight Gains – Female Toxicity Groups (continued)

1000 mg/kg/day	Day(s) Relative to Start Date (grams)				
	1 → 8	8 → 15	15 → 22	22 → 28	1 → 28
5284	20.7	10.6	10.6	13.0	54.9
5285	11.4	5.1	9.2	11.2	36.9
5286	7.1	3.7	10.8	12.1	33.7
5287	12.9	11.3	16.9	10.7	51.8
5288	3.1	15.1	14.9	-2.5	30.6
5289	3.3	19.4	10.1	-18.9	13.9
5290	16.8	17.9	12.3	7.9	54.9
5291	10.8	5.9	20.1	8.7	45.5
5292	11.9	8.1	6.9	22.1	49.0
5293	9.0	2.7	5.6	6.7	24.0
Mean	10.70	9.98	11.74	7.10	39.52
SD	5.50	5.93	4.46	10.99	14.01
N	10	10	10	10	10

Appendix I. Individual Body Weight Gains – Female Reproductive Groups

0 mg/kg/day	1-8 (g)	8-15 (g)	15-22 (g)	Gest 0-7 (g)	Gest 7-14 (g)	Gest 14-20 (g)	P-Partum 0-4 (g)
5214	33.8	18.0	.	31.7	47.0	88.8	23.4
5215	18.5	18.1	.	38.0	48.5	93.3	20.9
5216	0.2	18.1	.	43.1	53.4	85.6	4.3
5217	32.0	21.1	.	44.3	45.8	71.3	16.2
5218	15.0	16.8	.	26.2	46.7	93.9	-2.4
5219	22.8	7.7	.	26.8	38.8	80.7	-2.0
5220	19.6	18.6	.	38.2	46.7	110.6	5.9
5221	16.8	21.0	.	16.0	42.9	85.2	25.1
5222	18.9	11.9	.	34.8	36.7	92.9	10.1
5223	7.6	21.6	.	35.1 E	22.0 E	-10.1 E	.
Mean	18.52	17.29	.	33.23	45.17	89.14	11.28
SD	10.03	4.37	.	9.08	5.06	10.80	10.59
N	10	10	.	9	9	9	9

E = Excluded; 5223 was not pregnant.

Gest. = Gestational Day; P-Partum = PostPartum Day

Appendix I. Individual Body Weight Gains – Female Reproductive Groups (continued)

0 mg/kg/day	Total Change (g)
5214	161.4
5215	146.1
5216	132.2
5217	150.3
5218	123.2
5219	96.3
5220	144.5
5221	120.7
5222	121.0
5223	.
Mean	132.86
SD	19.84
N	9

Appendix I. Individual Body Weight Gains – Female Reproductive Groups (continued)

100 mg/kg/day	1-8 (g)	8-15 (g)	15-22 (g)	Gest 0-7 (g)	Gest 7-14 (g)	Gest 14-20 (g)	P-Partum 0-4 (g)
5244	17.2	17.5	.	27.3	35.6	87.6	26.8
5245	5.4	5.8	.	26.8	43.0	93.9	16.9
5246	8.4	13.8	.	17.9	41.5	92.1	-4.4
5247	18.2	29.8	.	24.4	39.9	95.4	29.2
5248	16.8	3.6	.	37.1	44.3	84.0	6.3
5249	13.0	25.4	.	42.0	42.4	84.1	-11.0
5250	22.6	10.7	.	26.1	46.3	103.8	-9.8
5251	18.6	11.2	.	23.4	39.0	72.9	14.5
5252	17.8	14.0	.	40.6	47.6	67.1	32.8
5253	14.7	8.4	.	31.9	38.2	88.6	-51.6
Mean	15.27	14.02	.	29.75	41.78	86.95	4.97
SD	5.12	8.28	.	7.91	3.72	10.76	25.46
N	10	10	.	10	10	10	10

Gest. = Gestational Day; P-Partum = Post-partum Day
. = No value present

Appendix I. Individual Body Weight Gains – Female Reproductive Groups (continued)

100 mg/kg/day	Total Change (g)
5244	120.9
5245	107.9
5246	102.2
5247	130.5
5248	133.3
5249	117.1
5250	124.1
5251	110.9
5252	146.2
5253	49.3
Mean	114.24
SD	26.27
N	10

Appendix I. Individual Body Weight Gains – Female Reproductive Groups (continued)

300 mg/kg/day	1-8 (g)	8-15 (g)	15-22 (g)	Gest 0-7 (g)	Gest 7-14 (g)	Gest 14-20 (g)	P-Partum 0-4 (g)
5274	4.9	17.9	.	26.4	41.3	88.8	2.2
5275	22.2	19.7	.	20.4	41.6	85.0	15.1
5276	14.3	13.3	46.1	39.3	32.3	71.6	9.7
5277	12.0	0.2	.	5.8 E	18.0 E	1.5 E	.
5278	6.3	22.8	.	36.1	10.8	112.6	2.3
5279	10.3	5.1	.	33.7	33.1	80.5	16.5
5280	2.5	13.5	.	42.8	46.8	104.6	7.7
5281	16.8	18.3	.	30.0	34.4	75.7	6.2
5282	21.9	11.4	.	31.2	44.2	84.7	13.6
5283	29.4	9.1	.	37.3	41.9	87.0	11.7
Mean	14.06	13.13	46.10	33.02	36.27	87.83	9.44
SD	8.61	6.97	.	6.88	10.82	13.13	5.26
N	10	10	1	9	9	9	9

E = Excluded; 5277 was not pregnant.
Gest. = Gestational Day
. = No value present

Appendix I. Individual Body Weight Gains – Female Reproductive Groups (continued)

300 mg/kg/day	Total Change (g)
5274	97.0
5275	109.4
5276	171.4
5277	
5278	100.4
5279	120.4
5280	130.2
5281	123.7
5282	122.8
5283	117.6
Mean	121.43
SD	21.74
N	9

Appendix I. Individual Body Weight Gains – Female Reproductive Groups (continued)

1000 mg/kg/day	1-8 (g)	8-15 (g)	15-22 (g)	Gest 0-7 (g)	Gest 7-14 (g)	Gest 14-20 (g)	P-Partum 0-4 (g)
5304	11.4	19.5	.	2.7	1.1	63.4	-23.6
5305	13.2	11.0	-6.5	[a] .	.	.	.
5306	6.7	12.8	.	17.0	36.1	78.2	-26.1 E[2]
5307	16.5	12.9	.	27.9	38.5	79.8	-49.8
5308	10.6	5.7	.	9.8	1.3	58.3	[b] .
5309	6.5	20.5	.	30.9	44.0	20.0	[c] .
5310	6.3	17.8	.	13.3 E	7.9 E	-16.9 E	.
5311	9.1	19.5	.	24.8	34.0	59.7	[c] .
5312	9.2	13.7	.	-0.9	8.8	72.0	-19.8
5313	6.5	12.9	.	31.6	32.9	74.1	28.9
Mean	9.60	14.63	-6.50	17.98	24.59	63.19	-16.08
SD	3.40	4.66	.	12.85	17.74	19.27	32.82
N	10	10	1	8	8	8	4

[a]5305 had no evidence of mating and was not pregnant; [b]5306 was euthanized on Gestational Day 24; [c]5309 and 5311 were euthanized on Post-Partum Day 0;
E = Excluded; 5310 had evidence of mating but was not pregnant; E[2] = Excluded; 5306 was euthanized Post-Partum Day 2;
Gest. = Gestational Day; P-Partum = Post–partum Day
. = No value present

Appendix I. Individual Body Weight Gains – Female Reproductive Groups (continued)

1000 mg/kg/day	1-8 (g)	8-15 (g)	15-22 (g)	Gest 0-7 (g)	Gest 7-14 (g)	Gest 14-20 (g)	P-Partum 0-4 (g)
5304	11.4	19.5	.	2.7	1.1	63.4	-23.6
5305	13.2	11.0	-6.5	[a]	.	.	.
5306	6.7	12.8	.	17.0	36.1	78.2	-26.1 E[2]
5307	16.5	12.9	.	27.9	38.5	79.8	-49.8
5308	10.6	5.7	.	9.8	1.3	58.3	[b]
5309	6.5	20.5	.	30.9	44.0	20.0	[c]
5310	6.3	17.8	.	13.3 E	7.9 E	-16.9 E	.
5311	9.1	19.5	.	24.8	34.0	59.7	[c]
5312	9.2	13.7	.	-0.9	8.8	72.0	-19.8
5313	6.5	12.9	.	31.6	32.9	74.1	28.9
Mean	9.60	14.63	-6.50	17.98	24.59	63.19	-16.08
SD	3.40	4.66	.	12.85	17.74	19.27	32.82
N	10	10	1	8	8	8	4

[a]5305 had no evidence of mating and was not pregnant; [b]5306 was euthanized on Gestational Day 24; [c]5309 and 5311 were euthanized on Post-Partum Day 0;
E = Excluded; 5310 had evidence of mating but was not pregnant; E[2] = Excluded; 5306 was euthanized Post-Partum Day 2;
Gest. = Gestational Day; P-Partum = Post–partum Day
. = No value present

Appendix I. Individual Body Weight Gains – Female Reproductive Groups (continued)

1000 mg/kg/day	Total Change (g)
5304	10.6
5305	[a].
5306	24.5 E
5307	19.9
5308	[b].
5309	[c].
5310	[a].
5311	[c].
5312	-8.4
5313	116.6
Mean	34.68
SD	55.87
N	4

[a]5305 and 5310 were not pregnant; [b]5308 was euthanized on Gestational Day 24; [c]5309 and 5311 were euthanized on Post-Partum Day 0;
E = Excluded; 5306 was euthanized Post-Partum Day 2;
. = No value present

Appendix J. Individual Food Consumption – Male Toxicity Groups

0 mg/kg/day	Day(s) Relative to Start Date		
	Food Consumption (g/day)	Food Consumption (g/day)	Total Food Consumption (g)
	1 → 8	8 → 15	1 → 15
5204	29.7	29.9	417.4
5205	23.2	23.6	327.4
5206	27.9	27.1	384.7
5207	27.4	26.2	375.4
5208	24.4	23.9	338.2
5209	27.7	29.1	397.9
5210	26.8	28.7	388.4
5211	25.1	29.3	380.7
5212	28.1	27.0	385.4
5213	23.2	24.1	331.1
Mean	26.35	26.88	372.66
SD	2.23	2.39	30.24
N	10	10	10

Appendix J. Individual Food Consumption – Male Toxicity Groups (continued)

100 mg/kg/day	Day(s) Relative to Start Date		
	Mean Food Consumption	Mean Food Consumption	Total Food Consumption
	1 → 8	8 → 15	1 → 15
5234	25.2	23.6	341.9
5235	25.5	26.4	363.6
5236	28.7	32.1	425.6
5237	26.3	26.4	369.0
5238	28.7	29.0	403.7
5239	23.3	25.8	343.8
5240	29.1	31.4	423.4
5241	30.1	32.5	438.5
5242	27.5	26.2	376.1
5243	25.1	26.4	360.5
Mean	26.94	28.00	384.61
SD	2.20	3.06	35.41
N	10	10	10

Appendix J. Individual Food Consumption – Male Toxicity Groups (continued)

300 mg/kg/day	Day(s) Relative to Start Date		
	Mean Food Consumption	Mean Food Consumption	Total Food Consumption
	1 → 8	8 → 15	1 → 15
5264	26.4	27.7	378.8
5265	25.4	26.6	364.0
5266	27.0	26.8	376.4
5267	27.1	27.2	379.9
5268	26.4	26.9	373.3
5269	26.4	23.7	350.4
5270	27.8	28.3	392.9
5271	28.4	30.4	412.1
5272	26.6	29.4	392.1
5273	26.8	27.9	382.8
Mean	26.83	27.49	380.27
SD	0.83	1.81	16.81
N	10	10	10

Appendix J. Individual Food Consumption – Male Toxicity Groups (continued)

1000 mg/kg/day	Day(s) Relative to Start Date		
	Mean Food Consumption	Mean Food Consumption	Total Food Consumption
	1 → 8	8 → 15	1 → 15
5294	27.8	29.4	400.3
5295	26.0	25.9	363.3
5296	23.6	21.9	318.1
5297	22.0	24.5	325.0
5298	29.0	34.3	443.0
5299	25.9	26.4	366.2
5300	30.2	28.5	411.2
5301	32.3	32.6	454.1
5302	24.6	25.9	353.2
5303	26.6	26.7	372.8
Mean	26.79	27.60	380.72
SD	3.12	3.72	45.87
N	10	10	10

Appendix K. Individual Food Consumption – Female Toxicity Groups

0 mg/kg/day	Day(s) Relative to Start Date				
	Mean Food Consumption	Mean Food Consumption	Mean Food Consumption	Mean Food Consumption	Total Food Consumption
	1 → 8	8 → 15	15 → 22	22 → 28	1 → 28
5194	19.9	21.2	22.0	19.0	555.6
5195	17.0	21.8	21.4	18.8	533.7
5196	19.0	19.7	19.8	19.1	523.7
5197	17.3	20.9	21.1	18.9	528.6
5198	19.8	22.9	24.1	21.1	594.4
5199	18.9	20.7	22.0	18.4	541.3
5200	19.2	22.4	22.0	20.8	569.6
5201	22.4	25.4	25.4	22.4	646.5
5202	23.3	23.6	23.0	21.3	617.5
5203	20.9	23.3	24.5	24.2	626.0
Mean	19.77	22.20	22.52	20.38	573.69
SD	2.01	1.68	1.72	1.89	44.61
N	10	10	10	10	10

Appendix K. Individual Food Consumption – Female Toxicity Groups (continued)

100 mg/kg/day	Day(s) Relative to Start Date				
	Mean Food Consumption	Mean Food Consumption	Mean Food Consumption	Mean Food Consumption	Total Food Consumption
	1 → 8	8 → 15	15 → 22	22 → 28	1 → 28
5224	20.5	22.8	21.9	21.4	585.1
5225	18.0	20.6	20.0	19.8	529.4
5226	20.4	23.6	23.7	21.4	602.6
5227	15.2	18.8	18.2	18.3	475.8
5228	19.4	21.6	21.7	20.1	559.3
5229	18.4	19.1	17.7	17.5	491.6
5230	21.2	23.3	23.0	22.3	605.9
5231	20.2	22.2	20.2	20.9	563.8
5232	17.3	18.3	17.5	18.4	483.0
5233	16.6	19.9	20.2	18.4	506.6
Mean	18.73	21.03	20.41	19.86	540.31
SD	1.96	1.94	2.16	1.63	49.64
N	10	10	10	10	10

Appendix K. Individual Food Consumption – Female Toxicity Groups (continued)

300 mg/kg/day	Day(s) Relative to Start Date				
	Mean Food Consumption	Mean Food Consumption	Mean Food Consumption	Mean Food Consumption	Total Food Consumption
	1 → 8	8 → 15	15 → 22	22 → 28	1 → 28
5254	19.0	22.4	22.7	19.9	568.3
5255	20.1	22.4	21.5	22.2	581.4
5256	18.1	20.6	22.1	19.3	540.7
5257	21.4	23.2	22.9	19.9	592.4
5258	19.5	21.1	21.3	19.7	552.5
5259	16.8	19.9	20.1	18.0	506.3
5260	17.5	20.9	20.0	18.6	520.5
5261	17.9	20.5	19.1	19.1	517.2
5262	19.0	21.5	20.0	18.5	534.4
5263	18.9	21.9	20.3	20.6	551.5
Mean	18.83	21.44	21.00	19.60	546.52
SD	1.34	1.03	1.29	1.20	28.27
N	10	10	10	10	10

Appendix K. Individual Food Consumption – Female Toxicity Groups (continued)

1000 mg/kg/day	Day(s) Relative to Start Date				
	Mean Food Consumption	Mean Food Consumption	Mean Food Consumption	Mean Food Consumption	Total Food Consumption
	1 → 8	8 → 15	15 → 22	22 → 28	1 → 28
5284	17.6	20.7	21.3	20.4	539.9
5285	16.0	17.2	17.6	17.9	463.3
5286	19.0	19.7	21.0	19.2	533.2
5287	20.2	22.6	22.7	23.2	598.0
5288	16.4	20.9	19.4	21.0	522.5
5289	16.2	20.6	19.9	15.2	488.7
5290	19.0	23.6	21.7	20.6	573.5
5291	16.7	18.7	20.5	18.3	501.0
5292	17.5	21.2	20.5	22.0	546.4
5293	17.8	20.9	17.7	19.9	513.9
Mean	17.64	20.61	20.23	19.77	528.04
SD	1.39	1.80	1.65	2.26	39.67
N	10	10	10	10	10

Appendix L. Individual Food Consumption – Female Reproductive Groups

0 mg/kg/day	1-8 (g/day)	8-15 (g/day)	Pre-Mating Total (g)	Gest 0-7 (g/day)	Gest 7-14 (g/day)	Gest 14-20 (g/day)	Gestational Total (g)
5214	22.0	21.8	306.5	23.1	25.3	30.0	518.8
5215	22.1	23.4	318.0	23.5	26.8	30.7	535.9
5216	16.4	19.0	248.0	22.0	25.4	27.8	498.5
5217	22.2	23.3	318.3	24.8	26.2	30.4	539.3
5218	19.9	21.0	286.0	20.5	22.4	27.3	463.8
5219	20.7	20.5	288.5	19.2	22.6	24.6	439.7
5220	17.6	19.8	262.3	21.2	24.1	28.2	485.6
5221	22.5	25.9	338.8	21.2	23.4	27.5	477.2
5222	18.4	20.8	274.9	22.0	24.2	25.6	477.0
5223	16.8	19.8	256.2	19.1 E	20.1 E	15.7 E	368.5 E
Mean	19.85	21.54	289.75	21.93	24.49	27.99	492.87
SD	2.37	2.10	30.11	1.68	1.55	2.10	33.42
N	10	10	10	9	9	9	9

Gest. = Gestational Day
E = Excluded, 5223 was not pregnant.

Appendix L. Individual Food Consumption – Female Reproductive Groups (continued)

0 mg/kg/day	P-Partum 0-4 (g/day)	P-Partum Total (g)
5214	40.4	161.7
5215	43.6	174.5
5216	35.9	143.4
5217	43.8	175.0
5218	28.8	115.2
5219	26.8	107.0
5220	32.9	131.5
5221	38.6	154.3
5222	29.2	116.7
5223	*	.
Mean	35.54	142.14
SD	6.48	25.93
N	9	9

*5223 was not pregnant.
P-Partum = Post–partum Day
. = No data collected.

Appendix L. Individual Food Consumption – Female Reproductive Groups (continued)

100 mg/kg/day	1-8 (g/day)	8-15 (g/day)	Pre-Mating Total (g)	Gest 0-7 (g/day)	Gest 7-14 (g/day)	Gest 14-20 (g/day)	Gestational Total (g)
5244	18.0	19.9	264.9	18.4	20.5	23.2	410.8
5245	16.2	18.7	244.0	19.3	23.7	26.3	458.8
5246	16.4	19.0	248.4	18.2	20.4	24.2	415.5
5247	18.8	23.6	296.6	21.3	22.4	24.1	450.3
5248	17.6	18.7	254.5	20.6	21.6	23.1	434.3
5249	19.4	22.0	289.6	22.3	23.4	25.3	472.0
5250	22.3	22.7	315.2	22.4	25.9	32.1	530.3
5251	19.1	20.3	276.1	19.8	20.9	25.0	435.2
5252	19.4	21.9	288.6	24.9	25.0	26.9	510.8
5253	19.2	22.0	288.6	21.5	23.8	25.4	469.7
Mean	18.64	20.88	276.65	20.87	22.77	25.55	458.77
SD	1.74	1.77	23.17	2.06	1.91	2.61	38.76
N	10	10	10	10	10	10	10

Gest. = Gestational Day

Appendix L. Individual Food Consumption – Female Reproductive Groups (continued)

100 mg/kg/day	P-Partum 0-4 (g/day)	P-Partum Total (g)
5244	34.3	137.3
5245	31.1	124.5
5246	23.5	93.8
5247	40.3	161.2
5248	29.8	119.3
5249	28.7	114.6
5250	26.5	106.0
5251	33.6	134.2
5252	38.2	152.8
5253	23.5	94.0
Mean	30.94	123.77
SD	5.74	22.95
N	10	10

P-Partum = Post–partum Day

Appendix L. Individual Food Consumption – Female Reproductive Groups (continued)

300 mg/kg/day	1-8 (g/day)	8-15 (g/day)	Pre-Mating Total (g)	Gest 0-7 (g/day)	Gest 7-14 (g/day)	Gest 14-20 (g/day)	Gestational Total (g)
5274	18.1	21.7	278.6	20.1	22.0	24.7	443.0
5275	21.2	24.1	316.9	19.2	21.9	26.3	444.9
5276	18.5	22.2	284.4	21.7	24.6	28.6	495.4
5277	17.9	20.1	266.0	17.8 E	18.1 E	16.9 E	352.8 E
5278	17.8	24.8	298.5	21.1	24.6	26.9	481.9
5279	19.0	20.6	277.2	19.9	21.3	23.8	431.8
5280	17.7	18.3	252.2	21.5	23.8	27.6	482.2
5281	17.9	20.6	269.2	18.5	20.3	23.4	412.0
5282	22.3	22.3	311.8	22.8	25.8	27.8	506.7
5283	24.0	24.7	340.7	24.3	27.3	30.0	541.2
Mean	19.43	21.93	289.55	21.01	23.52	26.56	471.01
SD	2.24	2.13	27.08	1.80	2.29	2.25	41.12
N	10	10	10	9	9	9	9

Gest = Gestational Day

E = Excluded, 5277 was not pregnant.

Appendix L. Individual Food Consumption – Female Reproductive Groups (continued)

300 mg/kg/day	P-Partum 0-4 (g/day)	P-Partum Total (g)
5274	28.1	112.2
5275	29.9	119.7
5276	38.8	155.2
5277	[a].	.
5278	31.4	125.7
5279	35.7	142.6
5280	30.2	120.7
5281	29.8	119.3
5282	29.9	119.7
5283	38.5	154.1
Mean	32.48	129.91
SD	4.07	16.29
N	9	9

[a]5277 was not pregnant.
P-Partum = Post-partum Day
. = No data collected.

Appendix L. Individual Food Consumption – Female Reproductive Groups (continued)

1000 mg/kg/day	1-8 (g/day)	8-15 (g/day)	Pre-Mating Total (g)	Gest 0-7 (g/day)	Gest 7-14 (g/day)	Gest 14-20 (g/day)	Gestational Total (g)
5304	16.8	22.0	271.1	16.9	15.7	21.4	356.4
5305	16.8	18.7	248.9	.	.	.	.
5306	16.1	15.6	222.1	19.4	19.7	21.6	403.2
5307	19.0	22.5	290.3	21.5	24.0	27.9	486.1
5308	17.6	16.9	241.7	17.7	16.3	20.0	357.2
5309	20.4	25.4	320.8	21.8	25.7	18.6	443.7
5310	19.0	21.4	282.6	17.9 E	17.9 E	13.8 E	333.2 E
5311	18.2	20.4	270.5	18.5	20.4	24.3	418.4
5312	19.6	21.1	284.7	16.9	14.9	19.9	342.0
5313	17.7	21.8	276.3	20.9	20.7	24.0	434.8
Mean	18.12	20.58	270.90	19.21	19.66	22.19	405.23
SD	1.37	2.84	27.77	2.02	3.90	3.05	50.37
N	10	10	10	8	8	8	8

*5305 was not pregnant.

E = Excluded; 5310 was not pregnant.

Gest = Gestational Day

. = No data collected.

Appendix L. Individual Food Consumption – Female Reproductive Groups (continued)

1000 mg/kg/day	P-Partum 0-4 (g/day)	P-Partum Total (g)
5304	16.1	64.4
5305	[a].	.
5306	[b].	.
5307	10.7	42.8
5308	[c].	.
5309	[d].	.
5310	[a].	.
5311	[d].	.
5312	11.1	44.2
5313	34.8	139.3
Mean	18.17	72.68
SD	11.37	45.50
N	4	4

P-Partum = Post--partum Day

[a]5305 and 5310 were not pregnant; [b]5306 was euthanized Post-Partum Day 2; [c]5308 was euthanized on Gestational Day 24; [d]5309 and 5311 were euthanized on Post-Partum Day 0;

. = No value present

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups

0 mg/kg/day	Terminal Body Wt (g)	Adrenal (g)	Adrenal / BW (%Ratio)	Brain (g)	Brain / BW (%Ratio)	Epipidymides (g)	Epipidymides / BW (%Ratio)
5204	432.6	0.0276	0.00638	1.991	0.4602	1.219	0.2818
5205	372.4	0.0405	0.01088	1.942	0.5215	1.309	0.3515
5206	373.2	0.0476	0.01275	1.912	0.5123	1.272	0.3408
5207	405.2	0.0384	0.00948	2.013	0.4968	1.125	0.2776
5208	410.3	0.0542	0.01321	2.177	0.5306	1.356	0.3305
5209	375.8	0 0456	0.01213	2.055	0.5468	1.239	0.3297
5210	414.4	0.0428	0.01033	2.038	0.4918	1.233	0.2975
5211	397.2	0.0457	0.01151	2.021	0.5088	1.313	0.3306
5212	385.2	0.0465	0.01207	2.100	0.5452	1.103	0.2863
5213	365.4	0.0373	0.01021	1.901	0.5203	1.404	0.3842
Mean	393.17	0.04262	0.010894	2.0150	0.51343	1.2573	0.32106
SD	22.18	0.00722	0.001980	0.0851	0.02609	0.0948	0.03456
N	10	10	10	10	10	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

0 mg/kg/day	Heart (g)	Heart / BW (%Ratio)	Kidney (g)	Kidney / BW (%Ratio)	Liver (g)	Liver / BW (%Ratio)	Prostate (g)
5204	1.424	0.3292	2.946	0.6810	12.338	2.8521	0.630
5205	1.124	0.3018	2.581	0.6931	9.797	2.6308	0.715
5206	1.310	0.3510	2.563	0.6868	9.872	2.6452	0.953
5207	1.262	0.3115	2.719	0.6710	9.946	2.4546	0.626
5208	1.259	0.3068	2.909	0.7090	9.608	2.3417	1.075
5209	1.152	0.3065	2.491	0.6629	9.377	2.4952	0.776
5210	1.399	0.3376	2.821	0.6807	10.568	2.5502	1.011
5211	1.268	0.3192	2.599	0.6543	9.498	2.3912	0.772
5212	1.245	0.3232	2.633	0.6835	10.276	2.6677	1.131
5213	1.424	0.3897	2.632	0.7203	9.071	2.4825	0.891
Mean	1.2867	0.32766	2.6894	0.68426	10.0351	2.55112	0.8580
SD	0.1048	0.02666	0.1542	0.01985	0.9171	0.15127	0.1812
N	10	10	10	10	10	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

0 mg/kg/day	Prostate / BW (%Ratio)	Seminal Vessicle (g)	Seminal Vess/ BW (%Ratio)	Spleen (g)	Spleen / BW (%Ratio)	Testes (g)	Testes / BW (%Ratio)
5204	0.1456	1.754	0.4055	0.749	0.1731	3.718	0.8595
5205	0.1920	1.653	0.4439	0.751	0.2017	3.419	0.9181
5206	0.2554	1.564	0.4191	0.786	0.2106	3.363	0.9011
5207	0.1545	1.289	0.3181	0.590	0.1456	3.132	0.7730
5208	0.2620	1.768	0.4309	0.740	0.1804	3.786	0.9227
5209	0.2065	2.033	0.5410	0.639	0.1700	3.422	0.9106
5210	0.2440	1.696	0.4093	0.634	0.1530	3.993	0.9636
5211	0.1944	1.605	0.4041	0.720	0.1813	3.597	0.9056
5212	0.2936	1.712	0.4444	0.615	0.1597	3.661	0.9504
5213	0.2438	1.805	0.4940	0.695	0.1902	3.498	0.9573
Mean	0.21918	1.6879	0.43102	0.6919	0.17655	3.5589	0.90618
SD	0.04832	0.1906	0.05882	0.0676	0.02073	0.2449	0.05603
N	10	10	10	10	10	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

0 mg/kg/day	Thymus (g)	Thymus / BW (%Ratio)
5204	0.439	0.1015
5205	0.324	0.0870
5206	0.288	0.0772
5207	0.632	0.1560
5208	0.402	0.0980
5209	0.392	0.1043
5210	0.327	0.0789
5211	0.446	0.1123
5212	0.451	0.1171
5213	0.234	0.0640
Mean	0.3935	0.09962
SD	0.1110	0.02588
N	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

100 mg/kg/day	Terminal Body Wt (g)	Adrenal (g)	Adrenal / BW (%Ratio)	Brain (g)	Brain / BW (%Ratio)	Epipidymides (g)	Epididymides- / BW (%Ratio)
5234	351.0	0.0423	0.01205	1.795	0.5114	1.281	0.3650
5235	410.7	0.0472	0.01149	2.066	0.5030	1.188	0.2893
5236	413.3	0.0698	0.01689	2.141	0.5180	1.239	0.2998
5237	431.2	0.0474	0.01099	2.096	0.4861	1.438	0.3335
5238	407.4	0.0355	0.00871	2.043	0.5015	1.112	0.2730
5239	381.8	0.0530	0.01388	1.957	0.5126	1.064	0.2787
5240	395.4	0.0527	0.01333	2.114	0.5346	1.314	0.3323
5241	451.1	0.0501	0.01111	2.104	0.4664	1.138	0.2523
5242	403.1	0.0508	0.01260	1.920	0 4763	1.309	0.3247
5243	406.5	0.0638	0.01569	2.047	0.5036	1.410	0.3469
Mean	405.15	0.05126	0.012675	2.0283	0.50135	1.2493	0.30953
SD	26.81	0.00982	0.002393	0.1073	0.02028	0.1246	0.03631
N	10	10	10	10	10	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

100 mg/kg/day	Heart (g)	Heart / BW (%Ratio)	Kidney (g)	Kidney / BW (%Ratio)	Liver (g)	Liver / BW (%Ratio)	Prostate (g)
5234	1.209	0.3444	2.523	0.7188	8.741	2.4903	0.535
5235	1.202	0.2927	2.551	0.6211	10.679	2.6002	0.886
5236	1.351	0.3269	3.142	0.7602	10.945	2.6482	0.782
5237	1.371	0.3179	2.587	0.6000	11.828	2.7430	0.714
5238	1.363	0.3346	2.787	0.6841	10.506	2.5788	0.878
5239	1.133	0.2968	2.624	0.6873	11.397	2.9851	0.581
5240	1.296	0.3278	2.956	0.7476	10.770	2.7238	0.651
5241	1.374	0.3046	3.278	0.7267	13.633	3.0222	0.662
5242	1.229	0.3049	2.956	0.7333	11.688	2.8995	0.798
5243	1.276	0.3139	2.874	0.7070	10.918	2.6859	0.827
Mean	1.2804	0.31644	2.8278	0.69861	11.1105	2.73770	0.7314
SD	0.0848	0.01695	0.2597	0.05243	1.2311	0.17782	0.1222
N	10	10	10	10	10	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

100 mg/kg/day	Prostate / BW (%Ratio)	Seminal Vessicle (g)	Seminal Vess/ BW (%Ratio)	Spleen (g)	Spleen / BW (%Ratio)	Testes (g)	Testes / BW (%Ratio)
5234	0.1524	1.438	0.4097	0.577	0.1644	3.627	1.0333
5235	0.2157	1.627	0.3962	0.719	0.1751	3.287	0.8003
5236	0.1892	1.869	0.4522	0.699	0.1691	3.641	0.8810
5237	0.1656	1.819	0.4218	0.722	0.1674	3.782	0.8771
5238	0.2155	1.768	0.4340	0.727	0.1784	3.535	0.8677
5239	0.1522	1.642	0.4301	0.752	0.1970	3.059	0.8012
5240	0.1646	1.906	0.4820	0.672	0.1700	3.716	0.9398
5241	0.1468	1.397	0.3097	0.571	0.1266	3.928	0.8708
5242	0.1980	1.956	0.4852	0.688	0.1707	3.508	0.8703
5243	0.2034	1.858	0.4571	0.822	0.2022	3.393	0.8347
Mean	0.18034	1.7280	0.42780	0.6949	0.17209	3.5476	0.87761
SD	0.02703	0.1948	0.05061	0.0757	0.02039	0.2528	0.06830
N	10	10	10	10	10	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

100 mg/kg/day	Thymus (g)	Thymus / BW (%Ratio)
5234	0.416	0.1185
5235	0.398	0.0969
5236	0.366	0.0886
5237	0.599	0.1389
5238	0.247	0.0606
5239	0.364	0.0953
5240	0.540	0.1366
5241	0.491	0.1088
5242	0.472	0.1171
5243	0.458	0.1127
Mean	0.4351	0.10740
SD	0.0999	0.02331
N	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

300 mg/kg/day	Terminal Body Wt (g)	Adrenal (g)	Adrenal / BW (%Ratio)	Brain (g)	Brain / BW (%Ratio)	Epididymides (g)	Epididymides / BW (%Ratio)
5264	393.3	0.0466	0.01185	2.063	0.5245	1.325	0.3369
5265	374.5	0.0456	0.01218	2.069	0.5525	1.084	0.2895
5266	431.8	0.0407	0.00943	2.193	0.5079	1.173	0.2717
5267	411.8	0.0564	0.01370	2.128	0.5168	1.117	0.2712
5268	402.5	0.0557	0.01384	1.962	0.4875	1.216	0.3021
5269	376.5	0.0484	0.01286	1.937	0.5145	1.201	0.3190
5270	421.5	0.0605	0.01435	1.981	0.4700	1.305	0.3096
5271	412.9	0.0525	0.01271	1.769	0.4284	1.334	0.3231
5272	408.1	0.0614	0.01505	2.389	0.5854	1.135	0.2781
5273	362.4	0.0552	0.01523	1.990	0.5491	1.095	0.3022
Mean	399.53	0.05230	0.013119	2.0481	0.51365	1.1985	0.30033
SD	22.39	0.00678	0.001730	0.1666	0.04463	0.0950	0.02255
N	10	10	10	10	10	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

300 mg/kg/day	Heart (g)	Heart / BW (%Ratio)	Kidney (g)	Kidney / BW (%Ratio)	Liver (g)	Liver / BW (%Ratio)	Prostate (g)
5264	1.396	0.3549	2.871	0.7300	11.935	3.0346	0.690
5265	1.168	0.3119	2.443	0.6523	10.336	2.7599	0.653
5266	1.291	0.2990	3.079	0.7131	11.747	2.7205	0.631
5267	1.293	0.3140	2.477	0.6015	11.869	2.8822	0.808
5268	1.323	0.3287	2.755	0.6845	10.944	2.7190	0.855
5269	1.152	0.3060	2.753	0.7312	11.057	2.9368	0.877
5270	1.317	0.3125	2.674	0.6344	11.490	2.7260	0.686
5271	1.364	0.3303	2.723	0.6595	12.592	3.0496	0.791
5272	1.232	0.3019	2.980	0.7302	11.952	2.9287	0.606
5273	1.336	0.3687	2.368	0.6534	9.963	2.7492	0.684
Mean	1.2872	0.32278	2.7123	0.67901	11.3885	2.85065	0.7281
SD	0.0802	0.02314	0.2316	0.04580	0.8084	0.13177	0.0965
N	10	10	10	10	10	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

300 mg/kg/day	Prostate / BW (%Ratio)	Seminal Vessicle (g)	Seminal Vess/ BW (%Ratio)	Spleen (g)	Spleen / BW (%Ratio)	Testes (g)	Testes / BW (%Ratio)
5264	0.1754	1.560	0.3966	0.596	0.1515	3.501	0.8902
5265	0.1744	1.354	0.3615	0.716	0.1912	3.354	0.8956
5266	0.1461	1.233	0.2855	0.653	0.1512	3.435	0.7955
5267	0.1962	1.668	0.4051	0.589	0.1430	3.279	0.7963
5268	0.2124	1.538	0.3821	0.642	0.1595	3.284	0.8159
5269	0.2329	2.086	0.5541	0.675	0.1793	3.903	1.0367
5270	0.1628	1.599	0.3794	0.781	0.1853	3.782	0.8973
5271	0.1916	1.806	0.4374	0.826	0.2000	3.288	0.7963
5272	0.1485	1.398	0.3426	0.638	0.1563	3.849	0.9432
5273	0.1887	1.425	0.3932	0.584	0.1611	3.191	0.8805
Mean	0.18291	1.5667	0.39375	0.6700	0.16786	3.4866	0.87473
SD	0.02735	0.2459	0.06948	0.0819	0.01950	0.2632	0.07757
N	10	10	10	10	10	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

300 mg/kg/day	Thymus (g)	Thymus / BW (%Ratio)
5264	0.466	0.1185
5265	0.572	0.1527
5266	0.317	0.0734
5267	0.273	0.0663
5268	0.435	0.1081
5269	0.411	0.1092
5270	0.371	0.0880
5271	0.396	0.0959
5272	0.633	0.1551
5273	0.531	0.1465
Mean	0.4405	0.11137
SD	0.1126	0.03194
N	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

1000 mg/kg/day	Terminal Body Wt (g)	Adrenal (g)	Adrenal / BW (%Ratio)	Brain (g)	Brain / BW (%Ratio)	Epididymides (g)	Epididymides / BW (%Ratio)
5294	382.2	0.0492	0.01287	2.008	0.5254	1.174	0.3072
5295	394.1	0.0591	0.01500	2.033	0.5159	1.262	0.3202
5296	358.8	0.0426	0.01187	2.057	0.5733	1.077	0.3002
5297	347.8	0.0523	0.01504	1.944	0.5589	1.142	0.3283
5298	385.2	0.0530	0.01376	2.020	0.5244	1.220	0.3167
5299	354.7	0.0518	0.01460	1.937	0.5461	1.083	0.3053
5300	434.5	0.0421	0.00969	1.933	0.4449	1.375	0.3165
5301	442.8	0.0523	0.01181	1.903	0.4298	1.323	0.2988
5302	386.8	0.0464	0.01200	1.915	0.4951	1.068	0.2761
5303	388.5	0.0506	0.01302	2.029	0.5223	1.179	0.3035
Mean	387.54	0.04994	0.012966	1.9779	0.51360	1.1903	0.30728
SD	31.31	0.00513	0.001698	0.0568	0.04607	0.1053	0.01452
N	10	10	10	10	10	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

1000 mg/kg/day	Heart (g)	Heart / BW (%Ratio)	Kidney (g)	Kidney / BW (%Ratio)	Liver (g)	Liver / BW (%Ratio)	Prostate (g)
5294	1.306	0.3417	2.724	0.7127	11.967	3.1311	0.562
5295	1.548	0.3928	2.705	0.6864	12.447	3.1583	0.747
5296	1.147	0.3197	2.644	0.7369	9.749	2.7171	0.571
5297	1.165	0.3350	2.464	0.7085	10.131	2.9129	0.683
5298	1.204	0.3126	2.914	0.7565	12.416	3.2233	0.873
5299	1.381	0.3893	2.478	0.6986	10.640	2.9997	0.777
5300	1.571	0.3616	2.758	0.6348	14.976	3.4467	0.720
5301	1.338	0.3022	2.601	0.5874	12.927	2.9194	0.823
5302	1.134	0.2932	2.845	0.7355	9.995	2.5840	0.759
5303	1.202	0.3094	2.595	0.6680	10.983	2.8270	0.728
Mean	1.2996	0.33573	2.6728	0.69252	11.6231	2.99195	0.7243
SD	0.1602	0.03537	0.1462	0.05125	1.6375	0.25562	0.0988
N	10	10	10	10	10	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

1000 mg/kg/day	Prostate / BW (%Ratio)	Seminal Vessicle (g)	Seminal Vess/ BW (%Ratio)	Spleen (g)	Spleen / BW (%Ratio)	Testes (g)	Testes / BW (%Ratio)
5294	0.1470	1.581	0.4137	0.723	0.1892	3.460	0.9053
5295	0.1895	2.145	0.5443	0.803	0.2038	3.584	0.9094
5296	0.1591	1.479	0.4122	0.626	0.1745	3.514	0.9794
5297	0.1964	1.806	0.5193	0.555	0.1596	3.373	0.9698
5298	0.2266	2.048	0.5317	0.744	0.1931	3.479	0.9032
5299	0.2191	1.504	0.4240	0.655	0.1847	3.197	0.9013
5300	0.1657	1.753	0.4035	0.726	0.1671	3.616	0.8322
5301	0.1859	1.793	0.4049	0.687	0.1551	3.394	0.7665
5302	0.1962	2.119	0.5478	0.644	0.1665	3.686	0.9529
5303	0.1874	1.709	0.4399	0.671	0.1727	3.416	0.8793
Mean	0.18730	1.7937	0.46412	0.6834	0.17662	3.4719	0.89993
SD	0.02495	0.2429	0.06294	0.0697	0.01562	0.1397	0.06408
N	10	10	10	10	10	10	10

Appendix M. Individual Organ and Organ / Body Weight Ratios – Male Toxicity Groups (continued)

1000 mg/kg/day	Thymus (g)	Thymus / BW (%Ratio)
5294	0.496	0.1298
5295	0.468	0.1188
5296	0.289	0.0805
5297	0.253	0.0727
5298	0.345	0.0896
5299	0.323	0.0911
5300	0.469	0.1079
5301	0.433	0.0978
5302	0.281	0.0726
5303	0.282	0.0726
Mean	0.3639	0.09334
SD	0.0929	0.02020
N	10	10

Appendix N. Individual Organ and Organ / Body Weight Ratios – Female Toxicity Groups

0 mg/kg/day	Terminal Body Wt (g)	Adrenal (g)	Adrenal / BW (%Ratio)	Brain (g)	Brain / BW (%Ratio)	Heart (g)	Heart / BW (%Ratio)
5194	249.7	0.0618	0.02475	2.069	0.8286	0.849	0.3400
5195	209.6	0.0595	0.02839	1.795	0.8564	0.797	0.3802
5196	237.5	0.0676	0.02846	1.874	0.7891	0.799	0.3364
5197	241.2	0.0596	0.02471	2.110 [a]	0.8748	0.849	0.3520
5198	261.6	0.0844	0.03226	1.871	0.7152	1.021	0.3903
5199	251.7	0.0643	0.02555	1.842	0.7318	0.909	0.3611
5200	237.2	0.0608	0.02563	2.001	0.8436	0.795	0.3352
5201	256.4	0.0756	0.02949	1.939	0.7562	0.858	0.3346
5202	268.1	0.0621	0.02316	1.947	0.7262	0.943	0.3517
5203	257.1	0.0773	0.03007	1.686	0.6558	0.854	0.3322
Mean	247.01	0.06730	0.027247	1.9134	0.77777	0.8674	0.35138
SD	16.66	0.00876	0.002901	0.1276	0.07201	0.0722	0.02030
N	10	10	10	10	10	10	10

[a]Fixed organ weight; 5197 brain inadvertently weighed late.

Appendix N. Individual Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

0 mg/kg/day	Kidney (g)	Kidney / BW (%Ratio)	Liver (g)	Liver / BW (%Ratio)	Ovaries (g)	Ovaries / BW (%Ratio)	Spleen (g)
5194	1.666	0.6672	6.905	2.7653	0.1365	0.05467	0.662
5195	1.536	0.7328	5.959	2.8430	0.1474	0.07032	0.511
5196	1.660	0.6989	6.300	2.6526	0.1441	0.06067	0.397
5197	1.614	0.6692	6.907	2.8636	0.1297	0.05377	0.569
5198	1.910	0.7301	8.191	3.1311	0.1848	0.07064	0.469
5199	1.983	0.7878	6.920	2.7493	0.1420	0.05642	0.605
5200	1.684	0.7099	6.739	2.8411	0.1528	0.06442	0.600
5201	1.819	0.7094	7.306	2.8495	0.1421	0.05542	0.583
5202	1.882	0.7020	7.523	2.8060	0.1590	0.05931	0.764
5203	1.639	0.6375	7.072	2.7507	0.1555	0.06048	0.655
Mean	1.7393	0.70450	6.9822	2.82522	0.14939	0.060612	0.5815
SD	0.1480	0.04167	0.6195	0.12528	0.01523	0.006127	0.1043
N	10	10	10	10	10	10	10

Appendix N. Individual Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

0 mg/kg/day	Spleen / BW (%Ratio)	Thymus (g)	Thymus / BW (%Ratio)	Uterus (g)	Uterus / BW (%Ratio)
5194	0.2651	0.513	0.2054	0.423	0.16940
5195	0.2438	0.291	0.1388	0.407	0.19418
5196	0.1672	0.318	0.1339	0.467	0.19663
5197	0.2359	0.323	0.1339	0.501	0.20771
5198	0.1793	0.421	0.1609	0.438	0.16743
5199	0.2404	0.400	0.1589	0.607	0.24116
5200	0.2530	0.240	0.1012	0.407	0.17159
5201	0.2274	0.362	0.1412	0.455	0.17746
5202	0.2850	0.443	0.1652	1.254	0.46774
5203	0.2548	0.304	0.1182	0.657	0.25554
Mean	0.23517	0.3615	0.14578	0.5616	0.224884
SD	0.03650	0.0823	0.02875	0.2575	0.090484
N	10	10	10	10	10

Appendix N. Individual Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

100 mg/kg/day	Terminal Body Wt (g)	Adrenal (g)	Adrenal / BW (%Ratio)	Brain (g)	Brain / BW (%Ratio)	Heart (g)	Heart / BW (%Ratio)
5224	255.8	0.0617	0.02412	1.974	0.7717	0.862	0.3370
5225	249.4	0.0545	0.02185	1.820	0.7298	0.912	0.3657
5226	239.5	0.0682	0.02848	1.867	0.7795	0.857	0.3578
5227	226.9	0.0565	0.02490	2.100	0.9255	0.825	0.3636
5228	239.8	0.0710	0.02961	1.858	0.7748	0.949	0.3957
5229	239.6	0.0728	0.03038	1.982	0.8272	0.965	0.4028
5230	274.1	0.0607	0.02215	1.965	0.7169	0.901	0.3287
5231	255.3	0.0731	0.02863	1.738	0.6808	0.883	0.3459
5232	216.5	0.0533	0.02462	1.871	0.8642	0.749	0.3460
5233	218.0	0.0541	0.02482	1.865	0.8555	0.763	0.3500
Mean	241.49	0.06259	0.025956	1.9040	0.79259	0.8666	0.35931
SD	18.02	0.00804	0.003080	0.1021	0.07532	0.0718	0.02394
N	10	10	10	10	10	10	10

Appendix N. Individual Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

100 mg/kg/day	Kidney (g)	Kidney / BW (%Ratio)	Liver (g)	Liver / BW (%Ratio)	Ovaries (g)	Ovaries / BW (%Ratio)	Spleen (g)
5224	1.748	0.6833	6.924	2.7068	0.1404	0.05489	0.490
5225	1.440	0.5774	6.942	2.7835	0.1193	0.04783	0.559
5226	1.596	0.6664	6.720	2.8058	0.1195	0.04990	0.469
5227	1.627	0.7171	6.305	2.7788	0.1482	0.06532	0.456
5228	1.655	0.6902	6.783	2.8286	0.1615	0.06735	0.521
5229	1.921	0.8018	6.557	2.7366	0.1201	0.05013	0.574
5230	1.772	0.6465	8.340	3.0427	0.4514	0.16468	1.358
5231	1.960	0.7677	7.723	3.0251	0.1316	0.05155	0.608
5232	1.661	0.7672	6.027	2.7838	0.1072	0.04952	0.383
5233	1.597	0.7326	6.057	2.7784	0.1260	0.05780	0.419
Mean	1.6977	0.70501	6.8378	2.82702	0.16252	0.065895	0.5837
SD	0.1570	0.06663	0.7230	0.11414	0.10275	0.035361	0.2810
N	10	10	10	10	10	10	10

Appendix N. Individual Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

100 mg/kg/day	Spleen / BW (%Ratio)	Thymus (g)	Thymus / BW (%Ratio)	Uterus (g)	Uterus / BW (%Ratio)
5224	0.1916	0.313	0.1224	0.961	0.37568
5225	0.2241	0.540	0.2165	0.415	0.16640
5226	0.1958	0.521	0.2175	1.059	0.44217
5227	0.2010	0.260	0.1146	0.423	0.18643
5228	0.2173	0.500	0.2085	0.407	0.16972
5229	0.2396	0.394	0.1644	0.975	0.40693
5230	0.4954	0.425	0.1551	0.166	0.06056
5231	0.2382	0.377	0.1477	0.703	0.27536
5232	0.1769	0.311	0.1436	0.712	0.32887
5233	0.1922	0.268	0.1229	0.440	0.20183
Mean	0.23720	0.3909	0.16133	0.6261	0.261396
SD	0.09311	0.1039	0.03966	0.3009	0.124096
N	10	10	10	10	10

Appendix N. Individual Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

300 mg/kg/day	Terminal Body Wt (g)	Adrenal (g)	Adrenal / BW (%Ratio)	Brain (g)	Brain / BW (%Ratio)	Heart (g)	Heart / BW (%Ratio)
5254	266.1	0.0367	0.01379	1.760	0.6614	0.912	0.3427
5255	263.8	0.0724	0.02745	1.853	0.7024	0.952	0.3609
5256	234.5	0.0625	0.02665	1.903	0.8115	0.770	0.3284
5257	259.6	0.0648	0.02496	1.823	0.7022	0.870	0.3351
5258	244.7	0.0715	0.02922	1.938	0.7920	0.832	0.3400
5259	222.0	0.0542	0.02441	1.903	0.8572	0.752	0.3387
5260	243.2	0.0638	0.02623	1.880	0.7730	0.851	0.3499
5261	220.0	0.0584	0.02655	1.814	0.8245	0.734	0.3336
5262	245.2	0.0552	0.02251	1.998	0.8148	0.787	0.3210
5263	238.3	0.0536	0.02249	1.941	0.8145	0.819	0.3437
Mean	243.74	0.05931	0.024427	1.8813	0.77537	0.8279	0.33940
SD	16.02	0.01037	0.004289	0.0705	0.06451	0.0703	0.01113
N	10	10	10	10	10	10	10

Appendix N. Individual Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

300 mg/kg/day	Kidney (g)	Kidney / BW (%Ratio)	Liver (g)	Liver / BW (%Ratio)	Ovaries (g)	Ovaries / BW (%Ratio)	Spleen (g)
5254	1.759	0.6610	8.456	3.1778	0.1162	0.04367	0.674
5255	1.631	0.6183	7.726	2.9287	0.1392	0.05277	0.684
5256	1.633	0.6964	7.078	3.0183	0.1091	0.04652	0.525
5257	1.703	0.6560	7.348	2.8305	0.1318	0.05077	0.496
5258	1.848	0.7552	7.871	3.2166	0.1663	0.06796	0.468
5259	1.401	0.6311	6.326	2.8495	0.1413	0.06365	0.490
5260	1.771	0.7282	7.262	2.9860	0.1367	0.05621	0.472
5261	1.524	0.6927	6.248	2.8400	0.0970	0.04409	0.440
5262	1.924	0.7847	6.958	2.8377	0.1279	0.05216	0.486
5263	1.681	0.7054	6.895	2.8934	0.1297	0.05443	0.684
Mean	1.6875	0.69290	7.2168	2.95786	0.12952	0.053223	0.5419
SD	0.1524	0.05321	0.6802	0.14183	0.01914	0.007910	0.0982
N	10	10	10	10	10	10	10

Appendix N. Individual Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

300 mg/kg/day	Spleen / BW (%Ratio)	Thymus (g)	Thymus / BW (%Ratio)	Uterus (g)	Uterus / BW (%Ratio)
5254	0.2533	0.624	0.2345	0.438	0.16460
5255	0.2593	0.581	0.2202	0.383	0.14519
5256	0.2239	0.344	0.1467	0.457	0.19488
5257	0.1911	0.296	0.1140	0.559	0.21533
5258	0.1913	0.525	0.2145	0.508	0.20760
5259	0.2207	0.415	0.1869	0.513	0.23108
5260	0.1941	0.312	0.1283	0.351	0.14433
5261	0.2000	0.351	0.1595	0.459	0.20864
5262	0.1982	0.409	0.1668	0.465	0.18964
5263	0.2870	0.351	0.1473	0.560	0.23500
Mean	0.22188	0.4208	0.17189	0.4693	0.193628
SD	0.03389	0.1160	0.04079	0.0686	0.032733
N	10	10	10	10	10

Appendix N. Individual Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

1000 mg/kg/day	Terminal Body Wt (g)	Adrenal (g)	Adrenal / BW (%Ratio)	Brain (g)	Brain / BW (%Ratio)	Heart (g)	Heart / BW (%Ratio)
5284	244.7	0.0581	0.02374	1.844	0.7536	0.764	0.3122
5285	199.9	0.0625	0.03127	1.780	0.8904	0.750	0.3752
5286	210.3	0.0599	0.02848	1.869	0.8887	0.877	0.4170
5287	232.6	0.0602	0.02588	2.017	0.8672	0.921	0.3960
5288	202.6	0.0576	0.02843	1.761	0.8692	0.797	0.3934
5289	198.8	0.0624	0.03139	1.768	0.8893	0.730	0.3672
5290	243.8	0.0448	0.01838	1.838	0.7539	0.854	0.3503
5291	220.3	0.0553	0.02510	1.844	0.8370	0.841	0.3818
5292	240.0	0.0719	0.02996	1.944	0.8100	0.859	0.3579
5293	216.5	0.0675	0.03118	1.777	0.8208	0.751	0.3469
Mean	220.95	0.06002	0.027381	1.8442	0.83802	0.8144	0.36978
SD	18.22	0.00725	0.004167	0.0829	0.05277	0.0647	0.02984
N	10	10	10	10	10	10	10

Appendix N. Individual Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

1000 mg/kg/day	Kidney (g)	Kidney / BW (%Ratio)	Liver (g)	Liver / BW (%Ratio)	Ovaries (g)	Ovaries / BW (%Ratio)	Spleen (g)
5284	1.634	0.6678	8.163	3.3359	0.1496	0.06114	0.528
5285	1.683	0.8419	7.004	3.5038	0.0873	0.04367	0.479
5286	1.701	0.8088	8.622	4.0999	0.1314	0.06248	0.483
5287	1.899	0.8164	8.509	3.6582	0.1203	0.05172	0.568
5288	1.666	0.8223	8.017	3.9571	0.1126	0.05558	0.435
5289	1.921	0.9663	7.774	3.9105	0.1019	0.05126	0.379
5290	1.773	0.7272	8.107	3.3253	0.1498	0.06144	0.562
5291	1.625	0.7376	7.310	3.3182	0.1429	0.06487	0.482
5292	2.043	0.8513	8.563	3.5679	0.1102	0.04592	0.607
5293	1.783	0.8236	7.391	3.4139	0.1321	0.06102	0.406
Mean	1.7728	0.80632	7.9460	3.60905	0.12381	0.055909	0.4929
SD	0.1401	0.08145	0.5639	0.28788	0.02100	0.007426	0.0738
N	10	10	10	10	10	10	10

Appendix N. Individual Organ and Organ / Body Weight Ratios – Female Toxicity Groups (continued)

1000 mg/kg/day	Spleen / BW (%Ratio)	Thymus (g)	Thymus / BW (%Ratio)	Uterus (g)	Uterus / BW (%Ratio)
5284	0.2158	0.331	0.1353	0.378	0.15447
5285	0.2396	0.233	0.1166	0.447	0.22361
5286	0.2297	0.243	0.1155	0.501	0.23823
5287	0.2442	0.314	0.1350	0.408	0.17541
5288	0.2147	0.248	0.1224	0.486	0.23988
5289	0.1906	0.313	0.1574	0.381	0.19165
5290	0.2305	0.320	0.1313	0.459	0.18827
5291	0.2188	0.332	0.1507	0.449	0.20381
5292	0.2529	0.344	0.1433	0.596	0.24833
5293	0.1875	0.352	0.1626	0.438	0.20231
Mean	0.22244	0.3030	0.13701	0.4543	0.206598
SD	0.02150	0.0444	0.01644	0.0641	0.030578
N	10	10	10	10	10

Appendix O. Individual Reproductive Parameter Data

Litter Data

Animal ID	Day 0 Live Male Pups	Day 0 Live Female Pups	Day 0 Dead Male Pups	Day 0 Dead Female Pups	Day 0 Dead Undetermined Sex	Day 0 Total Male/Female Ratio	Day 0 Total Live Pups	Day 0 Total Litter Size	Day 0 % Live Pups[1]	Day 0 Live Litter Weight (g)	Day 0 Live Average Pup weight (g)	Day 4 Live Male Pups	Day 4 Live Female Pups	Day 4 Total Male/Female Ratio	Day 4 Total Live Pups	Day 4 % Live Pups[1]	Day 4 Live Litter Weight (g)	Day 4 Live Average Pup weight (g)	Day 4 Average Pup Weight Change (g)
Group 1 0 mkd																			
D5214	7	8	0	0	0	0.9	15	15	100.0	99.7	6.6	7	8	0.9	15	100.0	176.4	11.8	5.2
D5215	8	10	0	0	0	0.8	18	18	100.0	110.2	6.1	8	10	0.8	18	100.0	184.6	10.3	4.2
D5216	8	8	0	0	0	1.0	16	16	100.0	109.5	6.8	8	8	1.0	16	100.0	181.2	11.3	4.5
D5217	10	10	0	0	0	1.0	20	20	100.0	129.9	6.5	10	10	1.0	20	100.0	215.1	10.8	4.3
D5218	7	8	0	0	0	0.9	15	15	100.0	89.7	6.0	7	8	0.9	15	100.0	138.2	9.2	3.2
D5219	5	10	0	0	0	0.5	15	15	100.0	85.2	5.7	5	10	0.5	15	100.0	141.4	9.4	3.7
D5220	9	8	0	0	0	1.1	17	17	100.0	102.1	6.0	9	8	1.1	17	100.0	161.7	9.5	3.5
D5221	9	6	0	0	0	1.5	15	15	100.0	102.3	6.8	9	6	1.5	15	100.0	168.5	11.2	4.4
D5222	10	7	0	0	0	1.4	17	17	100.0	98.6	5.8	10	7	1.4	17	100.0	157.5	9.3	3.5
D5223[a]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MEAN	**8.1**	**8.3**	**0.0**	**0.0**	**0.0**	**1.0**	**16.4**	**16.4**	**100.0**	**103.0**	**6.3**	**8.1**	**8.3**	**1.0**	**16.4**	**100.0**	**169.4**	**10.3**	**4.1**
SD	**1.6**	**1.4**	**0.0**	**0.0**	**0.0**	**0.3**	**1.7**	**1.7**	**0.0**	**13.0**	**0.4**	**1.6**	**1.4**	**0.3**	**1.7**	**0.0**	**23.6**	**1.0**	**0.6**
N	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**

[a] Evidence of mating but not pregnant

\- No data

[1] % Live Pups = (Total Live Pups/Total Litter Size)*100

Appendix O. Individual Reproductive Parameter Data (continued)

	Mating and Fertility Data			Loss of Offspring		
Animal ID	Length of Gestation	Implantations	Corpora Lutea	% Pre-Implantation[1]	% Post-Implantation[2]	% Post-Natal[3]
Group 1						
0 mkd						
D5214	22	16	18	11.1	6.3	0.0
D5215	22	18	24	25.0	0.0	0.0
D5216	22	16	21	23.8	0.0	0.0
D5217	21	22	22	0.0	9.1	0.0
D5218	21	17	17	0.0	11.8	0.0
D5219	21	16	16	0.0	6.3	0.0
D5220	21	18	18	0.0	5.6	0.0
D5221	22	17	18	5.6	11.8	0.0
D5222	21	17	17	0.0	0.0	0.0
D5223[a]	-	-	-	-	-	-
MEAN	**21.4**	**17.4**	**19.0**	**7.3**	**5.7**	**0.0**
SD	**0.5**	**1.9**	**2.7**	**10.4**	**4.8**	**0.0**
N	**9**	**9**	**9**	**9**	**9**	**9**

[a]Evidence of mating but not pregnant

\- No data

[1] % Preimplantation Loss = ((# Corpora Lutea - # Implantations) / # Corpora Lutea) * 100

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

[3] % Post-natal Loss = ((# live pups Day 0 - # live pups Day 4) / # Live pups Day 0) *100

Appendix O. Individual Reproductive Parameter Data (continued)

Litter Data

	Day 0											Day 4							
Animal ID	Live Male Pups	Live Female Pups	Dead Male Pups	Dead Female Pups	Dead Undetermined Sex	Total Male/Female Ratio	Total Live Pups	Total Litter Size	% Live Pups[1]	Live Litter Weight (g)	Live Average Pup weight (g)	Live Male Pups	Live Female Pups	Total Male/Female Ratio	Total Live Pups	% Live Pups[1]	Live Litter Weight (g)	Live Average Pup weight (g)	Average Pup Weight Change (g)
Group 2 100 mkd																			
D5244	6	10	0	0	0	0.6	16	16	100.0	96.6	6.0	6	9	0.7	15	93.8	148.7	9.9	3.9
D5245	9	5	0	0	0	1.8	14	14	100.0	98.6	7.0	9	5	1.8	14	100.0	162.8	11.6	4.6
D5246	10	5	0	0	0	2.0	15	15	100.0	89.7	6.0	10	5	2.0	15	100.0	139	9.3	3.3
D5247	12	5	0	0	0	2.4	17	17	100.0	112.3	6.6	12	5	2.4	17	100.0	173.8	10.2	3.6
D5248	7	7	0	0	0	1.0	14	14	100.0	93.2	6.7	7	7	1.0	14	100.0	144.7	10.3	3.6
D5249	6	8	0	0	0	0.8	14	14	100.0	85.5	6.1	6	8	0.8	14	100.0	147.5	10.5	4.4
D5250	9	7	0	0	0	1.3	16	16	100.0	90.7	5.7	9	7	1.3	16	100.0	144.2	9.0	3.3
D5251	5	6	0	0	0	0.8	11	11	100.0	79.6	7.2	5	6	0.8	11	100.0	126.6	11.5	4.3
D5252	11	4	0	0	0	2.8	15	15	100.0	100	6.7	11	4	2.8	15	100.0	162.2	10.8	4.1
D5253	9	5	0	0	0	1.8	14	14	100.0	91.7	6.6	9	5	1.8	14	100.0	135.6	9.7	3.1
MEAN	**8.4**	**6.2**	**0.0**	**0.0**	**0.0**	**1.5**	**14.6**	**14.6**	**100.0**	**93.8**	**6.5**	**8.4**	**6.1**	**1.5**	**14.5**	**99.4**	**148.5**	**10.3**	**3.8**
SD	**2.3**	**1.8**	**0.0**	**0.0**	**0.0**	**0.7**	**1.6**	**1.6**	**0.0**	**8.9**	**0.5**	**2.3**	**1.6**	**0.7**	**1.6**	**2.0**	**14.2**	**0.9**	**0.5**
N	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**

[1] % Live Pups = (Total Live Pups/Total Litter Size)*100

Appendix O. Individual Reproductive Parameter Data (continued)

	Mating and Fertility Data			Loss of Offspring		
Animal ID	Length of Gestation	Implantations	Corpora Lutea	% Pre-Implantation[1]	% Post-Implantation[2]	% Post-Natal[3]
Group 2 100 mkd						
D5244	22	16	16	0.0	0.0	6.3
D5245	22	15	17	11.8	6.7	0.0
D5246	21	15	15	0.0	0.0	0.0
D5247	22	18	19	5.3	5.6	0.0
D5248	22	15	16	6.3	6.7	0.0
D5249	21	16	23	30.4	12.5	0.0
D5250	21	16	16	0.0	0.0	0.0
D5251	22	13	16	18.8	15.4	0.0
D5252	22	16	23	30.4	6.3	0.0
D5253	22	14	15	6.7	0.0	0.0
MEAN	**21.7**	**15.4**	**17.6**	**11.0**	**5.3**	**0.6**
SD	**0.5**	**1.3**	**3.1**	**11.8**	**5.5**	**2.0**
N	**10**	**10**	**10**	**10**	**10**	**10**

[1] % Preimplantation Loss = ((# Corpora Lutea - # Implantations) / # Corpora Lutea) * 100
[2] % Post-Implantation Loss = ((# Implantations - # Live at First Litter Check) / # Implantations) *100
[3] % Post-natal Loss = ((# live pups Day 0 - # live pups Day 4) / # Live pups Day 0) *100

Appendix O. Individual Reproductive Parameter Data (continued)

Litter Data

	Day 0											Day 4							
Animal ID	Live Male Pups	Live Female Pups	Dead Male Pups	Dead Female Pups	Dead Undetermined Sex	Total Male/Female Ratio	Total Live Pups	Total Litter Size	% Live Pups[1]	Live Litter Weight (g)	Live Average Pup weight (g)	Live Male Pups	Live Female Pups	Total Male/Female Ratio	Total Live Pups	% Live Pups[1]	Live Litter Weight (g)	Live Average Pup weight (g)	Average Pup Weight Change (g)
Group 3 300 mkd																			
D5274	9	8	0	0	0	1.1	17	17	100.0	108.2	6.4	9	8	1.1	17	100.0	155.2	9.1	2.7
D5275	9	7	0	0	0	1.3	16	16	100.0	107	6.7	9	7	1.3	16	100.0	142.3	8.9	2.2
D5276	5	6	0	0	0	0.8	11	11	100.0	67	6.1	5	5	1.0	10	90.9	119.0	11.9	5.8
D5277[a]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D5278	9	6	0	0	0	1.5	15	15	100.0	88.3	5.9	9	5	1.8	14	93.3	131.5	9.4	3.5
D5279	6	7	0	0	0	0.9	13	13	100.0	95.7	7.4	6	7	0.9	13	100.0	154.2	11.9	4.5
D5280	8	7	0	0	0	1.1	15	15	100.0	94	6.3	8	7	1.1	15	100.0	139.2	9.3	3.0
D5281	5	6	0	0	0	0.8	11	11	100.0	81.1	7.4	5	6	0.8	11	100.0	134.2	12.2	4.8
D5282	9	7	0	0	0	1.3	16	16	100.0	89.5	5.6	9	6	1.5	15	93.8	141.7	9.4	3.8
D5283	10	7	0	0	0	1.4	17	17	100.0	112.6	6.6	10	7	1.4	17	100.0	175.9	10.3	3.7
MEAN	**7.8**	**6.8**	**0.0**	**0.0**	**0.0**	**1.1**	**14.6**	**14.6**	**100.0**	**93.7**	**6.5**	**7.8**	**6.4**	**1.2**	**14.2**	**97.6**	**143.7**	**10.3**	**3.8**
SD	**1.9**	**0.7**	**0.0**	**0.0**	**0.0**	**0.3**	**2.4**	**2.4**	**0.0**	**14.4**	**0.6**	**1.9**	**1.0**	**0.3**	**2.5**	**3.7**	**16.4**	**1.4**	**1.1**
N	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**

[a]Evidence of mating but not pregnant

\- No data

[1] % Live Pups = (Total Live Pups/Total Litter Size)*100

Appendix O. Individual Reproductive Parameter Data (continued)

	Mating and Fertility Data			Loss of Offspring		
Animal ID	Length of Gestation	Implantations	Corpora Lutea	% Pre-Implantation[1]	% Post-Implantation[2]	% Post-Natal[3]
Group 3 300 mkd						
D5274	22	17	23	26.1	0.0	0.0
D5275	22	17	17	0.0	5.9	0.0
D5276	22	17	21	19.0	35.3	9.1
D5277[a]	-	-	-	-	-	-
D5278	21	16	22	27.3	6.3	6.7
D5279	22	14	15	6.7	7.1	0.0
D5280	21	15	16	6.3	0.0	0.0
D5281	22	12	17	29.4	8.3	0.0
D5282	21	17	18	5.6	5.9	6.3
D5283	22	17	17	0.0	0.0	0.0
MEAN	**21.7**	**15.8**	**18.4**	**13.4**	**7.6**	**2.5**
SD	**0.5**	**1.8**	**2.8**	**12.0**	**10.9**	**3.8**
N	**9**	**9**	**9**	**9**	**9**	**9**

[a]Evidence of mating but not pregnant

\- No data

[1] % Preimplantation Loss = ((# Corpora Lutea - # Implantations) / # Corpora Lutea) * 100

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

[3] % Post-natal Loss = ((# live pups Day 0 - # live pups Day 4) / # Live pups Day 0) *100

Appendix O. Individual Reproductive Parameter Data (continued)

Litter Data

	Day 0											Day 4							
Animal ID	Live Male Pups	Live Female Pups	Dead Male Pups	Dead Female Pups	Dead Undetermined Sex	Total Male/Female Ratio	Total Live Pups	Total Litter Size	% Live Pups[1]	Live Litter Weight (g)	Live Average Pup weight (g)	Live Male Pups	Live Female Pups	Total Male/Female Ratio	Total Live Pups	% Live Pups[1]	Live Litter Weight (g)	Live Average Pup weight (g)	Average Pup Weight Change (g)
Group 4 1000 mkd																			
D5304	4	3	3	2	0	1.4	7	12	58.3	81.9	6.8	4	2	2.0	6	50.0	50	8.3	1.5
D5305[a]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D5306[b]	2	3	5	5	0	0.9	5	15	33.3	89.7	6.0	-	-	-	-	-	-	-	-
D5307	6	4	2	3	1	1.1	10	16	62.5	101.1	6.3	6	4	1.5	10	62.5	75.1	7.5	1.2
D5308[c]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D5309[d]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D5310[e]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D5311[d]	4	0	4	8	1	1.0	4	17	23.5	93.3	5.5	-	-	-	-	-	-	-	-
D5312	7	6	1	1	0	1.1	13	15	86.7	92.6	6.2	7	6	1.2	13	86.7	88.6	6.8	0.6
D5313	5	10	0	0	0	0.5	15	15	100.0	81.9	5.5	5	10	0.5	15	100.0	124.7	8.3	2.9
MEAN	**4.7**	**4.3**	**2.5**	**3.2**	**0.3**	**1.0**	**9.0**	**15.0**	**60.7**	**90.1**	**6.1**	**5.5**	**5.5**	**1.3**	**11.0**	**74.8**	**84.6**	**7.7**	**1.6**
SD	**1.8**	**3.4**	**1.9**	**2.9**	**0.5**	**0.3**	**4.4**	**1.7**	**29.5**	**7.4**	**0.5**	**1.3**	**3.4**	**0.6**	**3.9**	**22.7**	**31.2**	**0.7**	**1.0**
N	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**

- No data

[1] % Live Pups = (Total Live Pups/Total Litter Size)*100

[a] animal 5305 was not pregnant and had no evidence of mating

[b] animal 5306 euthanized on post-partum day 2

[c] animal 5308 was euthanized on gestation day 24

[d] animals 5309 and 5311 were euthanized on post-partum day 0

[e] animal 5310 was not pregnant but had evidence of mating

Appendix O. Individual Reproductive Parameter Data (continued)

	Mating and Fertility Data			Loss of Offspring		
	Length of Gestation	Implantations	Corpora Lutea	% Pre-Implantation[1]	% Post-Implantation[2]	% Post-Natal[3]
Group 4 1000 mkd						
D5304	22	12	12	0.0	41.7	14.29
D5305[a]	-	-	-	-	-	-
D5306[b]	23	15	15	0.0	66.7	-
D5307	23	17	22	22.7	41.2	0
D5308[c]	24	12	18	33.3	-	-
D5309[d]	22	19	21	9.5	-	-
D5310[e]	-	-	-	-	-	-
D5311[d]	23	17	19	10.5	76.5	-
D5312	22	15	16	6.3	13.3	0
D5313	22	15	15	0.0	0.0	0
MEAN	**22.6**	**15.3**	**17.3**	**10.3**	**39.9**	**3.6**
SD	**0.7**	**2.4**	**3.4**	**12.1**	**29.5**	**7.1**
N	**8**	**8**	**8**	**8**	**6**	**4**

\- No data

[a] animal 5305 was not pregnant and had no evidence of mating

[b] animal 5306 euthanized on post-partum day 2

[c] animal 5308 was euthanized on gestation day 24

[d] animals 5309 and 5311 were euthanized on post-partum day 0

[e] animal 5310 was not pregnant but had evidence of mating

[1] % Preimplantation Loss = ((# Corpora Lutea - # Implantations) / # Corpora Lutea) * 100

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

[3] % Post-natal Loss = ((# live pups Day 0 - # live pups Day 4) / # Live pups Day 0) * 100

APPENDIX P

Dow Corning Report Number: 2008-10000-58967

DOW CORNING CORPORATION
HEALTH & ENVIRONMENTAL SCIENCES
TECHNICAL REPORT

Title:	Characterization of Triethoxyoctylsilane (Lot Number 0005021818)
HES Study Number:	10900-102
Test Article:	Triethoxyoctylsilane
Study Director:	Jessica L. Mosey
Sponsor:	Silicones Environmental, Health and Safety Council (SEHSC) 2325 Dulles Corner Boulevard, Suite 500 Herndon, VA 20171
HES Group Supervisor:	Debra Stutts Health and Environmental Sciences (HES) Analytical and Commercialization Support
Testing Facility:	Health and Environmental Sciences Dow Corning Corporation 2200 W. Salzburg Road Auburn, MI 48611
Study Completion Date:	03-28-2008

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ABSTRACT

The test article, triethoxyoctylsilane (lot number 0005021818) was characterized in accordance with EPA (TSCA) Good Laboratory Practices 40 CFR Part 792. Characterization consisted of physical description, confirmation of structure by GC-MS, and determination of area percent purity by GC/FID.

The physical appearance of the test article was observed to be a colorless liquid. The mass spectrum contained peaks consistent with triethoxyoctylsilane. The area percent purity by GC/FID was 97.7 ± 0.06.

This test article meets the specification for physical description and identification by GC-MS as defined in the MSDS.

APPENDIX P

GLP COMPLIANCE STATEMENT

This study was conducted in accordance with EPA (TSCA) Good Laboratory Practices 40 CFR Part 792.

Jess Mosey

Jessica L. Mosey, B. S.
Associate Analytical Chemist
Study Director

28 Mar 2008
Date

Debra Stutts

Debra Stutts, B. S.
Health and Environmental Sciences (HES)
Supervisor - Analytical and Commercialization Support

28 Mar 2008
Date

APPENDIX P

QUALITY ASSURANCE STATEMENT

Title: Characterization of Triethoxyoctylsilane (Lot Number 0005021818)

Study Number: 10900-102

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 and Management
03 Mar 2008	Draft Protocol Review	03 Mar 2008
05 Mar 2008	Triplicate Injection by GC/FID	06 Mar 2008
10-12 Mar 2008	Draft Final Report with Raw Data	12 Mar 2008

Tom Brasseur

Tom Brasseur, B.S.
Quality Assurance Auditor
Dow Corning Corporation
Health & Environmental Sciences

31 Mar 2008
Date

APPENDIX P

APPROVAL SIGNATURES

This report consists of pages 1 through 14.

Jessica L. Mosey, B. S.
Associate Analytical Chemist
Study Director

28 Mar 2008
Date

Debra Stutts, B. S.
Health and Environmental Sciences (HES)
Supervisor - Analytical and Commercialization Support

28 Mar 2008
Date

APPENDIX P

STUDY INFORMATION

Study Initiation Date:	02-03-2008
Experimental Start Date:	03-04-2008
Experimental Termination Date:	03-05-2008
Study Completion Date:	03-28-2008

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A. Study Purpose
The objective of this study was to characterize the test article, triethoxyoctylsilane.

B. Test Article / Substance / Item
Identification: Triethoxyoctylsilane (Supplied as Dow Corning® Z-6341 Silane)
Lot Number: 0005021818
Expiration Date: August 06, 2010
Source: Dow Corning Corporation, Auburn, Michigan 48611
CAS Number: 2943-75-1
Physical Description: Colorless liquid, as determined by this study
Stability: Stable, will react with moisture, refer to MSDS
Purity: 97.7 ± 0.06 area % purity, as determined by this study
Solubility: Soluble in ethanol and methanol, refer to MSDS
Storage Conditions: Room temperature, refer to MSDS
Archive: A reserve sample was not retained for this study.

C. Labeling
The original test article container for this study was labeled with the following information: study number, name of test article, lot number, container accession number, concentration, storage conditions, expiration date, initials of the individual distributing the test article and date the test article was dispensed into the container.

D. Route of Exposure and Justification
As the test article is the test system, this is not applicable.

E. Experimental Procedures

1. **Physical Description**
The physical appearance of the test article was determined by visual examination.

2. **GC/FID Analysis**
A Hewlett Packard (HP) 6890 GC with flame ionization detector (FID) and HP 7673 autosampler was used to determine an area percent purity of triethoxyoctylsilane, based on the average of 3 replicate injections (0.2 µL). A solvent blank (hexane) was injected (1µL injection volume) prior to the test article solution analysis. The actual instrument parameters are shown in Table 1. The GC area percent results were calculated as the ratio of triethoxyoctylsilane peak area divided by the sum of all peak areas. The GC/FID performance was verified by conducting triplicate 1 µL injections of an Agilent checkout sample using the autosampler. Hewlett Packard Chemstation revision B.03.01-SR1 software was used for data acquisition and analysis. Prior to analyzing triethoxyoctylsilane, the oven temperature was increased to approximately 280 °C for 30 min to prevent carry over by heating the column to burn off any residual material left from previous analyses. Once a stable baseline was observed, the GC performance was considered acceptable for use.

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Table I. GC/FID Instrument Parameters

Parameter	Setting
Oven Temperature Program	50 °C (hold 3 min) to 250 °C at 20 °C/min (hold 5 min)
Inlet Temperature	280 °C
Detector Temperature	300 °C
Capillary Column	HP-1 (Methyl Siloxane), 0.32 mm inner diameter 30 m length, 0.25 µm film thickness
Mode	Constant flow, He carrier
Initial Flow	1.2 mL/min
Split Ratio	200:1

3. **GC-MS Analysis**
An HP 5890A Series II GC with an HP 5970B mass selective detector (MSD) was used to verify the identity of the major component in the test article as triethoxyoctylsilane by wet needle injection (< 0.2 µL). HP ChemStation version B.02.05 software and HP MS ChemStation version C.00.00 software were used for data acquisition and analysis. The standard autotune procedure was conducted prior to analyzing the test article. The standard autotune is an automated tuning program that uses perfluorotributylamine (PFTBA) to optimize the MS for general-purpose electron impact ionization (EI) operation. The GC oven temperature was increased to 280 °C for 30 min to prevent carry over by burning off residual material remaining from previous analyses. The actual instrument parameters used are shown in Table II.

Table II. GC-MS Instrument Parameters

Parameter	Setting
Oven Temperature Program	50 °C (hold 3 min) to 250 °C at 10 °C/min (hold 5 min)
Inlet Temperature	250 °C
Capillary Column	HP-5MS (Low Bleed 5%-Diphenyl-95%-dimethylsiloxane copolymer), 0.25 mm inner diameter, 30 m length, 0.25 µm film thickness
Mode	Constant flow, He carrier 2.2 psi at 50 °C, vacuum compensation on
Split Ratio	96.5:1
Mass Scan Range	15-550 atomic mass units

F. Data Analysis
Calculation of average and standard deviation for area percent purity determination was performed.

G. Deviations
There were no circumstances that affected the quality or integrity of the data.

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H. Results and Discussion

1. **Physical Description**
   The physical appearance of the test article was observed to be a colorless liquid, which is consistent with the physical form and color in the MSDS.

2. **GC/FID Analysis**
   The GC/FID area percent purity for triethoxyoctylsilane was 97.7 ± 0.06 based on the average of 3 replicate injections. The results are summarized in Table III. A representative GC/FID chromatogram of the test article is shown in Figure 1. The GC/FID performance verification passed the acceptance criteria described in protocol.

3. **GC-MS Analysis**
   The major peak in the total ion chromatogram (TIC) eluted at a retention time of 14.748 minutes and is shown in Figure 2. In the mass spectrum of triethoxyoctylsilane (parent molecule M = 276), the base peak occurred at m/z 163 and corresponds to the ion formed by the loss of the $-(CH_2)_7-CH_3$ sidechain from the parent molecule. The peak at m/z 135 was formed by $(M - (CH_2)_7-CH_3 - C_2H_4)^+$. The peak at m/z 119 was formed by $(M - (CH_2)_7-Me - OC_2H_4)^+$ by rearrangement. The molecular ion peak was seen at m/z 276.

   The mass spectrum for the major component in the total ion chromatogram (TIC) for the test article analysis was library searched and a reasonable match for triethoxyoctylsilane was not obtained.

I. Conclusions

The test article, triethoxyoctylsilane (lot number 0005021818) was characterized in accordance with EPA (TSCA) Good Laboratory Practices 40 CFR Part 792. The physical appearance of the test article was observed to be a colorless liquid. The mass spectrum contained peaks consistent with triethoxyoctylsilane. The area percent purity by GC/FID was 97.7 ± 0.06. This test article meets the specification for physical description and identification by GC-MS as defined in the MSDS.

J. Archive

Protocol, amendments and deviations, study authorization documentation, raw data, correspondence, samples/specimens as applicable, and final report (at minimum) will be retained for five (5) years in 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.

K. References

1. Moore, J. A. In The Analytical Chemistry of Silicones; A. L. Smith, ed.; Mass Spectrometry, Volume 112, Chapter 13; John Wiley & Sons, Inc.; New York, NY; 1991.
2. Material Safety Data Sheet (MSDS).

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Table III. GC/FID Purity Results for Triethoxyoctylsilane

Replicate	Peak #	Retention Time (min)	Area %	Peak Assignment
1	1	10.131	0.05528	Not Identified
	2	10.294	0.34598	Not Identified
	3	10.392	0.95017	Not Identified
	4	10.653	0.45665	Not Identified
	5	10.858	97.89019	Triethoxyoctylsilane
	6	11.895	0.06411	Not Identified
	7	15.014	0.42861	Not Identified
2	1	10.293	0.29867	Not Identified
	2	10.503	0.83861	Not Identified
	3	10.652	0.43728	Not Identified
	4	10.845	97.59317	Triethoxyoctylsilane
	5	11.895	0.08032	Not Identified
	6	15.013	0.73195	Not Identified
3	1	10.131	0.04962	Not Identified
	2	10.293	0.72030	Not Identified
	3	10.501	0.91082	Not Identified
	4	10.652	0.44759	Not Identified
	5	10.856	97.69755	Triethoxyoctylsilane
	6	10.969	0.04232	Not Identified
	7	11.895	0.07050	Not Identified
	8	15.014	0.43831	Not Identified
		Mean (n=3)	97.7	
		Standard Deviation	0.06	
		RSD (%)	0.06	

Dow...

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Figure 1. GC/FID Chromatogram of Triethoxyoctylsilane

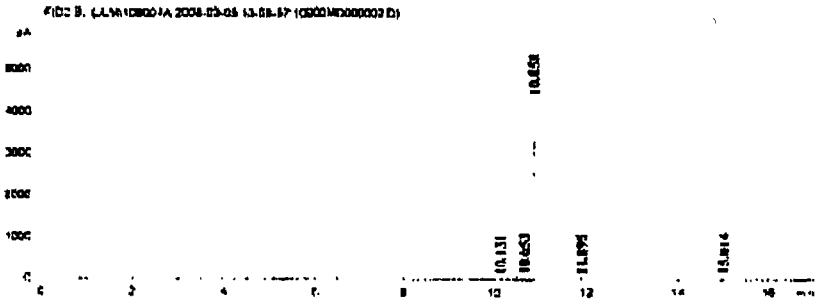

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Figure 2. Total Ion Chromatogram from GC-MS Analysis of Triethoxyoctylsilane

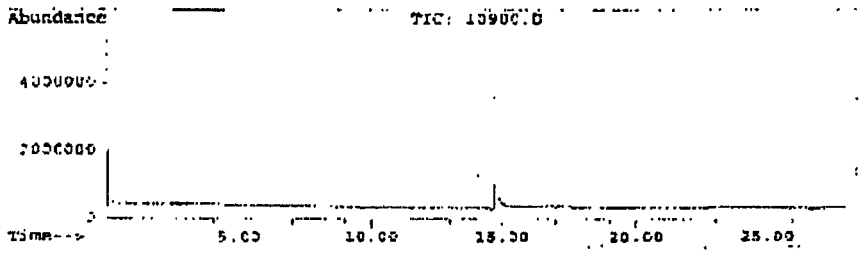

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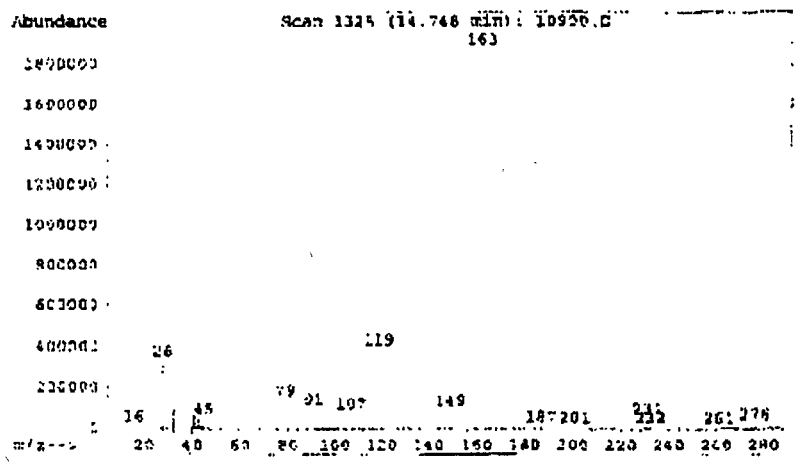
Figure 3. Mass Spectrum of Triethoxynetylsilane



DOW CORNING CORPORATION
HEALTH & ENVIRONMENTAL SCIENCES

CONTRIBUTING SCIENTIST REPORT

Report Title:	*Concentration Verification, Homogeneity and Stability of* Triethoxyoctylsilane Dosing Solutions
HES Study Number:	10709-102
Test Article:	Triethoxyoctylsilane , CAS: 2943-75-1
Contributing Scientist:	Paul S. Larson, B. S.
Sponsor:	Silicones Environmental, Health and Safety Council (SEHSC) 2325 Dulles Corner Boulevard, Suite 500 Herndon, VA 20171
HES Group Supervisor:	Debra Stutts, B.S. Health and Environmental Sciences (HES) Analytical and Commercialization Support
Testing Facility:	Health and Environmental Sciences Dow Corning Corporation 2200 West Salzburg Road Auburn, Michigan 48611
Analysis Start Date:	04 February 2008
Analysis End Date:	08 May 2008

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1. APPROVAL SIGNATURES

Approved by: Paul S. Larson — 11 Jan 2010

Paul S. Larson, B. S.
Associate Analytical Specialist
Date

Debra Stutts — 11 Jan 2010

Debra Stutts, B. S.
Health and Environmental Sciences (HES)
Group Supervisor - Analytical and Commercialization Support
Date

2. OBJECTIVE

This document describes the results from a gas chromatography with flame ionization detection (GC/FID) method for verifying the concentration, homogeneity and stability of triethoxyoctylsilane (TEOS) in dried, de-acidified peanut oil at three dose levels.

3. EXPERIMENTAL

Preparation of Solvent Standards:
Solvent standards of TEOS in hexane were prepared by weighing an amount of TEOS and mixing with a known volume of hexane (stock solution). Aliquots of the stock solution were then further diluted with hexane. The dilution for each set of standards was documented in the study data. An aliquot of each solvent standard was placed in an autosampler vial and analyzed by GC/FID using the run parameters listed below.

Preparation of Dose Solutions for Analysis by GC/FID:
For each analysis, a specified volume of the dose formulation was measured into a volumetric flask, diluted to volume with hexane and mixed well. Dose solution preparation was documented in the study data. A sample of the dose solution was placed in an autosampler vial and analyzed by GC/FID for TEOS concentration using the run parameters listed below.

Equipment (GC/FID)
Gas Chromatograph with Flame Ionization Detection System Components:
HP 6890 GC, G1530A, S/N US00001703
HP 7673 Autosampler, Injector 18593B, S/N 3537A44095
HP 7673 Autosampler, Controller G1512A, S/N 3537A02690
HP 7673 Autosampler, Sample Tray 18596C, S/N 3537A39913

Hardware System Components:
Dell Computer, Model Optiplex GX620, S/N 6J0NQ91

Software System Components:
HP Chemstation, Software, G1656B, Version B.03.01-SR1
Microsoft Windows XP

Gas Chromatography with Flame Ionization Detection Method
Run Parameters:
Column: J&W Scientific, DB-5 Capillary column, (5%-Phenyl)-methylpolysiloxane
Colum Dimensions: 0.25 µm film thickness, 30 m length x 0.320 mm I. D.
Oven Temperature Program: 50 °C (hold 2 min) to 250 °C at 20 °C/min (hold 3 min)
Mode: Constant flow, Helium carrier
Column Flow: 2.0 mL/min
Inlet Temperature: 250 °C
Inlet Mode: Splitless
Detector: Flame Ionization (FID)

Detector Temperature: 280 °C
Hydrogen Flow: 40 mL/min
Air Flow: 400 mL/min
Combined Flow (column + makeup): 25.0 mL min
Makeup Gas: Nitrogen
Injection Volume: 1.0 µL

4. DATA ANALYSIS

Statistical methods including mean, standard deviation, relative standard deviation (RSD) and linear regression analyses were performed.

5. DEVIATIONS

There were no circumstances that affected the quality or integrity of the data.

6. RESULTS / DISCUSSION / CONCLUSIONS

A set of solvent standards, comprised of four concentrations, was used to establish a calibration curve for TEOS and were prepared on the day of analysis. Trendlines and their mathematical equations were generated by linear regression analysis of the solvent standard data (peak area vs. concentration of standards) using Microsoft® Office Excel 2003 software. Verification of dose concentration was performed by comparing the target concentration of TEOS to the measured TEOS concentration by refitting the peak areas to the standard curve.

The initial TEOS dose solutions were prepared from lot number 0004908024 on February 4, 2008 for verification of each dose concentration, homogeneity and stability (through Day 32). The TEOS dose solutions were again prepared from lot number 0004908024 on February 18, 2008 for verification of dose concentration. However, the results from the GC/FID analysis showed mean measured concentrations of 94.2% and 949.0%, respectively, of target concentration for the 50 mg/mL (low) TEOS dose solution, mean measured concentrations of 95.8% and 92.9%, respectively, of target concentration for the 150 mg/mL (mid) TEOS dose solution and mean measured concentrations of 100.9%, 9.4%, respectively, of target concentration for the 500 mg/mL (high) TEOS dose solution (see Tables I and II). From these results the inference was that the low and high dose solutions were inadvertently switched, more specifically the low dose solution container was labeled as if it were the high dose solution and vice versa, which resulted in animals that initially were administered the correct dose to receive the wrong dose from the second preparation. The study was halted at this time.

The animals were replaced and a new lot of TEOS (lot number 0005021818) was received. Dose solutions from this lot of TEOS were prepared on April 10, 2008 and May 8, 2008.

From the new lot of TEOS (lot number 0005021818), verification of each dose concentration was conducted for each dose solution preparation. Each solution was analyzed by GC/FID. The mean

measured concentrations were 95.4% and 94.4%, respectively, of target concentration for the 50 mg/mL (low) TEOS dose solution. The mean measured concentrations were 96.2% and 96.0%, respectively, of target concentration for the 150 mg/mL (mid) TEOS dose solution. The mean measured concentrations were 98.9%, and 97.7%, respectively, of target concentration for the 500 mg/mL (high) TEOS dose solution (see Tables III and IV).

Homogeneity was determined for the 50 mg/mL, 150 mg/mL and 500 mg/mL TEOS concentration dose solution at time zero from lot number 0004908024 (see Table V). This was accomplished by collecting three aliquots, one each from the top, middle and bottom regions of the dose solution, diluting to a known volume with hexane and each solution mixed well. The % relative standard deviation was used as an indicator of homogeneity. The % relative standard deviation (% RSD) was 0.8% for the 50 mg/mL dose solution, 0.4% for the 150 mg/mL dose solution and 0.5% for the 500 mg/mL dose solution. The dose solutions were found to be homogeneous.

Stability of TEOS in dried, de-acidified peanut oil from lot number 0004908024 was assessed at time zero, on day 4, day 15, day 21 and on day 32 (see Table VI). Fresh calibration standards were prepared and analyzed on each day. Linear regression analysis was performed. The detector response was linear through the range of concentrations tested and the data confirms that TEOS is stable in dried, de-acidified peanut oil for at least thirty-two days.

7. REFERENCES

None

FIGURES

Figure I. Representative GC/FID Chromatogram of Triethoxyoctylsilane in Dried Deacidified Peanut Oil (Low Dose, 50 mg/mL)

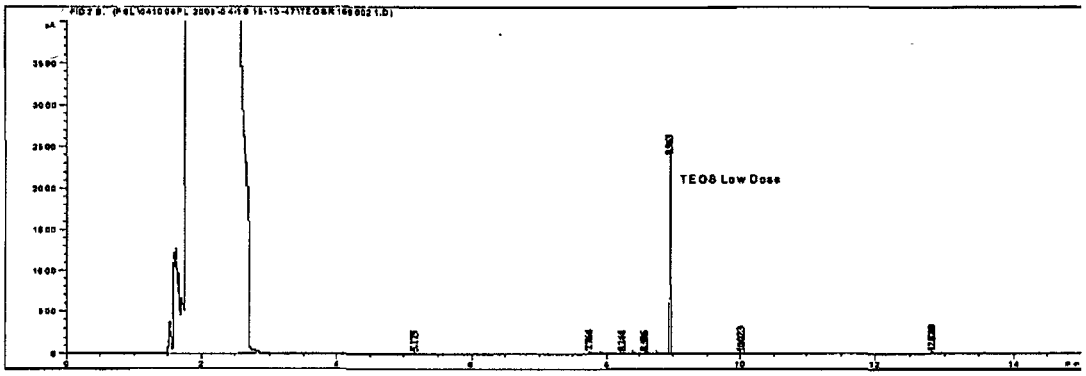


Figure II. Representative GC/FID Chromatogram of Triethoxyoctylsilane in Dried Deacidified Peanut Oil (Mid Dose, 150 mg/mL)

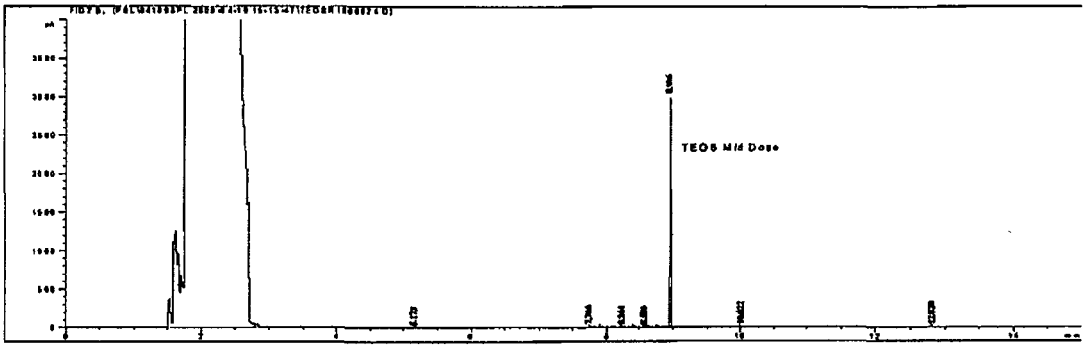
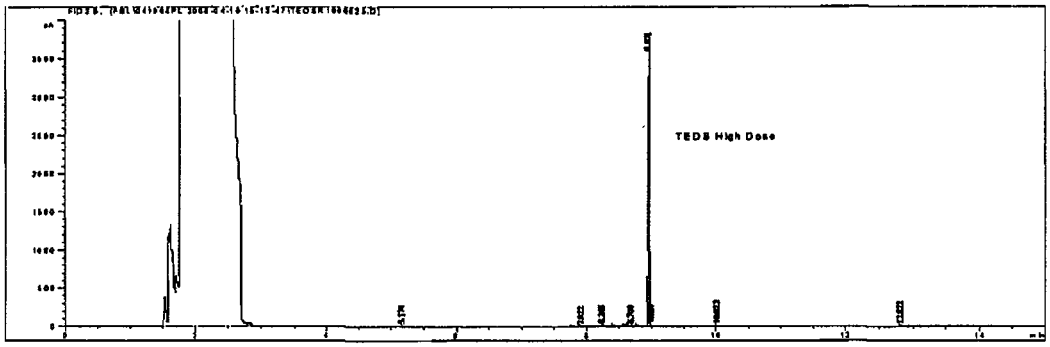


Figure III. Representative GC/FID Chromatogram of Triethoxyoctylsilane in Dried Deacidified Peanut Oil (High Dose, 500 mg/mL)



TABLES

Table I. Concentration Verification Triethoxyoctylsilane in Dried De-acidified Peanut Oil (from TEOS Lot Number 0004908024)

Dose Level (mg/mL)	Date Dosing Solution Prepared	Date Of Analysis	Target Concentration (mg/mL)	Mean Measured Concentration (mg/mL)[a, b]	Percent Of Target
Control	02/04/08	02/04/08	0	ND[c]	ND
50	02/04/08	02/04/08	50	47.1 ± 0.36	94.2
150	02/04/08	02/04/08	150	143.6 ± 0.55	95.8
500	02/04/08	02/04/08	500	504.6 ± 2.55	100.9

[a]*For reporting, mean measured concentration values were rounded to three significant digits*
[b] *Determined from the mean of the mean measured concentration, n = 9*
[c]*ND = not detected, Limit of Quantitation (LOQ) < 0.002 mg/mL*

Table II. Concentration Verification Triethoxyoctylsilane in Dried De-acidified Peanut Oil (from TEOS Lot Number 0004908024)

Dose Level (mg/mL)	Date Dosing Solution Prepared	Date Of Analysis	Target Concentration (mg/mL)	Mean Measured Concentration (mg/mL)[a, b]	Percent Of Target
Control	02/18/08	02/25/08	0	ND[c]	ND
50	02/18/08	02/25/08	50	474.5 ± 2.08	949.0
150	02/18/08	02/25/08	150	139.3 ± 0.91	92.9
500	02/18/08	02/25/08	500	46.9 ± 0.63	9.4

[a]*For reporting, mean measured concentration values were rounded to three significant digits*
[b] *Determined from the mean measured concentration, n = 3*
[c]*ND = not detected, Limit of Quantitation (LOQ) < 0.002 mg/mL*

Table III. Concentration Verification Triethoxyoctylsilane in Dried De-acidified Peanut Oil (from TEOS Lot Number 0005021818)

Dose Level (mg/mL)	Date Dosing Solution Prepared	Date Of Analysis	Target Concentration (mg/mL)	Mean Measured Concentration (mg/mL)[a, b]	Percent Of Target
Control	04/10/08	04/10/08	0	ND[c]	ND
50	04/10/08	04/10/08	50	47.7 ± 0.16	95.4
150	04/10/08	04/10/08	150	144.3 ± 0.73	96.2
500	04/10/08	04/10/08	500	494.5 ± 2.06	98.9

[a]*For reporting, mean measured concentration values were rounded to three significant digits*
[b] *Determined from the mean measured concentration, n = 3*
[c]*ND = not detected, Limit of Quantitation (LOQ) < 0.002 mg/mL*

Table IV. Concentration Verification Triethoxyoctylsilane in Dried De-acidified Peanut Oil (from TEOS Lot Number 0005021818)

Dose Level (mg/mL)	Date Dosing Solution Prepared	Date Of Analysis	Target Concentration (mg/mL)	Mean Measured Concentration (mg/mL)[a, b]	Percent Of Target
Control	05/08/08	05/08/08	0	ND[c]	ND
50	05/08/08	05/08/08	50	47.2 ± 0.26	94.4
150	05/08/08	05/08/08	150	144.0 ± 0.61	96.0
500	05/08/08	05/08/08	500	488.65 ± 3.01	97.7

[a]*For reporting, mean measured concentration values were rounded to three significant digits*
[b] *Determined from the mean measured concentration, n = 3*
[c]*ND = not detected, Limit of Quantitation (LOQ) < 0.002 mg/mL*

Table V. Homogeneity of Triethoxyoctylsilane in Dried De-acidified Peanut Oil (Dose Solutions Prepared on 02/04/2008 from TEOS Lot Number 0004908024)

Dose Level (mg/mL)	Date of Analysis	Sampling Number	Measured Concentration (mg/mL)[a]	Mean of the Mean Measured Concentration (mg/mL)[b]	Standard Deviation	% Relative Standard Deviation[c]
50	02/04/08	1	46.8	47.1	0.36	0.8
		2	47.0			
		3	47.5			
150	02/04/08	1	143.1	143.6	0.55	0.4
		2	143.6			
		3	144.2			
500	02/04/08	1	502.4	504.6	2.55	0.5
		2	507.4			
		3	504.0			

[a]*Determined from the mean of the measured concentration, n = 3*
[b] *Determined from the mean of the mean measured concentration, n = 9*
[c]*% RSD = (Standard Deviation/Mean Measured Concentration) x 100*

Table VI. Stability of Triethoxyoctylsilane in Dried De-acidified Peanut Oil

(Dose Solutions Prepared on 02/04/2008 from TEOS Lot Number 0004908024)

Dose Level	Date of Analysis	Target Concentration (mg/mL)	Mean Observed Concentration (mg/mL)	% of Time Zero Concentration
50 mg/mL	02/04/2008	50	47.1	---
50 mg/mL	02/07/2008	50	47.9	102
50 mg/mL	02/19/2008	50	46.7	99
50 mg/mL	02/25/2008	50	46.8	99
50 mg/mL	03/07/2008	50	47.7	101
150 mg/mL	02/04/2008	150	143.6	---
150 mg/mL	02/07/2008	150	142.5	99
150 mg/mL	02/19/2008	150	141.0	98
150 mg/mL	02/25/2008	150	141.5	99
150 mg/mL	03/07/2008	150	144.3	100
500 mg/mL	02/04/2008	500	504.6	---
500 mg/mL	02/07/2008	500	495.8	98
500 mg/mL	02/19/2008	500	500.0	99
500 mg/mL	02/25/2008	500	489.7	97
500 mg/mL	03/07/2008	500	491.2	97

APPENDIX R

DOW CORNING CORPORATION
HEALTH & ENVIRONMENTAL SCIENCES

CONTRIBUTING SCIENTIST REPORT

Report Title:	Statistical Analyses for Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Triethoxyoctylsilane in Sprague-Dawley Rats via Oral Gavage
HES Study Number:	10709-102
Test Article:	Triethoxyoctylsilane
Contributing Scientist:	Cynthia Van Landingham, M.S.
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Testing Facility:	Dow Corning Corporation Health and Environmental Sciences 2200 West Salzburg Road Auburn, Michigan 48611
Analysis Start Date:	August 13, 2008 (first analysis ran)
Analysis End Date:	May 5, 2009 (last analysis ran)

APPENDIX R

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1. APPROVAL SIGNATURES

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2. OBJECTIVE

The objective of this contributing scientist report is to provide statistical analysis of the study data.

3. EXPERIMENTAL

Not Applicable

4. DATA ANALYSIS

The data used in this analysis was based on the protocol for an OECD 422 study in Sprague Dawley rats. For this analysis, the data are arranged into three groups. These groups are the male toxicity group, the female toxicity group, and the female reproductive group. Data for each group were analyzed separately with the exception of the motor activity and continuous FOB data for the male and female toxicity groups. In the reproductive female group, one animal in the control and one animal in the 300 mg/kg/day group were excluded because they were not pregnant and six animals in the 1000 mg/kg/day were excluded from the analyses at various time points due to the following reasons: two animals were excluded starting with the first day of gestation because the animals were not pregnant (5305 and 5310), two animals were excluded from all post-partum data because clinical signs in these animals had warranted euthanasia prior to post – partum day 0 (5308 and 5309). Two additional animals were excluded from the post-partum day 4 analyses because clinical signs in these animals had warranted euthanasia prior to post-partum day 4 (5306 and 5311).

5. METHODS

All data analysis was carried out using SAS version 9.1.3 [1]. Statistically significant probabilities were reported for p-values of < 0.05, <0.02, and < 0.01.

Body weight, changes in body weight, and food consumption data, were analyzed using a one-way Analysis of Variance (ANOVA)[2] if the data satisfied the requirements of normality of the residuals and homogeneity of variance as determined using the Shapiro-Wilk[3] test for normality and Levene's test[4] for homogeneity of variance. If the data did not satisfy the parametric requirements, a Kruskal-Wallis test[5, 6] was used. If the ANOVA or Kruskal-Wallis test was significant, pair-wise comparisons of the exposed groups to control were made using the Dunnett's Test [7, 8] 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. See Motor Activity Statistical Tests flowchart (Attachment 1).

Reproductive Parameters with the exception of litter size were analyzed using an ANCOVA (Analysis of Covariance) with litter size as the covariate. Litter size was analyzed using an ANOVA.

Measured continuous Functional Observational Battery (FOB) data was analyzed using a combination of ANCOVA with baseline evaluations used as the covariate and repeated measures ANOVA. See FOB Continuous Data Statistical Tests flowchart (Attachment 2).

Categorical Functional Observational Battery (FOB) data was analyzed using the Jonckheere-Terpstra test[9]. This test is used to detect a shift in the categorical observations. See FOB Ranked Data Statistical Tests flowchart (Attachment 3).

Microscopic findings were analyzed using a Cochran-Armitage trend test[10] to indicate an increasing incidence trend regardless of grade with Fisher's Exact tests[11-13] 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[5, 6] 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 can be 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 was 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.

6. DEVIATIONS

There were no protocol deviations for this portion of the study.

7. RESULTS AND DISCUSSION/CONCLUSIONS

Body Weights

ANOVA was used for the analysis of body weight data for the reproductive group females for all days except gestation day 14 where a Kruskal Wallis test was used due to non-homogeneity of the variances (Table 1). Analysis of the day 22 data was not done due to lack of data in the control group for that day. There were no significant differences across treatment groups in the mean body weights from the start of the study through gestation day 0. However, from gestation days 7, 14 and 20, there were significant differences across groups with the 1000 mg/kg/day groups having significantly smaller average body weights on those days than the control group. This difference was also seen on post-partum day 0 and at terminal sacrifice on post-partum day 4. The repeated measures over time analysis did not show a significant interaction between treatment and time the reproductive female group (p=0.1491).

Change in Body Weights

ANOVA was used for the change in body weight analysis for each time period in the female reproductive group except for gestation week 2 which was analyzed with a Kruskal-Wallis test due to non-normality and non-homogeneity of the variance.

The female reproductive group had statistically significant differences between the treated and control groups in change in body weight for gestation weeks 1, 2 and 3 and the total post-partum change in body weight with the 1000 mg/kg/day group showing a significantly smaller mean change than the control group over those time periods (Table 2). There is also a significant difference between the control group and the 300 mg/kg/day group for gestation week 2 with the 300 mg/kg/day group's mean change in body weight being significantly smaller than in the control group.

Food Consumption

Analysis of food consumption data was done using an ANOVA for all three groups except for the food consumption in gestation week 2 in the female reproductive group, and the week 1 and total food consumption for the male toxicity group which were analyzed using a Kruskal-Wallis test due to non-homogeneity of variance in all cases. There were statistically significant differences seen in the average daily food

consumption across treatment groups in the female reproductive group (Table 3) for gestation weeks 1, 2 and 3 and during the post-partum period with the 1000 mg/kg/day group eating significantly less than the control group at all these time points and, in gestation week 2, the 100 mg/kg/day group also consumed significantly less than the control group. In addition, the average total grams consumed per animal showed statistically significant differences for the consumption during gestation and the consumption during the post-partum period. In both of these cases, the 1000 mg/kg/day group consumed significantly less than the control group. The week 3 mean food consumption was also significantly different across groups for the female toxicity group with both the 100 mg/kg/day group and the 1000 mg/kg/day group consuming significantly less than the control group (Table 4). There were no significant differences in food consumption among the male toxicity groups (Table 5). The repeated measures analysis of the average daily values (excluding the total grams reported in tables 3 and 4) showed a significant time by treatment interaction for the reproductive group females (p=0.0097) but not for the female toxicity group (p=0.1625). No repeated measures analysis was done on the male toxicity group food consumption data since there were only two time points.

Reproductive Values

Reproductive values (Table 6) from the female reproductive groups were analyzed using an ANOVA for the litter size and all pre-birth counts (corpora lutea, total implants, %pre-implantation loss, %post implantation loss, and length of gestation) and ANCOVA for all other endpoints using litter size as a covariate. Statistically significant differences in the dose groups were seen in the post implantation losses, length of gestation, live male pups day 0, live female pups day 0, dead male pups day 0, dead female pups day 0, dead undetermined sex day 0, male to female ratio day 0, total viable pups day 0, % viable at birth, live male pups day 4, total viable pups PND 4 day, % viable at day 4, litter weight day 4, average pup weight day 4, and average pup weight changes day 4. In all of these cases except the male to female ratio day 0 and the live male pups day 4, there was a statistically significant different between the response in the 1000 mg/kg/day group and the control group. For the male to female ratio and the live male pups day 4, the 100 mg/kg/day group had a larger mean response than the control group.

Clinical Signs

For the reproductive group females there were statistically significant differences in the clinical signs of decreased behavior activity; gait – both dragging of hindquarters, limbs flaccid, and incoordinated; rapid respiration, soiling of the nose or chin, and soiling of the muzzle. For the toxicity group females and the toxicity group males there were significant differences in the soiling of the nose or chin and soiling of the muzzle. In all these cases, there were significantly more of these clinical signs in the 1000 mg/kg/day group than in the control group.

Functional Observational Battery (FOB) Continuous Values

The FOB continuous data for toxicity group females (Table 8) and males (Table 9) were homogeneous and normally distributed with the sexes combined at the alpha = 0.01 level. The ANCOVA with treatment by sex and treatment by covariate (baseline measurement) showed a significant treatment by sex interaction for the hindlimb grip strength (p<0.0001), the rectal temperature (p=0.0337) and landing foot splay (p=0.0109) but not for the forelimb grip strength (p=0.0577). The analysis of the sex separated the hindlimb grip strength, rectal temperature and landing foot splay showed that the variances were homogeneous and the residuals were normal with an alpha greater than 0.01. The sexes combined forelimb grip strength did not have a significant baseline by treatment interaction (p=0.1190) nor were the baseline by treatment interactions significant for the sex separate hindlimb grip strength (female p=0.3102, male p = 0.9411), the rectal temperature (female p = 0.6656, male p=0.4234) or the landing foot splay (female p=0.4574, male p =0.1420), therefore the ANCOVA results were used to determine the treatment significance. There were no statistically significant treatment effects for the sexes combined forelimb grip strength (p=0.2727, nor for the sex separate hindlimb grip strength (female p=2700, male p = 0.8362), the rectal temperature (female p = 0.6646, male p=0.4175) or the landing foot splay (female p=0.5876, male p =0.1620).

Functional Observational Battery (FOB) Categorical Data

There were no statistically significant differences across dose groups in either the baseline or treated FOB categorical data for both the toxicity group females (Table 10) and the males (Table11).

Motor Activity

The baseline untransformed motor activity data for the toxicity group females (Table 12) and the toxicity group males (Table 13) was homogenous and the residuals from the ANOVAs were normally distributed with the sexes combined and although the treated data was homogeneous, the residuals from the ANOVA were not normally distributed (p=0.0007). A square root transformation of the data was done for the total baseline and treated data and the square root transformed data was both homogeneous and the residuals were normally distributed. For the square root transformed data, there was not a significant time*treatment*sex interaction for total count data (p=0.9130) nor a time*treatment*sex*interval interaction (p=0.2954). For the sexes combined, square root transformed total count data did not have a significant time by treatment interaction (p=0.6494) nor did the square root transformed combined sex interval data have a significant time*treatment* interval interaction (p=0.9166) or treatment*time interaction (p=0.6030).

Microscopic Findings

In the reproductive group females (Table 14), a significant Cochran-Armitage trend was seen for the brain white matter degeneration, liver centrilobular hypertrophy, sciatic and tibial nerve degeneration, skeletal muscle adductor degeneration, spinal cord white matter degeneration, spleen atrophy, thymus atrophy and urinary bladder hyperplasic epithelial diffuse with pair wise comparisons by the Fisher's Exact test showing significant differences between the control and the 1000 mg/kg/day group for all these endpoints and

significant differences between control and the 300 mg/kg/day group for the liver centrilobular hypertrophy. There were also significant trends by the Cochran Armitage test for the liver centrilobular vacuolation and the skeletal muscle gastrocnemius degeneration but these incidences were not significant by the Fisher's Exact test. There was also significant shift in grade for the skeletal muscle gastrocnemius degeneration.

For the toxicity group females (Table 15), there were significant trends in the liver centrilobular hypertrophy with the 300 and 1000 mg/kg/day groups having significantly more incidences than the control group and in the spinal cord white matter degeneration with only the 1000 mg/kg/day group being significantly different from control. There were also significant trends for the brain white matter degeneration and the sciatic nerve degeneration but neither of these showed pair wise differences between the control and treated groups by Fisher's Exact test.

The toxicity group males (Table 16) had a significant trend in the liver centrilobular hypertrophy and the urinary bladder hyperplasia epithelial diffuse with both having significantly higher incidence in the 1000 mg/kg/day group than in the control group and the liver centrilobular hypertrophy also being elevated in the 300 mg/kg/day group versus the control group.

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Table 1
Reproductive Females
Body Weight (g)

Time		Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
Day 1	Mean	206.5		203.5		204.7		206.4	
	Std	13.1		13.8		9.7		12.8	
	N	10		10		10		10	
Day 8	Mean	225.0		218.7		218.8		216.0	
	Std	20.7		14.5		16.2		12.9	
	N	10		10		10		10	
Day 15	Mean	242.3		232.8		231.9		230.6	
	Std	21.2		19.3		16.7		15.4	
	N	10		10		10		10	
Day 22	Mean					274.7		218.2	
	Std								
	N					1		1	
Gestation Day 0	Mean	254.4		242.3		246.7		237.6	
	Std	21.2		18.5		21.0		14.0	
	N	9		10		9		8	
Gestation Day 7	Mean	287.7	*	272.1		279.8		255.6	***
	Std	21.1		19.3		20.8		22.2	
	N	9		10		9		8	
Gestation Day 14	Mean	332.8	*	313.8		316.0		280.2	***
	Std	22.0		21.1		23.2		36.9	
	N	9		10		9		8	
Gestation Day 20	Mean	422.0	***	400.8		403.9		343.4	***
	Std	22.2		26.3		17.2		36.1	
	N	9		10		9		8	
Post-partum Day 0	Mean	329.4	***	312.7		318.4		259.4	***
	Std	21.4		24.8		22.2		35.2	
	N	9		10		9		7	
Term Sac	Mean	340.7	***	317.7		327.8		243.0	***
	Std	26.2		26.7		23.7		53.0	
	N	9		10		9		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 2
Reproductive Females
Change in Body Weight (g)

Time		Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
Week 1	Mean	18.5		15.3		14.1		9.6	
	Std	10.0		5.1		8.6		3.4	
	N	10		10		10		10	
Week 2	Mean	17.3		14.0		13.1		14.6	
	Std	4.4		8.3		7.0		4.7	
	N	10		10		10		10	
Week 3	Mean					46.1		-6.5	
	Std								
	N					1		1	
Gestation Week 1	Mean	33.2	***	29.8		33.0		18.0	***
	Std	9.1		7.9		6.9		12.8	
	N	9		10		9		8	
Gestation Week 2	Mean	45.2	***	41.8		36.3	*	24.6	***
	Std	5.1		3.7		10.8		17.7	
	N	9		10		9		8	
Gestation Week 3	Mean	89.1	***	87.0		87.8		63.2	***
	Std	10.8		10.8		13.1		19.3	
	N	9		10		9		8	
Post-partum	Mean	11.3		5.0		9.4		-16.1	
	Std	10.6		25.5		5.3		32.8	
	N	9		10		9		4	
Total-Post-partum Day 4	Mean	132.9	***	114.2		122.5		34.7	***
	Std	19.8		26.3		24.6		55.9	
	N	9		10		9		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
Reproductive Females
Average Daily Food Consumption (g/day)

Time		Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
PM Week 1	Mean	19.9		18.6		19.4		18.1	
	Std	2.4		1.8		2.2		1.4	
	N	10		10		10		10	
PM Week 2	Mean	21.5		20.9		21.9		20.6	
	Std	2.1		1.8		2.1		2.9	
	N	10		10		10		10	
Total PM grams	Mean	289.8		276.7		289.6		270.9	
	Std	30.1		23.2		27.1		27.8	
	N	10		10		10		10	
Gestation Week 1	Mean	21.9	*	20.9		21.0		19.2	**
	Std	1.7		2.1		1.8		2.0	
	N	9		10		9		8	
Gestation Week 2	Mean	24.5	*	22.8	*	23.5		19.7	**
	Std	1.5		1.9		2.3		3.9	
	N	9		10		9		8	
Gestation Week 3	Mean	28.0	***	25.6		26.6		22.2	***
	Std	2.1		2.6		2.2		3.0	
	N	9		10		9		8	
Total Gestational grams	Mean	492.9	***	458.8		471.0		405.2	***
	Std	33.4		38.8		41.1		50.4	
	N	9		10		9		8	
Post-partum Week	Mean	35.6	***	31.0		32.5		18.2	***
	Std	6.5		5.7		4.1		11.4	
	N	9		10		9		4	
Total Post-Partum grams	Mean	142.1	***	123.8		129.9		72.7	***
	Std	25.9		23.0		16.3		45.5	
	N	9		10		9		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 4
Toxicity Females
Average Daily Food Consumption (g/day)

Time		Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
Week 1	Mean	19.8		18.7		18.8		17.6	
	Std	2.0		2.0		1.3		1.4	
	N	10		10		10		10	
Week 2	Mean	22.2		21.0		21.4		20.6	
	Std	1.7		1.9		1.0		1.8	
	N	10		10		10		10	
Week 3	Mean	22.5	*	20.4	*	21.0		20.2	**
	Std	1.7		2.2		1.3		1.6	
	N	10		10		10		10	
Week 4	Mean	20.4		19.9		19.6		19.8	
	Std	1.9		1.6		1.2		2.3	
	N	10		10		10		10	
Total grams	Mean	573.7		540.3		546.5		528.0	
	Std	44.6		49.6		28.3		39.7	
	N	10		10		10		10	

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 5
Toxicity Males
Average Daily Food Consumption (g/day)

Time		Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
Week 1	Mean	26.4		27.0		26.8		26.8	
	Std	2.2		2.2		0.8		3.1	
	N	10		10		10		10	
Week 2	Mean	26.9		28.0		27.5		27.6	
	Std	2.4		3.1		1.8		3.7	
	N	10		10		10		10	
Total grams	Mean	372.7		384.6		380.3		380.7	
	Std	30.2		35.4		16.8		45.9	
	N	10		10		10		10	

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 6
Reproductive Females
Reproductive Measurements

		Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day		Litter Size
Corpora Lutea	Mean	19.0		17.6		18.4		17.3		NA
	Std	2.7		3.1		2.8		3.4		
	N	9		10		9		8		
Total Implants	Mean	17.4		15.4		15.8		15.3		NA
	Std	1.9		1.3		1.8		2.4		
	N	9		10		9		8		
% Pre-Implantation Loss	Mean	7.3		11.0		13.4		10.3		NA
	Std	10.4		11.8		12.0		12.1		
	N	9		10		9		8		
% Post-Implantation Loss	Mean	5.7	***	5.3		7.6		39.9	***	NA
	Std	4.8		5.5		10.9		29.5		
	N	9		10		9		6		
Length of Gestation	Mean	21.4	***	21.7		21.7		22.6	***	NA
	Std	0.5		0.5		0.5		0.7		
	N	9		10		9		8		
Total Litter Size Day 0	Mean	16.4		14.6		14.6		15.0		NA
	Std	1.7		1.6		2.4		1.7		
	N	9		10		9		6		
Live Male Pups Day 0	Mean	8.1	***	8.4		7.8		4.7	**	***
	Std	1.6		2.3		1.9		1.8		
	N	9		10		9		6		
Live Female Pups Day 0	Mean	8.3	***	6.2		6.8		4.3	***	
	Std	1.4		1.8		0.7		3.4		
	N	9		10		9		6		
Dead Male Pups Day 0	Mean	0.0	***	0.0		0.0		2.5	***	
	Std	0.0		0.0		0.0		1.9		
	N	9		10		9		6		
Dead Female Pups Day 0	Mean	0.0	***	0.0		0.0		3.2	***	
	Std	0.0		0.0		0.0		2.9		
	N	9		10		9		6		
Undertermined Sex (Dead) Day 0	Mean	0.0	**	0.0		0.0		0.3	***	
	Std	0.0		0.0		0.0		0.5		
	N	9		10		9		6		
Male/Female Ratio Day 0	Mean	1.0	*	1.5	*	1.1		1.0		
	Std	0.3		0.7		0.3		0.3		
	N	9		10		9		6		

Table 6 (continued)
Reproductive Females
Reproductive Measurements

		Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day		Litter Size
Total Viable Pups Day 0	Mean	16.4	***	14.6		14.6		9.0	***	***
	Std	1.7		1.6		2.4		4.4		
	N	9		10		9		6		
Total Dead Pups Day 0	Mean	0.0	***	0.0		0.0		6.0	***	
	Std	0.0		0.0		0.0		4.9		
	N	9		10		9		6		
% Post-Natal Loss	Mean	0.0		0.6		2.5		3.6		
	Std	0.0		2.0		3.8		7.1		
	N	9		10		9		4		
% Viable at Birth Day 0	Mean	100.0	***	100.0		100.0		60.7	***	
	Std	0.0		0.0		0.0		29.5		
	N	9		10		9		6		
Litter Weight (g) Day 0	Mean	103.0		93.8		93.7		90.1		***
	Std	13.0		8.9		14.4		7.4		
	N	9		10		9		6		
Average Pup weight (g) Day 0	Mean	6.3		6.5		6.5		6.0		**
	Std	0.4		0.5		0.6		0.5		
	N	9		10		9		6		
Live Male Pups Day 4	Mean	8.1	***	8.4	*	7.8		5.5		***
	Std	1.6		2.3		1.9		1.3		
	N	9		10		9		4		
Live Female Pups Day 4	Mean	8.3		6.1		6.4		5.5		
	Std	1.4		1.6		1.0		3.4		
	N	9		10		9		4		
Dead Male Pups Day 4	Mean	0.0		0.0		0.0		0.0		
	Std	0.0		0.0		0.0		0.0		
	N	9		10		9		4		
Dead Female Pups Day 4	Mean	0.0		0.1		0.3		0.3		
	Std	0.0		0.3		0.5		0.5		
	N	9		10		9		4		
Male/Female Ratio on Day 4 Day 4	Mean	1.0		1.5		1.2		1.3		
	Std	0.3		0.7		0.3		0.6		
	N	9		10		9		4		
Total Viable Pups on PND 4 Day 4	Mean	16.4	***	14.5		14.2		11.0	***	***
	Std	1.7		1.6		2.5		3.9		
	N	9		10		9		4		
% Viable Pups Day 4	Mean	100.0	***	99.4		97.6		74.8	***	
	Std	0.0		2.0		3.7		22.7		
	N	9		10		9		4		

Table 6 (continued)
Reproductive Females
Reproductive Measurements

		Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day		Litter Size
Litter Weight Day 4	Mean	169.4	***	148.5		143.7		84.6	***	***
	Std	23.6		14.2		16.4		31.2		
	N	9		10		9		4		
Average Pup Weight Day 4	Mean	10.3	***	10.3		10.3		7.7	***	***
	Std	1.0		0.9		1.3		0.7		
	N	9		10		9		4		
Average Pup Weight Change (g) Day 4	Mean	4.0	***	3.8		3.8		1.6	***	***
	Std	0.6		0.5		1.1		1.0		
	N	9		10		9		4		

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. . There are no significant differences between the control and the treated group by Dunnett's test.

Table 7
Clinical Signs

	Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
Reproductive Females								
No abnormalities detected	391/10		434/10		438/10		274/10	
Behavior activity: decreased	0/0	**	0/0		0/0		37/5	***
Excessive hair loss: hindlimb, bilateral	17/1		0/0		0/0		0/0	
Gait: dragging hindquarters, limbs flaccid	0/0	***	0/0		0/0		43/5	***
Gait: incoordinated	0/0	**	0/0		0/0		28/5	***
Misc.: thin	0/0		0/0		0/0		1/1	
Respiration: rapid	0/0	*	0/0		0/0		5/3	**
Skin: scab lower hindlimb, right, focal	18/1		0/0		0/0		0/0	
Skin: ungroomed appearance	0/0		0/0		0/0		1/1	
Soiling: abdomen, general (yellow)	1/1		0/0		0/0		4/1	
Soiling: nose, chin, (red, clear, or yellow)	0/0	***	0/0		2/1		77/10	***
Soiling: muzzle, general (red or clear)	0/0	***	0/0		0/0		50/9	***
Soiling: eye, bilateral red	0/0		0/0		0/0		4/2	
Soiling: urogenital, general (red or yellow)	2/2		0/0		0/0		1/1	
Toxicity Females								
No abnormalities detected	282/10		282/10		275/10		224/10	
Behavior activity: decreased	0/0		0/0		0/0		1/1	
Eye: increased lacrimation, bilateral	0/0		0/0		0/0		1/1	
Skin: scab head, top, focal	7/1		8/1		0/0		0/0	
Skin: scab muzzle, right, focal	1/1		0/0		0/0		0/0	
Skin: scab neck, right, focal	7/1		0/0		0/0		0/0	
Skin: scab shoulder, left, focal	0/0		0/0		8/1		7/1	
Soiling: nose, chin, (red, clear, or yellow)	0/0	***	0/0		5/1		20/7	***
Soiling: muzzle, general (red or clear)	0/0	***	0/0		3/2		41/7	***
Soiling: urogenital, general (red or yellow)	0/0		0/0		0/0		1/1	
Toxicity Males								
No abnormalities detected	299/10		296/10		259/10		204/10	
Skin: scab lower forelimb, right, focal	0/0		3/1		0/0		0/0	
Skin: scab shoulder, left, focal	0/0		0/0		7/1		0/0	
Skin: scab upper back, thoracic, right, focal	0/0		0/0		9/1		0/0	
Soiling: abdomen, general (yellow)	0/0		0/0		1/1		3/2	
Soiling: nose, chin, (red, clear, or yellow)	1/1	***	1/1		5/4		54/8	***
Soiling: muzzle, general (red or clear)	0/0	***	0/0		13/5		40/8	***
Soiling: urogenital, general (red or yellow)	0/0		0/0		11/4		11/4	

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 8
Toxicity Females
FOB Continuous

Endpoint	Time		Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Forelimb Grip Strength (g)	Baseline	Mean	700.0	714.3	749.2	782.5
		Std	73.2	148.3	93.3	118.0
		N	10	10	10	10
	Treated	Mean	966.8	1009.0	1025.0	887.3
		Std	150.4	276.1	159.9	154.2
		N	10	10	10	10
Hindlimb Grip Strength (g)	Baseline	Mean	608.3	653.0	665.8	624.7
		Std	89.4	112.2	123.2	116.6
		N	10	10	10	10
	Treated	Mean	987.0	959.5	985.3	868.2
		Std	101.4	125.7	153.7	157.1
		N	10	10	10	10
Landing Foot Splay (cm)	Baseline	Mean	11.1	10.6	10.6	9.4
		Std	1.8	2.0	1.9	2.3
		N	10	10	10	10
	Treated	Mean	10.5	9.1	10.0	8.8
		Std	2.0	1.6	1.4	2.1
		N	10	10	10	10
Rectal Temperature (oCelsius)	Baseline	Mean	38.4	38.2	38.4	38.0
		Std	0.4	0.4	0.4	0.4
		N	10	10	10	10
	Treated	Mean	38.6	38.4	38.3	38.4
		Std	0.5	0.4	0.6	0.3
		N	10	10	10	10

Table 9
Toxicity Males
FOB Continuous

Endpoint	Time		Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Forelimb Grip Strength (g)	Baseline	Mean	790.3	856.3	776.7	783.8
		Std	147.9	110.8	126.7	139.8
		N	10	10	10	10
	Treated	Mean	1197.8	1329.8	1088.7	1036.2
		Std	202.7	222.7	238.2	232.4
		N	10	10	10	10
Hindlimb Grip Strength (g)	Baseline	Mean	690.0	752.8	692.3	733.0
		Std	74.8	68.5	134.9	116.4
		N	10	10	10	10
	Treated	Mean	1272.5	1196.2	1140.5	1116.5
		Std	128.9	161.0	178.1	170.3
		N	10	10	10	10
Landing Foot Splay (cm)	Baseline	Mean	12.2	12.4	11.4	12.9
		Std	2.2	2.2	1.6	2.1
		N	10	10	10	10
	Treated	Mean	11.2	12.2	11.2	12.2
		Std	1.7	1.7	1.5	2.0
		N	10	10	10	10
Rectal Temperature (oCelsius)	Baseline	Mean	37.8	38.0	38.0	38.1
		Std	0.4	0.3	0.4	0.3
		N	10	10	10	10
	Treated	Mean	37.9	38.2	37.9	37.9
		Std	0.4	0.4	0.4	0.3
		N	10	10	10	10

Table 10
Toxicity Females
FOB Ranked

Endpoint	Time	#Examined / Response	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Resistance to Removal	Baseline	# Examined	10	10	10	10
		Moderate; actively avoids capture but is not aggressive	10	8	10	10
		Pronounced; actively avoids capture and/or is mildly aggressive	0	2	0	0
	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
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	10	10	10
	Treated	# Examined	10	10	10	10
		Moderate; clearly detectable	10	10	10	10

Table 10 (continued)
Toxicity Females
FOB Ranked

Endpoint	Time	#Examined / Response	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Reactivity to Handling	Baseline	# Examined	10	10	10	10
		Moderate struggling with little or no vocalization	9	9	10	10
		Pronounced struggling, animal may vocalize	1	1	0	0
	Treated	# Examined	10	10	10	10
		Moderate struggling with little or no vocalization	10	10	10	10
Level of Activity	Baseline	# Examined	10	10	10	10
		Moderate; inactive less than 50% of the time	10	10	9	9
		Pronounced; leaves circle, occasional inactivity.	0	0	1	1
	Treated	# Examined	10	10	10	10
		Minimal; inactive more than 50% of the time	1	1	2	0
		Moderate; inactive less than 50% of the time	8	9	8	10
		Pronounced; leaves circle, occasional inactivity.	1	0	0	0
Response to Sharp Noise	Baseline	# Examined	10	10	10	10
		Moderate; clear movement of the head, neck, ears and possibly shoulders/upper body	8	10	8	9
		Pronounced; clear movement of head, neck and ears, plus clear movement of whole body.	2	0	1	1
		Exaggerated; whole body response to stimulus more intense than "pronounced"; includes whole body going airborne	0	0	1	0
	Treated	# Examined	10	10	10	10
		Moderate; clear movement of the head, neck, ears and possibly shoulders/upper body	10	10	8	10
		Pronounced; clear movement of head, neck and ears, plus clear movement of whole body.	0	0	2	0

Table 10 (continued)
Toxicity Females
FOB Ranked

Endpoint	Time	#Examined / Response	Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
Response to Touch	Baseline	# Examined	10		10		10		10	
		Moderate; spontaneously lifts tail when touched	10		10		10		10	
	Treated	# Examined	10		10		10		10	
		Moderate; spontaneously lifts tail when touched	10		9		10		9	
		Pronounced; spontaneously lifts tail and acts startled	0		1		0		1	
Response to Tail Pinch	Baseline	# Examined	10		10		10		10	
		Moderate; animal flinches, moves rapidly and/or vocalizes	10		10		10		10	
	Treated	# Examined	10		10		10		10	
		Moderate; animal flinches, moves rapidly and/or vocalizes	9		10		10		10	
		Pronounced; animal moves vigorously in opposite direction of stimulation and vocalizes repeatedly and/or bends towards the tail and vocalizes	1		0		0		0	
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	4		3		5		2	
		Minimal; a few (1-4) small drops or a small pool (~1 cm)	3		5		2		2	
		Moderate; a few (1-4) small pools or a moderate pool (2-3 cm)	1		2		3		5	
		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	1		0		0		1	
	Treated	# Examined	10		10		10		10	
		No drops of urine	3		2		6		0	
		Minimal; a few (1-4) small drops or a small pool (~1 cm)	5		4		2		3	
		Moderate; a few (1-4) small pools or a moderate pool (2-3 cm)	2		3		0		5	
		Pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)	0		0		2		1	
		Exaggerated; >4 moderate pools or a single pool >5 cm	0		1		0		1	
Defecation	Baseline	# Examined	10		10		10		10	

Table 10 (continued)
Toxicity Females
FOB Ranked

Endpoint	Time	#Examined / Response	Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
		No pellets voided	8		10		9		7	
		Minimal; 1 or 2 pellets voided	2		0		1		3	
	Treated	# Examined	10		10		10		10	
		No pellets voided	9		9		7		7	
		Minimal; 1 or 2 pellets voided	1		1		1		1	
		Moderate; 3 pellets voided	0		0		0		2	
		Pronounced; 4 pellets voided	0		0		2		0	

Table 11
Toxicity Males
FOB Ranked

Endpoint	Time	#Examined / Response	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Resistance to Removal	Baseline	# Examined	10	10	10	10
		Moderate; actively avoids capture but is not aggressive	10	10	10	10
	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

Table 11 (continued)
Toxicity Males
FOB Ranked

Endpoint	Time	#Examined / Response	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
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
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	10	10	10
	Treated	# Examined	10	10	10	10
		Moderate; clearly detectable	10	10	8	10
		Pronounced; pushes vigorously	0	0	2	0
Reactivity to Handling	Baseline	# Examined	10	10	10	10
		Moderate struggling with little or no vocalization	10	10	10	10
	Treated	# Examined	10	10	10	10
		Moderate struggling with little or no vocalization	10	10	10	10
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
		None, rat doesn't leave the center circle (20 cm dia.)	0	0	0	1
		Minimal; inactive more than 50% of the time	6	3	5	5
		Moderate; inactive less than 50% of the time	4	7	5	4

Table II (continued)
Toxicity Males
FOB Ranked

Endpoint	Time	#Examined / Response	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Response to Sharp Noise	Baseline	# Examined	10	10	10	10
		Moderate; clear movement of the head, neck, ears and possibly shoulders/upper body	7	9	9	9
		Pronounced; clear movement of head, neck and ears, plus clear movement of whole body.	2	1	1	1
		Exaggerated; whole body response to stimulus more intense than "pronounced"; includes whole body going airborne	1	0	0	0
	Treated	# Examined	10	10	10	10
		Moderate; clear movement of the head, neck, ears and possibly shoulders/upper body	8	7	9	10
		Pronounced; clear movement of head, neck and ears, plus clear. movement of whole body.	2	3	1	0
Response to Touch	Baseline	# Examined	10	10	10	10
		Moderate; spontaneously lifts tail when touched	10	10	10	10
	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
		Moderate; animal flinches, moves rapidly and/or vocalizes	10	10	10	10
	Treated	# Examined	10	10	10	10
		Minimal; animal flinches and may vocalize slightly	1	0	1	0
		Moderate; animal flinches, moves rapidly and/or vocalizes	9	10	9	10
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

Table 11 (continued)
Toxicity Males
FOB Ranked

Endpoint	Time	#Examined / Response	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Urination	Baseline	# Examined	10	10	10	10
		No drops of urine	1	4	1	1
		Minimal; a few (1-4) small drops or a small pool (~1 cm)	3	2	1	0
		Moderate; a few (1-4) small pools or a moderate pool (2-3 cm)	3	1	2	3
		Pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)	1	0	3	2
		Exaggerated; >4 moderate pools or a single pool >5 cm	2	3	3	4
	Treated	# Examined	10	10	10	10
		No drops of urine	0	0	0	1
		Minimal; a few (1-4) small drops or a small pool (~1 cm)	1	1	0	1
		Moderate; a few (1-4) small pools or a moderate pool (2-3 cm)	2	1	3	2
		Pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)	2	3	3	4
		Exaggerated; >4 moderate pools or a single pool >5 cm	5	5	4	2
Defecation	Baseline	# Examined	10	10	10	10
		No pellets voided	4	5	4	6
		Minimal; 1 or 2 pellets voided	4	3	1	4
		Moderate; 3 pellets voided	2	2	4	0
		Pronounced; 4 pellets voided	0	0	1	0
	Treated	# Examined	10	10	10	10
		No pellets voided	3	2	6	2
		Minimal; 1 or 2 pellets voided	2	2	0	1
		Moderate; 3 pellets voided	1	2	1	3
		Pronounced; 4 pellets voided	1	3	2	4
		Exaggerated; 5 or more pellets voided	3	1	1	0

Table 12
Toxicity Females
Motor Activity

Endpoint	Time		Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Interval 1	Baseline	Mean	256	246	247	242
		Std	35	34	49	30
		N	10	10	10	10
	Treated	Mean	230	215	233	219
		Std	36	39	50	44
		N	10	10	10	10
Interval 2	Baseline	Mean	200	172	178	186
		Std	35	31	45	43
		N	10	10	10	10
	Treated	Mean	163	168	186	171
		Std	60	38	51	42
		N	10	10	10	10
Interval 3	Baseline	Mean	142	119	137	141
		Std	61	48	66	55
		N	10	10	10	10
	Treated	Mean	149	109	146	118
		Std	57	54	52	82
		N	10	10	10	10
Interval 4	Baseline	Mean	112	84	109	95
		Std	68	53	60	65
		N	10	10	10	10
	Treated	Mean	110	85	102	68
		Std	75	55	60	75
		N	10	10	10	10
Interval 5	Baseline	Mean	80	68	82	54
		Std	68	50	59	46
		N	10	10	10	10
	Treated	Mean	88	86	60	72
		Std	64	48	73	71
		N	10	10	10	10

Table 12 (continued)
Toxicity Females
Motor Activity

Endpoint	Time		Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Interval 6	Baseline	Mean	94	60	66	44
		Std	59	73	52	57
		N	10	10	10	10
	Treated	Mean	90	65	69	53
		Std	68	41	52	51
		N	10	10	10	10
Interval 7	Baseline	Mean	114	69	37	47
		Std	65	75	41	64
		N	10	10	10	10
	Treated	Mean	75	54	97	71
		Std	48	46	54	59
		N	10	10	10	10
Interval 8	Baseline	Mean	87	52	16	24
		Std	58	67	46	39
		N	10	10	10	10
	Treated	Mean	76	43	71	57
		Std	59	43	36	58
		N	10	10	10	10
Interval 9	Baseline	Mean	43	46	32	16
		Std	52	53	67	28
		N	10	10	10	10
	Treated	Mean	68	35	49	31
		Std	54	44	38	35
		N	10	10	10	10
Interval 10	Baseline	Mean	36	43	27	12
		Std	51	64	46	30
		N	10	10	10	10
	Treated	Mean	48	47	49	29
		Std	49	46	38	30
		N	10	10	10	10
Total	Baseline	Mean	1162	958	929	860
		Std	381	357	316	255
		N	10	10	10	10
	Treated	Mean	1096	908	1061	889
		Std	428	276	286	398
		N	10	10	10	10

Table 13
Toxicity Males
Motor Activity

Endpoint	Time		Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Interval 1	Baseline	Mean	235	215	229	234
		Std	34	40	49	55
		N	10	10	10	10
	Treated	Mean	221	217	220	192
		Std	56	42	36	38
		N	10	10	10	10
Interval 2	Baseline	Mean	153	151	138	145
		Std	46	34	40	64
		N	10	10	10	10
	Treated	Mean	154	161	126	143
		Std	39	38	25	34
		N	10	10	10	10
Interval 3	Baseline	Mean	120	119	96	122
		Std	49	49	25	65
		N	10	10	10	10
	Treated	Mean	106	74	79	91
		Std	30	27	51	40
		N	10	10	10	10
Interval 4	Baseline	Mean	88	68	54	77
		Std	63	58	47	63
		N	10	10	10	10
	Treated	Mean	61	42	50	60
		Std	54	29	37	37
		N	10	10	10	10
Interval 5	Baseline	Mean	60	31	28	56
		Std	47	29	46	54
		N	10	10	10	10
	Treated	Mean	54	36	45	23
		Std	48	47	46	29
		N	10	10	10	10

Table 13 (continued)
Toxicity Males
Motor Activity

Endpoint	Time		Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Interval 6	Baseline	Mean	31	27	18	28
		Std	53	66	34	54
		N	10	10	10	10
	Treated	Mean	41	22	41	55
		Std	38	27	37	56
		N	10	10	10	10
Interval 7	Baseline	Mean	13	13	16	22
		Std	17	41	38	53
		N	10	10	10	10
	Treated	Mean	24	23	32	32
		Std	36	26	24	48
		N	10	10	10	10
Interval 8	Baseline	Mean	6	2	5	7
		Std	11	6	14	17
		N	10	10	10	10
	Treated	Mean	18	23	18	27
		Std	41	40	22	48
		N	10	10	10	10
Interval 9	Baseline	Mean	1	2	4	9
		Std	2	5	13	28
		N	10	10	10	10
	Treated	Mean	16	20	12	17
		Std	35	37	20	18
		N	10	10	10	10
Interval 10	Baseline	Mean	1	9	12	11
		Std	2	28	36	20
		N	10	10	10	10
	Treated	Mean	18	16	18	24
		Std	37	25	34	34
		N	10	10	10	10
Total	Baseline	Mean	708	636	599	711
		Std	239	213	183	380
		N	10	10	10	10
	Treated	Mean	712	633	638	663
		Std	305	189	150	261
		N	10	10	10	10

Table 14
Reproductive Females
Microscopic Findings

Organ	Finding	Examined/Grade	Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
BONE MARROW, STERNUM	Atrophy	# Examined	10		0		0		9	
		All Grades	0		0		0		1	
		Moderate	0		0		0		1	
BRAIN	white matter Degeneration	# Examined	10		10		10		10	
		All Grades	0	+++	0		0		8	+++
		Minimal	0		0		0		4	
		Mild	0		0		0		1	
		Moderate	0		0		0		2	
		Marked	0		0		0		1	
KIDNEYS	Inflammation chronic	# Examined	10		0		0		10	
		All Grades	1		0		0		0	
		Minimal	1		0		0		0	
	pelvis Hyperplasia bilateral diffuse	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Mild	0		0		0		1	
	pelvis Inflammation chronic	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Mild	0		0		0		1	
	cortex Infarction chronic focal	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Mild	0		0		0		1	
	tubule Basophilia	# Examined	10		0		0		10	
		All Grades	3		0		0		0	
		Minimal	3		0		0		0	
LIVER	Inflammation chronic multifocal	# Examined	10		10		10		10	
		All Grades	0		1		0		2	
		Minimal	0		1		0		2	
	Extramedullary Hematopoiesis	# Examined	10		10		10		10	
		All Grades	0		1		0		0	
		Minimal	0		1		0		0	
	centrilobular Hypertrophy	# Examined	10		10		10		10	
		All Grades	0	+++	0		10	+++	10	+++
		Minimal	0		0		10		3	
		Mild	0		0		0		6	
		Moderate	0		0		0		1	
	centrilobular Vacuolation	# Examined	10		10		10		10	
		All Grades	0	+	0		0		2	
		Minimal	0		0		0		2	

Table 14 (continued)
Reproductive Females
Microscopic Findings

Organ	Finding	Examined/Grade	Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
LUNGS	Congestion	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Mild	0		0		0		1	
	Histocytosis	# Examined	10		0		0		10	
		All Grades	5		0		0		2	
		Minimal	5		0		0		2	
LYMPH NODE, MEDIASTINAL	Atrophy	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Mild	0		0		0		1	
NERVE, SCIATIC	Degeneration	# Examined	10		10		10		10	
		All Grades	0	+++	0		0		8	+++
		Minimal	0		0		0		1	
		Moderate	0		0		0		3	
		Marked	0		0		0		4	
NERVE, TIBIAL	Degeneration	# Examined	10		10		10		9	
		All Grades	0	+++	0		0		9	+++
		Minimal	0		0		0		2	
		Mild	0		0		0		3	
		Moderate	0		0		0		3	
		Marked	0		0		0		1	
SKELETAL MUSCLE, ADDUCTOR	Degeneration	# Examined	10		10		10		10	
		All Grades	4	+++	1		2		10	+++
		Minimal	3		0		1		4	
		Mild	1		1		1		3	
		Moderate	0		0		0		2	
		Marked	0		0		0		1	
	Inflammation, Chronic	# Examined	10		10		10		10	
		All Grades	2		0		0		0	
		Mild	2		0		0		0	
SKELETAL MUSCLE, GASTROCNEMIUS	Degeneration	# Examined	10		10		10		10	
		All Grades	5	++*	0		3		9	
		Minimal	5		0		3		3	
		Mild	0		0		0		3	
		Moderate	0		0		0		1	
		Marked	0		0		0		2	
	Inflammation, Chronic	# Examined	10		10		10		10	
		All Grades	0		2		1		0	
		Minimal	0		0		1		0	
		Mild	0		2		0		0	
SPINAL CORD	white matter Degeneration	# Examined	10		9		9		10	
		All Grades	0	+++	1		1		9	+++
		Minimal	0		1		1		2	
		Mild	0		0		0		2	
		Moderate	0		0		0		2	

Table 14 (continued)
Reproductive Females
Microscopic Findings

Organ	Finding	Examined/Grade	Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
		Marked	0		0		0		3	
SPLEEN	Atrophy	# Examined	10		10		10		10	
		All Grades	0	+++	0		0		5	++
		Mild	0		0		0		3	
		Moderate	0		0		0		2	
STOMACH	glandular Ulceration focal	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Mild	0		0		0		1	
THYMUS	Atrophy	# Examined	10		10		10		9	
		All Grades	0	+++	0		0		5	++
		Moderate	0		0		0		5	
THYROID GLANDS	Cyst ultimobranchial	# Examined	10		0		0		10	
		Present	1		0		0		2	
URINARY BLADDER	Hyperplasia epithelial diffuse	# Examined	10		10		10		10	
		All Grades	0	+++	2		0		7	+++
		Minimal	0		1		0		3	
		Mild	0		1		0		4	
	Inflammation chronic	# Examined	10		10		10		10	
		All Grades	0		1		0		0	
		Minimal	0		1		0		0	
UTERUS	Pregnant	# Examined	10		0		0		10	
		Present	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 15
Toxicity Females
Microscopic Findings

Organ	Finding	Examined/Grade	Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
BRAIN	Nematodiasis	# Examined	10		10		10		10	
		All Grades	1		0		0		0	
		Minimal	1		0		0		0	
	white matter Degeneration	# Examined	10		10		10		10	
		All Grades	1	+	0		1		4	
		Minimal	1		0		1		4	
HEART	Degeneration	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Minimal	0	–	0		0		1	
KIDNEYS	Chronic Progressive Nephropathy	# Examined	10		0		0		10	
		All Grades	2		0		0		2	
		Minimal	2		0		0		1	
		Mild	0		0		0		1	
	Inflammation chronic	# Examined	10		0		0		10	
		All Grades	3		0		0		0	
		Minimal	3		0		0		0	
	pelvis Hyperplasia bilateral diffuse	# Examined	10		0		0		10	
		All Grades	0		0		0		0	
	cortex Cyst	# Examined	10		0		0		10	
		Present	0		0		0		2	
	tubule Basophilia	# Examined	10		0		0		10	
		All Grades	0		0		0		2	
		Minimal	0		0		0		2	
LIVER	Inflammation chronic multifocal	# Examined	10		10		10		10	
		All Grades	7		10		5		9	
		Minimal	7		10		5		9	
	centrilobular Hypertrophy	# Examined	10		10		10		10	
		All Grades	0	+++	0		4	+	10	+++
		Minimal	0		0		4		1	
		Mild	0		0		0		9	
	periportal Vacuolation	# Examined	10		10		10		10	
		All Grades	3		1		3		2	
		Minimal	1		1		3		1	
		Mild	1		0		0		1	
		Moderate	1		0		0		0	
LUNGS	Inflammation chronic	# Examined	10		0		0		10	
		All Grades	1		0		0		0	
		Minimal	1		0		0		0	
	Histocytosis	# Examined	10		0		0		10	
		All Grades	3		0		0		4	
		Minimal	3		0		0		4	

Table 15 (continued)
Toxicity Females
Microscopic Findings

Organ	Finding	Examined/Grade	Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
NERVE, SCIATIC	Degeneration	# Examined	10		10		10		10	
		All Grades	0	+	1		0		3	
		Minimal	0		1		0		1	
		Mild	0		0		0		2	
SPINAL CORD	white matter Degeneration	# Examined	10		10		10		10	
		All Grades	0	+++	0		0		5	++
		Minimal	0		0		0		4	
		Mild	0		0		0		1	
STOMACH	Hyperkeratosis	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Mild	0		0		0		1	
	Edema	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Minimal	0		0		0		1	
	mucosa non-glandular Vacuolation	# Examined	10		0		0		10	
		All Grades	1		0		0		0	
		Mild	1		0		0		0	
THYMUS	Atrophy	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Minimal	0		0		0		1	
THYROID GLANDS	Cyst ultimobranchial	# Examined	10		0		0		10	
		Present	2		0		0		1	
	Ectopic Thymus	# Examined	10		0		0		10	
		Present	1		0		0		0	
	colloid Vacuolation	# Examined	10		0		0		10	
		All Grades	1		0		0		1	
		Minimal	1		0		0		1	
URINARY BLADDER	Hyperplasia epithelial diffuse	# Examined	10		10		10		10	
		All Grades	2		0		0		2	
		Minimal	2		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 16
Toxicity Males
Microscopic Findings

Organ	Finding	Examined/Grade	Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
ADRENAL GLANDS	cortex Hypertrophy focal	# Examined	10		0		0		10	
		All Grades	1		0		0		0	
		Minimal	1		0		0		0	
BRAIN	meninges Inflammation chronic	# Examined	10		0		0		10	
		All Grades	1		0		0		0	
		Minimal	1		0		0		0	
HEART	Inflammation chronic	# Examined	10		0		0		10	
		All Grades	2		0		0		2	
		Minimal	2		0		0		2	
KIDNEYS	Chronic Progressive Nephropathy	# Examined	10		10		10		10	
		All Grades	1		0		3		1	
		Minimal	1		0		3		1	
	Inflammation chronic	# Examined	10		10		10		10	
		All Grades	2		1		0		0	
		Minimal	1		1		0		0	
		Mild	1		0		0		0	
	Inflammation chronic-active	# Examined	10		10		10		10	
		All Grades	1		0		0		0	
		Mild	1		0		0		0	
	pelvis Hyperplasia bilateral diffuse	# Examined	10		10		10		10	
		All Grades	0		1		0		2	
		Minimal	0		0		0		1	
		Moderate	0		1		0		1	
	pelvis Inflammation chronic-active	# Examined	10		10		10		10	
		All Grades	0		1		0		1	
		Moderate	0		1		0		1	
	cortex Necrosis focal	# Examined	10		10		10		10	
		All Grades	0		0		1		0	
		Mild	0		0		1		0	
	cortex Cyst	# Examined	10		10		10		10	
		Present	1		0		0		0	
	tubule Basophilia	# Examined	10		10		10		10	
		All Grades	5		1		1		2	
		Minimal	5		1		1		2	
LIVER	Inflammation chronic multifocal	# Examined	10		10		10		10	
		All Grades	8		7		4		8	
		Minimal	8		7		4		8	
	Necrosis focal	# Examined	10		10		10		10	
		All Grades	0		0		0		1	
		Minimal	0		0		0		1	
	centrilobular Hypertrophy	# Examined	10		10		10		10	
		All Grades	0	+++	2		8	+++	10	+++
		Minimal	0		2		8		7	
		Mild	0		0		0		3	

Table 16 (continued)
Toxicity Males
Microscopic Findings

Organ	Finding	Examined/Grade	Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
LIVER (Continued)	midzonal Vacuolation	# Examined	10		10		10		10	
		All Grades	0		1		0		0	
		Mild	0		1		0		0	
	periportal Vacuolation	# Examined	10		10		10		10	
		All Grades	1		0		0		0	
		Minimal	1		0		0		0	
LUNGS	Inflammation chronic	# Examined	10		0		0		10	
		All Grades	1		0		0		0	
		Minimal	1		0		0		0	
	Inflammation subacute	# Examined	10		0		0		10	
		All Grades	1		0		0		1	
		Minimal	1		0		0		0	
		Mild	0		0		0		1	
	Histocytosis	# Examined	10		0		0		10	
		All Grades	4		0		0		5	
		Minimal	4		0		0		4	
		Mild	0		0		0		1	
	Hypertrophy vascular	# Examined	10		0		0		10	
		All Grades	0		0		0		1	
		Minimal	0		0		0		1	
NERVE, SCIATIC	Degeneration	# Examined	10		0		0		10	
		All Grades	1		0		0		2	
		Minimal	1		0		0		2	
PROSTATE GLAND	Hyperplasia focal	# Examined	10		0		0		10	
		All Grades	0		0		0		2	
		Mild	0		0		0		2	
	Inflammation chronic	# Examined	10		0		0		10	
		All Grades	2		0		0		1	
		Minimal	1		0		0		1	
		Mild	1		0		0		0	
	Inflammation chronic-active	# Examined	10		0		0		10	
		All Grades	1		0		0		2	
		Mild	1		0		0		2	
STOMACH	non-glandular Cyst	# Examined	10		0		0		10	
		Present	0		0		0		1	
THYROID GLANDS	Cyst ultimobranchial	# Examined	10		0		0		10	
		Present	0		0		0		2	

Table 16 (continued)
Toxicity Males
Microscopic Findings

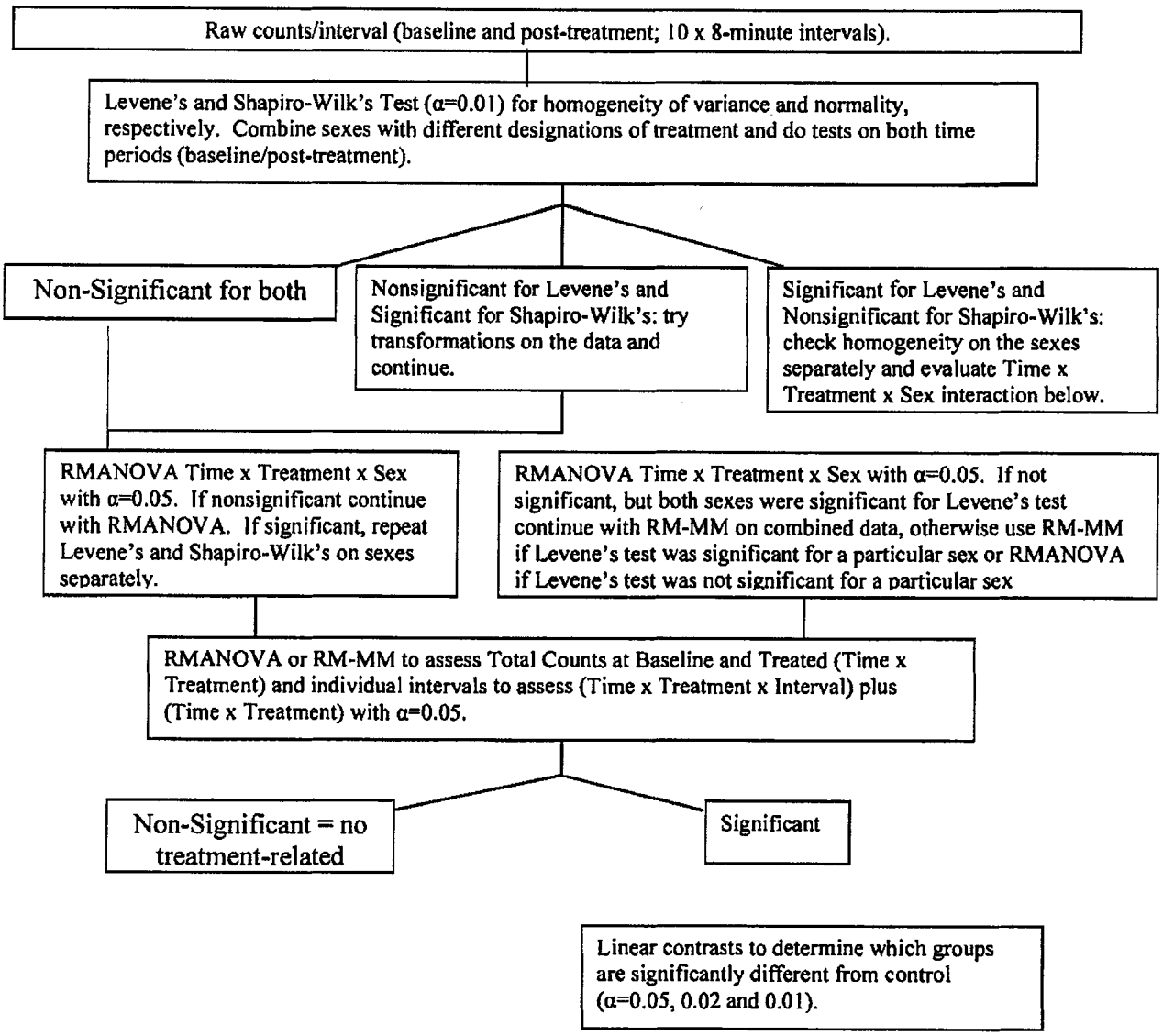
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)		100 mg/kg/day		300 mg/kg/day		1000 mg/kg/day	
URINARY BLADDER	Hyperplasia epithelial diffuse	# Examined	9		10		10		10	
		All Grades	0	+++	1		0		7	+++
		Minimal	0		0		0		4	
		Mild	0		1		0		3	
	Inflammation chronic	# Examined	9		10		10		10	
		All Grades	0		2		0		1	
		Minimal	0		2		0		1	
URINARY BLADDER (continued)	Inflammation chronic-active	# Examined	9		10		10		10	
		All Grades	0		0		0		1	
		Mild	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.

Attachments

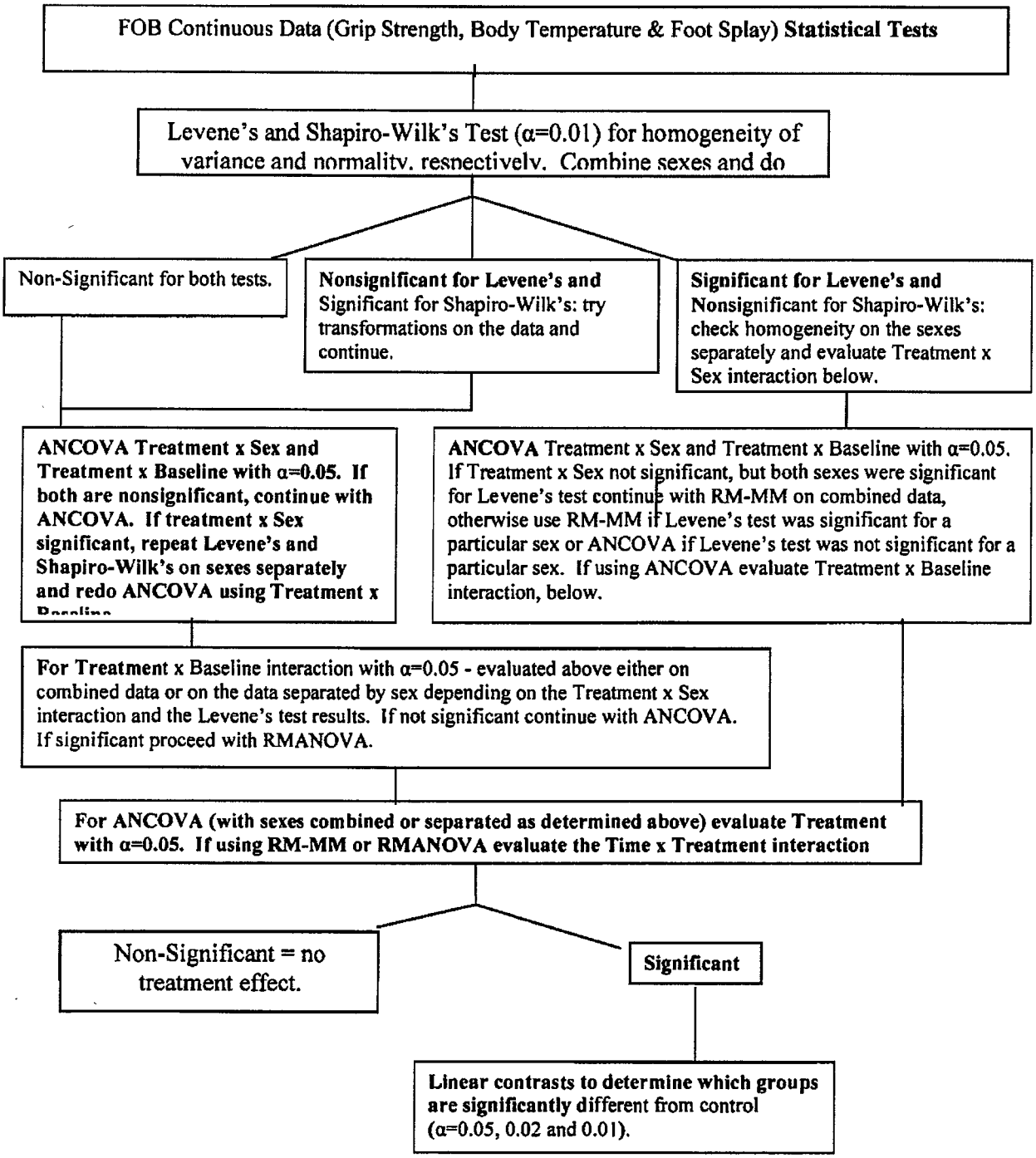
Attachment 1

Motor Activity Statistical Tests



APPENDIX R

Attachment 2



Note: ANCOVA = Analysis of Covariance; RM-MM = Repeated Measures Mixed Modeling; RMANOVA = Repeated Measures Analysis of Variance. The p-value given for the Type III SS is used for ANCOVA and RM-MM and Pillia's

APPENDIX R

Attachment 3

FOB Ranked Data Statistical Tests

Animals are scored from 1-5 (lowest to highest) based on the intensity level displayed by the animal for each observation.

Not tested for normality or equal variances. Uses baseline and post-treatment data separated by sex are analyzed separately. Baseline data analysis to be used as reference.

Jonckheere-Terpstra Test ($\alpha = 0.05$ for overall comparison and 0.02 for pair wise comparisons using two-sided p-values)

APPENDIX S

DOW CORNING CORPORATION
HEALTH & ENVIRONMENTAL SCIENCES (HES)

CONTRIBUTING SCIENTIST REPORT

Report Title:	Functional Observational Battery (FOB) and Motor Activity Results for a Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Triethoxyoctylsilane in Sprague-Dawley Rats via Oral Gavage
Study Number:	10709-102
Test Article:	Triethoxyoctylsilane
Contributing Scientist:	Teresa A. Cortner, B.G.S. HES Toxicologist
Study Director:	Tami S. McMullin, Ph.D.
Sponsor:	Silicones Environmental, Health and Safety Council 2325 Dulles Corner Blvd., Suite 500 Herndon, VA 20171
HES Group Manager:	Paul A. Jean, Ph.D. Team Leader, Toxicology Health and Environmental Sciences
Testing Facility:	Dow Corning Corporation Health and Environmental Sciences (HES) 2200 W. Salzburg Road Auburn, Michigan 48611
Analysis Start Date:	April 07, 2008
Analysis End Date:	May 09, 2008

APPENDIX S

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APPENDIX S

1. APPROVAL SIGNATURES

Report Title: Functional Observational Battery (FOB) and Motor Activity Results for a Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Triethoxyoctylsilane in Sprague-Dawley Rats via Oral Gavage

Submitted by: Dow Corning Corporation
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Approved by: Teresa A. Cortner 05 January 2010
Teresa A. Cortner, B.G.S. Date
HES Toxicologist
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Paul A. Jean, Ph.D. Date
Team Leader, Toxicology
Health and Environmental Sciences

2. OBJECTIVE

Functional Observational Battery (FOB) and Evaluation of motor activity were performed to screen for neurotoxic effects of the test article on the designated toxicity groups.

3. MATERIALS AND METHODS

In the week prior to exposure (baseline) and during week four of exposure (treated), all animals of the toxicity groups were screened for neurotoxic effects using a Functional Observational Battery (FOB) and evaluation of motor activity. The FOB was conducted blind to treatment, under red lighting, and consisted of 2 types of data, ranked and continuous. The room temperature and relative humidity in the FOB lab (Room 225) was continuously monitored during testing. The actual room temperature range was between (22.1°C - 24.4°C) and the humidity was maintained between (29% - 63% RH). The 29% RH is outside of the required RH range of (30% - 70%). This drop in humidity occurred at 11:00 am at a time when there were no animals present in the room and therefore did not negatively impact the study. The room temperature and relative humidity was also continuously monitored in the Motor Activity lab (Room 222), however the data from this monitoring is inadvertently not available for the treated testing which occurred the week of 5/5 thru 5/9. The actual room temperature range was between (21.0°C and 22.1°C) and the humidity was maintained between (28% - 57% RH) for baseline testing. The 28% RH is outside of the required RH range of (30% - 70%). This drop in humidity occurred while animals were being tested, but is only 2% below the required range, and is not believed to have negatively affected Motor Activity results. The first part of the FOB consisted of numerous hand-held and open field observations, which were ranked on a scale from 1-5 (none/low-exaggerated response). The second part of the FOB consisted of quantitative measurement of body temperature (rectal, Celsius), hindlimb/forelimb grip strength (grams), and landing foot splay (centimeters). Motor activity testing was conducted under reduced fluorescent lighting (approximately 121 lux) along with background noise (approximately 62 db white noise) to reduce the potential for distraction. The motor activity data (beam breaks or counts) were collected with a photobeam-type system and only ambulatory movement was assessed over 10, 8-minute intervals. To reduce any potential bias, the motor activity groups were counter-balanced across sessions and devices whenever possible (i.e., one animal from each group was tested in each session and in each device).

Pupil response was evaluated with a halogen penlite. An electronic solenoid valve (Skinner, Model #71315SN2GNJ1) was used to evaluate the response to sharp noise (measured at approximately 100 db). Rectal temperatures were measured using a YSI 4000 thermometer with a Model 402 probe. Grip strength was evaluated using a device manufactured for Dow Corning Corporation, which consisted of a horizontal coarse wire screen supported by four wheels attached to an electronic strain gauge (Chatillon, Model DFGS-R-ND with 10 kg load cell). Foot splay markings were measured with a digitizer (GTCO CalComp, Model Super L IV with a QuickRuler III measurement system). Motor Activity was measured with a Cage Rack Activity System (San Diego

Instruments), which consisted of 7 photobeams spaced equally down the long sides of the rectangular units and PAS V.2.03 Software.

4. DATA ANALYSIS

Motor activity data was analyzed using a repeated measurements ANOVA 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.

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 (Jonkheere-Terpstra, 1956).

5. PROTOCOL DEVIATIONS

There were no protocol deviations for neurotoxicity screening.

6. RESULTS AND DISCUSSION

6.1. FOB Ranked Tests

The incidence of the various ranked scores recorded during the FOB testing was tabulated by group and can be found in Tables 1 and 2. Individual data are listed in Attachments A-F. There were no statistically significant or biologically relevant differences between the control and treatment groups in either sex at either of the time points for the FOB ranked tests: resistance to removal, palpebral closure, pupil reactivity, pupil size, lacrimation, salivation, muscle tone, extensor thrust response, reactivity to handling, level of activity, responsiveness to sharp noise, touch, tail pinch, gait evaluation, urination, defecation and categorical observations.

6.2. FOB Continuous Tests

A summary of the FOB continuous tests can be found in Tables 3 and 4. The individual animal data are located in Attachments H-K. Statistical analysis followed the flow chart which can be found in the Statistical Contributing Scientist Report (see Appendix R of the main report).

Body Temperature

There were no differences between either the male or the female treatment groups and their respective control groups for body temperature that were statistically significant or considered to be biologically relevant.

Hindlimb Grip Strength

There were no statistically significant or biologically relevant differences between either the male or the female treatment groups and their respective control groups for hindlimb grip strength.

Forelimb Grip Strength

There were no statistically significant or biologically relevant differences between the treatment groups and the control group for forelimb grip strength. In addition, no difference was observed between the male and female treatment groups and their respective control groups.

Landing Foot Splay

There were no statistically significant or biologically relevant differences between male or female treatment groups and their respective control groups for landing foot splay.

6.3. Motor Activity

A summary of the motor activity data can be found in Tables 5 and 6. Individual animal data is located in Attachments L-O. Total counts and habituation (decrease in exploratory behavior over time) were analyzed statistically for differences compared to control. Statistical analysis followed the flow chart which can be found in the Statistical Contributing Scientist Report (see Appendix R of main report).

Total Counts

There were no statistically significant or biologically relevant differences between the treatment groups and the control group for motor activity.

Habituation

There were no statistically significant or biologically relevant differences noted between the treatment groups and the control group for motor activity habituation for either male or female.

7. CONCLUSIONS

Based on the evaluations performed, as described within the context of this contributing scientist report, there were no treatment-related effects associated with Triethoxyoctylsilane exposure on rat neurobiological function.

8. REFERENCES

1. OECD Guideline for Testing of Chemicals, "Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test", No. 422, Adopted March 22, 1996.

2. EPA Health Effects Test Guidelines, "OPPTS 870.6200 Neurotoxicity Screening Battery", August 1998.

Table 1 Summary of FOB Ranked/Categorical Incidence - Male Toxicity Groups

	Baseline				Treated			
Dose Group	1	2	3	4	1	2	3	4
Number of Animals Examined	10	10	10	10	10	10	10	10
Resistance to Removal								
(3) Moderate; actively avoids capture but is not aggressive	10	10	10	10	10	10	10	10
Palpebral Closure								
(3) Open	10	10	10	10	10	10	10	10
Pupil Reactivity								
(3) dilated, briskly reactive pupil	10	10	10	10	10	10	10	10
Pupil Size								
(3) Normal pupil size	10	10	10	10	10	10	10	10
Lacrimation								
(3) Glistening cornea	10	10	10	10	10	10	10	10
Salivation								
(3) glistening oral cavity/lips, no wetness	10	10	10	10	10	10	10	10
Muscle Tone								
(3) moderate; animal is neither very relaxed nor tense	10	10	10	10	10	10	10	10

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Table 1 Summary of FOB Ranked/Categorical Incidence - Male Toxicity Groups (continued)

	Baseline				Treated			
Dose Group	1	2	3	4	1	2	3	4
Number of Animals Examined	10	10	10	10	10	10	10	10
Extensor Thrust								
(3) moderate; clearly detectable	10	10	10	10	10	10	8	10
(4) Pronounced; pushes vigorously	0	0	0	0	0	0	2	0
Reactivity to Handling								
(3) moderate struggling with little or no vocalization	10	10	10	10	10	10	10	10
Level of Activity								
(1) None, animal doesn't leave the center circle (20 cm dia.)	0	0	0	0	0	0	0	1
(2) minimal, inactive more than 50% of the time	0	0	0	0	6	3	5	5
(3) moderate, inactive less than 50% of the time	10	10	10	10	4	7	5	4
Response to Noise								
(3) moderate; clear movement of the head, neck, ears and possibly front shoulders/upper body	7	9	9	9	8	7	9	10
(4) pronounced; clear movement of head, neck and ears, plus clear movement of whole body	2	1	1	1	2	3	1	0
(5) exaggerated; whole body response to stimulus, more intense than "pronounced"; includes whole body	1	0	0	0	0	0	0	0
Response to Touch								
(3) moderate; spontaneously lifts tail when touched	10	10	10	10	10	10	10	10

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Table 1 Summary of FOB Ranked/Categorical Incidence - Male Toxicity Groups (continued)

	Baseline				Treated			
Dose Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Number of Animals Examined	10	10	10	10	10	10	10	10
Response to Tail Pinch								
(2) minimal; animal flinches and may vocalize	0	0	0	0	1	0	1	0
(3) moderate; animal flinches, moves rapidly and/or vocalizes	10	10	10	10	9	10	9	10
Gait Evaluation								
(1) smooth and coordinated gait	10	10	10	10	10	10	10	10
Urination								
(1) no drops of urine	1	4	1	1	0	0	0	1
(2) minimal; a few (1-4) small drops or a small pool (~1 cm)	3	2	1	0	1	1	0	1
(3) moderate; a few (1-4) small pools or a moderate pool (2-3 cm)	3	1	2	3	2	1	3	2
(4) pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)	1	0	3	2	2	3	3	4
(5) Exaggerated; >4 moderate pools or single pool >5 cm.	2	3	3	4	5	5	4	2

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Table 1 Summary of FOB Ranked/Categorical Incidence - Male Toxicity Groups (continued)

	Baseline				Treated			
Dose Group	1	2	3	4	1	2	3	4
Number of Animals Examined	10	10	10	10	10	10	10	10
Defecation								
(1) no pellets voided	4	5	4	6	3	2	6	2
(2) minimal; 1 or 2 pellets voided	4	3	1	4	2	2	0	1
(3) moderate ; 3 pellets voided	2	2	4	0	1	2	1	3
(4) pronounced; 4 pellets voided	0	0	1	0	1	3	2	4
(5) Exaggerated; 5 or more pellets voided	0	0	0	0	3	1	1	0
Categorical Observations								
Behavior Repetitive (Head Sway)	0	0	0	0	0	1	0	0
No Abnormalities Detected	10	10	10	10	10	9	10	10

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Table 2 Summary of FOB Ranked/Categorical Incidence - Female Toxicity Groups

	Baseline				Treated			
Dose Group	1	2	3	4	1	2	3	4
Number of Animals Examined	10	10	10	10	10	10	10	10
Resistance to Removal								
(3) Moderate; actively avoids capture but is not aggressive	10	8	10	10	10	10	10	10
(4) Pronounced; actively avoids capture and/or is mildly aggressive	0	2	0	0	0	0	0	0
Palpebral Closure								
(3) Open	10	10	10	10	10	10	10	10
Pupil Reactivity								
(3) dilated, briskly reactive pupil	10	10	10	10	10	10	10	10
Pupil Size								
(3) Normal pupil size	10	10	10	10	10	10	10	10
Lacrimation								
(3) Glistening cornea	10	10	10	10	10	10	10	10
Salivation								
(3) glistening oral cavity/lips, no wetness	10	10	10	10	10	10	10	10
Muscle Tone								
(3) moderate; animal is neither very relaxed nor tense	10	10	10	10	10	10	10	10

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Table 2 Summary of FOB Ranked/Categorical Incidence - Female Toxicity Groups (continued)

	Baseline				Treated			
Dose Group	1	2	3	4	1	2	3	4
Number of Animals Examined	10	10	10	10	10	10	10	10
Extensor Thrust								
(3) moderate; clearly detectable	10	10	10	10	10	10	10	10
Reactivity to Handling								
(3) moderate struggling with little or no vocalization	9	9	10	10	10	10	10	10
(4) pronounced struggling, animal may vocalize	1	1	0	0	0	0	0	0
Level of Activity								
(2) minimal, inactive more than 50% of the time	0	0	0	0	1	1	2	0
(3) moderate, inactive less than 50% of the time	10	10	9	9	8	9	8	10
(4) pronounced; leaves circle, occasional inactivity	0	0	1	1	1	0	0	0
Response to Noise								
(3) moderate; clear movement of the head, neck, ears and possibly front shoulders/upper body	8	10	8	9	10	10	8	10
(4) pronounced; clear movement of head, neck and ears, plus clear movement of whole body	2	0	1	1	0	0	2	0
(5) exaggerated; whole body response to stimulus, more intense than "pronounced"; includes whole body	0	0	1	0	0	0	0	0

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Table 2 Summary of FOB Ranked/Categorical Incidence - Female Toxicity Groups (continued)

	Baseline				Treated			
Dose Group	1	2	3	4	1	2	3	4
Number of Animals Examined	10	10	10	10	10	10	10	10
Response to Touch								
(3) moderate; spontaneously lifts tail when touched	10	10	10	10	10	9	10	9
(4) Pronounced; spontaneously lifts tail and acts startled	0	0	0	0	0	1	0	1
Response to Tail Pinch								
(3) moderate; animal flinches, moves rapidly and/or vocalizes	10	10	10	10	9	10	10	10
(4) Pronounced; animal moves vigorously in opposite direction of source of stimulation and vocalized	0	0	0	0	1	0	0	0
Gait Evaluation								
(1) smooth and coordinated gait	10	10	10	10	10	10	10	10
Urination								
(1) no drops of urine	4	3	5	2	3	2	6	0
(2) minimal; a few (1-4) small drops or a small pool (~1 cm)	3	5	2	2	5	4	2	3
(3) moderate; a few (1-4) small pools or a moderate pool (2-3 cm)	1	2	3	5	2	3	0	5
(4) pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)	1	0	0	0	0	0	2	1
(5) Exaggerated; >4 moderate pools or single pool >5 cm.	1	0	0	1	0	1	0	1

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Table 2 Summary of FOB Ranked/Categorical Incidence - Female Toxicity Groups (continued)

	Baseline				Treated			
Dose Group	1	2	3	4	1	2	3	4
Number of Animals Examined	10	10	10	10	10	10	10	10
Defecation								
(1) no pellets voided	8	10	9	7	9	9	7	7
(2) minimal; 1 or 2 pellets voided	2	0	1	3	1	1	1	1
(3) moderate ; 3 pellets voided	0	0	0	0	0	0	0	2
(4) pronounced; 4 pellets voided	0	0	0	0	0	0	2	0
Categorical Observations								
Soiling Chin (Red)	0	0	0	0	0	0	0	1
No Abnormalities Detected	10	10	10	10	10	10	10	9

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Table 3 FOB Continuous Data Summary - Male Toxicity Groups

Group Sex		Baseline				Treated			
		Rectal Temperature (°C)	Hindlimb Grip Strength (g)	Forelimb Grip Strength (g)	Landing Foot Splay (cm)	Rectal Temperature (°C)	Hindlimb Grip Strength (g)	Forelimb Grip Strength (g)	Landing Foot Splay (cm)
1m	Mean	37.8	690.0	790.3	12.2	38.0	1272.5	1197.8	11.2
	S.D.	0.4	74.8	147.9	2.2	0.4	128.9	202.7	1.7
	N	10	10	10	10	10	10	10	10
2m	Mean	38.0	752.8	856.3	12.4	38.2	1196.2	1329.8	12.2
	S.D.	0.3	68.5	110.8	2.2	0.4	161.0	222.7	1.8
	N	10	10	10	10	10	10	10	10
3m	Mean	38.0	692.3	776.7	11.4	37.9	1140.5	1088.7	11.2
	S.D.	0.5	134.9	126.7	1.6	0.4	178.1	238.2	1.5
	N	10	10	10	10	10	10	10	10
4m	Mean	38.1	733.0	783.8	12.9	37.9	1116.5	1036.2	12.2
	S.D.	0.3	116.4	139.8	2.1	0.4	170.3	232.4	2.0
	N	10	10	10	10	10	10	10	10

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Table 4 FOB Continuous Data Summary - Female Toxicity Groups

Group Sex		Baseline				Treated			
		Rectal Temperature (°C)	Hindlimb Grip Strength (g)	Forelimb Grip Strength (g)	Landing Foot Splay (cm)	Rectal Temperature (°C)	Hindlimb Grip Strength (g)	Forelimb Grip Strength (g)	Landing Foot Splay (cm)
1f	Mean	38.4	608.3	700.0	11.1	38.6	987.0	966.8	10.5
	S.D.	0.4	89.4	73.2	1.8	0.5	101.5	150.4	2.0
	N	10	10	10	10	10	10	10	10
2f	Mean	38.2	653.0	714.3	10.6	38.4	959.5	1009.0	9.1
	S.D.	0.4	112.2	148.3	2.0	0.4	125.7	276.1	1.6
	N	10	10	10	10	10	10	10	10
3f	Mean	38.4	665.8	749.2	10.6	38.3	985.3	1025.0	10.0
	S.D.	0.4	123.2	93.3	1.9	0.6	153.7	159.9	1.4
	N	10	10	10	10	10	10	10	10
4f	Mean	38.0	624.7	782.5	9.4	38.4	868.2	887.3	8.8
	S.D.	0.4	116.7	118.1	1.5	0.3	157.1	154.2	2.1
	N	10	10	10	10	10	10	10	10

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Table 5 Motor Activity Summary - Male Toxicity Groups

		Baseline				Treated			
Interval	Group/Sex	1m	2m	3m	4m	1m	2m	3m	4m
(8 minutes)	N	10	10	10	10	10	10	10	10
1	Mean	234.8	215.3	228.5	233.9	220.6	216.5	219.6	191.5
	S.D.	34.5	39.8	48.8	55.2	56.2	41.7	35.5	38.5
2	Mean	152.8	151.3	137.5	145.1	154.1	160.5	125.7	142.5
	S.D.	46.2	34.1	40.5	64.3	39.1	38.3	25.3	33.6
3	Mean	120.4	118.5	95.9	121.8	105.5	74.1	78.9	91.0
	S.D.	48.5	49.1	24.5	65.1	29.8	26.9	51.3	40.0
4	Mean	87.6	68.0	54.3	77.1	61.1	42.2	49.6	59.9
	S.D.	62.5	58.1	47.4	62.7	54.3	29.3	37.2	37.1
5	Mean	59.8	30.6	28.0	55.8	53.7	35.8	44.7	23.0
	S.D.	46.8	29.1	45.5	54.2	47.6	47.0	46.4	29.1
6	Mean	31.3	26.8	18.0	28.4	41.0	22.3	40.5	55.3
	S.D.	53.5	65.8	33.6	54.2	38.3	27.3	37.2	55.9
7	Mean	13.4	12.9	15.8	22.0	24.3	22.7	31.7	31.8
	S.D.	17.0	40.8	37.6	52.8	35.6	26.2	24.5	48.2
8	Mean	6.2	2.3	5.1	6.5	18.0	22.8	17.6	27.1
	S.D.	10.9	5.7	14.1	17.2	41.0	39.5	21.5	48.2
9	Mean	0.8	1.8	4.2	9.0	16.0	20.2	12.1	16.9
	S.D.	2.2	5.0	13.3	27.8	34.6	37.4	19.9	17.7
10	Mean	0.9	8.9	11.6	10.9	17.8	15.6	17.7	24.2
	S.D.	2.2	27.8	36.3	19.9	36.9	25.3	34.2	33.5
Total	Mean	708.0	636.4	598.9	710.5	712.1	632.7	638.1	663.2
	S.D.	239.1	213.5	182.9	380.0	304.5	189.0	149.8	260.9

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Means and Standard Deviations were calculated using Microsoft Excel 2003(v.11.8169.8172)SP3

Table 6 Motor Activity Summary – Female Toxicity Groups

		Baseline				Treated			
Interval	Group/Sex	1f	2f	3f	4f	1f	2f	3f	4f
(8 minutes)	N	10	10	10	10	10	10	10	10
1	Mean	256.1	246.1	247.0	241.7	230.3	215.3	232.6	218.9
	S.D.	35.3	34.4	48.9	30.2	36.3	38.6	50.2	44.1
2	Mean	199.8	171.8	177.6	185.9	162.9	168.1	186.2	171.0
	S.D.	35.4	31.2	44.7	43.5	59.8	37.6	50.8	42.4
3	Mean	141.9	119.2	136.5	141.4	149.2	108.9	146.4	118.2
	S.D.	60.5	47.6	65.9	55.5	57.3	53.9	51.6	82.2
4	Mean	111.7	83.9	109.1	94.6	110.0	85.2	101.9	67.8
	S.D.	67.8	53.1	60.4	64.9	75.0	55.0	60.3	74.5
5	Mean	79.7	67.5	82.0	53.6	87.5	85.7	59.7	72.2
	S.D.	68.4	50.1	59.4	46.3	64.0	48.2	73.0	71.4
6	Mean	93.5	60.1	65.5	43.7	90.0	65.1	69.2	52.8
	S.D.	58.6	73.1	51.8	57.1	67.8	40.9	51.7	51.4
7	Mean	113.8	68.6	36.6	47.1	75.2	54.1	97.4	70.8
	S.D.	65.3	74.8	40.6	64.3	48.2	45.9	53.7	58.6
8	Mean	87.2	51.6	16.4	23.9	75.7	43.1	70.7	56.9
	S.D.	57.5	66.5	46.3	39.1	59.2	42.9	36.5	58.4
9	Mean	43.0	46.4	31.6	16.3	68.1	34.8	48.8	31.2
	S.D.	52.2	53.4	67.2	28.3	53.8	43.7	37.9	35.1
10	Mean	35.6	43.1	26.7	11.9	47.5	47.3	48.5	29.3
	S.D.	51.0	64.1	45.7	29.7	48.6	45.7	38.1	30.4
Total	Mean	1162.3	958.3	929.0	860.1	1096.4	907.6	1061.4	889.1
	S.D.	380.7	356.8	316.3	254.6	427.8	276.3	286.4	397.7

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
Means and Standard Deviations were calculated using Microsoft Excel 2003(v.11.8169.8172)SP3

Attachment A Individual FOB Ranked - Male Toxicity Groups (Baseline)

Group/Sex	Animal #	Resistance to Removal	Palpebral Closure	Pupil Reactivity	Pupil Size	Lacrimation	Salivation	Muscle Tone	Extensor Thrust	Reactivity to handling	Level of Activity	Response to Noise	Response to Touch	Response to Tail Pinch	Gait Evaluation	Urination	Defecation
1m	5204	3	3	3	3	3	3	3	3	3	3	4	3	3	1	2	1
1	5205	3	3	3	3	3	3	3	3	3	3	5	3	3	1	5	3
1	5206	3	3	3	3	3	3	3	3	3	3	3	3	3	1	4	2
1	5207	3	3	3	3	3	3	3	3	3	3	4	3	3	1	1	1
1	5208	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
1	5209	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	3
1	5210	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	2
1	5211	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
1	5212	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	2
1	5213	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	2
2m	5234	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	3
2	5235	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	2
2	5236	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	2
2	5237	3	3	3	3	3	3	3	3	3	3	4	3	3	1	5	3
2	5238	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
2	5239	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
2	5240	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	2
2	5241	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
2	5242	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
2	5243	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Attachment A Individual FOB Ranked - Male Toxicity Groups (Baseline) Continued

Group/Sex	Animal #	Resistance to Removal	Palpebral Closure	Pupil Reactivity	Pupil Size	Lacrimation	Salivation	Muscle Tone	Extensor Thrust	Reactivity to handling	Level of Activity	Response to Noise	Response to Touch	Response to Tail Pinch	Gait Evaluation	Urination	Defecation
3m	5264	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	1
3	5265	3	3	3	3	3	3	3	3	3	3	3	3	3	1	4	3
3	5266	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	4
3	5267	3	3	3	3	3	3	3	3	3	3	4	3	3	1	3	3
3	5268	3	3	3	3	3	3	3	3	3	3	3	3	3	1	4	1
3	5269	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
3	5270	3	3	3	3	3	3	3	3	3	3	3	3	3	1	4	2
3	5271	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	3
3	5272	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	3
3	5273	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	1
4m	5294	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
4	5295	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
4	5296	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	1
4	5297	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	2
4	5298	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
4	5299	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	2
4	5300	3	3	3	3	3	3	3	3	3	3	3	3	3	1	4	2
4	5301	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
4	5302	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	1
4	5303	3	3	3	3	3	3	3	3	3	3	4	3	3	1	4	2

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Attachment B Individual FOB Ranked - Male Toxicity Groups (Treated)

Group/Sex	Animal #	Resistance to Removal	Palpebral Closure	Pupil Reactivity	Pupil Size	Lacrimation	Salivation	Muscle Tone	Extensor Thrust	Reactivity to handling	Level of Activity	Response to Noise	Response to Touch	Response to Tail Pinch	Gait Evaluation	Urination	Defecation
1m	5204	3	3	3	3	3	3	3	3	3	3	4	3	3	1	5	1
1	5205	3	3	3	3	3	3	3	3	3	2	3	3	3	1	5	3
1	5206	3	3	3	3	3	3	3	3	3	2	3	3	3	1	4	5
1	5207	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
1	5208	3	3	3	3	3	3	3	3	3	2	4	3	3	1	5	2
1	5209	3	3	3	3	3	3	3	3	3	2	3	3	2	1	5	4
1	5210	3	3	3	3	3	3	3	3	3	3	3	3	3	1	4	2
1	5211	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
1	5212	3	3	3	3	3	3	3	3	3	2	3	3	3	1	5	5
1	5213	3	3	3	3	3	3	3	3	3	2	3	3	3	1	3	5
2m	5234	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	5
2	5235	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	1
2	5236	3	3	3	3	3	3	3	3	3	3	3	3	3	1	4	3
2	5237	3	3	3	3	3	3	3	3	3	2	4	3	3	1	4	3
2	5238	3	3	3	3	3	3	3	3	3	3	3	3	3	1	4	2
2	5239	3	3	3	3	3	3	3	3	3	2	4	3	3	1	5	1
2	5240	3	3	3	3	3	3	3	3	3	2	4	3	3	1	5	4
2	5241	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	2
2	5242	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	4
2	5243	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	4

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Attachment B Individual FOB Ranked - Male Toxicity Groups (Treated) Continued

Group/Sex	Animal #	Resistance to Removal	Palpebral Closure	Pupil Reactivity	Pupil Size	Lacrimation	Salivation	Muscle Tone	Extensor Thrust	Reactivity to handling	Level of Activity	Response to Noise	Response to Touch	Response to Tail Pinch	Gait Evaluation	Urination	Defecation
3m	5264	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	1
3	5265	3	3	3	3	3	3	3	3	3	2	3	3	3	1	3	3
3	5266	3	3	3	3	3	3	3	4	3	3	3	3	3	1	4	4
3	5267	3	3	3	3	3	3	3	3	3	3	3	3	2	1	5	1
3	5268	3	3	3	3	3	3	3	3	3	2	3	3	3	1	5	1
3	5269	3	3	3	3	3	3	3	3	3	2	3	3	3	1	4	5
3	5270	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	4
3	5271	3	3	3	3	3	3	3	3	3	2	3	3	3	1	3	1
3	5272	3	3	3	3	3	3	3	4	3	2	4	3	3	1	3	1
3	5273	3	3	3	3	3	3	3	3	3	3	3	3	3	1	4	1
4m	5294	3	3	3	3	3	3	3	3	3	2	3	3	3	1	2	1
4	5295	3	3	3	3	3	3	3	3	3	2	3	3	3	1	5	1
4	5296	3	3	3	3	3	3	3	3	3	1	3	3	3	1	3	4
4	5297	3	3	3	3	3	3	3	3	3	3	3	3	3	1	4	4
4	5298	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	4
4	5299	3	3	3	3	3	3	3	3	3	2	3	3	3	1	4	3
4	5300	3	3	3	3	3	3	3	3	3	2	3	3	3	1	4	4
4	5301	3	3	3	3	3	3	3	3	3	2	3	3	3	1	4	2
4	5302	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	3
4	5303	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	3

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Attachment C Individual FOB Ranked - Female Toxicity Groups (Baseline)

GroupSex	Animal #	Resistance to Removal	Palpebral Closure	Pupil Reactivity	Pupil Size	Lacrimation	Salivation	Muscle Tone	Extensor Thrust	Reactivity to handling	Level of Activity	Response to Noise	Response to Touch	Response to Tail Pinch	Gait Evaluation	Urination	Defecation
1f	5194	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
1	5195	3	3	3	3	3	3	3	3	3	3	4	3	3	1	3	1
1	5196	3	3	3	3	3	3	3	3	4	3	3	3	3	1	1	1
1	5197	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
1	5198	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
1	5199	3	3	3	3	3	3	3	3	3	3	4	3	3	1	2	2
1	5200	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	2
1	5201	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
1	5202	3	3	3	3	3	3	3	3	3	3	3	3	3	1	4	1
1	5203	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
2f	5224	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
2	5225	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
2	5226	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
2	5227	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
2	5228	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
2	5229	4	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
2	5230	3	3	3	3	3	3	3	3	4	3	3	3	3	1	1	1
2	5231	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
2	5232	4	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
2	5233	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Attachment C Individual FOB Ranked - Female Toxicity Groups (Baseline) Continued

GroupSex	Animal #	Resistance to Removal	Palpebral Closure	Pupil Reactivity	Pupil Size	Lacrimation	Salivation	Muscle Tone	Extensor Thrust	Reactivity to handling	Level of Activity	Response to Noise	Response to Touch	Response to Tail Pinch	Gait Evaluation	Urination	Defecation
3f	5254	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
3	5255	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
3	5256	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
3	5257	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
3	5258	3	3	3	3	3	3	3	3	3	3	5	3	3	1	3	2
3	5259	3	3	3	3	3	3	3	3	3	4	3	3	3	1	1	1
3	5260	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
3	5261	3	3	3	3	3	3	3	3	3	3	4	3	3	1	1	1
3	5262	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
3	5263	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
4f	5284	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
4	5285	3	3	3	3	3	3	3	3	3	4	3	3	3	1	1	1
4	5286	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
4	5287	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	2
4	5288	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
4	5289	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	2
4	5290	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
4	5291	3	3	3	3	3	3	3	3	3	3	4	3	3	1	2	1
4	5292	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	2
4	5293	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Attachment D Individual FOB Ranked - Female Toxicity Groups (Treated)

Group/Sex	Animal #	Resistance to Removal	Palpebral Closure	Pupil Reactivity	Pupil Size	Lacrimation	Salivation	Muscle Tone	Extensor Thrust	Reactivity to handling	Level of Activity	Response to Noise	Response to Touch	Response to Tail Pinch	Gait Evaluation	Urination	Defecation
1f	5194	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
1	5195	3	3	3	3	3	3	3	3	3	4	3	3	3	1	2	1
1	5196	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	2
1	5197	3	3	3	3	3	3	3	3	3	3	3	3	4	1	1	1
1	5198	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
1	5199	3	3	3	3	3	3	3	3	3	2	3	3	3	1	3	1
1	5200	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
1	5201	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
1	5202	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
1	5203	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
2f	5224	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
2	5225	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
2	5226	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
2	5227	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
2	5228	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
2	5229	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
2	5230	3	3	3	3	3	3	3	3	3	3	3	4	3	1	2	1
2	5231	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
2	5232	3	3	3	3	3	3	3	3	3	2	3	3	3	1	5	2
2	5233	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Attachment D Individual FOB Ranked - Female Toxicity Groups (Treated) Continued

Group/Sex	Animal #	Resistance to Removal	Palpebral Closure	Pupil Reactivity	Pupil Size	Lacrimation	Salivation	Muscle Tone	Extensor Thrust	Reactivity to handling	Level of Activity	Response to Noise	Response to Touch	Response to Tail Pinch	Gait Evaluation	Urination	Defecation
3f	5254	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
3	5255	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
3	5256	3	3	3	3	3	3	3	3	3	3	4	3	3	1	1	1
3	5257	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
3	5258	3	3	3	3	3	3	3	3	3	2	3	3	3	1	4	4
3	5259	3	3	3	3	3	3	3	3	3	3	4	3	3	1	1	1
3	5260	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
3	5261	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1
3	5262	3	3	3	3	3	3	3	3	3	2	3	3	3	1	4	4
3	5263	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	2
4f	5284	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
4	5285	3	3	3	3	3	3	3	3	3	3	3	3	3	1	5	1
4	5286	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
4	5287	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	3
4	5288	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
4	5289	3	3	3	3	3	3	3	3	3	3	3	3	3	1	4	3
4	5290	3	3	3	3	3	3	3	3	3	3	3	4	3	1	3	2
4	5291	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1
4	5292	3	3	3	3	3	3	3	3	3	3	3	3	3	1	3	1
4	5293	3	3	3	3	3	3	3	3	3	3	3	3	3	1	2	1

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Attachment E Individual FOB Categorical - Male Toxicity Groups

Day numbers relative to Start Date

Group Sex	Animal Number	Clinical Sign	Site	-7	-6	-5	-4	-3	22	23	24	25	26
1m	5204	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5205	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5206	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5207	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5208	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5209	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5210	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5211	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5212	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.
	5213	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.
2m	5234	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5235	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5236	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5237	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5238	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5239	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5240	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	.
		Behavior Repetitive		.	.	.	.	.	.	.	.	.	O
	5241	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5242	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.
	5243	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.

X = Present O = Other (Head Sway)

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – 100mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Attachment E Individual FOB Categorical – Male Toxicity Groups (continued)

Group Sex	Animal Number	Clinical Sign	Site	Day numbers relative to Start Date -7	-6	-5	-4	-3	22	23	24	25	26
3m	5264	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5265	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5266	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5267	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5268	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5269	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5270	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5271	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5272	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.
	5273	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.
4m	5294	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5295	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5296	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5297	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5298	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5299	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5300	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5301	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5302	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.
	5303	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.

X = Present

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – 100mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Attachment F Individual FOB Categorical – Female Toxicity Groups

Day numbers relative to Start Date

Group Sex	Animal Number	Clinical Sign	Site	-7	-6	-5	-4	-3	22	23	24	25	26
1f	5194	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5195	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5196	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5197	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5198	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5199	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5200	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5201	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5202	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.
	5203	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.
2f	5224	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5225	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5226	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5227	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5228	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5229	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5230	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5231	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5232	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.
	5233	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.

X= Present

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Attachment F Individual FOB Categorical – Female Toxicity Groups (continued)

Day numbers relative to Start Date

Group Sex	Animal Number	Clinical Sign	Site	-7	-6	-5	-4	-3	22	23	24	25	26
3f	5254	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5255	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5256	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5257	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5258	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5259	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5260	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5261	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5262	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.
	5263	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.
4f	5284	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5285	No Abnormalities Detected		.	X	.	.	.	.	X	.	.	.
	5286	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5287	No Abnormalities Detected		.	.	X	.	.	.	.	X	.	.
	5288	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5289	No Abnormalities Detected		.	.	.	X	.	.	.	.	X	.
	5290	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5291	No Abnormalities Detected		.	.	.	.	X	.	.	.	.	X
	5292	No Abnormalities Detected		X	.	.	.	.	X	.	.	.	.
	5293	No Abnormalities Detected		X	.	.	.	.	.	.	.	.	.
		Soiling	Chin	.	.	.	.	.	R	.	.	.	.

X = Present R = Red

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Attachment G FOB Ranked/Categorical Observations Definitions

Definitions:

Resistance to Removal:
1 = no resistance to capture and removal
2 = minimally avoids capture but is not aggressive
3 = moderate; actively avoids capture but is not aggressive
4 = pronounced; actively avoids capture and/or is mildly aggressive
5 = exaggerated; very difficult to capture and is very aggressive (i.e. tries to bite)

Pupil reactivity:
1 = dilated, nonreactive pupil
2 = dilated, slowly reactive pupil
3 = dilated, briskly reactive pupil
4 = constricted, cannot assess

Lacrimation:
1 = very dry appearance of cornea
2 = slightly dry appearance of cornea
3 = glistening cornea
4 = slight periocular wetness
5 = extensive periocular wetness

Muscle tone:
1 = scored as none but defined as limp
2 = slight; very relaxed, "soft"
3 = moderate; animal is neither very relaxed nor tense
4 = pronounced; animal feels slightly rigid or tense
5 = exaggerated; very rigid or stiff

Reactivity to handling:
1 = none, no struggling
2 = minimal struggling
3 = moderate struggling with little or no vocalization
4 = pronounced struggling, animal may vocalize
5 = exaggerated; aggressive escape behavior, tries to bite observer and usually vocalizes

Palpebral closure:
1 = closed
2 = 50% closed
3 = open
4 = protruding eyes

Pupil size:
1 = decreased pupil size (completely constricted)
2 = decreased pupil size (slightly constricted)
3 = normal pupil size
4 = increased pupil size (slightly dilated)
5 = increased pupil size (completely dilated)

Salivation:
1 = extensive oral dryness
2 = slight oral dryness
3 = gistening oral cavity/lips, no wetness
4 = slight perioral wetness
5 = extensive perioral wetness or drop(s) of fluid in or around mouth

Extensor-thrust response:
1 = no extensor thrust response
2 = slight; barely detectable response
3 = moderate; clearly detectable
4 = pronounced; pushes vigorously
5 = exaggerated; extreme thrust response

Level of activity:
1 = none, rat doesn't leave the center circle (20 cm dia.)
2 = minimal; inactive more than 50% of the time
3 = moderate; inactive less than 50% of the time
4 = pronounced; leaves circle, occasional inactivity.
5 = exaggerated; leaves circle, never inactive.

Attachment G FOB Ranked/Categorical Observations Definitions - Continued

Responsiveness to sharp noise:
1 = none, no response to click
2 = minimal; only the ears and/or head moves
3 = moderate; clear movement of the head, neck, ears and possibly shoulders/upper body
4 = pronounced; clear movement of head, neck and ears, plus clear movement of whole body.
5 = exaggerated; whole body response to stimulus, more intense than "pronounced", includes whole body going airborne.

Responsiveness to touch:
1 = no response to touch
2 = slight; does not spontaneously lift tail; but briefly holds tail in air when manually lifted
3 = moderate; spontaneously lifts tail when touched
4 = pronounced; spontaneously lifts tail and acts startled
5 = exaggerated; turns towards finger in an attack response

Responsiveness to tail pinch :
1 = none; no response to pinch
2 = minimal; animal flinches and may vocalize slightly
3 = moderate; animal flinches, moves rapidly and/or vocalizes
4 = pronounced; animal moves vigorously in opposite direction of stimulation and vocalizes repeatedly and/or bends towards the tail and vocalizes
5 = exaggerated response to pinch; same as "pronounced", but includes an attempt to attack the source of the stimulation

Gait evaluation:
1 = smooth and coordinated gait
2 = slight knuckling of the paws and/or slight tendency to stumble
3 = moderate; clear knuckling and stumbling; incoordination
4 = pronounced; to include but not limited to: poor coordination, falling, and/or clear and repetitive knuckling of paws, and/or dragging of one or more limbs
5 = exaggerated; animal is unable to walk

Urination:
1 = no drops of urine
2 = minimal; a few (1-4) small drops or a small pool (~1 cm)
3 = moderate; a few (1-4) small pools or a moderate pool (2-3 cm)
4 = pronounced; a few (1-4) moderate pools or a large pool (4-5 cm)
5 = exaggerated; >4 moderate pools or a single pool >5 cm

Defecation:
1 = no pellets voided
2 = minimal; 1 or 2 pellets voided
3 = moderate; 3 pellets voided
4 = pronounced; 4 pellets voided
5 = exaggerated; 5 or more pellets voided

Categoricals:

Positive Observations made at any time regarding the following categories:

Behavior	Urine or Feces	Other abnormalities
Skin/fur/mucous membranes	Soiling	
Respiration	Posture	
Muscle	Eyes	

Attachment H Individual FOB Continuous Data - Male Toxicity Groups (Baseline)

Group Sex	Animal ID	RectalTemperature (°Celsius)	Hindlimb Grip Strength (Grams)[1]	Forelimb Grip Strength (Grams)[1]	Landing Foot Splay (Centimeters)[1]
1m	5204	37.8	723.3	703.3	12.5
	5205	38.0	716.7	926.7	14.1
	5206	37.9	733.3	903.3	14.6
	5207	37.1	716.7	718.3	13.6
	5208	37.4	838.3	980.0	13.5
	5209	37.9	601.7	991.7	8.1
	5210	38.4	650.0	741.7	8.6
	5211	37.9	573.3	731.7	11.0
	5212	38.0	686.7	620.0	12.5
	5213	37.7	660.0	586.7	13.0
2m	5234	38.4	690.0	860.0	13.9
	5235	37.8	808.3	640.0	10.5
	5236	38.2	756.7	963.3	10.6
	5237	37.8	716.7	846.7	15.4
	5238	37.5	768.3	863.3	12.2
	5239	37.9	596.7	926.7	12.1
	5240	38.5	808.3	1015.0	9.3
	5241	37.9	815.0	831.7	10.9
	5242	37.6	770.0	900.0	15.3
	5243	37.9	798.3	716.7	14.2
3m	5264	38.7	873.3	805.0	13.4
	5265	37.6	700.0	676.7	13.5
	5266	38.3	728.3	733.3	11.7
	5267	37.4	653.3	705.0	12.6
	5268	38.2	571.7	961.7	10.5
	5269	38.0	696.7	835.0	10.3
	5270	38.4	665.0	861.7	9.6
	5271	38.1	951.7	915.0	10.7
	5272	38.0	548.3	528.3	9.0
	5273	37.3	535.0	745.0	12.8
4m	5294	38.4	741.7	690.0	14.0
	5295	38.2	643.3	705.0	12.8
	5296	38.3	715.0	766.7	11.3
	5297	38.0	711.7	730.0	14.4
	5298	38.4	660.0	1005.0	12.2
	5299	37.7	706.7	733.3	15.8
	5300	38.2	788.3	821.7	14.0
	5301	37.9	1026.7	1058.3	12.1
	5302	37.6	736.7	645.0	14.2
	5303	37.9	600.0	683.3	8.3

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
[1]Represents the mean of 3 trials

Attachment I Individual FOB Continuous Data - Male Toxicity Groups (Treated)

Group Sex	Animal ID	Rectal Temperature (°Celsius)	Hindlimb Grip Strength (Grams)[1]	Forelimb Grip Strength (Grams)[1]	Landing Foot Splay (Centimeters)[1]
1m	5204	37.6	1186.7	1321.7	11.8
	5205	37.2	1466.7	1148.3	12.1
	5206	37.6	1190.0	1415.0	13.3
	5207	37.5	1383.3	1338.3	12.7
	5208	38.1	1430.0	1306.7	10.9
	5209	38.2	1230.0	1346.7	8.2
	5210	38.4	1198.3	1228.3	9.8
	5211	38.3	1343.3	975.0	10.9
	5212	38.1	1055.0	753.3	9.3
	5213	38.4	1241.7	1145.0	13.2
2m	5234	38.0	1328.3	1393.3	11.6
	5235	37.8	1060.0	930.0	11.3
	5236	38.0	1388.3	1395.0	10.4
	5237	38.4	916.7	1541.7	14.3
	5238	38.5	1238.3	1275.0	12.9
	5239	39.0	1026.7	1728.3	11.9
	5240	37.7	1413.3	1323.3	10.2
	5241	38.7	1141.7	1298.3	10.5
	5242	38.1	1216.7	1348.3	15.4
	5243	38.1	1231.7	1065.0	13.2
3m	5264	37.8	1158.3	1086.7	10.1
	5265	37.4	1183.3	1295.0	13.2
	5266	37.3	1228.3	1230.0	12.4
	5267	37.6	1190.0	1055.0	9.6
	5268	37.8	1210.0	1356.7	11.3
	5269	38.2	1221.7	1290.0	8.9
	5270	38.0	1000.0	745.0	12.1
	5271	37.9	1445.0	1250.0	9.6
	5272	37.8	790.0	715.0	12.9
	5273	38.7	978.3	863.3	11.5
4m	5294	37.9	1163.3	643.3	12.7
	5295	38.1	953.3	1165.0	14.7
	5296	38.1	845.0	1256.7	11.3
	5297	37.6	1098.3	1003.3	14.1
	5298	38.0	1213.3	1431.7	12.1
	5299	37.3	1106.7	955.0	15.4
	5300	37.7	1230.0	868.3	11.1
	5301	38.3	1435.0	1221.7	11.1
	5302	38.5	941.7	968.3	10.4
	5303	37.9	1178.3	848.3	9.1

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
[1]Represents the mean of 3 trials

Attachment J Individual FOB Continuous Data - Female Toxicity Groups (Baseline)

Group Sex	Animal ID	RectalTemperature (°Celsius)	Hindlimb Grip Strength (Grams)[1]	Forelimb Grip Strength (Grams)[1]	Landing Foot Splay (Centimeters)[1]
1f	5194	38.7	600.0	641.7	11.7
	5195	38.6	583.3	721.7	8.6
	5196	37.9	638.3	695.0	9.8
	5197	38.4	743.3	671.7	11.3
	5198	38.2	508.3	593.3	12.1
	5199	38.6	681.7	680.0	10.9
	5200	38.8	648.3	731.7	13.9
	5201	38.4	608.3	873.3	7.8
	5202	38.9	646.7	713.3	12.2
	5203	37.7	425.0	678.3	12.2
2f	5224	38.6	505.0	585.0	10.1
	5225	38.4	625.0	553.3	9.2
	5226	38.3	716.7	830.0	9.8
	5227	37.6	675.0	1015.0	10.4
	5228	38.1	518.3	725.0	11.8
	5229	38.0	613.3	815.0	7.5
	5230	38.7	805.0	700.0	9.0
	5231	38.2	640.0	555.0	14.4
	5232	37.6	583.3	600.0	10.8
	5233	38.5	848.3	765.0	12.5
3f	5254	38.6	778.3	693.3	8.7
	5255	38.1	415.0	671.7	11.7
	5256	38.4	513.3	738.3	7.8
	5257	38.0	711.7	868.3	10.0
	5258	38.5	683.3	913.3	12.3
	5259	38.6	716.7	748.3	11.0
	5260	39.1	708.3	828.3	11.2
	5261	38.5	835.0	663.3	12.5
	5262	37.8	678.3	630.0	8.0
	5263	38.6	618.3	736.7	12.8
4f	5284	38.1	735.0	656.7	7.2
	5285	37.9	550.0	998.3	8.5
	5286	38.7	416.7	683.3	10.3
	5287	38.3	748.3	808.3	9.5
	5288	38.1	680.0	758.3	10.0
	5289	37.6	581.7	880.0	13.0
	5290	38.1	653.3	878.3	9.5
	5291	37.9	701.7	840.0	6.0
	5292	37.5	463.3	648.3	12.8
	5293	37.5	716.7	673.3	6.9

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
[1]Represents the mean of 3 trials

Attachment K Individual FOB Continuous Data - Female Toxicity Groups (Treated)

Group Sex	Animal ID	RectalTemperature (°Celsius)	Hindlimb Grip Strength (Grams)[1]	Forelimb Grip Strength (Grams)[1]	Landing Foot Splay (Centimeters)[1]
1f	5194	39.1	895.0	865.0	12.8
	5195	38.8	903.3	1035.0	8.6
	5196	37.6	906.7	723.3	12.2
	5197	38.8	981.7	873.3	10.6
	5198	38.9	1016.7	1106.7	8.9
	5199	38.1	1056.7	1080.0	10.6
	5200	39.1	1111.7	1106.7	12.2
	5201	38.7	1138.3	1133.3	6.4
	5202	38.7	1030.0	980.0	11.1
	5203	38.4	830.0	765.0	11.6
2f	5224	38.3	1053.3	1003.3	11.0
	5225	38.3	935.0	886.7	8.4
	5226	38.7	991.7	1373.3	11.3
	5227	38.8	1188.3	1510.0	10.2
	5228	38.1	831.7	923.3	8.3
	5229	38.5	948.3	1075.0	8.2
	5230	38.6	808.3	756.7	6.9
	5231	38.9	1093.3	718.3	10.6
	5232	37.4	813.3	685.0	8.8
	5233	38.3	931.7	1158.3	6.9
3f	5254	38.8	1131.7	1161.7	9.7
	5255	38.6	836.7	1161.7	10.6
	5256	38.2	706.7	836.7	6.9
	5257	38.6	1005.0	1000.0	9.5
	5258	37.2	1065.0	1323.3	11.6
	5259	38.1	1173.3	1100.0	9.8
	5260	39.0	961.7	945.0	8.8
	5261	38.2	945.0	996.7	11.5
	5262	37.6	1165.0	830.0	10.8
	5263	39.0	863.3	895.0	10.3
4f	5284	38.1	1013.3	841.7	10.1
	5285	38.3	848.3	1033.3	8.0
	5286	38.6	766.7	676.7	11.1
	5287	38.7	1213.3	930.0	8.4
	5288	38.0	896.7	1203.3	9.8
	5289	38.7	848.3	806.7	9.7
	5290	38.0	660.0	796.7	9.2
	5291	38.5	916.7	965.0	7.2
	5292	38.6	741.7	733.3	10.7
	5293	38.0	776.7	886.7	3.9

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day
[1]Represents the mean of 3 trials

APPENDIX S

Attachment L Individual Motor Activity by Interval - Male Toxicity Groups (Baseline)

Group Sex	Animal ID	Interval (8 minutes) 1	2	3	4	5	6	7	8	9	10	Total
1m	D5204	254	194	194	184	79	100	15	10	0	0	1030
	D5205	217	162	37	0	0	0	0	0	0	0	416
	D5206	221	80	100	58	110	0	13	0	0	0	582
	D5207	215	89	73	0	0	0	0	0	0	0	377
	D5208	269	202	154	54	34	3	0	1	0	0	717
	D5209	300	207	126	162	75	151	54	20	0	1	1096
	D5210	182	172	171	140	104	52	16	0	7	7	851
	D5211	255	137	123	101	113	6	28	31	1	1	796
	D5212	207	112	147	82	82	0	3	0	0	0	633
	D5213	228	173	79	95	1	1	5	0	0	0	582
2m	D5234	197	115	73	59	67	57	0	5	1	0	574
	D5235	180	108	84	93	5	0	0	0	16	88	574
	D5236	194	162	67	49	58	0	0	0	0	0	530
	D5237	236	178	151	54	2	0	0	0	0	0	621
	D5238	263	171	156	14	9	0	0	0	0	0	613
	D5239	219	150	156	178	48	207	129	18	1	0	1106
	D5240	149	110	38	0	2	0	0	0	0	0	299
	D5241	195	130	134	84	64	2	0	0	0	0	609
	D5242	279	203	188	142	51	0	0	0	0	0	863
	D5243	241	186	138	7	0	2	0	0	0	1	575
3m	D5264	290	167	109	2	0	6	0	0	0	0	574
	D5265	241	128	54	33	0	0	0	0	0	0	456
	D5266	208	156	121	153	73	102	32	0	0	0	845
	D5267	164	62	103	27	2	0	0	0	0	0	358
	D5268	212	80	78	25	0	2	1	0	42	115	555
	D5269	242	169	93	79	2	0	119	45	0	1	750
	D5270	258	177	135	52	33	0	0	0	0	0	655
	D5271	207	154	109	80	32	19	0	0	0	0	601
	D5272	157	113	69	0	0	0	0	0	0	0	339
	D5273	306	169	88	92	138	51	6	6	0	0	856
4m	D5294	206	193	125	123	110	117	44	2	0	0	920
	D5295	268	233	183	96	82	0	8	8	0	0	878
	D5296	176	105	53	0	0	0	0	0	0	2	336
	D5297	196	56	92	44	1	0	0	0	2	0	391
	D5298	261	170	136	99	28	0	0	0	0	0	694
	D5299	205	63	78	6	0	0	0	0	0	0	352
	D5300	289	182	194	133	121	17	0	0	0	11	947
	D5301	296	194	149	87	104	7	1	0	0	0	838
	D5302	144	73	4	0	0	0	0	0	0	49	270
	D5303	298	182	204	183	112	143	167	55	88	47	1479

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

APPENDIX S

Attachment M Individual Motor Activity by Interval - Male Toxicity Groups (Treated)

Group Sex	Animal ID	Intervals (8 minutes each) 1	2	3	4	5	6	7	8	9	10	Total
1m	D5204	251	158	161	158	108	94	95	130	111	112	1376
	D5205	190	82	93	9	17	46	31	0	0	1	469
	D5206	141	101	95	17	1	53	8	9	0	0	425
	D5207	191	177	115	46	31	0	0	0	0	6	566
	D5208	291	194	140	19	93	0	2	0	0	0	739
	D5209	259	147	85	85	143	10	0	0	3	0	732
	D5210	242	197	113	34	19	55	6	3	19	3	691
	D5211	275	182	113	120	56	48	83	37	25	53	992
	D5212	241	174	83	115	60	104	18	1	2	0	798
	D5213	125	131	57	8	9	0	0	0	0	3	333
2m	D5234	160	90	24	21	50	11	4	0	0	3	363
	D5235	191	139	81	67	23	75	33	5	0	0	614
	D5236	164	131	60	9	4	0	3	62	40	3	476
	D5237	227	160	97	25	1	7	63	0	0	0	580
	D5238	242	185	37	35	5	0	0	1	0	0	505
	D5239	174	161	85	78	30	37	25	17	0	0	607
	D5240	231	173	92	49	3	0	71	122	113	71	925
	D5241	260	187	105	94	61	60	24	9	0	42	842
	D5242	236	233	94	36	156	30	4	12	48	37	886
	D5243	280	146	66	8	25	3	0	0	1	0	529
3m	D5264	198	120	35	6	6	2	16	0	4	2	389
	D5265	236	118	84	17	44	69	50	50	32	0	700
	D5266	189	118	0	112	140	107	23	15	58	83	845
	D5267	255	180	135	67	30	36	67	20	0	1	791
	D5268	222	148	81	101	111	5	27	47	1	1	744
	D5269	218	133	161	57	43	15	0	0	0	0	627
	D5270	192	115	54	2	49	89	18	0	0	7	526
	D5271	194	113	130	53	15	32	67	0	1	1	606
	D5272	193	83	30	31	9	4	46	44	0	0	440
	D5273	299	129	79	50	0	46	3	0	25	82	713
4m	D5294	175	122	51	45	1	8	9	2	4	0	417
	D5295	238	166	135	85	0	0	40	135	42	62	903
	D5296	188	168	80	20	2	58	0	0	19	0	535
	D5297	193	93	35	71	52	56	6	4	0	2	512
	D5298	236	158	160	100	70	77	111	96	33	7	1048
	D5299	131	112	83	21	0	0	4	0	42	80	473
	D5300	210	206	122	77	38	173	129	27	26	14	1022
	D5301	209	148	96	116	62	97	18	0	3	0	749
	D5302	126	113	49	3	0	1	0	1	0	3	296
	D5303	209	139	99	61	5	83	1	6	0	74	677

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

APPENDIX S

Attachment N Individual Motor Activity by Interval - Female Toxicity Groups (Baseline)

Group Sex	Animal ID	Intervals (8 minutes each) 1	2	3	4	5	6	7	8	9	10	Total
1f	D5194	287	256	213	226	178	104	143	103	0	0	1510
	D5195	222	132	136	62	89	5	15	4	0	0	665
	D5196	266	192	147	124	90	134	134	130	4	0	1221
	D5197	276	197	11	0	12	0	0	0	0	0	496
	D5198	245	195	109	118	77	83	88	84	95	89	1183
	D5199	210	166	93	55	12	64	85	134	120	14	953
	D5200	265	236	209	165	8	160	173	43	0	4	1263
	D5201	222	204	143	142	134	85	161	87	17	15	1210
	D5202	242	191	179	57	14	169	148	107	112	103	1322
	D5203	326	229	179	168	183	131	191	180	82	131	1800
2f	D5224	297	183	137	36	0	0	0	0	5	0	658
	D5225	227	188	154	42	0	0	0	0	87	188	886
	D5226	227	180	118	135	106	153	148	176	142	75	1460
	D5227	237	163	122	87	58	3	13	15	0	0	698
	D5228	252	191	0	0	36	196	164	111	41	1	992
	D5229	295	177	125	122	66	78	148	84	100	65	1260
	D5230	190	107	137	37	43	0	0	0	0	0	514
	D5231	228	161	108	131	140	3	61	4	0	0	836
	D5232	229	144	108	89	92	51	1	0	1	0	715
	D5233	279	224	183	160	134	117	151	126	88	102	1564
3f	D5254	256	141	167	14	1	0	0	0	0	1	580
	D5255	264	200	128	120	119	46	58	1	7	0	943
	D5256	324	236	121	204	186	3	0	0	0	0	1074
	D5257	303	223	105	114	73	131	126	3	0	0	1078
	D5258	150	79	1	0	18	69	48	4	0	0	369
	D5259	252	201	143	135	54	128	59	148	117	128	1365
	D5260	208	182	189	102	35	20	0	0	0	0	736
	D5261	250	185	260	123	158	113	0	8	192	67	1356
	D5262	250	162	117	140	89	111	24	0	0	71	964
	D5263	213	167	134	139	87	34	51	0	0	0	825
4f	D5284	219	187	123	4	0	0	0	3	69	22	627
	D5285	247	97	145	101	0	0	0	1	0	0	591
	D5286	216	193	85	126	22	0	0	0	0	0	642
	D5287	260	186	154	30	3	89	88	27	0	0	837
	D5288	277	224	243	160	106	117	166	18	25	0	1336
	D5289	274	214	175	156	50	0	0	0	0	0	869
	D5290	280	241	191	153	119	3	0	0	0	0	987
	D5291	226	194	57	11	63	145	92	108	2	0	898
	D5292	193	126	88	48	68	7	0	0	0	94	624
	D5293	225	197	153	157	105	76	125	82	67	3	1190

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

APPENDIX S

Attachment O Individual Motor Activity by Interval - Female Toxicity Groups (Treated)

Group Sex	Animal ID	Intervals (8 minutes each) 1	2	3	4	5	6	7	8	9	10	Total
1f	D5194	244	185	169	136	148	117	127	109	74	25	1334
	D5195	317	295	238	241	199	224	165	189	0	152	2020
	D5196	217	122	67	56	88	110	60	111	121	74	1026
	D5197	192	151	128	109	92	94	36	33	132	8	975
	D5198	199	146	99	99	63	44	75	46	77	27	875
	D5199	202	102	98	6	0	27	66	61	55	61	678
	D5200	225	194	208	138	125	83	117	118	86	30	1324
	D5201	224	159	122	121	121	163	40	90	136	96	1272
	D5202	227	82	145	3	1	0	3	0	0	2	463
	D5203	256	193	218	191	38	38	63	0	0	0	997
2f	D5224	182	147	89	87	78	15	69	6	0	0	673
	D5225	187	169	107	118	148	81	70	83	124	54	1141
	D5226	225	165	118	119	160	92	147	83	10	7	1126
	D5227	191	172	135	133	92	94	69	86	9	10	991
	D5228	279	157	18	0	74	53	3	0	0	98	682
	D5229	260	238	202	104	56	99	61	13	74	94	1201
	D5230	165	98	50	7	62	4	0	56	73	53	568
	D5231	259	195	127	73	59	97	25	1	54	126	1016
	D5232	206	142	77	42	0	10	9	0	0	0	486
	D5233	199	198	166	169	128	106	88	103	4	31	1192
3f	D5254	196	161	116	84	20	74	76	60	30	75	892
	D5255	196	188	129	86	69	95	38	31	101	85	1018
	D5256	277	240	144	99	2	33	120	122	47	32	1116
	D5257	283	185	143	193	176	127	160	110	19	19	1415
	D5258	181	102	64	89	14	0	11	60	103	106	730
	D5259	300	252	243	54	5	1	173	66	0	0	1094
	D5260	272	243	196	205	179	139	131	93	70	89	1617
	D5261	248	208	178	128	123	117	56	0	0	51	1109
	D5262	153	124	92	5	0	25	131	73	76	4	683
	D5263	220	159	159	76	9	81	78	92	42	24	940
4f	D5284	213	161	98	116	47	46	64	51	58	60	914
	D5285	246	177	57	4	118	0	0	0	1	62	665
	D5286	168	169	194	86	56	79	47	18	10	75	902
	D5287	209	138	14	4	2	45	106	5	1	4	528
	D5288	220	181	80	1	0	0	122	113	75	33	825
	D5289	300	280	309	250	238	152	169	181	84	0	1963
	D5290	272	174	131	47	6	1	0	75	66	2	774
	D5291	170	164	108	77	92	114	84	40	0	52	901
	D5292	171	128	74	39	68	68	114	86	17	2	767
	D5293	220	138	117	54	95	23	2	0	0	3	652

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – 100 mg/kg/day Group 3 – 300 mg/kg/day Group 4 – 1000 mg/kg/day

Appendix T

Clinical Pathology

APPENDIX T

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APPENDIX T

1. METHODS

Female and male rats were exposed by repeated oral administration of triethoxyoctylsilane at concentrations of 0, 100, 300, and 1000 mg/kg/day (Groups 1, 2, 3, and 4, respectively). Only the toxicology groups were scheduled for clinical pathology analysis with 10 female and 10 male rats in groups 1, 2, 3, and 4 of the toxicology exposure groups. Whole blood, serum, and plasma samples were received from necropsy for analysis.

Analysis of the serum chemistry was conducted with the Cobas Integra 400 Plus®, Serial Number 39-5089 (Roche Diagnostics, Indianapolis, IN). Specific methodologies for the parameters measured are in Attachment 1 of this document. All samples were analyzed on the day of blood collection. Individual data are presented in Attachment 2.

Hematology analysis was conducted with the Cell Dyn 3700 Hematology Analyzer, Serial Number 1991AN96, (Abbott Laboratories, Dallas, TX). Specific methodologies for the parameters measured are in Attachment 1 of this document. All samples were analyzed on the day of blood collection. Individual data are presented in Attachment 2.

Prothrombin times were analyzed using rabbit brain calcium thromboplastin with the ACL 100 Coagulation Analyzer, Serial Number 030710733, (Instrumentation Laboratories, Lexington, MA) using nephalometry methodology. All samples were analyzed on the day of blood collection. Individual data are presented in Attachment 2.

2. DATA ANALYSIS

Clinical pathology data was analyzed with Provantis version 8.2 and SAS 9.13. Statistically significant probabilities were reported for p values of < 0.05 and < 0.01.

Serum chemistry, hematology data, and prothrombin times were analyzed using a One-way Analysis of Variance (ANOVA). Data was tested for homogeneity of variances (Bartlett's test) and normality of distributions (Wilks-Shapiro). If requirements for these tests were not met, a log or rank transformation was performed. If the ANOVA was significant, pair-wise comparisons of the exposed groups to control were made using the Dunnett's Test.

3. RESULTS

Serum Chemistry

The following parameters were analyzed for serum chemistry:

alkaline phosphatase	alanine aminotransferase	aspartate aminotransferase
total bilirubin	albumin	total protein
urea nitrogen (BUN)	creatinine	glucose
cholesterol	calcium	phosphorous (phosphate)
sodium	potassium	chloride

Statistical significant differences were noted in group 4 of the female toxicology rats (Table 1) for aspartate aminotransferase, creatinine, cholesterol ($p<0.01$), and albumin and sodium ($p<0.05$).

These parameters were initially analyzed using the one-way ANOVA, then a pairwise comparison by Dunnett's Test. Although these parameters were statistically significant, they were within historical control ranges of this laboratory (Attachment 3).

In male rats (Table 2), alkaline phosphatase was statistically different ($p<0.01$) in groups 2, 3 and 4 compared to control. A statistical difference was observed for aspartate aminotransferase in groups 2 and 4 ($p<0.01$) and group 3 ($p<0.05$). Total bilirubin was statistically different ($p<0.05$) in group 2. These parameters were all within the historical ranges (Attachment 3).

There were no significant differences noted in the other serum chemistry parameters across groups for either sex.

Hematology

The following parameters were analyzed for hematology:

white blood cells	red blood cells	hemoglobin
hematocrit	MCV	MCH
MCHC	platelets	neutrophils (% and absolute)
lymphocytes (% and absolute)	monocytes (% and absolute)	
eosinophils (% and absolute)	basophils (% and absolute)	

A statistically significant difference for platelets ($p<0.05$) was seen in group 4 for the female toxicology rats (Table 3). Although slightly lower than the control group, this parameter was within the historical range. There were no significant differences noted in the remaining hematology parameters for females.

There were no instances of statistically significant differences for hematology parameters noted in the male rats (Table 4).

Coagulation (Prothrombin Times)

There were no significant differences noted in prothrombin times across groups for either sex (Table 5 and 6).

APPENDIX T

4. REFERENCES

1. Cobas Integra 400 Plus® Methods Manual, Roche Diagnostics, Indianapolis, IN, 2004
2. Cell Dyn 3700 Operator Manual, Abbott Park, IL, 2003
3. Provantis™ Statistics User Guide, Instem LSS, Stone, England, 2007

APPENDIX T

TABLE 1: Summary of Serum Chemistry –Female Toxicity Groups

Sex: Female		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
ALP (U/L)	Mean	80.7	76.8	81.1	72.3
	SD	20.8	8.4	21.3	22.3
	N	10	10	10	10
ALT (U/L)	Mean	21.6	19.8	18.3	18.6
	SD	4.2	4.1	5.3	2.4
	N	10	10	10	10
AST (U/L)	Mean	89.5	87.2	73.9	61.4 **
	SD	13.3	18.4	15.0	14.8
	N	10	10	10	10
TBILI (mg/dL)	Mean	0.121	0.124	0.123	0.115
	SD	0.017	0.029	0.027	0.050
	N	10	10	10	10
ALB (g/dL)	Mean	4.22	4.16	4.14	3.91 *
	SD	0.25	0.29	0.26	0.14
	N	10	10	10	10
TP (g/dL)	Mean	5.97	5.96	5.85	5.66
	SD	0.36	0.34	0.48	0.26
	N	10	10	10	10
BUN (mg/dL)	Mean	14.6	15.5	15.7	12.9
	SD	2.2	2.1	3.0	2.6
	N	10	10	10	10
CREAT (mg/dL)	Mean	0.34	0.33	0.30	0.26 **
	SD	0.05	0.05	0.00	0.05
	N	10	10	10	10
GLUC (mg/dL)	Mean	125.4	125.0	122.8	136.0
	SD	12.8	10.4	11.6	22.6
	N	10	10	10	10
CHOL (mg/dL)	Mean	55.2	61.9	70.7	90.9 **
	SD	16.6	14.9	11.4	14.7
	N	10	10	10	10

** = p-values < 0.01 significance level

* = p-values < 0.05 significance level

APPENDIX T

TABLE 1: Summary of Serum Chemistry –Female Toxicity Groups (continued)

Sex: Female		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
CA (mg/dL)	Mean	9.86	9.79	10.03	10.04
	SD	0.25	0.30	0.28	0.28
	N	10	10	10	10
PHOS (mg/dL)	Mean	7.30	7.11	7.55	7.41
	SD	0.51	0.78	0.46	0.76
	N	10	10	10	10
NA (mmol/L)	Mean	140.9	140.8	140.1	139.4 *
	SD	1.3	1.1	0.9	1.1
	N	10	10	10	10
K (mmol/L)	Mean	4.09	4.00	4.16	4.01
	SD	0.21	0.22	0.37	0.28
	N	10	10	10	10
CL (mmol/L)	Mean	104.6	104.8	103.8	103.7
	SD	1.6	1.8	1.2	1.3
	N	10	10	10	10

* = p-values < 0.05 significance level

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TABLE 2: Summary of Serum Chemistry –Male Toxicity Groups

Sex: Male		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
ALP (U/L)	Mean	156.3	125.0 **	120.0 **	106.6 **
	SD	14.7	22.7	24.9	20.5
	N	10	10	10	10
ALT (U/L)	Mean	22.3	20.9	22.6	19.4
	SD	2.9	3.3	5.4	3.9
	N	10	10	10	10
AST (U/L)	Mean	91.0	66.9 **	73.2 *	63.1 **
	SD	20.5	9.0	23.2	8.1
	N	10	10	10	10
TBILI (mg/dL)	Mean	0.128	0.101 *	0.109	0.109
	SD	0.024	0.013	0.025	0.019
	N	10	10	10	10
ALB (g/dL)	Mean	3.77	3.75	3.74	3.67
	SD	0.14	0.12	0.18	0.21
	N	10	10	10	10
TP (g/dL)	Mean	5.70	5.70	5.68	5.60
	SD	0.17	0.19	0.18	0.34
	N	10	10	10	10
BUN (mg/dL)	Mean	12.4	12.8	12.9	13.0
	SD	1.3	1.8	1.9	1.5
	N	10	10	10	10
CREAT (mg/dL)	Mean	0.28	0.29	0.28	0.26
	SD	0.04	0.03	0.06	0.05
	N	10	10	10	10
GLUC (mg/dL)	Mean	119.9	132.3	127.5	116.8
	SD	12.8	13.6	16.1	10.3
	N	10	10	10	10
CHOL (mg/dL)	Mean	41.0	47.7	49.4	49.8
	SD	6.8	8.9	11.4	16.5
	N	10	10	10	10

** = p-values < 0.01 significance level
* = p-values < 0.05 significance level

APPENDIX T

TABLE 2: Summary of Serum Chemistry –Male Toxicity Groups (continued)

Sex: Male		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
CA (mg/dL)	Mean	9.57	9.63	9.71	9.81
	SD	0.23	0.16	0.22	0.34
	N	10	10	10	10
PHOS (mg/dL)	Mean	7.59	7.30	7.41	7.55
	SD	0.23	0.53	0.52	0.58
	N	10	10	10	10
NA (mmol/L)	Mean	142.8	143.0	142.3	142.7
	SD	1.2	2.1	0.5	1.5
	N	10	10	10	10
K (mmol/L)	Mean	4.44	4.34	4.40	4.28
	SD	0.16	0.25	0.18	0.32
	N	10	10	10	10
CL (mmol/L)	Mean	104.4	105.2	104.3	104.7
	SD	1.6	1.7	1.2	1.1
	N	10	10	10	10

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TABLE 3: Summary of Hematology Data –Female Toxicity Groups

Sex: Female		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
WBC (10^3/uL)	Mean	5.39	5.01	5.21	5.26
	SD	2.11	1.69	1.41	2.14
	N	10	10	10	10
RBC (10^6/uL)	Mean	7.585	7.618	7.704	7.761
	SD	0.117	0.336	0.375	0.224
	N	10	10	10	10
HGB (g/dL)	Mean	14.75	14.66	14.80	14.69
	SD	0.36	0.45	0.66	0.54
	N	10	10	10	10
HCT (%)	Mean	42.14	41.87	42.36	42.54
	SD	0.99	1.17	1.70	1.34
	N	10	10	10	10
MCV (fL)	Mean	55.56	55.02	55.02	54.83
	SD	1.87	2.20	1.99	1.55
	N	10	10	10	10
MCH (pg)	Mean	19.46	19.27	19.21	18.94
	SD	0.62	0.45	0.60	0.49
	N	10	10	10	10
MCHC (g/dL)	Mean	35.01	35.07	34.95	34.54
	SD	0.59	0.63	0.60	0.61
	N	10	10	10	10
PLT (10^3/uL)	Mean	995.70	976.00	971.70	869.50 *
	SD	92.31	47.59	105.20	117.05
	N	10	10	10	10

* = p-values < 0.05 significance level

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TABLE 3: Summary of Hematology Data –Female Toxicity Groups (continued)

Sex: Female		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Neutro (%)	Mean	15.80	17.06	15.97	18.66
	SD	8.44	9.67	11.41	15.07
	N	10	10	10	10
Abs Neut (10^3/uL)	Mean	0.8849	0.8496	0.9372	1.1269
	SD	0.5555	0.5097	0.7930	1.1661
	N	10	10	10	10
Lymph (%)	Mean	80.74	80.01	80.31	77.15
	SD	8.42	9.57	11.06	13.25
	N	10	10	10	10
Abs Lymph (10^3/uL)	Mean	4.3310	4.0050	4.0660	3.9320
	SD	1.6762	1.4340	0.8094	1.3785
	N	10	10	10	10
Mono (%)	Mean	0.64	0.70	1.07	1.33
	SD	0.34	0.50	1.17	1.80
	N	10	10	10	10
Abs Mono (10^3/uL)	Mean	0.0393	0.0309	0.0628	0.0581
	SD	0.0386	0.0170	0.0771	0.0672
	N	10	10	10	10
Eosin (%)	Mean	2.29	2.08	2.01	2.02
	SD	0.90	1.02	0.68	1.01
	N	10	10	10	10
Abs Eosin (10^3/uL)	Mean	0.1224	0.1001	0.1070	0.1044
	SD	0.0549	0.0528	0.0485	0.0568
	N	10	10	10	10
Baso (%)	Mean	0.55	0.16	0.62	0.84
	SD	1.08	0.14	0.96	1.70
	N	10	10	10	10
Abs Baso (10^3/uL)	Mean	0.0219	0.0088	0.0254	0.0306
	SD	0.0336	0.0106	0.0281	0.0553
	N	10	10	10	10

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TABLE 4: Summary of Hematology Data –Male Toxicity Groups

Sex: Male		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
WBC (10^3/uL)	Mean	5.77	5.45	5.89	4.96
	SD	1.09	0.99	1.20	1.32
	N	10	10	10	10
RBC (10^6/uL)	Mean	8.111	7.803	7.943	7.776
	SD	0.417	0.342	0.391	0.395
	N	10	10	10	10
HGB (g/dL)	Mean	15.14	14.78	14.96	14.62
	SD	0.74	0.34	0.77	0.74
	N	10	10	10	10
HCT (%)	Mean	43.37	42.47	43.04	41.93
	SD	2.02	0.90	2.34	2.20
	N	10	10	10	10
MCV (fL)	Mean	53.46	54.50	54.19	53.92
	SD	1.12	2.56	1.41	0.67
	N	10	10	10	10
MCH (pg)	Mean	18.69	18.96	18.85	18.81
	SD	0.40	0.82	0.52	0.28
	N	10	10	10	10
MCHC (g/dL)	Mean	34.93	34.81	34.79	34.88
	SD	0.21	0.30	0.43	0.39
	N	10	10	10	10
PLT (10^3/uL)	Mean	960.80	876.80	933.50	903.70
	SD	97.97	266.96	111.21	86.77
	N	10	10	10	10

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TABLE 4: Summary of Hematology Data –Male Toxicity Groups (continued)

Sex: Male		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Neutro (%)	Mean	20.84	17.79	20.20	18.59
	SD	5.99	7.28	8.98	5.06
	N	10	10	10	10
Abs Neut (10^3/uL)	Mean	1.2246	0.9712	1.1495	0.9132
	SD	0.5496	0.4857	0.4765	0.3875
	N	10	10	10	10
Lymph (%)	Mean	75.70	79.12	76.62	77.70
	SD	6.07	7.63	9.40	5.64
	N	10	10	10	10
Abs Lymph (10^3/uL)	Mean	4.3350	4.3100	4.5510	3.8710
	SD	0.7769	0.9051	1.1593	1.0977
	N	10	10	10	10
Mono (%)	Mean	0.90	1.02	1.01	1.04
	SD	0.74	1.04	1.53	1.21
	N	10	10	10	10
Abs Mono (10^3/uL)	Mean	0.0504	0.0532	0.0618	0.0490
	SD	0.0382	0.0517	0.0990	0.0521
	N	10	10	10	10
Eosin (%)	Mean	2.40	1.81	1.97	2.51
	SD	0.58	0.74	0.52	0.92
	N	10	10	10	10
Abs Eosin (10^3/uL)	Mean	0.1334	0.0995	0.1162	0.1185
	SD	0.0235	0.0460	0.0423	0.0336
	N	10	10	10	10
Baso (%)	Mean	0.15	0.28	0.19	0.19
	SD	0.18	0.20	0.19	0.17
	N	10	10	10	10
Abs Baso (10^3/uL)	Mean	0.0079	0.0143	0.0116	0.0090
	SD	0.0083	0.0090	0.0105	0.0058
	N	10	10	10	10

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TABLE 5: Summary of Prothrombin Times –Female Toxicity Groups

Sex: Female		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Prothrombin Time (Seconds)	Mean	13.84	13.83	13.96	13.90
	SD	0.47	0.54	0.38	0.63
	N	10	10	10	10

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TABLE 6: Summary of Prothrombin Times –Male Toxicity Groups

Sex: Male		0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Prothrombin Time (Seconds)	Mean	14.04	14.81	14.34	14.70
	SD	0.49	1.02	0.98	1.02
	N	10	10	10	10

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TABLE 7: Abbreviations- Serum Chemistry

Heading	Description
Measurement Descriptions	
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
TBILI	Total bilirubin
ALB	Albumin
TP	Total protein
BUN	Blood Urea Nitrogen
CREAT	Creatinine
GLUC	Glucose
CHOL	Cholesterol
CA	Calcium
PHOS	Phosphate (phosphorus)
NA	Sodium
K	Potassium
CL	Chloride
Unit Descriptions	
g/dL	grams/deciliter
mg/dL	milligrams/deciliter
mmol/L	millimole/liter
U/L	unit/liter

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TABLE 8: Abbreviations- Hematology

Heading	Description
Measurement Descriptions	
WBC	White blood cell
RBC	Red blood cell
PLT	Platelet
HGB	Hemoglobin
HCT	Hematocrit
MCV	Mean Cell Volume
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
Unit Descriptions	
$10^3/\mu L$	Thousand per microliter
$10^6/\mu L$	Million per microliter
%	Percent
g	Grams
fL	Femtoliter
pg	Picogram

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ATTACHMENT 1 - Serum Chemistry Methodologies

	Method	Unit	Reference
Albumin	BCG (bromcresol green)	g/dL	Doumas BT, et al, Clin Chim Acta. 1971;31:87-91
Total Protein	biuret	g/dL	Doumas BT, et al, Clin Chem. 1981;27:1642-1654
Glucose	hexokinase	mg/dL	Neely WE. Et al. Clin Chem. 1972;18:509-515
Cholesterol	enzymatic-(cholesterol oxidase)	mg/dL	Allain CC, et al, Clin Chem. 1974;20:470-475
Total Bilirubin	diazo	mg/dL	Malloy, HT, J Biol Chem. 1937;119:481-490
Calcium	o-creolphtalein complex	mg/dL	Schwarzenbach, G. Analyst 1955;80:713-729
Phosphate (Inorganic)	phosphomolybdate, direct	mg/dL	Daly, JS, et al, Clin Chem, 1972;18:263-265
Creatinine	Jaffe-kinetic	mg/dL	Fabiny DL, Clin Chem. 1971;32:81-85
Urea/BUN	urease-kinetic	mg/dL	Sampson EJ, et al, Clin chem. 1980;26:816-826
Alanine Aminotransferase	IFCC/wo pyridoxal phosphate activation	U/L	Bergmeyer HU, et al, J Clin Chem Clin Biochem. 1986;24:481-495
Aspartate Aminotransferase	IFCC/wo pyridoxal phosphate activation	U/L	Bergmeyer HU, et al, J Clin Chem Clin Biochem. 1986;24:497-510
Alkaline Phosphatase	IFCC	U/L	Tietz NW, et al, J Clin Chem Clin Biochem. 1983;21:731-748
Sodium	ISE-indirect	mmol/L	_____
Potassium	ISE-indirect	mmol/L	_____
Chloride	ISE-indirect	mmol/L	_____

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ATTACHMENT 1 - Hematology Methodologies

Parameter	Abbreviation	Method	Units
White Blood Cell	WBC	impedance (WIC)	# x $10^3/\mu L$
		optical (WOC) -flow cytometry	# x $10^3/\mu L$
WBC Differential	%Diff	optical -flow cytometry	%
	AbsDiff	calculation	# x $10^3/\mu L$
Red Blood Cell	RBC	impedance	# x $10^6/\mu L$
Platelet	PLT	impedance	# x $10^3/\mu L$
Hemoglobin	HGB	colorimetry	grams /dL (grams/deciliter)
Hematocrit	HCT	calculated (RBC x MCV) / 10	percent (%)
Mean Cell Volume	MCV	derived	femtoliters (fL)
Mean Cell Hemoglobin	MCH	calculated (HGB/RBC) x 10	picograms (pg)
Mean Cell Hemoglobin Concentration	MCHC	calculated (HGB/HCT) x 100	percent (%)

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ATTACHMENT 2

INDIVIDUAL CLINICAL PATHOLOGY DATA

APPENDIX T

Sex: Female

ATTACHMENT 2: Individual Serum Chemistry –Female Toxicity Groups

0 mg/kg/day	ALP (U/L)	ALT (U/L)	AST (U/L)	TBILI (mg/dL)	ALB (g/dL)	TP (g/dL)
5194	79	27	108	0.13	4.2	5.9
5195	120	22	103	0.14	4.4	6.3
5196	79	14	76	0.11	4.0	5.5
5197	85	21	92	0.10	3.8	5.4
5198	72	26	69	0.10	4.3	6.1
5199	72	17	76	0.14	4.4	6.0
5200	60	20	89	0.11	3.9	5.8
5201	112	19	102	0.11	4.2	5.9
5202	54	26	98	0.14	4.5	6.6
5203	74	24	82	0.13	4.5	6.2
Mean	80.7	21.6	89.5	0.121	4.22	5.97
SD	20.8	4.2	13.3	0.017	0.25	0.36
N	10	10	10	10	10	10

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ATTACHMENT 2: Individual Serum Chemistry –Female Toxicity Groups (continued)

Sex: Female

0 mg/kg/day	BUN (mg/dL)	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	CA (mg/dL)	PHOS (mg/dL)
5194	17	0.4	121	73	9.7	6.2
5195	16	0.3	129	48	9.7	7.8
5196	15	0.3	133	46	9.8	8.1
5197	17	0.4	108	92	9.4	7.2
5198	12	0.3	156	39	10.1	7.5
5199	13	0.3	123	41	9.9	7.4
5200	11	0.3	126	50	9.8	7.4
5201	16	0.4	123	65	10.0	7.3
5202	16	0.3	120	49	10.3	7.0
5203	13	0.4	115	49	9.9	7.1
Mean	14.6	0.34	125.4	55.2	9.86	7.30
SD	2.2	0.05	12.8	16.6	0.25	0.51
N	10	10	10	10	10	10

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ATTACHMENT 2: Individual Serum Chemistry –Female Toxicity Groups (continued)

Sex: Female

0 mg/kg/day	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
5194	142	4.3	106
5195	142	4.0	106
5196	143	3.9	107
5197	141	3.9	106
5198	139	3.9	102
5199	140	4.1	104
5200	140	4.2	103
5201	142	4.5	105
5202	140	3.9	104
5203	140	4.2	103
Mean	140.9	4.09	104.6
SD	1.3	0.21	1.6
N	10	10	10

Sex: Female

ATTACHMENT 2: Individual Serum Chemistry –Female Toxicity Groups (continued)

100 mg/kg/day	ALP (U/L)	ALT (U/L)	AST (U/L)	TBILI (mg/dL)	ALB (g/dL)	TP (g/dL)
5224	76	18	87	0.12	4.1	5.6
5225	59	28	82	0.12	4.3	6.4
5226	80	18	104	0.07	3.7	6.0
5227	91	23	123	0.14	4.1	5.9
5228	78	14	65	0.11	3.9	5.5
5229	78	22	99	0.16	4.5	5.8
5230	71	17	65	0.16	4.2	6.5
5231	72	23	73	0.14	4.7	6.3
5232	83	17	95	0.13	4.1	5.7
5233	80	18	79	0.09	4.0	5.9
Mean	76.8	19.8	87.2	0.124	4.16	5.96
SD	8.4	4.1	18.4	0.029	0.29	0.34
N	10	10	10	10	10	10

APPENDIX T

Sex: Female

ATTACHMENT 2: Individual Serum Chemistry –Female Toxicity Groups (continued)

100 mg/kg/day	BUN (mg/dL)	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	CA (mg/dL)	PHOS (mg/dL)
5224	19	0.4	131	66	9.6	5.7
5225	18	0.4	135	58	10.2	7.7
5226	13	0.3	118	42	9.3	7.8
5227	17	0.3	121	39	9.6	8.2
5228	17	0.3	123	76	9.7	7.2
5229	15	0.3	140	64	9.7	7.1
5230	14	0.3	128	86	10.1	7.3
5231	13	0.3	125	72	10.2	6.0
5232	14	0.3	127	66	9.9	6.8
5233	15	0.4	102	50	9.6	7.3
Mean	15.5	0.33	125.0	61.9	9.79	7.11
SD	2.1	0.05	10.4	14.9	0.30	0.78
N	10	10	10	10	10	10

Sex: Female **ATTACHMENT 2: Individual Serum Chemistry –Female Toxicity Groups (continued)**

100 mg/kg/day	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
5224	141	3.8	108
5225	141	4.4	104
5226	143	3.7	107
5227	141	4.2	105
5228	141	4.2	106
5229	140	4.1	103
5230	140	4.0	102
5231	140	3.8	104
5232	142	3.9	105
5233	139	3.9	104
Mean	140.8	4.00	104.8
SD	1.1	0.22	1.8
N	10	10	10

Sex: Female

ATTACHMENT 2: Individual Serum Chemistry –Female Toxicity Groups (continued)

300 mg/kg/day	ALP (U/L)	ALT (U/L)	AST (U/L)	TBILI (mg/dL)	ALB (g/dL)	TP (g/dL)
5254	110	17	80	0.12	4.5	6.4
5255	77	19	63	0.10	4.2	6.6
5256	95	17	69	0.13	4.5	6.1
5257	51	13	63	0.09	4.1	6.0
5258	109	20	52	0.09	4.0	5.8
5259	84	18	89	0.14	4.1	5.5
5260	67	16	79	0.13	4.3	5.9
5261	48	32	86	0.13	3.8	5.2
5262	83	13	99	0.18	4.2	5.9
5263	87	18	59	0.12	3.7	5.1
Mean	81.1	18.3	73.9	0.123	4.14	5.85
SD	21.3	5.3	15.0	0.027	0.26	0.48
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Serum Chemistry –Female Toxicity Groups (continued)

300 mg/kg/day	BUN (mg/dL)	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	CA (mg/dL)	PHOS (mg/dL)
5254	18	0.3	133	71	10.0	7.3
5255	19	0.3	135	59	10.2	7.9
5256	16	0.3	120	60	10.5	8.3
5257	20	0.3	126	68	9.9	7.9
5258	11	0.3	133	76	10.3	7.2
5259	13	0.3	108	64	9.9	8.0
5260	18	0.3	132	76	10.2	7.4
5261	13	0.3	125	72	9.8	6.8
5262	15	0.3	101	63	10.0	7.5
5263	14	0.3	115	98	9.5	7.2
Mean	15.7	0.30	122.8	70.7	10.03	7.55
SD	3.0	0.00	11.6	11.4	0.28	0.46
N	10	10	10	10	10	10

Sex: Female **ATTACHMENT 2: Individual Serum Chemistry –Female Toxicity Groups (continued)**

300 mg/kg/day	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
5254	139	4.3	102
5255	140	4.1	103
5256	142	4.0	105
5257	140	4.1	103
5258	140	3.5	104
5259	139	4.3	103
5260	140	4.5	103
5261	141	3.9	105
5262	140	4.9	104
5263	140	4.0	106
Mean	140.1	4.16	103.8
SD	0.9	0.37	1.2
N	10	10	10

Sex: Female

ATTACHMENT 2: Individual Serum Chemistry –Female Toxicity Groups (continued)

1000 mg/kg/day	ALP (U/L)	ALT (U/L)	AST (U/L)	TBILI (mg/dL)	ALB (g/dL)	TP (g/dL)
5284	84	19	56	0.10	4.2	6.1
5285	87	19	100	0.13	3.9	5.3
5286	111	22	60	0.10	3.9	5.5
5287	67	17	47	0.11	3.9	5.8
5288	55	20	55	0.09	3.8	5.7
5289	48	19	68	0.25	4.1	5.9
5290	76	16	63	0.11	3.9	5.8
5291	50	14	52	0.07	3.8	5.7
5292	97	19	54	0.09	3.9	5.5
5293	48	21	59	0.10	3.7	5.3
Mean	72.3	18.6	61.4	0.115	3.91	5.66
SD	22.3	2.4	14.8	0.050	0.14	0.26
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Serum Chemistry –Female Toxicity Groups (continued)

1000 mg/kg/day	BUN (mg/dL)	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	CA (mg/dL)	PHOS (mg/dL)
5284	15	0.3	115	82	9.9	6.8
5285	15	0.3	154	105	9.8	7.8
5286	11	0.2	126	100	9.6	7.4
5287	12	0.3	137	91	10.3	7.2
5288	10	0.2	129	91	10.5	7.6
5289	14	0.3	192	107	10.3	8.9
5290	10	0.3	136	96	9.9	7.2
5291	15	0.3	117	55	9.9	6.3
5292	10	0.2	131	94	10.0	6.7
5293	17	0.2	123	88	10.2	8.2
Mean	12.9	0.26	136.0	90.9	10.04	7.41
SD	2.6	0.05	22.6	14.7	0.28	0.76
N	10	10	10	10	10	10

Sex: Female **ATTACHMENT 2: Individual Serum Chemistry –Female Toxicity Groups (continued)**

1000 mg/kg/day	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
5284	139	4.0	103
5285	140	4.1	104
5286	140	4.3	106
5287	140	3.8	104
5288	139	3.7	102
5289	137	4.6	103
5290	139	3.9	102
5291	141	3.7	105
5292	140	3.9	104
5293	139	4.1	104
Mean	139.4	4.01	103.7
SD	1.1	0.28	1.3
N	10	10	10

Sex: Male

ATTACHMENT 2: Individual Serum Chemistry –Male Toxicity Groups

0 mg/kg/day	ALP (U/L)	ALT (U/L)	AST (U/L)	TBILI (mg/dL)	ALB (g/dL)	TP (g/dL)
5204	177	28	99	0.13	3.8	5.9
5205	157	22	80	0.13	3.8	5.7
5206	166	22	87	0.14	4.0	5.8
5207	164	20	67	0.08	3.6	5.8
5208	173	23	100	0.12	3.9	5.6
5209	131	26	128	0.17	3.9	5.8
5210	154	22	71	0.12	3.6	5.6
5211	142	22	68	0.11	3.6	5.7
5212	141	18	94	0.14	3.8	5.8
5213	158	20	116	0.14	3.7	5.3
Mean	156.3	22.3	91.0	0.128	3.77	5.70
SD	14.7	2.9	20.5	0.023	0.14	0.17
N	10	10	10	10	10	10

Sex: Male

ATTACHMENT 2: Individual Serum Chemistry –Male Toxicity Groups (continued)

0 mg/kg/day	BUN (mg/dL)	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	CA (mg/dL)	PHOS (mg/dL)
5204	13	0.3	142	39	9.8	8.0
5205	11	0.2	115	41	9.5	7.4
5206	14	0.3	114	44	9.6	7.4
5207	13	0.3	132	44	9.7	7.3
5208	13	0.3	103	47	10.0	7.7
5209	12	0.3	101	39	9.5	7.6
5210	12	0.3	118	48	9.6	7.4
5211	12	0.3	124	48	9.5	7.7
5212	10	0.2	131	33	9.3	7.5
5213	14	0.3	119	27	9.2	7.9
Mean	12.4	0.28	119.9	41.0	9.57	7.59
SD	1.3	0.04	12.8	6.8	0.23	0.23
N	10	10	10	10	10	10

ATTACHMENT 2: Individual Serum Chemistry –Male Toxicity Groups (continued)

Sex: Male

0 mg/kg/day	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
5204	141	4.5	101
5205	142	4.4	105
5206	142	4.4	103
5207	142	4.3	106
5208	145	4.2	106
5209	144	4.4	104
5210	143	4.3	104
5211	142	4.6	104
5212	144	4.7	105
5213	143	4.6	106
Mean	142.8	4.44	104.4
SD	1.2	0.16	1.6
N	10	10	10

ATTACHMENT 2: Individual Serum Chemistry –Male Toxicity Groups (continued)

Sex: Male

100 mg/kg/day	ALP (U/L)	ALT (U/L)	AST (U/L)	TBILI (mg/dL)	ALB (g/dL)	TP (g/dL)
5234	104	22	82	0.09	3.6	5.4
5235	160	27	77	0.10	3.8	5.8
5236	113	21	70	0.11	3.7	5.9
5237	167	22	68	0.10	3.8	5.7
5238	136	22	73	0.13	3.8	5.7
5239	110	24	67	0.09	3.6	5.8
5240	126	17	60	0.11	3.7	5.4
5241	105	19	61	0.09	3.8	6.0
5242	108	19	53	0.09	4.0	5.7
5243	121	16	58	0.10	3.7	5.6
Mean	125.0	20.9	66.9	0.101	3.75	5.70
SD	22.7	3.3	9.0	0.013	0.12	0.19
N	10	10	10	10	10	10

APPENDIX T

ATTACHMENT 2: Individual Serum Chemistry –Male Toxicity Groups (continued)

Sex: Male

100 mg/kg/day	BUN (mg/dL)	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	CA (mg/dL)	PHOS (mg/dL)
5234	14	0.3	156	35	9.4	8.0
5235	11	0.3	123	48	9.5	7.0
5236	13	0.3	120	45	9.5	7.3
5237	12	0.3	116	55	9.5	6.8
5238	11	0.2	125	42	9.7	7.5
5239	15	0.3	120	50	9.8	7.9
5240	16	0.3	140	34	9.7	7.2
5241	13	0.3	142	62	9.6	6.3
5242	12	0.3	148	52	9.7	7.2
5243	11	0.3	133	54	9.9	7.8
Mean	12.8	0.29	132.3	47.7	9.63	7.30
SD	1.8	0.03	13.6	8.9	0.16	0.53
N	10	10	10	10	10	10

APPENDIX T

ATTACHMENT 2: Individual Serum Chemistry –Male Toxicity Groups (continued)

Sex: Male

100 mg/kg/day	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
5234	144	4.3	107
5235	144	4.2	105
5236	140	4.7	104
5237	147	4.5	108
5238	144	4.2	106
5239	141	4.2	102
5240	144	3.9	106
5241	142	4.2	105
5242	141	4.5	104
5243	143	4.7	105
Mean	143.0	4.34	105.2
SD	2.1	0.25	1.7
N	10	10	10

APPENDIX T

ATTACHMENT 2: Individual Serum Chemistry –Male Toxicity Groups (continued)

Sex: Male

300 mg/kg/day	ALP (U/L)	ALT (U/L)	AST (U/L)	TBILI (mg/dL)	ALB (g/dL)	TP (g/dL)
5264	120	24	72	0.09	3.5	5.5
5265	128	21	74	0.13	3.8	5.7
5266	87	18	70	0.09	3.6	5.8
5267	163	22	67	0.11	3.8	5.7
5268	120	33	134	0.17	4.1	5.8
5269	147	21	62	0.10	3.8	5.8
5270	137	31	64	0.11	3.9	5.5
5271	88	19	58	0.09	3.7	6.0
5272	98	17	49	0.09	3.7	5.6
5273	112	20	82	0.11	3.5	5.4
Mean	120.0	22.6	73.2	0.109	3.74	5.68
SD	24.9	5.4	23.2	0.025	0.18	0.18
N	10	10	10	10	10	10

ATTACHMENT 2: Individual Serum Chemistry –Male Toxicity Groups (continued)

Sex: Male

300 mg/kg/day	BUN (mg/dL)	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	CA (mg/dL)	PHOS (mg/dL)
5264	14	0.3	137	48	9.5	7.1
5265	11	0.3	124	49	10.1	7.3
5266	12	0.3	135	44	9.9	8.1
5267	13	0.3	114	54	9.6	6.7
5268	12	0.3	107	53	10.0	8.3
5269	10	0.2	124	50	9.6	7.0
5270	16	0.4	122	52	9.6	7.4
5271	12	0.3	121	75	9.8	6.9
5272	15	0.2	166	36	9.5	7.7
5273	14	0.2	125	33	9.5	7.6
Mean	12.9	0.28	127.5	49.4	9.71	7.41
SD	1.9	0.06	16.1	11.4	0.22	0.52
N	10	10	10	10	10	10

APPENDIX T

ATTACHMENT 2: Individual Serum Chemistry –Male Toxicity Groups (continued)

Sex: Male

300 mg/kg/day	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
5264	142	4.3	104
5265	142	4.6	103
5266	142	4.6	106
5267	142	4.4	104
5268	143	4.5	103
5269	143	4.3	105
5270	142	4.4	103
5271	143	4.2	105
5272	142	4.1	104
5273	142	4.6	106
Mean	142.3	4.40	104.3
SD	0.5	0.18	1.2
N	10	10	10

ATTACHMENT 2: Individual Serum Chemistry –Male Toxicity Groups (continued)

Sex: Male

1000 mg/kg/day	ALP (U/L)	ALT (U/L)	AST (U/L)	TBILI (mg/dL)	ALB (g/dL)	TP (g/dL)
5294	140	18	65	0.11	3.6	5.4
5295	89	17	53	0.09	3.5	5.4
5296	102	19	68	0.11	3.5	5.5
5297	140	29	68	0.11	4.0	6.2
5298	88	18	58	0.08	3.6	5.4
5299	104	20	56	0.11	3.8	5.8
5300	84	15	53	0.12	3.6	5.7
5301	95	16	65	0.14	3.7	5.6
5302	103	21	79	0.13	3.4	5.0
5303	121	21	66	0.09	4.0	6.0
Mean	106.6	19.4	63.1	0.109	3.67	5.60
SD	20.5	3.9	8.1	0.019	0.21	0.34
N	10	10	10	10	10	10

APPENDIX T

ATTACHMENT 2: Individual Serum Chemistry –Male Toxicity Groups (continued)

Sex: Male

1000 mg/kg/day	BUN (mg/dL)	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	CA (mg/dL)	PHOS (mg/dL)
5294	13	0.2	129	42	9.7	7.1
5295	12	0.2	110	50	9.9	7.5
5296	13	0.2	110	39	9.3	7.0
5297	15	0.3	115	62	10.4	8.6
5298	14	0.3	101	43	9.6	6.7
5299	12	0.3	117	39	10.2	8.0
5300	15	0.3	128	92	9.8	8.2
5301	11	0.3	112	50	10.0	7.5
5302	11	0.2	134	40	9.4	7.6
5303	14	0.3	112	41	9.8	7.3
Mean	13.0	0.26	116.8	49.8	9.81	7.55
SD	1.5	0.05	10.3	16.5	0.34	0.58
N	10	10	10	10	10	10

ATTACHMENT 2: Individual Serum Chemistry –Male Toxicity Groups (continued)

Sex: Male

1000 mg/kg/day	NA (mmol/L)	K (mmol/L)	CL (mmol/L)
5294	142	4.0	105
5295	144	4.1	105
5296	140	4.2	104
5297	144	4.6	105
5298	141	3.9	105
5299	144	4.0	104
5300	144	4.8	103
5301	142	4.6	105
5302	144	4.5	107
5303	142	4.1	104
Mean	142.7	4.28	104.7
SD	1.5	0.32	1.1
N	10	10	10

APPENDIX T

ATTACHMENT 2: Individual Hematology –Female Toxicity Groups

Sex: Female

0 mg/kg/day	WBC (10^3/uL)	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)
5194	7.6	7.56	14.7	42.9	56.8	19.5
5195	4.4	7.50	14.7	43.0	57.2	19.6
5196	3.2	7.50	14.3	41.0	54.7	19.0
5197	3.4	7.74	14.7	41.6	53.7	19.0
5198	5.2	7.73	14.9	42.1	54.4	19.3
5199	4.8	7.61	14.9	42.1	55.3	19.6
5200	5.8	7.63	14.5	40.5	53.1	19.0
5201	6.4	7.49	14.4	42.0	56.1	19.2
5202	9.8	7.39	15.6	43.9	59.4	21.1
5203	3.3	7.70	14.8	42.3	54.9	19.3
Mean	5.39	7.585	14.75	42.14	55.56	19.46
SD	2.11	0.117	0.36	0.99	1.87	0.62
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Hematology –Female Toxicity Groups (continued)

0 mg/kg/day	MCHC (g/dL)	PLT (10^3/uL)	Neutro (%)	Abs Neut (10^3/uL)	Lymph (%)	Abs Lymph (10^3/uL)
5194	34.3	1013.0	9.6	0.731	87.2	6.660
5195	34.2	1047.0	26.4	1.160	70.0	3.060
5196	34.8	938.0	0.0	0.001	95.3	3.040
5197	35.4	939.0	11.0	0.377	86.7	2.960
5198	35.4	846.0	14.8	0.772	82.5	4.300
5199	35.5	1141.0	9.2	0.446	87.4	4.220
5200	35.7	1123.0	26.0	1.520	70.5	4.120
5201	34.2	978.0	20.2	1.300	77.0	4.940
5202	35.5	1018.0	18.4	1.800	77.7	7.590
5203	35.1	914.0	22.4	0.742	73.1	2.420
Mean	35.01	995.70	15.80	0.8849	80.74	4.3310
SD	0.59	92.31	8.44	0.5555	8.42	1.6762
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Hematology –Female Toxicity Groups (continued)

0 mg/kg/day	Mono (%)	Abs Mono (10^3/uL)	Eosin (%)	Abs Eosin (10^3/uL)	Baso (%)	Abs Baso (10^3/uL)
5194	0.9	0.065	2.1	0.160	0.3	0.022
5195	0.7	0.029	2.8	0.124	0.1	0.002
5196	0.4	0.012	0.7	0.021	3.6	0.115
5197	0.4	0.013	1.7	0.058	0.2	0.006
5198	0.6	0.029	1.8	0.093	0.4	0.020
5199	0.4	0.019	2.7	0.130	0.3	0.015
5200	0.9	0.052	2.4	0.139	0.2	0.009
5201	0.4	0.027	2.2	0.139	0.2	0.011
5202	1.4	0.137	2.3	0.220	0.2	0.019
5203	0.3	0.010	4.2	0.140	0.0	0.000
Mean	0.64	0.0393	2.29	0.1224	0.55	0.0219
SD	0.34	0.0386	0.90	0.0549	1.08	0.0336
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Hematology –Female Toxicity Groups (continued)

100 mg/kg/day	WBC (10^3/uL)	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)
5224	3.7	7.19	14.0	40.7	56.6	19.5
5225	5.5	7.08	14.4	42.4	59.9	20.3
5226	4.1	7.49	14.3	41.6	55.5	19.1
5227	6.2	7.64	14.6	41.7	54.6	19.1
5228	3.9	7.61	14.7	41.3	54.3	19.3
5229	4.0	7.79	14.5	40.8	52.3	18.7
5230	9.1	7.47	14.4	40.5	54.2	19.3
5231	5.2	7.75	15.0	42.6	55.0	19.4
5232	5.0	8.20	15.3	42.8	52.2	18.7
5233	3.4	7.96	15.4	44.3	55.6	19.3
Mean	5.01	7.618	14.66	41.87	55.02	19.27
SD	1.69	0.336	0.45	1.17	2.20	0.45
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Hematology –Female Toxicity Groups (continued)

100 mg/kg/day	MCHC (g/dL)	PLT (10^3/uL)	Neutro (%)	Abs Neut (10^3/uL)	Lymph (%)	Abs Lymph (10^3/uL)
5224	34.5	947.0	22.1	0.807	74.6	2.730
5225	34.0	970.0	18.1	1.000	79.3	4.370
5226	34.4	950.0	37.6	1.520	60.5	2.450
5227	35.0	961.0	21.8	1.350	74.5	4.630
5228	35.5	947.0	6.9	0.270	87.7	3.420
5229	35.6	971.0	6.1	0.246	91.9	3.680
5230	35.7	973.0	17.8	1.610	80.4	7.310
5231	35.3	1073.0	12.8	0.661	84.9	4.390
5232	35.9	1048.0	6.4	0.319	91.5	4.530
5233	34.8	920.0	21.0	0.713	74.8	2.540
Mean	35.07	976.00	17.06	0.8496	80.01	4.0050
SD	0.63	47.59	9.67	0.5097	9.57	1.4340
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Hematology –Female Toxicity Groups (continued)

100 mg/kg/day	Mono (%)	Abs Mono (10^3/uL)	Eosin (%)	Abs Eosin (10^3/uL)	Baso (%)	Abs Baso (10^3/uL)
5224	0.3	0.012	2.9	0.107	0.1	0.004
5225	0.5	0.028	2.0	0.110	0.1	0.004
5226	0.8	0.032	1.0	0.039	0.2	0.007
5227	0.1	0.007	3.6	0.224	0.0	0.003
5228	1.6	0.061	3.5	0.137	0.3	0.010
5229	0.4	0.016	1.5	0.059	0.1	0.005
5230	0.3	0.026	1.1	0.104	0.4	0.037
5231	0.8	0.040	1.4	0.073	0.1	0.005
5232	0.7	0.036	1.1	0.055	0.3	0.013
5233	1.5	0.051	2.7	0.093	0.0	0.000
Mean	0.70	0.0309	2.08	0.1001	0.16	0.0088
SD	0.50	0.0170	1.02	0.0528	0.13	0.0106
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Hematology –Female Toxicity Groups (continued)

300 mg/kg/day	WBC (10^3/uL)	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)
5254	6.6	7.38	14.4	42.5	57.6	19.5
5255	6.3	7.49	14.4	42.4	56.7	19.2
5256	6.9	7.70	14.6	42.1	54.6	19.0
5257	3.1	7.62	14.0	39.6	52.0	18.3
5258	5.9	7.52	14.5	41.2	54.7	19.3
5259	3.3	8.26	16.3	45.8	55.5	19.7
5260	4.7	7.13	14.5	41.0	57.4	20.3
5261	4.3	8.35	15.4	43.7	52.3	18.4
5262	4.5	7.77	15.1	43.5	56.0	19.5
5263	6.5	7.82	14.8	41.8	53.4	18.9
Mean	5.21	7.704	14.80	42.36	55.02	19.21
SD	1.41	0.375	0.66	1.70	1.99	0.60
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Hematology –Female Toxicity Groups (continued)

300 mg/kg/day	MCHC (g/dL)	PLT (10^3/uL)	Neutro (%)	Abs Neut (10^3/uL)	Lymph (%)	Abs Lymph (10^3/uL)
5254	33.9	1136.0	21.5	1.410	74.4	4.880
5255	33.9	1083.0	27.8	1.750	69.1	4.350
5256	34.8	936.0	35.2	2.420	62.7	4.300
5257	35.3	825.0	0.1	0.002	95.4	2.990
5258	35.3	1025.0	24.7	1.460	69.9	4.150
5259	35.5	947.0	10.9	0.354	86.1	2.810
5260	35.4	818.0	19.1	0.887	78.5	3.650
5261	35.2	1005.0	7.0	0.300	89.3	3.830
5262	34.8	1039.0	4.0	0.181	92.8	4.180
5263	35.4	903.0	9.4	0.608	84.9	5.520
Mean	34.95	971.70	15.97	0.9372	80.31	4.0660
SD	0.60	105.20	11.41	0.7930	11.06	0.8094
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Hematology –Female Toxicity Groups (continued)

300 mg/kg/day	Mono (%)	Abs Mono (10^3/uL)	Eosin (%)	Abs Eosin (10^3/uL)	Baso (%)	Abs Baso (10^3/uL)
5254	1.7	0.109	2.1	0.135	0.3	0.022
5255	0.2	0.012	2.8	0.179	0.1	0.005
5256	0.5	0.034	1.4	0.097	0.1	0.008
5257	0.4	0.014	0.8	0.025	3.3	0.102
5258	2.1	0.125	3.1	0.186	0.2	0.011
5259	0.2	0.007	2.3	0.076	0.5	0.017
5260	0.5	0.022	1.7	0.078	0.3	0.013
5261	1.1	0.048	2.1	0.092	0.4	0.018
5262	0.2	0.010	2.3	0.103	0.6	0.029
5263	3.8	0.247	1.5	0.099	0.4	0.029
Mean	1.07	0.0628	2.01	0.1070	0.62	0.0254
SD	1.17	0.0771	0.68	0.0485	0.96	0.0281
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Hematology –Female Toxicity Groups (continued)

1000 mg/kg/day	WBC (10^3/uL)	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)
5284	7.8	7.19	14.0	40.9	57.0	19.5
5285	2.4	7.75	14.4	42.4	54.8	18.6
5286	4.0	7.80	14.1	41.3	52.9	18.1
5287	7.4	7.78	14.7	42.0	54.0	18.9
5288	6.2	7.97	15.7	44.9	56.3	19.7
5289	2.8	7.72	14.8	44.2	57.2	19.2
5290	8.5	8.02	15.4	43.9	54.7	19.2
5291	4.0	7.73	14.4	42.1	54.5	18.6
5292	5.4	7.84	14.5	41.4	52.8	18.5
5293	4.1	7.81	14.9	42.3	54.1	19.1
Mean	5.26	7.761	14.69	42.54	54.83	18.94
SD	2.14	0.224	0.54	1.34	1.55	0.49
N	10	10	10	10	10	10

APPENDIX T

Sex: Female

ATTACHMENT 2: Individual Hematology –Female Toxicity Groups (continued)

1000 mg/kg/day	MCHC (g/dL)	PLT (10^3/uL)	Neutro (%)	Abs Neut (10^3/uL)	Lymph (%)	Abs Lymph (10^3/uL)
5284	34.2	987.0	41.3	3.210	56.3	4.380
5285	33.9	856.0	0.3	0.007	88.7	2.120
5286	34.1	1042.0	8.5	0.340	87.9	3.530
5287	35.0	916.0	37.0	2.730	61.3	4.530
5288	34.9	898.0	8.6	0.532	88.1	5.460
5289	33.6	614.0	33.6	0.951	63.6	1.800
5290	35.2	868.0	26.5	2.260	70.1	5.970
5291	34.2	839.0	14.1	0.559	82.3	3.260
5292	34.9	902.0	0.1	0.004	93.2	5.010
5293	35.4	773.0	16.6	0.676	80.0	3.260
Mean	34.54	869.50	18.66	1.1269	77.15	3.9320
SD	0.61	117.05	15.07	1.1661	13.25	1.3785
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Hematology –Female Toxicity Groups (continued)

1000 mg/kg/day	Mono (%)	Abs Mono (10^3/uL)	Eosin (%)	Abs Eosin (10^3/uL)	Baso (%)	Abs Baso (10^3/uL)
5284	0.2	0.016	2.2	0.168	0.1	0.006
5285	5.6	0.134	0.4	0.009	5.0	0.119
5286	0.5	0.019	3.1	0.123	0.1	0.005
5287	0.2	0.017	1.4	0.102	0.0	0.003
5288	0.2	0.012	3.0	0.189	0.1	0.005
5289	0.3	0.009	2.5	0.070	0.0	0.000
5290	1.7	0.144	1.5	0.131	0.1	0.011
5291	0.6	0.024	2.9	0.116	0.0	0.001
5292	3.4	0.183	0.5	0.025	2.8	0.150
5293	0.6	0.023	2.7	0.111	0.2	0.006
Mean	1.33	0.0581	2.02	0.1044	0.84	0.0306
SD	1.80	0.0672	1.01	0.0568	1.70	0.0553
N	10	10	10	10	10	10

APPENDIX T

ATTACHMENT 2: Individual Hematology –Male Toxicity Groups

Sex: Male

0 mg/kg/day	WBC (10^3/uL)	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)
5204	7.3	8.08	14.8	42.4	52.5	18.3
5205	7.7	7.64	14.3	41.6	54.4	18.8
5206	5.9	8.35	16.0	45.9	54.9	19.2
5207	5.5	7.68	14.4	40.9	53.2	18.7
5208	5.1	8.15	14.9	42.6	52.3	18.3
5209	4.7	7.69	14.9	42.4	55.1	19.4
5210	4.7	7.76	14.3	41.3	53.2	18.5
5211	4.7	8.44	16.0	45.5	53.9	18.9
5212	6.5	8.45	15.7	45.2	53.4	18.6
5213	5.6	8.87	16.1	45.9	51.7	18.2
Mean	5.77	8.111	15.14	43.37	53.46	18.69
SD	1.09	0.417	0.74	2.02	1.12	0.40
N	10	10	10	10	10	10

Sex: Male

ATTACHMENT 2: Individual Hematology –Male Toxicity Groups (continued)

0 mg/kg/day	MCHC (g/dL)	PLT (10^3/uL)	Neutro (%)	Abs Neut (10^3/uL)	Lymph (%)	Abs Lymph (10^3/uL)
5204	34.8	953.0	20.2	1.470	77.1	5.620
5205	34.5	1023.0	34.1	2.620	63.3	4.860
5206	35.0	852.0	18.1	1.060	79.5	4.650
5207	35.1	929.0	27.4	1.510	68.4	3.760
5208	34.9	894.0	19.7	1.010	74.5	3.810
5209	35.2	1016.0	19.8	0.922	75.8	3.520
5210	34.8	1018.0	15.2	0.718	81.0	3.820
5211	35.1	842.0	22.9	1.060	73.8	3.430
5212	34.8	1167.0	15.8	1.030	82.0	5.340
5213	35.1	914.0	15.2	0.846	81.6	4.540
Mean	34.93	960.80	20.84	1.2246	75.70	4.3350
SD	0.21	97.97	5.99	0.5496	6.07	0.7769
N	10	10	10	10	10	10

APPENDIX T

Sex: Male

ATTACHMENT 2: Individual Hematology –Male Toxicity Groups (continued)

0 mg/kg/day	Mono (%)	Abs Mono (10^3/uL)	Eosin (%)	Abs Eosin (10^3/uL)	Baso (%)	Abs Baso (10^3/uL)
5204	1.0	0.073	1.8	0.129	0.0	0.000
5205	0.5	0.040	1.9	0.145	0.1	0.007
5206	0.5	0.031	1.9	0.110	0.1	0.005
5207	1.9	0.104	2.2	0.120	0.1	0.008
5208	2.2	0.113	3.5	0.177	0.1	0.005
5209	1.6	0.076	2.2	0.100	0.6	0.028
5210	0.5	0.024	2.9	0.138	0.3	0.013
5211	0.5	0.023	2.8	0.131	0.0	0.001
5212	0.1	0.009	1.9	0.121	0.2	0.011
5213	0.2	0.011	2.9	0.163	0.0	0.001
Mean	0.90	0.0504	2.40	0.1334	0.15	0.0079
SD	0.74	0.0382	0.58	0.0235	0.18	0.0083
N	10	10	10	10	10	10

APPENDIX T

ATTACHMENT 2: Individual Hematology –Male Toxicity Groups (continued)

Sex: Male

100 mg/kg/day	WBC (10^3/uL)	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)
5234	6.8	7.78	14.8	42.4	54.5	18.9
5235	6.5	7.99	15.1	43.2	54.1	18.9
5236	5.4	7.81	14.7	41.9	53.6	18.8
5237	3.9	7.84	14.3	41.7	53.1	18.2
5238	4.9	8.16	15.1	42.9	52.6	18.5
5239	5.7	7.84	14.2	40.6	51.7	18.2
5240	6.4	7.11	14.8	42.7	60.1	20.8
5241	4.2	7.40	14.6	42.3	57.2	19.7
5242	5.9	8.30	15.1	43.5	52.4	18.2
5243	4.8	7.80	15.1	43.5	55.7	19.4
Mean	5.45	7.803	14.78	42.47	54.50	18.96
SD	0.99	0.342	0.34	0.90	2.56	0.82
N	10	10	10	10	10	10

Sex: Male

ATTACHMENT 2: Individual Hematology –Male Toxicity Groups (continued)

100 mg/kg/day	MCHC (g/dL)	PLT (10^3/uL)	Neutro (%)	Abs Neut (10^3/uL)	Lymph (%)	Abs Lymph (10^3/uL)
5234	34.8	712.0	16.6	1.130	80.0	5.410
5235	34.9	848.0	32.4	2.110	65.7	4.290
5236	35.1	1002.0	16.6	0.899	79.2	4.300
5237	34.3	1045.0	15.6	0.599	80.7	3.110
5238	35.3	901.0	23.1	1.140	70.9	3.500
5239	35.1	1019.0	22.0	1.250	74.4	4.220
5240	34.6	182.0	6.6	0.422	91.9	5.880
5241	34.5	965.0	21.4	0.902	77.3	3.270
5242	34.7	1057.0	12.0	0.707	84.9	5.000
5243	34.8	1037.0	11.6	0.553	86.2	4.120
Mean	34.81	876.80	17.79	0.9712	79.12	4.3100
SD	0.30	266.96	7.28	0.4857	7.63	0.9051
N	10	10	10	10	10	10

Sex: Male

ATTACHMENT 2: Individual Hematology –Male Toxicity Groups (continued)

100 mg/kg/day	Mono (%)	Abs Mono (10^3/uL)	Eosin (%)	Abs Eosin (10^3/uL)	Baso (%)	Abs Baso (10^3/uL)
5234	1.0	0.067	2.2	0.151	0.2	0.014
5235	0.3	0.018	1.6	0.106	0.0	0.001
5236	1.7	0.091	2.1	0.114	0.4	0.023
5237	0.8	0.029	2.4	0.091	0.6	0.023
5238	3.7	0.183	1.8	0.086	0.6	0.028
5239	0.6	0.035	2.8	0.159	0.2	0.012
5240	0.3	0.017	0.9	0.057	0.3	0.020
5241	0.5	0.023	0.7	0.030	0.1	0.003
5242	0.3	0.019	2.6	0.154	0.2	0.011
5243	1.0	0.050	1.0	0.047	0.2	0.008
Mean	1.02	0.0532	1.81	0.0995	0.28	0.0143
SD	1.04	0.0517	0.74	0.0460	0.20	0.0090
N	10	10	10	10	10	10

ATTACHMENT 2: Individual Hematology –Male Toxicity Groups (continued)

300 mg/kg/day	WBC (10^3/uL)	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)
5264	4.1	7.67	14.1	40.3	52.6	18.4
5265	6.9	8.06	14.9	43.9	54.5	18.5
5266	7.5	7.14	13.5	38.6	54.1	19.0
5267	6.5	8.64	15.8	45.4	52.6	18.3
5268	6.0	7.78	15.4	43.5	55.9	19.8
5269	5.3	7.96	15.1	43.7	54.8	19.0
5270	6.9	8.30	16.0	46.3	55.8	19.3
5271	4.9	7.96	14.9	43.0	54.0	18.7
5272	6.6	7.96	15.4	44.3	55.6	19.3
5273	4.2	7.96	14.5	41.4	52.0	18.2
Mean	5.89	7.943	14.96	43.04	54.19	18.85
SD	1.20	0.391	0.77	2.34	1.41	0.52
N	10	10	10	10	10	10

APPENDIX T

Sex: Male

ATTACHMENT 2: Individual Hematology –Male Toxicity Groups (continued)

300 mg/kg/day	MCHC (g/dL)	PLT (10^3/uL)	Neutro (%)	Abs Neut (10^3/uL)	Lymph (%)	Abs Lymph (10^3/uL)
5264	35.0	857.0	34.7	1.420	63.1	2.590
5265	33.9	1077.0	13.5	0.928	83.3	5.740
5266	35.1	1006.0	28.6	2.150	69.3	5.210
5267	34.7	1018.0	24.9	1.610	67.6	4.390
5268	35.5	802.0	15.3	0.915	81.4	4.860
5269	34.7	809.0	15.6	0.826	81.8	4.340
5270	34.5	887.0	11.6	0.794	84.3	5.770
5271	34.7	1000.0	11.8	0.585	86.3	4.270
5272	34.7	811.0	13.7	0.907	85.1	5.650
5273	35.1	1068.0	32.3	1.360	64.0	2.690
Mean	34.79	933.50	20.20	1.1495	76.62	4.5510
SD	0.43	111.21	8.98	0.4765	9.40	1.1593
N	10	10	10	10	10	10

Sex: Male

ATTACHMENT 2: Individual Hematology –Male Toxicity Groups (continued)

300 mg/kg/day	Mono (%)	Abs Mono (10^3/uL)	Eosin (%)	Abs Eosin (10^3/uL)	Baso (%)	Abs Baso (10^3/uL)
5264	0.3	0.014	1.9	0.078	0.0	0.000
5265	0.4	0.028	2.6	0.176	0.2	0.016
5266	0.2	0.017	1.8	0.135	0.0	0.003
5267	5.2	0.336	2.1	0.136	0.2	0.014
5268	0.8	0.047	2.0	0.118	0.5	0.029
5269	0.2	0.009	2.5	0.131	0.0	0.000
5270	1.1	0.076	2.6	0.177	0.4	0.025
5271	0.3	0.014	1.4	0.071	0.1	0.006
5272	0.2	0.016	1.0	0.063	0.1	0.004
5273	1.4	0.061	1.8	0.077	0.4	0.019
Mean	1.01	0.0618	1.97	0.1162	0.19	0.0116
SD	1.53	0.0990	0.52	0.0423	0.19	0.0105
N	10	10	10	10	10	10

Sex: Male

ATTACHMENT 2: Individual Hematology –Male Toxicity Groups (continued)

1000 mg/kg/day	WBC (10^3/uL)	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)
5294	4.4	7.71	14.2	41.2	53.4	18.5
5295	5.4	7.24	13.6	39.3	54.3	18.7
5296	4.5	7.46	14.2	40.3	54.0	19.1
5297	4.2	7.99	15.2	43.9	54.9	19.0
5298	5.8	8.07	15.4	43.9	54.4	19.1
5299	3.5	8.35	15.8	44.8	53.6	18.9
5300	6.2	7.55	14.2	40.7	53.9	18.8
5301	7.7	7.26	13.7	38.5	53.1	18.9
5302	4.4	7.88	14.9	43.1	54.7	18.9
5303	3.5	8.25	15.0	43.6	52.9	18.2
Mean	4.96	7.776	14.62	41.93	53.92	18.81
SD	1.32	0.395	0.74	2.20	0.67	0.28
N	10	10	10	10	10	10

Sex: Male

ATTACHMENT 2: Individual Hematology –Male Toxicity Groups (continued)

1000 mg/kg/day	MCHC (g/dL)	PLT (10^3/uL)	Neutro (%)	Abs Neut (10^3/uL)	Lymph (%)	Abs Lymph (10^3/uL)
5294	34.6	893.0	16.6	0.738	81.0	3.590
5295	34.5	908.0	14.7	0.793	83.1	4.500
5296	35.3	1083.0	23.5	1.070	73.6	3.340
5297	34.7	811.0	19.4	0.810	77.5	3.250
5298	35.1	803.0	17.6	1.030	79.8	4.660
5299	35.2	875.0	20.1	0.696	72.3	2.500
5300	34.8	969.0	7.7	0.475	88.9	5.480
5301	35.6	986.0	24.9	1.910	71.5	5.480
5302	34.5	850.0	17.9	0.781	77.2	3.370
5303	34.5	859.0	23.5	0.829	72.1	2.540
Mean	34.88	903.70	18.59	0.9132	77.70	3.8710
SD	0.39	86.77	5.06	0.3875	5.64	1.0977
N	10	10	10	10	10	10

Sex: Male

ATTACHMENT 2: Individual Hematology –Male Toxicity Groups (continued)

1000 mg/kg/day	Mono (%)	Abs Mono (10^3/uL)	Eosin (%)	Abs Eosin (10^3/uL)	Baso (%)	Abs Baso (10^3/uL)
5294	0.9	0.038	1.3	0.059	0.2	0.010
5295	0.2	0.009	1.8	0.099	0.2	0.012
5296	0.3	0.011	2.6	0.116	0.1	0.006
5297	0.2	0.008	2.9	0.120	0.1	0.003
5298	0.3	0.015	2.2	0.128	0.2	0.011
5299	4.1	0.141	2.9	0.100	0.6	0.022
5300	1.5	0.094	1.7	0.105	0.1	0.008
5301	1.7	0.129	1.9	0.146	0.1	0.006
5302	0.3	0.015	4.3	0.188	0.3	0.011
5303	0.9	0.030	3.5	0.124	0.0	0.001
Mean	1.04	0.0490	2.51	0.1185	0.19	0.0090
SD	1.21	0.0521	0.92	0.0336	0.17	0.0058
N	10	10	10	10	10	10

Sex: Female

ATTACHMENT 2: Individual Prothrombin Times –Female Toxicity Groups

0 mg/kg/day	Prothrombin Time (Seconds)
5194	14.1
5195	14.2
5196	14.4
5197	14.5
5198	13.2
5199	13.6
5200	14.0
5201	13.2
5202	13.6
5203	13.6
Mean	13.84
SD	0.47
N	10

ATTACHMENT 2: Individual Prothrombin Times –Female Toxicity Groups (continued)

Sex: Female

100 mg/kg/day	Prothrombin Time (Seconds)
5224	14.2
5225	13.5
5226	14.4
5227	14.7
5228	13.7
5229	13.0
5230	13.6
5231	13.2
5232	13.8
5233	14.2
Mean	13.83
SD	0.54
N	10

ATTACHMENT 2: Individual Prothrombin Times –Female Toxicity Groups (continued)

Sex: Female

300 mg/kg/day	Prothrombin Time (Seconds)
5254	14.5
5255	14.2
5256	14.3
5257	13.5
5258	13.7
5259	13.6
5260	13.7
5261	13.9
5262	13.7
5263	14.5
Mean	13.96
SD	0.38
N	10

ATTACHMENT 2: Individual Prothrombin Times –Female Toxicity Groups (continued)

Sex: Female

1000 mg/kg/day	Prothrombin Time (Seconds)
5284	14.4
5285	14.1
5286	14.7
5287	14.9
5288	13.4
5289	13.1
5290	13.2
5291	13.5
5292	13.7
5293	14.0
Mean	13.90
SD	0.63
N	10

ATTACHMENT 2: Individual Prothrombin Times –Male Toxicity Groups

Sex: Male

0 mg/kg/day	Prothrombin Time (Seconds)
5204	13.5
5205	13.5
5206	13.7
5207	13.8
5208	13.8
5209	14.1
5210	15.1
5211	14.2
5212	14.3
5213	14.4
Mean	14.04
SD	0.49
N	10

ATTACHMENT 2: Individual Prothrombin Times –Male Toxicity Groups (continued)

Sex: Male

100 mg/kg/day	Prothrombin Time (Seconds)
5234	14.8
5235	13.7
5236	13.9
5237	13.7
5238	14.9
5239	16.1
5240	15.7
5241	14.2
5242	14.5
5243	16.6
Mean	14.81
SD	1.02
N	10

ATTACHMENT 2: Individual Prothrombin Times –Male Toxicity Groups (continued)

300 mg/kg/day	Prothrombin Time (Seconds)
5264	13.6
5265	14.4
5266	13.9
5267	13.7
5268	14.4
5269	15.2
5270	14.0
5271	13.3
5272	14.2
5273	16.7
Mean	14.34
SD	0.98
N	10

ATTACHMENT 2: Individual Prothrombin Times –Male Toxicity Groups (continued)

1000 mg/kg/day	Prothrombin Time (Seconds)
5294	15.4
5295	13.6
5296	15.3
5297	15.5
5298	14.5
5299	16.5
5300	13.4
5301	13.4
5302	14.9
5303	14.5
Mean	14.70
SD	1.02
N	10

ATTACHMENT 3: HISTORICAL CONTROL DATA

Serum Chemistry

FEMALE (Sprague Dawley 8-12 weeks)

Parameter (Unit)	N	Mean	SD	Range
ALB (g/dL)	88	3.9	0.52	2.9-5.2
ALP (U/L)	88	76.5	18.8	36-125
ALT (U/L)	88	22.2	7.1	11-56
AST (U/L)	88	77.3	17.7	49-119
TBILI (mg/dL)	88	0.16	0.0	0.09-0.34
CA (mg/dL)	88	10.0	0.4	9.4-10.9
CREAT (mg/dL)	88	0.4	0.1	0.3-0.6
CHOL (mg/dL)	88	50.6	12.6	31-99
GLUC (mg/dL)	88	129.9	16.4	97-179
PHOS (mg/dL)	88	7.0	0.8	5.0-9.2
TP (g/dL)	88	6.1	0.4	5.4-7.3
BUN (mg/dL)	88	13.6	2.5	9-20
NA (mmol/L)	88	140.9	1.5	137-144
K (mmol/L)	88	4.2	0.3	3.6-6.3
CL (mmol/L)	88	103.8	2.2	98-109

MALE (Sprague Dawley 8-12 weeks)

Parameter (Unit)	N	Mean	SD	Range
ALB (g/dL)	89	3.6	0.3	2.8-4.2
ALP (U/L)	89	135.8	28.6	80-227
ALT (U/L)	89	23.8	4.4	13.0-36.0
AST (U/L)	89	83.8	18.6	55.0-129.0
TBILI (mg/dL)	89	0.14	0.05	0.07-0.31
CA (mg/dL)	89	9.9	0.4	9.2-11.2
CREAT (mg/dL)	89	0.4	0.1	0.2-0.6
CHOL (mg/dL)	89	42.2	11.0	21.0-68.0
GLUC (mg/dL)	89	131.7	23.1	97.0-249.0
PHOS (mg/dL)	89	7.6	1.0	6.1-13.0
TP (g/dL)	89	5.8	0.3	5.2-6.7
BUN (mg/dL)	89	12.0	1.8	9.0-17.0
NA (mmol/L)	89	142.0	1.5	139.0-146.0
K (mmol/L)	89	4.6	0.6	3.9-8.4
CL (mmol/L)	89	103.4	1.7	99.0-108.0

Unaudited reference information

March 13, 2009

APPENDIX T

ATTACHMENT 3: HISTORICAL CONTROL DATA

Hematology

FEMALE (Sprague Dawley 8-12 weeks)

Parameter (Unit)	N	Mean	SD	Range
WBC (10^3/µL)	55	6.6	2.5	2.9-13.5
RBC (10^6/µL)	55	7.50	0.3	6.80-8.20
HGB (g/dL)	55	14.6	0.5	13.8-15.8
HCT (%)	55	42.0	1.7	38.5-46.3
MCV (fL)	55	56.1	2.2	52.8-64.2
MCH (pg)	55	19.6	0.7	17.7-21.4
MCHC (g/dL)	55	34.9	0.9	32.7-36.6
PLT (10^6/uL)	55	1026	133.6	768-1336
Neutrophil (%)	55	14.0	6.8	0-29
Neutrophil (10^3/µL)	55	0.9	0.5	0.0-3.5
Lymphocyte (%)	55	78.6	8.1	60.3-95.3
Lymphocyte (10^3/µL)	55	5.2	2.2	2.1-12.0
Monocyte (%)	55	4.3	3.0	0.2-12.0
Monocyte (10^3/µL)	55	0.3	0.2	0.0-1.0
Eosinophil (%)	55	2.1	0.9	0.7-4.4
Eosinophil (10^3/µL)	55	0.1	0.1	0.1-0.5
Basophil (%)	55	1.0	0.9	4.0
Basophil (10^3/µL)	55	0.1	0.1	0.0-0.3

MALE (Sprague Dawley 8-12 weeks)

Parameter (Unit)	N	Mean	SD	Range
WBC (10^3/µL)	59	7.6	2.04	4.7-15.4
RBC (10^6/µL)	59	7.81	0.41	7.2-8.9
HGB (g/dL)	59	15.0	0.60	13.6-16.1
HCT (%)	59	42.7	1.51	40.0-45.9
MCV (fL)	59	54.7	1.86	50.4-59.2
MCH (pg)	59	19.2	0.66	18.0-20.9
MCHC (g/dL)	59	35.2	0.62	33.3-36.5
PLT (10^6/uL)	59	929	97.2	728-1167
Neutrophil (%)	59	15.7	5.81	4.7-34.1
Neutrophil (10^3/µL)	59	1.2	0.48	0.4-2.7
Lymphocyte (%)	59	76.8	6.2	63.3-87.4
Lymphocyte (10^3/µL)	59	5.9	1.7	3.4-11.2
Monocyte (%)	59	4.7	3.1	0.1-10.7
Monocyte (10^3/µL)	59	0.4	0.26	0-1.0
Eosinophil (%)	59	1.9	0.7	0.7-3.6
Eosinophil (10^3/µL)	59	0.14	0.05	0.1-0.3
Basophil (%)	59	0.9	1.03	0.0-3.8
Basophil (10^3/µL)	59	0.8	0.11	0.0-0.6

APPENDIX T

ATTACHMENT 3: HISTORICAL CONTROL DATA

Prothrombin Time

FEMALE (Sprague Dawley 8-12 weeks

Parameter (Unit)	N	Mean	SD	Range
Prothrombin Time (seconds)	56	14.3	1.4	10.7-17.5

MALE (Sprague Dawley 8-12 weeks

Parameter (Unit)	N	Mean	SD	Range
Prothrombin Time (seconds)	61	14.8	1.5	11.6-19.5

APPENDIX U

DOW CORNING CORPORATION
HEALTH & ENVIRONMENTAL SCIENCES

CONTRIBUTING SCIENTIST REPORT

Report Title:	Gross Pathology and Histopathology for the Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Triethoxyoctylsilane in Sprague-Dawley Rats via Oral Gavage
HES Study Number:	10709-102
Test Article:	Triethoxyoctylsilane
Contributing Scientist:	James W. Crissman, DVM, PhD, D.A.C.V.P. Pathologist Crissman Toxicologic Pathology, LLC 2887 Oakhaven Ct Midland, MI 48642-7869
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HES Group Manager:	Paul A. Jean, Ph.D. Team Leader, Toxicology
Testing Facility:	Dow Corning Corporation Health and Environmental Sciences 2200 West Salzburg Road Auburn, Michigan 48611
Analysis Start Date:	May 12, 2008
Analysis End Date:	May 5, 2009

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1 APPROVAL SIGNATURES

Report Title: Gross Pathology and Histopathology for the Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Triethoxyoctylsilane in Sprague-Dawley Rats via Oral Gavage

Submitted by:

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2 OBJECTIVE

The objective of this contributing scientist report is to provide gross and histopathology data for the Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test of Triethoxyoctylsilane in Sprague-Dawley Rats via Oral Gavage.

3 EXPERIMENTAL

Groups of 10 rats per sex per dose were orally administered 0, 100, 300, or 1000 mg/kg/day of triethoxyoctylsilane in peanut oil by gavage for four weeks. Additionally, groups of 10 female rats at the same dose levels were assigned to reproductive replicates and administered the same levels of the test article during a 2-week pre-mating period, through mating (up to 2 weeks), gestation, and day-3 post-partum. Three reproductive group females (D5306, D5309, D5311) displayed signs of distress during or after delivery that warranted euthanasia prior to schedule termination. The remaining reproductive group females were necropsied on day-4 post-partum or 26 days after the end of the mating period in the case of animals that failed to deliver pups. The total days on study for the reproductive group females varied from 38 to 54 days. All males and 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. Based on in-life clinical findings, the 1000 mg/kg/day reproductive group females were also included for gross necropsy and tissues processed for histological evaluation by protocol amendment. Tissues collected, weighed and processed for histological evaluation of the control and 100 mg/kg/day dose groups are listed in Table 1. The clinical signs in the 1000 mg/kg/day reproductive group females warranted collection of the hindlimb and a section of mammary tissue of the reproductive group females at the unscheduled and scheduled necropsies. The hindlimb was further processed for histological evaluation to obtain sections of the adductor and gastrocnemius muscles of the hindlimb and the tibial nerve of the hindlimb (Table 1). Upon further evaluation of the clinical signs, it was determined that the mammary tissue did not represent a possible target organ and was therefore, not processed for histological evaluation. Based on histopathology findings in the 1000 mg/kg/day dose group, various target tissues for the toxicity group males and females and reproductive group females were examined at the mid and low dose groups (Table 2).

4 DATA ANALYSIS

Microscopic examination was performed on all tissues listed in Table 1 for control and 1000 mg/kg/day toxicity males and females and reproductive group females, with the exception of the mammary tissue from the reproductive group females. For animals administered 100 or 300 mg/kg/day, microscopic examination was performed as indicated in Table 2.

5 DEVIATIONS

There were no protocol deviations for this portion of the study.

6 RESULTS AND DISCUSSION

23.1 Gross Pathology

Intergroup comparisons of gross pathology findings are summarized in Attachment 1 and individual animal gross pathology observations are presented in attachments 2 and 5. There were no gross findings attributable to treatment in the male or female toxicity study rats. Among reproductive group females administered 1000 mg/kg/day, most were thin and the spleen and thymus were decreased in size, half of these animals had a notable decrease in skeletal muscle mass, noted especially in the hind legs, and two animals had decreased ingesta in all or parts of their gastrointestinal tracts. Other findings either occurred only once or were considered typical of rats of this age and stock and unrelated to test article dosage.

23.2 Microscopic Pathology

Microscopic pathology findings for tissues identified with visible lesions and data are summarized in Tables 3, 4, and 5 for females, males and reproductive group females, respectively. Intergroup comparisons of histopathology observations are presented in Attachment 3 and individual animal data are presented in Attachments 4 and 6 for all animals.

Liver

In the liver there was dose-related minimal to mild centrilobular hypertrophy in all high dose and most mid-dose animals of both sexes, including the reproductive groups. This is a common effect of xenobiotic administration and is considered an adaptive change.

Urinary Tract

In the urinary bladder there was minimal to mild diffuse epithelial hyperplasia in most males administered 1000 mg/kg/day; one male administered 100 mg/kg/day also had the finding. The effect was not attributable to the test article in toxicity group females; however, the finding was present in most reproductive group females administered 1000 mg/kg/day and was considered a test article effect. There were related findings in the kidneys of two high dose males with minimal or moderate bilateral epithelial hyperplasia in the renal pelvis. The finding was also present in the moderate degree in one 100 mg/kg/day male, but none at the next higher dosage. The kidney finding was not observed in male control group rats and in only one high-dose reproductive group female. These urinary bladder and kidney findings affect similar transitional epithelium directly exposed to urine and are consistent with a likely irritant effect of crystalluria at high test material concentrations (Cohen, et al, 2002).

Lymphoreticular system

In reproductive group females administered 1000 mg/kg/day, there was mild to moderate atrophy of the spleen and thymus in 5/10 animals; moderate bone marrow atrophy was also observed in one rat in this group. These findings were not observed at lower dosage levels. In toxicity group animals minimal thymic atrophy was identified in 1/10 high dosage group females, a finding that is not observed in young untreated animals without significant concurrent disease, and so is attributed to treatment in the absence of statistical significance. These findings were not observed in lower dosage groups, control groups, or any male rats. These findings are likely secondary effects of stress since they were not seen to a significant extent until after the onset of the neuromuscular effects described below.

Neuromuscular findings

Following the clinical finding of hindquarter weakness in the reproductive group females, there were also gross findings of muscle atrophy in many of these rats at necropsy. These findings correlate with prominent histopathological findings in the brain, spinal cord, peripheral nerves, and skeletal muscle. The neuromuscular findings were notable only in female rats and were much more pronounced in the reproductive group. There were no observed neuromuscular effects clearly attributable to the test article among male rats. The skeletal muscle findings are considered secondary to the nerve changes.

In the brain and spinal cord, findings were tabulated as white matter degeneration, and in the peripheral nerves, simply as degeneration. The lesions appeared to represent a primary effect on myelin. In the central nervous system (CNS) the subtlest change was white matter vacuolization, which was difficult to differentiate from artifactual vacuolar change; it was recorded only when there were corroborating features such as occasional axonal swelling or a glial cell(s) visible within a vacuole. Because of the difficulty in discriminating between real and artifactual vacuolization (Greaves, 2000), there may be some under diagnosis in the lower dose groups. In the more severe degrees, vacuolization was pronounced; vacuoles tended to be more oblong or linear and followed myelinated tracts. There were occasional minor axonal changes, myelin folds, and oligodendroglial cells visible in the vacuoles. In the brain, the effect was observed primarily in the most caudal of the three standard sections examined. Within that section, the most severely affected areas were in the white matter surrounding the fourth ventricle, including the cerebellum and the pons or medulla oblongata, depending on the exact location of the section. In the spinal cord, in more severe cases the white matter degeneration was diffuse and was observed in both sensory and motor nerve roots within the spinal canal.

The degenerative changes observed in the two examined peripheral nerves, the sciatic and tibial, were similar in appearance, incidence, and severity. Effects clearly attributable to the test article were confined to females given 1000 mg/kg/day, and were substantially increased in incidence and severity among the reproductive group animals. The lesion was characterized by segmental dilation of myelin sheaths. The dilated segments were filled with macrophages with abundant clear foamy cytoplasm, consistent in appearance with degenerating myelin. Any axonal changes were minimal, suggesting that the primary effect was on the myelin sheath.

There were degenerative changes secondarily attributable to treatment in sections of the two examined skeletal muscles sections, the adductor muscles of the inner thigh and the gastrocnemius (calf) muscle. The degenerative changes were statistically significantly increased in incidence and severity in reproductive group females administered 1000 mg/kg/day. Affected animals showed gross muscle atrophy, with diffusely decreased muscle fiber size, fiber fragmentation, increased density of myofiber nuclei, and focal areas of inflammation around necrotic fibers. The changes are consistent with denervation atrophy. Minimal muscle fiber degeneration was also observed as a background change in a number of control animals; in the minimal degree the finding consists of widely scattered swollen or degenerate muscle fibers, findings common enough in this pathologist's experience to be considered normal; however as a target tissue these sections were read with "zero tolerance" for the smallest deviations from perfection. The background change in control animals is of no clinical significance and is a far milder change than that seen as a secondary treatment effect in many of the reproductive group females administered 1000 mg/kg/day.

Other Findings

Other findings either occurred only once or were generally typical of rats of this age, stock, and test article administration method and considered unrelated to test article administration.

7 CONCLUSIONS

Effects attributable to the oral administration of triethoxyoctylsilane were observed in three systems, the liver, the urinary tract, and the neuromuscular system. The finding in the liver, centrilobular hypertrophy, is considered an adaptive change and affected animals of both sexes administered the test article at 300 and 1000 mg/kg/day. Urinary tract findings attributable to the test article involved hyperplasia with inflammation in the epithelium lining the urinary bladder and to a much lesser extent the renal pelvis. Urinary tract changes affected male rats and the reproductive group females administered 1000 mg/kg/day. Neuromuscular effects attributable to the test article were confined to females administered 1000 mg/kg/day and were markedly increased in incidence and severity in the reproductive group. The change was characterized as a probable myelin-based effect involving white matter of the hind brain and spinal cord, and peripheral nerves, with secondary denervation atrophy of skeletal muscle.

8 REFERENCES

Cohen SM, Wanibuchi H, Fukushima S (2002). Lower Urinary Tract, in *Handbook of Toxicologic Pathology, 2nd Edition* (Eds. WM Haschek, CG Rousseaux, MA Wallig). Academic Press, San Diego. Vol. 2, pp 340-344.

Greaves P (2000). *Histopathology of Preclinical Toxicity Studies: Interpretation and Relevance in Drug Safety Evaluation.* Elsevier, Amsterdam. pp 834-837.

Table 1: Tissues Weighed and Collected for Histopathology Examination

Organ Weights [1,2]	Organs Collected[@]
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
X	Testes
X	Thymus
	Thyroid
	Trachea
	Urinary bladder
X	Uterus (horns and cervix)
	Hind limb[3]
	Mammary Tissue (including mammary skin)[3]

[1]Paired organs were weighed together.

[2]Organ weights were only conducted on the toxicity group male and females.

[3]Reproductive females only.

[@]The testes and epididymides will be preserved in Bouin's solution. All other tissues collected were placed in 10% neutral buffered formalin for preservation.

Table 2: Selected Target Tissues Examined for Mid and Low Dose Groups

Toxicity Groups		Reproductive Group Females
Males	Females	
liver, kidneys, urinary bladder	brain, spinal cord, sciatic nerve, liver, urinary bladder	brain, spinal cord, sciatic nerve, hindlimb (tibial nerve, adductor muscle, gastrocnemius muscle) liver, urinary bladder, spleen, thymus

Table 3: Summary of Microscopic Findings: Female Toxicity Groups

Toxicity Females Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
BRAIN	Nematodiasis	# Examined	10	10	10	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
	white matter Degeneration	# Examined	10	10	10	10
		All Grades	1 +	0	1	4
		Minimal	1	0	1	4
HEART	Degeneration	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Minimal	0	0	0	1
KIDNEYS	Chronic Progressive Nephropathy	# Examined	10	0	0	10
		All Grades	2	0	0	2
		Minimal	2	0	0	1
		Mild	0	0	0	1
	Inflammation chronic	# Examined	10	0	0	10
		All Grades	3	0	0	0
		Minimal	3	0	0	0
	pelvis Hyperplasia bilateral diffuse	# Examined	10	0	0	10
		All Grades	0	0	0	0
	cortex Cyst	# Examined	10	0	0	10
		Present	0	0	0	2
	tubule Basophilia	# Examined	10	0	0	10
		All Grades	0	0	0	2
		Minimal	0	0	0	2
LIVER	Inflammation chronic multifocal	# Examined	10	10	10	10
		All Grades	7	10	5	9
		Minimal	7	10	5	9
	centrilobular Hypertrophy	# Examined	10	10	10	10
		All Grades	0 +++	0	4 +	10 +++
		Minimal	0	0	4	1
		Mild	0	0	0	9
	periportal Vacuolation	# Examined	10	10	10	10
		All Grades	3	1	3	2
		Minimal	1	1	3	1
		Mild	1	0	0	1
		Moderate	1	0	0	0

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 3: Summary of Microscopic Findings: Female Toxicity Groups (continued)

Toxicity Females Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
LUNGS	Inflammation chronic	# Examined	10	0	0	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
	Histocytosis	# Examined	10	0	0	10
		All Grades	3	0	0	4
		Minimal	3	0	0	4
NERVE, SCIATIC	Degeneration	# Examined	10	10	10	10
		All Grades	0 +	1	0	3
		Minimal	0	1	0	1
		Mild	0	0	0	2
SPINAL CORD	white matter Degeneration	# Examined	10	10	10	10
		All Grades	0 +++	0	0	5 ++
		Minimal	0	0	0	4
		Mild	0	0	0	1
STOMACH	Hyperkeratosis	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Mild	0	0	0	1
	Edema	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Minimal	0	0	0	1
	mucosa non-glandular Vacuolation	# Examined	10	0	0	10
		All Grades	1	0	0	0
		Mild	1	0	0	0
THYMUS	Atrophy	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Minimal	0	0	0	1
	Cyst ultimobranchial	# Examined	10	0	0	10
		Present	2	0	0	1
THYROID GLANDS	Ectopic Thymus	# Examined	10	0	0	10
		Present	1	0	0	0
	colloid Vacuolation	# Examined	10	0	0	10
		All Grades	1	0	0	1
		Minimal	1	0	0	1
URINARY BLADDER	Hyperplasia epithelial diffuse	# Examined	10	10	10	10
		All Grades	2	0	0	2
		Minimal	2	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 4: Summary of Microscopic Findings: Male Toxicity Groups

Toxicity Males Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
ADRENAL GLANDS	cortex Hypertrophy focal	# Examined	10	0	0	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
BRAIN	meninges Inflammation chronic	# Examined	10	0	0	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
HEART	Inflammation chronic	# Examined	10	0	0	10
		All Grades	2	0	0	2
		Minimal	2	0	0	2
KIDNEYS	Chronic Progressive Nephropathy	# Examined	10	10	10	10
		All Grades	1	0	3	1
		Minimal	1	0	3	1
	Inflammation chronic	# Examined	10	10	10	10
		All Grades	2	1	0	0
		Minimal	1	1	0	0
		Mild	1	0	0	0
	Inflammation chronic-active	# Examined	10	10	10	10
		All Grades	1	0	0	0
		Mild	1	0	0	0
	pelvis Hyperplasia bilateral diffuse	# Examined	10	10	10	10
		All Grades	0	1	0	2
		Minimal	0	0	0	1
		Moderate	0	1	0	1
	pelvis Inflammation chronic-active	# Examined	10	10	10	10
		All Grades	0	1	0	1
		Moderate	0	1	0	1
	cortex Necrosis focal	# Examined	10	10	10	10
		All Grades	0	0	1	0
		Mild	0	0	1	0
	cortex Cyst	# Examined	10	10	10	10
		Present	1	0	0	0
	tubule Basophilia	# Examined	10	10	10	10
		All Grades	5	1	1	2
		Minimal	5	1	1	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 4: Summary of Microscopic Findings: Male Toxicity Groups (continued)

Toxicity Males Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
LIVER	Inflammation chronic multifocal	# Examined	10	10	10	10
		All Grades	8	7	4	8
		Minimal	8	7	4	8
	Necrosis focal	# Examined	10	10	10	10
		All Grades	0	0	0	1
		Minimal	0	0	0	1
	centrilobular Hypertrophy	# Examined	10	10	10	10
		All Grades	0 +++	2	8 +++	10 +++
		Minimal	0	2	8	7
		Mild	0	0	0	3
	midzonal Vacuolation	# Examined	10	10	10	10
		All Grades	0	1	0	0
		Mild	0	1	0	0
	periportal Vacuolation	# Examined	10	10	10	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
LUNGS	Inflammation chronic	# Examined	10	0	0	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
	Inflammation subacute	# Examined	10	0	0	10
		All Grades	1	0	0	1
		Minimal	1	0	0	0
		Mild	0	0	0	1
	Histocytosis	# Examined	10	0	0	10
		All Grades	4	0	0	5
		Minimal	4	0	0	4
		Mild	0	0	0	1
	Hypertrophy vascular	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Minimal	0	0	0	1
NERVE, SCIATIC	Degeneration	# Examined	10	0	0	10
		All Grades	1	0	0	2
		Minimal	1	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 4: Summary of Microscopic Findings: Male Toxicity Groups (continued)

Toxicity Males Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
PROSTATE GLAND	Hyperplasia focal	# Examined	10	0	0	10
		All Grades	0	0	0	2
		Mild	0	0	0	2
	Inflammation chronic	# Examined	10	0	0	10
		All Grades	2	0	0	1
		Minimal	1	0	0	1
		Mild	1	0	0	0
	Inflammation chronic-active	# Examined	10	0	0	10
		All Grades	1	0	0	2
		Mild	1	0	0	2
STOMACH	non-glandular Cyst	# Examined	10	0	0	10
		Present	0	0	0	1
THYROID GLANDS	Cyst ultimobranchial	# Examined	10	0	0	10
		Present	0	0	0	2
URINARY BLADDER	Hyperplasia epithelial diffuse	# Examined	9	10	10	10
		All Grades	0 +++	1	0	7 +++
		Minimal	0	0	0	4
		Mild	0	1	0	3
	Inflammation chronic	# Examined	9	10	10	10
		All Grades	0	2	0	1
		Minimal	0	2	0	1
	Inflammation chronic-active	# Examined	9	10	10	10
		All Grades	0	0	0	1
		Mild	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 5: Summary of Microscopic Findings: Female Reproductive Group

Reproductive Females Microscopic Findings						
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
BONE MARROW, STERNUM	Atrophy	# Examined	10	0	0	9
		All Grades	0	0	0	1
		Moderate	0	0	0	1
BRAIN	white matter Degeneration	# Examined	10	10	10	10
		All Grades	0 +++	0	0	8 +++
		Minimal	0	0	0	4
		Mild	0	0	0	1
		Moderate	0	0	0	2
		Marked	0	0	0	1
KIDNEYS	Inflammation chronic	# Examined	10	0	0	10
		All Grades	1	0	0	0
		Minimal	1	0	0	0
	pelvis Hyperplasia bilateral diffuse	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Mild	0	0	0	1
	pelvis Inflammation chronic	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Mild	0	0	0	1
	cortex Infarction chronic focal	# Examined	10	0	0	10
		All Grades	0	0	0	1
		Mild	0	0	0	1
	tubule Basophilia	# Examined	10	0	0	10
		All Grades	3	0	0	0
		Minimal	3	0	0	0
LIVER	Inflammation chronic multifocal	# Examined	10	10	10	10
		All Grades	0	1	0	2
		Minimal	0	1	0	2
	Extramedullary Hematopoiesis	# Examined	10	10	10	10
		All Grades	0	1	0	0
		Minimal	0	1	0	0
	centrilobular Hypertrophy	# Examined	10	10	10	10
		All Grades	0 +++	0	10 +++	10 +++
		Minimal	0	0	10	3
		Mild	0	0	0	6
		Moderate	0	0	0	1
	centrilobular Vacuolation	# Examined	10	10	10	10
		All Grades	0 +	0	0	2
		Minimal	0	0	0	2

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Table 5: Summary of Microscopic Findings: Female Reproductive Group (continued)

Reproductive Females Microscopic Findings								
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)		100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	
LUNGS	Congestion	# Examined	10		0	0	10	
		All Grades	0		0	0	1	
		Mild	0		0	0	1	
	Histocytosis	# Examined	10		0	0	10	
		All Grades	5		0	0	2	
		Minimal	5		0	0	2	
LYMPH NODE, MEDIASTINAL	Atrophy	# Examined	10		0	0	10	
		All Grades	0		0	0	1	
		Mild	0		0	0	1	
NERVE, SCIATIC	Degeneration	# Examined	10		10	10	10	
		All Grades	0	+++	0	0	8	+++
		Minimal	0		0	0	1	
		Moderate	0		0	0	3	
		Marked	0		0	0	4	
NERVE, TIBIAL	Degeneration	# Examined	10		10	10	9	
		All Grades	0	+++	0	0	9	+++
		Minimal	0		0	0	2	
		Mild	0		0	0	3	
		Moderate	0		0	0	3	
		Marked	0		0	0	1	
SKELETAL MUSCLE, ADDUCTOR	Degeneration	# Examined	10		10	10	10	
		All Grades	4	+++	1	2	10	+++
		Minimal	3		0	1	4	
		Mild	1		1	1	3	
		Moderate	0		0	0	2	
		Marked	0		0	0	1	
	Inflammation, Chronic	# Examined	10		10	10	10	
		All Grades	2		0	0	0	
		Mild	2		0	0	0	
SKELETAL MUSCLE, GASTROCNEMIUS	Degeneration	# Examined	10		10	10	10	
		All Grades	5	++*	0	3	9	
		Minimal	5		0	3	3	
		Mild	0		0	0	3	
		Moderate	0		0	0	1	
		Marked	0		0	0	2	
	Inflammation, Chronic	# Examined	10		10	10	10	
		All Grades	0		2	1	0	
		Minimal	0		0	1	0	
		Mild	0		2	0	0	

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Table 5: Summary of Microscopic Findings: Female Reproductive Group (continued)

Reproductive Females Microscopic Findings									
Organ	Finding	Examined/Grade	Control (0 mg/kg/day)		100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	
SPINAL CORD	white matter Degeneration	# Examined	10		9	9	10	
		All Grades	0	+++	1	1	9	+++
		Minimal	0		1	1	2	
		Mild	0		0	0	2	
		Moderate	0		0	0	2	
		Marked	0		0	0	3	
SPLEEN	Atrophy	# Examined	10		10	10	10	
		All Grades	0	+++	0	0	5	++
		Mild	0		0	0	3	
		Moderate	0		0	0	2	
STOMACH	glandular Ulceration focal	# Examined	10		0	0	10	
		All Grades	0		0	0	1	
		Mild	0		0	0	1	
THYMUS	Atrophy	# Examined	10		10	10	9	
		All Grades	0	+++	0	0	5	++
		Moderate	0		0	0	5	
THYROID GLANDS	Cyst ultimobranchial	# Examined	10		0	0	10	
		Present	1		0	0	2	
URINARY BLADDER	Hyperplasia epithelial diffuse	# Examined	10		10	10	10	
		All Grades	0	+++	2	0	7	+++
		Minimal	0		1	0	3	
		Mild	0		1	0	4	
	Inflammation chronic	# Examined	10		10	10	10	
		All Grades	0		1	0	0	
		Minimal	0		1	0	0	
UTERUS	Pregnant	# Examined	10		0	0	10	
		Present	0		0	0	2	

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Attachment 1 - Intergroup Comparison of Gross Pathology Observations

Removal Reasons: All of those SELECTED

	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
ANIMAL IDENTIFICATION;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
ADRENAL GLANDS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
BONE MARROW, STERNUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
BRAIN;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
EPIDIDYMIDES;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	10	10	10	10	-	-	-	-
HEART;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
INTESTINE, CECUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
INTESTINE, COLON;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
INTESTINE, DUODENUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
INTESTINE, ILEUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)

Attachment 1 - Intergroup Comparison of Gross Pathology Observations (continued)

Removal Reasons: All of those SELECTED	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
INTESTINE, ILEUM; (continued)								
No Visible Lesions	10	10	10	10	10	10	10	10
INTESTINE, JEJUNUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
KIDNEYS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
LIVER;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
LUNGS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
LYMPH NODE, MEDIASTINAL;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
LYMPH NODE, MESENTERIC;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
NERVE, SCIATIC;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
OVARIES;								
Submitted	(-)	(-)	(-)	(-)	(10)	(10)	(10)	(10)
No Visible Lesions	-	-	-	-	10	10	10	10
PROSTATE GLAND;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	10	10	10	10	-	-	-	-

Attachment 1 - Intergroup Comparison of Gross Pathology Observations (continued)

Removal Reasons: All of those SELECTED	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
SEMINAL VESICLES;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	10	10	10	10	-	-	-	-
SPINAL CORD;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
SPLEEN;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	9	10	10
Enlarged	0	0	0	0	0	1	0	0
STOMACH;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
TESTES;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	10	10	10	10	-	-	-	-
THYMUS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	9	10
Discoloration; red; focal	0	0	0	0	0	0	1	0
THYROID GLAND;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
TRACHEA;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10
URINARY BLADDER;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	10	10	10	10	10	10	10	10

Attachment 1 - Intergroup Comparison of Gross Pathology Observations (continued)

Removal Reasons: All of those SELECTED	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
UTERUS;								
Submitted	(-)	(-)	(-)	(-)	(10)	(10)	(10)	(10)
No Visible Lesions	-	-	-	-	10	10	10	10

Attachment 1 - Intergroup Comparison of Gross Pathology Observations (continued)

Removal Reasons: All of those SELECTED

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
ADRENAL GLANDS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
BONE MARROW, STERNUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
BRAIN;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
HEART;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
INTESTINE, CECUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	9
Not Examined: NOT COLLECTED	0	1	0	0
Decreased Ingesta	0	0	0	1
INTESTINE, COLON;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	9
Not Examined: NOT COLLECTED	0	1	0	0
Decreased Ingesta	0	0	0	1
INTESTINE, DUODENUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	8
Not Examined: NOT COLLECTED	0	1	0	0
Decreased Ingesta	0	0	0	2
INTESTINE, ILEUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	7
Not Examined: NOT COLLECTED	0	1	0	0
Contents Abnormal	0	0	0	1

Attachment 1 - Intergroup Comparison of Gross Pathology Observations (continued)

Removal Reasons: All of those SELECTED

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
INTESTINE, ILEUM; (continued)				
Decreased Ingesta	0	0	0	2
INTESTINE, JEJUNUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	8
Not Examined: NOT COLLECTED	0	1	0	0
Decreased Ingesta	0	0	0	2
KIDNEYS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	9
Not Examined: NOT COLLECTED	0	1	0	0
Discoloration	0	0	0	1
LIVER;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	9
Not Examined: NOT COLLECTED	0	1	0	0
Accentuated Lobular Pattern	0	0	0	1
LUNGS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
LYMPH NODE, MEDIASTINAL;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
LYMPH NODE, MESENTERIC;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
SKELETAL MUSCLE;				
Submitted	(0)	(0)	(0)	(5)
No Visible Lesions	0	0	0	0
Decreased Size	0	0	0	5
NERVE, SCIATIC;				
Submitted	(10)	(9)	(10)	(10)

Attachment 1 - Intergroup Comparison of Gross Pathology Observations (continued)

Removal Reasons: All of those SELECTED

	--------REPRODUCTIVE FEMALES----------			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
NERVE, SCIATIC; (continued)				
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
OVARIES;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
SPINAL CORD;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
SPLEEN;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	3
Not Examined: NOT COLLECTED	0	1	0	0
Decreased Size	0	0	0	7
STOMACH;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	8
Not Examined: NOT COLLECTED	0	1	0	0
Ulcer	0	0	0	1
Decreased Ingesta	0	0	0	1
THYMUS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	4
Not Examined: NOT COLLECTED	0	1	0	0
Small	0	0	0	6
THYROID GLANDS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
TRACHEA;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0

Attachment 1 - Intergroup Comparison of Gross Pathology Observations (continued)

Removal Reasons: All of those SELECTED

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
URINARY BLADDER;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0
UTERUS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	9
Not Examined: NOT COLLECTED	0	1	0	0
Pregnant	0	0	0	1
WHOLE BODY;				
Submitted	(0)	(0)	(0)	(8)
No Visible Lesions	0	0	0	0
Not Examined: NOT COLLECTED	0	1*	0	0
Thin	0	0	0	8
Soiling	0	0	0	1
RIGHT HINDLIMB;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	10	9	10	10
Not Examined: NOT COLLECTED	0	1	0	0

*Gross necropsy data for animal 5251 was inadvertently not documented. Tissues were collected and animal is included in histopathology data.

Attachment 2 - Gross Pathology Observations – Animal Cross Reference

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
ANIMAL IDENTIFICATION;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5228	5258	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5282	5292
	5213	5243	5273	5303	5203	5233	5263	5293
ADRENAL GLANDS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
BONE MARROW, STERNUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5264
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5238	5266	5296	5196	5226	5256	5266
	5207	5237	5267	5297	5197	5227	5257	5267
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5269
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
BRAIN;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
EPIDIDYMIDES;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	5204	5234	5264	5294				
	5205	5235	5265	5295				
	5206	5236	5266	5296				
	5207	5237	5267	5297				
	5208	5238	5268	5298				
	5209	5239	5269	5299				
	5210	5240	5270	5300				
	5211	5241	5271	5301				
	5212	5242	5272	5302				
	5213	5243	5273	5303				
HEART;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5228	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
INTESTINE, CECUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5238	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5289	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5281	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
INTESTINE, COLON;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5288	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5281	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
INTESTINE, DUODENUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5267
	5208	5238	5268	5298	5196	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5269
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
INTESTINE, ILEUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
INTESTINE, JEJUNUM;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
KIDNEYS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5236	5268	5298	5198	5228	5258	5286
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
LIVER;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
LUNGS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
LYMPH NODE, MEDIASTINAL;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5208	5236	5266	5298	5196	5226	5256	5288
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
LYMPH NODE, MESENTERIC;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5266
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
NERVE, SCIATIC;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5208	5238	5266	5296	5196	5226	5256	5288
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
OVARIES;								
Submittad	(-)	(-)	(-)	(-)	(10)	(10)	(10)	(10)
No Visible Lesions					5194	5224	5254	5284
					5195	5225	5255	5285
					5196	5226	5256	5266
					5197	5227	5257	5287
					5198	5228	5258	5288
					5199	5229	5259	5289
					5200	5230	5260	5290
					5201	5231	5261	5291
					5202	5232	5262	5292
					5203	5233	5263	5293

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
PROSTATE GLAND;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	5204	5234	5264	5294				
	5205	5235	5265	5295				
	5206	5236	5266	5296				
	5207	5237	5267	5297				
	5208	5238	5268	5298				
	5209	5239	5269	5299				
	5210	5240	5270	5300				
	5211	5241	5271	5301				
	5212	5242	5272	5302				
	5213	5243	5273	5303				
SEMINAL VESICLES;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	5204	5234	5264	5294				
	5205	5235	5265	5295				
	5206	5236	5266	5296				
	5207	5237	5267	5297				
	5208	5238	5268	5298				
	5209	5239	5269	5299				
	5210	5240	5270	5300				
	5211	5241	5271	5301				
	5212	5242	5272	5302				
	5213	5243	5273	5303				
SPINAL CORD;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
SPLEEN;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5231	5260	5290
	5211	5241	5271	5301	5201	5232	5261	5291
	5212	5242	5272	5302	5202	5233	5262	5292
	5213	5243	5273	5303	5203		5263	5293
Enlarged						5230		
STOMACH;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
TESTES;								
Submitted	(10)	(10)	(10)	(10)	(-)	(-)	(-)	(-)
No Visible Lesions	5204	5234	5264	5294				
	5205	5235	5265	5295				
	5206	5236	5266	5296				
	5207	5237	5267	5297				
	5208	5238	5268	5298				
	5209	5239	5269	5299				
	5210	5240	5270	5300				
	5211	5241	5271	5301				
	5212	5242	5272	5302				
	5213	5243	5273	5303				

Attachment 2 - Gross Patbology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
THYMUS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5261	5290
	5211	5241	5271	5301	5201	5231	5262	5291
	5212	5242	5272	5302	5202	5232	5263	5292
	5213	5243	5273	5303	5203	5233		5293
Discoloration; red; focal							5260	
THYROID GLANDS;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5266	5296	5196	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
TRACHEA;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
URINARY BLADDER;								
Submitted	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
No Visible Lesions	5204	5234	5264	5294	5194	5224	5254	5284
	5205	5235	5265	5295	5195	5225	5255	5285
	5206	5236	5266	5296	5196	5226	5256	5286
	5207	5237	5267	5297	5197	5227	5257	5287
	5208	5238	5268	5298	5198	5228	5258	5288
	5209	5239	5269	5299	5199	5229	5259	5289
	5210	5240	5270	5300	5200	5230	5260	5290
	5211	5241	5271	5301	5201	5231	5261	5291
	5212	5242	5272	5302	5202	5232	5262	5292
	5213	5243	5273	5303	5203	5233	5263	5293
UTERUS;								
Submitted	(-)	(-)	(-)	(-)	(10)	(10)	(10)	(10)
No Visible Lesions					5194	5224	5254	5284
					5195	5225	5255	5285
					5196	5226	5256	5286
					5197	5227	5257	5287
					5198	5228	5258	5288
					5199	5229	5259	5289
					5200	5230	5260	5290
					5201	5231	5281	5291
					5202	5232	5282	5292
					5203	5233	5263	5293

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES 0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
ADRENAL GLANDS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5261	5311
	5222	5253	5282	5312
	5223		5283	5313
BONE MARROW, STERNUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5281	5311
	5222	5253	5282	5312
	5223		5283	5313
BRAIN;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5278	5306
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5281	5311
	5222	5253	5282	5312
	5223		5283	5313
HEART;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
HEART; (continued)				
No Visible Lesions (continued)	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5281	5311
	5222	5253	5282	5312
	5223		5283	5313
INTESTINE, CECUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5309
	5219	5249	5279	5310
	5220	5250	5280	5311
	5221	5252	5281	5312
	5222	5253	5282	5313
	5223		5283	
Decreased Ingesta				5308
INTESTINE, COLON;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5310
	5220	5250	5280	5311
	5221	5252	5281	5312
	5222	5253	5282	5313
	5223		5283	
Decreased Ingesta				5309
INTESTINE, DUODENUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
INTESTINE, DUODENUM; (continued)				
No Visible Lesions (continued)	5217	5247	5277	5307
	5218	5248	5278	5310
	5219	5249	5279	5311
	5220	5250	5280	5312
	5221	5252	5281	5313
	5222	5253	5282	
	5223		5283	
Decreased Ingesta				5308
				5309
INTESTINE, ILEUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5308
	5217	5247	5277	5310
	5218	5248	5278	5311
	5219	5249	5279	5312
	5220	5250	5280	5313
	5221	5252	5281	
	5222	5253	5282	
	5223		5283	
Contents Abnormal				5307
Decreased Ingesta				5308
				5309
INTESTINE, JEJUNUM;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5310
	5219	5249	5279	5311
	5220	5250	5280	5312
	5221	5252	5281	5313
	5222	5253	5282	
	5223		5283	
Decreased Ingesta				5308

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
INTESTINE, JEJUNUM; (continued)				
Decreased Ingesta (continued)				5309
KIDNEYS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5278	5308
	5217	5247	5277	5308
	5218	5248	5278	5309
	5219	5249	5279	5310
	5220	5250	5280	5311
	5221	5252	5281	5312
	5222	5253	5282	5313
	5223		5283	
Discoloration				5307
LIVER;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5278	5306
	5217	5247	5277	5307
	5218	5248	5278	5309
	5219	5249	5279	5310
	5220	5250	5280	5311
	5221	5252	5281	5312
	5222	5253	5282	5313
	5223		5283	
Accentuated Lobular Pattern				5308
LUNGS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5248	5278	5306
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5281	5311
	5222	5253	5282	5312

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
LUNGS; (continued)				
No Visible Lesions (continued)	5223		5283	5313
LYMPH NODE, MEDIASTINAL;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5281	5311
	5222	5253	5282	5312
	5223		5283	5313
LYMPH NODE, MESENTERIC;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5281	5311
	5222	5253	5282	5312
	5223		5283	5313
SKELETAL MUSCLE;				
Submitted	(0)	(0)	(0)	(5)
Decreased Size				5308
				5308
				5309
				5311
				5312
NERVE, SCIATIC;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
NERVE, SCIATIC; (continued)				
No Visible Lesions (continued)	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5281	5311
	5222	5253	5282	5312
	5223		5283	5313
OVARIES;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5281	5311
	5222	5253	5282	5312
	5223		5283	5313
SPINAL CORD;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5281	5311
	5222	5253	5282	5312
	5223		5283	5313
SPLEEN;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5305
	5215	5245	5275	5310
	5216	5246	5276	5313
	5217	5247	5277	
	5218	5248	5278	
	5219	5249	5279	
	5220	5250	5280	
	5221	5252	5281	

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
SPLEEN; (continued)				
No Visible Lesions (continued)	5222 5223	5253	5282 5283	
Decreased Size				5304 5306 5307 5308 5309 5311 5312
STOMACH;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214 5215 5216 5217 5218 5219 5220 5221 5222 5223	5244 5245 5248 5247 5248 5249 5250 5252 5253	5274 5275 5276 5277 5278 5279 5280 5281 5282 5283	5304 5305 5306 5308 5310 5311 5312 5313
Ulcer				5307
Decreased Ingesta				5309
THYMUS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214 5215 5216 5217 5218 5219 5220 5221 5222 5223	5244 5245 5246 5247 5248 5249 5250 5252 5253	5274 5275 5276 5277 5278 5279 5280 5281 5282 5283	5304 5305 5310 5313
Small				5306 5307

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
THYMUS; (continued)				
Small (continued)				5308
				5309
				5311
				5312
THYROID GLANDS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5281	5311
	5222	5253	5282	5312
	5223		5283	5313
TRACHEA;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5308
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5260	5310
	5221	5252	5281	5311
	5222	5253	5282	5312
	5223		5283	5313
URINARY BLADDER;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5281	5311
	5222	5253	5282	5312
	5223		5263	5313

Attachment 2 - Gross Pathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
UTERUS;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5309
	5219	5249	5279	5310
	5220	5250	5280	5311
	5221	5252	5281	5312
	5222	5253	5282	5313
	5223		5283	
Pregnant				5308
WHOLE BODY;				
Submitted	(0)	(0)	(0)	(8)
Thin				5304
				5306
				5307
				5308
				5309
				5311
				5312
				5313
Soiling				5308
RIGHT HINDLIMB;				
Submitted	(10)	(9)	(10)	(10)
No Visible Lesions	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5307
	5218	5248	5278	5308
	5219	5249	5279	5309
	5220	5250	5280	5310
	5221	5252	5281	5311
	5222	5253	5282	5312
	5223		5283	5313

Attachment 3 - Intergroup Comparison of Histopathology Observations

Observations: Neo-Plastic and Non Neo-Plastic	MALES				TOXICITY FEMALES			
Removal Reasons: All of those SELECTED	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
ADRENAL GLANDS;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	9	0	0	10	10	0	0	10
Hypertrophy; cortex; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0
BONE MARROW, STERNUM;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10	10	0	0	10
BRAIN;								
Examined	(10)	(0)	(0)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	9	0	0	10	6	10	9	6
Degeneration; white matter	(0)	(0)	(0)	(0)	(1)	(0)	(1)	(4)
minimal	0	0	0	0	1	0	1	4
Inflammation; chronic; meninges	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0
Nematodiasis	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
minimal	0	0	0	0	1	0	0	0
EPIDIDYMIDES;								
Examined	(10)	(0)	(0)	(10)	(-)	(-)	(-)	(-)
Within Normal Limits	10	0	0	10	-	-	-	-
HEART;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	8	0	0	8	10	0	0	8
Degeneration	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
minimal	0	0	0	0	0	0	0	1
Inflammation; chronic	(2)	(0)	(0)	(2)	(0)	(0)	(0)	(0)
minimal	2	0	0	2	0	0	0	0

Attachment 3 - Intergroup Comparison of Histopathology Observations (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				TOXICITY FEMALES			
Removal Reasons: All of those SELECTED	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
INTESTINE, CECUM;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10	10	0	0	10
INTESTINE, COLON;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10	10	0	0	10
INTESTINE, DUODENUM;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10	10	0	0	10
INTESTINE, ILEUM;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10	10	0	0	10
INTESTINE, JEJUNUM;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10	10	0	0	10
KIDNEYS;								
Examined	(10)	(10)	(10)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	2	7	5	6	5	0	0	6
Chronic Progressive Nephropathy	(1)	(0)	(3)	(1)	(2)	(0)	(0)	(2)
minimal	1	0	3	1	2	0	0	1
mild	0	0	0	0	0	0	0	1
Hyperplasia; pelvis; bilateral; diffuse	(0)	(1)	(0)	(2)	(0)	(0)	(0)	(0)
minimal	0	0	0	1	0	0	0	0
moderate	0	1	0	1	0	0	0	0
Inflammation; chronic	(2)	(1)	(0)	(0)	(3)	(0)	(0)	(0)
minimal	1	1	0	0	3	0	0	0
mild	1	0	0	0	0	0	0	0
Inflammation; chronic-active	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

Attachment 3 - Intergroup Comparison of Histopathology Observations (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				TOXICITY FEMALES			
Removal Reasons: All of those SELECTED	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
KIDNEYS; (continued)								
mild	1	0	0	0	0	0	0	0
Inflammation; chronic-active; pelvis	(0)	(1)	(0)	(1)	(0)	(0)	(0)	(0)
moderate	0	1	0	1	0	0	0	0
Necrosis; cortex; focal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
mild	0	0	1	0	0	0	0	0
Cyst; cortex	1	0	0	0	0	0	0	2
Basophilia; tubule	(5)	(1)	(1)	(2)	(0)	(0)	(0)	(2)
minimal	5	1	1	2	0	0	0	2
LIVER;								
Examined	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	2	2	2	0	3	0	2	0
Hypertrophy; centrilobular	(0)	(2)	(8)	(10)	(0)	(0)	(4)	(10)
minimal	0	2	8	7	0	0	4	1
mild	0	0	0	3	0	0	0	9
Inflammation; chronic; multifocal	(8)	(7)	(4)	(8)	(7)	(10)	(5)	(9)
minimal	8	7	4	8	7	10	5	9
Necrosis; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
minimal	0	0	0	1	0	0	0	0
Vacuolation; midzonal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	1	0	0	0	0	0	0
Vacuolation; periportal	(1)	(0)	(0)	(0)	(3)	(1)	(3)	(2)
minimal	1	0	0	0	1	1	3	1
mild	0	0	0	0	1	0	0	1
moderate	0	0	0	0	1	0	0	0
LUNGS;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	4	0	0	3	6	0	0	6
Inflammation; chronic	(1)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
minimal	1	0	0	0	1	0	0	0
Inflammation; subacute	(1)	(0)	(0)	(1)	(0)	(0)	(0)	(0)

Attachment 3 - Intergroup Comparison of Histopathology Observations (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				TOXICITY FEMALES			
Removal Reasons: All of those SELECTED	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
LUNGS; (continued)								
minimal	1	0	0	0	0	0	0	0
mild	0	0	0	1	0	0	0	0
Histocytosis	(4)	(0)	(0)	(5)	(3)	(0)	(0)	(4)
minimal	4	0	0	4	3	0	0	4
mild	0	0	0	1	0	0	0	0
Hypertrophy; vascular	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
minimal	0	0	0	1	0	0	0	0
LYMPH NODE, MEDIASTINAL;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10	10	0	0	10
LYMPH NODE, MESENTERIC;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10	10	0	0	10
NERVE, SCIATIC;								
Examined	(10)	(0)	(0)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	9	0	0	8	10	9	10	7
Degeneration	(1)	(0)	(0)	(2)	(0)	(1)	(0)	(3)
minimal	1	0	0	2	0	1	0	1
mild	0	0	0	0	0	0	0	2
OVARIES;								
Examined	(-)	(-)	(-)	(-)	(10)	(0)	(0)	(10)
Within Normal Limits	-	-	-	-	10	0	0	10
PROSTATE GLAND;								
Examined	(10)	(0)	(0)	(10)	(-)	(-)	(-)	(-)
Within Normal Limits	7	0	0	7	-	-	-	-
Hyperplasia; focal	(0)	(0)	(0)	(2)	(-)	(-)	(-)	(-)
mild	0	0	0	2	-	-	-	-

Attachment 3 - Intergroup Comparison of Histopathology Observations (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				TOXICITY FEMALES			
Removal Reasons: All of those SELECTED	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
PROSTATE GLAND; (continued)								
Inflammation; chronic	(2)	(0)	(0)	(1)	(-)	(-)	(-)	(-)
minimal	1	0	0	1	-	-	-	-
mild	1	0	0	0	-	-	-	-
Inflammation; chronic-active	(1)	(0)	(0)	(2)	(-)	(-)	(-)	(-)
mild	1	0	0	2	-	-	-	-
SEMINAL VESICLES;								
Examined	(10)	(0)	(0)	(10)	(-)	(-)	(-)	(-)
Within Normal Limits	10	0	0	10	-	-	-	-
SPINAL CORD;								
Examined	(10)	(0)	(0)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	10	0	0	10	10	10	10	5
Degeneration; white matter	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(5)
minimal	0	0	0	0	0	0	0	4
mild	0	0	0	0	0	0	0	1
SPLEEN;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10	10	0	0	10
STOMACH;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	9	9	0	0	9
Vacuolation; mucosa; non-glandular	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	0	0	1	0	0	0
Hyperkeratosis	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
mild	0	0	0	0	0	0	0	1
Edema	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
minimal	0	0	0	0	0	0	0	1
Cyst; non-glandular	0	0	0	1	0	0	0	0

Attachment 3 - Intergroup Comparison of Histopathology Observations (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				TOXICITY FEMALES			
Removal Reasons: All of those SELECTED	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
TESTES;								
Examined	(10)	(0)	(0)	(10)	(-)	(-)	(-)	(-)
Within Normal Limits	10	0	0	10	-	-	-	-
THYMUS;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10	10	0	0	9
Atrophy	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
minimal	0	0	0	0	0	0	0	1
THYROID GLANDS;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	8	7	0	0	9
Cyst; ultimobranchial	0	0	0	2	2	0	0	1
Vacuolation; colloid	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(1)
minimal	0	0	0	0	1	0	0	1
Ectopic Thymus	0	0	0	0	1	0	0	0
TRACHEA;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10	10	0	0	10
URINARY BLADDER;								
Examined	(9)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	9	8	10	2	8	10	10	8
Not Examined: INSUFFICIENT TISSUE TO EVALUATE	1	0	0	0	0	0	0	0
Hyperplasia; epithelial; diffuse	(0)	(1)	(0)	(7)	(2)	(0)	(0)	(2)
minimal	0	0	0	4	2	0	0	2
mild	0	1	0	3	0	0	0	0
Inflammation; chronic	(0)	(2)	(0)	(1)	(0)	(0)	(0)	(0)
minimal	0	2	0	1	0	0	0	0
Inflammation; chronic-active	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
mild	0	0	0	1	0	0	0	0

Attachment 3 - Intergroup Comparison of Histopathology Observations (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTEO

	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
UTERUS;								
Examined	(-)	(-)	(-)	(-)	(10)	(0)	(0)	(10)
Within Normal Limits	-	-	-	-	10	0	0	10

Attachment 3 - Intergroup Comparison of Histopathology Observations (continued)

Observations: Neo-Plastic and Non Neo-Plastic	REPRODUCTIVE FEMALES			
Removal Reasons: All of those SELECTED	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
ADRENAL GLANDS;				
Examined	(9)	(0)	(0)	(10)
Within Normal Limits	9	0	0	10
Not Examined: NO SECTION	1	0	0	0
BONE MARROW, STERNUM;				
Examined	(10)	(0)	(0)	(9)
Within Normal Limits	10	0	0	8
Not Examined: INSUFFICIENT TISSUE TO EVALUATE	0	0	0	1
Atrophy	(0)	(0)	(0)	(1)
moderate	0	0	0	1
BRAIN;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	10	10	10	2
Degeneration; white matter	(0)	(0)	(0)	(8)
minimal	0	0	0	4
mild	0	0	0	1
moderate	0	0	0	2
marked	0	0	0	1
HEART;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10
INTESTINE, CECUM;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10
INTESTINE, COLON;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10

Attachment 3 - Intergroup Comparison of Histopathology Observations (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	---------REPRODUCTIVE FEMALES ----------			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
INTESTINE, DUODENUM;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10
INTESTINE, ILEUM;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10
INTESTINE, JEJUNUM;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10
KIDNEYS;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	6	0	0	8
Hyperplasia; pelvis; bilateral; diffuse	(0)	(0)	(0)	(1)
mild	0	0	0	1
Infarction; chronic; cortex; focal	(0)	(0)	(0)	(1)
mild	0	0	0	1
Inflammation; chronic	(1)	(0)	(0)	(0)
minimal	1	0	0	0
Inflammation; chronic; pelvis	(0)	(0)	(0)	(1)
mild	0	0	0	1
Basophilia; tubule	(3)	(0)	(0)	(0)
minimal	3	0	0	0
LIVER;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	10	8	0	0
Hypertrophy; centrilobular	(0)	(0)	(10)	(10)
minimal	0	0	10	3
mild	0	0	0	6
moderate	0	0	0	1

Attachment 3 - Intergroup Comparison of Histopathology Observations (continued)

Observations: Neo-Plastic and Non Neo-Plastic Removal Reasons: All of those SELECTED	---------REPRODUCTIVE FEMALES ----------			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
LIVER; (continued)				
Inflammation; chronic; multifocal	(0)	(1)	(0)	(2)
minimal	0	1	0	2
Vacuolation; centrilobular	(0)	(0)	(0)	(2)
minimal	0	0	0	2
Extramedullary Hematopoiesis	(0)	(1)	(0)	(0)
minimal	0	1	0	0
LUNGS;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5	0	0	7
Congestion	(0)	(0)	(0)	(1)
mild	0	0	0	1
Histocytosis	(5)	(0)	(0)	(2)
minimal	5	0	0	2
LYMPH NODE, MEDIASTINAL;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	9
Atrophy	(0)	(0)	(0)	(1)
mild	0	0	0	1
LYMPH NODE, MESENTERIC;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10
SKELETAL MUSCLE, GASTROCNEMIUS;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	5	6	6	1
Degeneration	(5)	(0)	(3)	(9)
minimal	5	0	3	3
mild	0	0	0	3
moderate	0	0	0	1

Attachment 3 - Intergroup Comparison of Histopathology Observations (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
SKELETAL MUSCLE, GASTROCNEMIUS; (continued)				
marked	0	0	0	2
Inflammation, Chronic	(0)	(2)	(1)	(0)
minimal	0	0	1	0
mild	0	2	0	0
NERVE, SCIATIC;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	10	10	10	2
Degeneration	(0)	(0)	(0)	(8)
minimal	0	0	0	1
moderate	0	0	0	3
marked	0	0	0	4
NERVE, TIBIAL;				
Examined	(10)	(10)	(10)	(9)
Within Normal Limits	10	10	10	0
Not Examined: NOT PRESENT	0	0	0	1
Degeneration	(0)	(0)	(0)	(9)
minimal	0	0	0	2
mild	0	0	0	3
moderate	0	0	0	3
marked	0	0	0	1
OVARIES;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	10
SPINAL CORD;				
Examined	(10)	(9)	(9)	(10)
Within Normal Limits	10	8	8	1
Not Examined: NO SECTION	0	1	1	0
Degeneration; white matter	(0)	(1)	(1)	(9)

Attachment 3 - Intergroup Comparison of Histopathology Observations (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	---------REPRODUCTIVE FEMALES ----------			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
SPINAL CORD; (continued)				
minimal	0	1	1	2
mild	0	0	0	2
moderate	0	0	0	2
marked	0	0	0	3
SPLEEN;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	10	10	10	5
Atrophy	(0)	(0)	(0)	(5)
mild	0	0	0	3
moderate	0	0	0	2
STOMACH;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	9
Ulceration; glandular; focal	(0)	(0)	(0)	(1)
mild	0	0	0	1
THYMUS;				
Examined	(10)	(10)	(10)	(9)
Within Normal Limits	10	10	10	4
Not Examined: NO SECTION	0	0	0	1
Atrophy	(0)	(0)	(0)	(5)
moderate	0	0	0	5
THYROID GLANDS;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	9	0	0	8
Cyst; ultimobranchial	1	0	0	2
TRACHEA;				
Examined	(10)	(0)	(0)	(10)

Attachment 3 - Intergroup Comparison of Histopathology Observations (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	---------REPRODUCTIVE FEMALES ----------			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
Number of Animals on Study :	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)
TRACHEA; (continued)				
Within Normal Limits	10	0	0	10
URINARY BLADDER;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	10	8	10	3
Hyperplasia; epithelial; diffuse	(0)	(2)	(0)	(7)
minimal	0	1	0	3
mild	0	1	0	4
Inflammation; chronic	(0)	(1)	(0)	(0)
minimal	0	1	0	0
UTERUS;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	10	0	0	8
Pregnant	0	0	0	2
SKELETAL MUSCLE, ADDUCTOR;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	6	9	8	0
Degeneration	(4)	(1)	(2)	(10)
minimal	3	0	1	4
mild	1	1	1	3
moderate	0	0	0	2
marked	0	0	0	1
Inflammation, Chronic	(2)	(0)	(0)	(0)
mild	2	0	0	0

Attachment 4 - Histopathology Observations – Animal Cross Reference

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
ADRENAL GLANDS;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5206			5295	5195			5285
	5207			5296	5196			5286
	5208			5297	5197			5287
	5209			5298	5198			5288
	5210			5299	5199			5289
	5211			5300	5200			5290
	5212			5301	5201			5291
	5213			5302	5202			5292
				5303	5203			5293
cortex; Hypertrophy; focal; minimal	5205							
BONE MARROW, STERNUM;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5195			5285
	5206			5296	5196			5286
	5207			5297	5197			5287
	5208			5298	5198			5288
	5209			5299	5199			5289
	5210			5300	5200			5290
	5211			5301	5201			5291
	5212			5302	5202			5292
	5213			5303	5203			5293
BRAIN;								
Examined	(10)	(0)	(0)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	5204			5294	5194	5224	5254	5284
	5206			5295	5195	5225	5256	5285
	5207			5296	5196	5226	5257	5289
	5208			5297	5197	5227	5258	5290
	5209			5298	5198	5228	5259	5291
	5210			5299	5200	5229	5260	5292
	5211			5300	5201	5230	5261	
	5212			5301	5203	5231	5262	
	5213			5302		5232	5263	

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
BRAIN; (continued)								
Within Normal Limits (continued)				5303		5233		
Nematodiasis;								
minimal					5202			
white matter; Degeneration;								
minimal					5199		5255	5286
								5287
								5288
								5293
meninges; Inflammation; chronic;								
minimal	5205							
EPIDIDYMIDES;								
Examined	(10)	(0)	(0)	(10)	(-)	(-)	(-)	(-)
Within Normal Limits	5204			5294				
	5205			5295				
	5206			5296				
	5207			5297				
	5208			5298				
	5209			5299				
	5210			5300				
	5211			5301				
	5212			5302				
	5213			5303				
HEART;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5206			5296	5195			5285
	5207			5297	5196			5286
	5208			5298	5197			5287
	5209			5299	5198			5288
	5210			5300	5199			5289
	5211			5301	5200			5290
	5213			5302	5201			5291
					5202			5292
					5203			

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
HEART; (continued)								
Degeneration;								
minimal								5293
Inflammation; chronic;								
minimal	5205			5295				
	5212			5303				
INTESTINE, CECUM;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5195			5285
	5206			5296	5196			5286
	5207			5297	5197			5287
	5208			5298	5198			5288
	5209			5299	5199			5289
	5210			5300	5200			5290
	5211			5301	5201			5291
	5212			5302	5202			5292
	5213			5303	5203			5293
INTESTINE, COLON;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5195			5285
	5206			5296	5196			5286
	5207			5297	5197			5287
	5208			5298	5198			5288
	5209			5299	5199			5289
	5210			5300	5200			5290
	5211			5301	5201			5291
	5212			5302	5202			5292
	5213			5303	5203			5293
INTESTINE, DUODENUM;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5195			5285
	5206			5296	5196			5286
	5207			5297	5197			5287

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
INTESTINE, DUODENUM; (continued)								
Within Normal Limits (continued)	5208			5298	5198			5288
	5209			5299	5199			5289
	5210			5300	5200			5290
	5211			5301	5201			5291
	5212			5302	5202			5292
	5213			5303	5203			5293
INTESTINE, ILEUM;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5195			5285
	5206			5296	5196			5286
	5207			5297	5197			5287
	5208			5296	5198			5288
	5209			5299	5199			5289
	5210			5300	5200			5290
	5211			5301	5201			5291
	5212			5302	5202			5292
	5213			5303	5203			5293
INTESTINE, JEJUNUM;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5195			5285
	5206			5296	5196			5286
	5207			5297	5197			5287
	5208			5298	5198			5288
	5209			5299	5199			5289
	5210			5300	5200			5290
	5211			5301	5201			5291
	5212			5302	5202			5292
	5213			5303	5203			5293
KIDNEYS;								
Examined	(10)	(10)	(10)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5205	5234	5284	5295	5194			5285
	5208	5235	5287	5297	5197			5286
		5236	5269	5298	5198			5288
		5237	5270	5299	5199			5289

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected

	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
KIDNEYS; (continued)								
Within Normal Limits (continued)		5238 5240 5242	5271	5300 5303	5203			5280 5283
Chronic Progressive Nephropathy;								
minimal	5210		5265 5272 5273	5301	5195 5196			5284
mild								5287
Inflammation; chronic;								
minimal	5206	5243			5200 5201 5202			
mild	5208							
Inflammation; chronic-active;								
mild	5207							
pelvis; Hyperplasia; bilateral; diffuse;								
minimal				5301				
moderate		5239		5302				
pelvis; Inflammation; chronic-active;								
moderate		5239		5302				
cortex; Necrosis; focal;								
mild			5268					
cortex; Cyst	5209							5284 5287
tubule; Basophilia;								
minimal	5204 5209 5211	5241	5266	5294 5296				5291 5292

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
KIDNEYS; (continued)								
minimal (continued)	5212 5213							
LIVER;								
Examined	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	5205 5207	5242 5243	5266 5267		5196 5199 5200		5258 5259	
Inflammation; chronic; multifocal;								
minimal	5204 5206 5208 5209 5210 5211 5212 5213	5234 5235 5236 5238 5239 5240 5241	5268 5269 5270 5273	5294 5296 5297 5298 5299 5300 5302 5303	5194 5195 5197 5198 5201 5202 5203	5224 5225 5228 5227 5228 5229 5230 5231 5232 5233	5256 5257 5260 5261 5263	5284 5285 5286 5287 5289 5290 5291 5292 5293
Necrosis; focal;								
minimal				5298				
centrilobular; Hypertrophy;								
minimal		5240 5241	5264 5265 5268 5269 5270 5271 5272 5273	5295 5296 5297 5298 5299 5301 5303			5254 5256 5260 5282	5281
mild				5294 5300 5302				5284 5285 5288 5287 5286

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
LIVER; (continued)								
mild (continued)								5289 5290 5292 5293
midzonal; Vacuolation;								
mild		5237						
periportal; Vacuolation;								
minimal	5212				5201	5225	5255 5257 5263	5288
mild					5197			5290
moderate					5198			
LUNGS;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5206 5209 5212 5213			5300 5301 5302	5195 5197 5198 5199 5200 5203			5285 5286 5288 5289 5290 5291
Inflammation; chronic;								
minimal	5210				5202			
Inflammation; subacute;								
minimal	5206							
mild				5296				
Histocytosis;								
minimal	5204 5205 5207 5211			5294 5297 5299 5303	5194 5196 5201			5284 5287 5292 5293

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
LUNGS; (continued)								
mild				5295				
Hypertrophy; vascular;								
minimal				5298				
LYMPH NODE, MEDIASTINAL;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5195			5285
	5206			5296	5196			5286
	5207			5297	5197			5287
	5208			5298	5198			5288
	5209			5299	5199			5289
	5210			5300	5200			5290
	5211			5301	5201			5291
	5212			5302	5202			5292
	5213			5303	5203			5293
LYMPH NODE, MESENTERIC;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5195			5285
	5206			5296	5196			5286
	5207			5297	5197			5287
	5208			5298	5198			5288
	5209			5299	5199			5289
	5210			5300	5200			5290
	5211			5301	5201			5291
	5212			5302	5202			5292
	5213			5303	5203			5293
NERVE, SCIATIC;								
Examined	(10)	(0)	(0)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	5204			5294	5194	5224	5254	5285
	5205			5295	5195	5225	5255	5286
	5206			5296	5196	5226	5256	5287
	5207			5297	5197	5227	5257	5288
	5208			5298	5198	5229	5258	5290
	5210			5299	5199	5230	5259	5291

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected

	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
NERVE, SCIATIC; (continued)								
Within Normal Limits (continued)	5211 5212 5213			5302 5303	5200 5201 5202 5203	5231 5232 5233	5260 5261 5262 5263	5292
Degeneration;								
minimal	5209			5300 5301		5228		5284
mild								5289 5293
OVARIES;								
Examined	(-)	(-)	(-)	(-)	(10)	(0)	(0)	(10)
Within Normal Limits					5194 5195 5196 5197 5198 5199 5200 5201 5202 5203			5284 5285 5286 5287 5288 5289 5290 5291 5292 5293
PROSTATE GLAND;								
Examined	(10)	(0)	(0)	(10)	(-)	(-)	(-)	(-)
Within Normal Limits	5204 5205 5206 5207 5208 5210 5211			5295 5296 5297 5298 5299 5300 5303				
Hyperplasia; focal;								
mild				5301 5302				

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
PROSTATE GLAND; (continued)								
Inflammation; chronic;								
minimal	5212			5294				
mild	5209							
Inflammation; chronic-active;								
mild	5213			5301				
				5302				
SEMINAL VESICLES;								
Examined	(10)	(0)	(0)	(10)	(-)	(-)	(-)	(-)
Within Normal Limits	5204			5294				
	5205			5295				
	5206			5296				
	5207			5297				
	5208			5298				
	5209			5299				
	5210			5300				
	5211			5301				
	5212			5302				
	5213			5303				
SPINAL CORD;								
Examined	(10)	(0)	(0)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	5204			5294	5194	5224	5254	5284
	5205			5295	5195	5225	5255	5285
	5206			5296	5196	5226	5256	5286
	5207			5297	5197	5227	5257	5287
	5208			5298	5198	5228	5258	5290
	5209			5299	5199	5229	5259	
	5210			5300	5200	5230	5260	
	5211			5301	5201	5231	5261	
	5212			5302	5202	5232	5262	
	5213			5303	5203	5233	5263	
white matter; Degeneration;								
minimal								5289
								5291
								5292

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
SPINAL CORD; (continued)								
minimal (continued)								5293
mild								5288
SPLEEN;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5195			5285
	5206			5296	5196			5286
	5207			5297	5197			5287
	5208			5298	5198			5288
	5209			5299	5199			5289
	5210			5300	5200			5290
	5211			5301	5201			5291
	5212			5302	5202			5292
	5213			5303	5203			5293
STOMACH;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5195			5285
	5206			5297	5198			5287
	5207			5298	5197			5288
	5208			5299	5199			5289
	5209			5300	5200			5290
	5210			5301	5201			5291
	5211			5302	5202			5292
	5212			5303	5203			5293
	5213							
Hyperkeratosis;								
mild								5286
Edema;								
minimal								5286
mucosa; Vacuolation; non-glandular;								
mild					5198			

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
STOMACH; (continued)								
non-glandular; Cyst				5295				
TESTES;								
Examined	(10)	(0)	(0)	(10)	(-)	(-)	(-)	(-)
Within Normal Limits	5204			5294				
	5205			5295				
	5206			5296				
	5207			5297				
	5208			5298				
	5209			5299				
	5210			5300				
	5211			5301				
	5212			5302				
	5213			5303				
THYMUS;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5195			5285
	5206			5296	5196			5286
	5207			5297	5197			5287
	5208			5298	5198			5288
	5209			5299	5199			5289
	5210			5300	5200			5290
	5211			5301	5201			5291
	5212			5302	5202			5292
	5213			5303	5203			
Atrophy;								
minimal								5293
THYROID GLANDS;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5196			5285
	5206			5298	5197			5286
	5207			5297	5198			5288
	5208			5299	5200			5289
	5209			5300	5202			5290

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
THYROID GLANDS; (continued)								
Within Normal Limits (continued)	5210			5301	5203			5291
	5211			5303				5292
	5212							5293
	5213							
Cyst; ultimobranchial				5298	5195			5287
				5302	5201			
Ectopic Thymus					5195			
colloid; Vacuolation; minimal					5199			5287
TRACHEA;								
Examined	(10)	(0)	(0)	(10)	(10)	(0)	(0)	(10)
Within Normal Limits	5204			5294	5194			5284
	5205			5295	5195			5285
	5206			5296	5198			5286
	5207			5297	5197			5287
	5208			5298	5198			5288
	5209			5299	5199			5289
	5210			5300	5200			5290
	5211			5301	5201			5291
	5212			5302	5202			5292
	5213			5303	5203			5293
URINARY BLADDER;								
Examined	(9)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	5204	5234	5264	5299	5194	5224	5254	5284
	5205	5235	5265	5300	5195	5225	5255	5286
	5206	5236	5266		5198	5226	5256	5287
	5207	5237	5267		5197	5227	5257	5288
	5208	5238	5268		5198	5228	5258	5289
	5209	5240	5269		5200	5229	5259	5291
	5210	5241	5270		5201	5230	5260	5292
	5212	5243	5271		5202	5231	5261	5293
	5213		5272			5232	5262	
			5273			5233	5263	

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected

	MALES				TOXICITY FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
URINARY BLADDER; (continued)								
Hyperplasia; epithelial; diffuse;								
minimal				5294 5295 5301 5303	5199 5203			5285 5290
mild		5239		5297 5298 5302				
Inflammation; chronic;								
minimal		5239 5242		5296				
Inflammation; chronic-active;								
mild				5298				
UTERUS;								
Examined	(-)	(-)	(-)	(-)	(10)	(0)	(0)	(10)
Within Normal Limits					5194 5195 5196 5197 5198 5199 5200 5201 5202 5203			5284 5285 5286 5287 5288 5289 5290 5291 5292 5293

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
ADRENAL GLANDS;				
Examined	(9)	(0)	(0)	(10)
Within Normal Limits	5215			5304
	5216			5305
	5217			5306
	5218			5307
	5219			5308
	5220			5309
	5221			5310
	5222			5311
	5223			5312
				5313
BONE MARROW, STERNUM;				
Examined	(10)	(0)	(0)	(9)
Within Normal Limits	5214			5304
	5215			5305
	5216			5307
	5217			5309
	5216			5310
	5219			5311
	5220			5312
	5221			5313
	5222			
	5223			
Atrophy;				
moderate				5308
BRAIN;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	5214	5244	5274	5307
	5215	5245	5275	5313
	5216	5246	5276	
	5217	5247	5277	
	5218	5248	5278	
	5219	5249	5279	
	5220	5250	5280	
	5221	5251	5281	
	5222	5252	5282	

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	---------REPRODUCTIVE FEMALES----------			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
BRAIN; (continued)				
Within Normal Limits (continued)	5223	5253	5283	
white matter; Degeneration;				
minimal				5306
				5309
				5310
				5311
mild				5308
moderate				5304
				5312
marked				5305
HEART;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5307
	5218			5308
	5219			5309
	5220			5310
	5221			5311
	5222			5312
	5223			5313
INTESTINE, CECUM;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5307
	5218			5308
	5219			5309
	5220			5310
	5221			5311
	5222			5312

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
INTESTINE, CECUM; (continued)				
Within Normal Limits (continued)	5223			5313
INTESTINE, COLON;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5307
	5218			5308
	5219			5309
	5220			5310
	5221			5311
	5222			5312
	5223			5313
INTESTINE, DUODENUM;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5307
	5218			5308
	5219			5309
	5220			5310
	5221			5311
	5222			5312
	5223			5313
INTESTINE, ILEUM;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5307
	5218			5306
	5219			5309
	5220			5310
	5221			5311
	5222			5312

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
INTESTINE, ILEUM; (continued)				
Within Normal Limits (continued)	5223			5313
INTESTINE, JEJUNUM;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5307
	5218			5308
	5219			5309
	5220			5310
	5221			5311
	5222			5312
	5223			5313
KIDNEYS;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5216			5304
	5217			5305
	5219			5306
	5220			5307
	5222			5308
	5223			5311
				5312
				5313
Inflammation; chronic;				
minimal	5214			
pelvis; Hyperplasia; bilateral; diffuse;				
mild				5309
pelvis; Inflammation; chronic;				
mild				5309
cortex; Infarction; chronic; focal;				
mild				5310

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
KIDNEYS; (continued)				
tubule; Basophilia;				
minimal	5215 5218 5221			
LIVER;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	5214 5215 5216 5217 5218 5219 5220 5221 5222 5223	5244 5245 5247 5249 5250 5251 5252 5253		
Inflammation; chronic; multifocal;				
minimal		5248		5304 5305
Extramedullary Hematopoiesis;				
minimal		5246		
centrilobular; Hypertrophy;				
minimal			5274 5275 5276 5277 5278 5279 5280 5281 5282 5283	5304 5310 5311

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
LIVER; (continued)				
mild				5305
				5306
				5307
				5309
				5312
				5313
moderate				5308
centrilobular; Vacuolation;				
minimal				5308
				5309
LUNGS;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5305
	5216			5306
	5221			5307
	5222			5308
	5223			5309
				5310
				5313
Congestion;				
mild				5304
Histocytosis;				
minimal	5215			5311
	5217			5312
	5218			
	5219			
	5220			
LYMPH NODE, MEDIASTINAL;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5307

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES 0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
LYMPH NODE, MEDIASTINAL; (continued)				
Within Normal Limits (continued)	5218			5309
	5219			5310
	5220			5311
	5221			5312
	5222			5313
	5223			
Atrophy;				
mild				5308
LYMPH NODE, MESENTERIC;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5307
	5218			5308
	5219			5309
	5220			5310
	5221			5311
	5222			5312
	5223			5313
SKELETAL MUSCLE, GASTROCNEMIUS;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	5214	5244	5274	5313
	5215	5245	5279	
	5217	5247	5280	
	5221	5248	5281	
	5223	5249	5282	
		5250	5283	
		5251		
		5253		
Degeneration;				
minimal	5216		5278	5306
	5218		5277	5307
	5219		5278	5308
	5220			

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
SKELETAL MUSCLE, GASTROCNEMIUS; (continued)				
minimal (continued)	5222			
mild				5309 5310 5311
moderate				5305
marked				5304 5312
Inflammation, Chronic;				
minimal			5275	
mild		5246 5252		
NERVE, SCIATIC;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	5214 5215 5216 5217 5218 5219 5220 5221 5222 5223	5244 5245 5246 5247 5248 5249 5250 5251 5252 5253	5274 5275 5276 5277 5278 5279 5280 5281 5282 5283	5311 5313
Degeneration;				
minimal				5306
moderate				5307 5309 5310

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES 0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
NERVE, SCIATIC; (continued)				
marked				5304
				5305
				5308
				5312
NERVE, TIBIAL;				
Examined	(10)	(10)	(10)	(9)
Within Normal Limits	5214	5244	5274	
	5215	5245	5275	
	5216	5246	5276	
	5217	5247	5277	
	5218	5248	5278	
	5219	5249	5279	
	5220	5250	5280	
	5221	5251	5281	
	5222	5252	5282	
	5223	5253	5283	
Degeneration;				
minimal				5304
				5306
mild				5307
				5310
				5311
moderate				5305
				5308
				5309
marked				5312
OVARIES;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5307
	5218			5308

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
OVARIES; (continued)				
Within Normal Limits (continued)	5219			5309
	5220			5310
	5221			5311
	5222			5312
	5223			5313
SPINAL CORD;				
Examined	(10)	(9)	(9)	(10)
Within Normal Limits	5214	5244	5274	5313
	5215	5245	5277	
	5216	5246	5278	
	5217	5247	5279	
	5218	5249	5280	
	5219	5250	5281	
	5220	5251	5282	
	5221	5252	5283	
	5222			
	5223			
white matter; Degeneration;				
minimal		5248	5276	5306
				5311
mild				5307
				5309
moderate				5308
				5310
marked				5304
				5305
				5312
SPLEEN;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	5214	5244	5274	5304
	5215	5245	5275	5305
	5216	5246	5276	5306
	5217	5247	5277	5310

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
SPLEEN; (continued)				
Within Normal Limits (continued)	5218	5248	5278	5313
	5219	5249	5279	
	5220	5250	5280	
	5221	5251	5281	
	5222	5252	5282	
	5223	5253	5283	
Atrophy;				
mild				5309
				5311
				5312
moderate				5307
				5308
STOMACH;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5307
	5218			5309
	5219			5310
	5220			5311
	5221			5312
	5222			5313
	5223			
glandular; Ulceration; focal;				
mild				5308
THYMUS;				
Examined	(10)	(10)	(10)	(9)
Within Normal Limits	5214	5244	5274	5305
	5215	5245	5275	5306
	5216	5246	5276	5310
	5217	5247	5277	5313
	5218	5248	5278	
	5219	5249	5279	

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
THYMUS; (continued)				
Within Normal Limits (continued)	5220	5250	5280	
	5221	5251	5281	
	5222	5252	5282	
	5223	5253	5283	
Atrophy;				
moderate				5304
				5307
				5308
				5311
				5312
THYROID GLANDS;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5308
	5218			5310
	5219			5311
	5221			5312
	5222			5313
	5223			
Cyst; ultimobranchial	5220			5307
				5309
TRACHEA;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5307
	5218			5308
	5219			5309
	5220			5310
	5221			5311
	5222			5312
	5223			5313

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
URINARY BLADDER;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	5214	5244	5274	5304
	5215	5245	5275	5306
	5216	5247	5276	5311
	5217	5248	5277	
	5218	5249	5278	
	5219	5250	5279	
	5220	5251	5260	
	5221	5253	5281	
	5222		5282	
	5223		5283	
Hyperplasia; epithelial; diffuse;				
minimal		5246		5305
				5312
				5313
mild		5252		5307
				5308
				5309
				5310
Inflammation; chronic;				
minimal		5252		
UTERUS;				
Examined	(10)	(0)	(0)	(10)
Within Normal Limits	5214			5304
	5215			5305
	5216			5306
	5217			5307
	5218			5310
	5219			5311
	5220			5312
	5221			5313
	5222			
	5223			
Pregnant				5308

Attachment 4 - Histopathology Observations – Animal Cross Reference (continued)

Removal Reason: All of those selected

	REPRODUCTIVE FEMALES			
	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
UTERUS; (continued)				
Pregnant (continued)				5309
SKELETAL MUSCLE, ADDUCTOR;				
Examined	(10)	(10)	(10)	(10)
Within Normal Limits	5214	5244	5274	
	5219	5246	5275	
	5220	5247	5276	
	5221	5248	5277	
	5222	5249	5278	
	5223	5250	5279	
		5251	5280	
		5252	5282	
		5253		
Degeneration;				
minimal	5216		5283	5306
	5217			5308
	5218			5309
				5313
mild	5215	5245	5281	5307
				5310
				5311
moderate				5304
				5305
marked				5312
Inflammation, Chronic;				
mild	5215			
	5217			

Attachment 5 - Individual Gross Pathology Data

SEX: MALE

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Attachment 5 - Individual Gross Pathology Data (continued)

SEX: MALE

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Attachment 5 - Individual Gross Pathology Data (continued)

SEX: FEMALE

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Attachment 5 - Individual Gross Pathology Data (continued)

SEX: FEMALE

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Attachment 5 - Individual Gross Pathology Data (continued)

SEX: FEMALE

| | | |

Attachment 5 - Individual Gross Pathology Data (continued)

SEX: FEMALE

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Attachment 5 - Individual Gross Pathology Data (continued)

SEX: FEMALE

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Attachment 5 - Individual Gross Pathology Data (continued)

SEX: FEMALE

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Attachment 5 - Individual Gross Pathology Data (continued)

Key Page

Group

Code	Description
1	0 mg/kg/day
2	100 mg/kg/day
3	300 mg/kg/day
4	1000 mg/kg/day

Removal Reason

Code	Description
R1	Scheduled Necropsy - Isoflurane/Exsanguination
R15	Moribund
R3	Scheduled Necropsy- CO2

Tissue Result

Code	Description
N	N.V.L
.	Not Recorded
+	Tissue Observation Present
X	Not Examined

Grade

Code	Description
.	not recorded
#	duplicate
P	present - no grade or classification

Attachment 6 - Individual Histopathology Data

SEX: MALE

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Attachment 6 - Individual Histopathology Data (continued)

SEX: MALE

| | | |

Attachment 6 - Individual Histopathology Data (continued)

SEX: MALE

| | | |

Attachment 6 - Individual Histopathology Data (continued)

SEX: FEMALE

| | | |

Attachment 6 - Individual Histopathology Data (continued)

SEX: FEMALE

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Attachment 6 - Individual Histopathology Data (continued)

SEX: FEMALE

| | | |

Attachment 6 - Individual Histopathology Data (continued)

SEX: FEMALE

| | | |

Attachment 6 - Individual Histopathology Data (continued)

SEX: FEMALE

| | | |

Attachment 6 - Individual Histopathology Data (continued)

SEX: FEMALE

| | | |

Attachment 6 - Individual Histopathology Data (continued)

Key Page

Group

Code	Description
1	0 mg/kg/day
2	100 mg/kg/day
3	300 mg/kg/day
4	1000 mg/kg/day

Removal Reason

Code	Description
R1	Scheduled Necropsy - Isoflurane/Exsanguination
R15	Moribund
R3	Scheduled Necropsy- CO2

Tissue Result

Code	Description
N	N.V.L
.	Not Recorded
+	Tissue Observation Present
X	Not Examined

Grade

Code	Description
.	not recorded
1	minimal
2	mild
3	moderate
4	marked
#	duplicate
P	present - no grade or classification