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Toxicology & Product Regulatory Compliance

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8EHQ-0904-15661

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November 3, 2004

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Washington, DC 20460-0001

Phone# (202) 564-8930

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REFERENCE: 8EHQ-04-15661

Dear Sir/Madam:

As a follow-up to our previous 8(e) submission dated, September 1, 2004, submitted for 6-(t-butyl)-2,4-dimethyl-3-chloromethylphenol, I am enclosing a copy of the following final report entitled:

“A-1846: Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test in Rats”

This report **does not** contain confidential business information; therefore, a sanitized version is not necessary.

If you have any questions or comments please contact me at (973) 357-3375.

Sincerely,



Patricia Ann Vernon
Manager, Regulatory Toxicology Programs



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MARYBELL RODRIGUEZ
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UNITED STATES US

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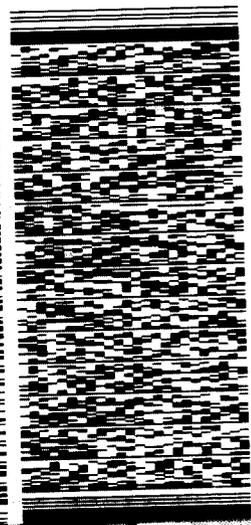
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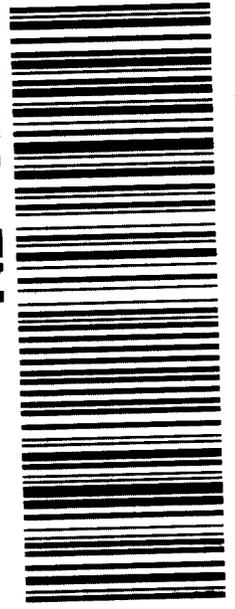
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Study Title

A-1846: Combined Repeated Dose Toxicity Study With the
Reproduction/Developmental Toxicity Screening Test in Rats

Volume 1 of 2

Laboratory Project ID: DuPont-14109

TEST GUIDELINES: Organisation for Economic Cooperation and Development
(OECD/OCDE). Guidelines for Testing of Chemicals,
Section 4 (Part 422): Health Effects (MAR-1996)

United States Environmental Protection Agency (EPA),
Office of Prevention, Pesticides, and Toxic Substances
(OPPTS) OPPTS 870.3650 Combined Repeated Dose
Toxicity Study With the Reproduction/Developmental
Toxicity Screening Test (JULY-2000)

AUTHOR: Eve Mylchreest, Ph.D.

STUDY COMPLETED ON: October 19, 2004

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

SPONSOR: Cytec Industries Inc.
Five Garret Mountain Plaza
West Paterson, New Jersey 07424

WORK REQUEST NUMBER: 15031

SERVICE CODE NUMBER: 1422

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are compatible with the OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM(98)17, OECD, Paris, 1998 and MAFF Japan Good Laboratory Practice Standards (11 NohSan Number 6283), except for the item documented below. The item listed does not impact the validity of the study.

- The bulk test substance characterization was performed by the sponsor, at a non-GLP laboratory. All of the analyses are considered valid and sufficient for the purposes of this study.

Applicant / Sponsor: Cytex Industries Inc.
Five Garret Mountain Plaza
West Paterson, New Jersey 07424

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Study Director: _____


Eys Mylchreest, Ph.D.
Senior Research Toxicologist

19-Oct-2004
Date

Applicant / Sponsor: _____

Applicant/Sponsor Representative

Date

QUALITY ASSURANCE STATEMENT

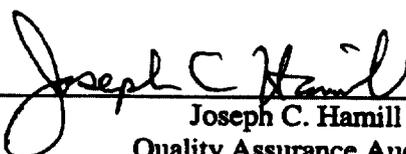
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The conduct of this study has been subjected to periodic Quality Assurance inspections. The dates of inspection are indicated below.

<i>Phase Audited</i>	<i>Audit Dates</i>	<i>Dates Reported to Study Director and Management</i>
Conduct:	March 8, 26, 30, 31, 2004; April 15, 2004	March 8, 26, 30, 31, 2004; April 15, 1004
Tables/Appendices:	May 25-28, 2004; June 1-4, 14, 16, 22-25, 2004; July 21, 22, 2004	May 28, 2004; June 21, 25, 2004; July 22, 2004
Report/Records:	July 25, 26, 2004	July 26, 2004

Reported by:



Joseph C. Hamill
Quality Assurance Auditor

19-Oct-2004

Date

CERTIFICATION

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

Analytical Evaluations by: Janet C. Maslanka 18-Oct-2004
Janet C. Maslanka, B.S. Date
Senior Staff Chemist

Neurobehavioral Evaluations by: Linda A. Malley 18 Oct-2004
Linda A. Malley, Ph.D., D.A.B.T. Date
Senior Research Toxicologist

Clinical Pathology Evaluations by: Nancy E. Everds 19-Oct-2004
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Diplomate A.C.V.P.
Principal Research Clinical Pathologist

Anatomic Pathology Evaluations by: Greg P. Sykes for 19-Oct-2004
Greg P. Sykes, V.M.D. Date
Diplomate A.C.V.P., A.C.L.A.M., A.B.T.
Veterinary Pathologist

Anatomic Pathology Evaluations Peer Review by: Steven R. Frame 19-Oct-2004
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Diplomate A.C.V.P.
Principal Research Pathologist

Approved by: Scott E. Loveless 19-Oct-2004
Scott E. Loveless, Ph.D. Date
Research Manager and Director

Issued by Study Director: Ed Mylchreest 19-Oct-2004
Ed Mylchreest, Ph.D. Date
Senior Research Toxicologist

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STUDY INFORMATION

9th Collective Nomenclature: Phenol, 3-(chloromethyl)-6-(1,1-dimethylethyl)-2,4-dimethyl-

- Synonyms/Codes:
- 6-tert-Butyl-3-(chloromethyl)-2,4-xyleneol
 - A-1846
 - 2,4-dimethyl-3-(chloromethyl)-6-tert-butylphenol
 - 3-(chloromethyl)-6-(1,1-dimethylethyl)-2,4-dimethylphenol
 - 4-tert-butyl-3-hydroxy-2,6-dimethylbenzyl chloride
 - 6-tert-butyl-2,4-dimethyl-3-chloromethyl phenol
 - 6-tert-butyl-3-chloromethyl-2,4-dimethylphenol phenol, 3-(chloromethyl)-6-(1,1-dimethylethyl)-2,4-dimethyl phenol, 6-tert-butyl-3-chloromethyl-2,4-xyleneol
 - S19650-123 (Lot No.)

Haskell Number: 26200

CAS Registry Number: 23500-79-0

Purity: >98%

Known Impurities: None

Physical Characteristics: Off-white crystal

Stability: The test substance was stable under the conditions of the study.

Study Initiated/Completed: March 2, 2004 / (see report cover page)

In-Life Initiated/Completed: March 3, 2004 / April 28, 2004

SUMMARY

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test was conducted with A-1846. CrI:CD[®](SD)IGS BR rats (10/sex/dose level) were dosed with A-1846 once daily by gavage at dose levels of 0, 15, 50, or 200 mg/kg/day. The vehicle was PEG 400 and the dose volume was 8 mL/kg/day. Following 2 weeks of dosing (pre mating), the P₁ generation males and females were cohoused within their respective treatment groups to produce F₁ litters. Dams were allowed to deliver and rear their offspring until postpartum day 4. General clinical observations were recorded once daily during dosing; detailed clinical observations were recorded once during pretest and weekly thereafter. Body weights and food consumption were recorded weekly throughout the study in P₁ rats; food consumption was not measured during cohabitation or thereafter for males or females with no evidence of copulation. A neurobehavioral evaluation consisting of a functional observational battery and motor activity was conducted in P₁ rats (5/sex/group). Clinical pathology parameters (hematology, clinical chemistry, coagulation) were measured in P₁ rats (5/sex/group). F₁ litter examinations (pup viability, individual pup weights, clinical observations) were performed at birth and on lactation day 4.

After litter production, all P₁ rats were given a gross pathological examination. The testes and epididymides from all males were weighed. The liver, kidneys, adrenals, thymus, spleen, brain, and heart from 5 animals/sex/group were weighed. Liver, small and large intestines, kidneys, bladder, lungs, trachea, heart, spleen, thymus, lymph nodes, bone marrow, thyroid, adrenals, brain, spinal cord, sciatic nerve, and femur were saved from 5 animals/sex/group. Gross observations, potential target organs (liver, stomach), and reproductive organs were saved from all animals. Uterine implantation sites and ovarian *corpora lutea* were counted in P₁ female rats. A histological examination of saved tissues was conducted for the control and 200 mg/kg/day groups and for unscheduled deaths. Examination of tissues from the remaining groups was limited to relevant gross lesions and those tissues that demonstrated treatment-related histological effects in the 200 mg/kg/day group.

Effects considered to be related to the test substance at 200 mg/kg/day include:Adverse effects:

- Dystocia (difficult or prolonged labor) in P₁ females
- Clinical signs of toxicity in P₁ males
- Mortality and clinical signs of toxicity, including those associated with dystocia (difficult or prolonged labor) in P₁ females
- Reductions in body weight gain, food consumption and food efficiency in P₁ males
- Reductions in body weight gain, food consumption and food efficiency in P₁ females during pre mating
- Reductions in body weight gain and food consumption in P₁ females during gestation
- Reduction in mean pup weight in F₁ litters during lactation days 0-4

- Decreased hindlimb grip strength (males) and decreased motor activity (males and females)
- Potentially adverse, test substance-related hypertrophy of thyroid follicular epithelium in P₁ males and females

Non-adverse effects:

- Increased liver weight and hepatocellular hypertrophy in P₁ males and females
- Decreased platelet counts in males
- Increased cholesterol concentration in males and females

Effects considered to be related to the test substance at 50 mg/kg/day include:

Adverse effects:

- Dystocia in P₁ females
- Mortality and clinical observations associated with dystocia in P₁ females
- Reduction in body weight gain and food consumption in P₁ females during gestation
- Reduction in mean pup weight in F₁ litters on lactation day 4

Non-adverse effects:

- Increased liver weight in P₁ males and females, and hepatocellular hypertrophy in P₁ males
- Increased cholesterol concentration in males and females

Effects considered to be related to the test substance at 15 mg/kg/day group include:

Adverse effects:

- Dystocia in P₁ females
- Mortality and clinical observations associated with dystocia in P₁ females
- Reduction in body weight gain in P₁ females during gestation

Non-adverse effects:

- Increased cholesterol concentration in males and females

Under the conditions of this study, a no-observed-effect level (NOEL)^a was not determined for systemic toxicity in P₁ rats, based on mortality and clinical signs of toxicity associated with dystocia, and reduced body weight gain in females during gestation at all dose levels. The NOEL for F₁ offspring was 15 mg/kg/day, based on reduced pup weights during lactation at 50 and 200 mg/kg/day. A NOEL for reproductive parameters was not established, based on the occurrence of dystocia in P₁ females at all dose levels.

^a The NOEL for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Thus, for this study, the NOEL is equivalent to the NOEL as defined by the United States Environmental Protection Agency (1985) and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union (1994).

INTRODUCTION AND OBJECTIVE

The objective of this study was to evaluate the potential subchronic and reproductive toxicity of the test substance when administered by gavage to male and female rats during premating, cohabitation, gestation, until lactation day 3. Clinical pathology, neurobehavioral function, gross pathology, histopathology, and reproductive function were evaluated.

MATERIALS AND METHODS

A. Sponsor

Sponsor (approval effective on the date authorized on the contract):

Cytec Industries Inc.
Five Garret Mountain Plaza
West Paterson, New Jersey 07424
U.S.A.

Sponsor study monitor:

Patricia A. Vernon
Manager, Regulatory Toxicology Programs
Cytec Industries Inc.
Five Garret Mountain Plaza
West Paterson, NJ 07424
U.S.A.
(P) 973-357-3375
(F) 973-357-3057
Patricia.Vernon@cytec.com

B. Testing Facility

DuPont Haskell Laboratory for Health and Environmental Sciences
E.I. du Pont de Nemours and Company
Newark, Delaware 19714
U.S.A.

C. Regulatory Compliance

1. Test Guidelines

The study design complies with the following test guidelines:

- Organisation for Economic Cooperation and Development (OECD/OCDE). Guidelines for the Testing of Chemicals, Section 4 (Part 422): Health Effects (MAR-1996).
- United States (U.S.) Environmental Protection Agency (EPA), Office of Prevention, Pesticides, and Toxic Substances (OPPTS) Health Effects Test Guidelines, OPPTS 870.3650 Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test (JULY-2000).

D. Study Design

1. Experimental Design

Treatment Groups and Daily Dosage

Group		Number/Group		Exposure	Test Formulation Concentration
Male	Female	Male	Female	(mg/kg/day) ^a	(mg/mL) ^b
I-0	II-0	10	10	0 ^c	0
III-0	IV-0	10	10	15	1.88
V-0	VI-0	10	10	50	6.25
VII-0	VIII-0	10	10	200	25

- a Formulations of test substance in PEG 400 (Technical Grade) were administered once daily by gavage at a dosing volume of 8 mL/kg.
- b To achieve these concentrations of active ingredient, the formulations were adjusted for sample purity.
- c The control group animals received vehicle PEG 400 (Technical Grade) only at 8 mL/kg.

Sacrifice Schedule

Animals	Schedule
Adult Males	Test Day 34
Pregnant Females	Day 4 of lactation (Test days 43-57)
Nonpregnant Females	Not Applicable (All females were pregnant)
Offspring	Day 4 of lactation

2. Selection of Dose Levels

In a previous 2-week range-finding study⁽¹⁾ groups of 5 male and 5 female rats were administered the test substance by gavage at dosages of 0, 250, 500, or 1000 mg/kg/day. Test substance-related mortality and clinical signs of toxicity occurred at 500 and 1000 mg/kg/day. Test substance-related reductions in body weight gain and weight loss occurred at 250, 500, and

1000 mg/kg/day. Test substance-related gross lesions in the liver and stomach were observed in animals in these groups.

Dosages of 0, 15, 50, and 200 mg/kg/day were selected for the current study. The 50 mg/kg/day level was expected to produce no or minimal toxic effects. The 200 mg/kg/day level was expected to produce some systemic toxicity but no mortality. The 15 mg/kg/day level was expected to be the no-observed-effect level (NOEL).

E. Analytical

1. Vehicle

The vehicle was PEG 400 (Technical Grade). Lot number(s) and expiration date(s) are recorded in the study records.

2. Test Substance

The test substance, an off-white crystal, was supplied by the sponsor. The test substance was assigned Haskell Laboratory Number H-26200.

3. Preparation, Administration, and Analysis of Test Formulations

a. Test Formulation Preparation

Formulations of the test substance in the vehicle (PEG 400) were prepared daily and stored refrigerated until used. Once 10-day refrigerated storage stability was established (Appendix C), formulations were prepared once a week and stored refrigerated. The method of mixing the test substance with the vehicle was documented in the study records.

b. Test Formulation Administration

The test substance was administered once daily by oral intubation (gavage) the route recommended by test guidelines. The volume of test substance or vehicle given to each rat was based on the most recently recorded body weight. The dose volume was 8 mL/kg. Male and female control rats were similarly treated with the vehicle at the same dose volume as used in the other groups.

Dosing Schedule

- All animals were dosed once daily by gavage for 14 days prior to cohabitation and during the cohabitation period (up to 2 weeks).
- Male rats and female rats showing no evidence of copulation continued to be dosed after the end of the cohabitation period until sacrifice.
- Females showing evidence of copulation were dosed throughout gestation.
- Pregnant females in the process of delivery or showing signs of delivery were not dosed.
- Females were dosed after delivering litters, until day 3 postpartum.

c. Test Formulation Sampling

Type	Collected From	Storage Conditions Until Analysis
Control	Mixing Vessel	Room temperature

Homogeneity, Initial Concentration Verification, and 5 Hour Stability of the Test Substance in the Vehicle^{a,b,c}

Top	Mixing Vessel - Top	Room temperature
Middle	Mixing Vessel - Middle	Room temperature
Bottom	Mixing Vessel - Bottom	Room temperature
5 Hour Stability	Mixing Vessel	Room temperature for approximately 5 hours

10-Day Stability – All samples listed above were taken at the initial formulation preparation.

The remaining formulations after dosing were refrigerated for 10 days and then analyzed for concentration verification (duplicate samples) and 5-hour room temperature stability.^c

Concentration Verification: ^{a,c,d}	Mixing Vessel	Room temperature
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- a Whenever samples were collected, a sample of the vehicle was also collected and analyzed.
- b Four samples (approximately 3 ml each) were taken from each concentration of the initial test formulations near the beginning of the study.
- c Remaining formulation samples after dosing were stored refrigerated for 10 days, then sampled, and discarded when the final results from the analysis were accepted.
- d Duplicate samples were taken near the middle and end of the study.

The samples were analyzed by the Haskell Laboratory Analytical Chemistry Group on the day the samples were collected. On days samples were taken, the formulations remaining after dosing were stored in the refrigerator for possible additional analysis and then discarded.

F. Test Species

The CrI:CD[®](SD)IGS BR strain was chosen because of the consistently acceptable health status and extensive experience with this strain at Haskell Laboratory.

On February 19, 2004, 45 male and 45 female CrI:CD[®](SD)IGS BR rats, with an assigned birth date of December 29, 2003 were received from Charles River Laboratories, Inc., Raleigh, North Carolina for use on this study. The rats were approximately 52 days old upon arrival and weighed approximately 210.1-241.9 grams (males) and approximately 176.5-211.0 grams (females) the day after arrival. Male and female rats were nonsiblings; females were nulliparous.

The rats were approximately 65 days old at the start of treatment (March 3, 2004), and in the body weight ranges of 276.6–385.6 grams (males) and 216.0-248.5 grams (females).

G. Animal Husbandry

1. Identification

During the pretest period, a unique number was assigned to each animal which was tattooed on the animal's tail and included on the animal's cage label.

2. Housing

All male rats were housed individually during non-mating periods in stainless steel, wire-mesh cages suspended above cageboards.

a. Pretest and Premating

All rats were housed individually in stainless steel, wire-mesh cages suspended above cageboards.

b. Cohabitation Period

All rats were housed as breeding pairs in stainless steel, wire-mesh cages suspended above cageboard. At the end of the cohabitation period, females without evidence of copulation were housed individually in polycarbonate pans.

c. Gestation Period (Females with evidence of copulation)

- Days 0-19: Dams were housed individually in stainless steel, wire-mesh cages suspended above cageboards.
- Day 20-Delivery: Females were housed individually in polycarbonate pans with bedding.

d. Lactation Period

Dams were housed with their litters in polycarbonate pans with bedding.

3. Environmental Conditions – Animal Rooms

a. Temperature

Animal rooms were maintained at an acceptable temperature of 18-26°C (targeted at 22°-24°C).

b. Humidity

Animal rooms were maintained at an acceptable relative humidity of 30%-70% (targeted at 40%-60%).

c. Lighting

Animal rooms were artificially illuminated (fluorescent light) on a 12-hour light/dark cycle (approximately 0600-1800 hours).

Occasional excursions outside the accepted ranges were minor and did not affect the study.

4. Feed and Water

a. Feed

All rats were fed pelleted PMI[®] Nutrition International, Certified Rodent LabDiet[®] 5002 *ad libitum*, except when fasted.

b. Water

Tap water from United Water Delaware was provided *ad libitum*.

5. Health Monitoring Program

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

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Samples from freshly washed cages and cage racks are analyzed for sentinel bacteria to ensure adequate sanitation by the cagewashers.

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

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

H. Pretest and Quarantine Period

Upon arrival at Haskell Laboratory, the rats were quarantined for 6 days of the 13-day pretest period. The rats were observed daily for any clinically apparent signs of disease or injury and weighed once.

On the basis of acceptable body weight gains and clinical observations, all surviving rats were released from quarantine on test day -8 (February 24, 2004) by the laboratory animal veterinarian designee.

I. Assignment to Groups and Study Start - Randomization

Rats of each sex were ranked by their most recently recorded body weight and randomly assigned to control and experimental groups. The randomization resulted in a distribution in which the mean body weights for all groups within a sex were not statistically different ($p > 0.05$).

Rats not assigned to a test group, at the discretion of the study director were sacrificed by carbon dioxide euthanasia and discarded without pathological evaluation, except for 2 males that were sent to necropsy for a gross examination and blood collection for serology.

Subgroup Designations: First 5 surviving rats – Clinical and Anatomic Pathology Evaluations
Last 5 surviving rats – Neurobehavioral Evaluations

J. Clinical Observations and Mortality – P₁ Rats

1. Health Observations

Cage-site examinations to detect moribund or dead animals and abnormal behavior and/or appearance were performed on all animals at least once daily during quarantine and predosing and twice daily thereafter.

2. General Clinical Observations

All animals were examined daily at approximately the same time of day (± 2 hours) for acute/systemic toxicity.

3. Detailed Clinical Observations

Once during pretest (baseline), and weekly thereafter at approximately the same time of day (± 2 hours), animals were individually handled and examined for abnormal behavior and appearance in a standardized arena. Observations included (but were not limited to) evaluation of fur, skin, eyes, mucous membranes, occurrence of secretions and excretions, autonomic nervous system activity (lacrimation, piloerection, and unusual respiratory pattern), changes in gait, posture, response to handling, presence of clonic, tonic, stereotypical, or bizarre behavior.

K. Body Weights and Body Weight Gains - P₁ Rats

1. Premating Period

All P₁ rats were weighed once a week and at terminal sacrifice.

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2. Gestation and Lactation Periods

P₁ females were weighed on days 0, 7, 14, and 21 of gestation.

P₁ females were weighed on days 0 and 4 of lactation.

Females without evidence of copulation, those that copulated and did not deliver a litter, and males were weighed on a weekly schedule.

L. Food Consumption and Food Efficiency - P₁ Rats

Each feeder was weighed at the beginning and end of the weekly food consumption interval and the final weight of the feeder and the amount of spillage from the feeder during the interval was subtracted from the initial feeder weight. From the food consumption and body weight data, the mean daily food efficiency was calculated.

1. Premating and Cohabitation Periods

Individual food consumption was determined weekly throughout the period, ending on test day 15. Food consumption was not measured during cohabitation for males and females or after cohabitation for males.

2. Gestation and Lactation Periods

Individual food consumption of pregnant P₁ females was recorded on gestation days 0, 7, 14, and 21, and for lactating females on lactation days 0 and 4. Food consumption was not measured for females without evidence of copulation, females that did not deliver a litter, or for males.

M. Breeding

1. Cohousing

Each female was continually housed on a 1:1 basis with a randomly selected, nonsibling male of the same dosage level, in the male's cage. On the day copulation was confirmed, the female was transferred back to individual cage housing.

A second pairing with a proven male of the same dose group was performed for 2 pairs each in the 50 and 200 mg/kg/day groups due to lack of evidence of copulation during the first pairing.

Due to severe clinical signs of toxicity on test day 15, the start of cohabitation, Animal Number 792 (Group VIII-0), was not cohoused and was subsequently found dead on test day 16.

2. Start of Cohabitation

Animals were cohoused after approximately 2 weeks of exposure to the test substance. The day animals were first cohoused (test day 15) was designated as day 1 of cohabitation.

3. Duration of Cohabitation Period

Animals were cohoused until evidence of copulation was observed (designated as day 0 of gestation) or until 2 weeks had elapsed. The cohabitation period ended in the morning of day 15 of cohabitation.

4. Evidence of Copulation

Once daily, each female was examined for an intravaginal copulation plug or sperm in the vaginal lavage sample, either of which was considered evidence of copulation. The day evidence of copulation was observed was designated as day 0 of gestation.

N. Gestation Procedures

After being transferred into polycarbonate pans (on day 20 of gestation for mated females, or at the end of the cohabitation period for females without evidence of copulation), female rats were observed at least twice daily for signs of delivery and offspring.

O. Lactation Procedures

The day when delivery was complete was designated day 0 postpartum. At each examination period (days 0 and 4 postpartum), offspring were individually handled and examined for abnormal behavior and appearance; any dead or abnormal pups were recorded. Dams that had no live pups remaining during lactation were sacrificed.

1. Day 0 Postpartum

Live and dead pups in each litter were counted by sex as soon as possible after delivery was completed. Live pups in each litter were individually weighed.

2. Day 4 Postpartum

Live pups in each litter were counted by sex and individually weighed and a gross external examination was performed. All pups were euthanized (by decapitation).

P. Neurobehavioral Evaluation

Neurobehavioral evaluations were conducted once on 5 randomly selected male rats per group on day 29 (near the end of the dosing period), and once on 5 randomly selected female rats per group on day 14 (near the end of the pre mating period).

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

1. Functional Observational Battery (FOB)

For the FOB evaluation, the rats were distributed into 2 replicates with approximately equal representation of each group within a replicate. Replicate identity was recorded in the study records. Precautions were taken to ensure that the experimenter who assessed the behavioral characteristics during the FOB was unaware of the group designation of the rats.

FOB testing consisted of a series of quantified behavioral observations conducted in a sequence that proceeded from the least interactive to the most interactive.

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

2. Motor Activity (MA)

Motor activity (MA) measurement was conducted immediately following the FOB assessment. Rats were individually tested in one of 30 nominally identical, automated activity monitors (Coulbourn® Instruments). Groups were counterbalanced across the monitors and time of day to the fullest extent possible. The infrared monitoring device enabled measurement of 2 dependent variables, duration of movement and number of movements. A continuous movement was counted as one movement regardless of duration. Each test session was 60 minutes in duration, and the results were expressed for the total session as well as for 6 successive 10-minute blocks.

3. Functional Observational Battery and Motor Activity Parameters

Phase	Order	Procedure	Parameters or Methods	
	1	Acclimation to the Home Cage for at least 10 minutes ^a	NA	
FOB	2	Home Cage Assessments	posture palpebral closure tremors	convulsions gait/coordination
FOB	3	Removal from Home Cage and Handling Assessments	ease of removal ease of handling muscle tone vocalizations piloerection palpebral closure fur/skin appearance	lacrimation salivation exophthalmus mucous membranes dehydration emaciation
FOB	4	Open Field Arena (approx. 85 x 59 x 20 cm)	righting reflex posture tremors gait/coordination rate of respiration convulsions muscle spasms/fasciculation	vocalizations palpebral closure diarrhea polyuria ease of respiration rearing arousal
FOB	5	Manipulations in Open Field	approach and touch response auditory response	tail pinch response foot splay ^b
FOB	6	Fore- and hindlimb grip strength Strain gauge device (Chatillion [®] Digital Force gauge)	forelimb grip strength	hindlimb grip strength
MA	7	Motor Activity	Duration of movement and number of movements were evaluated in 6 consecutive blocks of 10 minutes each as well as for the total 60-minute session.	
MA	8	Assessments in MA monitor ^c	diarrhea	polyuria
FOB	9	Pupillary Constriction or Response ^d	Light beam in each eye in the darkened MA room	
	10	Body weight ^e		

a The "Home Cage" was defined as the cage on the transport rack to which an individual animal was assigned. This cage was similar in design to the home cage.

b Hindlimb splay was assessed by inking the hind paws and releasing the rat from a height of approximately 32 cm onto a piece of paper that covered a padded surface. Heel-to-heel distance was measured from the inked impressions and recorded.

c The presence of diarrhea and polyuria on the cageboards below the motor activity cages was evaluated following each motor activity session.

d Conducted at the conclusion of motor activity immediately prior to removing the rats from the motor activity cages because the darkened room in which the apparatus was located facilitated observing the response. The presence or absence of pupillary constriction was recorded after a beam of light was directed into each eye.

e Data not included in the final report

Q. Clinical Pathology Evaluation

A clinical pathology evaluation was conducted on the first 5 surviving rats/sex/group approximately 14 days after initiation of the study (hematology and clinical chemistry) and at terminal sacrifice (coagulation only). Only 4 males could be evaluated in the high-dose group on day 14 (hematology and clinical chemistry) due to the death of 1 male on test day 3 and because the 5 last males in the group were undergoing neurobehavioral evaluation on that day.

The day before collection of samples for hematology and clinical chemistry, these animals were fasted after 3 p.m. (at least 15 hours). Blood samples for hematology and clinical chemistry measurements were collected from the orbital sinus of each animal while the animal was under carbon dioxide anesthesia. Blood samples for coagulation parameters were collected at sacrifice (day 34 for males, and day 4 of lactation [days 43-57] for females) from the abdominal *vena cava* of each animal (non-fasted) while the animal was under carbon dioxide anesthesia. Additional blood collected from the *vena cava* was placed in a serum tube, processed to serum, and frozen at -80°C. Serum was discarded without analysis because further tests were not required to support experimental findings. All blood samples were evaluated for quality by visual examination prior to analysis. Results were maintained in the study records and reported only if the sample was analyzed.

1. Hematology and Coagulation

Complete blood counts, including reticulocytes, were determined on a Bayer® Advia 120 hematology analyzer or determined from microscopic evaluation of the blood smear. Wright-Giemsa-stained blood smears from all animals were examined microscopically for confirmation of automated results. Blood smears, stained with new methylene blue, were prepared from each animal undergoing a hematology evaluation, but were not needed for examination. Coagulation times were determined on a Sysmex® CA-1000 Coagulation Analyzer.

The following parameters were determined:

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

2. Clinical Chemistry

Serum clinical chemistry parameters were determined on an Olympus® AU640 clinical chemistry analyzer.

The following parameters were determined:

aspartate aminotransferase	total protein
alanine aminotransferase	albumin
urea nitrogen	total bile acids
creatinine	sodium
cholesterol	potassium
glucose	

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R. Anatomic Pathology

Surviving male rats (up to 10/sex/group) were sacrificed and necropsied on test day 34. Surviving female rats (up to 10/sex/group) were sacrificed and necropsied on day 4 of lactation. Both the male and female rats utilized for pathology (gross pathology, organ weights, and histopathology) were also used as the P₁ sires and dams in the Reproductive/Developmental Toxicity Screening Test.

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

The following tissues were collected from rats that were found dead or accidentally killed, sacrificed *in extremis*, and the first 5 males and 5 females sacrificed by design. Gross observations, suspected target organs (liver and stomach), and organs of the reproductive system were collected from all rats sacrificed by design.

<u>Digestive System</u> ^a	<u>Hematopoietic System</u>	<u>Reproductive System</u>
liver ^b	spleen	<u>Male</u>
stomach ^b	thymus	testes
duodenum	mandibular lymph node	epididymides
jejunum	mesenteric lymph node	prostate
ileum	bone marrow ^c	seminal vesicles
cecum		coagulating glands
colon	<u>Endocrine System</u>	
rectum	thyroid gland	
	adrenal glands	<u>Female</u> ^d
<u>Urinary System</u>	<u>Nervous System</u>	ovaries (with oviducts)
kidneys	brain (3 sections)	cervix
urinary bladder	spinal cord (3 levels)	uterus
<u>Respiratory System</u>	sciatic nerve	vagina
lungs		
trachea		
<u>Cardiovascular System</u>	<u>Musculoskeletal System</u>	<u>Miscellaneous</u>
heart	femur ^c	gross observations ^e

-
- Peyer's patches were collected from sections of the digestive tract.
 - Potential target organ (based on previous 2-week range-finding study)
 - Bone marrow was collected with the femur and sternum.
 - Females were examined for the presence and number of implantation sites and ovarian *corpora lutea*.
 - Gross observations made at necropsy for which histopathology was not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) were generally not collected. Gross lesions for which a microscopic diagnosis would not be additive (e.g., osteoarthritis, pododermatitis, chronic dermatitis of the tail, urinary calculi, and deformity of the teeth, toe, tail, or pinna) were saved but were generally not processed for microscopic evaluation.

The testes and epididymides of all males sacrificed by design were weighed. The following tissues were weighed from the first 5 rats from each group sacrificed by design: liver, kidneys, adrenal glands, thymus, spleen, brain, and heart. Relative organ weights (percent of final body weight; ratio to brain weight) were calculated. Final body weights, determined just prior to necropsy, were used in the assessment of organ weight changes. Organs from rats found dead, sacrificed *in extremis*, or accidentally killed were not weighed. Organs were inadvertently weighed from an additional (i.e., 6th) 15 mg/kg/day rat (Animal Number 832) that was sacrificed by design but was not one of the first 5 rats. These data were included in the weight data tables and were used in the calculation of the means.

Testes and epididymides were fixed in Bouin's solution. All other tissues were fixed in 10% neutral buffered formalin. Processed tissues were embedded in paraffin, sectioned approximately 5-6 microns thick, stained with hematoxylin and eosin (H&E), and examined microscopically by a veterinary pathologist.

All collected tissues from the first 5 rats/sex sacrificed by design in the control and high-dose (200 mg/kg/day) groups were examined microscopically. All tissues from rats found dead, sacrificed *in extremis* (i.e., unscheduled sacrifice), or accidentally killed were similarly examined. Reproductive tissues and gross observations were examined from all males and females. Target organs that were collected from all rats (liver) were examined from all rats. Target organs that were not collected from all rats (thyroid) were examined for the rats from which they were collected (the first 5 rats/sex/dose sacrificed by design and all unscheduled deaths). Non-target organs that were initially suspected to be target organs based on the previous 2-week range-finding study⁽¹⁾ (stomach) were examined from all control and high-dose males and females (10/sex/group).

DATA ANALYSES

The following table lists the indices of reproductive function that will be calculated for the Parental animals.

Reproductive Function Calculations

Mating Index (%)	=	$\frac{\text{Number copulated}^a}{\text{Number cohabited}}$	x 100
Fertility Index (%)	=	$\frac{\text{Number pregnant}^b}{\text{Number copulated}^a}$	x 100
Gestation Index (%)	=	$\frac{\text{Number of litters with at least one live pup}}{\text{Number of litters}}$	x 100
Implantation Efficiency (%) ^c	=	$\frac{\text{Number of pups born}}{\text{Number of implantation sites}}$	x 100
Pups Born Alive (%) ^c	=	$\frac{\text{Number of pups born alive}}{\text{Number of pups born}}$	x 100
0-4 Day Viability (%) ^{c,d}	=	$\frac{\text{Number of pups alive day 4}}{\text{Number of pups born alive}}$	x 100

a Evidence of copulation = intravaginal copulatory plug, sperm in vaginal lavage, found dead pregnant, or delivery of a litter.

b Including those found dead pregnant during gestation.

c Determined for each litter. Mean and standard deviation for each dose level were calculated.

d Excluding litters sacrificed due to death of dam during lactation.

Statistical Methods

Parameter	Preliminary Test	Method of Statistical Analysis	
		If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Food Efficiency Gestation Length Implantation Site Numbers Corpora Lutea Counts Implantation Efficiency Mean Number of Pups Per Litter Percent Born Alive 0-4 Day Viability Clinical Pathology ^c Organ Weight	Levene's test for homogeneity ⁽²⁾ and Shapiro-Wilk test ⁽³⁾ for normality ^a	One-way analysis of variance ⁽⁴⁾ and Dunnett's test ^(5,6,7)	Kruskal-Wallis test ⁽⁸⁾ and Dunn's test ⁽⁹⁾
Incidence of Clinical Observations Incidence of FOB Descriptive Parameters Mating Index Fertility Index Gestation Index	None	Cochran-Armitage test for trend ^{(4)b}	
Sex Ratio Mean Pup Weights (Covariates: litter size, sex ratio)	None	Exact Mann-Whitney with a Bonferroni-Holm adjustment ^(10,11)	
Motor Activity ^d Grip Strength Foot Splay Rearing	Levene's test for homogeneity ⁽²⁾ and Shapiro-Wilk test ⁽³⁾ for normality ^a	Repeated measures analysis of variance ⁽¹²⁾ followed by Linear contrasts ⁽¹³⁾	Sequential application ⁽¹⁴⁾ of the Jonckheere-Terpstra trend test ⁽¹⁵⁾ unless a normalizing, variance stabilizing transformation can be found and the repeated measures analysis of variance repeated.

- a If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used. If the Shapiro-Wilk test was significant, Kruskal-Wallis test was followed with Dunn's test.
- b If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test⁽¹⁶⁾ with a Bonferroni correction was used.
- c When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that bilirubin data.
- d Test day and 10-minute interval were used as repeated-measure factors.

Male and female parental data were evaluated separately. For litter parameters, the proportion of affected pups per litter or the litter mean were used as the experimental unit for statistical evaluation.⁽¹⁷⁾ The level of significance selected was $p < 0.05$.

RECORDS AND SAMPLE STORAGE

All data and records for analytical characterizations conducted by the Sponsor will be retained by the Sponsor. Laboratory-specific or site-specific raw data, such as personnel files and equipment records will be retained by the facility where the work was done.

Specimens and raw data will be retained at Haskell Laboratory, Newark, Delaware. All original study data and samples will be returned to the Sponsor upon request within 6 months following issuance of the final report. The study data will be sent to a GLP-compliant archive designated by the Sponsor.

A draft final report was prepared and finalized in consultation with the Sponsor. Upon finalization, the final report was provided to the Sponsor's Study Monitor. Electronic copies of the final protocol (and any amendments and deviations) and the final report were provided as a Portable Document Format (PDF) image.

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RESULTS AND DISCUSSION

ANALYTICAL

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A. Test Formulation Analysis (Appendix C)

The analytical method used is described in Appendix C. Results from the analysis of the test formulation samples indicated that the test substance was uniformly mixed, at the expected concentrations, and stable in the vehicle for 5 hours at room temperature at all dose levels.

A. Test Substance Stability (Appendices C and D)

The stability of the test substance over the course of the study was confirmed by analyses conducted near the beginning and end of the study (Appendices C and D). No evidence of instability, such as a change in color or physical state, was observed.

REPRODUCTIVE TOXICOLOGY

A. P₁ Rats - Clinical Observations and Mortality

1. P₁ Males: (Tables 1 and 5, Appendices E and I)

There was no test substance-related mortality during the study; convulsions preceded death on test day 3 in 1 animal; however this death was not considered test substance-related (refer to Anatomic Pathology, Section A, for more details). There were test substance-related clinical observations at 200 mg/kg/day, which consisted of lung noise (3/10 animals), diarrhea (3/10 animals), hunched over posture (2/10 animals) and stained fur (6/10 animals). In addition to displaying these signs, one animal also had irregular respiration and dehydration.

Clinical signs of toxicity observed during the weekly detailed clinical observations session were consistent with those observed during the daily clinical observations sessions. There were no test substance-related clinical observations at 15 or 50 mg/kg/day.

2. P₁ Females: (Tables 2-4 and 6-8, Appendices F-H and J-L)

There was test substance-related mortality during the study at all dose levels with 0, 1, 2, and 4 deaths at 0, 15, 50, and 200 mg/kg/day, respectively (refer to Anatomic Pathology, Section A, for more details). Most of the deaths occurred during gestation (1, 2, and 3 deaths at 15, 50, and 200 mg/kg/day, respectively), were associated with dystocia (difficult or prolonged parturition), and were considered test substance-related due to the high incidence and dose-related trend for

the relatively rare occurrence of dystocia in rats of this strain and age. One additional death in the 200 mg/kg/day group on test day 16 was also considered test substance-related. Another death in the 200 mg/kg/day group was considered to be a dosing accident.

There were test substance-related clinical observations during pre mating at 200 mg/kg/day, which consisted of stained fur (4/10 animals), and diarrhea and hunched over posture (1/10 animals). Other clinical signs of toxicity observed during pre mating occurred in 1 animal (Animal Number 792, 200 mg/kg/day) immediately prior to death on test day 16, and included irregular respiration, stained/wet fur, diarrhea, and dehydration. During pre mating (days 1-15) this animal also lost 44 grams of body weight and had low food consumption (12.5 grams/day). There were test substance-related clinical observations during gestation at all dose levels; these signs were associated with dystocia in one animal at each level and included dehydration, diarrhea, immobility/lethargy, pallor, ptosis and stained/wet fur. Other test substance-related clinical observations were observed in a few animals during gestation and lactation at 200 mg/kg/day and included irregular respiration, lung noise, and stained/wet fur.

Clinical signs of toxicity observed during the weekly detailed clinical observations session were consistent with those observed during the daily clinical observations sessions.

B. P₁ Rats - Body Weights and Body Weight Gains

1. P₁ Males: (Tables 9-10, Appendices M-N)

There were test substance-related effects on body weight and body weight gain at 200 mg/kg/day. Body weight gain was 45% lower than control for the entire dosing period (days 1-34) as well as for the pre mating period (65% lower than control for days 1-15) at this dose level. Although weekly mean body weight gain was generally lower throughout dosing, it was most marked during the first week (97% lower than control for days 1-8). In addition, weekly mean body weights were 8%-10% lower than control throughout the study and were consistent with the reduced weight gain at this dose level.

There were no test substance-related effects on body weights and body weight gains at 15 or 50 mg/kg/day.

2. P₁ Females: (Tables 11-16, Appendices O-T)

There were reductions in body weight gain during pre mating at 200 mg/kg/day and during gestation at all dose levels; these effects were considered test substance-related despite lack of statistical significance. The lower mean weight gain during pre mating (days 1-15) at 200 mg/kg/day was due to one animal (Animal Number 792) that displayed marked weight loss during this period and was subsequently found dead on test day 16. The reduced weight gain during gestation was also confounded by high interindividual variability in body weight gain and maternal mortality/morbidity. Maternal body weight gain for the entire gestation period (days 0-21) was 16%, 16%, and 27% lower than control at 15, 50, and 200 mg/kg/day, respectively, as a

result of a few animals in each group displaying low weight gain. There was no appreciable effect of test substance administration on weekly mean body weights during pre-mating or gestation at any dose level. There were no test substance-related effects on maternal body weight or weight gain during lactation days 0-4 at any dose level. There were no test substance-related effects on body weights and body weight gains at 15 or 50 mg/kg/day.

C. P₁ Rats - Food Consumption and Food Efficiency

1. P₁ Males:
(Tables 17-18, Appendix U)

There were test substance-related effects food consumption and food efficiency at 200 mg/kg/day. Food consumption was 17% lower than control for the pre-mating period (days 1-15) at this dose level, as a result of lower food consumption during the first week of dosing (29% lower than control for days 1-8). The lower food efficiency during pre-mating (days 1-8 and 1-15) at 200 mg/kg/day is consistent with the reduced weight gain and food consumption at this dose level.

2. P₁ Females:
(Tables 19-24, Appendices V-X)

There were reductions in food consumption and food efficiency during pre-mating at 200 mg/kg/day and on food consumption during gestation at 50 and 200 mg/kg/day; these effects were considered test substance-related despite lack of statistical significance. The lower mean food consumption during pre-mating (days 1-15) at 200 mg/kg/day was mainly due to one animal (Animal Number 792) that displayed marked weight loss and reduced food consumption during this period and was subsequently found dead on test day 16. The lower food efficiency during pre-mating (days 1-8 and 1-15) at 200 mg/kg/day is consistent with the reduced weight gain and food consumption at this dose level. Maternal food consumption for the entire gestation period (days 0-21) was 10%-12% lower than control at 50 and 200 mg/kg/day, as a result of weekly food consumption that was 8%-15% lower than the mean weekly values for the control group. There was no appreciable effect of test substance administration on weekly food efficiency during gestation at any dose level. There were no test substance-related effects on food consumption or food efficiency during lactation days 0-4 at any dose level.

D. Reproductive Indices in P₁ Rats (Table 25, Appendices Y-Z)

There were no test substance-related effects on the length of the pre-coital interval, mating, fertility (females that had dystocia were included), gestation length (females that had dystocia not included), number of implantation sites, implantation efficiency, or number of *corpora lutea* at any dose level. The lower mean implantation efficiency in the 15 mg/kg/day group was not considered test substance-related since there was no dose-response relationship for this parameter.

E. F₁ Offspring Data

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1. Litter Size, Sex Ratio and Pup Survival
(Table 26, Appendix AA)

There were no test substance-related effects on the number of pups born, born alive, and alive on day 4, nor were there any effects on sex ratio, or survival indices during lactation days 0-4 at any dose level. The smaller litter size and survival indices in the 15 mg/kg/day group were not considered test substance-related since there was no dose-response relationship for these parameters.

2. Clinical Observations in F₁ Pups
(Table 27, Appendix BB)

There were no test substance-related clinical observations at any dose level.

3. Pup Weights
(Table 28, Appendix CC)

There were test substance-related effects on pup weights at birth at 200 mg/kg/day and on day 4 of lactation at 50 and 200 mg/kg/day. Although not statistically significant, mean pup weights at these dose levels were 6%-8% lower than the control group and thus of significant magnitude to be considered test-substance related. The apparent lower mean pup weight at 15 mg/kg/day on day 4 of lactation was not considered test substance-related since the group mean was considerably skewed by one litter (containing only one emaciated pup).

F. Reproductive Toxicology Conclusions

There were clinical signs of toxicity, and reductions in body weight gain, food consumption and food efficiency in P₁ males at 200 mg/kg/day. Dystocia (difficult or prolonged parturition), mortality, and clinical signs of toxicity including those associated with dystocia, occurred at all dose levels in P₁ females. There were reductions in body weight gain, food consumption and food efficiency during premating at 200 mg/kg/day in P₁ females. There were reductions in body weight gain at all dose levels and food consumption at 50 and 200 mg/kg/day in P₁ females during gestation. There were reductions in pup weights at birth at 200 mg/kg/day and on day 4 of lactation at 50 and 200 mg/kg/day in F₁ litters.

There were no effects on the length of the precoital interval, mating, fertility (females that had dystocia were included), gestation length (females that had dystocia not included), number of implantation sites, implantation efficiency, or number of *corpora lutea* at any dose level. There were no test substance-related effects on the number of pups born, born alive, and alive on day 4, nor were there any effects on sex ratio or survival indices during lactation days 0-4 in F₁ litters at any dose level. There were no test substance-related clinical observations during lactation days 0-4 in F₁ litters at any dose level.

NEUROBEHAVIORAL EVALUATION

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A. Functional Observational Battery

1. Forelimb Grip Strength (Table 29, Appendix DD)

There were no statistically significant or test substance-related effects on forelimb grip strength in either males or females administered any dosage.

2. Hindlimb Grip Strength (Table 29, Appendix DD)

A test substance-related, statistically significant decrease in hindlimb grip strength occurred in males administered 200 mg/kg/day. There were no test substance-related effects in hindlimb grip strength for females administered any dosage of the test substance. The decreased hindlimb grip strength correlated with decreased body weight/weight gain and decreased motor activity in the 200 mg/kg/day males, and was considered to be adverse.

3. Hindlimb Footsplay (Table 29, Appendix DD)

There were no test substance-related or statistically significant differences in footsplay in either males or females administered any dosage of the test substance.

4. Rearing (Table 29, Appendix DD)

There were no test substance-related or statistically significant differences for incidence of rearing in either males or females administered any dosage of the test substance.

5. Other Functional Observational Battery (FOB) Endpoints (Table 30, Appendix EE)

Although there were no test substance-related or statistically significant differences observed in the incidences of any of the FOB parameters for males or females administered any dosage of the test substance, the incidence of lung noise in 200 mg/kg/day males was significantly increased compared to the control group. The rate of respiration and ease of respiration were not affected by the test substance.

B. Motor Activity (Tables 31-32, Appendix FF)

A test substance-related decrease in motor activity was observed in males and females administered 200 mg/kg/day of the test substance. Duration of movement in 200 mg/kg/day males was significantly decreased during the 4th and 6th 10-minute intervals, and total duration of movement was 41% lower than the control value (statistically significant). In addition, total

number of movements for 200 mg/kg/day males was 35% lower than the control value (statistically significant).

Although not statistically significant, total duration of movement and number of movements in 200 mg/kg/day females were also 37% and 25% lower than the control values, respectively.

The decreased duration of movements and number of movements in 200 mg/kg/day males and females was considered to be adverse.

Duration of movement was significantly decreased during the 6th 10-minute interval in males administered 15 mg/kg/day. However, a dose-response relationship was not evident and therefore, the statistically decreased duration of movement during the 6th 10-minute interval for 15 mg/kg/day males was not considered to be test substance-related.

In males, total duration of movement was lower in the 15 and 50 mg/kg/day groups; however, a dose response-relationship was not present, values were within historical control range, and the lower total duration of movement in 15 and 50 mg/kg/day males was not considered to be test substance-related. There were no test substance-related effects on duration of movement or number of movements in females administered 15 or 50 mg/kg/day.

C. Neurobehavioral Evaluation Conclusions

Test substance-related decreases in hindlimb grip strength (males only) and motor activity (males and females) occurred at 200 mg/kg/day. There were no effects at any dosage in P₁ males or females on forelimb grip strength, hindlimb foot splay, rearing, or any of the other behavioral parameters evaluated in the FOB.

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A. Hematology (Tables 33-34, Appendix GG)

There were no adverse changes in hematologic parameters. The following statistically significant change in mean hematologic parameters was not considered to be adverse:

- Platelets were mildly decreased in males dosed with 200 mg/kg/day (mean was 79% of control group mean; statistically significant). Numerical platelet counts were only available on 2 of the rats in this group (Animal Numbers 753 and 765). The platelet counts in these 2 males were lower than those of any other male on this study. The 2 other males (Animal Numbers 754 and 775) had inaccurate and low platelet counts due to platelet clumps. Historical platelet counts from approximate age-matched controls range from 925-1447 $\times 10^3/\mu\text{L}$ (mean of 1149 $\times 10^3/\mu\text{L}$). The platelet count of 1 of the 2 males dosed with 200 mg/kg/day was minimally below the historical range for individual values, while the other one was just inside the range. The minimally decreased platelet counts in this 1 male was of uncertain relationship to treatment; regardless of the relationship to treatment, this effect was not adverse, due to the small magnitude of change.

B. Coagulation (Tables 35-36, Appendix GG)

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

C. Clinical Chemistry (Tables 37-38, Appendix GG)

There were no adverse changes in clinical chemistry parameters in male or female rats. The following changes in mean clinical chemistry parameters were not adverse:

- Cholesterol concentration was minimally increased in some males dosed with 15, 50, or 200 mg/kg/day (not statistically significant at any dose, and not dose-related across the treatment groups). Cholesterol concentrations of individual males generally fell in the upper part of the range of control values. In addition, three males in each treated group were above the highest individual male in the concurrent control group. Therefore, increased cholesterol concentrations in some males of all three treated groups were considered to be treatment-related. However, due to the minimal degree of change, these effects were considered to be non-adverse.
- Cholesterol concentration was also minimally increased in some females dosed with 15 or 50 mg/kg/day, and in all females dosed with 200 mg/kg/day (statistically significant only at 200 mg/kg/day). Cholesterol concentrations of most of the rats treated with test substance

were greater than the highest individual female in the concurrent control group. Therefore, increased cholesterol concentrations in most females of all 3 treated groups were considered to be treatment-related. However, due to the minimal degree of change, these effects were considered to be non-adverse.

D. Clinical Pathology Conclusions

In conclusion, administration of the test substance to rats resulted in mildly decreased platelet counts in males dosed with 200 mg/kg/day, and minimally increased cholesterol in some males and females dosed with 15, 50, or 200 mg/kg/day. None of the effects were considered to be adverse.

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ANATOMICAL PATHOLOGY

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A. Mortality
 (Appendix II)

One male and 8 females died before their scheduled sacrifice. The male death (200 mg/kg/day) and 1 female death (200 mg/kg/day) were dosing accidents; 1 female death (200 mg/kg/day) was possibly test substance-related; and 6 female deaths (15 mg/kg/day, 50 mg/kg/day, and 200 mg/kg/day) were due to test substance-related dystocia.

The individual male death (200 mg/kg/day, Animal Number 758) was accidentally killed in a dosing accident. The cause of death was determined by gross findings (tracheal fluid) and microscopic observations (tracheal exudates and hemorrhage).

The incidence of unscheduled female deaths (found dead, sacrificed *in extremis* [i.e., unscheduled sacrifice], and accidentally killed) was dose-related and included 0/10, 1/10, 2/10, and 5/10 females in the 0, 15, 50, and 200 mg/kg/day dose groups, respectively. The causes of death were, based on gross and microscopic pathology, recorded as dystocia (15 mg/kg/day - Animal Number 820, 50 mg/kg/day - Animal Numbers 795 and 826, 200 mg/kg/day - Animal Numbers 813, 817, and 818), undetermined (200 mg/kg/day - Animal Number 792), and dosing accident (200 mg/kg/day - Animal Number 810). Therefore, the incidence of dystocia-related deaths was 0/10, 1/10, 2/10, and 3/10 in the 0, 15, 50, and 200 mg/kg/day dose groups, respectively. The 200 mg/kg/day female with an “undetermined” cause of death was found dead on day 16 with severe autolysis. This death was interpreted to be most likely test substance-related.

B. Organ Weight Data
 (Tables 39-40, Appendix HH)

A test substance-related increase in mean liver weights parameters was observed in male and female rats given 50 mg/kg/day or more of the test substance.

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

Dose (mg/kg/day):	Male				Female			
	0	15	50	200	0	15	50	200
Final Body Weight (grams)	422	430	411	380	306	304	299	306
<u>Liver</u>								
absolute wt. (grams)	15.87	18.06	18.17 ^a	21.80 ^{*a}	13.15	13.18	14.14 ^a	15.69 ^{*a}
liver wt./body wt. x 100	3.82	4.07	4.43 ^{*a}	5.53 ^{*a}	4.24	4.39	4.69 ^a	5.12 ^{*a}
liver wt./brain wt. x 100	777	868	913 ^a	1069 ^{*a}	658	667	749 ^a	830 ^{*a}

Statistics were run on non-rounded weight data.

* Pair-wise test (Dunnett/Tamhane-Dunnett) significant.

a Interpreted to be test substance-related effects.

In males, mean relative (liver/body) liver weights were increased 7%, 16%, and 45% in rats given 15, 50, and 200 mg/kg/day, respectively, as compared to control values. In females, mean relative (liver/body) liver weights were increased 3%, 11%, and 21% in rats given 15, 50, and 200 mg/kg/day, respectively, as compared to control values. The increased values were statistically significant in both sexes at 200 mg/kg/day (absolute and relative weights) and in males at 50 mg/kg/day (relative weight). Increased liver weight parameters were considered test substance-related in males and females given 50 and 200 mg/kg/day. The liver weight effect correlated with hepatocellular hypertrophy observed microscopically in males given ≥ 50 mg/kg/day and females given 200 mg/kg/day (see Microscopic Findings).

All other differences in organ weight values were considered unrelated to test substance administration.

C. Gross Observations
 (Tables 41-44, Appendix II)

There were no test substance-related gross observations in this study. All gross observations at necropsy were interpreted to be either naturally occurring background lesions that are typical of rats of this age and stock or gross lesions associated with dosing accidents or dystocia.

D. Microscopic Findings
 (Tables 45-48; Appendix II)

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

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

Dose (mg/kg/day):	<u>Male</u>				<u>Female</u>			
	0	15	50	200	0	15	50	200
<u>Liver</u>								
Tissues examined:	10	10	10	10	10	10	10	10
Hypertrophy, hepatocellular, centrilob.	0	0	3 ^a	6 ^a	0	0	0	10 ^a
<u>Thyroid</u>								
Tissues examined ^b :	5	5	5	6	5	7	7	10
Hypertrophy, follicular cell	0	0	0	4 ^a	0	0	0	1 ^a

a Interpreted to be test substance-related effects.

b Includes the first 5 rats/sex/dose sacrificed by design (SD), early decedents, and one additional SD female rat (15 mg/kg/day).

Liver

Hypertrophy of centrilobular hepatocytes was observed in the livers of 6/10 males and 10/10 females given 200 mg/kg/day and 3/10 males given 50 mg/kg/day of the test substance. In all cases, the hepatocellular hypertrophy was graded as minimal (grade 1 out of 4). Microscopically, hepatocellular hypertrophy was characterized by an increased amount of finely granular eosinophilic cytoplasm within centrilobular hepatocytes. There was no histomorphologic evidence of hepatocellular damage, and hepatic serum enzyme levels were not elevated (see Clinical Pathology section). Thus, hepatocellular hypertrophy (and the associated increase in liver weights) was considered a test substance-related pharmacological response to the metabolism of a xenobiotic and not adverse.

Thyroid

Hypertrophy of thyroid follicular cells was present in 4/6 males and 1/9 females given 200 mg/kg/day of the test substance, in which the thyroid was examined. In all cases, the follicular cell hypertrophy was graded as minimal. Although the incidence of minimal hypertrophy observed in the high-dose females (1/9) was within the range of normal, it was considered to be most likely treatment related since there was no hypertrophy observed in any other group in this study and the effect in males was unequivocal. Follicular cell hypertrophy was characterized by an increase in the height of the columnar epithelium of the thyroid follicles. Follicles were decreased in size, irregular in shape, and contained decreased amounts of normal pink colloid.

An increase in the incidence and severity of thyroid follicular cell hypertrophy is indicative of altered thyroid gland homeostasis. Although the follicular cell response observed in this study (minimal hypertrophy) was within the range of normal physiological response, the effect is potentially proliferative and adverse, especially in the rat. Since follicular cell hypertrophy is consistent with several different mechanisms of altered thyroid gland homeostasis, the specific cause of the hypertrophic response in this study is not clear. In rats, a common cause of thyroid follicular cell hypertrophy is an increase in the rate of hepatic thyroxine (T_4) glucuronidation and subsequent biliary excretion.⁽¹⁸⁾ An increased rate of T_4 excretion results in lower T_4 blood levels which triggers an increase in the release of pituitary-derived thyroid stimulating hormone (TSH), resulting in thyroid follicular cell hypertrophy. Many inducers of hepatic cytochrome P₄₅₀ isoenzymes in the rat are known to secondarily cause thyroid follicular cell hypertrophy by this mechanism. In this study, the presence of test substance-related hepatocellular hypertrophy in the males and females demonstrates that hepatocellular enzyme systems have been induced and that T_4 excretion may have been secondarily increased. Due to differences in T_4 half-life, thyroglobulin binding, and the ease of UDP-glucuronyl-transferase induction, rats are much more susceptible than humans to secondary thyroid follicular cell hypertrophy.⁽¹⁸⁾

Other

All other microscopic observations in this study were: a) known to occur naturally in rats of this stock and age; b) considered non-specific effects of morbidity (e.g., lymphoid necrosis and depletion in the thymus, spleen and lymph nodes); or c) related to dosing accidents (e.g., tracheal inflammation and exudates). There were no treatment-related microscopic findings in the stomachs of any rats.

E. Anatomic Pathology Conclusions

Exposure to 15, 50, and 200 mg/kg/day of the test substance for 34 (males) or approximately 45 (females) days, produced a dose-related increase in mortality, liver weights, hepatocellular hypertrophy, and thyroid follicular cell hypertrophy.

Test substance-related dystocia resulted in the death of 1/10, 2/10, and 3/10 females given 15, 50, and 200 mg/kg/day, respectively. An additional high-dose female died on test day 16, probably of test substance-related toxicity. There was no test substance-related mortality in male rats.

Mean liver weight parameters were increased in male and female rats given 50 mg/kg/day or more of the test substance. An associated minimal hypertrophy of centrilobular hepatocytes was observed in the livers of 6/10 males and 10/10 females given 200 mg/kg/day and 3/10 males given 50 mg/kg/day of the test substance. Both the increased liver weights and the hepatocellular hypertrophy were considered to be indicative of the pharmacological induction of hepatocellular enzymes by a xenobiotic and were therefore not adverse.

Hypertrophy of thyroid follicular cells was present in 4/6 males and 1/9 females given 200 mg/kg/day of the test substance, in which the thyroid was examined. While the thyroid follicular cell hypertrophy was most likely secondary to the hepatic enzyme induction, it was regarded as potentially adverse.

CONCLUSIONS

Under the conditions of this study, a no-observed-effect level (NOEL)^a was not determined for systemic toxicity in P₁ rats, based on mortality and clinical signs of toxicity associated with dystocia, and reduced body weight gain in females during gestation at all dose levels. The NOEL for F₁ offspring was 15 mg/kg/day, based on reduced pup weights during lactation at 50 and 200 mg/kg/day. A NOEL for reproductive parameters was not established, based on the occurrence of dystocia in P₁ females at all dose levels.

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^a The NOEL for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Thus, for this study, the NOEL is equivalent to the NOEL as defined by the United States Environmental Protection Agency⁽¹⁹⁾ and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union.⁽²⁰⁾

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TABLES

TABLES

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating period
Test Days 15-34 = Cohabitation period

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Abbreviations

BW = Body Weight
BWG = Body Weight Gain
FC = Food Consumption
FE = Food Efficiency
G = Gestation
N/n = Number

CLINICAL PATHOLOGY TABLES

Notes:

Summary of Hematology Values

Summary of Coagulation Values

Summary of Clinical Chemistry Values

Groups with identical values may vary in statistical significance, because tabulated statistics are rounded to fewer decimal places than the values used for statistical determination.

TABLES

EXPLANATORY NOTES (Continued)

CLINICAL PATHOLOGY TABLES

Abbreviations

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Summary of Hematology Values

- RBC - red blood cell count
- HGB - hemoglobin
- HCT - hematocrit
- MCV - mean corpuscular volume
- MCH - mean corpuscular hemoglobin
- MCHC - mean corpuscular hemoglobin concentration
- RDW - red cell distribution width
- ARET - absolute reticulocyte count
- PLT - platelet count
- WBC - white blood cell count
- ANEU - absolute neutrophil (all forms)
- ALYM - absolute lymphocyte
- AMON - absolute monocyte
- AEOS - absolute eosinophil
- ABAS - absolute basophil
- ALUC - absolute large unstained cell

Summary of Coagulation Values

- PT - prothrombin time
- APTT - activated partial thromboplastin time

Summary of Clinical Chemistry Values

- AST - aspartate aminotransferase
- ALT - alanine aminotransferase
- BUN - urea nitrogen
- CREA - creatinine
- CHOL - cholesterol
- GLUC - glucose
- TP - total protein
- ALB - albumin
- TBA - total bile acids
- NA - sodium
- K - potassium

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TABLE 1

SUMMARY OF CLINICAL OBSERVATIONS IN P₁ MALE RATS

OBSERVATION	GROUP: DOSE (MG/KG/DAY): N:	NUMBER OF RATS WITH GIVEN SIGN			
		I-0	III-0	V-0	VII-0
		0	15	50	200
		10	10	10	10
ALOPECIA		1	0	0	0
CONVULSIONS		0	0	0	1
DEHYDRATED		0	0	0	1
DIARRHEA		1	0	0	3
HUNCHED OVER		0	0	0	2
IRREGULAR RESPIRATION		0	0	0	1
LUNG NOISE		0	0	0	3 [^]
STAINED FUR ^a		0	0	1	6 [^]

a Includes: Stained chin, stained face, stained perineum, stained underbody.

Statistical Analysis: Statistical significance is indicated by the following
 (p < 0.05):

[^] Cochran-Armitage test for trend

* Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

@ Nonparametric comparison to control (Dunn's) significant

Trend test (Jonckheere-Terpstra) significant

~ next to control mean indicates no analyses were performed

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TABLE 2

SUMMARY OF CLINICAL OBSERVATIONS IN P₁ FEMALE RATS DURING PREMATING
 (Includes Data Collected After Premating (Days 1-15),
 And Not Included In Gestation For Group VIII-0)

NUMBER OF RATS WITH GIVEN SIGN

	GROUP:	II-0	IV-0	VI-0	VIII-0
DOSE (MG/KG/DAY):		0	15	50	200
N:		10	10	10	10
OBSERVATION					
COLORED DISCHARGE LEFT EYE(S)		0	1	0	0
DEHYDRATED		0	0	0	1
DIARRHEA		0	0	0	2
GASPING ^a		0	0	0	1 ^a
HUNCHED OVER		0	0	0	1
HYPERREACTIVE		0	0	0	1
IRREGULAR RESPIRATION		0	0	0	1
STAINED FUR ^b		0	0	0	4 ^{b,^}
WET FUR ^c		0	0	0	1

a Observed on Day 17 after Premating (Days 1-15) and not included in Gestation.

b Includes: Stained chin, stained face, stained perineum, stained underbody.
 Stained face brown observed for one animal on Days 28-29 after Premating
 (Days 1-15) and not included in Gestation.

c Includes: Wet chin, wet underbody.

Statistical Analysis: Statistical significance is indicated by the following
 (p < 0.05):

^ Cochran-Armitage test for trend

* Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

@ Nonparametric comparison to control (Dunn's) significant

Trend test (Jonckheere-Terpstra) significant

~ next to control mean indicates no analyses were performed

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TABLE 3

SUMMARY OF CLINICAL OBSERVATIONS IN P₁ FEMALE RATS DURING GESTATION

OBSERVATION	GROUP: DOSE (MG/KG/DAY): N:	NUMBER OF RATS WITH GIVEN SIGN			
		II-0	IV-0	VI-0	VIII-0
		0	15	50	200
		10	10	8	7
ALOPECIA		3	1	4	0
DEHYDRATED		0	1	1	0
DIARRHEA		0	1	0	1
DYSTOCIA		0	1	1	1
IMMOBILE		0	0	1	0
IRREGULAR RESPIRATION		0	0	0	2 [^]
LETHARGY		0	1	0	1
LUNG NOISE		0	0	1	3 [^]
PALLOR		0	0	1	0
PTOSIS		0	0	1	0
STAINED FUR ^a		0	2	1	3 [^]
WET FUR ^b		0	0	1	2 [^]

- a Includes: Stained abdomen, stained face, stained nose, stained perineum, stained underbody.
 b Includes: Wet perineum, wet underbody.

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- [^] Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

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

TABLE 4

SUMMARY OF CLINICAL OBSERVATIONS IN P₁ FEMALE RATS DURING LACTATION

	NUMBER OF RATS WITH GIVEN SIGN			
	II-0	IV-0	VI-0	VIII-0
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSE (MG/KG/DAY):	0	15	50	200
N:	10	9	8	5
OBSERVATION				
ALOPECIA	3	1	2	1
DISCHARGE VAGINAL OPENING	0	1	0	0
IRREGULAR RESPIRATION	0	0	0	1
LUNG NOISE	0	0	0	1
STAINED FUR ^a	0	1	1	1

a Includes: Stained abdomen, stained face.

Statistical Analysis: Statistical significance is indicated by the following
 (p < 0.05):

^ Cochran-Armitage test for trend

* Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

@ Nonparametric comparison to control (Dunn's) significant

Trend test (Jonckheere-Terpstra) significant

~ next to control mean indicates no analyses were performed

TABLE 5

SUMMARY OF DETAILED CLINICAL OBSERVATIONS IN P₁ MALE RATS

	GROUP:	NUMBER OF RATS WITH GIVEN SIGN			
		I-0	III-0	V-0	VII-0
DOSE (MG/KG/DAY):		0	15	50	200
N:		10	10	10	10
OBSERVATION					
ALOPECIA		1	0	0	0
DEHYDRATED		0	0	0	1
IRREGULAR RESPIRATION		0	0	0	1
LUNG NOISE		0	0	0	1
STAINED PERINEUM		0	0	0	2

Statistical Analysis: Statistical significance is indicated by the following
 (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

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TABLE 6

SUMMARY OF DETAILED CLINICAL OBSERVATIONS IN P₁ FEMALE RATS
 DURING PREMATING

	GROUP:	NUMBER OF RATS WITH GIVEN SIGN			
		II-0	IV-0	VI-0	VIII-0
DOSE (MG/KG/DAY):		0	15	50	200
N:		10	10	10	10
OBSERVATION					
HYPERREACTIVE		0	0	0	1
STAINED FACE		0	0	0	1

Statistical Analysis: Statistical significance is indicated by the following
 (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

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TABLE 7

SUMMARY OF DETAILED CLINICAL OBSERVATIONS IN P₁ FEMALE RATS
 DURING GESTATION

	GROUP:	NUMBER OF RATS WITH GIVEN SIGN			
		II-0	IV-0	VI-0	VIII-0
DOSE (MG/KG/DAY):		0	15	50	200
N:		10	10	8	7
OBSERVATION					
ALOPECIA		1	1	4	0
IRREGULAR RESPIRATION		0	0	0	1
LUNG NOISE		0	0	0	2 [^]

Statistical Analysis: Statistical significance is indicated by the following
 (p < 0.05):

- [^] Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

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TABLE 8

SUMMARY OF DETAILED CLINICAL OBSERVATIONS IN P₁ FEMALE RATS
 DURING LACTATION

	GROUP: DOSE (MG/KG/DAY): N:	NUMBER OF RATS WITH GIVEN SIGN			
		II-0	IV-0	VI-0	VIII-0
		0	15	50	200
		9	8	8	4
OBSERVATION					
ALOPECIA		3	1	2	0
DISCHARGE VAGINAL OPENING		0	1	0	0
IRREGULAR RESPIRATION		0	0	0	1
LUNG NOISE		0	0	0	1
STAINED FUR		0	0	1	1

a Includes: Stained abdomen, stained face.

Statistical Analysis: Statistical significance is indicated by the following
 (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

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TABLE 9
 MEAN BODY WEIGHTS (grams) OF P₁ MALE RATS

Group: Dose (mg/kg/day)	I-0 0	III-0 15	V-0 50	VII-0 200
Test				
BW:Day 1	331.1 19.3 (10)	330.1 20.2 (10)	330.8 31.9 (10)	330.1 12.4 (10)
BW:Day 8	360.0 25.8 (10)	363.0 29.1 (10)	354.6 35.9 (10)	331.0 17.8 (9)
BW:Day 15	376.5 25.6 (10)	379.0 30.2 (10)	373.1 42.2 (10)	346.0 25.8 (9)
BW:Day 22	392.7 28.0 (10)	401.6 34.7 (10)	390.4 47.0 (10)	360.2 33.7 (9)
BW:Day 29	415.7 35.0 (10)	423.2 38.6 (10)	410.8 50.5 (10)	382.1 40.8 (9)
BW:Day 34	422.4 34.9 (10)	430.1 41.4 (10)	411.0 50.3 (10)	380.5 48.3 (9)
Data summarized as:	Mean	Standard Deviation (n)		

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: Test Day 15 = Last day of premating period that data were recorded.

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TABLE 10
 MEAN BODY WEIGHT GAINS (grams) OF P₁ MALE RATS

Group: Dose (mg/kg/day)	I-0 0	III-0 15	V-0 50	VII-0 200
Test				
BWG:Day 1-8	28.9 10.5(10)	33.0 9.9(10)	23.7 8.0(10)	0.9* 12.4(9)
BWG:Day 8-15	16.5 12.3(10)	16.0 10.7(10)	18.6 9.7(10)	14.9 17.7(9)
BWG:Day 15-22	16.2 6.0(10)	22.5 7.3(10)	17.3 7.8(10)	14.2 19.4(9)
BWG:Day 22-29	23.0 9.8(10)	21.6 11.4(10)	20.4 9.1(10)	21.9 13.5(9)
BWG:Day 29-34	6.7 4.5(10)	7.0 12.9(10)	0.2 7.0(10)	-1.6 10.7(9)
BWG:Day 1-15	45.4 16.6(10)	49.0 13.1(10)	42.3 14.3(10)	15.8* 24.0(9)
BWG:Day 1-34	91.3 24.0(10)	100.1 23.8(10)	80.2 22.8(10)	50.3@ 51.4(9)
Data summarized as:	Mean	Standard Deviation (n)		

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: Test Day 15 = Last day of prenatting period that data were recorded.

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TABLE 11
 MEAN BODY WEIGHTS (grams) OF P₁ FEMALE RATS DURING PREMATING

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day)	0	15	50	200
Test				
BW:Day 1	234.6 9.4 (10)	230.8 10.5 (10)	231.3 9.5 (10)	232.8 11.6 (10)
BW:Day 8	241.4 10.5 (10)	240.2 13.7 (10)	241.9 8.9 (10)	235.1 18.1 (10)
BW:Day 15	241.7 10.1 (10)	244.1 18.0 (10)	247.7 11.1 (10)	238.0 24.5 (10)

Data summarized as: Mean
 Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: Test Day 15 = Last day of prematuring period that data were recorded.

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TABLE 12
 MEAN BODY WEIGHT GAINS (grams) OF P₁ FEMALE RATS DURING PREMATING

Group: Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
Test				
BWG:Day 1-8	6.8 6.7 (10)	9.4 6.3 (10)	10.7 6.7 (10)	2.3 10.6 (10)
BWG:Day 8-15	0.3 8.5 (10)	3.9 7.8 (10)	5.8 6.3 (10)	2.9 15.2 (10)
BWG:Day 1-15	7.1 5.0 (10)	13.3 12.1 (10)	16.4 7.5 (10)	5.2 19.3 (10)

Data summarized as: Mean
 Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: Test Day 15 = Last day of prematuring period that data were recorded.

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TABLE I3
 MEAN BODY WEIGHTS (grams) OF P₁ FEMALE RATS DURING GESTATION

Group: Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
Test				
BW:Day 0	249.8 11.7 (10)	251.8 13.7 (10)	250.1 12.3 (8)	250.3 15.6 (7)
BW:Day 7	284.2 14.4 (10)	285.2 19.6 (10)	279.7 16.2 (8)	276.8 15.7 (7)
BW:Day 14	315.3 16.0 (10)	314.8 21.1 (10)	308.9 21.4 (8)	309.3 16.4 (7)
BW:Day 21	394.5 23.2 (10)	373.2 40.3 (10)	372.1 32.4 (8)	355.8 40.0 (7)

Data summarized as: Mean

Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: This table contains data from animals with evidence of copulation that delivered a litter.

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TABLE 14
 MEAN BODY WEIGHT GAINS (grams) OF P₁ FEMALE RATS DURING GESTATION

Group: Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
Test				
BWG:Day 0-7	34.3 6.5(10)	33.4 6.6(10)	29.7 11.5(8)	26.5 5.7(7)
BWG:Day 7-14	31.2 7.4(10)	29.6 5.3(10)	29.2 8.7(8)	32.6 5.3(7)
BWG:Day 14-21	79.1 15.6(10)	58.4 30.2(10)	63.2 21.8(8)	46.4 32.8(7)
BWG:Day 0-21	144.6 17.4(10)	121.4 32.7(10)	122.0 30.1(8)	105.5@ 34.7(7)

Data summarized as: Mean

Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: This table contains data from animals with evidence of copulation that delivered a litter.

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TABLE 15
 MEAN BODY WEIGHTS (grams) OF P₁ FEMALE RATS DURING LACTATION

Group: Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
Test				
BW:Day 0	299.1 17.1 (10)	291.5 30.4 (9)	283.9 23.4 (8)	289.3 17.3 (5)
BW:Day 4	305.6 17.3 (10)	309.1 23.7 (8)	299.1 18.1 (8)	305.6 15.7 (5)

Data summarized as:

Mean
 Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnnett/Tamhane-Dunnnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

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TABLE 16
 MEAN BODY WEIGHT GAINS (grams) OF P₁ FEMALE RATS DURING LACTATION

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day)	0	15	50	200
Test				
BWG:Day 0-4	6.5	14.5	15.2	16.3
	16.6(10)	14.7(8)	11.9(8)	13.2(5)

Data summarized as: Mean
 Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following ($p < 0.05$):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

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TABLE 17
 MEAN DAILY FOOD CONSUMPTION (grams/day) OF P₁ MALE RATS DURING PREMATING

Group: Dose (mg/kg/day)	I-0 0	III-0 15	V-0 50	VII-0 200
Test				
FC:Day 1-8	25.7 3.3(10)	26.6 1.7(10)	24.9 3.1(10)	18.2* 2.6(9)
FC:Day 8-15	25.1 2.7(10)	24.7 2.5(10)	24.5 2.2(10)	23.9 2.4(9)
FC:Day 1-15	25.4 2.8(10)	25.6 1.8(10)	24.7 2.5(10)	21.1* 2.2(9)

Data summarized as: Mean Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):
 ^ Cochran-Armitage test for trend
 * Parametric comparison to control (Dunnett/Tamhane-Dunnnett) significant
 @ Nonparametric comparison to control (Dunn's) significant
 # Trend test (Jonckheere-Terpstra) significant
 ~ next to control mean indicates no analyses were performed
 Note: Test Day 15 = Last day of premating period that data were recorded.

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TABLE 18

MEAN DAILY FOOD EFFICIENCY (grams weight gain/grams food consumed) OF P₁ MALE RATS DURING PREMATING

Group: Dose (mg/kg/day)	I-0 0	III-0 15	V-0 50	VII-0 200
Test				
FE:Day 1-8	0.158 0.041 (10)	0.175 0.047 (10)	0.135 0.036 (10)	-0.001* 0.087 (9)
FE:Day 8-15	0.091 0.064 (10)	0.089 0.053 (10)	0.106 0.048 (10)	0.085 0.104 (9)
FE:Day 1-15	0.126 0.038 (10)	0.135 0.030 (10)	0.121 0.032 (10)	0.049@ 0.075 (9)

Data summarized as: Mean
 Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
 - * Parametric comparison to control (Dunnett/Tamhane-Dunnnett) significant
 - @ Nonparametric comparison to control (Dunn's) significant
 - # Trend test (Jonckheere-Terpstra) significant
 - ~ next to control mean indicates no analyses were performed
- Note: Test Day 15 = Last day of premating period that data were recorded.

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TABLE 19
 MEAN DAILY FOOD CONSUMPTION (grams) OF P₁ FEMALE RATS DURING PREMATING

Group: Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
Test				
FC:Day 1-8	18.0 1.8(10)	18.5 2.6(10)	17.9 1.7(10)	15.8 2.3(10)
FC:Day 8-15	19.1 1.5(10)	19.2 3.0(10)	18.6 1.0(10)	18.2 2.6(10)
FC:Day 1-15	18.5 1.4(10)	18.9 2.8(10)	18.2 0.9(10)	17.0 2.1(10)

Data summarized as: Mean
 Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: Test Day 15 = Last day of prematuring period that data were recorded.

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TABLE 20

MEAN DAILY FOOD EFFICIENCY (grams weight gain/grams food consumed) OF P₁ FEMALE RATS DURING PREMATING

Group: Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
Test				
FE:Day 1-8	0.054 0.052 (10)	0.069 0.040 (10)	0.086 0.058 (10)	0.014 0.106 (10)
FE:Day 8-15	0.000 0.062 (10)	0.023 0.056 (10)	0.044 0.050 (10)	0.008 0.144 (10)
FE:Day 1-15	0.027 0.018 (10)	0.046 0.038 (10)	0.065@ 0.031 (10)	0.014 0.100 (10)

Data summarized as: Mean
 Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: Test Day 15 = Last day of prematuring period that data were recorded.

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TABLE 21
 MEAN DAILY FOOD CONSUMPTION (grams) OF P₁ FEMALE RATS DURING GESTATION

Group: Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
Test				
FC:Day 0-7	25.4 2.9(10)	24.9 2.9(10)	23.2 3.5(8)	22.4 2.3(7)
FC:Day 7-14	27.0 2.1(10)	26.1 3.2(10)	23.8* 2.3(8)	24.8 1.4(7)
FC:Day 14-21	28.1 2.1(10)	26.6 2.8(10)	25.3 2.5(8)	23.8* 4.9(7)
FC:Day 0-21	26.8 2.1(10)	25.9 2.8(10)	24.1 2.4(8)	23.7* 2.0(7)

Data summarized as: Mean
 Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: This table contains data from animals with evidence of copulation that delivered a litter.

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TABLE 22

MEAN FOOD EFFICIENCY (grams weight gain/grams food consumed) OF P₁ FEMALE RATS DURING GESTATION

Group: Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
Test				
FE:Day 0-7	0.192 0.021 (10)	0.191 0.022 (10)	0.176 0.062 (8)	0.168 0.031 (7)
FE:Day 7-14	0.164 0.031 (10)	0.162 0.024 (10)	0.174 0.045 (8)	0.187 0.029 (7)
FE:Day 14-21	0.403 0.075 (10)	0.306 0.150 (10)	0.353 0.101 (8)	0.249 0.176 (7)
FE:Day 0-21	0.257 0.025 (10)	0.222 0.053 (10)	0.240 0.048 (8)	0.208 0.056 (7)

Data summarized as: Mean
 Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: This table contains data from animals with evidence of copulation that delivered a litter.

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TABLE 23
 MEAN DAILY FOOD CONSUMPTION (grams) OF P₁ FEMALE RATS DURING LACATION

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day)	0	15	50	200
Test				
FC:Day 0-4	27.1	27.4	32.1	33.5
	5.8(10)	7.6(8)	6.5(8)	4.9(5)

Data summarized as: Mean
 Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: This table contains data from animals with evidence of copulation that delivered a litter.

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TABLE 24

MEAN FOOD EFFICIENCY (grams weight gain/grams food consumed) OF P₁ FEMALE RATS DURING LACTATION

Group: Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
Test				
FE:Day 0-4	0.063 0.147 (10)	0.177 0.217 (8)	0.116 0.100 (8)	0.114 0.081 (5)

Data summarized as: Mean
 Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

- ^ Cochran-Armitage test for trend
- * Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant
- @ Nonparametric comparison to control (Dunn's) significant
- # Trend test (Jonckheere-Terpstra) significant
- ~ next to control mean indicates no analyses were performed

Note: This table contains data from animals with evidence of copulation that delivered a litter.

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TABLE 25

SUMMARY OF REPRODUCTIVE INDICES: P₁ GENERATION

MATERNAL GROUP: DOSE (MG/KG/DAY):	II-0 0	IV-0 15	VI-0 50	VIII-0 200
MATING INDEX (%)^a (No. copulated/cohoused)	100.0 (10/10)	100.0 (10/10)	100.0 (10/10)	100.0 (8/8)
FERTILITY INDEX (%)^b (No. pregnant/copulated)	100.0 (10/10)	100.0 (10/10)	100.0 (8/8)	100.0 (8/8)
GESTATION LENGTH (days)^c (No. in group)	22.2 (10)	22.6 (9)	22.2 (6)	22.4 (5)
NUMBER OF IMPLANTATION SITES per pregnant female	13.9	13.9	14.4	13.0
Standard Deviation (No. in group)	0.9(10)	1.1(10)	1.3(10)	2.3(8)
IMPLANTATION EFFICIENCY (%)^d Standard Deviation (No. in group)	90.1 9.2(10)	78.8 19.1(9)	94.3 7.8(8)	96.0 8.9(5)
NUMBER OF CORPORA LUTEA Standard Deviation (No. in group)	14.4 1.1(10)	14.6 1.4(10)	14.9 1.3(10)	13.9 1.6(7)

^a Evidence of copulation = Intra vaginal copulation plug, sperm in vaginal lavage, implantations observed at necropsy, or delivery of a litter.

^b Pregnant = Delivery of a litter or implantation sites at necropsy.

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

^d Number of pups born/number of implantation sites X 100.

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

[^] Cochran-Armitage test for trend

* Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

@ Nonparametric comparison to control (Dunn's) significant

Trend test (Jonckheere-Terpstra) significant

~ next to control mean indicates no analyses were performed

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TABLE 26

MEAN PUP NUMBERS AND SURVIVAL: F₁ GENERATION

MATERNAL GROUP: DOSE (MG/KG/DAY): N:	II-0 0 10	IV-0 15 9	VI-0 50 8	VIII-0 200 5
MEAN NUMBER OF PUPS/LITTER				
Born	12.5	11.0	13.4	13.2
Born Alive	11.9	10.1	13.4	13.0
Day 4	11.0	9.8	13.1	11.8
MEAN NUMBER OF MALE PUPS/LITTER				
Born	6.1	5.7	6.1	6.8
Born Alive	5.7	5.2	6.1	6.5
Day 4	5.1	5.9	6.0	6.0
MEAN NUMBER OF FEMALE PUPS/LITTER				
Born	6.4	5.0	7.3	6.4
Born Alive	6.2	4.9	7.3	6.2
Day 4	5.9	4.6	7.1	5.8
SURVIVAL (%)				
Sex Ratio (males)	0.49	0.54	0.45	0.53
Gestation Index ^a	100.0	88.9	100.0	100.0
Mean % Born Alive	95.1	86.6	100.0	98.8
0-4 Day Viability	91.1	85.2	98.3	90.8

a Percent litters delivered having at least one live pup.

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

^ Cochran-Armitage test for trend

* Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

@ Nonparametric comparison to control (Dunn's) significant

Trend test (Jonckheere-Terpstra) significant

~ next to control mean indicates no analyses were performed

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

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TABLE 27

SUMMARY OF PUP CLINICAL OBSERVATIONS: F₁ GENERATION

MATERNAL GROUP: DOSE (MG/KG/DAY):	II-0 0	IV-0 15	VI-0 50	VIII-0 200
OBSERVATIONS				
TOTAL NUMBER OF SIGNS	0	0	0	0
NUMBER OF LITTERS AFFECTED	0	0	0	0
TOTAL NUMBER OF LITTERS	10	8	8	5

Statistical Analysis: Statistical significance is indicated by the following
(p < 0.05):

^ Cochran-Armitage test for trend

* Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

@ Nonparametric comparison to control (Dunn's) significant

Trend test (Jonckheere-Terpstra) significant

~ next to control mean indicates no analyses were performed

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TABLE 28

MEAN PUP WEIGHTS: F₁ GENERATION

MATERNAL GROUP:	II-0	IV-0	VI-0	VIII-0
DOSE (MG/KG/DAY):	0	15	50	200
N:	10	8	8	5
	<u>MEAN PUP WEIGHTS (grams)</u>			
Day 0	6.5 (0.6)	6.4 (1.0)	6.3 (0.4)	6.1 (0.7)
Day 4	10.6 (1.0)	10.0 (2.1)	9.9 (1.0)	9.7 (1.2)
	<u>MEAN MALE PUP WEIGHTS (grams)</u>			
Day 0	6.8 (0.6)	6.8 (1.0) ^a	6.4 (0.3)	6.3 (0.7)
Day 4	10.9 (0.9)	11.0 (1.5)	10.0 (1.0)	9.9 (1.4)
	<u>MEAN FEMALE PUP WEIGHTS (grams)</u>			
Day 0	6.3 (0.6)	6.3 (1.0) ^a	6.2 (0.4)	5.8 (0.6)
Day 4	10.4 (1.1)	9.8 (2.5)	9.8 (1.0)	9.3 (1.0)

Data summarized as: Mean (Standard Deviation)

a N = 7; One missexed litter was excluded.

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

! Exact Mann-Whitney with a Bonferroni-Holm adjustment
 (Covariates: litter size, sex ratio)

Note: Statistical analyses were conducted on the combined pup weights. Male and female data are presented for information only.

TABLE 29

MEAN FORELIMB AND HINDLIMB GRIP STRENGTH, HINDLIMB SPLAY, AND REARING IN P₁ RATS

GROUP	DOSE (mg/kg/day)	FORELIMB GRIP STRENGTH (kg) (Mean of Three Trials)		HINDLIMB GRIP STRENGTH (kg)		HINDLIMB SPLAY (cm)	REARING (Number)
		FORELIMB GRIP STRENGTH (kg)	HINDLIMB GRIP STRENGTH (kg)	FORELIMB GRIP STRENGTH (kg)	HINDLIMB GRIP STRENGTH (kg)		
MALE							
I-0	0	0.93(0.23)	0.59(0.04)	0.59(0.04)	0.59(0.04)	8.3(2.2)	4(3)
III-0	15	1.02(0.22)	0.62(0.11)	0.62(0.11)	0.62(0.11)	7.9(1.1)	4(2)
V-0	50	0.99(0.13)	0.58(0.10)	0.58(0.10)	0.58(0.10)	9.7(2.0)	2(2)
VII-0	200	0.86(0.16)	0.42(0.12)&	0.42(0.12)&	0.42(0.12)&	7.8(2.8)	6(3)
FEMALE							
II-0	0	0.73(0.07)	0.49(0.07)	0.49(0.07)	0.49(0.07)	6.4(1.8)	7(4)
IV-0	15	0.76(0.07)	0.46(0.08)	0.46(0.08)	0.46(0.08)	8.4(1.2)	5(3)
VI-0	50	0.78(0.15)	0.45(0.09)	0.45(0.09)	0.45(0.09)	7.1(2.4)	5(2)
VIII-0	200	0.73(0.17)	0.44(0.08)	0.44(0.08)	0.44(0.08)	8.6(1.9)	4(3)

N = 5.

Data arranged as: Mean (Standard Deviation).

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

& Statistically significant difference from control at p < 0.05 by repeated measures analysis of variance.

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TABLE 30

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS IN P₁ RATS

GROUP	I-0	III-0	V-0	VII-0	II-0	IV-0	VI-0	VIII-0
DOSE: (mg/kg/day)	0	15	50	200	0	15	50	200
NUMBER EXAMINED:	5	5	5	5	5	5	5	5
HOME CAGE:								
POSTURE:								
limbs spread out or lying on one side	0	0	0	0	0	0	0	0
curled up,	0	1	0	2	0	0	0	0
sitting, standing or rearing normally, alert	5	4	5	3	5	5	5	5
jumping	0	0	0	0	0	0	0	0
PALPEBRAL CLOSURE:								
eyelids wide open	5	5	5	4	5	5	5	5
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
rat appears to be sleeping	0	0	0	1	0	0	0	0
GAIT/COORDINATION:								
normal	5	5	5	5	5	5	5	5
unbalanced, swaying, uncoordinated	0	0	0	0	0	0	0	0
ataxic	0	0	0	0	0	0	0	0
unable to move	0	0	0	0	0	0	0	0
TREMORS:								
none	5	5	5	5	5	5	5	5
slight - paws	0	0	0	0	0	0	0	0
mild - limbs	0	0	0	0	0	0	0	0
severe - multiple sites	0	0	0	0	0	0	0	0
CONVULSIONS:								
absent	5	5	5	5	5	5	5	5
present	0	0	0	0	0	0	0	0

TABLE 30 (Continued)

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SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS IN P₁ RATS

GROUP	I-0	III-0	V-0	VII-0	II-0	IV-0	VI-0	VIII-0
DOSE: (mg/kg/day)	0	15	50	200	0	15	50	200
NUMBER EXAMINED:	5	5	5	5	5	5	5	5

REMOVAL FROM CAGE:

EASE OF REMOVAL:

too easy (rat sits quietly, no resistance)	0	0	0	0	0	0	0	0
some resistance (rears, follows observer's hand)	5	5	5	5	5	5	5	5
difficult (runs around cage, may attack)	0	0	0	0	0	0	0	0

EASE OF HANDLING:

too easy	0	0	0	0	0	0	0	0
easy (alert, limbs pulled up against body)	5	5	5	5	5	5	5	5
difficult	0	0	0	0	0	0	0	0

VOCALIZATIONS:

absent	5	5	5	4	5	5	5	5
present	0	0	0	1	0	0	0	0

MUSCLE TONE:

limp	0	0	0	0	0	0	0	0
normal	5	5	5	5	5	5	5	5
rigid	0	0	0	0	0	0	0	0

PILOERECTION:

absent	5	5	5	5	5	5	5	5
present	0	0	0	0	0	0	0	0

FUR APPEARANCE:

normal	5	5	5	5	5	5	5	5
stained	0	0	0	0	0	0	0	0
soiled	0	0	0	0	0	0	0	0

MUCOUS MEMBRANES:

normal	5	5	5	5	5	5	5	5
pale, discolored	0	0	0	0	0	0	0	0
colored discharge, or crusty deposits	0	0	0	0	0	0	0	0

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TABLE 30 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS IN P₁ RATS

GROUP	I-0	III-0	V-0	VII-0	II-0	IV-0	VI-0	VIII-0
DOSE: (mg/kg/day)	0	15	50	200	0	15	50	200
NUMBER EXAMINED:	5	5	5	5	5	5	5	5
PALPEBRAL CLOSURE:								
none	5	5	5	5	5	5	5	5
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
EXOPHTHALAMUS:								
absent	5	5	5	5	5	5	5	5
present	0	0	0	0	0	0	0	0
LACRIMATION:								
none	5	5	5	5	5	5	5	5
slight	0	0	0	0	0	0	0	0
severe	0	0	0	0	0	0	0	0
SALIVATION:								
none	5	5	5	5	5	5	5	5
slight (wet chin)	0	0	0	0	0	0	0	0
severe (active salivation, drooling)	0	0	0	0	0	0	0	0
DEHYDRATION:								
absent	5	5	5	5	5	5	5	5
present	0	0	0	0	0	0	0	0
EMACIATION:								
absent	5	5	5	5	5	5	5	5
present	0	0	0	0	0	0	0	0

TABLE 30 (Continued)

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SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS IN P₁ RATS

GROUP	I-0	III-0	V-0	VII-0	II-0	IV-0	VI-0	VIII-0
DOSE: (mg/kg/day)	0	15	50	200	0	15	50	200
NUMBER EXAMINED:	5	5	5	5	5	5	5	5
OPEN FIELD:								
RIGHTING REFLEX:								
present	5	5	5	5	5	5	5	5
slow	0	0	0	0	0	0	0	0
absent	0	0	0	0	0	0	0	0
PALPEBRAL CLOSURE:								
none	5	5	5	5	5	5	5	5
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
POSTURE:								
normal	5	5	5	5	5	5	5	5
abnormal	0	0	0	0	0	0	0	0
GAIT/COORDINATION:								
normal	5	5	5	5	5	5	5	5
unbalanced, swaying, uncoordinated	0	0	0	0	0	0	0	0
ataxic	0	0	0	0	0	0	0	0
unable to move	0	0	0	0	0	0	0	0
TREMORS:								
none	5	5	5	5	5	5	5	5
slight - paws	0	0	0	0	0	0	0	0
mild - limbs	0	0	0	0	0	0	0	0
severe - multiple sites	0	0	0	0	0	0	0	0
CONVULSIONS:								
absent	5	5	5	5	5	5	5	5
present	0	0	0	0	0	0	0	0
MUSCLE SPASMS/FASCICULATION:								
absent	5	5	5	5	5	5	5	5
present	0	0	0	0	0	0	0	0
RESPIRATION EASE:								
normal	5	5	5	5	5	5	5	5
labored breathing	0	0	0	0	0	0	0	0

TABLE 30 (Continued)

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SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS IN P₁ RATS

GROUP	I-0	III-0	V-0	VII-0	II-0	IV-0	VI-0	VIII-0
DOSE: (mg/kg/day)	0	15	50	200	0	15	50	200
NUMBER EXAMINED:	5	5	5	5	5	5	5	5
RATE OF RESPIRATION:								
slow	0	0	0	0	0	0	0	0
normal	5	5	5	5	5	5	5	5
rapid	0	0	0	0	0	0	0	0
AROUSAL:								
very low (stupor, little or no responsiveness)	0	0	0	0	0	0	0	0
low	0	0	1	0	0	0	0	0
normal (alert, exploratory movements)	5	5	4	5	5	5	5	5
high (slight excitement, tense, sudden movements)	0	0	0	0	0	0	0	0
VOCALIZATIONS:								
present	0	0	0	0	0	0	0	0
absent	5	5	5	5	5	5	5	4
vocalizes only when handled	0	0	0	0	0	0	0	1
DIARRHEA:								
absent	5	5	5	5	5	5	5	5
present	0	0	0	0	0	0	0	0
POLYURIA:								
absent	5	5	5	5	5	5	5	5
present	0	0	0	0	0	0	0	0

TABLE 30 (Continued)

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SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS IN P₁ RATS

GROUP	I-0	III-0	V-0	VII-0	II-0	IV-0	VI-0	VIII-0
DOSE: (mg/kg/day)	0	15	50	200	0	15	50	200
NUMBER EXAMINED:	5	5	5	5	5	5	5	5

MANIPULATIONS:

APPROACH & TOUCH:

no reaction	0	0	0	0	0	0	0	0
normal	5	5	5	5	5	5	5	5
increased reaction (jumps away or attacks)	0	0	0	0	0	0	0	0

AUDITORY STIMULUS:

no reaction	0	0	0	0	0	0	0	0
normal reaction (rat flinches or flicks ear)	5	5	5	5	5	5	5	5
exaggerated reaction (rat jumps, flips)	0	0	0	0	0	0	0	0

TAIL PINCH:

no response	0	0	0	0	0	0	0	0
normal (turns toward site)	5	4	5	5	5	5	5	5
exaggerated response	0	1	0	0	0	0	0	0

IN MOTOR ACTIVITY MONITOR:

PUPILLARY RESPONSE:

present	5	5	5	5	5	5	5	5
absent	0	0	0	0	0	0	0	0

DIARRHEA:

absent	5	5	5	5	5	5	5	5
present	0	0	0	0	0	0	0	0

POLYURIA:

absent	5	5	5	5	5	5	5	5
present	0	0	0	0	0	0	0	0

TABLE 30 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS IN P₁ RATS

GROUP	I-0	III-0	V-0	VII-0	II-0	IV-0	VI-0	VIII-0
DOSE: (mg/kg/day)	0	15	50	200	0	15	50	200
NUMBER EXAMINED:	5	5	5	5	5	5	5	5

FOOTNOTES

SORE TOE

absent	5	5	5	5	5	4	5	4
present	0	0	0	0	0	1	0	1

LUNG NOISE

absent	5	5	5	2	5	5	5	5
present	0	0	0	3 [^]	0	0	0	0

Statistical Analysis: Statistical significance is indicated by the following ($p < 0.05$):

[^] Cochran-Armitage test for trend

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TABLE 31

MOTOR ACTIVITY ASSESSEMENT: MEAN DURATION OF MOVEMENT (seconds) IN P₁ RATS

GROUP	DOSE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						TOTAL
		1	2	3	4	5	6	
MALE								
I-0	0	394(39)	365(47)	314(24)	296(67)	203(124)	230(162)	1803(333)
III-0	15	376(72)	299(93)	231(147)	226(51)	110(106)	59(57)+	1302(472)
V-0	50	367(42)	270(63)	265(54)	215(77)	136(107)	115(123)	1369(306)
VII-0	200	371(71)	236(147)	204(98)	136(127)+	83(74)	39(62)+	1069(344)+
FEMALE								
II-0	0	328(45)	256(74)	183(89)	122(105)	105(70)	206(72)	1200(347)
IV-0	15	360(55)	251(60)	219(108)	193(65)	185(119)	96(111)	1304(390)
VI-0	50	303(31)	189(63)	157(84)	129(73)	137(126)	125(86)	1041(387)
VIII-0	200	284(29)	160(88)	101(80)	73(85)	63(113)	80(104)	760(435)

Data arranged as: Mean (Standard Deviation).

N = 5.

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

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

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TABLE 32
 MOTOR ACTIVITY ASSESSEMENT: MEAN NUMBER OF MOVEMENTS IN P₁ RATS

GROUP	DOSE (mg/kg/day)	SUCCESSIVE 10-MINUTE INTERVALS						TOTAL
		1	2	3	4	5	6	
MALE								
I-0	0	150(22)	144(24)	136(22)	133(30)	100(39)	100(59)	762(123)
III-0	15	144(20)	138(17)	109(65)	123(26)	69(61)	33(29)	616(158)
V-0	50	137(11)	129(22)	127(7)	117(19)	86(59)	62(57)	659(140)
VII-0	200	136(18)	101(44)	114(48)	68(45)	52(52)	29(44)	499(183)+
FEMALE								
II-0	0	137(19)	119(12)	109(43)	82(49)	71(35)	124(21)	644(98)
IV-0	15	127(17)	120(17)	111(37)	100(8)	101(55)	56(59)	615(142)
VI-0	50	125(20)	121(38)	97(45)	94(57)	77(64)	82(52)	597(217)
VIII-0	200	143(12)	123(29)	83(54)	53(58)	34(48)	49(65)	484(221)

N = 5.

Statistical Analysis: Statistical significance is indicated by the following ($p < 0.05$):

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

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TABLE 33

SUMMARY OF HEMATOLOGY VALUES FOR P₁ MALE RATS

Group	I-0	III-0	V-0	VII-0
Dose (mg/kg/day)	0	15	50	200
RBC (x10 ⁶ /μL)				
DAY 14	8.11 0.38(5)	7.72 0.38(5)	8.16 0.64(5)	8.06 0.50(4)
HGB (g/dL)				
DAY 14	15.8 0.6(5)	15.0 0.5(5)	15.8 1.0(5)	15.9 0.5(4)
HCT (%)				
DAY 14	50.5 1.8(5)	48.2 1.8(5)	49.8 2.8(5)	50.5 2.0(4)
MCV (fL)				
DAY 14	62.3 1.1(5)	62.5 2.1(5)	61.1 1.8(5)	62.8 2.9(4)
MCH (pg)				
DAY 14	19.5 0.5(5)	19.5 0.8(5)	19.3 0.7(5)	19.8 1.0(4)
MCHC (g/dL)				
DAY 14	31.3 0.4(5)	31.2 0.6(5)	31.6 0.7(5)	31.5 0.4(4)
RDW (%)				
DAY 14	11.7 0.4(5)	11.6 0.1(5)	11.3 0.3(5)	11.4 0.4(4)
ARET (x10 ³ /μL)				
DAY 14	200.3 16.8(5)	173.4 19.7(5)	180.0 42.9(5)	192.5 23.3(4)
PLT (x10 ³ /μL)				
DAY 14	1147 99(5)	1092 96(3)	1253 103(4)	910* 30(2)
WBC (x10 ³ /μL)				
DAY 14	15.54 2.83(5)	13.19 0.88(5)	13.71 2.74(5)	16.61 3.01(4)
ANEU (x10 ³ /μL)				
DAY 14	1.96 0.45(5)	1.51 0.24(5)	1.71 0.55(5)	2.09 0.37(4)
ALYM (x10 ³ /μL)				
DAY 14	12.93 3.04(5)	11.15 0.68(5)	11.41 2.17(5)	13.75 3.24(4)

TABLE 33 (Continued)

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SUMMARY OF HEMATOLOGY VALUES FOR P₁ MALE RATS

Group	I-0	III-0	V-0	VII-0
Dose (mg/kg/day)	0	15	50	200
AMON (x10 ³ /μL)				
DAY 14	0.31 0.09(5)	0.25 0.05(5)	0.26 0.04(5)	0.37 0.10(4)
AEOS (x10 ³ /μL)				
DAY 14	0.14 0.08(5)	0.12 0.06(5)	0.12 0.06(5)	0.25 0.17(4)
ABAS (x10 ³ /μL)				
DAY 14	0.07 0.02(5)	0.07 0.03(5)	0.07 0.03(5)	0.08 0.06(4)
ALUC (x10 ³ /μL)				
DAY 14	0.12 0.06(5)	0.09 0.03(5)	0.14 0.07(5)	0.09 0.06(4)

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

* Statistically significant difference from control at p < 0.05 by Dunnett/Tamhane-Dunnett test.

TABLE 34

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SUMMARY OF HEMATOLOGY VALUES FOR P₁ FEMALE RATS

Group Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
RBC (x10 ⁶ /μL)				
DAY 14	7.60 0.44(5)	7.59 0.44(5)	7.73 0.27(5)	7.59 0.76(5)
HGB (g/dL)				
DAY 14	14.9 0.6(5)	14.9 0.9(5)	14.9 0.6(5)	14.7 1.0(5)
HCT (%)				
DAY 14	45.7 1.8(5)	45.9 3.0(5)	45.9 1.4(5)	45.5 2.9(5)
MCV (fL)				
DAY 14	60.2 2.2(5)	60.4 1.5(5)	59.4 1.7(5)	60.2 2.8(5)
MCH (pg)				
DAY 14	19.6 0.5(5)	19.6 0.3(5)	19.4 0.5(5)	19.4 0.8(5)
MCHC (g/dL)				
DAY 14	32.6 0.6(5)	32.4 0.4(5)	32.6 0.9(5)	32.3 0.3(5)
RDW (%)				
DAY 14	11.8 0.8(5)	11.4 0.3(5)	11.6 0.7(5)	12.2 0.7(5)
ARET (x10 ³ /μL)				
DAY 14	215.8 47.3(5)	196.1 44.9(5)	233.2 33.4(5)	280.0 58.3(5)
PLT (x10 ³ /μL)				
DAY 14	1204 50(3)	1322 315(2)	1211 212(3)	1295 195(4)
WBC (x10 ³ /μL)				
DAY 14	9.33 1.75(5)	10.32 3.34(5)	10.11 3.11(5)	9.01 1.88(5)
ANEU (x10 ³ /μL)				
DAY 14	1.22 0.28(5)	1.32 0.46(5)	1.12 0.45(5)	1.36 0.51(5)
ALYM (x10 ³ /μL)				
DAY 14	7.74 1.59(5)	8.59 2.99(5)	8.53 2.56(5)	7.14 1.97(5)

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TABLE 34 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR P₁ FEMALE RATS

Group Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
AMON (x10 ³ /μL) DAY 14	0.17 0.04(5)	0.19 0.10(5)	0.23 0.07(5)	0.30 0.10(5)
AEOS (x10 ³ /μL) DAY 14	0.09 0.01(5)	0.11 0.05(5)	0.10 0.04(5)	0.09 0.05(5)
ABAS (x10 ³ /μL) DAY 14	0.04 0.01(5)	0.04 0.02(5)	0.04 0.03(5)	0.04 0.01(5)
ALUC (x10 ³ /μL) DAY 14	0.07 0.01(5)	0.07 0.04(5)	0.09 0.06(5)	0.06 0.02(5)

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

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

TABLE 35

SUMMARY OF COAGULATION VALUES FOR P₁ MALE RATS

Group Dose (mg/kg/day)	I-0 0	III-0 15	V-0 50	VII-0 200
PT (sec)				
DAY 34	15.0 1.2(4)	15.1 0.6(5)	15.4 0.2(5)	15.7 0.4(5)
APTT (sec)				
DAY 34	16.3 2.9(4)	16.3 1.3(5)	16.6 1.7(5)	18.4 2.8(5)

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

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

TABLE 36

SUMMARY OF COAGULATION VALUES FOR P₁ FEMALE RATS

Group Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
PT (sec)				
DAY 43 - 57	15.7 0.7(5)	15.7 0.3(5)	15.7 0.4(5)	15.2 0.6(5)
APTT (sec)				
DAY 43 - 57	17.4 2.5(5)	18.3 1.9(5)	17.5 2.4(5)	17.0 2.8(5)

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

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

TABLE 37

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR P₁ MALE RATS

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Group Dose (mg/kg/day)	I-0 0	III-0 15	V-0 50	VII-0 200
AST (U/L) DAY 14	74 11(5)	75 5(5)	83 20(5)	70 6(4)
ALT (U/L) DAY 14	29 4(5)	25 2(5)	29 3(5)	24 3(4)
BUN (mg/dL) DAY 14	16 2(5)	13 2(5)	14 1(5)	15 3(4)
CREA (mg/dL) DAY 14	0.34 0.02(5)	0.33 0.02(5)	0.34 0.03(5)	0.31 0.03(4)
CHOL (mg/dL) DAY 14	50 8(5)	64 11(5)	68 20(5)	73 20(4)
GLUC (mg/dL) DAY 14	91 18(5)	101 47(5)	85 12(5)	80 8(4)
TP (g/dL) DAY 14	6.5 0.3(5)	6.6 0.2(5)	6.5 0.2(5)	6.8 0.1(4)
ALB (g/dL) DAY 14	3.4 0.1(5)	3.5 0.1(5)	3.5 0.2(5)	3.5 0.1(4)
TBA (μmol/L) DAY 14	20.0 7.2(5)	15.0 7.4(5)	16.9 11.9(5)	15.9 22.4(4)
NA (mmol/L) DAY 14	146.6 0.9(5)	146.2 1.0(5)	145.1 1.6(5)	144.9 2.3(4)
K (mmol/L) DAY 14	6.38 0.21(5)	6.57 0.38(5)	6.31 0.50(5)	6.28 0.20(4)

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

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

TABLE 38

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR P₁ FEMALE RATS

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Group Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
AST (U/L)				
DAY 14	77 14(5)	73 13(5)	69 3(5)	74 15(5)
ALT (U/L)				
DAY 14	21 4(5)	22 5(5)	25 2(5)	27 5(5)
BUN (mg/dL)				
DAY 14	18 2(5)	18 2(5)	17 4(5)	19 3(5)
CREA (mg/dL)				
DAY 14	0.38 0.04(5)	0.41 0.05(5)	0.40 0.05(5)	0.41 0.03(5)
CHOL (mg/dL)				
DAY 14	67 6(5)	73 10(5)	87 18(5)	110* 18(5)
GLUC (mg/dL)				
DAY 14	110 16(5)	106 14(5)	101 16(5)	97 16(5)
TP (g/dL)				
DAY 14	7.2 0.4(5)	7.0 0.3(5)	7.2 0.4(5)	7.4 0.2(5)
ALB (g/dL)				
DAY 14	3.9 0.3(5)	3.7 0.2(5)	3.9 0.3(5)	3.8 0.1(5)
TBA (µmol/L)				
DAY 14	16.0 8.7(5)	19.2 6.5(5)	18.5 9.9(5)	12.9 11.0(5)
NA (mmol/L)				
DAY 14	143.4 0.8(5)	144.3 1.4(5)	143.3 0.9(5)	144.8 2.5(5)
K (mmol/L)				
DAY 14	5.41 0.30(5)	5.76 0.73(5)	5.61 0.43(5)	5.98 0.21(5)

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

* Statistically significant difference from control at p < 0.05 by Dunnett/Tamhane-Dunnett test.

TABLE 39

MEAN FINAL BODY AND ORGAN WEIGHTS FROM MALE RATS - P₁ ADULTS

Group: Dose (mg/kg/day)	MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)				
	I-0 0	III-0 15	V-0 50	VII-0 200	
FINAL BODY WEIGHT	422.4 34.9(10)	430.1 41.4(10)	411.0 50.3(10)	380.4 48.3(9)	
BRAIN	2.049 0.091(5)	2.086 0.092(5)	1.983 0.115(5)	2.040 0.116(5)	
ADRENAL GLANDS	0.055 0.010(5)	0.054 0.009(5)	0.055 0.009(5)	0.056 0.005(5)	
EPIDIDYMIDES	1.282 0.093(10)	1.287 0.103(10)	1.295 0.084(10)	1.185 0.209(9)	
HEART	1.298 0.122(5)	1.478 0.089(5)	1.388 0.204(5)	1.285 0.076(5)	
KIDNEYS	3.292 0.479(5)	3.648 0.185(5)	3.349 0.567(5)	3.453 0.504(5)	
LIVER	15.868 2.282(5)	18.055 0.699(5)	18.169 3.114(5)	21.797* 1.887(5)	
SPLEEN	0.739 0.052(5)	0.806 0.076(5)	0.714 0.110(5)	0.729 0.149(5)	
TESTES	3.315 0.225(10)	3.383 0.278(10)	3.389 0.279(10)	3.102 0.277(9)	
THYMUS	0.391 0.067(5)	0.427 0.074(5)	0.363 0.078(5)	0.414 0.129(5)	

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TABLE 39 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS FROM MALE RATS - P₁ ADULTS

Group: Dose (mg/kg/day)	MEAN RELATIVE ORGAN WEIGHTS (% of body weight)			
	I-0 0	III-0 15	V-0 50	VII-0 200
ADRENAL GLANDS/ FINAL BODY * 100	0.013 0.002 (5)	0.012 0.002 (5)	0.014 0.002 (5)	0.014 0.002 (5)
BRAIN/ FINAL BODY * 100	0.498 0.049 (5)	0.470 0.021 (5)	0.488 0.039 (5)	0.518 0.038 (5)
EPIDIDYMIDES/ FINAL BODY * 100	0.304 0.023 (10)	0.301 0.028 (10)	0.318 0.028 (10)	0.310 0.029 (9)
HEART/ FINAL BODY * 100	0.313 0.015 (5)	0.332 0.011 (5)	0.339* 0.018 (5)	0.326 0.015 (5)
KIDNEYS/ FINAL BODY * 100	0.792 0.068 (5)	0.822 0.043 (5)	0.816 0.059 (5)	0.873 0.087 (5)
LIVER/ FINAL BODY * 100	3.819 0.304 (5)	4.068 0.193 (5)	4.429* 0.395 (5)	5.525* 0.333 (5)
SPLEEN/ FINAL BODY * 100	0.179 0.020 (5)	0.181 0.011 (5)	0.177 0.037 (5)	0.184 0.029 (5)
TESTES/ FINAL BODY * 100	0.789 0.070 (10)	0.792 0.087 (10)	0.830 0.078 (10)	0.822 0.069 (9)
THYMUS/ FINAL BODY * 100	0.096 0.023 (5)	0.096 0.014 (5)	0.088 0.012 (5)	0.104 0.029 (5)

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TABLE 39 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS FROM MALE RATS - P₁ ADULTS

MEAN RELATIVE ORGAN WEIGHTS (% of brain weight)		I-0	III-0	V-0	VII-0
Group:	Dose (mg/kg/day)	0	15	50	200
ADRENAL GLANDS/ BRAIN * 100	2.686 0.381 (5)	2.601 0.326 (5)	2.786 0.347 (5)	2.752 0.177 (5)	
EPIDIDYMIDES/ BRAIN * 100	60.568 3.333 (5)	62.036 4.341 (5)	64.787 3.456 (5)	59.814 8.155 (5)	
HEART/ BRAIN * 100	63.557 7.793 (5)	70.978 5.676 (5)	69.759 6.542 (5)	63.145 5.339 (5)	
KIDNEYS/ BRAIN * 100	160.940 25.291 (5)	175.092 9.613 (5)	168.154 20.024 (5)	169.350 22.563 (5)	
LIVER/ BRAIN * 100	776.802 128.847 (5)	867.801 65.021 (5)	912.610 115.897 (5)	1069.329* 83.845 (5)	
SPLEEN/ BRAIN * 100	36.084 2.819 (5)	38.661 3.777 (5)	36.027 5.512 (5)	35.584 5.734 (5)	
TESTES/ BRAIN * 100	164.146 14.574 (5)	166.781 12.875 (5)	167.906 6.177 (5)	152.502 8.040 (5)	
THYMUS/ BRAIN * 100	19.066 3.292 (5)	20.438 3.056 (5)	18.220 3.090 (5)	20.156 5.464 (5)	

Data summarized as: Mean
Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

* Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant

@ Nonparametric comparison to control (Dunn's) significant

Trend test (Jonckheere-Terpstra) significant

~ next to control mean indicates no analyses were performed

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TABLE 40

MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE RATS - P₁ ADULTS

Group: Dose (mg/kg/day)	MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)			
	II-0 0	IV-0 15	VI-0 50	VIII-0 200
FINAL BODY WEIGHT	305.6 17.3(10)	304.4 26.3(9)	299.1 18.1(8)	305.6 15.7(5)
BRAIN	1.996 0.115(5)	1.976 0.039(6)	1.888 0.140(5)	1.891 0.035(5)
ADRENAL GLANDS	0.081 0.020(5)	0.078 0.007(6)	0.068 0.009(5)	0.083 0.014(5)
HEART	1.195 0.193(5)	1.043 0.055(6)	1.054 0.145(5)	1.040 0.051(5)
KIDNEYS	2.284 0.142(5)	2.326 0.192(6)	2.210 0.185(5)	2.406 0.062(5)
LIVER	13.152 1.168(5)	13.178 0.846(6)	14.136 1.243(5)	15.687* 2.041(5)
SPLEEN	0.639 0.098(5)	0.598 0.107(6)	0.667 0.172(5)	0.554 0.103(5)
THYMUS	0.246 0.077(5)	0.232 0.056(6)	0.230 0.052(5)	0.191 0.067(5)

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TABLE 40 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE RATS - P₁ ADULTS

Group: Dose (mg/kg/day)	II-0 0	IV-0 15	VI-0 50	VIII-0 200
ADRENAL GLANDS/ FINAL BODY * 100	0.026 0.006 (5)	0.026 0.004 (6)	0.022 0.001 (5)	0.027 0.005 (5)
BRAIN/ FINAL BODY * 100	0.645 0.027 (5)	0.659 0.031 (6)	0.626 0.042 (5)	0.620 0.033 (5)
HEART/ FINAL BODY * 100	0.388 0.076 (5)	0.348 0.017 (6)	0.348 0.029 (5)	0.341 0.028 (5)
KIDNEYS/ FINAL BODY * 100	0.739 0.064 (5)	0.778 0.100 (6)	0.732 0.030 (5)	0.789 0.046 (5)
LIVER/ FINAL BODY * 100	4.241 0.203 (5)	4.389 0.164 (6)	4.688 0.361 (5)	5.124* 0.492 (5)
SPLEEN/ FINAL BODY * 100	0.207 0.038 (5)	0.198 0.028 (6)	0.220 0.047 (5)	0.181 0.026 (5)
THYMUS/ FINAL BODY * 100	0.079 0.023 (5)	0.077 0.016 (6)	0.076 0.015 (5)	0.062 0.019 (5)

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TABLE 40 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE RATS - P₁ ADULTS

MEAN RELATIVE ORGAN WEIGHTS (% of brain weight)

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day)	0	15	50	200
Test				
ADRENAL GLANDS/ BRAIN * 100	4.043 0.907 (5)	3.937 0.436 (6)	3.582 0.424 (5)	4.374 0.681 (5)
HEART/ BRAIN * 100	60.289 12.634 (5)	52.801 2.689 (6)	55.718 5.159 (5)	54.975 1.765 (5)
KIDNEYS/ BRAIN * 100	114.592 7.702 (5)	117.863 11.625 (6)	117.181 6.990 (5)	127.338 4.837 (5)
LIVER/ BRAIN * 100	658.190 30.387 (5)	666.913 40.958 (6)	749.394 45.730 (5)	829.800* 107.267 (5)
SPLEEN/ BRAIN * 100	32.218 6.030 (5)	30.209 5.026 (6)	35.175 7.933 (5)	29.339 5.442 (5)
THYMUS/ BRAIN * 100	12.384 3.940 (5)	11.708 2.618 (6)	12.093 2.119 (5)	10.091 3.543 (5)

Data summarized as: Mean

Standard Deviation (n)

Statistical Analysis: Statistical significance is indicated by the following (p < 0.05):

* Parametric comparison to control (Dunnett/Tamhane-Dunnnett) significant

@ Nonparametric comparison to control (Dunn's) significant

Trend test (Jonckheere-Terpstra) significant

~ next to control mean indicates no analyses were performed

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TABLE 41

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS (ALL ANIMALS) - P₁ ADULTS

LESION	LESION INCIDENCE (Numeric)						
	TREATMENT	Males					
	per day	0	15	50	200		
		I-0	III-0	V-0	VII-0		
LIVER		(10)	(10)	(10)	(10)		
NO ABNORMALITY DETECTED		10	10	10	10		
KIDNEYS		(10)	(10)	(10)	(10)		
NO ABNORMALITY DETECTED		10	10	10	10		
LUNGS		(10)	(10)	(10)	(10)		
NO ABNORMALITY DETECTED		10	10	10	10	9	1
EXPANDED.							1
DISCOLORATION, DARK, RED.							1
HEART		(10)	(10)	(10)	(10)		
NO ABNORMALITY DETECTED		10	10	10	10		
SPLEEN		(10)	(10)	(10)	(10)		
NO ABNORMALITY DETECTED		10	10	10	10		

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

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TABLE 41 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT				LESION INCIDENCE (Numeric)				
	0	15	50	200	Males				
	mg/kg	mg/kg	mg/kg	mg/kg	I-0	III-0	V-0	VII-0	
	per day								
BRAIN	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED	10	10	10	10					
SPINAL CORD	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED	10	10	10	10					
STOMACH	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED	10	10	10	10					
DUODENUM	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED	10	10	10	10					
JEJUNUM	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED	10	10	10	10					

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

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TABLE 41 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS (ALL ANIMALS)- P₁ ADULTS

LESIONS	TREATMENT per day	LESION INCIDENCE (Numeric)			
		Males			
		0 mg/kg I-0	15 mg/kg III-0	50 mg/kg V-0	200 mg/kg VII-0
ILEUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
CECUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
COLON		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
RECTUM		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
MESENTERIC LYMPH NODE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

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

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TABLE 41 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT per day	LESION INCIDENCE (Numeric)			
		Males			
		0 mg/kg I-0	15 mg/kg III-0	50 mg/kg V-0	200 mg/kg VII-0
MANDIBULAR LYMPH NODE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
THYMUS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
ADRENAL GLANDS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SCIATIC NERVE		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
THYROID GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

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

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TABLE 41 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT				LESION INCIDENCE (Numeric)				
	0	15	50	200	Males				
	mg/kg I-0	mg/kg III-0	mg/kg V-0	mg/kg VII-0					
PAPATHYROID GLANDS	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED	10	10	10	10					
TRACHEA	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED FLUID, CLEAR.	10	10	10	9					1
PROSTATE	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED SMALL.	10	10	10	9					1
SEMINAL VESICLES	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED SMALL, BILATERAL.	10	10	10	9					1

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

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TABLE 41 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT				LESION INCIDENCE (Numeric)			
	0	15	50	200	Males			
	mg/kg I-0	mg/kg III-0	mg/kg V-0	mg/kg VII-0				
URINARY BLADDER	(10)	(10)	(10)	(10)				
NO ABNORMALITY DETECTED	10	10	10	10				
TESTES	(10)	(10)	(10)	(10)				
NO ABNORMALITY DETECTED DEFORMITY, SOFT, BILATERAL.	10	10	10	9				1
EPIDIDYMIDES	(10)	(10)	(10)	(10)				
NO ABNORMALITY DETECTED SMALL, BILATERAL.	10	10	10	9				1
FEMUR/KNEE JOINT	(10)	(10)	(10)	(10)				
NO ABNORMALITY DETECTED	10	10	10	10				
COAGULATING GLANDS	(10)	(10)	(10)	(10)				
NO ABNORMALITY DETECTED	10	10	10	10				

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TABLE 42

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT per day	0 mg/kg I-0	15 mg/kg III-0	50 mg/kg V-0	200 mg/kg VII-0	
LIVER		(10)	(10)	(10)	(9)	
NO ABNORMALITY DETECTED		10	10	10	9	
KIDNEYS		(10)	(10)	(10)	(9)	
NO ABNORMALITY DETECTED		10	10	10	9	
LUNGS		(10)	(10)	(10)	(9)	
NO ABNORMALITY DETECTED		10	10	10	9	
HEART		(10)	(10)	(10)	(9)	
NO ABNORMALITY DETECTED		10	10	10	9	
SPLEEN		(10)	(10)	(10)	(9)	
NO ABNORMALITY DETECTED		10	10	10	9	

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TABLE 42 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	LESION INCIDENCE (Numeric)					
	Males					
TREATMENT per day	0 mg/kg I-0	15 mg/kg III-0	50 mg/kg V-0	200 mg/kg VII-0		
BRAIN	(10)	(10)	(10)	(9)		
NO ABNORMALITY DETECTED	10	10	10	9		
SPINAL CORD	(10)	(10)	(10)	(9)		
NO ABNORMALITY DETECTED	10	10	10	9		
STOMACH	(10)	(10)	(10)	(9)		
NO ABNORMALITY DETECTED	10	10	10	9		
DUODENUM	(10)	(10)	(10)	(9)		
NO ABNORMALITY DETECTED	10	10	10	9		
JEJUNUM	(10)	(10)	(10)	(9)		
NO ABNORMALITY DETECTED	10	10	10	9		

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TABLE 42 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT				Males				LESION INCIDENCE (Numeric)
	0	15	50	200	0	15	50	200	
	mg/kg	mg/kg	mg/kg	mg/kg	I-0	III-0	V-0	VII-0	
	per day								
ILEUM	(10)	(10)	(10)	(9)	(10)	(10)	(10)	(9)	(9)
NO ABNORMALITY DETECTED	10	10	10	9					
CECUM	(10)	(10)	(10)	(9)	(10)	(10)	(10)	(9)	(9)
NO ABNORMALITY DETECTED	10	10	10	9					
COLON	(10)	(10)	(10)	(9)	(10)	(10)	(10)	(9)	(9)
NO ABNORMALITY DETECTED	10	10	10	9					
RECTUM	(10)	(10)	(10)	(9)	(10)	(10)	(10)	(9)	(9)
NO ABNORMALITY DETECTED	10	10	10	9					
MESENTERIC LYMPH NODE	(10)	(10)	(10)	(9)	(10)	(10)	(10)	(9)	(9)
NO ABNORMALITY DETECTED	10	10	10	9					

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TABLE 42 (Continued)
 INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT		Males			
	per day	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
		I-0	III-0	V-0	VII-0	
MANDIBULAR LYMPH NODE		(10)	(10)	(10)	(10)	(9)
NO ABNORMALITY DETECTED		10	10	10	10	9
THYMUS		(10)	(10)	(10)	(10)	(9)
NO ABNORMALITY DETECTED		10	10	10	10	9
ADRENAL GLANDS		(10)	(10)	(10)	(10)	(9)
NO ABNORMALITY DETECTED		10	10	10	10	9
SCIATIC NERVE		(10)	(10)	(10)	(10)	(9)
NO ABNORMALITY DETECTED		10	10	10	10	9
THYROID GLAND		(10)	(10)	(10)	(10)	(9)
NO ABNORMALITY DETECTED		10	10	10	10	9

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TABLE 42 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT						LESION INCIDENCE (Numeric)									
	0		15		50		200		Males							
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	I-0	III-0	V-0	VII-0						
PARATHYROID GLANDS	(10)	(10)	(10)	(10)	(10)	(10)										
NO ABNORMALITY DETECTED	10	10	10	10	10	9										
TRACHEA	(10)	(10)	(10)	(10)	(10)	(9)										
NO ABNORMALITY DETECTED	10	10	10	10	10	9										
PROSTATE	(10)	(10)	(10)	(10)	(10)	(9)										
NO ABNORMALITY DETECTED	10	10	10	10	10	8										
SEMINAL VESICLES	(10)	(10)	(10)	(10)	(10)	(9)										
NO ABNORMALITY DETECTED	10	10	10	10	10	8										
URINARY BLADDER	(10)	(10)	(10)	(10)	(10)	(9)										
NO ABNORMALITY DETECTED	10	10	10	10	10	9										

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TABLE 42 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT				LESION INCIDENCE (Numeric)				
	0	15	50	200	Males				
	mg/kg	mg/kg	mg/kg	mg/kg	I-0	III-0	V-0	VII-0	
TESTES	(10)	(10)	(10)	(9)					
NO ABNORMALITY DETECTED DEFORMITY, SOFT, BILATERAL.	10	10	10	8					1
EPIDIDYMIDES	(10)	(10)	(10)	(9)					
NO ABNORMALITY DETECTED SMALL, BILATERAL.	10	10	10	8					1
FEMUR/KNEE JOINT	(10)	(10)	(10)	(9)					
NO ABNORMALITY DETECTED	10	10	10	9					
COAGULATING GLANDS	(10)	(10)	(10)	(9)					
NO ABNORMALITY DETECTED	10	10	10	9					

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TABLE 43

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	LESION INCIDENCE (Numeric)					
	Females					
TREATMENT	0	15	50	200		
per day	mg/kg	mg/kg	mg/kg	mg/kg		
	II-0	IV-0	VI-0	VIII-0		
LIVER	(10)	(10)	(10)	(10)		(10)
NO ABNORMALITY DETECTED	10	10	10	10		10
KIDNEYS	(10)	(10)	(10)	(10)		(10)
NO ABNORMALITY DETECTED	10	10	10	10		10
LUNGS	(10)	(10)	(10)	(10)		(10)
NO ABNORMALITY DETECTED EXPANDED.	10	10	10	10	9	1
HEART	(10)	(10)	(10)	(10)		(10)
NO ABNORMALITY DETECTED	10	10	10	10		10
SPLEEN	(10)	(10)	(10)	(10)		(10)
NO ABNORMALITY DETECTED	10	10	10	10		10

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TABLE 43 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT				LESION INCIDENCE (Numeric)				
	0	15	50	200	Females				
	mg/kg	mg/kg	mg/kg	mg/kg	II-0	IV-0	VI-0	VIII-0	
BRAIN	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED	10	10	10	10					
SPINAL CORD	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED	10	10	10	10					
STOMACH	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED	10	10	9	10					
			1						
DUODENUM	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED	10	10	10	10					
JEJUNUM	(10)	(10)	(10)	(10)					
NO ABNORMALITY DETECTED	10	10	10	10					

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TABLE 43 (Continued)
 INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT						LESION INCIDENCE (Numeric)					
	0	15	50	200	mg/kg	mg/kg	0	15	50	200	mg/kg	mg/kg
	II-0	IV-0	VI-0	VIII-0	mg/kg	mg/kg	II-0	IV-0	VI-0	VIII-0	mg/kg	mg/kg
ILEUM	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10	10	10	10	10	10	10
CECUM	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10	10	10	10	10	9	1
DISTENDED WITH FLUID, BROWN.												
COLON	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10	10	10	10	10	10	10
RECTUM	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10	10	10	10	10	10	10
MESENTERIC LYMPH NODE	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10	10	10	10	10	10	10

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TABLE 43 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	LESION INCIDENCE (Numeric)					
	Females					
TREATMENT per day	0 mg/kg II-0	15 mg/kg IV-0	50 mg/kg VI-0	200 mg/kg VIII-0		
MANDIBULAR LYMPH NODE	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10
THYMUS	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10
ADRENAL GLANDS	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10
SCIATIC NERVE	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10
PITUITARY GLAND					(1)	(1)
DISCOLORATION, DARK.					1	1

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TABLE 43 (Continued)
 INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	LESION INCIDENCE (Numeric)					
	Females					
TREATMENT	0	15	50	200		
per day	mg/kg	mg/kg	mg/kg	mg/kg		
	II-0	IV-0	VI-0	VIII-0		
THYROID GLAND	(10)	(10)	(10)	(10)		(10)
NO ABNORMALITY DETECTED	10	10	10	10		10
PARATHYROID GLANDS	(10)	(10)	(10)	(10)		(10)
NO ABNORMALITY DETECTED	10	10	10	10		10
TRACHEA	(10)	(10)	(10)	(10)		(10)
NO ABNORMALITY DETECTED	10	10	10	10	9	1
MAMMARY GLAND (FEMALE)	(10)	(10)	(10)	(10)		(10)
NO ABNORMALITY DETECTED	10	10	10	10		10
OVARIES	(10)	(10)	(10)	(10)		(10)
NO ABNORMALITY DETECTED	10	10	10	10		10

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TABLE 43 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	LESION INCIDENCE (Numeric)					
	TREATMENT		Females			
	per day	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
		II-0	IV-0	VI-0	VIII-0	
UTERUS		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED THICK, BILATERAL, HORNS. FETUS IN BIRTH CANAL.		10	9	9	10	10
			1	1		
VAGINA		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10
URINARY BLADDER		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10
FEMUR/KNEE JOINT		(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10

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TABLE 44

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT				LESION INCIDENCE (Numeric)				
	0	15	50	200	Females				
	mg/kg II-0	mg/kg IV-0	mg/kg VI-0	mg/kg VIII-0					
LIVER	(10)	(9)	(8)	(5)					
NO ABNORMALITY DETECTED	10	9	8	5					
KIDNEYS	(10)	(9)	(8)	(5)					
NO ABNORMALITY DETECTED	10	9	8	5					
LUNGS	(10)	(9)	(8)	(5)					
NO ABNORMALITY DETECTED	10	9	8	5					
HEART	(10)	(9)	(8)	(5)					
NO ABNORMALITY DETECTED	10	9	8	5					
SPLEEN	(10)	(9)	(8)	(5)					
NO ABNORMALITY DETECTED	10	9	8	5					

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TABLE 44 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT						Females						LESION INCIDENCE (Numeric)
	0	15	50	200	mg/kg II-0	mg/kg IV-0	mg/kg VI-0	mg/kg VIII-0	mg/kg mg/kg	mg/kg mg/kg	mg/kg mg/kg	mg/kg mg/kg	
BRAIN	(10)	(9)	(8)	(5)									
NO ABNORMALITY DETECTED	10	9	8	5									
SPINAL CORD	(10)	(9)	(8)	(5)									
NO ABNORMALITY DETECTED	10	9	8	5									
STOMACH	(10)	(9)	(8)	(5)									
NO ABNORMALITY DETECTED	10	9	8	5									
DUODENUM	(10)	(9)	(8)	(5)									
NO ABNORMALITY DETECTED	10	9	8	5									
JEJUNUM	(10)	(9)	(8)	(5)									
NO ABNORMALITY DETECTED	10	9	8	5									

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TABLE 44 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT per day	LESION INCIDENCE (Numeric)			
		Females			
		0 mg/kg II-0	15 mg/kg IV-0	50 mg/kg VI-0	200 mg/kg VIII-0
ILEUM		(10)	(9)	(8)	(5)
NO ABNORMALITY DETECTED		10	9	8	5
CECUM		(10)	(9)	(8)	(5)
NO ABNORMALITY DETECTED		10	9	8	5
COLON		(10)	(9)	(8)	(5)
NO ABNORMALITY DETECTED		10	9	8	5
RECTUM		(10)	(9)	(8)	(5)
NO ABNORMALITY DETECTED		10	9	8	5
MESENTERIC LYMPH NODE		(10)	(9)	(8)	(5)
NO ABNORMALITY DETECTED		10	9	8	5

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TABLE 44 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT						LESION INCIDENCE (Numeric)								
	0 mg/kg II-0		15 mg/kg IV-0		50 mg/kg VI-0		200 mg/kg VIII-0		Females						
MANDIBULAR LYMPH NODE	(10)	(9)	(8)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	10	9	8	5	5	5	5	5	5	5	5	5	5	5	5
THYMUS	(10)	(9)	(8)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	10	9	8	5	5	5	5	5	5	5	5	5	5	5	5
ADRENAL GLANDS	(10)	(9)	(8)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	10	9	8	5	5	5	5	5	5	5	5	5	5	5	5
SCIATIC NERVE	(10)	(9)	(8)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	10	9	8	5	5	5	5	5	5	5	5	5	5	5	5
THYROID GLAND	(10)	(9)	(8)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED	10	9	8	5	5	5	5	5	5	5	5	5	5	5	5

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TABLE 44 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT per day	LESION INCIDENCE (Numeric)				
		Females				
		0 mg/kg II-0	15 mg/kg IV-0	50 mg/kg VI-0	200 mg/kg VIII-0	
PARATHYROID GLANDS		(10)	(9)	(8)	(5)	
NO ABNORMALITY DETECTED		10	9	8	5	
TRACHEA		(10)	(9)	(8)	(5)	
NO ABNORMALITY DETECTED		10	9	8	5	
MAMMARY GLAND (FEMALE)		(10)	(9)	(8)	(5)	
NO ABNORMALITY DETECTED		10	9	8	5	
OVARIES		(10)	(9)	(8)	(5)	
NO ABNORMALITY DETECTED		10	9	8	5	
UTERUS		(10)	(9)	(8)	(5)	
NO ABNORMALITY DETECTED		10	8	8	5	
THICK, BILATERAL, HORNS.			1			

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TABLE 44 (Continued)

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT						LESION INCIDENCE (Numeric)					
	per day		mg/kg		mg/kg		mg/kg		mg/kg		mg/kg	
	II-0	IV-0	VI-0	VIII-0	0	15	50	200	0	15	50	200
VAGINA	(10)	(9)	(8)	(5)								
NO ABNORMALITY DETECTED					10	9	8	5				
URINARY BLADDER	(10)	(9)	(8)	(5)								
NO ABNORMALITY DETECTED					10	9	8	5				
FEMUR/KNEE JOINT	(10)	(9)	(8)	(5)								
NO ABNORMALITY DETECTED					10	9	8	5				

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TABLE 45

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT per day	LESION INCIDENCE (NUMERIC)			
		0 mg/kg I-0	15 mg/kg III-0	50 mg/kg V-0	200 mg/kg VII-0
Males					
DIGESTIVE SYSTEM					
LIVER		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		2	1	2	1
INFLAMMATION, SUBACUTE/CHRONIC.		8	9	8	7
HYPERTROPHY, HEPATOCELLULAR, CENTRILOBULAR.		1		3	6
FATTY CHANGE, MEDIAN CLEFT.		2	1		
FATTY CHANGE, HEPATOCELLULAR, CENTRILOBULAR.					
STOMACH		(10)			(10)
NO ABNORMALITY DETECTED		10			10
DUODENUM		(5)			(6)
NO ABNORMALITY DETECTED		5			6
JEJUNUM		(5)			(6)
NO ABNORMALITY DETECTED		5			6
ILEUM		(5)			(6)
NO ABNORMALITY DETECTED		5			6

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TABLE 45 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	LESION INCIDENCE (NUMERIC)			
	TREATMENT per day	0 mg/kg I-0	15 mg/kg III-0	50 mg/kg V-0
DIGESTIVE SYSTEM				
CECUM		(5)		(6)
NO ABNORMALITY DETECTED		5		6
COLON		(5)		(6)
NO ABNORMALITY DETECTED LYMPHATIC CONGESTION.		5		5
RECTUM		(5)		1
NO ABNORMALITY DETECTED				(6)
URINARY SYSTEM		5		6
KIDNEYS		(5)		(6)
NO ABNORMALITY DETECTED		1		3
CHRONIC PROGRESSIVE NEPHROPATHY. HYDRONEPHROSIS, UNILATERAL. AGGREGATES, LYMPHOID.		1		2
		4		1
				2

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TABLE 45 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	LESION INCIDENCE (NUMERIC)					
	Males					
	TREATMENT	0	15	50	200	
	per day	mg/kg	mg/kg	mg/kg	mg/kg	
		I-0	III-0	V-0	VII-0	
URINARY SYSTEM						
URINARY BLADDER		(5)				(6)
NO ABNORMALITY DETECTED		5				6
RESPIRATORY SYSTEM						
LUNGS		(5)				(6)
NO ABNORMALITY DETECTED						
INFLAMMATION, PERIVASCULAR.		3				4
INFLAMMATION, ALVEOLAR, ACUTE.		1				1
HEMORRHAGE.		1				1
TRACHEA		(5)				(6)
NO ABNORMALITY DETECTED						
INFLAMMATION, ACUTE, MUCOSAL.		5				5
EXUDATE.						1
						1

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TABLE 45 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT						LESION INCIDENCE (NUMERIC)									
	0		15		50		200		0		15		50		200	
	mg/kg		mg/kg		mg/kg		mg/kg		mg/kg		mg/kg		mg/kg		mg/kg	
	I-0		III-0		V-0		VII-0		I-0		III-0		V-0		VII-0	
	per day		per day		per day		per day		per day		per day		per day		per day	
CARDIOVASCULAR SYSTEM																
HEART									(5)						(6)	
NO ABNORMALITY DETECTED INFLAMMATION, SUBACUTE/CHRONIC.									4						6	
LYMPHATIC AND HEMATOPOIETIC SYSTEM																
SPLEEN									(5)						(6)	
NO ABNORMALITY DETECTED									5						6	
THYMUS									(5)						(6)	
NO ABNORMALITY DETECTED HEMORRHAGE.									3						2	
MANDIBULAR LYMPH NODE									2						4	
NO ABNORMALITY DETECTED ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS.									(5)						(6)	
MESENTERIC LYMPH NODE									5						5	
NO ABNORMALITY DETECTED									(5)						(6)	
									4						5	

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TABLE 45 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (ALL ANIMALS) - P₁ ADULTS

LESION	TREATMENT				LESION INCIDENCE (NUMERIC)				
	0	15	50	200	Males				
	mg/kg	mg/kg	mg/kg	mg/kg	I-0	III-0	V-0	VII-0	
	per day								
LYMPHATIC AND HEMATOPOIETIC SYSTEM									
MESENTERIC LYMPH NODE	(5)								(6)
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS.	1								1
BONE MARROW	(5)								(6)
NO ABNORMALITY DETECTED	5								6
PEYER'S PATCH	(5)								(6)
NO ABNORMALITY DETECTED	5								6
ENDOCRINE SYSTEM									
THYROID GLAND	(5)	(5)	(5)	(6)					(6)
NO ABNORMALITY DETECTED	5	5	5	2					2
HYPERTROPHY, FOLLICULAR CELL.				4					4
ADRENAL GLANDS	(5)								(6)
NO ABNORMALITY DETECTED	5			6					6

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TABLE 45 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT				LESION INCIDENCE (NUMERIC)			
	per day	mg/kg I-0	mg/kg III-0	mg/kg V-0	0	15	50	200
NERVOUS SYSTEM								
BRAIN					(5)			(6)
NO ABNORMALITY DETECTED					5			6
SPINAL CORD					(5)			(6)
NO ABNORMALITY DETECTED					5			6
SCIATIC NERVE					(5)			(6)
NO ABNORMALITY DETECTED					5			6
MUSCULAR AND SKELETAL SYSTEM								
FEMUR/KNEE JOINT					(5)			(6)
NO ABNORMALITY DETECTED					5			6
REPRODUCTIVE SYSTEM								
TESTES					(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED					10	9	9	10
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, UNILATERAL.						1	1	

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TABLE 46

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT per day	LESION INCIDENCE (NUMERIC)			
		Males			
		0 I-0	15 III-0	50 V-0	200 VII-0
		mg/kg	mg/kg	mg/kg	mg/kg
DIGESTIVE SYSTEM					
LIVER		(10)	(10)	(10)	(9)
NO ABNORMALITY DETECTED		2	1	2	
INFLAMMATION, SUBACUTE/CHRONIC.		8	9	8	7
HYPERTROPHY, HEPATOCELLULAR, CENTRILOBULAR.		1		3	6
FATTY CHANGE, MEDIAN CLEFT.		2	1		
FATTY CHANGE, HEPATOCELLULAR, CENTRILOBULAR.		(10)			(9)
STOMACH					
NO ABNORMALITY DETECTED		10			9
DUODENUM		(5)			(5)
NO ABNORMALITY DETECTED		5			5
JEJUNUM		(5)			(5)
NO ABNORMALITY DETECTED		5			5
ILEUM		(5)			(5)
NO ABNORMALITY DETECTED		5			5

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TABLE 46 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT					LESION INCIDENCE (NUMERIC)								
	per day	0 mg/kg I-0	15 mg/kg III-0	50 mg/kg V-0	200 mg/kg VII-0	Males								
DIGESTIVE SYSTEM														
CECUM			(5)										(5)	
NO ABNORMALITY DETECTED			5										5	
COLON			(5)										(5)	
NO ABNORMALITY DETECTED LYMPHATIC CONGESTION.			5										4	
RECTUM			(5)										(5)	
NO ABNORMALITY DETECTED			5										5	
URINARY SYSTEM														
KIDNEYS			(5)										(5)	
NO ABNORMALITY DETECTED			1										2	
CHRONIC PROGRESSIVE NEPHROPATHY.			1										2	
HYDRONEPHROSIS, UNILATERAL.													1	
AGGREGATES, LYMPHOID.			4										2	

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TABLE 46 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT					LESION INCIDENCE (NUMERIC)				
	0	15	50	200		Males				
	mg/kg	mg/kg	mg/kg	mg/kg	per day	I-0	III-0	V-0	VII-0	
URINARY SYSTEM										
URINARY BLADDER	(5)									(5)
NO ABNORMALITY DETECTED	5									5
RESPIRATORY SYSTEM										
LUNGS	(5)									(5)
NO ABNORMALITY DETECTED	3									4
INFLAMMATION, PERIVASCULAR.	1									1
INFLAMMATION, ALVEOLAR, ACUTE.	1									1
TRACHEA	(5)									(5)
NO ABNORMALITY DETECTED	5									5
CARDIOVASCULAR SYSTEM										
HEART	(5)									(5)
NO ABNORMALITY DETECTED	4									5
INFLAMMATION, SUBACUTE/CHRONIC.	1									

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TABLE 46 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESION	TREATMENT					LESION INCIDENCE (NUMERIC)							
	per day	0 mg/kg I-0	15 mg/kg III-0	50 mg/kg V-0	200 mg/kg VII-0	Males							
LYMPHATIC AND HEMATOPOIETIC SYSTEM													
SPLEEN		(5)			(5)								(5)
NO ABNORMALITY DETECTED		5			5								5
THYMUS		(5)			(5)								(5)
NO ABNORMALITY DETECTED		3			2								2
HEMORRHAGE.		2			3								3
MANDIBULAR LYMPH NODE		(5)			(5)								(5)
NO ABNORMALITY DETECTED		5			4								4
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS.		(5)			(5)								1
MESENTERIC LYMPH NODE		(5)			(5)								(5)
NO ABNORMALITY DETECTED		4			4								4
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS.		1			1								1
BONE MARROW		(5)			(5)								(5)
NO ABNORMALITY DETECTED		5			5								5
PEYER'S PATCH		(5)			(5)								(5)
NO ABNORMALITY DETECTED		5			5								5

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TABLE 46 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT per day	LESION INCIDENCE (NUMERIC)			
		Males			
		0 mg/kg I-0	15 mg/kg III-0	50 mg/kg V-0	200 mg/kg VII-0
ENDOCRINE SYSTEM					
THYROID GLAND		(5)	(5)	(5)	(5)
NO ABNORMALITY DETECTED HYPERTROPHY, FOLLICULAR CELL.		5	5	5	1 4
ADRENAL GLANDS		(5)			(5)
NO ABNORMALITY DETECTED		5			5
NERVOUS SYSTEM					
BRAIN		(5)			(5)
NO ABNORMALITY DETECTED		5			5
SPINAL CORD		(5)			(5)
NO ABNORMALITY DETECTED		5			5
SCIATIC NERVE		(5)			(5)
NO ABNORMALITY DETECTED		5			5

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TABLE 46 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESION	TREATMENT per day	LESION INCIDENCE (NUMERIC)			
		Males			
		0 mg/kg I-0	15 mg/kg III-0	50 mg/kg V-0	200 mg/kg VII-0
MUSCULAR AND SKELETAL SYSTEM					
FEMUR/KNEE JOINT		(5)			(5)
NO ABNORMALITY DETECTED		5			5
REPRODUCTIVE SYSTEM					
TESTES		(10)	(10)	(10)	(9)
NO ABNORMALITY DETECTED		10	9	9	9
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, UNILATERAL.			1	1	
EPIDIDYMIDES		(10)	(10)	(10)	(9)
NO ABNORMALITY DETECTED		10	10	10	9
PROSTATE		(10)	(10)	(10)	(9)
NO ABNORMALITY DETECTED		2	6	4	3
INFLAMMATION, SUBACUTE/CHRONIC.			2	2	
AGGREGATES, LYMPHOID.		8	4	6	6
SEMINAL VESICLES		(10)	(10)	(10)	(9)
NO ABNORMALITY DETECTED		10	10	10	9

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TABLE 46 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT per day	LESION INCIDENCE (NUMERIC)			
		Males			
		0 mg/kg I-0	15 mg/kg III-0	50 mg/kg V-0	200 mg/kg VII-0
REPRODUCTIVE SYSTEM					
COAGULATING GLANDS		(10)	(10)	(10)	(9)
NO ABNORMALITY DETECTED		10	10	10	9
TISSUES NOT INCLUDED WITHIN BODY SYSTEMS					
CAUSE OF DEATH		(10)	(10)	(10)	(9)
TERMINAL SACRIFICE.		10	10	10	9

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TABLE 47

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT per day	LESION INCIDENCE (NUMERIC)			
		Males		Females	
		0 mg/kg II-0	15 mg/kg IV-0	50 mg/kg VI-0	200 mg/kg VIII-0
DIGESTIVE SYSTEM					
LIVER		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		1	1	2	3
NECROSIS, FOCAL.					1
NECROSIS, CENTRILOBULAR.					2
INFLAMMATION, SUBACUTE/CHRONIC.		4	2	5	10
HYPERTROPHY, HEPATOCELLULAR, CENTRILOBULAR.		8	5	4	3
HEMATOPOIESIS, EXTRAMEDULLARY.		1			
FATTY CHANGE, HEPATOCELLULAR, PERIPORTAL.			2	1	
FATTY CHANGE, HEPATOCELLULAR, MIDZONAL.					
STOMACH		(10)	(1)	(2)	(9)
NO ABNORMALITY DETECTED		10	1	2	8
EROSION/ULCER, NONGLANDULAR.					1
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.					1
DUODENUM		(5)	(1)	(2)	(10)
NO ABNORMALITY DETECTED		5	1	2	10

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TABLE 47 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESION	TREATMENT				LESION INCIDENCE (NUMERIC)				
	0	15	50	200	Females				
	mg/kg II-0	mg/kg IV-0	mg/kg VI-0	mg/kg VIII-0					
DIGESTIVE SYSTEM									
JEJUNUM	(5)	(1)	(2)	(10)					
NO ABNORMALITY DETECTED AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.	5	1	2	10					1
ILEUM	(5)	(1)	(2)	(9)					
NO ABNORMALITY DETECTED	5	1	2	9					
CECUM	(5)	(1)	(2)	(7)					
NO ABNORMALITY DETECTED INFLAMMATION, MUCOSAL.	5	1	2	6					1
COLON	(5)	(1)	(2)	(10)					
NO ABNORMALITY DETECTED AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.	5	1	2	10					3

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TABLE 47 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESION	TREATMENT				LESION INCIDENCE (NUMERIC)				
	0	15	50	200	Females				
	mg/kg	mg/kg	mg/kg	mg/kg	II-0	IV-0	VI-0	VIII-0	
	per day								
DIGESTIVE SYSTEM									
RECTUM	(5)	(1)	(2)	(10)					
NO ABNORMALITY DETECTED	5	1	2	10					2
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.									
URINARY SYSTEM									
KIDNEYS	(5)	(1)	(2)	(10)					
NO ABNORMALITY DETECTED	3		1	3					
CHRONIC PROGRESSIVE NEPHROPATHY.	1			1					
HYDRONEPHROSIS, UNILATERAL.									2
FATTY CHANGE, TUBULAR, DIFFUSE.		1	1	3					
DILATATION, TUBULAR, FOCAL.									
DILATATION, TUBULAR, DIFFUSE.									
DEGENERATION/NECROSIS, TUBULAR, EPITHELIAL.									1
AGGREGATES, LYMPHOID.	1			1					3
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.									

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TABLE 47 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESION	TREATMENT					LESION INCIDENCE (NUMERIC)				
	0	15	50	200		Females				
	mg/kg	mg/kg	mg/kg	mg/kg		II-0	IV-0	VI-0	VIII-0	
	per day	per day	per day	per day						
URINARY SYSTEM										
URINARY BLADDER						(5)	(1)	(2)	(10)	
NO ABNORMALITY DETECTED AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.						5	1	2	10	1
RESPIRATORY SYSTEM										
LUNGS						(5)	(1)	(2)	(10)	
NO ABNORMALITY DETECTED INFLAMMATION, PERIVASCULAR.						4	1	2	8	
INFLAMMATION, ALVEOLAR, SUBACUTE/CHRONIC.						1			1	1
INFLAMMATION, ALVEOLAR, ACUTE.										1
TRACHEA						(5)	(1)	(2)	(10)	
NO ABNORMALITY DETECTED INFLAMMATION, ACUTE, MUCOSAL. EXUDATE.						5	1	2	8	2
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.										2

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TABLE 47 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT					LESION INCIDENCE (NUMERIC)				
	0	15	50	200		Females				
	mg/kg	mg/kg	mg/kg	mg/kg		II-0	IV-0	VI-0	VIII-0	
	per day									
CARDIOVASCULAR SYSTEM										
HEART	(5)	(1)	(2)	(10)						
NO ABNORMALITY DETECTED	5	1	2	10						
LYMPHATIC AND HEMATOPOIETIC SYSTEM										
SPLEEN	(5)	(1)	(2)	(10)						
NO ABNORMALITY DETECTED	1			1						
PIGMENT INCREASED.				2						
HYPERPLASIA, LYMPHOID.				1						
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED.	4			5						
DEPLETION/ATROPHY, LYMPHOID.		1	2	4						
THYMUS	(5)	(1)	(2)	(10)						
NO ABNORMALITY DETECTED										
NECROSIS, ACUTE, LYMPHOID.	2			3						
HEMORRHAGE.	1	1	2	4						
DEPLETION/ATROPHY, LYMPHOID.	2	1	1	3						

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TABLE 47 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESION	TREATMENT				LESION INCIDENCE (NUMERIC)				
	0	15	50	200	Females				
	mg/kg	mg/kg	mg/kg	mg/kg	II-0	IV-0	VI-0	VIII-0	
	per day								
LYMPHATIC AND HEMATOPOIETIC SYSTEM									
MANDIBULAR LYMPH NODE					(5)	(1)	(2)	(10)	
NO ABNORMALITY DETECTED					4	1	1	7	
NECROSIS, ACUTE, LYMPHOID.									
INFLAMMATION, ACUTE.					1			2	
HYPERPLASIA, PLASMA CELL.							1	1	
DEPLETION/ATROPHY, LYMPHOID.					(5)	(1)	(2)	(10)	
MESENTERIC LYMPH NODE					5	1	1	8	
NO ABNORMALITY DETECTED									
NECROSIS, ACUTE, LYMPHOID.							1	1	
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS.							1	1	
DEPLETION/ATROPHY, LYMPHOID.					(5)	(1)	(2)	(10)	
BONE MARROW					2	1	2	7	
NO ABNORMALITY DETECTED					3			3	
HEMATOPOIESIS, INCREASED.									

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TABLE 47 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT					LESION INCIDENCE (NUMERIC)				
	0	15	50	200		Females				
	mg/kg	mg/kg	mg/kg	mg/kg		II-0	IV-0	VI-0	VIII-0	
	per day									
LYMPHATIC AND HEMATOPOIETIC SYSTEM										
PEYER'S PATCH	(5)	(1)	(2)	(9)						
NO ABNORMALITY DETECTED	5	1	2	9						
ENDOCRINE SYSTEM										
PITUITARY GLAND			(1)	(1)						
CONGESTION.										
THYROID GLAND	(5)	(7)	(7)	(10)						
NO ABNORMALITY DETECTED	5	7	7	9						
HYPERTROPHY, FOLLICULAR CELL.										
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED.										
ADRENAL GLANDS	(5)	(1)	(2)	(10)						
NO ABNORMALITY DETECTED	5	1	2	10						

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

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TABLE 47 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT				LESION INCIDENCE (NUMERIC)	
	0	15	50	200	Females	
	mg/kg II-0	mg/kg IV-0	mg/kg VI-0	mg/kg VIII-0		
NERVOUS SYSTEM						
BRAIN	(5)	(1)	(2)	(10)		
NO ABNORMALITY DETECTED	5	1	2	10		
SPINAL CORD	(5)	(1)	(2)	(10)		
NO ABNORMALITY DETECTED	5	1	2	10		
SCIATIC NERVE	(5)	(1)	(2)	(10)		
NO ABNORMALITY DETECTED	5	1	2	10		
MUSCULAR AND SKELETAL SYSTEM						
FEMUR/KNEE JOINT	(5)	(1)	(2)	(10)		
NO ABNORMALITY DETECTED	5	1	1	10		
FIBROUS OSTEODYSTROPHY.			1	1		

Figure in parentheses is number of animals microscopically examined for this tissue
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TABLE 47 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT					LESION INCIDENCE (NUMERIC)				
	0	15	50	200		Females				
	mg/kg	mg/kg	mg/kg	mg/kg		II-0	IV-0	VI-0	VIII-0	
	per day	per day	per day	per day						
REPRODUCTIVE SYSTEM										
OVARIES	(10)	(10)	(10)	(10)						
NO ABNORMALITY DETECTED	10	10	10	10						
UTERUS	(10)	(10)	(10)	(10)						
NO ABNORMALITY DETECTED	1									3
INFLAMMATION, SUBACUTE/CHRONIC, MUCOSAL. IMPLANTATION SITES.	9	10	10	10						7
VAGINA	(10)	(10)	(10)	(10)						
INFLAMMATION, MUCOSAL. DILATATION.			1							
Diestrus/Anestrus.	10	10	10	10						10

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TABLE 47 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (ALL ANIMALS) - P₁ ADULTS

LESIONS	TREATMENT					Females					LESION INCIDENCE (NUMERIC)								
	0	15	50	100	200	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	II-0	IV-0	VI-0	VIII-0	(10)	(10)	(10)	(10)	(10)
CERVIX															(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED															10	10	10	10	10
TISSUES NOT INCLUDED WITHIN BODY SYSTEMS																			
CAUSE OF DEATH															(10)	(10)	(10)	(10)	(10)
DOSING ACCIDENT.																			1
UNDETERMINED.																			1
TERMINAL SACRIFICE.															10	9	8	5	5
DYSTOCIA.																1	2	3	3

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

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TABLE 48

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESION	TREATMENT				LESION INCIDENCE (NUMERIC)				
	0	15	50	200	Females				
	mg/kg II-0	mg/kg IV-0	mg/kg VI-0	mg/kg VIII-0					
DIGESTIVE SYSTEM									
LIVER	(10)	(9)	(8)	(5)					
NO ABNORMALITY DETECTED	1	1	1						
NECROSIS, FOCAL.				1					
INFLAMMATION, SUBACUTE/CHRONIC.	4	2	5	2					
HYPERTROPHY, HEPATOCELLULAR, CENTRILOBULAR.	8	5	4	5					
HEMATOPOIESIS, EXTRAMEDULLARY.	1			3					
FATTY CHANGE, HEPATOCELLULAR, PERIPORTAL.									
FATTY CHANGE, HEPATOCELLULAR, MIDZONAL.		1							
STOMACH									
NO ABNORMALITY DETECTED	(10)			(5)					
EROSION/ULCER, NONGLANDULAR.	10			4					
DUODENUM	(5)			1					
NO ABNORMALITY DETECTED	5			5					

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TABLE 48 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT				LESION INCIDENCE (NUMERIC)				
	0	15	50	200	Females				
	mg/kg	mg/kg	mg/kg	mg/kg	II-0	IV-0	VI-0	VIII-0	
	per day								
DIGESTIVE SYSTEM									
JEJUNUM					(5)				(5)
NO ABNORMALITY DETECTED					5				5
ILEUM					(5)				(5)
NO ABNORMALITY DETECTED					5				5
CECUM					(5)				(5)
NO ABNORMALITY DETECTED					5				4
NO ABNORMALITY DETECTED									1
NO ABNORMALITY DETECTED					(5)				(5)
NO ABNORMALITY DETECTED					5				5
NO ABNORMALITY DETECTED					(5)				(5)
NO ABNORMALITY DETECTED					5				5

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 The absence of a number indicates the lesion specified was not identified

TABLE 48 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT					LESION INCIDENCE (NUMERIC)				
	0	15	50	200		Females				
	mg/kg II-0	mg/kg IV-0	mg/kg VI-0	mg/kg VIII-0	per day					
URINARY SYSTEM										
KIDNEYS	(5)			(5)						
NO ABNORMALITY DETECTED										
CHRONIC PROGRESSIVE NEPHROPATHY.	3			2						
DILATATION, TUBULAR, FOCAL.	1			1						
AGGREGATES, LYMPHOID.	1			3						
URINARY BLADDER				1						
NO ABNORMALITY DETECTED	(5)			(5)						
RESPIRATORY SYSTEM										
LUNGS										
NO ABNORMALITY DETECTED										
INFLAMMATION, PERIVASCULAR.	5			5						
INFLAMMATION, ALVEOLAR, SUBACUTE/CHRONIC.	(5)			(5)						
	4			4						
	1			1						

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

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TABLE 48 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT				LESION INCIDENCE (NUMERIC)			
	0	15	50	200	Females			
	mg/kg II-0	mg/kg IV-0	mg/kg VI-0	mg/kg VIII-0	0	15	50	200
	per day	per day	per day	per day	mg/kg II-0	mg/kg IV-0	mg/kg VI-0	mg/kg VIII-0
RESPIRATORY SYSTEM								
TRACHEA					(5)			(5)
NO ABNORMALITY DETECTED					5			5
CARDIOVASCULAR SYSTEM								
HEART					(5)			(5)
NO ABNORMALITY DETECTED					5			5
LYMPHATIC AND HEMATOPOIETIC SYSTEM								
SPLEEN					(5)			(5)
NO ABNORMALITY DETECTED					1			1
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED.					4			4
THYMUS					(5)			(5)
NO ABNORMALITY DETECTED					2			2
HEMORRHAGE.					1			1

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TABLE 48 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESION	LESION INCIDENCE (NUMERIC)				
	TREATMENT	0	15	50	200
	per day	mg/kg	mg/kg	mg/kg	mg/kg
		II-0	IV-0	VI-0	VIII-0
LYMPHATIC AND HEMATOPOIETIC SYSTEM					
THYMUS		(5)			(5)
DEPLETION/ATROPHY, LYMPHOID.		2			2
MANDIBULAR LYMPH NODE		(5)			(5)
NO ABNORMALITY DETECTED		4			3
HYPERPLASIA, PLASMA CELL.		1			2
MESENTERIC LYMPH NODE		(5)			(5)
NO ABNORMALITY DETECTED		5			4
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS.					1
BONE MARROW		(5)			(5)
NO ABNORMALITY DETECTED		2			3
HEMATOPOIESIS, INCREASED.		3			2

Figure in parentheses is number of animals microscopically examined for this tissue
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TABLE 48 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT				LESION INCIDENCE (NUMERIC)				
	0 mg/kg II-0	15 mg/kg IV-0	50 mg/kg VI-0	200 mg/kg VIII-0	Females				
LYMPHATIC AND HEMATOPOIETIC SYSTEM									
PEYER'S PATCH		(5)		(5)					(5)
NO ABNORMALITY DETECTED		5							5
ENDOCRINE SYSTEM									
THYROID GLAND		(5)	(6)	(5)					(5)
NO ABNORMALITY DETECTED		5	6	5					4
HYPERTROPHY, FOLLICULAR CELL.									1
ADRENAL GLANDS		(5)							(5)
NO ABNORMALITY DETECTED		5							5
NERVOUS SYSTEM									
BRAIN		(5)							(5)
NO ABNORMALITY DETECTED		5							5

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

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TABLE 48 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT				LESION INCIDENCE (NUMERIC)				
	0 mg/kg II-0	15 mg/kg IV-0	50 mg/kg VI-0	200 mg/kg VIII-0	Females				
NERVOUS SYSTEM									
SPINAL CORD					(5)				(5)
NO ABNORMALITY DETECTED					5				5
SCIATIC NERVE					(5)				(5)
NO ABNORMALITY DETECTED					5				5
MUSCULAR AND SKELETAL SYSTEM									
FEMUR/KNEE JOINT					(5)				(5)
NO ABNORMALITY DETECTED					5				5
REPRODUCTIVE SYSTEM									
OVARIES					(10)	(9)	(8)		(5)
NO ABNORMALITY DETECTED					10	9	8		5

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

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TABLE 48 (Continued)

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS (SACRIFICED BY DESIGN) - P₁ ADULTS

LESIONS	TREATMENT per day	LESION INCIDENCE (NUMERIC)			
		Females			
		0 mg/kg II-0	15 mg/kg IV-0	50 mg/kg VI-0	200 mg/kg VIII-0
REPRODUCTIVE SYSTEM					
UTERUS		(10)	(9)	(8)	(5)
NO ABNORMALITY DETECTED INFLAMMATION, SUBACUTE/CHRONIC, MUCOSAL, IMPLANTATION SITES.		1	1		1
VAGINA		9	9	8	4
Diestrus/Anestrus.		(10)	(9)	(8)	(5)
CERVIX		10	9	8	5
NO ABNORMALITY DETECTED		(10)	(9)	(8)	(5)
TISSUES NOT INCLUDED WITHIN BODY SYSTEMS		10	9	8	5
CAUSE OF DEATH		(10)	(9)	(8)	(5)
TERMINAL SACRIFICE.		10	9	8	5

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

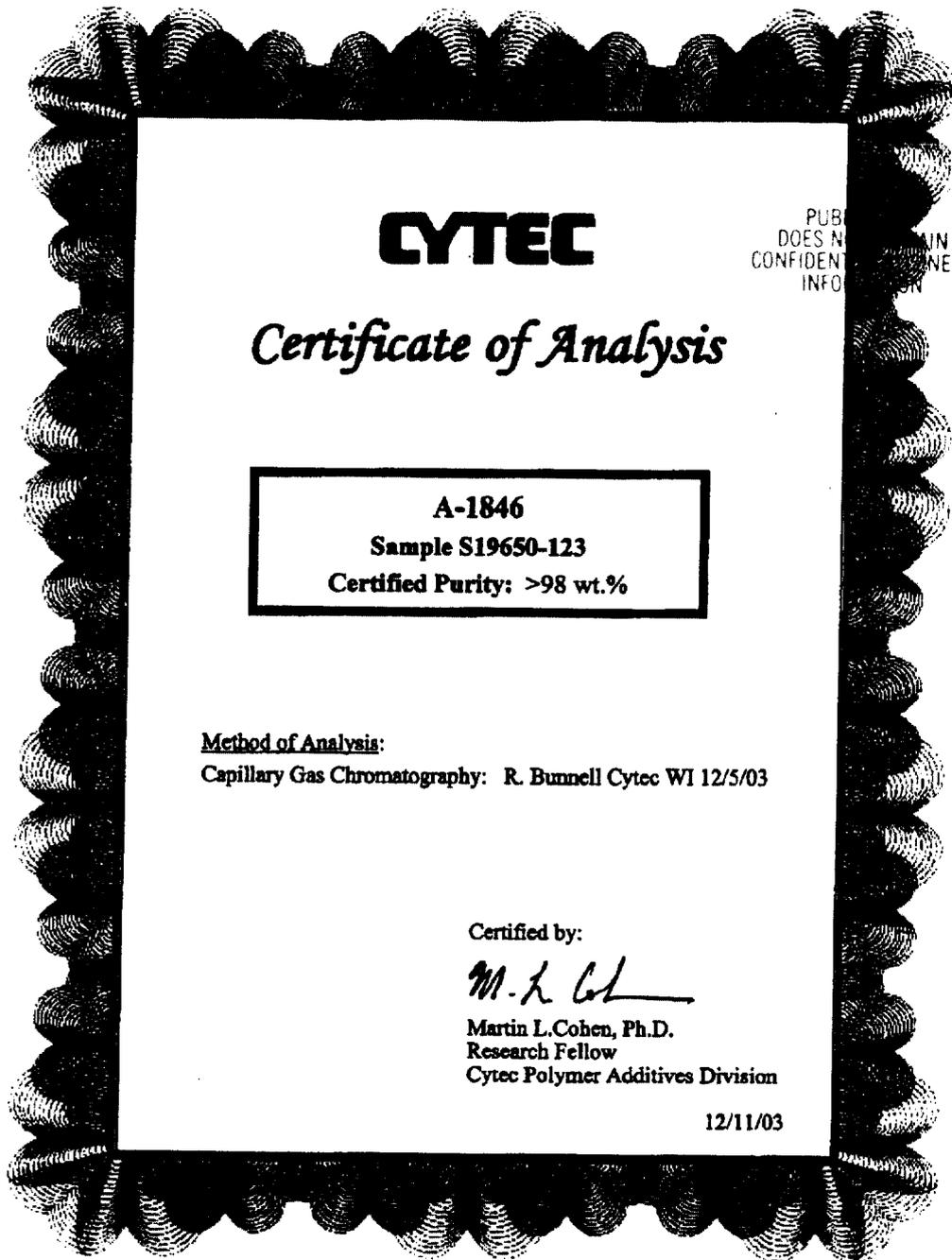
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APPENDICES

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APPENDIX A
CERTIFICATE OF ANALYSIS



CYTEC

PUB
DOES N
CONFIDENT
INFO
IN
BUSINESS
OR

Certificate of Analysis

A-1846
Sample S19650-123
Certified Purity: >98 wt.%

Method of Analysis:

Capillary Gas Chromatography: R. Bunnell Cytec WI 12/5/03

Certified by:

Martin L. Cohen, Ph.D.
Research Fellow
Cytec Polymer Additives Division

12/11/03

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APPENDIX B
PROTOCOL AND PROTOCOL AMENDMENTS

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

A-1846: Combined Repeated Dose Toxicity Study With the Reproduction/Developmental
Toxicity Screening Test in Rats

Work Request Number 15031

Service Code 1422

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Protocol

Haskell Animal Welfare Committee Number: DGRT-153GP

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INTRODUCTION AND OBJECTIVE

The objective of this study is to evaluate the potential subchronic and reproductive toxicity of the test substance when administered by gavage to male and female rats during pre-mating, cohabitation, gestation, until lactation day 3. Clinical pathology, neurobehavioral function, gross pathology, histopathology, and reproductive function will be evaluated.

MATERIALS AND METHODS

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A. Sponsor And Test Facility

Sponsor (approval effective on the date authorized on the contract):

Cytec Industries, Inc.
Five Garret Mountain Plaza
West Paterson, NJ 07424

Sponsor study monitor:

Patricia A. Vernon
Manager, Regulatory Toxicology Programs & Asia-Pacific Regulatory Compliance
Cytec Industries Inc.
Five Garret Mountain Plaza
West Paterson, NJ 07424
(P) 973-357-3375
(F) 973-357-3057
Patricia.Vernon@cytec.com

Test Facility:

DuPont Haskell Laboratory for Health and Environmental Sciences
E.I. du Pont de Nemours and Company
Newark, Delaware.

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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B. Regulatory Compliance

1. Good Laboratory Practice Standards

This study will be conducted in compliance with United States (U.S.) Environmental Protection Agency (EPA), Toxic Substances Control Act (TSCA) (40 CFR part 792) Good Laboratory Practice Standards (1989) which are consistent with the Organisation for Economic Cooperation and Development (OECD/OCDE) Principles of Good Laboratory Practice Standards (as revised in 1997) published in ENV/MC/CHEM(98)17 (OCDE/GD(92)32).

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2. Test Guidelines

This study will be conducted in compliance with the following guidelines:

- Organisation for Economic Cooperation and Development (OECD/OCDE). Guidelines for the Testing of Chemicals, Section 4 (Part 422): Health Effects (MAR-1996).
- United States (U.S.) Environmental Protection Agency (EPA), Office of Prevention, Pesticides, and Toxic Substances (OPPTS) Health Effects Test Guidelines, OPPTS 870.3650 Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test (JULY-2000).

C. Experimental Design

Study Parameter	Study Dates
Initiation of test substance administration	March 3, 2004
In-life Completion Date	April 22, 2004 (Approximate)

Treatment Groups and Daily Dosage

Group		Number/Group		Exposure	Test Formulation Concentration
Male	Female	Male	Female	(mg/kg/day) ^a	(mg/mL) ^b
I-0	II-0	10	10	0 ^c	0
III-0	IV-0	10	10	15	1.88
V-0	VI-0	10	10	50	6.25
VII-0	VIII-0	10	10	200	25

- a Formulations of test substance in PEG 400 (Technical Grade) will be administered once daily by oral gavage at a dosing volume of 8 mL/kg.
- b To achieve these concentrations of active ingredient, the formulations will be adjusted for sample purity.
- c The control group animals will receive vehicle PEG 400 (Technical Grade) only at 8 mL/kg.

Dosing Schedule

- All animals will be dosed once daily by gavage for approximately 14 days prior to cohabitation and during the cohabitation period (up to 2 weeks).
- Male rats and female rats showing no evidence of copulation will continue to be dosed after the end of the cohabitation period until sacrifice.
- Females showing evidence of copulation will be dosed throughout gestation.
- Pregnant females in the process of delivery or showing signs of delivery will not be dosed.
- Females will be dosed after delivering litters, until day 3 postpartum.
- Females that do not deliver a litter will continue to be dosed until the day before sacrifice.

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Sacrifice Schedule

<u>Animals</u>	<u>Schedule</u>
Adult Males	Test Day 28 (at the earliest)
Pregnant Females	Day 4 of lactation
Nonpregnant Females	Approximately Day 25 after the end of cohabitation
Offspring	Day 4 of lactation

1. Selection of Dose Levels

In a previous 2-week range-finding study⁽¹⁾ groups of 5 male and 5 female rats were administered the test substance by gavage at dosages of 0, 250, 500, or 1000 mg/kg/day. Test substance-related mortality and clinical signs of toxicity occurred at 500 and 1000 mg/kg/day. Test substance-related reductions in body weight gain and weight loss occurred at 250, 500, and 1000 mg/kg/day. Test substance-related gross lesions in the liver and stomach were observed in animals in these groups.

Dosages of 0, 15, 50, and 200 mg/kg/day were selected for the current study. The 50 mg/kg/day level is expected to produce no or minimal toxic effects. The 200 mg/kg/day level is expected to produce some systemic toxicity but no mortality. The 15 ppm level is expected to be the no-observed-effect level (NOEL).

2. Route of Administration

The test substance will be administered by oral intubation (gavage) as it is the route recommended by test guidelines. The volume of test substance or vehicle given to each rat will be based on the most recently recorded body weight.

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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D. Analytical

1. Vehicle

Name: PEG 400 (Technical Grade)

Manufacturer,
Production Code, Lot

Number, and Purity: Recorded in study records

Known Contaminants: none

2. Test Substance

Test Substance: A-1846, supplied by the sponsor

Identity: Reported by the sponsor

Purity: 98%, reported by sponsor

Haskell Number: 26200

Analytical Standard: Test substance sample, supplied by the sponsor

Stability of Test Substance: Confirmed by analyses near the beginning and end of the study

Additional Information: Off-white crystal

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A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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3. Test Formulation Preparation

Frequency of Preparation: Test formulations will be mixed daily for at least the first 10 days to establish the ability to mix weekly.

Preparation Method: Documented in the study records

Storage Conditions: Prepared formulations refrigerated

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4. Test Formulation Sampling

Type	Collected From	Storage Conditions Until Analysis
Control	Mixing Vessel	Room temperature

Homogeneity, Initial Concentration Verification, and 5 Hour Stability of the Test Substance in the Vehicle^{a,b,c}

Top	Mixing Vessel - Top	Room temperature
Middle	Mixing Vessel - Middle	Room temperature
Bottom	Mixing Vessel - Bottom	Room temperature
5 Hour Stability	Mixing Vessel	Room temperature for approximately 5 hours

10-Day Stability – All samples listed above will be taken at the initial formulation preparation. The remaining formulation after dosing will be refrigerated for 10 days and then analyzed for concentration verification (duplicate samples) and a 5-hour room temperature stability.^c

Concentration Verification:^{a,c,d} Mixing Vessel Room temperature

- a Whenever samples are collected, a sample of the vehicle will also be collected and analyzed.
- b Four samples (approximately 3 ml each) will be taken from each concentration of the initial test formulations near the beginning of the study.
- c Remaining formulation samples after dosing will be stored refrigerated for 10 days, then sampled, and discarded when the final results from the analysis have been accepted.
- d Duplicate samples will be taken near the middle and end of the study.

The samples will be analyzed by the Haskell Laboratory Analytical Chemistry Group on the day the samples are collected. If samples cannot be analyzed at the specified times, they will be refrigerated until analyses can be conducted. On days samples are taken, the formulations remaining after dosing will be stored in the refrigerator for additional analysis. The Analytical Method used will be documented in the Analytical Study Group records and may be included in the final report.

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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E. Test Species

Species: CrI:CD[®](SD)IGS BR, nulliparous, nonpregnant rats

Sex: Male and female nonsibling

Source: Charles River Laboratories, Inc
City/State will be documented in study records and final report

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Number of Rats Requested: 45 per sex

Age at Arrival: 52 days

Age at Start of Study: Approximately 66 days

Weight at Arrival: 201-225 grams (males); 176-200 grams (females)
The weight range is not a factor for the purposes of this study and, therefore, deviations outside of this range are expected not to have any impact on the study. The body weight range will be documented in the study records and provided in the final report.

Identification: Number assigned to each animal which will be tattooed on the tail during pretest period and included on cage label.

Selection Criteria: Consistently acceptable health status and extensive experience with this strain at Haskell Laboratory

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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F. Animal Husbandry

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Housing - Female

Quarantine - Premating: Singly in stainless steel, wire-mesh cages suspended above cage boards; sexes on separate racks

Cohabitation: With males in male's cage on a 1:1 basis in stainless steel, wire-mesh cages suspended above cage boards

G Day 0 - 19: Singly in stainless steel, wire-mesh cages suspended above cage boards; sexes on separate racks.

G Day 20 - L Day 4: Females assumed pregnant will be housed singly in polycarbonate pans with bedding material. Females assumed not pregnant will be housed in the same manner on the day that mating pairs are separated.

Housing - Male

All Phases: Singly in stainless steel, wire-mesh cages suspended above cage boards; sexes on separate racks except during cohabitation

Cage Rack Positioning: Cage racks will not be relocated within the animal room.

Climate: Temperature of 18-26°C (targeted to 22-24°C)
Relative humidity of 30-70% (targeted to 40-60%).

Unless judged by the study director or the laboratory veterinarian to have affected the results of the study, the relative humidity and temperature ranges in the housing rooms will be recorded but will not be included in the final report.

Illumination: Artificial (fluorescent light) on an approximate 12-hour light/dark cycle.

Water: Tap water *ad libitum* from United Water Delaware

Feed: PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002 *ad libitum* except when fasted.

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G. Animal Health and Environmental Monitoring Program

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

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Water Screening Tests: Total bacterial counts, and the presence of coliforms, lead, and other contaminants

Cage and Cage Rack Screening Tests: Analyzed for sentinel bacteria to ensure adequate sanitation by the cagewashers

Feed: Certified animal feed is used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates.

Program Administration: Laboratory animal veterinarian

Data: Maintained separately from study records and may be included in the final report at the discretion of the study director

H. Quarantine

Quarantine Period: Minimum of 3 days

Quarantine Release: Performed by the laboratory animal veterinarian or designee on the basis of adequate body weight gain and freedom of clinical signs

I. Pretest

Pretest Period: Minimum of 5 days

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J. Assignment to Groups

Selection Criteria: Animals with adequate body weight gain and free of any clinical signs of disease or injury; any animals with preexisting ophthalmology abnormalities may be eliminated from consideration for use in the study; weight variation of individual rats will not exceed $\pm 20\%$ of the mean weight for each sex

Replacement Criteria: On test day 1, if necessary and possible, animals outside this range will be replaced with others fitting the study criteria above

Randomization: Computerized, stratified randomization so that no statistically significant group mean body weight differences occur within a sex

Disposition of Remaining Animals: To be sent to Animal Resources or sacrificed by carbon dioxide asphyxiation, at the discretion of the study director

Subgroup Designations: First 5 surviving rats – Clinical and Anatomic Pathology Evaluations
Last 5 surviving rats – Neurobehavioral Evaluations

K. Health Observations

Frequency: All animals – At least once daily during quarantine and predosing and twice daily thereafter

Scope: Cage-site examination to detect moribund or dead animals and abnormal behavior and/or appearance

L. General Clinical Observations

Frequency: All animals - daily at approximately the same time of day (± 2 hours)

Scope: Acute/systemic toxicity

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M. Detailed Clinical Observations

Frequency: Once during pretest (baseline), and weekly thereafter at approximately the same time of day (± 2 hours)

Scope: Animals individually handled and examined for abnormal behavior and appearance in a standardized arena; observations will include (but are not limited to) evaluation of fur, skin, eyes, mucous membranes, occurrence of secretions and excretions, autonomic nervous system activity (lacrimation, piloerection, and unusual respiratory pattern), changes in gait, posture, response to handling, presence of clonic, tonic, stereotypical, or bizarre behavior.

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N. Body Weight

Frequency

Quarantine: All animals - at least once

Predosing: Weekly

Premating: Weekly

Cohabitation: Weekly

Gestation: 0, 7, 14, 21 G

Lactation: 0, 4 L

Post-cohabitation^a: Weekly and at Terminal Sacrifice

^a Males and females that are not pregnant or assumed not pregnant

O. Food Consumption and Food Efficiency

Frequency

Premating: Weekly

Cohabitation: None

Gestation: 0, 7, 14, 21 G

Lactation: 0, 4 L

Post-cohabitation^a: None

Calculation of Food Consumption: Weigh each feeder at the beginning and end of interval and subtract final weight and amount of spillage from the feeder from initial weight

Calculation of Mean

Daily Food Efficiency: From food consumption and body weight data

^a Males and females that are not pregnant or assumed not pregnant

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P. Cohabitation Procedures

Frequency^a: Once after approximately 2 weeks of exposure to the test substance

Scope: Each female will be continually housed on a 1:1 basis with a randomly selected, nonsibling male of the same concentration level.

Duration: Until evidence of copulation is observed or the cohabitation period has ended, at which time the mating pairs will be separated.

Evidence of Copulation^b: Daily examination of each female for an intravaginal copulation plug or sperm in the vaginal lavage sample.

- a First day of cohousing = Day 1 of cohabitation; End of cohousing = Day 15 of cohabitation
b Evidence of copulation = Day 0 of gestation

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Q. Lactation Procedures

At each examination period, offspring will be individually handled and examined for abnormal behavior and appearance; any dead or abnormal pups will be recorded.

Day 0^a: Live and dead pups in each litter will be counted by sex and individually weighed as soon as possible after delivery is completed.

Day 4^b: Pups in each litter will be counted by sex and individually weighed and a gross external examination will be performed.

- a Day of delivery = Day 0 of lactation
b Litter Sacrifice

If litters die prior to Day 4 of lactation, the female will be sacrificed. If the female dies prior to Day 4 of lactation, the litter will be sacrificed.

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R. Neurobehavioral Evaluation

Frequency: Males - Once near the end of the dosing period
(prior to fasting for clinical pathology evaluation)
Females - Once near the end of the premating period.

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Scope: Neurobehavioral test battery consisting of functional
observational battery assessments (FOB) and motor activity
(MA).

Number of Animals: 5/sex/group, randomly selected.

Animal Identification: Experimenter will be unaware of treatment group of the animals.

Replicate Identification: Animals will be assigned to 2 replicates to correspond to
assessments conducted over a 2-day period. Replicate
designations will not be reported in the final report, but will be
recorded in the study records.

Assignment to Replicates: Counterbalanced by all groups within a sex.

Order of FOB Assessment: Counterbalanced by sex and dose over time; same order used at
all time points.

Order of MA Assessment: Counterbalanced by group and sex across the 30 MA monitors
and time of day to the fullest extent possible.

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1. Parameters

Phase	Order	Procedure	Parameters or Methods
	1	Acclimation to the Home cage for at least 10 minutes ^a	NA
FOB	2	Home Cage Assessments	posture palpebral closure tremors convulsions gait/coordination
FOB	3	Removal from Home Cage and Handling Assessments	ease of removal ease of handling muscle tone vocalizations piloerection palpebral closure fur/skin appearance lacrimation salivation exophthalmus mucous membranes dehydration emaciation
FOB	4	Open Field Arena (approx. 85 x 59 x 20 cm)	righting reflex posture tremors gait/coordination rate of respiration convulsions muscle spasms/fasciculation vocalizations palpebral closure diarrhea polyuria
FOB	5	Manipulations in Open Field	approach and touch response auditory response tail pinch response foot splay
FOB	6	Fore- and hindlimb grip strength Strain gauge (Chatillon [®])	forelimb grip strength hindlimb grip strength
MA	7	Motor Activity	Duration of movement and number of movements will be evaluated in 6 consecutive blocks of 10 minutes each as well as for the total 60-minute session.
MA	8	Assessments in MA monitor	diarrhea polyuria
FOB	9	Pupillary Constriction or Response ^b	Light beam in each eye in the darkened MA room
	10	Body weight ^c	

- a The "home cage" will be defined as the cage on the transport rack to which an individual animal is assigned. This cage will be similar in design to the home cage.
- b Conducted at the conclusion of motor activity while the animals are still in the motor activity monitor.
- c Data will not be included in the final report

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S. Clinical Pathology Evaluation

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Frequency: - Once before the cohabitation period
(Hematology, Clinical Chemistry)
- At terminal sacrifice (Coagulation)
- Selected tests on animals showing clinical evidence of toxicity
or sacrificed *in extremis*, if deemed necessary by the clinical
pathologist and study director

Number of Animals: 5/sex/group, randomly selected

Fasting: After 3 p.m. (for at least 15 hours) the day before the evaluation
(hematology, clinical chemistry).

Anesthesia: Carbon dioxide

1. Collection Sites and Samples

Hematology: Orbital sinus (0.5 mL into EDTA tube)

Coagulation: Abdominal *vena cava* at sacrifice (1.8 mL into sodium citrate
tube)

Clinical Chemistry: Orbital sinus (0.75 mL into serum separator tube)

Additional Saved Serum: Abdominal *vena cava* at sacrifice (all remaining blood into
serum separator tube); processed to serum, and frozen at
approximately -80°C. Serum may be used for additional testing
as documented by protocol amendment, or will be discarded
when the final report issues

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2. Collection Parameters

All blood samples will be evaluated for quality by visual examination prior to analysis. Results will be maintained in the study records and reported only if the sample is analyzed. The following indicated parameters will be determined according to Disposition of Animals (if appropriate due to sample volume, priority indicated by number in front of test):

<p>Hematology</p> <input checked="" type="checkbox"/> red blood cell count <input checked="" type="checkbox"/> hemoglobin <input checked="" type="checkbox"/> hematocrit <input checked="" type="checkbox"/> mean corpuscular volume <input checked="" type="checkbox"/> mean corpuscular hemoglobin <input checked="" type="checkbox"/> mean corpuscular hemoglobin concentration <input checked="" type="checkbox"/> red cell distribution width <input checked="" type="checkbox"/> absolute reticulocyte count <input checked="" type="checkbox"/> platelet count <input checked="" type="checkbox"/> mean platelet volume <input checked="" type="checkbox"/> white blood cell count <input checked="" type="checkbox"/> differential white blood cell count <input type="checkbox"/> Heinz bodies <input type="checkbox"/> methemoglobin <input checked="" type="checkbox"/> Wright's-stained, blood smear prepared ^a <input checked="" type="checkbox"/> red blood cell, white blood cell, and platelet morphology <input checked="" type="checkbox"/> new-methylene-blue-stained, blood smear prepared ^a	<p>Clinical Chemistry^b</p> <input type="checkbox"/> globulin <input type="checkbox"/> calcium <input type="checkbox"/> inorganic phosphorus <input checked="" type="checkbox"/> sodium <input checked="" type="checkbox"/> potassium <input type="checkbox"/> chloride <input type="checkbox"/> albumin/globulin ratio <input type="checkbox"/> creatinine kinase <input type="checkbox"/> bicarbonate <input type="checkbox"/> high-density lipoprotein cholesterol <input type="checkbox"/> low-density lipoprotein cholesterol <input type="checkbox"/> serum osmolality <input checked="" type="checkbox"/> total bile acids <input type="checkbox"/> fluoride (EDTA plasma)
<p>Cosagulation</p> <input checked="" type="checkbox"/> prothrombin time <input checked="" type="checkbox"/> activated partial thromboplastin time <input type="checkbox"/> thrombin clotting time <input type="checkbox"/> fibrinogen	<p>Urinalysis</p> <input type="checkbox"/> quality <input type="checkbox"/> color <input type="checkbox"/> clarity <input type="checkbox"/> volume <input type="checkbox"/> osmolality <input type="checkbox"/> specific gravity <input type="checkbox"/> pH <input type="checkbox"/> glucose <input type="checkbox"/> ketone <input type="checkbox"/> bilirubin <input type="checkbox"/> blood <input type="checkbox"/> urobilinogen <input type="checkbox"/> protein <input type="checkbox"/> fluoride <input type="checkbox"/> microscopic urine sediment examination
<p>Clinical Chemistry^b</p> <input checked="" type="checkbox"/> aspartate aminotransferase <input checked="" type="checkbox"/> alanine aminotransferase <input type="checkbox"/> sorbitol dehydrogenase <input type="checkbox"/> alkaline phosphatase <input type="checkbox"/> gamma glutamyltransferase <input type="checkbox"/> total bilirubin <input checked="" type="checkbox"/> urea nitrogen <input checked="" type="checkbox"/> creatinine <input checked="" type="checkbox"/> cholesterol <input type="checkbox"/> triglycerides <input checked="" type="checkbox"/> glucose <input checked="" type="checkbox"/> total protein <input checked="" type="checkbox"/> albumin	<p>Other Determinations</p> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

^a Examined if required to substantiate or clarify the results of hematology findings.
^b All parameters will be analyzed on serum unless indicated.

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T. Anatomic Pathology Evaluation

1. Quarantine/Predosing

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

2. Study Animals

a. Adult Rats

All rats found dead, accidentally killed, sacrificed *in extremis*, or sacrificed by design will undergo a gross evaluation. Rats will be euthanatized by carbon dioxide asphyxiation and exsanguination. The order of sacrifice for scheduled deaths will be random among all treatment groups within a sex.

The following tissues will be collected from rats that are found dead or accidentally killed (tissue integrity permitting), sacrificed *in extremis*, and 5 males and 5 females, randomly selected from each group that are sacrificed by design. Gross observations, target organs, and organs of the reproductive system will be collected from the last 5 males and the last 5 females per group that are sacrificed by design.

<u>Digestive System</u> ^a	<u>Cardiovascular System</u>	<u>Musculoskeletal System</u>
liver ^b	heart	femur ^c
stomach ^b		
duodenum	<u>Hematopoietic System</u>	<u>Reproductive System</u>
jejunum	spleen	Male
ileum	thymus	testes
cecum	mandibular lymph node	epididymides
colon	mesenteric lymph node	prostate
rectum	bone marrow ^f	seminal vesicles
		coagulating glands
<u>Urinary System</u>	<u>Endocrine System</u>	Female ^d
kidneys	thyroid gland	ovaries (with oviducts)
urinary bladder	adrenal glands	cervix
		uterus
<u>Respiratory System</u>	<u>Nervous System</u>	vagina
lungs	brain (3 sections)	
trachea	spinal cord (3 levels)	<u>Miscellaneous</u>
	sciatic nerve	gross observations ^e

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

b Potential Target Organ.

c Bone marrow will be collected with the femur.

d Females will be examined for the presence and number of uterine implantation sites and ovarian *corpora lutea*.

e Gross observations made at necropsy for which histopathology is not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) will generally not be collected.

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All tissues will be placed in the appropriate fixative.

The testes and epididymides of all males sacrificed by design will be weighed. For 5 males and females, randomly selected from each group, that are sacrificed by design, the following organs will be weighed: liver, kidneys, adrenal glands, thymus, spleen, brain, and heart. Relative organ weights (percent of final body weight; ratio to brain weight) will be calculated. Final body weights determined just prior to necropsy will be used in the assessment of organ weight changes. Organs from rats found dead, sacrificed *in extremis*, or accidentally killed may be weighed at the discretion of the pathologist or Study Director.

Histologic examination of all the tissues in the table above will be conducted for the high-treatment and control groups (10 sex/group for target organs). Examination of tissues from the remaining groups will be limited to relevant gross lesions and those tissues that demonstrate treatment-related histologic effects in the high-treatment group.

The uteri of females will be examined for the number of implantation sites and the ovaries will be examined for the number of *corpora lutea*. The uteri of mated females that did not deliver litters will be visually examined for implantation sites in order to verify pregnancy status.

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

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

b. Pups

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

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DATA ANALYSES

The following table lists the indices of reproductive function that will be calculated for the Parental animals.

<u>Reproductive Function Calculations</u>			
Mating Index (%)	=	$\frac{\text{Number copulated}^a}{\text{Number cohabited}}$	x 100
Fertility Index (%)	=	$\frac{\text{Number pregnant}^b}{\text{Number copulated}^a}$	x 100
Gestation Index (%)	=	$\frac{\text{Number of litters with at least one live pup}}{\text{Number of litters}}$	x 100
Implantation Efficiency (%) ^c	=	$\frac{\text{Number of pups born}}{\text{Number of implantation sites}}$	x 100
Pups Born Alive (%) ^c	=	$\frac{\text{Number of pups born alive}}{\text{Number of pups born}}$	x 100
0-4 Day Viability (%) ^{c,d}	=	$\frac{\text{Number of pups alive day 4}}{\text{Number of pups born alive}}$	x 100

a Evidence of copulation = intravaginal copulatory plug, sperm in vaginal lavage, found dead pregnant, or delivery of a litter.

b Including those found dead pregnant during gestation.

c To be determined for each litter. Mean and standard deviation for each dose level will be calculated.

d Excluding litters sacrificed due to death of dam during lactation.

e Restricted to pregnant dams.

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Statistical Methods

Parameter	Preliminary Test	Method of Statistical Analysis	
		If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Food Efficiency Gestation Length Organ Weight Implantation Site Numbers Corpora Lutea Counts Implantation Efficiency Mean Number of Pups Per Litter Percent Born Alive 0-4 Day Viability Preimplantation Loss	Levene's test for homogeneity ⁽²⁾ and Shapiro-Wilk test ⁽³⁾ for normality ^a	One-way analysis of variance ⁽⁴⁾ and Dunnett's test ^(5,6,7)	Kruskal-Wallis test ⁽⁸⁾ and Dunn's test ⁽⁹⁾
Incidence of Clinical Observations Incidence of FOB Descriptive Parameters Mating Index Fertility Index Gestation Index Litter Survival	None	Cochran-Armitage test for trend ^(4,b)	
Sex Ratio Mean Pup Weights (Covariates: litter size, sex ratio)	None	Exact Mann-Whitney with a Bonferroni-Holm adjustment ^(10,11)	
Motor Activity ^d Grip Strength Foot Splay Rearing	Levene's test for homogeneity ⁽²⁾ and Shapiro-Wilk test ⁽³⁾ for normality ^a	Repeated measures analysis of variance ⁽¹²⁾ followed by Linear contrasts ⁽¹³⁾	Sequential application ⁽¹⁴⁾ of the Jonckheere-Terpstra trend test ⁽¹⁵⁾ unless a normalizing, variance stabilizing transform can be found and the repeated measures analysis of variance repeated.
Clinical Pathology ^d	Levene's test for homogeneity ⁽²⁾ and Shapiro-Wilk test ⁽³⁾ for normality ^a	One-way analysis of variance ⁽⁴⁾ followed with Dunnett's test ^(5,6,7)	Kruskal-Wallis test ⁽⁸⁾ followed with Dunn's test ⁽⁹⁾

- a If the Shapiro-Wilk test is not significant but Levene's test is significant, a robust version of Dunnett's test will be used. If the Shapiro-Wilk test is significant, Kruskal-Wallis test is followed with Dunn's test.
- b If the incidence is not significant, but a significant lack of fit occurs, then Fisher's Exact test⁽¹⁶⁾ with a Bonferroni correction is used.
- c Test day and 10-minute interval will be used as repeated-measure factors.
- d When an individual observation is recorded as being less than a certain value, calculations are performed on half the recorded value. For example, if bilirubin is reported as <0.1, 0.05 is used for any calculations performed with that bilirubin data.

Male and female parental data will be evaluated separately. For litter parameters, the proportion of affected pups per litter or the litter mean will be used as the experimental unit for statistical evaluation.⁽¹⁷⁾ The level of significance selected is $p < 0.05$. Additional statistical tests will be used, and other parameters analyzed, if deemed necessary.

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SAFETY AND HOUSEKEEPING

Good housekeeping procedures will be practiced to avoid contamination of dose formulation preparation facilities and potential health hazards. To avoid skin contact, gloves will be worn when handling either the test substance or dose formulations. In addition, the test substance will be handled in a chemical hood. Dose formulations will be prepared in properly ventilated areas. Animal carcasses, feces, and unused dose formulations will be incinerated.

RECORDS AND SAMPLE STORAGE

All data and records for analytical characterizations conducted by the Sponsor will be retained by the Sponsor. Laboratory-specific or site-specific raw data, such as personnel files and equipment records will be retained by the facility where the work was done.

Specimens and raw data will be retained at Haskell Laboratory, Newark, Delaware. All original study data and samples will be returned to the Sponsor upon request within 6 months following issuance of the final report.

A draft final report will be prepared and finalized in consultation with the Sponsor. Upon finalization, the final report shall be provided to the Sponsor's Study Monitor. Electronic copies of the final protocol (and any amendments and deviations) and the final report will be provided as a Portable Document Format (PDF) image.

The study data will be sent to a GLP-compliant archive designated by the Sponsor.

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Approved by:



Eve Mychroest, Ph.D.
Study Director

02-Mar-2004
Date

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Work Request Number 15031

Service Code Number 1422

PROTOCOL AMENDMENT 1

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The Protocol is amended as follows:

1. Page 17, Materials and Methods, S. Clinical Pathology Evaluation, 2. Collection Parameters, in the Hematology list after the first paragraph, delete "mean platelet volume."

Rationale: This hematology parameter was inadvertently included in the protocol and will not be determined.

Approved by:



26-Mar-2004

Eric Mylonreest, Ph.D.
Study Director

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A-1846: Combined Repeated Dose Toxicity Study With The Reproduction/Developmental
Toxicity Screening Test In Rats
Work Request Number 15031
Service Code Number 1422
PROTOCOL AMENDMENT 2

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The Protocol is amended as follows:

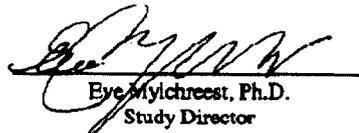
1. Page 13, Materials and Methods, P. Cohabitation Procedures, add the following paragraph at the end of the section, after the footnotes: "If the first pairing does not result in copulation, a second pairing with a proven male of the same dose group may be performed at the discretion of the study director."

Rationale: To include the procedure for a second pairing.

2. Page 14, Materials and Methods, R. Neurobehavioral Evaluation, Frequency, delete the second line under Males, in parentheses: "(prior to fasting for clinical pathology evaluation)."

Rationale: To correct typographical error. This statement was included in error.

Approved by:


Eve Mychreest, Ph.D.
Study Director

5-APR-1994

A-1846: Combined Repeated Dose Toxicity Study
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PROTOCOL AMENDMENT 3

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The Protocol is amended as follows:

1. Page 4, Materials and Methods, B. Regulatory Compliance, 1. Good Laboratory Practice Standards, replace with (changes are in bold):

This study will be conducted in compliance with United States (U.S.) Environmental Protection Agency (EPA), Toxic Substances Control Act (TSCA) (40 CFR part 792) Good Laboratory Practice Standards (1989) which are **compatible** with the Organisation for Economic Cooperation and Development (OECD/OCDE) Principles of Good Laboratory Practice Standards (as revised in 1997) published in ENV/MC/CHEM(98)17, **OECD, Paris, 1998**, and the Ministry of Agriculture, Forestry, and Fisheries, MAFF Japan Good Laboratory Practice Standards (**11 NohSan Number 6283**).

Rationale: To update Good Laboratory Practice Standards for OECD and to add Good Laboratory Practice Standards for MAFF Japan.

2. Page 13, Materials and Methods, Q. "Lactation Procedures,"
 - ♦ change the heading from "Lactation Procedures" to Gestation and Lactation Procedures," and replace with the following:

Gestation Procedures

After being transferred into polycarbonate pans (on day 20 of gestation for mated females, or at the end of the cohabitation period for females without evidence of copulation), female rats will be observed at least twice daily for signs of delivery and offspring.

Lactation Procedures

At each examination period, offspring will be individually handled and examined for abnormal behavior and appearance; any dead or abnormal pups will be recorded.

Day 0^a: Live and dead pups in each litter will be counted by sex and individually weighed as soon as possible after delivery is completed.

Day 4^b: Pups in each litter will be counted by sex and individually weighed and a gross external examination will be performed.

a Day of delivery = Day 0 of lactation
b Litter Sacrifice

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Toxicity Screening Test In Rats

Work Request Number 15031

Service Code Number 1422

PROTOCOL AMENDMENT 3 (Continued)

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If litters die prior to Day 4 of lactation, the female will be sacrificed. If the female dies prior to Day 4 of lactation, the litter will be sacrificed.

Rationale: To include the procedure for Gestation.

3. Page 18, Materials and Methods, T. Anatomic Pathology Evaluation, 2. Study Animals, a. Adult Rats, second paragraph, last sentence, change from:

“Gross observations, target organs, and organs of the reproductive system will be collected from the last 5 males and the last 5 females per group that are sacrificed by design.”

To (changes are in bold):

“Gross observations, target organs, and organs of the reproductive system will be collected from **all rats** sacrificed by design.”

Rationale: To clarify pathology procedures for all animals sacrificed by design.

4. Page 20, Data Analyses, delete Footnote “e” at the bottom of the table.

Rationale: To correct typographical error.

Approved:


Eve M. McCreest, Ph.D.
Study Director

29 Jul 2004

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APPENDIX C
ANALYSIS OF DOSING FORMULATIONS

A-1846: Combined Repeated Dose Toxicity Study With the Reproduction/Developmental
Toxicity Screening Test in Rats

ANALYSIS FOR A-1846 IN DOSING FORMULATIONS

Medical Research Project Number:	15031	PUBLIC COPY DOES NOT CONTAIN CONFIDENTIAL BUSINESS INFORMATION
Haskell Sample Number:	26200	
Analytical Report Number:	DuPont-14109_AN	

SUMMARY

Samples from dosing formulations prepared March 3, 2004 containing A-1846 at concentrations of 1.88, 6.25 and 25.0 mg/mL were collected for homogeneity/concentration verification and 5-hour room temperature stability analysis. Samples from the same preparation of the dosing formulations were collected on March 12, 2004 after 10 days of refrigeration for concentration verification and 5-hour room temperature stability analysis. This was to establish stability for the test substance in the vehicle stored refrigerated for a period of time to allow weekly preparation of the dosing formulations. Concentration verification samples at all levels were collected on March 18, 2004 and April 1, 2004. The 0 mg/mL control samples were submitted with each set of samples.

The vehicle for the formulations is PEG 400 (polyethylene glycol, molecular weight 400).

Concentrations of A-1846 in dosing formulations were measured by high performance liquid chromatography (HPLC).

The data for samples collected on March 3, 2004 indicates that the test substance was homogeneously mixed in the vehicle at all levels (C.V.'s = 0.3, 0.6, and 1.3, respectively). The test substance was at the targeted concentration in the samples ($\pm 2.4\%$ of nominal) and was stable in the vehicle when held 5 hours at room temperature.

The data for samples collected on March 12, 2004 after 10 days of refrigeration indicates that the test substance was at the targeted concentration in the samples ($\pm 7.8\%$ of nominal) and uniformly mixed with CV's = 1, 3, and 1, respectively. The data also indicated that the test substance was stable in the vehicle for the 10 days of refrigeration followed by 5 hours at room temperature.

The data for samples collected on March 18, 2004 indicates that the test substance was at the targeted concentration in the samples ($\pm 7.0\%$ of nominal) and uniformly mixed with CV's = 7, 4, and 8, respectively. The data for samples collected on April 1, 2004 indicates that the test substance was at the targeted concentration in the samples ($\pm 7.2\%$ of nominal) and uniformly mixed with CV's = 1, 7, and 0.3, respectively.

A-1846 was not detected in the 0 mg/mL samples.

SAMPLE SUBMITTAL

Samples from dosing formulations prepared March 3, 2004 containing A-1846 at concentrations of 1.88, 6.25 and 25.0 mg/mL were collected for homogeneity/concentration verification and 5-hour room temperature stability analysis. Samples from the same preparation of the dosing formulations were collected on March 12, 2004 after 10 days of refrigeration for concentration verification and 5-hour room temperature stability analysis. This was to establish stability for the test substance in the vehicle stored refrigerated for a period of time to allow weekly preparation of the dosing formulations. Concentration verification samples at all levels were collected on March 18, 2004 and April 1, 2004. The 0 mg/mL control samples were submitted with each set of samples.

The formulation vehicle for the study was PEG 400 (polyethylene glycol, molecular weight 400).

METHODS

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1. Analytical Methods

a. Recovery Sample Analysis

Concurrent with dosing formulation analyses, recovery of A-1846 from the vehicle (PEG 400) was tested at the low (1.88 mg/mL), mid (6.25 mg/mL) and high (25 mg/mL) levels to confirm the analytical method. The appropriate amount of the test substance was weighed for each concentration and added to 3 mL of the vehicle. All recovery samples were then mixed for dispersion of the test material in the vehicle. The samples were then processed and analyzed in the same manner as the dosing samples at similar concentrations.

b. Dosing Formulation Treatment

Each dosing sample (3 mL) was diluted to 100 mL with acetonitrile and mixed to dissolve the test substance. The samples were further diluted with acetonitrile to give nominal concentrations of approximately 0.028 or 0.030 mg/mL of A-1846. This final dilution for all samples was matrix corrected to contain an equivalent concentration 0 mg/mL (control) sample.

Submitted samples were analyzed the day the formulations were received or when reanalysis was necessary.

c. Chromatographic Conditions

Instrument: Hewlett-Packard 1100 liquid chromatograph
Column: Zorbax® SB-C18, 4.6 mm x 150 mm
Flow Rate: 1.0 mL/min.
Column Temperature: 47°C
Detection: UV absorbance at 210 nm
Mobile Phase: 70% acetonitrile/30% 3.1 mM H₃PO₄
Injection Volume: 2 µL

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d. Calibration and Quantitation

A separate sample of the test material, A-1846 (H-26200, 98.0% pure), was obtained to use as analytical reference in the study. A stock solution of this material was made in acetonitrile. Appropriate aliquots of the stock were further diluted to make calibration standards that bracketed the target concentration of the diluted dosing formulations. This final dilution for all standards was corrected to contain an equivalent concentration 0 mg/mL sample (vehicle) as the samples. Peak heights from HPLC analysis of these standards were used to construct a calibration curve by least squares regression (see Figure 1 for a representative calibration curve). Measured concentrations for dosing formulations were determined by applying the peak heights from replicate injections of each sample to the calibration curve.

Homogeneity of test material in dosing formulations was evaluated by calculating the coefficient of variation (C.V. = standard deviation/mean x 100) of the measured concentration in the top, middle, and bottom samples for each concentration. Normally a C.V. less than 10% implies homogeneity.

The mean result of the homogeneity samples (top, middle and bottom) was used to determine the concentration of the test substance for the respective dosing levels.

Stability of test material in dosing formulations was evaluated by using the mean result of the homogeneity samples as the baseline for comparing the corresponding results for the refrigerated and room temperature samples.

ANALYTICAL RESULTS

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A. Test Substance Stability Analyses (Appendix D)

Samples of the test substance were analyzed near the beginning and end of the study. These analyses indicated that the A-1846 was stable over the course of the study.

The average of the active ingredient was $98.8\% \pm 1.0$ and $99.8\% \pm 2.0$ for samples analyzed March 5, 2004 and April 30, 2004, respectively. This work is reported in analytical reports Dupont-14917 and Dupont-14985 (Appendix D), and can be found in Haskell Laboratory Records (MR 5672). The A-1846 was reported by the sponsor to be 98.0% pure. The difference between the sponsor reported purity and the experimental data represent analytical variability.

B. Chromatography

A-1846 eluted from the HPLC column as a resolved peak with a retention time of approximately 4.8 to 5.1 minutes. Representative HPLC chromatograms are shown in Figures 2 (a - d).

C. Recovery Samples

Detailed analytical results of recovery samples are summarized in Table I. The variability of the analytical method was demonstrated by the coefficients of variation of the recovery results at the targeted dosing concentrations over the course of the study. The measured concentrations A-1846 for the 1.88 mg/mL level ranged from 97.4% and 101.0% of nominal (mean percent recovery = $99.7\% \pm 1.7$, C.V. = 2%). The measured concentrations A-1846 for the 6.25 mg/mL level ranged from 83.8% and 103.2% of nominal (mean percent recovery = $97.5\% \pm 9.2$, C.V. = 9%). The measured concentrations A-1846 for the 25.0 mg/mL level ranged from 98.8% and 105.0% of nominal (mean percent recovery = $102.2\% \pm 2.6$, C.V. = 3%). Based on this data, the analytical method performed satisfactory for the concentration of the samples in the study.

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D. Homogeneity (concentration verification) and Stability Samples

Analytical results from dosing formulations collected March 3, 2004 for homogeneity (concentration verification) analysis and stability are shown in Summary Table 1 and Table II.

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

Preparation Day Sample Type	Nominal mg/mL	Measured T,M,B ^a mg/mL	Mean (T,M,B) % Nominal	C.V. (%)	Stability ^b % Nominal
3-Mar-04					
Homogeneity	0	ND ^c	---	---	---
	1.88	1.86, 1.86, 1.85	98.9	0.3	104.8 ^d
	6.25	6.26, 6.27, 6.33	100.6	0.6	100.2
	25.0	24.3, 24.1, 24.7	97.6	1.3	106.6 ^d

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

b Samples held 5 hours at room temperature.

c Denotes none detected.

d Mean result of duplicate reanalysis of the original diluted sample. Original analysis is not reported due to aliquot error in preparing sample for analysis.

The data for samples collected on March 3, 2004 indicate that the test substance was homogeneously mixed in the vehicle at all levels (C.V.'s = 0.3, 0.6, and 1.3, respectively). The test substance was at the targeted concentration in the samples ($\pm 2.4\%$ of nominal) and was stable in the vehicle when held 5 hours at room temperature.

A-1846 was not detected in the 0 mg/mL formulation.

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E. Concentration Verification Samples

Analytical results from dosing formulations collected March 18, 2004 and April 1, 2004 for concentration verification analysis are shown in Summary Table 1 and Table IV.

The following table summarizes the results for concentration verification samples.

Sample Day	Nominal mg/mL	Measured ^a mg/mL	Mean % Nominal	C.V. (%)
18-Mar-04	0	ND ^b	---	---
	1.88	1.66 ^c , 1.83	93.0	7
	6.25	5.80, 6.14	95.5	4
	25.0	22.1 ^c , 24.6	93.6	8
1-April-04	0	ND ^b	---	---
	1.88	1.76, 1.73	92.8	1
	6.25	5.86, 6.45	98.5	7
	25.0	25.2, 25.3	101.0	0.3

a Mean results for the analysis of duplicate samples. CV reported for duplicate sample to show uniformity of mixing.

b Denotes none detected.

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

The data for samples collected on March 18, 2004 indicates that the test substance was at the targeted concentration in the samples ($\pm 7.0\%$ of nominal) and uniformly mixed with CV's = 7, 4, and 8, respectively.

The data for samples collected on April 1, 2004 indicates that the test substance was at the targeted concentration in the samples ($\pm 7.2\%$ of nominal) and uniformly mixed with CV's = 1, 7, and 0.3, respectively.

A-1846 was not detected in the 0 mg/mL formulation.

F. Conclusions

Data from the analysis of the samples at the start of the study indicate that the test substance was mixed homogeneously, was at the targeted levels and stable for 5 hours at room temperature. The data from the 10 days refrigerated samples indicated that the test substance was stable in the vehicle for the period of time refrigerated followed by 5 hours at room temperature. The data for the concentration verification indicated that the test substance remained mixed uniformly in the vehicle and at the targeted concentration during the study. Test substance was not found in the 0 mg/mL samples.

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Table I. Recovery of A-1846 Added to Dosing Vehicle

Sample Type	mg/ml A-1846		Percent Nominal
	Nominal	Measured	
RECOVERY ^(A)	1.89	1.84	97.4
RECOVERY ^(B)	2.06	2.05	99.5
RECOVERY ^(D)	2.78	2.81	101.1
RECOVERY ^(F)	2.78	2.80	100.7
			Mean: 99.7 ± 1.7, C.V. 2%
RECOVERY ^(A)	6.14	6.28 ^(C)	102.3
RECOVERY ^(B)	6.83	6.87	100.6
RECOVERY ^(D)	7.97	6.68 ^(E)	83.8
RECOVERY ^(F)	6.83	7.05	103.2
			Mean: 97.5 ± 9.2, C.V. 9%
RECOVERY ^(A)	24.8	24.5	98.8
RECOVERY ^(B)	24.8	25.4	102.4
RECOVERY ^(D)	25.8	27.1	105.0
RECOVERY ^(F)	26.6	27.3	102.6
			Mean: 102.2 ± 2.6, C.V. 3%

- (A) Processed with homogeneity/concentration verification and 5-hour room temperature stability samples from dosing prepared March 3, 2004.
- (B) Processed with 10-day refrigerated and 10-day refrigerated followed by 5-hour stability samples on March 12, 2004 from dosing prepared March 3, 2004.
- (C) Mean result of duplicate reanalysis of the original diluted sample. Original analysis is not reported due to aliquot error in preparing sample for analysis.
- (D) Processed with concentration verification samples from dosing prepared March 18, 2004.
- (E) Mean result of the original analysis and duplicate reanalysis of the original diluted sample..
- (F) Processed with concentration verification samples from dosing prepared April 1, 2004.

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Table II. Homogeneity and Room Temperature Stability of A-1846 in Dosing Formulations

Sample Type	mg/mL A-1846		Percent Nominal
	Nominal	Measured	
<u>Homogeneity</u>			
CONTROL	0.00	ND(A)	---
TOP	1.88	1.86	98.9
MIDDLE	1.88	1.86	98.9
BOTTOM	1.88	<u>1.85</u>	98.4
		<i>Mean(B): 1.86 ± 0.01</i>	<i>(98.9%)</i>
		<i>C.V. 0.3%</i>	
TOP	6.25	6.26	100.2
MIDDLE	6.25	6.27	100.3
BOTTOM	6.25	<u>6.33</u>	101.3
		<i>Mean(B): 6.29 ± 0.04</i>	<i>(100.6%)</i>
		<i>C.V. 0.6%</i>	
TOP	25.0	24.3	97.2
MIDDLE	25.0	24.1	96.4
BOTTOM	25.0	<u>24.7</u>	98.8
		<i>Mean(B): 24.4 ± 0.31</i>	<i>(97.6%)</i>
		<i>C.V. 1.3%</i>	
<u>Stability(C)</u>			
	1.88	1.97(D)	104.8
	6.25	6.26	100.2
	25.0	26.7(D)	106.6

(A) Denotes not detected.

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

(C) Sample held 5 hours at room temperature.

(D) Mean result of duplicate reanalysis of the original diluted sample. Original analysis is not reported due to aliquot error in preparing sample for analysis.

Table III. Concentration Verification and Refrigerated Stability of A-1846 in Dosing Formulations

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Sample Type	mg/mL A-1846		Percent Nominal
	Nominal	Measured	
<u>Concentration</u>			
12-Mar-04			
CONTROL	0.00	ND(A)	---
#1	1.88	1.79	95.2
#2	1.88	<u>1.77(B)</u>	94.1
		Mean(C): <u>1.78 ± 0.01</u>	(94.7%)
		C.V. 1%	
#1	6.25	5.63	90.1
#2	6.25	<u>5.89</u>	94.2
		Mean(C): <u>5.76 ± 0.18</u>	(92.2%)
		C.V. 3%	
#1	25.0	23.6	94.4
#2	25.0	<u>23.8</u>	95.2
		Mean(C): <u>23.7 ± 0.14</u>	(94.8%)
		C.V. 1%	
<u>Stability</u>			
	1.88	1.72	91.5
	6.25	5.43	86.9
	25.0	21.4(B)	85.6

(A) Denotes not detected.

(B) Mean result of duplicate reanalysis of the original diluted sample. Original analysis is not reported due to aliquot error in preparing sample for analysis.

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

Table IV. Concentration Verification of A-1846 in Dosing Formulations

Sample Type	mg/mL A-1846		Percent Nominal
	Nominal	Measured	
Concentration			
18-Mar-04			
CONTROL	0.00	ND(A)	---
#1	1.88	1.66(B)	88.3
#2	1.88	<u>1.83</u>	97.3
		<i>Mean(C): 1.75 ± 0.12</i>	<i>(93.0%)</i>
		<i>C.V. 7%</i>	
#1	6.25	5.80	92.8
#2	6.25	<u>6.14</u>	98.2
		<i>Mean(C): 5.97 ± 0.24</i>	<i>(95.5%)</i>
		<i>C.V. 4%</i>	
#1	25.0	22.1(B)	88.4
#2	25.0	<u>24.6</u>	98.4
		<i>Mean(C): 23.4 ± 1.8</i>	<i>(93.6%)</i>
		<i>C.V. 8%</i>	
1-April-04			
CONTROL	0.00	ND(A)	---
#1	1.88	1.76	93.6
#2	1.88	<u>1.73</u>	92.0
		<i>Mean(C): 1.75 ± 0.02</i>	<i>(92.8%)</i>
		<i>C.V. 1%</i>	
#1	6.25	5.86	93.8
#2	6.25	<u>6.45</u>	103.2
		<i>Mean(C): 6.16 ± 0.42</i>	<i>(98.5%)</i>
		<i>C.V. 7%</i>	
#1	25.0	25.2	100.8
#2	25.0	<u>25.3</u>	101.2
		<i>Mean(C): 25.3 ± 0.07</i>	<i>(101.0%)</i>
		<i>C.V. 0.3%</i>	

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- (A) Denotes not detected.
 (B) Mean result of the original analysis and duplicate reanalysis of the original diluted sample.
 (C) The average measured concentration, average percent of nominal (in parentheses), standard deviation, and coefficient of variation of duplicate samples.

Figure 1
Representative Analytical Calibration Curve

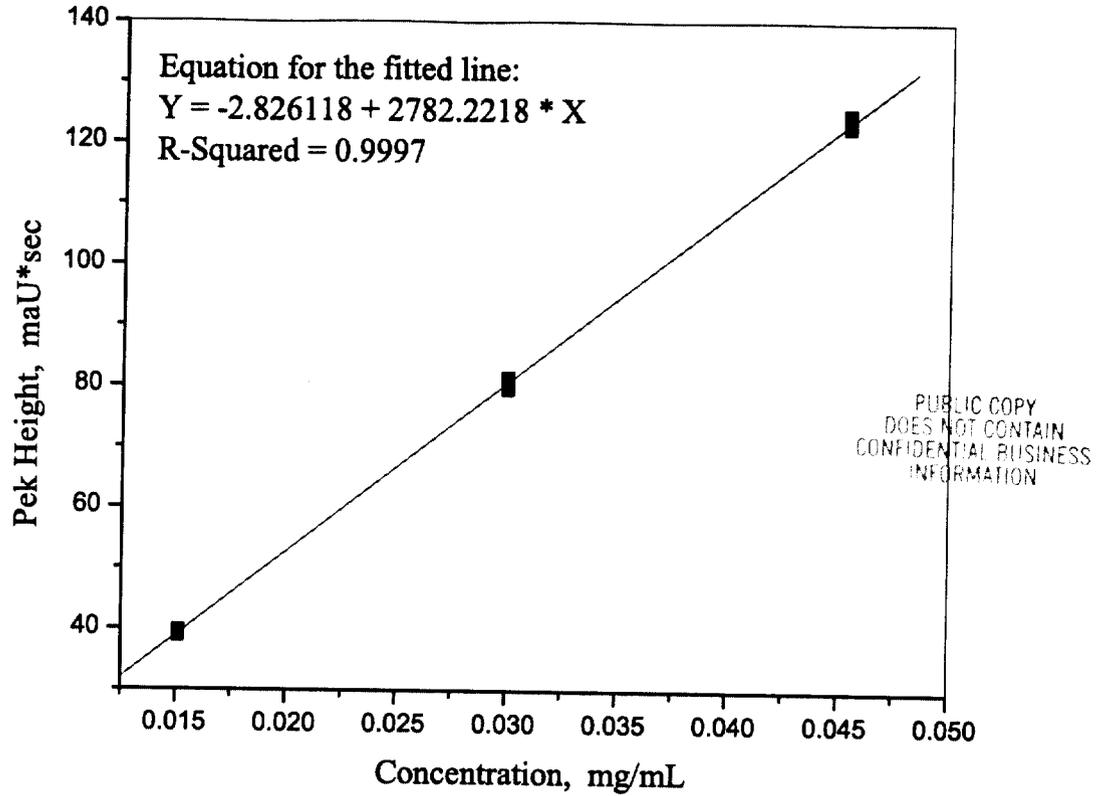


Figure 1: Calibration curve showing linear fit (line) to replicate peak height measurements (squares) for calibration solutions of A-1846 in acetonitrile (corrected for 0 mg/mL sample matrix) over a concentration range of 0.0151 to 0.0454 mg/mL.

Figure 2

Representative HPLC Chromatograms

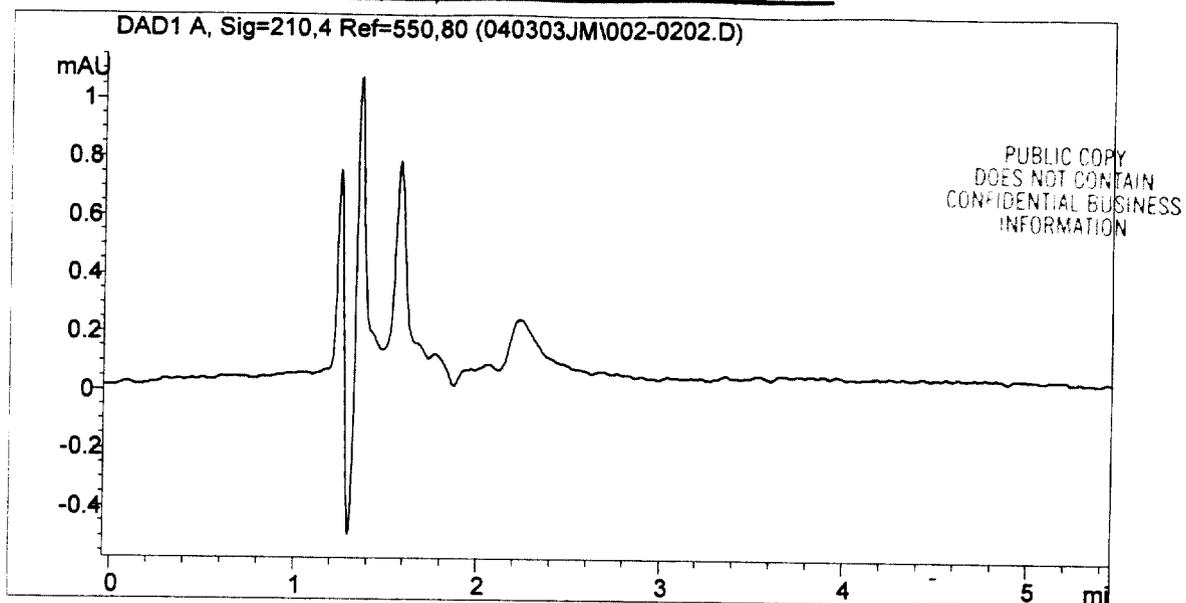


Figure 2a: Representative HPLC chromatogram of 0 mg/mL control dosing formulation. Retention time of A-1846 is approximately 4.8 to 5.1 minutes.

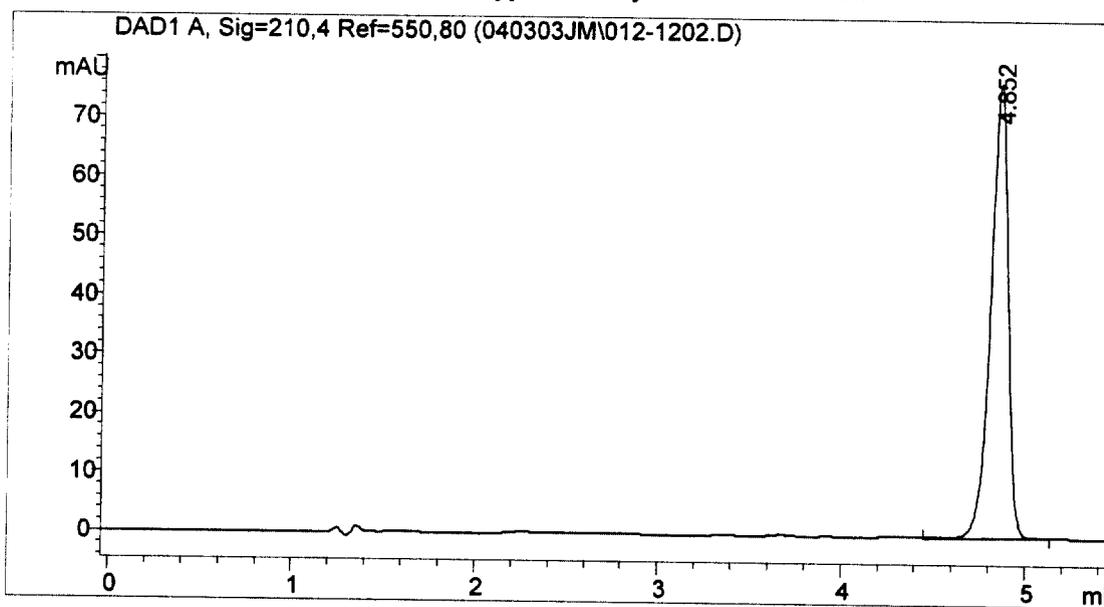
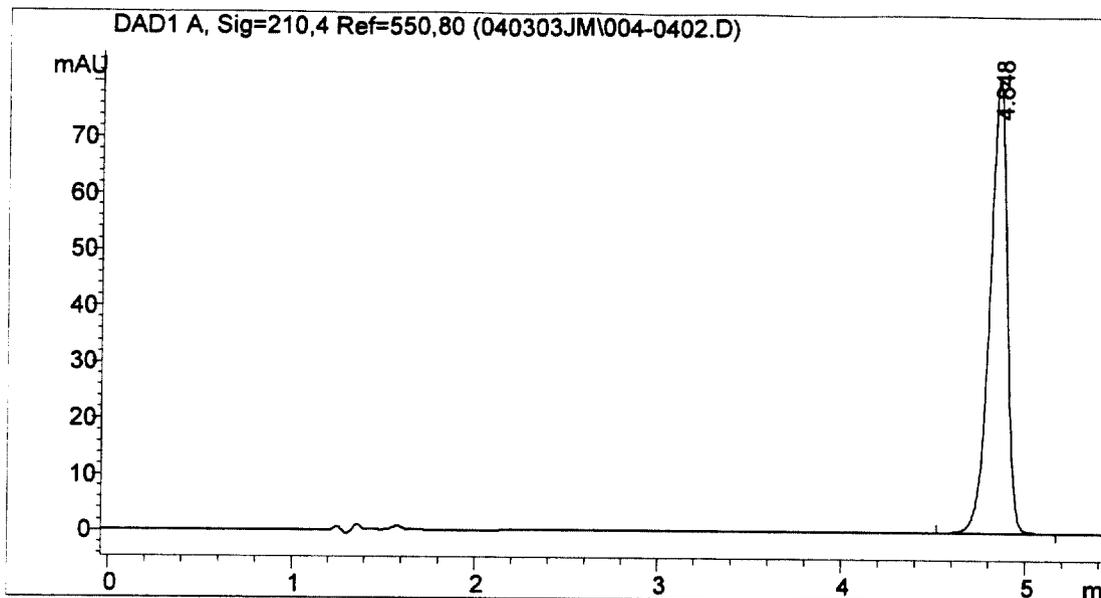


Figure 2b: Representative HPLC chromatogram of 6.25 mg/mL A-1846 dosing formulation diluted to a nominal concentration of 0.0281 mg/mL for analysis. The measured concentration of the sample shown is 6.26 mg/mL.

Figure 2 (continued)
Representative HPLC Chromatograms



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Figure 2c: Representative HPLC chromatogram of 0.030 mg/mL A-1846 analytical reference standard in acetonitrile with 0 mg/mL dosing sample matrix correction.

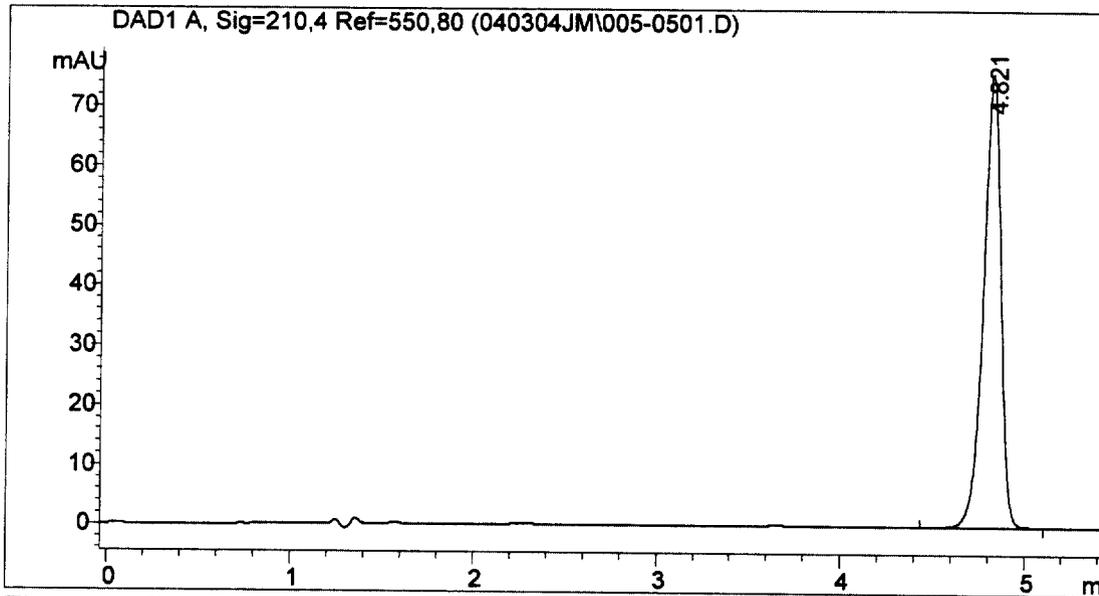


Figure 2d: Representative HPLC chromatogram of 6.14 mg/mL spiked dosing formulation diluted to nominal concentration of 0.0281 mg/mL of A-1846. The measured concentration of the representative solution is 6.26 mg/mL.

TABLE 1
 SUMMARY OF DOSING MIXING AND STABILITY ANALYSES

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Sample Type	Dosing Concentration of A-1846 (mg/mL)			
	Nominal	1.88	6.25	25.0
<u>Homogeneity</u>				
3/3/2004				
Top		1.86 (98.9) ^a	6.26 (100.2)	24.3 (97.2)
Middle		1.86 (98.9)	6.27 (100.3)	24.1 (96.4)
Bottom		1.85 (98.4)	6.33 (101.3)	24.7 (98.8)
Mean Concentration (mg/mL) ^b		1.86	6.29	24.4
Average % Nominal		(98.9)	(100.6)	(97.6)
Standard Deviation ^b		±0.01	±0.04	±0.31
Coefficient of Variation (%) ^b		0.3	0.6	1.3
<u>Stability Samples^c</u>				
		1.97 ^d (104.8)	6.26 (100.2)	26.7 ^d (106.6)
<u>Concentration/Refrigerated</u>				
<u>Stability</u>				
3/12/2004				
#1		1.79 (95.2)	5.63 (90.1)	23.6 (94.4)
#2		1.77 ^d (94.1)	5.89 (94.2)	23.8 (95.2)
Mean Concentration (mg/mL) ^e		1.78	5.76	23.7
Average % Nominal		(94.7)	(92.2)	(94.8)
Standard Deviation ^e		±0.01	±0.18	±0.14
Coefficient of Variation (%) ^e		1	3	1
<u>Stability Samples^c</u>				
		1.72 (91.5)	5.43 (86.9)	21.4 ^d (85.6)

- a Numbers in parentheses are the respective percent of nominal.
- b Standard deviation and coefficient of variation values based on mean concentration (mg/mL) of top, middle, and bottom homogeneity samples.
- c Samples held at room temperature for 5 hours.
- d Mean result of duplicate reanalysis of the original diluted sample. Original analysis is not reported due to aliquot error in preparing sample for analysis.
- e Standard deviation and coefficient of variation values based on mean concentration (mg/mL) of duplicate samples.
- f Mean result of the original analysis and duplicate reanalysis of the original diluted sample.

TABLE 1 (Continued)

SUMMARY OF DOSING MIXING AND STABILITY ANALYSES

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Sample Type	Dosing Concentration of A-1846 (mg/mL)			
	Nominal	1.88	6.25	25.0
Concentration				
3/18/2004				
#1		1.66 ^f (88.3)	5.80 (92.8)	22.1 ^f (88.4)
#2		1.83 (97.3)	6.14 (98.2)	24.6 (98.4)
Mean Concentration (mg/mL)^e		1.75	5.97	23.4
Average % Nominal		(93.0)	(95.5)	(93.6)
Standard Deviation^e		±0.12	±0.24	±1.8
Coefficient of Variation (%)^e		7	4	8
4/1/2004				
#1		1.76 (93.6)	5.86 (93.8)	25.2 (100.8)
#2		1.73 (92.0)	6.45 (103.2)	25.3 (101.2)
Mean Concentration (mg/mL)^e		1.75	6.16	25.3
Average % Nominal		(92.8)	(98.5)	(101.0)
Standard Deviation^e		±0.02	±0.42	±0.07
Coefficient of Variation (%)^e		1	7	0.3

- a Numbers in parentheses are the respective percent of nominal.
- b Standard deviation and coefficient of variation values based on mean concentration (mg/mL) of top, middle, and bottom homogeneity samples.
- c Samples held at room temperature for 5 hours.
- d Mean result of duplicate reanalysis of the original diluted sample. Original analysis is not reported due to aliquot error in preparing sample for analysis.
- e Standard deviation and coefficient of variation values based on mean concentration (mg/mL) of duplicate samples.
- f Mean result of the original analysis and duplicate reanalysis of the original diluted sample.

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APPENDIX D

TEST SUBSTANCE STABILITY REPORTS

DuPont-14917

DuPont-14985

DuPont Haskell Laboratory for Health
and Environmental Sciences

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June 9, 2004

cc: MR-15031
Eve Mylchreest

TO: MR FILE 5672, POCKET H-26200
FROM: Janet C. Maslanka

TEST SUBSTANCE STABILITY OF A-1846

Medical Research Project Number:	5672
Haskell Sample Number:	26200
Haskell Number (Analytical Reference):	26200
Analytical Test Code:	432
Analytical Report Number:	DuPont-14917
Notebook References:	E78240-YY

Attached is the analytical report to satisfy protocol requirements for toxicology studies with A-1846 but may also be used for other purposes.

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TEST SUBSTANCE STABILITY OF A1846

Medical Research Project Number: 5672
Haskell Sample Number: 26200
Analytical Report Number: DuPont-14917

A sample of A1846 was received on March 5, 2004 and analyzed on March 9, 2004. The percentage of active ingredient (a.i.) was measured to be $98.8\% \pm 1.0$ with a range of 97.6 to 99.5% of nominal for replicate analyses (n = 3). The sponsor reported a purity of 98.0% when the sample was submitted.

SIGNATURES

Analysis by: Sheila A. Riley 09-June-2004
Sheila A Riley
Associate Chemist Date

Report by: Janet C. Maslanka 09-June-2004
Janet C. Maslanka
Analytical Staff Chemist Date

Date Issued: 09-June-2004

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DuPont-14917 page 2 of 2

METHODS

Analysis for the percentage of a.i. in a sample of A-1846 was by high-performance liquid chromatography (HPLC).

SAMPLE PREPARATION & ANALYSIS

Aliquots (0.0136, 0.0145, and 0.0148 grams) of A-1846 were dissolved in acetonitrile (10 mL) to give a nominal concentration of 1360, 1450, and 1480 ppm, respectively. The aliquots were further diluted with acetonitrile to 34, 36 and 37 ppm respectively, and analyzed according to the following method.

CHROMATOGRAPHIC CONDITIONS

Instrument:	Hewlett-Packard 1100 HPLC
Column:	Zorbax [®] SB-C18, 4.5 mm x 150mm, 5um
Mobile Phase:	70% Acetonitrile/30% 3.1 H ₃ PO ₄
Flow Rate:	1.0 mL/min
Injection Volume:	2 µl
Column Temperature:	47 °C
Detection:	UV absorbance at 210 nm

CALIBRATION & QUANTITATION

A stock solution of the A-1846 (separate sample of H-26200, used as analytical reference) was made in acetonitrile. Appropriate aliquots of the stock were diluted with acetonitrile to make calibration standards that bracketed the target concentration of the diluted sample solutions. Peak heights from replicate HPLC analyses of each calibration solution were used to construct a calibration curve by least-squares regression. Measured concentrations for each purity solution were determined by applying respective peak heights to the calibration curve.

RESULTS

A-1846 eluted from the HPLC column as a resolved peak with a retention time of about 5.0 minutes. The sponsor reported a purity of 98.0% when the sample was submitted.

Table 1. The percent of a.i. in the A-1846 sample analyzed March 9, 2004.

Aliquot	ppm A-1846		Percent Nominal
	Targeted	Measured	
1	34.0	33.2	97.6
2	36.0	35.7	99.2
3	37.0	36.8	99.5
Average Percent Nominal			98.8
Standard Deviation			± 1.0
Coefficient of Variation			1%

DuPont Haskell Laboratory for Health
and Environmental Sciences

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June 9, 2004

cc: MR-15031
Eve Mylchreest

TO: MR FILE 5672, POCKET H-26200
FROM: Janet C. Maslanka

TEST SUBSTANCE STABILITY OF A-1846

Medical Research Project Number:	5672
Haskell Sample Number:	26200
Haskell Number (Analytical Reference):	26200
Analytical Test Code:	432
Analytical Report Number:	DuPont-14985
Notebook References:	E78240-ZH

Attached is the analytical report to satisfy protocol requirements for toxicology studies with A-1846 but may also be used for other purposes.

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TEST SUBSTANCE STABILITY OF A1846

Medical Research Project Number: 5672
Haskell Sample Number: 26200
Analytical Report Number: DuPont-14985

A sample of A1846 was received on April 22, 2004 and analyzed on April 30, 2004. The percentage of active ingredient (a.i.) was measured to be $99.8\% \pm 2.0$ with a range of 98.3 to 102.0% of nominal for replicate analyses (n = 3). The sponsor reported a purity of 98.0% when the sample was submitted.

SIGNATURES

Analysis by: Sheila A. Riley 09-June-2004
Sheila A Riley
Associate Chemist Date

Report by: Janet C. Maslanka 09-June-2004
Janet C. Maslanka
Analytical Staff Chemist Date

Date Issued: 09-June-2004

DuPont-14985 page 2 of 2

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METHODS

Analysis for the percentage of a.i. in a sample of A-1846 was by high-performance liquid chromatography (HPLC).

SAMPLE PREPARATION & ANALYSIS

Aliquots (0.0158, 0.0166, and 0.0147 grams) of A-1846 were dissolved in acetonitrile (10 mL) to give a nominal concentration of 1580, 1660, and 1470 ppm, respectively. The aliquots were further diluted with acetonitrile to 30.0, 29.9 and 29.4 ppm respectively, and analyzed according to the following method.

CHROMATOGRAPHIC CONDITIONS

Instrument:	Hewlett-Packard 1100 HPLC
Column:	Zorbax [®] SB-C18, 4.5 mm x 150mm
Mobile Phase:	70% Acetonitrile/30% 3.1 H ₃ PO ₄
Flow Rate:	1.0 mL/min
Injection Volume:	2 µl
Column Temperature:	47 °C
Detection:	UV absorbance at 210 nm

CALIBRATION & QUANTTITATION

A stock solution of the A-1846 (separate sample of H-26200, used as analytical reference) was made in acetonitrile. Appropriate aliquots of the stock were diluted with acetonitrile to make calibration standards that bracketed the target concentration of the diluted sample solutions. Peak heights from replicate HPLC analyses of each calibration solution were used to construct a calibration curve by least-squares regression. Measured concentrations for each purity solution were determined by applying respective peak heights to the calibration curve.

RESULTS

A-1846 eluted from the HPLC column as a resolved peak with a retention time of about 5.1 minutes. The sponsor reported a purity of 98.0% when the sample was submitted.

Table 1. The percent of a.i. in the A-1846 sample analyzed April 30, 2004.

Aliquot	ppm A-1846		Percent Nominal
	Targeted	Measured	
1	30.0	30.6	102.0
2	29.9	29.4	98.3
3	29.4	29.1	99.0
Average Percent Nominal			99.8
Standard Deviation			± 2.0
Coefficient of Variation			2%

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APPENDIX E

**INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN P₁ MALE RATS**

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 MALE RATS

GROUP: I-0 DOSE: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
748	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
749	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
756	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
760	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
762	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
767	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
777	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
780	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
782	DIARRHEA SACRIFICED BY DESIGN TEST DAY 34	33	33
786	ALOPECIA RIGHT FRONT PAW(S) ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 34	27 31 31	30 34 34

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 MALE RATS

GROUP: III-0 DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
750	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
752	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
757	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
759	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
769	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
770	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
773	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
776	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
790	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
791	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
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INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 MALE RATS

GROUP: V-0 DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
747	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
751	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
755	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
764	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
766	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
772	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
774	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
778	STAINED UNDERBODY YELLOW SACRIFICED BY DESIGN TEST DAY 34	16	19
783	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
784	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		

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A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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H# 26,200
 MR 15031
 HC 42

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 MALE RATS

GROUP: VII-0 DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
753	STAINED UNDERBODY YELLOW	3	4
	STAINED FACE BROWN	3	3
	DIARRHEA	4	4
	HUNCHED OVER	4	4
	STAINED PERINEUM YELLOW	5	6
	SACRIFICED BY DESIGN TEST DAY 34		
754	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 34		
758	CONVULSIONS	3	3
	FOUND DEAD TEST DAY 3		
765	STAINED UNDERBODY YELLOW	4	6
	STAINED FACE BROWN	4	5
	DIARRHEA	4	6
	HUNCHED OVER	4	4
	SACRIFICED BY DESIGN TEST DAY 34		
775	STAINED PERINEUM YELLOW	6	7
	SACRIFICED BY DESIGN TEST DAY 34		
779	LUNG NOISE	24	26
	LUNG NOISE	28	28
	SACRIFICED BY DESIGN TEST DAY 34		
781	LUNG NOISE	6	6
	LUNG NOISE	15	19
	SACRIFICED BY DESIGN TEST DAY 34		
785	STAINED FACE BROWN	3	3
	STAINED CHIN BROWN	3	4
	STAINED PERINEUM YELLOW	3	3
	SACRIFICED BY DESIGN TEST DAY 34		

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

H# 26,200
MR 15031
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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 MALE RATS

GROUP: VII-0 DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
787	DEHYDRATED	15	19
	STAINED UNDERBODY YELLOW	16	19
	STAINED FACE BROWN	16	16
	DIARRHEA	16	16
	IRREGULAR RESPIRATION	17	34
	LUNG NOISE	17	34
	DEHYDRATED	27	30
	STAINED PERINEUM YELLOW	33	34
	DEHYDRATED	34	34
	SACRIFICED BY DESIGN TEST DAY 34		
788	STAINED UNDERBODY YELLOW	16	19
	SACRIFICED BY DESIGN TEST DAY 34		

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APPENDIX F

INDIVIDUAL CLINICAL OBSERVATIONS IN P₁ FEMALE RATS DURING PREMATING (Includes Data Collected After Premating [Days 1-15], And Not Included In Gestation For Group VIII-0)

INDIVIDUAL CLINICAL OBSERVATIONS IN P₁ FEMALE RATS DURING PREMATING
(Includes Data Collected After Premating [Days 1-15],
And Not Included In Gestation For Group VIII-0)

EXPLANATORY NOTES

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Notes

Test Day 15 = Last day of premating period that data were recorded.

Test days for animal fates are determined from the initiation of test substance administration, designated as Day 1 of test.

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS DURING PREMATING

GROUP: II-0 DOSE: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
793	NO ABNORMALITIES DETECTED		
794	NO ABNORMALITIES DETECTED		
796	NO ABNORMALITIES DETECTED		
797	NO ABNORMALITIES DETECTED		
798	NO ABNORMALITIES DETECTED		
806	NO ABNORMALITIES DETECTED		
809	NO ABNORMALITIES DETECTED		
814	NO ABNORMALITIES DETECTED		
819	NO ABNORMALITIES DETECTED		
829	NO ABNORMALITIES DETECTED		

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HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN F1 FEMALE RATS DURING PREMATING

GROUP: IV-0 DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
800	NO ABNORMALITIES DETECTED		
807	NO ABNORMALITIES DETECTED		
808	NO ABNORMALITIES DETECTED		
812	NO ABNORMALITIES DETECTED		
820	COLOR DISCHARGE LEFT EYE(S) BROWN	2	3
821	NO ABNORMALITIES DETECTED		
823	NO ABNORMALITIES DETECTED		
825	NO ABNORMALITIES DETECTED		
831	NO ABNORMALITIES DETECTED		
832	NO ABNORMALITIES DETECTED		

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS DURING PREMATING

GROUP: VI-0 DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
795	NO ABNORMALITIES DETECTED		
799	NO ABNORMALITIES DETECTED		
801	NO ABNORMALITIES DETECTED		
815	NO ABNORMALITIES DETECTED		
826	NO ABNORMALITIES DETECTED		
828	NO ABNORMALITIES DETECTED		
830	NO ABNORMALITIES DETECTED		
834	NO ABNORMALITIES DETECTED		
835	NO ABNORMALITIES DETECTED		
836	NO ABNORMALITIES DETECTED		

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 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
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 HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS DURING PREMATING
 (Includes Data Collected After Premating [Days 1-15]
 And Not Included In Gestation For Group VIII-0)

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
792 ^a	IRREGULAR RESPIRATION	14	15
	STAINED FACE BROWN	15	15
	WET CHIN	15	15
	STAINED UNDERBODY YELLOW	15	15
	WET UNDERBODY	15	15
	DIARRHEA	15	15
	DEHYDRATED	15	15
	FOUND DEAD TEST DAY 16 ^a		
805	NO ABNORMALITIES DETECTED		
810 ^a	HYPERREACTIVE	7	7
	GASPING ^a	17	17
	SACRIFICED IN EXTREMIS TEST DAY 17 ^a		
811	NO ABNORMALITIES DETECTED		
813 ^a	NO ABNORMALITIES DETECTED	1	15
	STAINED FACE BROWN ^a	28	29
	FOUND DEAD TEST DAY 37 ^a		
816	NO ABNORMALITIES DETECTED		
817	NO ABNORMALITIES DETECTED		
818	NO ABNORMALITIES DETECTED		
822	STAINED FACE BROWN	3	3
	STAINED CHIN BROWN	3	3
	STAINED UNDERBODY YELLOW	3	5
	DIARRHEA	4	5
	HUNCHED OVER	5	5
	STAINED PERINEUM YELLOW	6	6
	STAINED FACE BROWN	6	6
824	STAINED FACE BROWN	7	8

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^a Includes data observed after Premating (Days 1-15) and not included in Gestation.

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APPENDIX G

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P₁ FEMALE RATS DURING GESTATION

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN P₁ FEMALE RATS DURING GESTATION

EXPLANATORY NOTES

Notes

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

Test days for animal fates are determined from the initiation of test substance administration, designated as Day 1 of test.

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS DURING GESTATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
793	SPERM POSITIVE	0	0
794	SPERM POSITIVE	0	0
796	SPERM POSITIVE	0	0
797	SPERM POSITIVE	0	0
798	SPERM POSITIVE ALOPECIA RIGHT FRONT LEG(S)	0 20	0 22
806	SPERM POSITIVE	0	0
809	SPERM POSITIVE ALOPECIA BOTH FRONT PAW(S)	0 18	0 21
814	SPERM POSITIVE	0	0
819	SPERM POSITIVE	0	0
829	VAGINAL PLUG ALOPECIA BOTH FRONT PAW(S)	0 14	0 21

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A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
 MR 15031
 HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS DURING GESTATION

GROUP: IV-0 DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
800	VAGINAL PLUG	0	0
807	VAGINAL PLUG	0	0
808	VAGINAL PLUG	0	0
812	VAGINAL PLUG	0	0
	ALOPECIA LEFT FRONT LEG(S)	7	21
	ALOPECIA LEFT FRONT PAW(S)	7	21
820	SPERM POSITIVE	0	0
	DEHYDRATED	23	23
	LETHARGY	23	23
	DIARRHEA	23	23
	DYSTOCIA	23	23
	SACRIFICED IN EXTREMIS TEST DAY 39 (day 23 of gestation)		
821	SPERM POSITIVE	0	0
823	SPERM POSITIVE	0	0
825	SPERM POSITIVE	0	0
	STAINED FACE BROWN	22	23
831	SPERM POSITIVE	0	0
	STAINED FACE BROWN	21	21
832	SPERM POSITIVE	0	0

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
 MR 15031
 HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS DURING GESTATION

GROUP: VI-0 DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
795	SPERM POSITIVE FOUND DEAD TEST DAY 39 (day 23 of gestation)	0	0
799	VAGINAL PLUG ALOPECIA BOTH FRONT PAW(S)	0 13	0 22
815	VAGINAL PLUG	0	0
826	VAGINAL PLUG ALOPECIA BOTH FRONT PAW(S) LUNG NOISE STAINED FACE BROWN WET UNDERBODY STAINED UNDERBODY BROWN DEHYDRATED IMMOBILE PTOSIS PALLOR DYSTOCIA SACRIFICED IN EXTREMIS TEST DAY 40 (day 24 of gestation)	0 7 16 22 23 24 24 24 24 24 24 24 24	0 24 17 24 24 24 24 24 24 24 24 24
828	VAGINAL PLUG ALOPECIA ABDOMEN	0 14	0 21
830	SPERM POSITIVE	0	0
834	VAGINAL PLUG ALOPECIA CHEST	0 10	0 21
836	SPERM POSITIVE	0	0

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A-1846: Combined Repeated Dose Toxicity Study
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 INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS DURING GESTATION

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
805	SPERM POSITIVE	0	0
811	SPERM POSITIVE	0	0
816	VAGINAL PLUG	0	0
	LUNG NOISE	20	20
817	SPERM POSITIVE	0	0
	STAINED NOSE BROWN	21	22
	IRREGULAR RESPIRATION	21	21
	STAINED UNDERBODY YELLOW	22	22
	WET UNDERBODY	22	22
	DIARRHEA	22	22
	LETHARGY	22	22
	DYSTOCIA	22	22
	SACRIFICED IN EXTREMIS TEST DAY 38 (day 22 of gestation)		
818	SPERM POSITIVE	0	0
	STAINED PERINEUM YELLOW	0	2
	LUNG NOISE	0	2
	LUNG NOISE	16	17
	STAINED PERINEUM YELLOW	21	21
	WET PERINEUM	21	21
	FOUND DEAD TEST DAY 39 (day 22 of gestation)		
822	LUNG NOISE	0	8
	IRREGULAR RESPIRATION	0	8
	SPERM POSITIVE	0	0
	IRREGULAR RESPIRATION	19	22
	LUNG NOISE	21	22
	STAINED ABDOMEN BROWN	21	22
824	SPERM POSITIVE	0	0

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APPENDIX H

**INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN P₁ FEMALE RATS DURING LACTATION**

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN P₁ FEMALE RATS DURING LACTATION

EXPLANATORY NOTES

Note

Test days for animal fates are determined from the initiation of test substance administration, designated as Day 1 of test.

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
 MR 15031
 HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
 DURING LACTATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
793	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		
794	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 46		
796	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
797	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
798	ALOPECIA RIGHT FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 44	0	4
806	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		
809	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 45	0 0	4 4
814	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
819	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
829	ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 44	0	3

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
 MR 15031
 HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
 DURING LACTATION

GROUP: IV-0 DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
800	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
807	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 44		
808	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
812	ALOPECIA LEFT FRONT LEG(S) ALOPECIA LEFT FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 45	0 0	4 4
821	DISCHARGE VAGINAL OPENING RED SACRIFICED BY DESIGN TEST DAY 45	0	0
823	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		
825	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 44		
831	STAINED FACE BROWN SACRIFICED BY DESIGN TEST DAY 42	0	1
832	NO SURVIVING PUPS SACRIFICED BY DESIGN TEST DAY 40	0	0

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN F1 FEMALE RATS
DURING LACTATION

GROUP: VI-0 DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
799	ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 45	0	4
801	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 44		
815	STAINED FACE BROWN SACRIFICED BY DESIGN TEST DAY 45	0	0
828	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
830	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 49		
834	ALOPECIA CHEST SACRIFICED BY DESIGN TEST DAY 44	0	4
835	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 44		
836	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN F1 FEMALE RATS
DURING LACTATION

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
805	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 49		
811	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 44		
816	ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 45	4	4
822	IRREGULAR RESPIRATION LUNG NOISE STAINED ABDOMEN BROWN SACRIFICED BY DESIGN TEST DAY 57	0 0 0	1 4 1
824	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 46		

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APPENDIX I

**INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA
IN P₁ MALE RATS**

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
 MR 15031
 HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 MALE RATS

GROUP: I-0 DOSE: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
748	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
749	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
756	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
760	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
762	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
767	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
777	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
780	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
782	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
786	ALOPECIA RIGHT FRONT PAW(S) ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 34	27 34 34	27 34 34

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 MALE RATS

GROUP: III-0 DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
750	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
752	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
757	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
759	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
769	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
770	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
773	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
776	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
790	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
791	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 MALE RATS

GROUP: V-0 DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
747	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
751	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
755	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
764	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
766	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
772	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
774	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
778	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
783	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
784	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
 MR 15031
 HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 MALE RATS

GROUP: VII-0 DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
753	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
754	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
758	FOUND DEAD TEST DAY 3		
765	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
775	STAINED PERINEUM YELLOW SACRIFICED BY DESIGN TEST DAY 34	7	7
779	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
781	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
785	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		
787	IRREGULAR RESPIRATION LUNG NOISE DEHYDRATED STAINED PERINEUM YELLOW SACRIFICED BY DESIGN TEST DAY 34	20 20 27 34	34 34 34 34
788	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 34		

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APPENDIX J

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P₁ FEMALE RATS DURING PREMATING (Includes Data Collected After Premating [Days 1-15], And Not Included In Gestation For Group VIII-0)

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA
IN P₁ FEMALE RATS DURING PREMATING
(Includes Data Collected After Premating [Days 1-15],
And Not Included In Gestation For Group VIII-0)

EXPLANATORY NOTES

Note

Test days for animal fates are determined from the initiation of test substance administration, designated as Day 1 of test.

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
DURING PREMATING

GROUP: II-0 DOSE: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
793	NO ABNORMALITIES DETECTED		
794	NO ABNORMALITIES DETECTED		
796	NO ABNORMALITIES DETECTED		
797	NO ABNORMALITIES DETECTED		
798	NO ABNORMALITIES DETECTED		
806	NO ABNORMALITIES DETECTED		
809	NO ABNORMALITIES DETECTED		
814	NO ABNORMALITIES DETECTED		
819	NO ABNORMALITIES DETECTED		
829	NO ABNORMALITIES DETECTED		

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
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HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
DURING PREMATING

GROUP: IV-0 DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
800	NO ABNORMALITIES DETECTED		
807	NO ABNORMALITIES DETECTED		
808	NO ABNORMALITIES DETECTED		
812	NO ABNORMALITIES DETECTED		
820	NO ABNORMALITIES DETECTED		
821	NO ABNORMALITIES DETECTED		
823	NO ABNORMALITIES DETECTED		
825	NO ABNORMALITIES DETECTED		
831	NO ABNORMALITIES DETECTED		
832	NO ABNORMALITIES DETECTED		

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
DURING PREMATING

GROUP: VI-0 DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
795	NO ABNORMALITIES DETECTED		
799	NO ABNORMALITIES DETECTED		
801	NO ABNORMALITIES DETECTED		
815	NO ABNORMALITIES DETECTED		
826	NO ABNORMALITIES DETECTED		
828	NO ABNORMALITIES DETECTED		
830	NO ABNORMALITIES DETECTED		
834	NO ABNORMALITIES DETECTED		
835	NO ABNORMALITIES DETECTED		
836	NO ABNORMALITIES DETECTED		

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
DURING PREMATING

(Includes Data Collected After Premating [Days 1-15]
And Not Included In Gestation For Group VIII-0)

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

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ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
792	NO ABNORMALITIES DETECTED FOUND DEAD TEST DAY 16		
805	NO ABNORMALITIES DETECTED		
810	HYPERREACTIVE SACRIFICED IN EXTREMIS TEST DAY 17	7	7
811	NO ABNORMALITIES DETECTED		
813 ^a	NO ABNORMALITIES DETECTED FOUND DEAD TEST DAY 37 ^a		
816	NO ABNORMALITIES DETECTED		
817	NO ABNORMALITIES DETECTED		
818	NO ABNORMALITIES DETECTED		
822	NO ABNORMALITIES DETECTED		
824	STAINED FACE BROWN	7	7

^a Includes data observed after Premating (Days 1-15) and not included in Gestation.

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APPENDIX K

**INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA
IN P₁ FEMALE RATS DURING GESTATION**

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA
IN P₁ FEMALE RATS DURING GESTATION

EXPLANATORY NOTES

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Notes

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

Test days for animal fates are determined from the initiation of test substance administration, designated as Day 1 of test.

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
DURING GESTATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

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ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
793	NO ABNORMALITIES DETECTED		
794	NO ABNORMALITIES DETECTED		
796	NO ABNORMALITIES DETECTED		
797	NO ABNORMALITIES DETECTED		
798	NO ABNORMALITIES DETECTED		
806	NO ABNORMALITIES DETECTED		
809	NO ABNORMALITIES DETECTED		
814	NO ABNORMALITIES DETECTED		
819	NO ABNORMALITIES DETECTED		
829	ALOPECIA BOTH FRONT PAW(S)	16	16

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
DURING GESTATION

GROUP: IV-0 DOSE: 15 MG/KG/DAY

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ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
800	NO ABNORMALITIES DETECTED		
807	NO ABNORMALITIES DETECTED		
808	NO ABNORMALITIES DETECTED		
812	ALOPECIA LEFT FRONT PAW(S) ALOPECIA LEFT FRONT LEG(S)	8 8	15 15
820	NO ABNORMALITIES DETECTED SACRIFICED IN EXTREMIS TEST DAY 39		
821	NO ABNORMALITIES DETECTED		
823	NO ABNORMALITIES DETECTED		
825	NO ABNORMALITIES DETECTED		
831	NO ABNORMALITIES DETECTED		
832	NO ABNORMALITIES DETECTED		

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
DURING GESTATION

GROUP: VI-0 DOSE: 50 MG/KG/DAY

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ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
795	NO ABNORMALITIES DETECTED FOUND DEAD TEST DAY 39		
799	ALOPECIA BOTH FRONT PAW(S)	16	16
815	NO ABNORMALITIES DETECTED		
826	ALOPECIA BOTH FRONT PAW(S) SACRIFICED IN EXTREMIS TEST DAY 40	11	18
828	ALOPECIA ABDOMEN	15	15
830	NO ABNORMALITIES DETECTED		
834	ALOPECIA CHEST	16	16
836	NO ABNORMALITIES DETECTED		

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
DURING GESTATION

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
805	NO ABNORMALITIES DETECTED		
811	NO ABNORMALITIES DETECTED		
816	NO ABNORMALITIES DETECTED		
817	NO ABNORMALITIES DETECTED SACRIFICED IN EXTREMIS TEST DAY 38		
818	LUNG NOISE FOUND DEAD TEST DAY 39	17	17
822	LUNG NOISE IRREGULAR RESPIRATION	4 4	4 4
824	NO ABNORMALITIES DETECTED		

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APPENDIX L

**INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA
IN P₁ FEMALE RATS DURING LACTATION**

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA
IN P₁ FEMALE RATS DURING LACTATION

EXPLANATORY NOTES

Notes

Test days for animal fates are determined from the initiation of test substance administration, designated as Day 1 of test.

Some females did not have detailed clinical observations performed during Lactation (Days 0-4) because they were sacrificed prior to the scheduled weekly observations.

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
 MR 15031
 HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
 DURING LACTATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

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ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
793	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		
794 ^a	SACRIFICED BY DESIGN TEST DAY 46		
796	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
797	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
798	ALOPECIA RIGHT FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 44	1	1
806	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		
809	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 45	0 0	0 0
814	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
819	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
829	ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 44	1	1

^a No detailed clinical observations were recorded; female was sacrificed as scheduled (Lactation Day 4) prior to the scheduled weekly detailed clinical observations.

H# 26,200
 MR 15031
 HC 42

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
 DURING LACTATION

GROUP: IV-0 DOSE: 15 MG/KG/DAY

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ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
800	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
807	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 44		
808	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
812	ALOPECIA LEFT FRONT PAW(S) ALOPECIA LEFT FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 45	0 0	0 0
821	DISCHARGE VAGINAL OPENING RED SACRIFICED BY DESIGN TEST DAY 45	0	0
823	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		
825	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 44		
831	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 42		
832 ^a	SACRIFICED BY DESIGN TEST DAY 40		

^a No detailed clinical observations were recorded; female was sacrificed as scheduled (Lactation Day 4) prior to the scheduled weekly detailed clinical observations.

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

H# 26,200
MR 15031
HC 42

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
DURING LACTATION

GROUP: VI-0 DOSE: 50 MG/KG/DAY

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ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
799	ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 45	0	0
801	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 44		
815	STAINED FACE BROWN SACRIFICED BY DESIGN TEST DAY 45	0	0
828	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
830	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 49		
834	ALOPECIA CHEST SACRIFICED BY DESIGN TEST DAY 44	1	1
835	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 44		
836	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26,200
MR 15031
HC 42

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS AND MORTALITY DATA IN P1 FEMALE RATS
DURING LACTATION

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

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ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
805	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 49		
811	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 44		
816	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
822	IRREGULAR RESPIRATION LUNG NOISE STAINED ABDOMEN BROWN SACRIFICED BY DESIGN TEST DAY 57	0 0 0	0 4 0
824 ^a	SACRIFICED BY DESIGN TEST DAY 46		

^a No detailed clinical observations were recorded; female was sacrificed as scheduled (Lactation Day 4) prior to the scheduled weekly detailed clinical observations.

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APPENDIX M

INDIVIDUAL BODY WEIGHTS AND MORTALITY DATA OF P₁ MALE RATS

INDIVIDUAL BODY WEIGHTS AND MORTALITY DATA OF P₁ MALE RATS

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating period
Test Days 15-34 = Cohabitation period

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Abbreviations

FD = Found dead
SD = Sacrificed by design

Summary Section

S.D. = Standard Deviation
S.E. = Standard Error
N = Number in Group

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) AND MORTALITY DATA OF P1 MALE RATS

GROUP: I-0 DOSE: 0 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	34	
ANIMAL NUMBER							
748	356.5	404.9	397.9	417.3	447.1	447.3	SD (DAY 34)
749	321.4	334.5	339.1	345.5	358.4	366.2	SD (DAY 34)
756	320.6	340.1	356.3	376.2	391.6	397.1	SD (DAY 34)
760	323.8	352.2	375.8	385.3	412.0	412.8	SD (DAY 34)
762	353.9	376.3	391.2	415.1	437.7	448.6	SD (DAY 34)
767	340.2	373.7	393.5	408.5	442.4	445.2	SD (DAY 34)
777	345.0	387.2	423.9	437.5	475.7	485.8	SD (DAY 34)
780	291.2	319.5	348.6	359.5	383.3	390.6	SD (DAY 34)
782	324.5	354.8	371.9	393.0	399.0	406.9	SD (DAY 34)
786	334.1	356.9	366.6	388.9	409.5	423.6	SD (DAY 34)
MEAN	331.1	360.0	376.5	392.7	415.7	422.4	
S.D.	19.3	25.8	25.6	28.0	35.0	34.9	
S.E.	6.1	8.2	8.1	8.8	11.1	11.1	
N	10	10	10	10	10	10	

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) AND MORTALITY DATA OF P1 MALE RATS

GROUP: III-0

DOSE: 15 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	34	
ANIMAL NUMBER							
750	340.3	385.1	390.0	415.5	441.5	442.8	SD (DAY 34)
752	329.2	354.4	362.7	381.1	399.1	414.4	SD (DAY 34)
757	343.9	387.7	388.0	422.3	460.7	453.8	SD (DAY 34)
759	348.8	389.3	400.6	427.8	448.8	447.1	SD (DAY 34)
769	343.5	380.5	399.3	417.3	449.8	463.5	SD (DAY 34)
770	323.9	350.1	368.8	388.8	415.4	408.4	SD (DAY 34)
773	340.2	370.6	403.6	430.4	427.0	461.8	SD (DAY 34)
776	324.3	359.8	386.4	416.2	441.1	452.1	SD (DAY 34)
790	328.0	362.0	389.2	402.1	421.8	432.7	SD (DAY 34)
791	278.5	290.9	301.6	314.0	326.7	324.8	SD (DAY 34)
MEAN	330.1	363.0	379.0	401.5	423.2	430.1	
S.D.	20.2	29.1	30.2	34.7	38.6	41.4	
S.E.	6.4	9.2	9.5	11.0	12.2	13.1	
N	10	10	10	10	10	10	

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) AND MORTALITY DATA OF P1 MALE RATS

GROUP: V-0

DOSE: 50 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	34	
ANIMAL NUMBER							
747	276.6	300.5	313.6	329.6	351.0	344.8	SD (DAY 34)
751	328.7	356.5	364.9	371.0	387.6	378.0	SD (DAY 34)
755	327.8	352.5	361.6	379.6	417.1	418.8	SD (DAY 34)
764	336.9	353.0	367.9	392.5	414.9	417.3	SD (DAY 34)
766	385.6	412.7	450.0	474.1	499.1	488.8	SD (DAY 34)
772	332.7	344.4	353.7	377.5	390.0	390.9	SD (DAY 34)
774	372.4	408.6	436.6	463.5	494.3	497.4	SD (DAY 34)
778	299.9	320.4	338.3	344.6	359.1	361.8	SD (DAY 34)
783	337.4	371.4	391.0	408.5	414.7	426.4	SD (DAY 34)
784	310.4	325.6	353.6	363.0	380.2	386.2	SD (DAY 34)
MEAN	330.8	354.6	373.1	390.4	410.8	411.0	
S.D.	31.9	35.9	42.2	47.0	50.5	50.3	
S.E.	10.1	11.4	13.3	14.9	16.0	15.9	
N	10	10	10	10	10	10	

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) AND MORTALITY DATA OF P1 MALE RATS

GROUP: VII-0

DOSE: 200 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	34	
ANIMAL NUMBER							
753	307.0	309.6	319.3	330.4	353.1	363.2	SD (DAY 34)
754	333.8	322.2	346.9	380.7	425.8	423.4	SD (DAY 34)
758	329.3	FD (DAY 3)					
765	309.9	310.0	333.6	350.7	384.1	390.0	SD (DAY 34)
775	329.7	323.1	330.3	374.7	393.2	393.8	SD (DAY 34)
779	344.8	351.7	370.0	384.3	401.2	402.5	SD (DAY 34)
781	333.2	341.1	358.8	377.4	397.1	401.4	SD (DAY 34)
785	337.2	324.0	353.2	366.0	398.0	395.6	SD (DAY 34)
787	342.1	337.0	309.8	285.6	285.9	258.5	SD (DAY 34)
788	333.5	360.7	391.9	392.0	400.4	395.7	SD (DAY 34)
MEAN	330.1	331.0	346.0	360.2	382.1	380.5	
S.D.	12.4	17.8	25.8	33.7	40.8	48.3	
S.E.	3.9	5.9	8.6	11.2	13.6	16.1	
N	10	9	9	9	9	9	

APPENDIX N
INDIVIDUAL BODY WEIGHT GAINS OF P₁ MALE RATS

INDIVIDUAL BODY WEIGHT GAINS OF P₁ MALE RATS

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating period
Test Days 15-34 = Cohabitation period

Abbreviations

FD = Found dead

Summary Section

S.D. = Standard Deviation
S.E. = Standard Error
N = Number in Group

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) OF P1 MALE RATS

GROUP: I-0 DOSE: 0 MG/KG/DAY

DAYS ON TEST:	ANIMAL NUMBER					
	1-8	8-15	15-22	22-29	29-34	1-34
748	48.4	-7.0	19.4	29.8	0.2	90.8
749	13.1	4.6	6.4	12.9	7.8	44.8
756	19.5	16.2	19.9	15.4	5.5	76.5
760	28.4	23.6	9.5	26.7	0.8	89.0
762	22.4	14.9	23.9	22.6	10.9	94.7
767	33.5	19.8	15.0	33.9	2.8	105.0
777	42.2	36.7	13.6	38.2	10.1	140.8
780	28.3	29.1	10.9	23.8	7.3	99.4
782	30.3	17.1	21.1	6.0	7.9	82.4
786	22.8	9.7	22.3	20.6	14.1	89.5
MEAN	28.9	16.5	16.2	23.0	6.7	91.3
S.D.	10.5	12.3	6.0	9.8	4.5	24.0
S.E.	3.3	3.9	1.9	3.1	1.4	7.6
N	10	10	10	10	10	10

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) OF P1 MALE RATS

GROUP: III-0 DOSE: 15 MG/KG/DAY

DAYS ON TEST:	ANIMAL NUMBER					
	1-8	8-15	15-22	22-29	29-34	1-34
750	44.8	4.9	25.5	26.0	1.3	102.5
752	25.2	8.3	18.4	18.0	15.3	85.2
757	43.8	0.3	34.3	38.4	-6.9	109.9
759	40.5	11.3	27.2	21.0	-1.7	98.3
769	37.0	18.8	18.0	32.5	13.7	120.0
770	26.2	18.7	20.0	26.6	-7.0	84.5
773	30.4	33.0	26.8	-3.4	34.8	121.6
776	35.5	26.6	29.8	24.9	11.0	127.8
790	34.0	27.2	12.9	19.7	10.9	104.7
791	12.4	10.7	12.4	12.7	-1.9	46.3
MEAN	33.0	16.0	22.5	21.6	6.9	100.1
S.D.	9.9	10.7	7.3	11.4	12.9	23.8
S.E.	3.1	3.4	2.3	3.6	4.1	7.5
N	10	10	10	10	10	10

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) OF P1 MALE RATS

GROUP: V-0 DOSE: 50 MG/KG/DAY

DAYS ON TEST:	ANIMAL NUMBER					
	1-8	8-15	15-22	22-29	29-34	1-34
747	23.9	13.1	16.0	21.4	-6.2	68.2
751	27.8	8.4	6.1	16.6	-9.6	49.3
755	24.7	9.1	18.0	37.5	1.7	91.0
764	16.1	14.9	24.6	22.4	2.4	80.4
766	27.1	37.3	24.1	25.0	-10.3	103.2
772	11.7	9.3	23.8	12.5	0.9	58.2
774	36.2	28.0	26.9	30.8	3.1	125.0
778	20.5	17.9	6.3	14.5	2.7	61.9
783	34.0	19.6	17.5	6.2	11.7	89.0
784	15.2	28.0	9.4	17.2	6.0	75.8
MEAN	23.7	18.6	17.3	20.4	0.2	80.2
S.D.	8.0	9.7	7.8	9.1	7.0	22.8
S.E.	2.5	3.1	2.5	2.9	2.2	7.2
N	10	10	10	10	10	10

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) OF P1 MALE RATS

GROUP: VII-0 DOSE: 200 MG/KG/DAY

DAYS ON TEST:	ANIMAL NUMBER					
	1-8	8-15	15-22	22-29	29-34	1-34
753	2.6	9.7	11.1	22.7	10.1	56.2
754	-11.6	24.7	33.8	45.1	-2.4	89.6
758	FD (DAY 3)					
765	0.1	23.6	17.1	33.4	5.9	80.1
775	-6.6	7.2	44.4	18.5	0.6	64.1
779	6.9	18.3	14.3	16.9	1.3	57.7
781	7.9	17.7	18.6	19.7	4.3	68.2
785	-13.2	29.2	12.8	32.0	-2.4	58.4
787	-5.1	-27.2	-24.2	0.3	-27.4	-83.6
788	27.2	31.2	0.1	8.4	-4.7	62.2
MEAN	0.9	14.9	14.2	21.9	-1.6	50.3
S.D.	12.4	17.7	19.4	13.5	10.7	51.4
S.E.	4.1	5.9	6.5	4.5	3.6	17.1
N	9	9	9	9	9	9

APPENDIX O

**INDIVIDUAL BODY WEIGHTS AND MORTALITY DATA OF P₁ FEMALE RATS
DURING PREMATING**

INDIVIDUAL BODY WEIGHTS AND MORTALITY DATA OF P₁ FEMALE RATS
DURING PREMATING

EXPLANATORY NOTES

Note

Test Day 15 = Last day of pre mating period that data were recorded.

Abbreviations

FD = Found dead
SD = Sacrificed by design
SE = Sacrificed *in extremis*

Summary Section

S.D. = Standard Deviation
S.E. = Standard Error
N = Number in Group

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) AND MORTALITY DATA OF P1 FEMALE RATS DURING PREMATING

GROUP: II-0 DOSE: 0 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:			
	1	8	15	
793	239.7	234.7	241.2	SD (DAY 43)
794	236.8	245.8	236.1	SD (DAY 46)
796	238.5	249.9	241.8	SD (DAY 45)
797	240.6	253.5	250.8	SD (DAY 45)
798	247.9	244.1	258.0	SD (DAY 44)
806	229.3	233.5	245.7	SD (DAY 43)
809	236.2	251.7	241.7	SD (DAY 45)
814	216.7	223.0	224.5	SD (DAY 45)
819	239.0	248.4	248.8	SD (DAY 45)
829	221.7	229.7	228.4	SD (DAY 44)
MEAN	234.6	241.4	241.7	
S.D.	9.4	10.5	10.1	
S.E.	3.0	3.3	3.2	
N	10	10	10	

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) AND MORTALITY DATA OF P1 FEMALE RATS DURING PREMATING

GROUP: IV-0 DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:			
	1	8	15	
800	224.4	236.3	226.9	SD (DAY 45)
807	232.8	245.7	248.6	SD (DAY 44)
808	226.0	230.1	232.3	SD (DAY 45)
812	231.0	237.7	234.4	SD (DAY 45)
820	238.9	237.5	234.6	SE (DAY 39)
821	218.7	229.1	233.1	SD (DAY 45)
823	246.7	269.8	284.6	SD (DAY 43)
825	246.6	256.2	263.6	SD (DAY 44)
831	217.0	225.1	233.9	SD (DAY 42)
832	225.5	234.4	248.8	SD (DAY 40)
MEAN	230.8	240.2	244.1	
S.D.	10.5	13.7	18.0	
S.E.	3.3	4.3	5.7	
N	10	10	10	

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 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) AND MORTALITY DATA OF P1 FEMALE RATS DURING PREMATING

GROUP: VI-0 DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:			
	1	8	15	
795	244.6	255.2	268.6	FD (DAY 39)
799	241.1	241.3	256.6	SD (DAY 45)
801	224.3	239.5	249.9	SD (DAY 44)
815	236.3	239.5	244.6	SD (DAY 45)
826	237.7	246.7	253.5	SE (DAY 40)
828	226.1	242.1	245.9	SD (DAY 45)
830	232.4	242.7	242.0	SD (DAY 49)
834	216.0	237.0	243.5	SD (DAY 44)
835	235.4	252.5	247.1	SD (DAY 44)
836	218.9	222.9	225.4	SD (DAY 45)
MEAN	231.3	241.9	247.7	
S.D.	9.6	8.9	11.1	
S.E.	3.0	2.8	3.5	
N	10	10	10	

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) AND MORTALITY DATA OF P1 FEMALE RATS DURING PREMATING

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:			
	1	8	15	
792	225.6	211.9	181.4	FD (DAY 16)
805	242.4	251.6	250.6	SD (DAY 49)
810	244.8	254.7	250.0	SE (DAY 17)
811	230.2	231.5	243.6	SD (DAY 44)
813	217.6	206.5	219.5	FD (DAY 37)
816	229.9	243.2	235.7	SD (DAY 45)
817	245.4	246.3	247.5	SE (DAY 38)
818	218.3	213.2	227.9	FD (DAY 39)
822	225.4	244.7	252.6	SD (DAY 57)
824	248.5	247.8	271.2	SD (DAY 46)
MEAN	232.8	235.1	238.0	
S.D.	11.6	18.1	24.5	
S.E.	3.7	5.7	7.7	
N	10	10	10	

APPENDIX P

INDIVIDUAL BODY WEIGHT GAINS OF P₁ FEMALE RATS DURING PREMATING

INDIVIDUAL BODY WEIGHT GAINS OF P₁ FEMALE RATS DURING PREMATING
EXPLANATORY NOTES

Note

Test Day 15 = Last day of pre mating period that data were recorded.

Abbreviations

Summary Section

S.D. = Standard Deviation
S.E. = Standard Error
N = Number in Group

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) OF P1 FEMALE RATS DURING PREMATING

GROUP: II-0

DOSE: 0 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:		
	1-8	8-15	1-15
793	-5.0	6.5	1.5
794	9.0	-9.7	-0.7
796	11.4	-8.1	3.3
797	12.9	-2.7	10.2
798	-3.8	13.9	10.1
806	4.2	12.2	16.4
809	15.5	-10.0	5.5
814	6.3	1.5	7.8
819	9.4	0.4	9.8
829	8.0	-1.3	6.7
MEAN	6.8	0.3	7.1
S.D.	6.7	8.5	5.0
S.E.	2.1	2.7	1.6
N	10	10	10

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) OF P1 FEMALE RATS DURING PREMATING

GROUP: IV-0

DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:		
	1-8	8-15	1-15
800	11.9	-9.4	2.5
807	12.9	2.9	15.8
808	4.1	2.2	6.3
812	6.7	-3.3	3.4
820	-1.4	-2.9	-4.3
821	10.4	4.0	14.4
823	23.1	14.8	37.9
825	9.6	7.4	17.0
831	8.1	8.8	16.9
832	8.9	14.4	23.3
MEAN	9.4	3.9	13.3
S.D.	6.3	7.8	12.1
S.E.	2.0	2.5	3.8
N	10	10	10

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) OF P1 FEMALE RATS DURING PREMATING

GROUP: VI-0

DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:		
	1-8	8-15	1-15
795	10.6	13.4	24.0
799	0.2	15.3	15.5
801	15.2	10.4	25.6
815	3.2	5.1	8.3
826	9.0	6.8	15.8
828	16.0	3.8	19.8
830	10.3	-0.7	9.6
834	21.0	6.5	27.5
835	17.1	-5.4	11.7
836	4.0	2.5	6.5
MEAN	10.7	5.8	16.4
S.D.	6.7	6.3	7.5
S.E.	2.1	2.0	2.4
N	10	10	10

**A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats**

DuPont-14109

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) OF P1 FEMALE RATS DURING PREMATING

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:		
	1-8	8-15	1-15
792	-13.7	-30.5	-44.2
805	9.2	-1.0	8.2
810	9.9	-4.7	5.2
811	1.3	12.1	13.4
813	-11.1	13.0	1.9
816	13.3	-7.5	5.8
817	0.9	1.2	2.1
818	-5.1	14.7	9.6
822	19.3	7.9	27.2
824	-0.7	23.4	22.7
MEAN	2.3	2.9	5.2
S.D.	10.6	15.2	19.3
S.E.	3.4	4.8	6.1
N	10	10	10

APPENDIX Q

INDIVIDUAL BODY WEIGHTS OF P₁ FEMALE RATS DURING GESTATION

INDIVIDUAL BODY WEIGHTS OF P₁ FEMALE RATS DURING GESTATION

EXPLANATORY NOTES

Note

This appendix contains data from females with evidence of copulation observed. No gestation data were collected for females with no evidence of copulation (whether a litter was delivered or not).

Test days for animal fates:

- Determined as days of gestation for rats with evidence of copulation
- Determined as days on test from the initiation of test substance administration for rats dying during pre mating or cohabitation, or for those showing no evidence of copulation.

Abbreviations

FD = Found Dead
G = Gestation
SE = Sacrificed *in extremis*
- = No Data

Summary Section

S.D. = Standard Deviation
S.E. = Standard Error
N = Number in Group

**A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats**

DuPont-14109

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) OF P1 FEMALE RATS DURING GESTATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

GESTATION DAYS:	0	7	14	21
ANIMAL NUMBER				
793	241.3	281.3	323.4	368.3
794	258.4	300.4	325.1	409.4
796	263.2	287.5	322.4	419.2
797	253.8	283.6	308.9	372.4
798	254.3	298.1	337.3	431.9
806	247.7	279.9	320.0	404.9
809	256.6	295.5	316.2	390.8
814	241.6	270.9	298.0	372.4
819	257.9	292.1	321.5	406.8
829	223.6	252.3	280.6	368.7
MEAN	249.8	284.2	315.3	394.5
S.D.	11.7	14.4	16.0	23.2
S.E.	3.7	4.6	5.1	7.3
N	10	10	10	10

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) OF P1 FEMALE RATS DURING GESTATION

GROUP: IV-0 DOSE: 15 MG/KG/DAY

GESTATION DAYS:	0	7	14	21	
ANIMAL NUMBER					
800	243.5	269.2	302.9	387.9	
807	256.1	293.5	312.5	356.3	
808	240.9	272.3	301.6	386.8	
812	257.7	292.0	323.4	414.3	
820	237.1	269.4	299.6	315.4	SE (DAY 23G)
821	248.7	277.3	306.6	399.9	
823	280.7	323.3	362.3	437.2	
825	265.4	309.7	337.9	377.3	
831	237.3	261.5	292.9	321.5	
832	251.0	283.7	308.3	335.3	
MEAN	251.8	285.2	314.8	373.2	
S.D.	13.7	19.6	21.1	40.3	
S.E.	4.3	6.2	6.7	12.8	
N	10	10	10	10	

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) OF P1 FEMALE RATS DURING GESTATION

GROUP: VI-0 DOSE: 50 MG/KG/DAY

GESTATION DAYS:	0	7	14	21	
ANIMAL NUMBER					
795	272.6	307.1	335.1	377.3	FD (DAY 23G)
799	254.3	293.0	331.8	413.6	
801	-	-	-	-	
815	249.7	282.5	316.1	411.7	
826	255.8	286.2	318.7	360.7	SE (DAY 24G)
828	249.0	274.3	301.7	379.5	
830	250.2	254.1	271.6	332.8	
834	237.5	268.1	307.2	376.9	
835	-	-	-	-	
836	231.5	272.6	288.9	324.3	
MEAN	250.1	279.7	308.9	372.1	
S.D.	12.3	16.2	21.4	32.4	
S.E.	4.4	5.7	7.6	11.5	
N	8	8	8	8	

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) OF P1 FEMALE RATS DURING GESTATION

GROUP: VIII-0

DOSE: 200 MG/KG/DAY

GESTATION DAYS:	0	7	14	21	
ANIMAL NUMBER					
792	-	-	-	-	FD (DAY 16)
805	260.6	286.5	318.7	385.5	
810	-	-	-	-	FD (DAY 17)
811	241.6	257.6	292.2	352.5	
813	-	-	-	-	FD (DAY 37)
816	251.6	283.4	318.0	397.4	
817	255.8	280.6	302.4	325.3	SE (DAY 22G)
818	218.9	251.2	284.3	307.6	FD (DAY 22G)
822	260.9	291.2	323.7	318.2	
824	262.4	286.8	326.0	403.9	
MEAN	250.3	276.8	309.3	355.8	
S.D.	15.6	15.7	16.4	40.0	
S.E.	5.9	5.9	6.2	15.1	
N	7	7	7	7	

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**A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats**

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APPENDIX R

INDIVIDUAL BODY WEIGHT GAINS OF P₁ FEMALE RATS DURING GESTATION

INDIVIDUAL BODY WEIGHT GAINS OF P₁ FEMALE RATS DURING GESTATION

EXPLANATORY NOTES

Note

This appendix contains data from females with evidence of copulation observed. No gestation data were collected for females with no evidence of copulation (whether a litter was delivered or not).

Test days for animal fates:

- Determined as days of gestation for rats with evidence of copulation
- Determined as days on test from the initiation of test substance administration for rats dying during premating or cohabitation, or for those showing no evidence of copulation.

Abbreviations

FD = Found Dead
G = Gestation
SE = Sacrificed *in extremis*
- = No Data

Summary Section

S.D. = Standard Deviation
S.E. = Standard Error
N = Number in Group

**A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats**

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) OF P1 FEMALE RATS DURING GESTATION

GROUP: II-0

DOSE: 0 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NUMBER				
793	40.0	42.1	44.9	127.0
794	42.0	24.7	84.3	151.0
796	24.3	34.9	96.8	156.0
797	29.8	25.3	63.5	118.6
798	43.8	39.2	94.6	177.6
806	32.2	40.1	84.9	157.2
809	38.9	20.7	74.6	134.2
814	29.3	27.1	74.4	130.8
819	34.2	29.4	85.3	148.9
829	28.7	28.3	88.1	145.1
MEAN	34.3	31.2	79.1	144.6
S.D.	6.5	7.4	15.6	17.4
S.E.	2.1	2.3	4.9	5.5
N	10	10	10	10

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) OF P1 FEMALE RATS DURING GESTATION

GROUP: IV-0

DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	GESTATION DAYS:				SE (DAY 23G)
	0-7	7-14	14-21	0-21	
800	25.7	33.7	85.0	144.4	
807	37.4	19.0	43.8	100.2	
808	31.4	29.3	85.2	145.9	
812	34.3	31.4	90.9	156.6	
820	32.3	30.2	15.8	78.3	
821	28.6	29.3	93.3	151.2	
823	42.6	39.0	74.9	156.5	
825	44.3	28.2	39.4	111.9	
831	24.2	31.4	28.6	84.2	
832	32.7	24.6	27.0	84.3	
MEAN	33.3	29.6	58.4	121.3	
S.D.	6.6	5.3	30.2	32.7	
S.E.	2.1	1.7	9.6	10.4	
N	10	10	10	10	

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 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) OF F1 FEMALE RATS DURING GESTATION

GROUP: VI-0

DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	GESTATION DAYS:				
	0-7	7-14	14-21	0-21	
795	34.5	28.0	42.2	104.7	FD (DAY 23G)
799	38.7	38.8	81.8	159.3	
801	-	-	-	-	SE (DAY 24G)
815	32.8	33.6	95.6	162.0	
826	30.4	32.5	42.0	104.9	
828	25.3	27.4	77.8	130.5	
830	3.9	17.5	61.2	82.6	
834	30.6	39.1	69.7	139.4	
835	-	-	-	-	
836	41.1	16.3	35.4	92.8	
MEAN	29.7	29.2	63.2	122.0	
S.D.	11.5	8.7	21.8	30.1	
S.E.	4.1	3.1	7.7	10.7	
N	8	8	8	8	

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) OF P1 FEMALE RATS DURING GESTATION

GROUP: VIII-0

DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	GESTATION DAYS:				
	0-7	7-14	14-21	0-21	
792	-	-	-	-	FD (DAY 16)
805	25.9	32.2	66.8	124.9	
810	-	-	-	-	FD (DAY 17)
811	16.0	34.6	60.3	110.9	
813	-	-	-	-	FD (DAY 37)
816	31.8	34.6	79.4	145.8	
817	24.8	21.8	22.9	69.5	SE (DAY 22G)
818	32.3	33.1	23.3	88.7	FD (DAY 22G)
822	30.3	32.5	-5.5	57.3	
824	24.4	39.2	77.9	141.5	
MEAN	26.5	32.6	46.4	105.5	
S.D.	5.7	5.3	32.8	34.7	
S.E.	2.1	2.0	12.4	13.1	
N	7	7	7	7	

APPENDIX S
**INDIVIDUAL BODY WEIGHTS AND MORTALITY DATA OF P₁ FEMALE RATS
DURING LACTATION**

INDIVIDUAL BODY WEIGHTS AND MORTALITY DATA OF P₁ FEMALE RATS
DURING LACTATION

EXPLANATORY NOTES

Notes

Unless stated otherwise, animals with no data did not deliver a litter and therefore had no lactation data collected.

Test days for animal fates are determined from the initiation of test substance administration.

Abbreviations

FD = Found Dead
SE = Sacrificed *in extremis*
- = No Data

Summary Section

S.D. = Standard Deviation
S.E. = Standard Error
N = Number in Group

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) AND MORTALITY DATA OF P1 FEMALE RATS DURING LACTATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

ANIMAL NUMBER	LACTATION DAYS:		
	0	4	
793	279.6	290.3	SD (DAY 43)
794	318.3	331.2	SD (DAY 46)
796	311.6	298.8	SD (DAY 45)
797	289.8	305.7	SD (DAY 45)
798	301.8	322.7	SD (DAY 44)
806	321.0	294.3	SD (DAY 43)
809	290.3	321.9	SD (DAY 45)
814	289.3	294.8	SD (DAY 45)
819	316.2	318.5	SD (DAY 45)
829	272.6	277.5	SD (DAY 44)
MEAN	299.1	305.6	
S.D.	17.1	17.3	
S.E.	5.4	5.5	
N	10	10	

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) AND MORTALITY DATA OF P1 FEMALE RATS DURING LACTATION

GROUP: IV-0 DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	LACTATION DAYS:		
	0	4	
800	292.2	308.5	SD (DAY 45)
807	271.3	309.5	SD (DAY 44)
808	285.7	303.1	SD (DAY 45)
812	304.9	310.1	SD (DAY 45)
820	-	-	SE (DAY 39)
821	315.1	303.9	SD (DAY 45)
823	344.6	350.3	SD (DAY 43)
825	302.9	322.8	SD (DAY 44)
831	240.3	264.4	SD (DAY 42)
832	266.6	-	SD (DAY 40)
MEAN	291.5	309.1	
S.D.	30.4	23.7	
S.E.	10.1	8.4	
N	9	8	

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) AND MORTALITY DATA OF P1 FEMALE RATS DURING LACTATION

GROUP: VI-0 DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	LACTATION DAYS:		
	0	4	
795	-	-	FD (DAY 39)
799	319.9	338.3	SD (DAY 45)
801	265.9	293.2	SD (DAY 44)
815	309.1	301.8	SD (DAY 45)
826	-	-	SE (DAY 40)
828	299.3	302.1	SD (DAY 45)
830	250.4	274.7	SD (DAY 49)
834	274.2	299.0	SD (DAY 44)
835	272.8	289.0	SD (DAY 44)
836	279.9	294.6	SD (DAY 45)
MEAN	283.9	299.1	
S.D.	23.4	18.1	
S.E.	8.3	6.4	
N	8	8	

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL BODY WEIGHTS (g) AND MORTALITY DATA OF P1 FEMALE RATS DURING LACTATION

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	LACTATION DAYS:		
	0	4	
792	-	-	FD (DAY 16)
805	301.1	304.3	SD (DAY 49)
810	-	-	SE (DAY 17)
811	292.1	298.8	SD (DAY 44)
813	-	-	FD (DAY 37)
816	300.0	331.2	SD (DAY 45)
817	-	-	SE (DAY 38)
818	-	-	FD (DAY 39)
822	259.1	288.8	SD (DAY 57)
824	294.3	305.0	SD (DAY 46)
MEAN	289.3	305.6	
S.D.	17.3	15.7	
S.E.	7.7	7.0	
N	5	5	

APPENDIX T
INDIVIDUAL BODY WEIGHT GAINS AND MORTALITY DATA
OF P₁ FEMALE RATS DURING LACTATION

INDIVIDUAL BODY WEIGHT GAINS AND MORTALITY DATA
OF P₁ FEMALE RATS DURING LACTATION

EXPLANATORY NOTES

Notes

Unless stated otherwise, animals with no data did not deliver a litter and therefore had no lactation data collected.

Abbreviations

FD = Found Dead
SE = Sacrificed *in extremis*
- = No Data

Summary Section

S.D. = Standard Deviation
S.E. = Standard Error
N = Number in Group

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
MR# 15031
HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) AND MORTALITY DATA OF P1 FEMALE RATS DURING LACTATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

LACTATION
DAYS: 0-4

ANIMAL NUMBER

793	10.7	SD (DAY 43)
794	12.9	SD (DAY 46)
796	-12.8	SD (DAY 45)
797	15.9	SD (DAY 45)
798	20.9	SD (DAY 44)
806	-26.7	SD (DAY 43)
809	31.6	SD (DAY 45)
814	5.5	SD (DAY 45)
819	2.3	SD (DAY 45)
829	4.9	SD (DAY 44)
MEAN	6.5	
S.D.	16.6	
S.E.	5.2	
N	10	

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
MR# 15031
HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) AND MORTALITY DATA OF P1 FEMALE RATS DURING LACTATION

GROUP: IV-0 DOSE: 15 MG/KG/DAY

LACTATION		
DAYS:	0-4	
ANIMAL NUMBER		
800	16.3	SD (DAY 45)
807	38.2	SD (DAY 44)
808	17.4	SD (DAY 45)
812	5.2	SD (DAY 45)
820	-	SE (DAY 39)
821	-11.2	SD (DAY 45)
823	5.7	SD (DAY 43)
825	19.9	SD (DAY 44)
831	24.1	SD (DAY 42)
832	-	SD (DAY 40)
MEAN	14.4	
S.D.	14.7	
S.E.	5.2	
N	8	

**A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats**

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
MR# 15031
HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) AND MORTALITY DATA OF P1 FEMALE RATS DURING LACTATION

GROUP: VI-0

DOSE: 50 MG/KG/DAY

LACTATION		
DAYS:	0-4	
ANIMAL NUMBER		
795	-	FD (DAY 39)
799	18.4	SD (DAY 45)
801	27.3	SD (DAY 44)
815	-7.3	SD (DAY 45)
826	-	SE (DAY 40)
828	2.8	SD (DAY 45)
830	24.3	SD (DAY 49)
834	24.8	SD (DAY 44)
835	16.2	SD (DAY 44)
836	14.7	SD (DAY 45)
MEAN	15.2	
S.D.	11.9	
S.E.	4.2	
N	8	

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
MR# 15031
HC# 42

INDIVIDUAL BODY WEIGHT GAINS (g) AND MORTALITY DATA OF P1 FEMALE RATS DURING LACTATION

GROUP: VIII-0

DOSE: 200 MG/KG/DAY

LACTATION	
DAYS:	0-4
ANIMAL NUMBER	
792	- FD (DAY 16)
805	3.2 SD (DAY 49)
810	- SE (DAY 17)
811	6.7 SD (DAY 44)
813	- FD (DAY 37)
816	31.2 SD (DAY 45)
817	- SE (DAY 38)
818	- FD (DAY 39)
822	29.7 SD (DAY 57)
824	10.7 SD (DAY 46)
MEAN	16.3
S.D.	13.2
S.E.	5.9
N	5

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APPENDIX U

INDIVIDUAL FOOD CONSUMPTION BY P₁ MALE RATS DURING PREMATING

INDIVIDUAL FOOD CONSUMPTION BY P₁ MALE RATS DURING PREMATING

EXPLANATORY NOTES

Notes

- Test Days 1-15 = Premating period
Test Days 15-34 = Cohabitation period
Test Day 15 = Last day of premating period that data were recorded.

Abbreviations

FD = Found dead

Summary Section

- S.D. = Standard Deviation
S.E. = Standard Error
N = Number in Group

**A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats**

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 MALE RATS DURING PREMATING

GROUP: I-0 DOSE: 0 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:		
	1-8	8-15	1-15
748	31.5	25.1	28.3
749	22.8	20.4	21.6
756	22.2	22.9	22.6
760	23.6	23.1	23.3
762	25.6	25.7	25.7
767	25.8	26.5	26.1
777	30.0	30.8	30.4
780	24.2	25.7	25.0
782	28.5	26.1	27.3
786	22.4	24.3	23.3
MEAN	25.7	25.1	25.4
S.D.	3.3	2.7	2.8
S.E.	1.0	0.9	0.9
N	10	10	10

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 MALE RATS DURING PREMATING

GROUP: III-0

DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:		
	1-8	8-15	1-15
750	26.8	22.2	24.5
752	26.8	22.5	24.6
757	28.0	24.1	26.1
759	27.8	24.4	26.1
769	28.0	24.2	26.1
770	25.7	25.5	25.6
773	26.9	29.0	27.9
776	27.7	27.8	27.8
790	25.6	26.1	25.8
791	22.5	21.0	21.7
MEAN	26.6	24.7	25.6
S.D.	1.7	2.5	1.8
S.E.	0.5	0.8	0.6
N	10	10	10

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 MALE RATS DURING PREMATING

GROUP: V-0 DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:		
	1-8	8-15	1-15
747	23.6	23.6	23.6
751	27.5	23.3	25.4
755	23.3	21.2	22.3
764	26.7	24.9	25.8
766	28.4	27.9	28.2
772	21.4	23.8	22.6
774	29.1	28.1	28.6
778	20.5	22.7	21.6
783	26.1	26.1	26.1
784	22.0	23.7	22.8
MEAN	24.9	24.5	24.7
S.D.	3.1	2.2	2.5
S.E.	1.0	0.7	0.8
N	10	10	10

**A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats**

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 MALE RATS DURING PREMATING

GROUP: VII-0 DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:		
	1-8	8-15	1-15
753	17.7	20.3	19.0
754	19.7	23.8	21.7
758	FD (DAY 3)		
765	16.1	24.1	20.1
775	15.3	21.3	18.3
779	19.8	24.5	22.1
781	18.9	24.2	21.5
785	16.2	26.4	21.3
787	16.9	22.8	19.9
788	23.6	28.1	25.9
MEAN	18.2	23.9	21.1
S.D.	2.6	2.4	2.2
S.E.	0.9	0.8	0.7
N	9	9	9

APPENDIX V

INDIVIDUAL FOOD CONSUMPTION BY P₁ FEMALE RATS DURING PREMATING

INDIVIDUAL FOOD CONSUMPTION BY P₁ FEMALE RATS DURING PREMATING
EXPLANATORY NOTES

Note

Test Day 15 = Last day of pre mating period that data were recorded.

Abbreviations

Summary Section

S.D. = Standard Deviation
S.E. = Standard Error
N = Number in Group

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
MR# 15031
HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 FEMALE RATS DURING PREMATING

GROUP: II-0

DOSE: 0 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL NUMBER			
793	17.1	17.7	17.4
794	19.9	17.6	18.7
796	16.1	18.5	17.3
797	18.4	18.0	18.2
798	19.0	20.2	19.6
806	18.3	20.9	19.6
809	21.2	20.3	20.7
814	17.6	19.5	18.6
819	17.1	20.8	19.0
829	15.0	17.0	16.0
MEAN	18.0	19.1	18.5
S.D.	1.8	1.5	1.4
S.E.	0.6	0.5	0.4
N	10	10	10

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 FEMALE RATS DURING PREMATING

GROUP: IV-0 DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:		
	1-8	8-15	1-15
800	17.5	16.3	16.9
807	18.9	19.0	19.0
808	18.0	17.0	17.5
812	16.8	17.8	17.3
820	15.2	15.2	15.2
821	17.9	19.5	18.7
823	24.7	26.0	25.4
825	20.5	21.3	20.9
831	17.0	19.3	18.1
832	18.8	20.4	19.6
MEAN	18.5	19.2	18.9
S.D.	2.6	3.0	2.8
S.E.	0.8	1.0	0.9
N	10	10	10

**A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats**

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 FEMALE RATS DURING PREMATING

GROUP: VI-0 DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:		
	1-8	8-15	1-15
795	20.1	18.8	19.4
799	17.9	17.6	17.7
801	16.2	18.8	17.5
815	16.3	19.8	18.1
826	19.1	20.1	19.6
828	16.8	18.4	17.6
830	20.1	18.5	19.3
834	16.2	18.0	17.1
835	19.5	16.8	18.1
836	16.5	18.8	17.6
MEAN	17.9	18.5	18.2
S.D.	1.7	1.0	0.9
S.E.	0.5	0.3	0.3
N	10	10	10

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
MR# 15031
HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 FEMALE RATS DURING PREMATING

GROUP: VIII-0

DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	DAYS ON TEST:		
	1-8	8-15	1-15
792	12.6	12.5	12.5
805	19.0	18.3	18.7
810	18.6	20.4	19.5
811	16.2	18.5	17.4
813	13.9	16.1	15.0
816	18.5	18.0	18.2
817	16.3	17.4	16.8
818	13.9	19.2	16.6
822	13.6	19.6	16.6
824	14.9	22.2	18.6
MEAN	15.8	18.2	17.0
S.D.	2.3	2.6	2.0
S.E.	0.7	0.8	0.6
N	10	10	10

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APPENDIX W

INDIVIDUAL FOOD CONSUMPTION BY P₁ FEMALE RATS DURING GESTATION

INDIVIDUAL FOOD CONSUMPTION BY P₁ FEMALE RATS DURING GESTATION

EXPLANATORY NOTES

Notes

This appendix contains data from females with evidence of copulation observed. No gestation data were collected for females with no evidence of copulation (whether a litter was delivered or not).

Test days for animal fates:

- Determined as days of gestation for rats with evidence of copulation
- Determined as days on test from the initiation of test substance administration for rats dying during pre mating or cohabitation, or for those showing no evidence of copulation.

Abbreviations

FD = Found Dead
G = Gestation
SE = Sacrificed *in extremis*
- = No Data

Summary Section

S.D. = Standard Deviation
S.E. = Standard Error
N = Number in Group

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
MR# 15031
HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 FEMALE RATS DURING GESTATION

GROUP: II-0

DOSE: 0 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NUMBER				
793	26.2	29.5	29.3	28.3
794	29.9	27.1	28.8	28.6
796	21.3	28.3	29.4	26.3
797	21.2	24.0	23.7	22.9
798	27.8	30.0	31.3	29.7
806	25.6	27.3	28.9	27.3
809	27.8	26.6	28.5	27.6
814	26.3	25.3	27.2	26.3
819	25.4	28.0	28.2	27.2
829	22.3	24.1	25.5	24.0
MEAN	25.4	27.0	28.1	26.8
S.D.	2.9	2.1	2.2	2.1
S.E.	0.9	0.7	0.7	0.7
N	10	10	10	10

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 FEMALE RATS DURING GESTATION

GROUP: IV-0

DOSE: 15 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21	
ANIMAL NUMBER					
800	22.7	25.3	26.9	25.0	
807	25.9	24.6	27.0	25.9	
808	23.1	24.8	28.5	25.5	
812	25.7	26.3	27.9	26.6	
820	21.6	22.7	21.9	22.1	SE (DAY 23G)
821	23.7	24.7	26.0	24.8	
823	30.6	33.4	31.4	31.8	
825	28.8	29.6	28.7	29.1	
831	22.7	26.4	24.8	24.6	
832	24.1	23.4	22.9	23.5	
MEAN	24.9	26.1	26.6	25.9	
S.D.	2.9	3.2	2.8	2.8	
S.E.	0.9	1.0	0.9	0.9	
N	10	10	10	10	

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 FEMALE RATS DURING GESTATION

GROUP: VI-0 DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	GESTATION DAYS:				
	0-7	7-14	14-21	0-21	
795	27.1	25.0	26.3	26.1	FD (DAY 23G)
799	25.3	27.4	28.8	27.2	
801	-	-	-	-	
815	24.4	25.4	29.0	26.3	
826	24.5	23.4	23.0	23.6	SE (DAY 24G)
828	22.1	22.4	25.7	23.4	
830	15.8	19.6	23.8	19.7	
834	21.5	23.1	22.8	22.5	
835	-	-	-	-	
836	24.6	23.9	23.2	23.9	
MEAN	23.1	23.8	25.3	24.1	
S.D.	3.5	2.3	2.6	2.4	
S.E.	1.2	0.8	0.9	0.9	
N	8	8	8	8	

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
 MR# 15031
 HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 FEMALE RATS DURING GESTATION

GROUP: VIII-0

DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	GESTATION DAYS:				
	0-7	7-14	14-21	0-21	
792	-	-	-	-	FD (DAY 16)
805	23.5	27.4	26.8	25.9	
810	-	-	-	-	FD (DAY 17)
811	17.9	24.5	27.3	23.2	
813	-	-	-	-	FD (DAY 37)
816	24.3	25.6	26.7	25.6	
817	23.6	23.3	21.9	22.9	SE (DAY 22G)
818	20.9	24.9	22.9	22.9	FD (DAY 22G)
822	23.1	23.5	13.9	20.1	
824	23.5	24.7	27.4	25.2	
MEAN	22.4	24.9	23.8	23.7	
S.D.	2.2	1.4	4.9	2.0	
S.E.	0.8	0.5	1.9	0.8	
N	7	7	7	7	

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APPENDIX X

INDIVIDUAL FOOD CONSUMPTION BY P₁ FEMALE RATS DURING LACTATION

INDIVIDUAL FOOD CONSUMPTION BY P₁ FEMALE RATS DURING LACTATION

EXPLANATORY NOTES

Notes

Unless stated otherwise, animals with no data did not deliver a litter and therefore had no lactation data collected.

Test days for animal fates are determined from the initiation of test substance administration.

Abbreviations

FD = Found Dead
SD = Sacrificed by Design
SE = Sacrificed *in extremis*
- = No Data

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846
H# 26200
MR# 15031
HC# 42
INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 FEMALE RATS DURING LACTATION
GROUP: II-0 DOSE: 0 MG/KG/DAY

LACTATION
DAYS: 0-4

ANIMAL NUMBER

793	15.8
794	31.6
796	24.0
797	27.0
798	22.4
806	29.7
809	37.0
814	27.4
819	30.8
829	24.9

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
MR# 15031
HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 FEMALE RATS DURING LACTATION

GROUP: IV-0

DOSE: 15 MG/KG/DAY

LACTATION
DAYS: 0-4

ANIMAL NUMBER

800	26.9	
807	27.0	
808	35.9	
812	30.3	
820	-	SE (DAY 39)
821	30.7	
823	30.4	
825	27.9	
831	9.9	
832	-	SD (DAY 40)

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
MR# 15031
HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 FEMALE RATS DURING LACTATION

GROUP: VI-0

DOSE: 50 MG/KG/DAY

LACTATION
DAYS: 0-4

ANIMAL NUMBER

795	-	FD (DAY 39)
799	46.2	
801	33.8	
815	26.0	
826	-	SE (DAY 40)
828	29.0	
830	25.8	
834	34.1	
835	31.4	
836	30.1	

A-1846: Combined Repeated Dose Toxicity Study
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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H# 26200
MR# 15031
HC# 42

INDIVIDUAL FOOD CONSUMPTION (g/day) BY P1 FEMALE RATS DURING LACTATION

GROUP: VIII-0

DOSE: 200 MG/KG/DAY

LACTATION
DAYS: 0-4

ANIMAL NUMBER

792	-	FD (DAY 16)
805	30.9	
810	-	SE (DAY 17)
811	28.6	
813	-	FD (DAY 37)
816	41.1	
817	-	SE (DAY 38)
818	-	FD (DAY 39)
822	35.6	
824	31.3	

APPENDIX Y

INDIVIDUAL MATING DATA AND GESTATION LENGTH: P₁ RATS

INDIVIDUAL MATING DATA AND GESTATION LENGTH: P₁ RATS

EXPLANATORY NOTES

Note

Test days for animal fates:

- Determined as days of gestation for rats with evidence of copulation
- Determined as days on test from the initiation of test substance administration for rats dying during pre mating or cohabitation, or for those showing no evidence of copulation.

Abbreviations

- FD = Found Dead
G = Gestation
SE = Sacrificed *in extremis*
- = No Plug/Sperm Observed or No Litter Produced
-- = No Data

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H-26200
MR-15031
HC-42

APPENDIX

INDIVIDUAL MATING DATA AND GESTATION LENGTH: F1A GENERATION

GROUPS: II-0, I-0 DOSE: 0 MG/KG/DAY

FEMALE ANIMAL#	MALE #1 ANIMAL#	PLUG/SPERM OBSERVED	MALE #2 ANIMAL#	PLUG/SPERM OBSERVED	LITTER PRODUCED	GESTATION LENGTH (days)
793	748	+				
794	749	+			+	22
796	756	+			+	23
797	760	+			+	22
798	762	+			+	22
806	767	+			+	23
809	777	+			+	22
814	780	+			+	22
819	782	+			+	22
829	786	+			+	22

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H-26200
MR-15031
HC-42

APPENDIX (continued)

INDIVIDUAL MATING DATA AND GESTATION LENGTH: F1A GENERATION

GROUPS: IV-0, III-0 DOSE: 15 MG/KG/DAY

FEMALE ANIMAL#	MALE #1 ANIMAL#	PLUG/SPERM OBSERVED	MALE #2 ANIMAL#	PLUG/SPERM OBSERVED	LITTER PRODUCED	GESTATION LENGTH(days)
800	750	+				
807	752	+			+	22
808	757	+			+	22
812	759	+			+	23
820	769	+			+	22
821	770	+			-	-- SE (DAY 23G) a
823	773	+			+	22
825	776	+			+	22
831	790	+			+	24
832	791	+			+	22

a No litter delivered; however, animal was pregnant.

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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H-26200
MR-15031
HC-42

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

APPENDIX (continued)

INDIVIDUAL MATING DATA AND GESTATION LENGTH: F1A GENERATION

GROUPS: VI-0,V-0 DOSE: 50 MG/KG/DAY

FEMALE ANIMAL#	MALE #1 ANIMAL#	PLUG/SPERM OBSERVED	MALE #2 ANIMAL#	PLUG/SPERM OBSERVED	LITTER PRODUCED	GESTATION LENGTH(days)	
795	747	+			-	--	FD (DAY 23G)a
799	751	+			+	23	
801	755	-	747	-	+	--	
815	764	+			+	22	
826	766	+			-	--	SE (DAY 24G)a
828	772	+			+	22	
830	774	+			+	22	
834	778	+			+	22	
835	783	-	751	-	+	--	
836	784	+			+	22	

a No litter delivered; however, animal was pregnant.

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H-26200
MR-15031
HC-42

APPENDIX (continued)

INDIVIDUAL MATING DATA AND GESTATION LENGTH: F1A GENERATION

GROUPS: VIII-0, VII-0 DOSE: 200 MG/KG/DAY

FEMALE ANIMAL#	MALE #1 ANIMAL#	PLUG/SPERM OBSERVED	MALE #2 ANIMAL#	PLUG/SPERM OBSERVED	LITTER PRODUCED	GESTATION LENGTH(days)
792	--	--	--	--	--	--
805	753	+			+	22 FD (DAY 16)
810	754	-			-	22
811	765	+			+	FD (DAY 17)
813	775	-	753	-	-	23
816	779	+			+	FD (DAY 37) a
817	781	+			-	22
818	785	+			-	SE (DAY 22G) a
822	787	-	754	+	+	FD (DAY 22G) a
824	788	+			+	23
						22

a No litter delivered, however, animal was pregnant.

APPENDIX Z
INDIVIDUAL IMPLANTATION SITE, IMPLANTATION EFFICIENCY,
AND *CORPOR LUTEA* DATA: P₁ RATS

INDIVIDUAL IMPLANTATION SITE, IMPLANTATION EFFICIENCY,
AND *CORPOR LUTEA* DATA: P₁ RATS

EXPLANATORY NOTES

Note

When the number of pups born was greater than the number of implantation sites found in the uterus at necropsy, implantation efficiency could not be calculated and the number of implantation sites was excluded from the statistical analysis.

Abbreviations

FD = Found Dead
G = Gestation
SE = Sacrificed *in extremis*
- = No Data

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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INDIVIDUAL IMPLANTATION SITE, IMPLANTATION EFFICIENCY,
AND CORPORA LUTEA DATA: P₁ RATS

GROUP: II-0 DOSE: 0 MG/KG/DAY

Animal Number	Pups Born	Number of Implantation Sites	Implantation Efficiency (%)	Number of Corpora Lutea
793	11	14	78.6	15
794	11	12	91.7	12
796	15	15	100.0	15
797	12	14	85.7	14
798	11	15	73.3	15
806	14	14	100.0	14
809	13	13	100.0	15
814	12	14	85.7	14
819	13	14	92.9	14
829	13	14	92.9	16

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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INDIVIDUAL IMPLANTATION SITE, IMPLANTATION EFFICIENCY,
AND CORPORA LUTEA DATA: P₁ RATS

GROUP: IV-0 DOSE: 15 MG/KG/DAY

Animal Number	Pups Born	Number of Implantation Sites	Implantation Efficiency (%)	Number of Corpora Lutea	Animal Status
800	11	13	84.6	13	
807	12	13	92.3	13	
808	10	12	83.3	16	
812	15	15	100.0	15	
820	-	13	-	13	SE (DAY 23G)
821	13	14	92.9	14	
823	13	15	86.7	17	
825	8	15	53.3	16	
831	11	15	73.3	15	
832	6	14	42.9	14	

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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INDIVIDUAL IMPLANTATION SITE, IMPLANTATION EFFICIENCY,
 AND CORPORA LUTEA DATA: P₁ RATS

GROUP: VI-0 DOSE: 50 MG/KG/DAY

Animal Number	Pups Born	Number of Implantation Sites	Implantation Efficiency (%)	Number of Corpora Lutea	Animal Status
795	-	15	-	15	FD (DAY 23G)
799	13	13	100.0	13	
801	14	14	100.0	14	
815	15	15	100.0	15	
826	-	16	-	17	SE (DAY 24G)
828	12	14	85.7	16	
830	10	12	83.3	13	
834	16	16	100.0	16	
835	15	15	100.0	15	
836	12	14	85.7	15	

**A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats**

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INDIVIDUAL IMPLANTATION SITE, IMPLANTATION EFFICIENCY,
 AND CORPORA LUTEA DATA: P₁ RATS

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

Animal Number	Pups Born	Number of Implantation Sites	Implantation Efficiency (%)	Number of Corpora Lutea	Animal Status
792	-	-	-	-	FD (DAY 16)
805	12	12	100.0	12	
810	-	-	-	-	FD (DAY 17)
811	8	10	80.0	9a	
813	-	10	-	12	FD (DAY 37)
816	15	15	100.0	15	
817	-	12	-	13	SE (DAY 22G)
818	-	14	-	14	FD (DAY 22G)
822	15	15	100.0	15	
824	16	16	100.0	16	

a Number of implantation sites was greater than the number of corpora lutea; data excluded from statistical analyses.

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Study Title

A-1846: Combined Repeated Dose Toxicity Study With the
Reproduction/Developmental Toxicity Screening Test in Rats

Volume 2 of 2

Laboratory Project ID: DuPont-14109

TEST GUIDELINES: Organisation for Economic Cooperation and Development
(OECD/OCDE). Guidelines for Testing of Chemicals,
Section 4 (Part 422): Health Effects (MAR-1996)

United States Environmental Protection Agency (EPA),
Office of Prevention, Pesticides, and Toxic Substances
(OPPTS) OPPTS 870.3650 Combined Repeated Dose
Toxicity Study With the Reproduction/Developmental
Toxicity Screening Test (JULY-2000)

AUTHOR: Eve Mylchreest, Ph.D.

STUDY COMPLETED ON: October 19, 2004

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

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WORK REQUEST NUMBER: 15031

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APPENDIX AA
INDIVIDUAL PUP SURVIVAL: F₁ GENERATION

INDIVIDUAL PUP SURVIVAL: F₁ GENERATION

EXPLANATORY NOTES

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Note

Unless stated otherwise, a dash ("-") indicates that there was no litter delivered.

Abbreviations

FD = Found Dead
G = Gestation
SE = Sacrificed *in extremis*
- = No Data

Summary Section

S.D. = Standard Deviation
S.E. = Standard Error
N = Number in Group

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

H-26200
MR-15031
HC-42

APPENDIX

INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

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NUMBER OF PUPS

ANIMAL #	BORN	BORN ALIVE	DAY 4
793	11	9	5
794	11	11	11
796	15	14	14
797	12	11	11
798	11	11	7
806	14	13	13
809	13	13	13
814	12	11	11
819	13	13	13
829	13	13	12
Mean	12.5	11.9	11.0
S.D.	1.35	1.52	2.87
S.E.	0.43	0.48	0.91
N	10	10	10

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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APPENDIX (continued)

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL #	BORN	BORN ALIVE	DAY 4
793	6	5	2
794	3	3	3
796	8	8	8
797	4	3	3
798	7	7	4
806	8	7	7
809	5	5	5
814	7	6	6
819	7	7	7
829	6	6	6
Mean	6.1	5.7	5.1
S.D.	1.66	1.70	2.02
S.E.	0.53	0.54	0.64
N	10	10	10

NUMBER OF FEMALE PUPS

ANIMAL #	BORN	BORN ALIVE	DAY 4
793	5	4	3
794	8	8	8
796	7	6	6
797	8	8	8
798	4	4	3
806	6	6	6
809	8	8	8
814	5	5	5
819	6	6	6
829	7	7	6
Mean	6.4	6.2	5.9
S.D.	1.43	1.55	1.85
S.E.	0.45	0.49	0.59
N	10	10	10

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

NUMBER OF PUPS

ANIMAL #	SEX RATIO (MALES)	% BORN ALIVE	0-4 DAY VIABILITY
793	0.55	81.8	55.6
794	0.27	100.0	100.0
796	0.53	93.3	100.0
797	0.33	91.7	100.0
798	0.64	100.0	63.6
806	0.57	92.9	100.0
809	0.38	100.0	100.0
814	0.58	91.7	100.0
819	0.54	100.0	100.0
829	0.46	100.0	92.3
Mean	0.49	95.1	91.1
S.D.	0.119	6.04	16.91
S.E.	0.038	1.91	5.35
N	10	10	10

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL #	% BORN ALIVE	0-4 DAY VIABILITY
793	83.3	40.0
794	100.0	100.0
796	100.0	100.0
797	75.0	100.0
798	100.0	57.1
806	87.5	100.0
809	100.0	100.0
814	85.7	100.0
819	100.0	100.0
829	100.0	100.0
Mean	93.2	89.7
S.D.	9.40	22.06
S.E.	2.97	6.98
N	10	10

NUMBER OF FEMALE PUPS

ANIMAL #	% BORN ALIVE	0-4 DAY VIABILITY
793	80.0	75.0
794	100.0	100.0
796	85.7	100.0
797	100.0	100.0
798	100.0	75.0
806	100.0	100.0
809	100.0	100.0
814	100.0	100.0
819	100.0	100.0
829	100.0	85.7
Mean	96.6	93.6
S.D.	7.35	10.75
S.E.	2.33	3.40
N	10	10

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: IV-0 DOSE: 15 MG/KG/DAY

NUMBER OF PUPS			
ANIMAL #	BORN	BORN ALIVE	DAY 4
800	11	11	11
807	12	11	8
808	10	10	10
812	15	15	15
820	-	-	-
821	13	13	13
823	13	13	13
825	8	7	7
831	11	11	1
832	6	0	-
Mean	11.0	10.1	9.8
S.D.	2.74	4.40	4.43
S.E.	0.91	1.47	1.57
N	9	9	8

SE (DAY 23G)

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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APPENDIX (continued)

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: IV-0 DOSE: 15 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL #	BORN	BORN ALIVE	DAY 4	
800	3	3	3	
807	6	5	4	
808	6	6	6	
812	8	8	8	
820	-	-	-	SE (DAY 23G)
821	8	8	8	
823	9	9	9	
825	4	3	3	
831	5	5	-	
832	2	0	-	
Mean	5.7	5.2	5.9	
S.D.	2.40	2.91	2.54	
S.E.	0.80	0.97	0.96	
N	9	9	7	

NUMBER OF FEMALE PUPS

ANIMAL #	BORN	BORN ALIVE	DAY 4	
800	8	8	8	
807	6	6	4	
808	4	4	4	
812	7	7	7	
820	-	-	-	SE (DAY 23G)
821	5	5	5	
823	4	4	4	
825	4	4	4	
831	6	6	1	
832	1	0	-	
Mean	5.0	4.9	4.6	
S.D.	2.06	2.32	2.13	
S.E.	0.69	0.77	0.75	
N	9	9	8	

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: IV-0 DOSE: 15 MG/KG/DAY

NUMBER OF PUPS

ANIMAL #	SEX RATIO (MALES)	% BORN ALIVE	0-4 DAY VIABILITY
800	0.27	100.0	100.0
807	0.50	91.7	72.7
808	0.60	100.0	100.0
812	0.53	100.0	100.0
820	-	-	-
821	0.62	100.0	100.0
823	0.69	100.0	100.0
825	0.50	87.5	100.0
831	0.45	100.0	9.1
832	0.67	0.0	-
Mean	0.54	86.6	85.2
S.D.	0.128	32.79	32.21
S.E.	0.043	10.93	11.39
N	9	9	8

SE (DAY 23G)

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: IV-0 DOSE: 15 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL #	% BORN ALIVE	0-4 DAY VIABILITY	
800	100.0	100.0	
807	83.3	80.0	
808	100.0	100.0	
812	100.0	100.0	
820	-	-	
821	100.0	100.0	SE (DAY 23G)
823	100.0	100.0	
825	75.0	100.0	
831	100.0	-	
832	0.0	-	
Mean	84.3	97.1	
S.D.	32.93	7.56	
S.E.	10.98	2.86	
N	9	7	

NUMBER OF FEMALE PUPS

ANIMAL #	% BORN ALIVE	0-4 DAY VIABILITY	
800	100.0	100.0	
807	100.0	66.7	
808	100.0	100.0	
812	100.0	100.0	
820	-	-	
821	100.0	100.0	SE (DAY 23G)
823	100.0	100.0	
825	100.0	100.0	
831	100.0	16.7	
832	0.0	-	
Mean	88.9	85.4	
S.D.	33.33	30.13	
S.E.	11.11	10.65	
N	9	8	

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: VI-0 DOSE: 50 MG/KG/DAY

NUMBER OF PUPS

ANIMAL #	BORN	BORN ALIVE	DAY 4	
795	-	-	-	FD (DAY 23G)
799	13	13	13	
801	14	14	13	
815	15	15	15	
826	-	-	-	SE (DAY 24G)
828	12	12	12	
830	10	10	10	
834	16	16	16	
835	15	15	14	
836	12	12	12	
Mean	13.4	13.4	13.1	
S.D.	2.00	2.00	1.89	
S.E.	0.71	0.71	0.67	
N	8	8	8	

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: VI-0 DOSE: 50 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL #	BORN	BORN ALIVE	DAY 4	
795	-	-	-	FD (DAY 23G)
799	4	4	4	
801	5	5	4	
815	11	11	11	
826	-	-	-	SE (DAY 24G)
828	5	5	5	
830	3	3	3	
834	8	8	8	
835	7	7	7	
836	6	6	6	
Mean	6.1	6.1	6.0	
S.D.	2.53	2.53	2.62	
S.E.	0.90	0.90	0.93	
N	8	8	8	

NUMBER OF FEMALE PUPS

ANIMAL #	BORN	BORN ALIVE	DAY 4	
795	-	-	-	FD (DAY 23G)
799	9	9	9	
801	9	9	9	
815	4	4	4	
826	-	-	-	SE (DAY 24G)
828	7	7	7	
830	7	7	7	
834	8	8	8	
835	8	8	7	
836	6	6	6	
Mean	7.3	7.3	7.1	
S.D.	1.67	1.67	1.64	
S.E.	0.59	0.59	0.58	
N	8	8	8	

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: VI-0 DOSE: 50 MG/KG/DAY

NUMBER OF PUPS

ANIMAL #	SEX RATIO (MALES)	% BORN ALIVE	0-4 DAY VIABILITY	
795	-	-	-	FD (DAY 23G)
799	0.31	100.0	100.0	
801	0.36	100.0	92.9	
815	0.73	100.0	100.0	
826	-	-	-	SE (DAY 24G)
828	0.42	100.0	100.0	
830	0.30	100.0	100.0	
834	0.50	100.0	100.0	
835	0.47	100.0	93.3	
836	0.50	100.0	100.0	
Mean	0.45	100.0	98.3	
S.D.	0.140	0.00	3.20	
S.E.	0.050	0.00	1.13	
N	8	8	8	

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: VI-0 DOSE: 50 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL #	% BORN ALIVE	0-4 DAY VIABILITY	
795	-	-	FD (DAY 23G)
799	100.0	100.0	
801	100.0	80.0	
815	100.0	100.0	
826	-	-	SE (DAY 24G)
828	100.0	100.0	
830	100.0	100.0	
834	100.0	100.0	
835	100.0	100.0	
836	100.0	100.0	
Mean	100.0	97.5	
S.D.	0.00	7.07	
S.E.	0.00	2.50	
N	8	8	

NUMBER OF FEMALE PUPS

ANIMAL #	% BORN ALIVE	0-4 DAY VIABILITY	
795	-	-	FD (DAY 23G)
799	100.0	100.0	
801	100.0	100.0	
815	100.0	100.0	
826	-	-	SE (DAY 24G)
828	100.0	100.0	
830	100.0	100.0	
834	100.0	100.0	
835	100.0	87.5	
836	100.0	100.0	
Mean	100.0	98.4	
S.D.	0.00	4.42	
S.E.	0.00	1.56	
N	8	8	

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

NUMBER OF PUPS				
ANIMAL #	BORN	BORN ALIVE	DAY 4	
792	-	-	-	FD (DAY 16)
805	12	12	12	
810	-	-	-	FD (DAY 17)
811	8	8	7	
813	-	-	-	FD (DAY 37)
816	15	15	15	
817	-	-	-	SE (DAY 22G)
818	-	-	-	FD (DAY 22G)
822	15	15	11	
824	16	15	14	
Mean	13.2	13.0	11.8	
S.D.	3.27	3.08	3.11	
S.E.	1.46	1.38	1.39	
N	5	5	5	

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL #	BORN	BORN ALIVE	DAY 4	
792	-	-	-	FD (DAY 16)
805	8	8	8	
810	-	-	-	FD (DAY 17)
811	5	5	5	
813	-	-	-	FD (DAY 37)
816	6	6	6	
817	-	-	-	SE (DAY 22G)
818	-	-	-	FD (DAY 22G)
822	7	7	4	
824	8	8	7	
Mean	6.8	6.8	6.0	
S.D.	1.30	1.30	1.58	
S.E.	0.58	0.58	0.71	
N	5	5	5	

NUMBER OF FEMALE PUPS

ANIMAL #	BORN	BORN ALIVE	DAY 4	
792	-	-	-	FD (DAY 16)
805	4	4	4	
810	-	-	-	FD (DAY 17)
811	3	3	2	
813	-	-	-	FD (DAY 37)
816	9	9	9	
817	-	-	-	SE (DAY 22G)
818	-	-	-	FD (DAY 22G)
822	8	8	7	
824	8	7	7	
Mean	6.4	6.2	5.8	
S.D.	2.70	2.59	2.77	
S.E.	1.21	1.16	1.24	
N	5	5	5	

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

NUMBER OF PUPS

ANIMAL #	SEX RATIO (MALES)	% BORN ALIVE	0-4 DAY VIABILITY	
792	-	-	-	FD (DAY 16)
805	0.67	100.0	100.0	
810	-	-	-	FD (DAY 17)
811	0.63	100.0	87.5	
813	-	-	-	FD (DAY 37)
816	0.40	100.0	100.0	
817	-	-	-	SE (DAY 22G)
818	-	-	-	FD (DAY 22G)
822	0.47	100.0	73.3	
824	0.50	93.8	93.3	
Mean	0.53	98.8	90.8	
S.D.	0.111	2.80	11.09	
S.E.	0.050	1.25	4.96	
N	5	5	5	

REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL PUP SURVIVAL: F1A GENERATION

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

NUMBER OF MALE PUPS

ANIMAL #	% BORN ALIVE	0-4 DAY VIABILITY	
792	-	-	FD (DAY 16)
805	100.0	100.0	
810	-	-	FD (DAY 17)
811	100.0	100.0	
813	-	-	FD (DAY 37)
816	100.0	100.0	
817	-	-	SE (DAY 22G)
818	-	-	FD (DAY 22G)
822	100.0	57.1	
824	100.0	87.5	
Mean	100.0	88.9	
S.D.	0.00	18.57	
S.E.	0.00	8.31	
N	5	5	

NUMBER OF FEMALE PUPS

ANIMAL #	% BORN ALIVE	0-4 DAY VIABILITY	
792	-	-	FD (DAY 16)
805	100.0	100.0	
810	-	-	FD (DAY 17)
811	100.0	66.7	
813	-	-	FD (DAY 37)
816	100.0	100.0	
817	-	-	SE (DAY 22G)
818	-	-	FD (DAY 22G)
822	100.0	87.5	
824	87.5	100.0	
Mean	97.5	90.8	
S.D.	5.59	14.55	
S.E.	2.50	6.51	
N	5	5	

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APPENDIX BB

INDIVIDUAL LITTER CLINICAL OBSERVATIONS: F₁ GENERATION

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL LITTER CLINICAL OBSERVATIONS: F1A GENERATION

GROUP: II-0 DOSE: 0 MG/KG/DAY

ANIMAL NUMBER	LACTATION DAY	SIGN INCIDENCE	OBSERVATIONS
------------------	------------------	-------------------	--------------

793	NO	ABNORMALITIES	DETECTED
794	NO	ABNORMALITIES	DETECTED
796	NO	ABNORMALITIES	DETECTED
797	NO	ABNORMALITIES	DETECTED
798	NO	ABNORMALITIES	DETECTED
806	NO	ABNORMALITIES	DETECTED
809	NO	ABNORMALITIES	DETECTED
814	NO	ABNORMALITIES	DETECTED
819	NO	ABNORMALITIES	DETECTED
829	NO	ABNORMALITIES	DETECTED

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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APPENDIX (continued)

INDIVIDUAL LITTER CLINICAL OBSERVATIONS: F1A GENERATION

GROUP: IV-0 DOSE: 15 MG/KG/DAY

ANIMAL NUMBER	LACTATION DAY	SIGN INCIDENCE	OBSERVATIONS
------------------	------------------	-------------------	--------------

800	NO	ABNORMALITIES	DETECTED
807	NO	ABNORMALITIES	DETECTED
808	NO	ABNORMALITIES	DETECTED
812	NO	ABNORMALITIES	DETECTED
821	NO	ABNORMALITIES	DETECTED
823	NO	ABNORMALITIES	DETECTED
825	NO	ABNORMALITIES	DETECTED
831	NO	ABNORMALITIES	DETECTED
832	NO	PUPS BORN	ALIVE

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL LITTER CLINICAL OBSERVATIONS: F1A GENERATION

GROUP: VI-0 DOSE: 50 MG/KG/DAY

ANIMAL NUMBER	LACTATION DAY	SIGN INCIDENCE	OBSERVATIONS
------------------	------------------	-------------------	--------------

799			NO ABNORMALITIES DETECTED
801			NO ABNORMALITIES DETECTED
815			NO ABNORMALITIES DETECTED
828			NO ABNORMALITIES DETECTED
830			NO ABNORMALITIES DETECTED
834			NO ABNORMALITIES DETECTED
835			NO ABNORMALITIES DETECTED
836			NO ABNORMALITIES DETECTED

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REPRODUCTIVE AND FERTILITY EFFECTS WITH A1846

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INDIVIDUAL LITTER CLINICAL OBSERVATIONS: F1A GENERATION

GROUP: VIII-0 DOSE: 200 MG/KG/DAY

ANIMAL NUMBER	LACTATION DAY	SIGN INCIDENCE	OBSERVATIONS
------------------	------------------	-------------------	--------------

805 NO ABNORMALITIES DETECTED

811 NO ABNORMALITIES DETECTED

816 NO ABNORMALITIES DETECTED

822 NO ABNORMALITIES DETECTED

824 NO ABNORMALITIES DETECTED

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INDIVIDUAL PUP WEIGHTS: F₁ GENERATION

INDIVIDUAL PUP WEIGHTS: F₁ GENERATION

EXPLANATORY NOTES

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Abbreviations

FD = Found dead
G = Gestation
SE = Sacrificed *in extremis*

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Individual Pup Weights (grams): F₁ Generation
 Lactation Day 0
 Group: II-0 Dose: 0 mg/kg/day

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Animal Number	Pup Sex	Pup Number												
		1	2	3	4	5	6	7	8					
793	♂	5.5	5.8	5.5	5.9	5.8								
	♀	5.7	4.9	5.3	4.9									
794	♂	8.3	8.1	7.2										
	♀	6.6	7.2	7.4	7.8	7.2	7.3	7.3	7.3					
796	♂	6.8	6.7	6.3	7.4	7.4	7.3	6.6	7.2					
	♀	6.9	6.4	6.7	6.6	6.7	6.0							
797	♂	6.9	6.7	7.2										
	♀	6.9	6.0	6.3	6.3	6.6	6.5	7.0	6.3					
798	♂	6.2	6.4	6.0	6.0	5.8	5.9	6.3						
	♀	5.8	5.4	5.3	5.4									
806	♂	6.6	6.6	6.5	7.4	7.2	7.1	6.4						
	♀	6.4	6.6	7.1	6.5	6.5	6.3							
809	♂	6.3	7.1	6.6	7.1	7.0								
	♀	6.9	6.3	6.4	6.8	7.0	6.1	6.3	5.4					
814	♂	7.3	7.5	7.3	6.6	7.0	6.9							
	♀	6.9	6.7	6.9	7.0	6.8								
819	♂	6.7	6.9	6.4	6.6	6.4	7.6	6.7						
	♀	6.6	6.6	6.3	6.0	7.1	6.5							
829	♂	5.9	5.9	7.1	6.7	7.0	6.3							
	♀	5.9	6.6	4.8	6.5	3.9	6.5	5.3						

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Individual Pup Weights (grams): F₁ Generation

Lactation Day 0

Group: IV-0

Dose: 15 mg/kg/day

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Animal Number	Pup Sex	Pup Number													
		1	2	3	4	5	6	7	8	9					
800	♂	7.4	7.2	7.2											
	♀	6.7	7.3	7.0	6.9	7.0	7.3	6.5	6.4						
807	♂	5.4	5.5	5.7	5.6	5.3									
	♀	5.0	4.8	4.3	5.2	4.8	4.9								
808	♂	8.4	8.4	8.3	7.9	8.1	8.7								
	♀	6.8	7.5	7.5	7.8										
812	♂	6.9	6.9	6.5	7.4	6.8	6.6	7.1	6.8						
	♀	6.8	6.8	6.8	6.7	6.7	6.6	6.9							
820	♂	SE (DAY 23G)													
	♀	SE (DAY 23G)													
821	♂	7.5	7.0	7.3	7.1	6.7	6.6	6.9	7.1						
	♀	6.3	7.1	6.5	6.6	6.1									
823	♂	7.1	7.3	7.3	7.0	7.1	7.4	7.3	7.6	6.8					
	♀	6.7	6.5	6.4	6.9										
825 ^a	♂	6.2	5.2	5.6	5.7	5.6	5.4								
	♀	5.3													
831	♂	5.4	5.4	5.2	5.6	5.5									
	♀	5.0	4.9	5.5	5.1	5.0	5.2								
832	♂	NO LIVE PUPS													
	♀	NO LIVE PUPS													

^a Two pups were missexed at birth; litter was excluded from group means, male and female pup weights.

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Individual Pup Weights (grams): F₁ Generation

Lactation Day 0

Group: VI-0

Dose: 50 mg/kg/day

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Animal Number	Pup Sex	Pup Number											
		1	2	3	4	5	6	7	8	9	10	11	
795	♂	FD (DAY 23G)											
	♀	FD (DAY 23G)											
799	♂	6.1	7.5	7.5	6.8								
	♀	6.6	6.9	7.2	7.1	7.3	7.0	7.0	7.4	6.5			
801	♂	6.6	6.2	7.0	6.0	6.8							
	♀	6.8	6.2	6.6	5.9	6.5	6.6	6.4	6.7	6.5			
815	♂	7.0	6.9	6.6	6.6	6.3	6.8	5.7	6.6	6.8	6.2	5.7	
	♀	6.3	6.2	6.3	6.6								
826	♂	SE (DAY 24G)											
	♀	SE (DAY 24G)											
828	♂	6.8	6.8	6.7	6.5	6.4							
	♀	6.7	6.9	6.1	6.3	6.0	6.0	6.1					
830	♂	6.7	6.0	6.4									
	♀	6.3	6.3	5.4	6.4	6.0	5.9	5.6					
834	♂	6.0	5.7	6.1	5.9	6.2	5.9	6.2	6.0				
	♀	6.1	5.3	5.0	6.1	6.2	5.7	6.5	5.5				
835	♂	6.4	6.3	6.2	6.2	6.4	6.6	6.2					
	♀	5.5	5.8	5.7	5.5	6.3	5.5	5.8	5.8				
836	♂	6.5	6.1	6.2	5.9	6.0	6.3						
	♀	6.5	5.5	6.1	6.0	6.7	6.0						

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Individual Pup Weights (grams): F1 Generation
 Lactation Day 0
 Group: VIII-0 Dose: 200 mg/kg/day

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Animal Number	Pup Sex	Pup Number											
		1	2	3	4	5	6	7	8	9			
792	♂	FD (DAY 16)											
	♀	FD (DAY 16)											
805	♂	6.6	6.8	6.2	6.8	6.9	7.0	6.5	5.4				
	♀	6.3	6.3	6.0	6.3								
810	♂	FD (DAY 17)											
	♀	FD (DAY 17)											
811	♂	6.9	6.6	7.6	7.4	7.6							
	♀	6.5	6.2	6.4									
813	♂	FD (DAY 37)											
	♀	FD (DAY 37)											
816	♂	6.6	6.0	5.9	6.7	5.9	5.6						
	♀	5.7	6.1	5.9	6.0	5.5	5.3	6.4	5.5	5.6			
817	♂	SE (DAY 22G)											
	♀	SE (DAY 22G)											
818	♂	FD (DAY 22G)											
	♀	FD (DAY 22G)											
822	♂	4.4	4.8	5.9	5.1	5.1	5.1	5.7					
	♀	5.3	5.3	4.4	5.1	4.0	5.1	4.2	5.2				
824	♂	6.2	6.4	6.1	6.7	6.3	6.6	6.2	6.6				
	♀	5.8	5.9	5.8	6.2	6.1	5.6	5.8					

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Individual Pup Weights (grams): F₁ Generation

Lactation Day 4

Group: II-0

Dose: 0 mg/kg/day

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Animal Number	Pup Sex	Pup Number							
		1	2	3	4	5	6	7	8
793	♂	11.1	10.8						
	♀	11.1	12.5	11.8					
794	♂	10.9	13.8	11.5					
	♀	12.2	10.7	12.2	11.7	11.3	11.4	11.8	12.3
796	♂	10.4	9.3	10.7	10.5	10.8	9.8	10.0	11.0
	♀	9.1	9.4	10.0	10.2	9.2	10.1		
797	♂	9.7	11.2	10.3					
	♀	9.9	10.5	10.3	10.2	10.5	10.0	9.8	10.6
798	♂	10.2	8.5	9.4	8.9				
	♀	9.1	9.7	9.0					
806	♂	12.2	11.4	11.8	12.8	11.5	12.1	11.6	
	♀	11.8	11.9	10.9	11.1	10.1	12.1		
809	♂	12.0	11.3	11.3	12.0	11.5			
	♀	10.4	7.2	10.9	11.0	10.8	11.1	11.6	10.7
814	♂	12.1	12.0	11.3	10.9	11.3	12.0		
	♀	10.7	11.7	10.6	11.5	11.4			
819	♂	10.5	10.2	11.0	10.3	10.1	9.8	10.4	
	♀	9.7	9.6	10.2	9.4	11.0	9.4		
829	♂	9.3	10.2	11.3	10.8	10.8	8.7		
	♀	7.5	5.8	10.1	9.7	10.0	9.2		

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Individual Pup Weights (grams): F₁ Generation
 Lactation Day 4
 Group: IV-0 Dose: 15 mg/kg/day

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Animal Number	Pup Sex	Pup Number											
		1	2	3	4	5	6	7	8	9			
800	♂	10.5	10.6	10.6									
	♀	10.1	10.6	10.3	10.2	10.0	10.6	10.6	10.0				
807	♂	10.7	10.4	10.7	10.9								
	♀	9.2	10.4	9.4	9.0								
808	♂	14.1	13.6	13.6	13.7	13.4	12.1						
	♀	12.8	10.8	12.8	13.2								
812	♂	10.5	10.5	10.2	10.2	10.7	9.7	10.9	10.2				
	♀	9.6	10.1	10.3	9.4	10.4	10.2	9.7					
820	♂	SE (DAY 23G)											
	♀	SE (DAY 23G)											
821	♂	11.6	11.0	11.3	9.5	10.9	11.5	10.8	11.2				
	♀	10.4	11.4	9.5	10.2	10.5							
823	♂	11.9	12.7	12.1	11.5	11.8	12.0	12.9	11.9	12.1			
	♀	11.7	10.6	10.8	11.7								
825	♂	10.4	8.0	7.5									
	♀	8.4	11.5	10.6	12.6								
831	♂	NO LIVE MALE PUPS											
	♀	4.0											
832	♂	NO LIVE PUPS											
	♀	NO LIVE PUPS											

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Individual Pup Weights (grams): F₁ Generation

Lactation Day 4

Group: VI-0

Dose: 50 mg/kg/day

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Animal Number	Pup Sex	Pup Number										
		1	2	3	4	5	6	7	8	9	10	11
795	♂	FD (DAY 23G)										
	♀	FD (DAY 23G)										
799	♂	12.8	12.8	12.2	10.7							
	♀	12.5	12.2	11.9	11.8	11.5	12.8	11.2	10.8	12.2		
801	♂	9.0	9.6	10.1	9.2							
	♀	9.4	9.3	9.3	9.9	10.7	9.9	9.1	10.1	10.1		
815	♂	11.1	10.0	9.3	9.2	10.8	8.9	10.1	10.9	9.8	10.6	10.6
	♀	10.3	9.8	10.0	10.0							
826	♂	SE (DAY 24G)										
	♀	SE (DAY 24G)										
828	♂	9.9	10.5	10.8	10.2	9.9						
	♀	9.6	10.3	9.9	9.5	10.5	8.9	9.9				
830	♂	9.6	10.1	9.5								
	♀	9.2	9.7	9.1	8.9	10.5	9.2	10.6				
834	♂	9.6	9.0	9.1	8.4	8.6	8.3	8.5	8.1			
	♀	7.7	7.2	7.3	8.2	9.0	9.8	8.8	8.7			
835	♂	10.0	9.8	9.7	10.3	10.5	10.2	9.7				
	♀	9.0	9.6	9.8	9.3	8.7	8.7	9.7				
836	♂	9.5	8.9	9.4	9.7	9.3	9.6					
	♀	9.4	9.8	9.4	9.0	9.4	9.7					

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Individual Pup Weights (grams): F₁ Generation
 Lactation Day 4
 Group: VIII-0 Dose: 200 mg/kg/day

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Animal Number	Pup Sex	Pup Number											
		1	2	3	4	5	6	7	8	9			
792	♂	FD (DAY 16)											
	♀	FD (DAY 16)											
805	♂	10.6	11.1	10.2	10.3	8.2	10.4	9.4	10.8				
	♀	10.1	9.7	8.9	8.9								
810	♂	FD (DAY 17)											
	♀	FD (DAY 17)											
811	♂	13.3	12.8	10.8	11.6	12.0							
	♀	10.5	11.2										
813	♂	FD (DAY 37)											
	♀	FD (DAY 37)											
816	♂	9.1	9.3	10.7	10.0	10.2	8.6						
	♀	9.7	8.7	10.1	8.9	8.7	8.4	8.6	9.7	9.0			
817	♂	SE (DAY 22G)											
	♀	SE (DAY 22G)											
818	♂	FD (DAY 22G)											
	♀	FD (DAY 22G)											
822	♂	8.0	8.0	7.7	9.8								
	♀	9.0	8.0	8.3	8.9	6.7	9.2	7.3					
824	♂	9.6	9.8	9.2	9.5	9.2	9.1	8.7					
	♀	8.4	8.4	8.8	9.3	9.8	9.5	9.2					

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APPENDIX DD

**INDIVIDUAL FORELIMB AND HINDLIMB GRIP STRENGTH,
HINDLIMB SPLAY, AND REARING COUNT IN P₁ RATS**

INDIVIDUAL FORELIMB AND HINDLIMB GRIP STRENGTH, HINDLIMB SPLAY,
AND REARING COUNT IN P₁ RATS

EXPLANATORY NOTES

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Note

Rearing Count = the number of times both forelimbs are lifted off the cageboard.

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Individual Forelimb and Hindlimb Grip Strength, Hindlimb Splay, and Rearing Count in P₁ Rats

MALE	ANIMAL NUMBER	FORELIMB GRIP STRENGTH (kg)			HINDLIMB GRIP STRENGTH (kg)			HINDLIMB FOOT SPLAY (CM)	REARING COUNT
		Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3		
GROUP I-0 0 mg/kg/day	767	0.73	0.69	0.92	0.63	0.53	0.58	4.7	9
	777	0.90	1.00	1.14	0.51	0.61	0.65	9.0	5
	780	0.90	1.19	1.10	0.65	0.64	0.67	10.7	1
	782	0.59	0.68	0.54	0.59	0.45	0.58	8.0	4
	786	1.34	1.23	0.94	0.68	0.63	0.52	9.2	2
GROUP III-0 15 mg/kg/day	770	1.34	1.20	1.28	0.73	0.80	0.75	9.4	7
	773	0.55	0.80	1.11	0.48	0.54	0.45	8.7	2
	776	1.00	1.15	0.97	0.69	0.62	0.71	7.1	4
	790	1.22	1.17	1.18	0.69	0.62	0.61	7.1	4
	791	0.75	0.82	0.75	0.52	0.58	0.52	7.4	4
GROUP V-0 50 mg/kg/day	772	0.83	1.53	1.02	0.52	0.69	0.69	11.4	0
	774	0.87	1.10	1.25	0.61	0.74	0.81	11.2	4
	778	1.08	0.89	0.93	0.50	0.45	0.47	6.4	2
	783	0.77	1.08	1.09	0.54	0.58	0.56	9.4	2
	784	0.68	1.02	0.69	0.51	0.65	0.42	9.9	4
GROUP VII-0 200 mg/kg/day	779	0.81	0.71	1.31	0.27	0.31	0.25	11.2	6
	781	0.90	0.76	1.11	0.49	0.37	0.28	5.2	9
	785	1.11	0.95	0.95	0.52	0.56	0.54	9.6	2
	787	0.75	0.53	0.51	0.28	0.46	0.32	4.7	5
	788	0.74	0.83	0.98	0.55	0.52	0.57	8.3	6

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Individual Forelimb and Hindlimb Grip Strength, Hindlimb Splay, and Rearing Count in P₁ Rats

FEMALE	ANIMAL NUMBER	FORELIMB GRIP STRENGTH (kg)			HINDLIMB GRIP STRENGTH (kg)			HINDLIMB FOOT SPLAY (CM)	REARING COUNT
		Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3		
GROUP II-0 0 mg/kg/day	806	0.58	1.00	0.46	0.68	0.42	0.62	8.1	9
	809	0.74	0.70	0.81	0.75	0.39	0.55	4.4	11
	814	0.75	0.96	0.84	0.85	0.47	0.42	5.4	7
	819	0.66	0.54	0.90	0.70	0.42	0.37	5.7	8
	829	0.77	0.59	0.65	0.67	0.56	0.59	8.5	1
GROUP IV-0 15 mg/kg/day	821	0.53	1.00	0.72	0.75	0.66	0.53	7.9	8
	823	0.66	0.80	0.96	0.81	0.31	0.45	9.2	8
	825	0.80	0.64	0.49	0.64	0.50	0.49	9.4	2
	831	0.80	0.81	0.64	0.75	0.51	0.32	9.1	4
	832	0.92	0.61	0.97	0.83	0.37	0.46	6.5	4
GROUP VI-0 50 mg/kg/day	828	0.85	0.68	0.79	0.77	0.31	0.35	4.5	6
	830	0.56	0.45	0.61	0.54	0.38	0.48	8.2	5
	834	0.87	0.91	0.67	0.82	0.37	0.53	10.1	4
	835	1.05	0.85	0.95	0.95	0.55	0.65	7.7	7
	836	0.65	0.94	0.86	0.82	0.39	0.39	4.9	3
GROUP VIII-0 200 mg/kg/day	816	0.84	0.66	0.86	0.79	0.42	0.54	9.3	5
	817	0.76	0.81	0.74	0.77	0.46	0.45	6.2	0
	818	0.62	1.12	0.75	0.83	0.49	0.36	8.4	8
	822	0.98	1.01	0.49	0.83	0.38	0.33	11.2	5
	824	0.43	0.45	0.41	0.43	0.54	0.53	7.7	4

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APPENDIX EE

**INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY ASSESSMENT
IN P₁ RATS**

INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY ASSESSMENT
IN P₁ RATS

EXPLANATORY NOTES

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INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY SCORING SYSTEM

Home Cage Observations:

POSTURE:	-2 = limbs spread out or lying on one side
	-1 = curled up, often asleep, or sitting with head hung down
	0 = sitting, standing or rearing normally, alert
	1 = jumping
PALPEBRAL CLOSURE:	-2 = eyelids completely shut
	-1 = eyelids drooping (ptosis)
	0 = eyelids wide open
	S = rat appears to be sleeping
GAIT/COORDINATION:	0 = normal
	1 = unbalanced, swaying, uncoordinated
	2 = ataxic (unable to coordinate voluntary muscles, dragging limbs, hopping)
	3 = unable to move
TREMORS	0 = none
	1 = slight - localized to fingers or paws
	2 = mild - limbs
	3 = severe - multiple locations
CONVULSIONS	0 = none
	1 = present - violent involuntary series of muscle contractions; may be accompanied by pupillary dilation, vomiting, salivation, defecation, urination, chewing, and/or loss of consciousness

Outside the Home Cage (Removal from Cage):

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

INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY ASSESSMENTS
IN P₁ RATS

EXPLANATORY NOTES (Continued)

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INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY SCORING SYSTEM (Continued)

Outside the Home Cage (Removing from Cage): (Continued)

LACRIMATION: 0 = none
 1 = slight
 2 = severe

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

DEHYDRATION 0 = absent
 1 = present

EMACIATION 0 = absent
 1 = present

Open Field Arena (in Free-Roaming Space):

RIGHTING REFLEX: -2 = absent
 -1 = slow
 0 = present

PALPEBRAL CLOSURE: -2 = eyelids completely shut
 -1 = eyelids drooping (ptosis)
 0 = none

POSTURE: 0 = normal
 1 = abnormal (add description)

GAIT/COORDINATION: 0 = normal
 1 = unbalanced, swaying, uncoordinated
 2 = ataxic (unable to coordinate voluntary muscles, dragging limbs,
 hopping)
 3 = unable to move

TREMORS: 0 = none
 1 = slight - localized to fingers or paws
 2 = mild - limbs
 3 = severe - multiple locations

CONVULSIONS: 0 = none
 1 = present - violent involuntary series of muscle contractions;
 may be accompanied by pupillary dilation, vomiting, salivation,
 defecation, urination, chewing, and/or loss of consciousness

MUSCLE SPASMS/
FASCICULATION: 0 = none
 1 = present - twitching or rippling of muscle or skin

RESPIRATION EASE: 0 = normal
 1 = labored breathing

RATE OF RESPIRATION: -1 = slow
 0 = normal
 1 = rapid

AROUSAL
(LEVEL OF ACTIVITY): -2 = very slow (stupor, little or no responsiveness)
 -1 = low (some exploratory movements with periods of immobility)
 0 = normal (alert, exploratory movements)
 1 = high (slight excitement, tense, sudden movements)

INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY ASSESSMENTS
IN P₁ RATS

EXPLANATORY NOTES (Continued)

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INDIVIDUAL FUNCTIONAL OBSERVATIONAL BATTERY SCORING SYSTEM (Continued)

Open Field Area (in Free-Roaming Space): (Continued)

VOCALIZATIONS: 0 = absent
 1 = present
 2 = vocalizes only when handled

DIARRHEA: 0 = absent
 1 = present

POLYURIA: 0 = absent
 1 = present

Manipulations in Open Field Area (Free-Roaming Space):

APPROACH & TOUCH: -1 = no reaction
 0 = normal
 1 = increased reaction (jumps away or attacks)

AUDITORY STIMULUS: -1 = no reaction
 0 = normal reaction
 1 = increased reaction (rat jumps, flips)

TAIL PINCH: -1 = no response
 0 = normal (turns toward site)
 1 = exaggerated response (vocalizations, rapid turning)

Motor Activity Monitor:

PUPILLARY RESPONSE: 0 = present
 1 = absent

DIARRHEA: 0 = absent
 1 = present

POLYURIA: 0 = absent
 1 = present

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Functional Battery Assessment in P₁ Rats

ANIMAL NUMBER	HOME CAGE				REMOVAL FROM CAGE										OPEN FIELD				IN MOTOR ACTIVITY MONITOR																							
	POSTURE	PALPEBRAL CLOSURE	GAIT/COORDINATION	TREMORS	CONVULSIONS	EASE OF REMOVAL	EASE OF HANDLING	VOCALIZATIONS	MUSCLE TONE	PILORECTION	FUR/SKIN APPEARANCE	MUCOUS MEMBRANES	PALPEBRAL CLOSURE	EXOPHTHALMUS	LACRIMATION	SALIVATION	DEHYDRATION	EMACIATION	RIGHTING REFLEX	PALPEBRAL CLOSURE	POSTURE	GAIT/COORDINATION	TREMORS	CONVULSIONS	MUSCLE SPASMS/ FASCICULATION	RESPIRATION EASE	RATE OF RESPIRATION	AROUSAL	VOCALIZATIONS	DIARRHEA	POLYURIA	APPROACH & TOUCH	AUDITORY STIMULUS	TAIL PINCH	PUPILLARY RESPONSE	DIARRHEA	POLYURIA					
	(-2,-1,0,1)	(0,-1,-2,S)	(0,1,2,3)	(0,1,2,3)	(0,1)	(-1,0,1)	(0,1)	(-1,0,1)	(0,1)	(0,-1,-2)	(0,-1,-2)	(0,-1,-2)	(0,-1,-2)	(0,1)	(0,1,2)	(0,1,2)	(0,1)	(0,1)	(0,-1,-2)	(0,-1,-2)	(0,1)	(0,1,2,3)	(0,1,2,3)	(0,1)	(0,1)	(0,1)	(-1,0,1)	(-1,0,1)	(-1,0,1)	(0,1)	(0,1)	(0,1)	(-1,0,1)	(0,1)	(0,1)	(0,1)	(0,1)					
Female Group II-0 - 0 mg/kg/day																																										
806	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
809	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
814	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
819	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
829	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Female Group IV-0 - 15 mg/kg/day																																										
821	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
823	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
825a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
831	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
832	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Female Group VI-0 - 50 mg/kg/day																																										
828	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
836	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
830	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
834	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
835	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Female Group VIII-0 - 200 mg/kg/day																																										
816	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
817	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
818	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
822b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
824	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

a Sore toe, left front paw.
 b Sore toe, right front paw.

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APPENDIX FF

**INDIVIDUAL MOTOR ACTIVITY:
DURATION OF MOVEMENT AND NUMBER OF MOVEMENTS
IN P₁ RATS**

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Motor Activity:

Duration of Movement and Number of Movements in P₁ Rats

Successive 10-Minute Intervals

Animal Number	DURATION OF MOVEMENT (seconds)							NUMBER OF MOVEMENTS						
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>TOTAL</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>TOTAL</u>
Male, Group I-0 0 mg/kg/day														
767	387	355	352	377	319	302	2092	168	166	157	164	137	165	957
777	454	435	292	247	335	439	2202	115	112	102	98	130	112	669
780	344	304	299	356	152	237	1692	152	129	136	162	102	125	806
782	390	361	307	225	169	170	1622	144	147	131	110	90	90	712
786	397	371	322	277	40	1	1408	170	167	155	129	39	6	666
Male, Group III-0 15 mg/kg/day														
770	438	331	262	275	218	121	1645	139	166	164	152	137	68	826
773	261	144	0	147	24	0	576	177	121	0	132	25	1	456
776	434	383	320	221	80	112	1550	122	135	136	114	44	46	597
790	364	289	193	220	3	4	1073	144	135	106	83	6	6	480
791	384	349	382	268	227	56	1666	137	134	141	136	131	44	723
Male, Group V-0 50 mg/kg/day														
772	331	268	264	334	264	200	1661	138	163	125	143	156	93	818
774	381	350	327	251	59	4	1372	130	134	135	117	47	3	566
778	317	188	198	157	116	47	1023	150	120	125	108	87	48	638
783	420	236	227	172	13	36	1104	145	102	118	91	11	22	489
784	386	310	310	162	226	289	1683	124	126	134	126	128	144	782
Male, Group VII-0 200 mg/kg/day														
779	287	197	144	140	175	142	1085	164	116	118	106	117	105	726
781	381	266	270	27	11	1	956	140	118	136	36	5	4	439
785	421	242	212	315	140	0	1330	132	125	163	115	96	2	633
787	312	32	74	4	79	52	553	128	23	35	9	34	31	260
788	456	443	319	192	11	1	1422	114	121	119	72	6	4	436

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Individual Motor Activity:

Duration of Movement and Number of Movements in P₁ Rats

Successive 10-Minute Intervals

Animal Number	DURATION OF MOVEMENT (seconds)							NUMBER OF MOVEMENTS						
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>TOTAL</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>TOTAL</u>
Female, Group II-0 0 mg/kg/day														
806	306	153	168	33	47	165	872	142	115	132	40	41	139	609
809	393	288	254	261	215	246	1657	124	112	128	125	118	139	746
814	306	218	50	14	51	193	832	147	124	33	23	48	117	492
819	281	349	274	195	131	119	1349	113	108	128	133	100	90	672
829	354	272	169	107	82	305	1289	160	137	126	90	50	137	700
Female, Group IV-0 15 mg/kg/day														
821	291	167	107	104	5	2	676	129	101	78	93	7	4	412
823	310	238	100	180	308	51	1187	111	134	70	110	140	33	598
825	408	238	309	170	251	265	1641	142	128	146	91	143	138	788
831	390	287	257	233	230	148	1545	144	135	110	105	109	97	700
832	403	326	321	276	129	14	1469	108	102	151	100	105	9	575
Female, Group VI-0 50 mg/kg/day														
828	266	132	99	117	163	146	923	103	71	66	65	79	95	479
830	284	112	54	6	4	10	470	123	92	34	9	9	10	277
834	295	250	153	180	258	237	1373	122	144	114	135	151	150	816
835	331	211	225	158	8	77	1010	158	162	143	145	17	59	684
836	339	241	255	182	253	157	1427	121	137	126	117	130	96	727
Female, Group VIII-0 200 mg/kg/day														
816	308	186	157	211	42	154	1058	161	142	136	150	37	94	720
817	245	131	92	60	3	0	531	145	147	84	44	4	0	424
818	304	299	200	85	263	226	1377	137	136	132	52	117	142	716
822	261	70	53	1	1	19	405	130	77	55	6	4	5	277
824	302	113	1	6	6	0	428	140	112	8	11	10	3	284

APPENDIX GG
INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES

ABBREVIATIONS:

General:

NSR - no sample received for testing
NP - not taken or not performed
OK - sample condition OK for testing

Individual Hematology Values:

COND - sample condition
RBC - red blood cell count
HGB - hemoglobin
HCT - hematocrit
MCV - mean corpuscular volume
MCH - mean corpuscular hemoglobin
MCHC - mean corpuscular hemoglobin concentration
RDW - red cell distribution width
ARET - absolute reticulocyte count
PLT - platelet count
WBC - white blood cell count
ANEU - absolute neutrophil (all forms)
ALYM - absolute lymphocyte
AMON - absolute monocyte
AEOS - absolute eosinophil
ABAS - absolute basophil
ALUC - absolute large unstained cell

Individual Coagulation Values:

PHEM - plasma hemolysis
PLIP - plasma lipemia
PICT - plasma icterus
PT - prothrombin time
APTT - activated partial thromboplastin time

Individual Clinical Chemistry Values:

HEM - hemolysis
LIP - lipemia
ICT - icterus
AST - aspartate aminotransferase
ALT - alanine aminotransferase
BUN - urea nitrogen
CREA - creatinine
CHOL - cholesterol
GLUC - glucose
TP - total protein
ALB - albumin
TBA - total bile acids
NA - sodium
K - potassium

NOTES:

When individual animal data are not reported, it may be due to one of the following reasons or other reasons, all of which are explained in the study records:

the sample was clotted (CLOT)
there was insufficient sample for testing (QNS)
a valid result could not be obtained (RNV)
the sample was not suitable for testing
the animal died prior to sample collection
no sample was available for testing (NSR)

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Individual Animal Clinical Pathology Data

Male, Animal	Group	I-0	0 mg/kg/day	Day	14	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $\times 10^3/\mu\text{L}$	PLT $\times 10^3/\mu\text{L}$
748	OK	8.56	16.6	52.9	61.8	19.4	31.4	12.0	187.1	1110	
749	OK	8.43	15.8	51.5	61.1	18.8	30.7	12.0	183.7	1128	
756	OK	7.66	15.3	48.9	63.9	20.0	31.4	11.1	205.9	1047	
760	OK	7.82	15.1	48.6	62.1	19.4	31.2	11.5	199.0	1312	
762	OK	8.09	16.1	50.8	62.8	20.0	31.8	12.1	225.8	1137	
Male, Animal	Group	III-0	15 mg/kg/day	Day	14	MCV fL	MCH pg	MCHC g/dL	RDW % <td>ARET $\times 10^3/\mu\text{L}$ <td>PLT $\times 10^3/\mu\text{L}$</td> </td>	ARET $\times 10^3/\mu\text{L}$ <td>PLT $\times 10^3/\mu\text{L}$</td>	PLT $\times 10^3/\mu\text{L}$
750	OK	7.71	15.3	48.4	62.7	19.8	31.6	11.6	161.9	NP	
752	OK	8.19	15.6	51.2	62.5	19.0	30.4	11.4	150.2	1003	
757	OK	7.88	15.0	47.6	60.4	19.1	31.6	11.7	187.9	1193	
759	OK	7.67	14.3	46.8	61.0	18.7	30.6	11.6	168.4	1081	
769	OK	7.16	14.9	47.0	65.7	20.8	31.7	11.7	198.8	NP	

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A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal Clinical Pathology Data

Male, Animal	Group	V-O	50 mg/kg/day	Day	14	RBC x10 ⁶ /μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET x10 ³ /μL	PLT x10 ³ /μL
747	OK	8.58	16.7	51.1	59.5	19.4	32.6	11.0	254.7	NP				
751	OK	8.78	16.9	53.3	60.7	19.2	31.6	11.5	161.0	1146				
755	OK	7.92	15.4	49.4	62.3	19.4	31.1	11.0	147.5	1185				
764	OK	8.35	15.4	49.7	59.5	18.4	31.0	11.4	161.9	1323				
766	OK	7.18	14.5	45.6	63.5	20.3	31.9	11.5	174.9	1358				
Male, Animal	Group	VII-O	200 mg/kg/day	Day <td>14</td> <th>RBC x10⁶/μL</th> <th>HGB g/dL</th> <th>HCT %</th> <th>MCV fL</th> <th>MCH pg</th> <th>MCHC g/dL</th> <th>RDW %</th> <th>ARET x10³/μL</th> <th>PLT x10³/μL</th>	14	RBC x10 ⁶ /μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET x10 ³ /μL	PLT x10 ³ /μL
753	OK	8.66	16.2	51.5	59.4	18.6	31.4	11.0	173.9	888				
754	OK	7.45	15.3	47.8	64.2	20.6	32.1	12.0	222.6	NP				
758	NSR	NP	NP	NP	NP	NP	NP	NP	NP	NP				
765	OK	7.96	16.3	52.5	65.9	20.5	31.1	11.2	199.1	931				
775	OK	8.16	15.7	50.2	61.6	19.3	31.3	11.4	174.3	NP				

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A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal Clinical Pathology Data

Male, Animal	Group	I-0	0 mg/kg/day	Day	14	ANEU $\times 10^3/\mu\text{L}$	ALYM $\times 10^3/\mu\text{L}$	AMON $\times 10^3/\mu\text{L}$	AEOS $\times 10^3/\mu\text{L}$	ABAS $\times 10^3/\mu\text{L}$	ALUC $\times 10^3/\mu\text{L}$
748	WBC $\times 10^3/\mu\text{L}$	16.40	2.47	13.19	0.28	0.26	0.07	0.13	0.10	0.07	0.13
749		19.59	1.42	17.52	0.35	0.04	0.10	0.16	0.10	0.10	0.16
756		14.76	1.89	12.31	0.24	0.17	0.08	0.07	0.07	0.07	0.07
760		11.79	2.38	9.01	0.22	0.09	0.04	0.05	0.04	0.04	0.05
762		15.15	1.66	12.63	0.45	0.14	0.08	0.19	0.08	0.08	0.19

Male, Animal	Group	III-0	15 mg/kg/day	Day	14	ANEU $\times 10^3/\mu\text{L}$	ALYM $\times 10^3/\mu\text{L}$	AMON $\times 10^3/\mu\text{L}$	AEOS $\times 10^3/\mu\text{L}$	ABAS $\times 10^3/\mu\text{L}$	ALUC $\times 10^3/\mu\text{L}$
750	WBC $\times 10^3/\mu\text{L}$	11.97	1.12	10.26	0.23	0.14	0.11	0.12	0.11	0.11	0.12
752		13.34	1.67	11.15	0.24	0.12	0.07	0.11	0.07	0.07	0.11
757		14.42	1.62	12.17	0.26	0.21	0.05	0.11	0.05	0.05	0.11
759		12.92	1.45	11.16	0.19	0.04	0.04	0.05	0.04	0.04	0.05
769		13.28	1.68	11.03	0.33	0.09	0.07	0.07	0.09	0.07	0.07

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Individual Animal Clinical Pathology Data

Male, Animal	Group	V-0	50 mg/kg/day	Day	14	AEU $\times 10^3/\mu\text{L}$	ALYM $\times 10^3/\mu\text{L}$	AMON $\times 10^3/\mu\text{L}$	AEOS $\times 10^3/\mu\text{L}$	ABAS $\times 10^3/\mu\text{L}$	ALUC $\times 10^3/\mu\text{L}$
747		18.18	2.48	14.80	0.32	0.21	0.12	0.08	0.05	0.10	0.15
751		13.93	1.16	12.17	0.25	0.12	0.08	0.07	0.04	0.04	0.05
755		10.81	1.21	9.19	0.23	0.07	0.04	0.09	0.04	0.04	0.10
764		12.69	1.93	10.32	0.22	0.09	0.04	0.09	0.04	0.05	0.15
766		12.92	1.77	10.59	0.26	0.09	0.05	0.09	0.05	0.05	0.15
Male, Animal	Group	VII-0	200 mg/kg/day	Day <td>14</td> <td>ANEU $\times 10^3/\mu\text{L}$</td> <td>ALYM $\times 10^3/\mu\text{L}$</td> <td>AMON $\times 10^3/\mu\text{L}$</td> <td>AEOS $\times 10^3/\mu\text{L}$</td> <td>ABAS $\times 10^3/\mu\text{L}$</td> <td>ALUC $\times 10^3/\mu\text{L}$</td>	14	ANEU $\times 10^3/\mu\text{L}$	ALYM $\times 10^3/\mu\text{L}$	AMON $\times 10^3/\mu\text{L}$	AEOS $\times 10^3/\mu\text{L}$	ABAS $\times 10^3/\mu\text{L}$	ALUC $\times 10^3/\mu\text{L}$
753		16.76	2.16	14.07	0.30	0.06	0.08	0.06	0.06	0.08	0.11
754		15.82	1.90	13.13	0.32	0.47	0.00	0.47	0.00	0.00	0.00
758		NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
765		13.31	2.58	9.96	0.34	0.25	0.09	0.25	0.09	0.09	0.09
775		20.56	1.72	17.83	0.52	0.21	0.14	0.21	0.14	0.14	0.14

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A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal Clinical Pathology Data

Female, Animal	Group	COND	II-0	0 mg/kg/day	Day	14	RBC x10 ⁶ /μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET x10 ³ /μL	PLT x10 ³ /μL
793	OK	OK	7.18	14.4	45.5	63.4	20.0	31.6	13.1	296.5	1189				
794	OK	OK	8.17	15.8	47.7	58.4	19.3	33.1	11.2	182.8	1164				
796	OK	OK	7.17	14.5	43.9	61.2	20.2	33.0	11.4	206.4	NP				
797	OK	OK	7.91	15.3	47.3	59.8	19.4	32.4	11.2	180.4	1260				
798	OK	OK	7.57	14.4	43.9	58.0	19.0	32.9	12.1	213.1	NP				
Female, Animal	Group	COND	IV-0	15 mg/kg/day	Day	14	RBC x10 ⁶ /μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET x10 ³ /μL	PLT x10 ³ /μL
800	OK	OK	7.45	14.7	45.2	60.7	19.7	32.5	11.4	189.5	1545				
807	OK	OK	7.69	15.4	48.2	62.8	20.0	31.8	11.7	264.7	NP				
808	OK	OK	7.04	13.6	41.5	59.0	19.3	32.7	11.6	196.6	NP				
812	OK	OK	7.53	14.6	45.2	60.0	19.4	32.4	11.3	191.0	1099				
820	OK	OK	8.25	16.1	49.3	59.7	19.5	32.6	10.9	138.7	NP				

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A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal Clinical Pathology Data

Female, Animal	Group	VI-0	50 mg/kg/day	Day	14	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET x10 ³ /μL	PLT x10 ³ /μL
795	OK	RBC x10 ⁶ /μL	HGB g/dL	HCT %	7.70	14.8	44.3	57.6	11.3	199.6	1248
799	OK	7.74	15.2	47.3	61.2	19.7	32.1	10.6	198.6	983	
801	OK	7.96	15.7	46.9	58.9	19.8	33.6	11.7	236.9	NP	
815	OK	7.97	14.8	46.4	58.2	18.6	32.0	11.9	269.4	1402	
826	OK	7.30	14.2	44.6	61.1	19.4	31.8	12.4	261.5	NP	

Female, Animal	Group	VIII-0200	mg/kg/day	Day	14	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET x10 ³ /μL	PLT x10 ³ /μL
792	OK	RBC x10 ⁶ /μL	HGB g/dL	HCT %	8.94	16.4	50.3	56.3	11.4	311.4	1554
805	OK	7.42	14.6	45.1	60.7	19.7	32.4	12.2	207.9	1152	
810	OK	7.10	14.3	44.7	63.0	20.1	31.9	12.1	252.6	1138	
811	OK	7.24	13.6	42.3	58.5	18.7	32.1	11.8	267.3	1336	
813	OK	7.24	14.6	45.1	62.3	20.2	32.4	13.4	360.7	NP	

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 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal Clinical Pathology Data

Male, Animal	Group	I-0	0 mg/kg/day	Day	34	PT Sec	APTT Sec
	PHEM	PLIP	PICT	PT Sec	APTT Sec		
748	Small	None	None	NP	NP		
749	Trace	None	None	15.2	17.0		
756	None	None	None	16.2	17.9		
760	Trace	None	None	15.3	18.4		
762	None	None	None	13.4	12.0		
Male, Animal	Group	III-0	15 mg/kg/day	Day	34	PT Sec	APTT Sec
	PHEM	PLIP	PICT	PT Sec	APTT Sec		
750	None	None	None	15.6	16.4		
752	None	None	None	14.2	15.0		
757	Trace	None	None	15.6	18.4		
759	None	None	None	15.4	15.6		
769	Trace	None	None	14.7	16.3		

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Individual Animal Clinical Pathology Data

Male, Animal	Group	V-0	50 mg/kg/day	Day	34	PT Sec	APTT Sec
747	Trace	None	None	15.1	14.5		
751	None	None	None	15.5	17.4		
755	None	None	None	15.6	17.7		
764	None	None	None	15.4	15.0		
766	None	None	None	15.5	18.3		
Male, Animal	Group	VII-0	200 mg/kg/day <th>Day</th> <th>34</th> <th>PT Sec</th> <th>APTT Sec</th>	Day	34	PT Sec	APTT Sec
753	Trace	None	None	15.4	18.8		
754	Trace	None	None	15.1	16.0		
758	NSR	NP	NP	NP	NP		
765	Trace	None	None	15.9	22.3		
775	None	None	None	15.8	15.3		
779	None	None	None	16.1	19.5		

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Individual Animal Clinical Pathology Data

Female, Animal	Group	II-0	0 mg/kg/day	Day	43 - 57	PT Sec	APTT Sec
793	None	Trace	None	16.7	14.4		
794	Trace	None	None	15.6	15.3		
796	None	None	None	14.7	20.3		
797	None	Trace	None	15.7	18.8		
798	None	None	None	15.8	18.0		
Female, Animal	Group	IV-0	15 mg/kg/day	Day	43 - 57	PT Sec	APTT Sec
800	Trace	None	None	15.5	18.8		
807	None	None	None	15.5	15.4		
808	None	None	None	15.8	18.8		
812	None	None	None	16.2	20.7		
821	None	None	None	15.7	17.9		

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A-1846: Combined Repeated Dose Toxicity Study
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Individual Animal Clinical Pathology Data

Female, Animal	Group	PHEM	PLIP	PICT	PT Sec	Day	APT Sec
	VI-0					43	57
799		None	None	None	16.3		20.0
801		Trace	Trace	None	15.2		15.2
815		None	None	None	15.4		18.1
828		None	None	None	15.8		19.3
830		Trace	None	None	16.0		14.7
Female, Animal	Group	PHEM	PLIP	PICT <td>PT Sec</td> <td>Day</td> <td>APT Sec</td>	PT Sec	Day	APT Sec
	VIII-0200					43	57
805		None	None	None	14.8		12.1
811		None	None	None	15.6		17.7
816		None	None	None	14.3		18.8
822		None	None	None	15.7		18.6
824		Trace	None	None	15.7		18.0

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A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal Clinical Pathology Data

Male, Animal	Group	HEM	LIP	ICT	AST U/L	ALT U/L	BUN mg/dL	CREA mg/dL	CHOL mg/dL	GLUC mg/dL	TP g/dL	ALB g/dL
	I-0							14				
748		Trace	None	None	70	30	15	0.33	40	90	7.0	3.5
749		Trace	None	None	59	23	16	0.35	61	122	6.3	3.3
756		Trace	None	None	83	29	15	0.35	47	80	6.4	3.3
760		None	None	None	85	33	14	0.37	53	77	6.6	3.4
762		None	None	None	75	28	18	0.32	50	88	6.2	3.3
Male, Animal	Group	HEM	LIP	ICT <td>AST U/L</td> <td>ALT U/L</td> <td>BUN mg/dL</td> <td>CREA mg/dL</td> <td>CHOL mg/dL</td> <td>GLUC mg/dL</td> <td>TP g/dL</td> <td>ALB g/dL</td>	AST U/L	ALT U/L	BUN mg/dL	CREA mg/dL	CHOL mg/dL	GLUC mg/dL	TP g/dL	ALB g/dL
	III-0							14				
750		None	None	None	77	26	13	0.33	59	64	6.8	3.5
752		None	None	None	74	26	12	0.31	64	83	6.9	3.6
757		None	None	None	78	28	12	0.36	77	183	6.5	3.3
759		None	None	None	80	22	13	0.35	49	87	6.5	3.5
769		None	None	None	68	23	16	0.32	70	87	6.3	3.4

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 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal Clinical Pathology Data

Male, Animal	Group	HEM	LIP	ICT	AST U/L	ALT U/L	BUN mg/dL	CREA mg/dL	CHOL mg/dL	GLUC mg/dL	TP g/dL	ALB g/dL
	V-0						Day	14				
747	None	None	None	None	110	33	15	0.34	42	69	6.5	3.4
751	None	None	None	None	99	27	15	0.39	61	82	6.3	3.6
755	None	None	None	None	75	32	15	0.33	65	81	6.5	3.4
764	None	None	None	None	69	26	12	0.31	78	98	6.9	3.7
766	None	None	None	None	63	26	14	0.32	95	97	6.4	3.3
Male, Animal	Group	HEM	LIP	ICT <td>AST U/L</td> <td>ALT U/L</td> <td>BUN mg/dL</td> <td>CREA mg/dL</td> <td>CHOL mg/dL</td> <td>GLUC mg/dL</td> <td>TP g/dL</td> <td>ALB g/dL</td>	AST U/L	ALT U/L	BUN mg/dL	CREA mg/dL	CHOL mg/dL	GLUC mg/dL	TP g/dL	ALB g/dL
	VII-0						Day	14				
753	Trace	None	None	None	73	26	16	0.33	44	72	6.7	3.5
754	Trace	None	None	None	65	20	12	0.27	73	91	6.7	3.4
758	NSR	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
765	None	None	None	None	64	23	13	0.29	90	76	6.9	3.5
775	None	None	None	None	77	27	18	0.33	83	81	6.8	3.5

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A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal Clinical Pathology Data

Male, Animal	Group	I-0	-	0 mg/kg/day	-	Day	14
	TBA μmol/L	NA mmol/L	K	mmol/L			
748	26.0	147.4		6.28			
749	28.6	145.6		6.31			
756	13.5	146.6		6.15			
760	12.7	145.8		6.70			
762	19.1	147.7		6.48			

Male, Animal	Group	III-0	-	15 mg/kg/day	-	Day	14
	TBA μmol/L	NA mmol/L	K	mmol/L			
750	27.1	147.2		6.19			
752	17.1	147.1		6.24			
757	11.1	144.9		6.75			
759	9.4	146.1		7.12			
769	10.1	145.5		6.57			

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A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal Clinical Pathology Data

Male,	Group	V-0	50 mg/kg/day	-	Day	14
Animal	TBA μmol/L	NA mmol/L	K mmol/L			
747	33.9	142.3	6.15			
751	3.2	146.4	6.04			
755	8.7	145.9	6.04			
764	17.1	145.5	6.12			
766	21.5	145.6	7.19			
Male,	Group	VII-0	200 mg/kg/day	-	Day	14
Animal	TBA μmol/L	NA mmol/L	K mmol/L			
753	3.2	144.5	6.16			
754	6.9	141.7	6.42			
758	NP	NP	NP			
765	3.9	146.9	6.06			
775	49.4	146.3	6.48			

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A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal Clinical Pathology Data

Female, Animal	Group	HEM	LIP	ICT	AST U/L	ALT U/L	BUN mg/dL	CREA mg/dL	CHOL mg/dL	GLUC mg/dL	TP g/dL	ALB g/dL
	VI-0							14				
795		None	None	None	74	23	16	0.42	79	88	6.9	3.6
799		None	None	None	69	23	23	0.47	92	124	7.3	4.2
801		None	None	None	65	26	19	0.40	107	103	7.8	4.3
815		None	None	None	67	26	14	0.35	97	84	7.5	3.9
826		None	None	None	69	28	15	0.34	60	104	6.7	3.7
Female, Animal	Group	HEM	LIP	ICT	AST U/L	ALT U/L	BUN mg/dL	CREA mg/dL	CHOL mg/dL	GLUC mg/dL	TP g/dL	ALB g/dL
	VIII-0							14				
792		None	None	None	96	33	23	0.38	137	122	7.6	3.9
805		None	None	None	74	31	19	0.42	88	100	7.4	3.7
810		None	None	None	76	23	19	0.45	106	97	7.3	3.8
811		None	None	None	68	26	16	0.37	105	81	7.0	3.7
813		None	None	None	55	22	17	0.41	115	87	7.6	3.8

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 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal Clinical Pathology Data

Female, Animal	Group	TBA μmol/L	II-0 NA mmol/L	- K mmol/L	0 mg/kg/day	-	Day	14
793		17.8	143.9	5.51				
794		29.9	142.0	4.88				
796		12.5	143.4	5.47				
797		13.4	143.8	5.67				
798		6.5	144.1	5.51				
Female, Animal	Group	TBA μmol/L	IV-0 NA mmol/L	- K mmol/L	15 mg/kg/day	-	Day	14
800		25.2	144.5	6.28				
807		27.3	145.6	4.71				
808		15.6	142.1	6.45				
812		15.1	145.5	6.04				
820		12.9	144.0	5.32				

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A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal Clinical Pathology Data

Female, Animal	Group	TBA μmol/L	VI-0 NA mmol/L	K mmol/L	50 mg/kg/day	Day
795	8.0	142.4	5.44			14
799	22.4	143.5	5.16			
801	25.8	142.5	5.32			
815	28.5	144.3	6.13			
826	8.0	144.0	6.00			

Female, Animal	Group	TBA μmol/L	VIII-0 NA mmol/L	K mmol/L	200 mg/kg/day	Day
792	5.2	147.2	5.83			14
805	8.0	145.8	5.89			
810	7.3	146.5	5.97			
811	11.9	141.1	5.85			
813	32.0	143.3	6.34			

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APPENDIX HH

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHT DATA

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Organ Weight Listing
Study:15031/26200/1422

Individual Animal & Summary Stats Report
PLACES 2000 v1.400

Group : I-0 Treatment : 0 mg/kg I-0 Sex :MALES

ANIMAL	FBW (Gms)	BRAIN		ADRENAL GLANDS		EPIDIDYIMIDES		HEART		KIDNEYS					
		(Gms)	%FBW	(Gms)	%BRAIN	(Gms)	%BRAIN	(Gms)	%BRAIN	(Gms)	%BRAIN				
748	447.30	1.982	0.4431	0.049	0.0110	2.4723	1.220	0.2727	61.554	1.416	0.3166	71.443	3.817	0.8533	192.58
749	366.20	2.025	0.5530	0.047	0.0128	2.3210	1.222	0.3337	60.346	1.181	0.3225	58.321	2.956	0.8072	145.98
756	397.10	2.009	0.5059	0.049	0.0123	2.4390	1.150	0.2896	57.242	1.278	0.3218	63.614	2.682	0.6754	133.50
760	412.80	2.209	0.5351	0.068	0.0165	3.0783	1.282	0.3106	58.035	1.183	0.2866	53.554	3.317	0.8035	150.16
762	448.60	2.021	0.4505	0.063	0.0140	3.1173	1.327	0.2958	65.661	1.432	0.3192	70.856	3.688	0.8221	182.48
767	445.20						1.282	0.2880							
777	485.80						1.388	0.2857							
780	390.60						1.228	0.3144							
782	406.90						1.250	0.3072							
786	423.60						1.471	0.3473							
Mean	422.41	2.049	0.4975	0.055	0.0133	2.6856	1.282	0.3045	60.568	1.298	0.3133	63.557	3.292	0.7923	160.94
S.D.	34.944	0.091	0.0493	0.010	0.0021	0.3807	0.093	0.0230	3.3328	0.122	0.0151	7.7934	0.479	0.0682	25.291

Group : III-0 Treatment : 15 mg/kg III-0 Sex :MALES

ANIMAL	FBW (Gms)	BRAIN		ADRENAL GLANDS		EPIDIDYIMIDES		HEART		KIDNEYS					
		(Gms)	%FBW	(Gms)	%BRAIN	(Gms)	%BRAIN	(Gms)	%BRAIN	(Gms)	%BRAIN				
750	442.80	2.168	0.4896	0.057	0.0129	2.6292	1.279	0.2888	58.994	1.426	0.3220	65.775	3.576	0.8076	164.94
752	414.40	1.961	0.4732	0.046	0.0111	2.3457	1.334	0.3219	68.027	1.394	0.3364	71.086	3.564	0.8600	181.74
757	453.80	2.156	0.4751	0.068	0.0150	3.1540	1.356	0.2988	62.894	1.483	0.3268	68.785	3.966	0.8740	183.95
759	447.10	2.127	0.4757	0.052	0.0116	2.4448	1.350	0.3019	63.470	1.461	0.3268	68.688	3.496	0.7819	164.36
769	463.50	2.016	0.4350	0.049	0.0106	2.4306	1.145	0.2470	56.796	1.624	0.3504	80.556	3.638	0.7849	180.46
770	408.40						1.142	0.2796							
773	461.80						1.415	0.3064							
776	452.10						1.362	0.3013							
790	432.70						1.339	0.3095							
791	324.80						1.150	0.3541							
Mean	430.14	2.086	0.4697	0.054	0.0122	2.6008	1.287	0.3009	62.036	1.478	0.3325	70.978	3.648	0.8217	175.09
S.D.	41.404	0.092	0.0205	0.009	0.0018	0.3260	0.103	0.0276	4.3414	0.089	0.0113	5.6760	0.185	0.0428	9.6125

FBW - Final Body Weight

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With the Reproduction/Developmental Toxicity Screening Test in Rats

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Organ Weight Listing
Study: 15031/26200/1422
Individual Animal & Summary Stats Report
PLACES 2000 VI.400

Group : V-0 Treatment : 50 mg/kg V-0 Sex : MALES

ANIMAL	FBW (Gms)	BRAIN		ADRENAL GLANDS		EPIDIDYMIDES		HEART		KIDNEYS					
		(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW				
747	344.80	1.867	0.5415	0.049	0.0142	2.6245	1.244	0.3608	66.631	1.235	0.3582	66.149	2.901	0.8414	155.38
751	378.00	1.942	0.5138	0.057	0.0151	2.9351	1.269	0.3357	65.345	1.228	0.3249	63.234	2.762	0.7307	142.22
755	418.80	1.948	0.4651	0.044	0.0105	2.2587	1.198	0.2861	61.499	1.442	0.3443	74.025	3.277	0.7825	168.22
764	417.30	1.986	0.4759	0.062	0.0149	3.1219	1.376	0.3297	69.285	1.318	0.3158	66.365	3.657	0.8763	184.14
766	488.80	2.174	0.4448	0.065	0.0133	2.9899	1.330	0.2721	61.178	1.718	0.3515	79.025	4.148	0.8486	190.80
772	390.90						1.307	0.3344							
774	497.40						1.409	0.2833							
778	361.80						1.140	0.3151							
783	426.40						1.375	0.3225							
784	386.20						1.302	0.3371							
Mean	411.04	1.983	0.4882	0.055	0.0136	2.7860	1.295	0.3177	64.788	1.388	0.3389	69.759	3.349	0.8159	168.15
S.D.	50.295	0.115	0.0389	0.009	0.0019	0.3467	0.084	0.0284	3.4563	0.204	0.0179	6.5419	0.567	0.0586	20.024

Group : VII-0 Treatment : 200 mg/kg VII-0 Sex : MALES

ANIMAL	FBW (Gms)	BRAIN		ADRENAL GLANDS		EPIDIDYMIDES		HEART		KIDNEYS					
		(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW				
753	363.20	2.109	0.5807	0.059	0.0162	2.7975	1.050	0.2891	49.787	1.189	0.3274	56.377	2.850	0.7847	135.14
754	423.40	2.183	0.5156	0.059	0.0139	2.7027	1.331	0.3144	60.971	1.366	0.3226	62.574	4.212	0.9948	192.95
765	390.00	1.883	0.4828	0.047	0.0121	2.4960	1.230	0.3154	65.321	1.342	0.3441	71.269	3.476	0.8913	184.60
775	393.20	2.049	0.5211	0.057	0.0145	2.7818	1.096	0.2787	53.490	1.304	0.3316	63.641	3.540	0.9003	172.77
779	402.50	1.977	0.4912	0.059	0.0147	2.9843	1.374	0.3414	69.499	1.223	0.3039	61.861	3.189	0.7923	161.31
781	401.40						1.197	0.2982							
785	395.60						1.167	0.2950							
787	258.50						0.754	0.2917							
788	395.70						1.464	0.3700							
Mean	380.39	2.040	0.5183	0.056	0.0143	2.7525	1.185	0.3104	59.814	1.285	0.3259	63.145	3.453	0.8727	169.35
S.D.	48.289	0.116	0.0384	0.005	0.0015	0.1767	0.209	0.0290	8.1551	0.076	0.0147	5.3391	0.504	0.0869	22.563

FBW - Final Body Weight

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Individual Animal & Summary Stats Report
PLACES 2000 VI.400

Organ Weight Listing
Study:15031/26200/1422

Group : I-0 Treatment : 0 mg/kg I-0 Sex : MALES

ANIMAL	LIVER		SPLEEN		TESTES		THYMUS	
	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW
748	19.510	4.3617	0.798	0.1784	3.359	0.7510	0.284	0.0635
749	13.645	3.7261	0.729	0.1991	3.191	0.8714	0.469	0.1281
756	14.580	3.6716	0.739	0.1861	3.340	0.8411	0.393	0.0990
760	15.113	3.6611	0.768	0.1860	3.182	0.7708	0.392	0.0950
762	16.490	3.6759	0.659	0.1469	3.706	0.8261	0.415	0.0925
767					3.559	0.7994		
777					3.001	0.6177		
780					3.050	0.7808		
782					3.260	0.8012		
786					3.505	0.8274		
Mean	15.868	3.8193	0.739	0.1793	3.315	0.7887	0.391	0.0956
S.D.	2.282	0.3043	0.052	0.0196	0.225	0.0697	0.067	0.0229

Group : III-0 Treatment : 15 mg/kg III-0 Sex : MALES

ANIMAL	LIVER		SPLEEN		TESTES		THYMUS	
	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW
750	17.823	4.0251	0.746	0.1685	3.524	0.7958	0.422	0.0953
752	18.056	4.3571	0.708	0.1708	3.596	0.8678	0.335	0.0808
757	17.661	3.8918	0.844	0.1860	3.534	0.7788	0.537	0.1183
759	17.488	3.9114	0.837	0.1872	3.714	0.8307	0.399	0.0892
769	19.249	4.1530	0.893	0.1927	3.013	0.6501	0.443	0.0956
770					2.991	0.7324		
773					3.246	0.7029		
776					3.445	0.7620		
790					3.688	0.8523		
791					3.082	0.9489		
Mean	18.055	4.0677	0.806	0.1810	3.383	0.7922	0.427	0.0959
S.D.	0.699	0.1925	0.076	0.0107	0.278	0.0871	0.074	0.0139

FBW - Final Body Weight

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Organ Weight Listing
Study:15031/26200/1422

Individual Animal & Summary Stats Report
PLACES 2000 V1.400

Group : V-0 Treatment : 50 mg/kg V-0 Sex : MALES

ANIMAL	LIVER		SPLEEN		TESTES		THYMUS	
	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW
747	16.122	4.6758	0.832	0.2413	3.221	0.9342	0.282	0.0818
751	14.416	3.8138	0.597	0.1579	3.284	0.8688	0.351	0.0929
755	17.949	4.2858	0.659	0.1574	3.403	0.8126	0.297	0.0709
764	20.093	4.8150	0.650	0.1558	3.239	0.7762	0.430	0.1030
766	22.263	4.5546	0.832	0.1702	3.481	0.7122	0.457	0.0935
772					3.774	0.9655		
774					3.767	0.7573		
778					2.877	0.7952		
783					3.610	0.8466		
784					3.229	0.8361		
Mean	18.169	4.4290	0.714	0.1765	3.389	0.8305	0.363	0.0884
S.D.	3.114	0.3952	0.110	0.0367	0.279	0.0779	0.078	0.0123

Group : VII-0 Treatment : 200 mg/kg VII-0 Sex : MALES

ANIMAL	LIVER		SPLEEN		TESTES		THYMUS	
	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW
753	20.419	5.6220	0.622	0.1713	3.195	0.8797	0.419	0.1154
754	24.809	5.8595	0.977	0.2308	3.267	0.7716	0.612	0.1445
765	22.018	5.6456	0.621	0.1592	3.136	0.8041	0.323	0.0828
775	21.739	5.5287	0.751	0.1910	3.030	0.7706	0.277	0.0704
779	20.002	4.9694	0.673	0.1672	2.905	0.7217	0.439	0.1091
781					3.301	0.8224		
785					3.220	0.8140		
787					2.471	0.9559		
788					3.389	0.8565		
Mean	21.797	5.5251	0.729	0.1839	3.102	0.8218	0.414	0.1044
S.D.	1.887	0.3333	0.149	0.0287	0.277	0.0690	0.129	0.0290

*** Listing Complete ***

FBW - Final Body Weight

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Organ Weight Listing
Study:15031/26200/1422
Individual Animal & Summary Stats Report
PLACES 2000 V1.400

Group : II-0 Treatment : 0 mg/kg II-0 Sex : FEMALES

ANIMAL	FBW (Gms)	BRAIN		ADRENAL GLANDS		HEART		KIDNEYS		LIVER					
		(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW				
793	290.30	1.831	0.6307	0.083	0.0286	4.5330	1.509	0.5198	82.414	2.298	0.7916	125.51	11.362	3.9139	620.54
794	331.20	2.001	0.6042	0.064	0.0193	3.1984	1.123	0.3391	56.122	2.091	0.6313	104.50	14.054	4.2434	702.35
796	298.80	1.978	0.6620	0.088	0.0295	4.4489	1.080	0.3614	54.601	2.304	0.7711	116.48	13.075	4.3758	661.02
797	305.70	2.016	0.6595	0.060	0.0196	2.9762	1.022	0.3343	50.694	2.240	0.7327	111.11	12.939	4.2326	641.82
798	322.70	2.154	0.6675	0.109	0.0338	5.0604	1.241	0.3846	57.614	2.485	0.7701	115.37	14.329	4.4403	665.23
806	294.30														
809	321.90														
814	294.80														
819	318.50														
829	277.50														
Mean	305.57	1.996	0.6448	0.081	0.0262	4.0434	1.195	0.3878	60.289	2.284	0.7394	114.59	13.152	4.2412	658.19
S.D.	17.302	0.115	0.0268	0.020	0.0064	0.9071	0.193	0.0764	12.634	0.142	0.0640	7.7019	1.168	0.2031	30.387

Group : IV-0 Treatment : 15 mg/kg IV-0 Sex : FEMALES

ANIMAL	FBW (Gms)	BRAIN		ADRENAL GLANDS		HEART		KIDNEYS		LIVER					
		(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW				
800	308.50	1.948	0.6314	0.081	0.0263	4.1581	1.069	0.3465	54.877	2.471	0.8010	126.85	14.315	4.6402	734.86
807	309.50	1.979	0.6394	0.075	0.0242	3.7898	1.122	0.3625	56.695	2.382	0.7696	120.36	13.460	4.3489	680.14
808	303.10	1.991	0.6569	0.069	0.0228	3.4656	0.977	0.3223	49.071	2.034	0.6711	102.16	12.576	4.1491	631.64
812	310.10	2.010	0.6482	0.076	0.0245	3.7811	1.063	0.3428	52.886	2.176	0.7017	108.26	13.676	4.4102	680.40
821	303.90	2.014	0.6627	0.075	0.0247	3.7239	1.043	0.3432	51.787	2.336	0.7687	115.99	13.121	4.3175	651.49
823	350.30														
825	322.80														
831	264.40														
832	266.60	1.913	0.7176	0.090	0.0338	4.7047	0.985	0.3695	51.490	2.555	0.9584	133.56	11.917	4.4700	622.95
Mean	304.36	1.976	0.6594	0.078	0.0260	3.9372	1.043	0.3478	52.801	2.326	0.7784	117.86	13.178	4.3893	666.91
S.D.	26.343	0.039	0.0307	0.007	0.0039	0.4363	0.055	0.0166	2.6886	0.192	0.1005	11.625	0.846	0.1639	40.958

FBW - Final Body Weight

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With the Reproduction/Developmental Toxicity Screening Test in Rats

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Organ Weight Listing
Study: 15031/26200/1422
Individual Animal & Summary Stats Report
PLACES 2000 V1.400

Group : VI-0 Treatment : 50 mg/kg VI-0 Sex : FEMALES

ANIMAL	FBW (Gms)	BRAIN		ADRENAL GLANDS		HEART		KIDNEYS		LIVER					
		(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW				
799	338.30	1.921	0.5678	0.083	0.0245	4.3207	1.211	0.3580	63.040	2.436	0.7201	126.81	14.587	4.3119	759.34
801	293.20	1.783	0.6081	0.061	0.0208	3.4212	0.968	0.3302	54.291	2.063	0.7036	115.70	13.845	4.7220	776.50
815	301.80	1.998	0.6620	0.065	0.0215	3.2533	1.175	0.3893	58.809	2.363	0.7830	118.27	15.929	5.2780	797.25
828	302.10	2.031	0.6723	0.069	0.0228	3.3973	1.054	0.3489	51.896	2.178	0.7210	107.24	13.777	4.5604	678.34
830	274.70	1.705	0.6207	0.060	0.0218	3.5191	0.862	0.3138	50.557	2.010	0.7317	117.89	12.541	4.5653	735.54
834	299.00														
835	289.00														
836	294.60														
Mean	299.09	1.888	0.6262	0.068	0.0223	3.5823	1.054	0.3480	55.718	2.210	0.7319	117.18	14.136	4.6875	749.39
S.D.	18.148	0.140	0.0423	0.009	0.0014	0.4236	0.145	0.0287	5.1587	0.185	0.0303	6.9898	1.243	0.3613	45.730

Group : VIII-0 Treatment : 200 mg/kgVIII-0 Sex : FEMALES

ANIMAL	FBW (Gms)	BRAIN		ADRENAL GLANDS		HEART		KIDNEYS		LIVER					
		(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW	(Gms)	%FBW				
805	304.30	1.858	0.6106	0.060	0.0197	3.2293	0.986	0.3240	53.068	2.347	0.7713	126.32	13.764	4.5232	740.80
811	298.80	1.851	0.6195	0.082	0.0274	4.4300	0.998	0.3340	53.917	2.510	0.8400	135.60	16.591	5.5525	896.33
816	331.20	1.909	0.5764	0.087	0.0263	4.5574	1.042	0.3146	54.584	2.396	0.7234	125.51	18.832	5.6860	986.49
822	288.80	1.933	0.6693	0.089	0.0308	4.6042	1.114	0.3857	57.631	2.375	0.8224	122.87	14.592	5.0526	754.89
824	305.00	1.902	0.6236	0.096	0.0315	5.0473	1.059	0.3472	55.678	2.404	0.7882	126.39	14.655	4.8049	770.50
Mean	305.62	1.891	0.6199	0.083	0.0271	4.3736	1.040	0.3411	54.975	2.406	0.7891	127.34	15.687	5.1239	829.80
S.D.	15.699	0.035	0.0333	0.014	0.0047	0.6807	0.051	0.0277	1.7647	0.062	0.0456	4.8366	2.041	0.4918	107.27

FBW - Final Body Weight

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Individual Animal & Summary Stats Report
 PLACES 2000 V1.400

Organ Weight Listing
 Study:15031/26200/1422

Group : II-0 Treatment : 0 mg/kg II-0 Sex : FEMALES

ANIMAL	SPLEEN		THYMUS	
	(Gms)	%FBW	(Gms)	%FBW
793	0.673	0.2318	0.192	0.0661
794	0.660	0.1993	0.350	0.1057
796	0.775	0.2594	0.301	0.1007
797	0.536	0.1753	0.224	0.0733
798	0.551	0.1707	0.164	0.0508
806				
809				
814				
819				
829				
Mean	0.639	0.2073	0.246	0.0793
S.D.	0.098	0.0379	0.077	0.0233

Group : IV-0 Treatment : 15 mg/kg IV-0 Sex : FEMALES

ANIMAL	SPLEEN		THYMUS	
	(Gms)	%FBW	(Gms)	%FBW
800	0.584	0.1893	0.196	0.0635
807	0.687	0.2220	0.248	0.0801
808	0.652	0.2151	0.238	0.0785
812	0.610	0.1967	0.273	0.0880
821	0.662	0.2178	0.296	0.0974
823				
825				
831				
832	0.394	0.1478	0.142	0.0533
Mean	0.598	0.1981	0.232	0.0768
S.D.	0.107	0.0278	0.056	0.0161

FBW - Final Body Weight

A-1846: Combined Repeated Dose Toxicity Study
 With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

Organ Weight Listing
 Study: 15031/26200/1422
 Individual Animal & Summary Stats Report
 PLACES 2000 VI.400

Group : VI-0 Treatment : 50 mg/kg VI-0 Sex : FEMALES

ANIMAL	SPLEEN (Gms)	%FBW	%BRAIN	(Gms)	THYMUS (Gms)	%FBW	%BRAIN
799	0.865	0.2557	45.029	0.271	0.0801	14.107	
801	0.418	0.1426	23.444	0.167	0.0570	9.3662	
815	0.777	0.2575	38.889	0.228	0.0755	11.411	
828	0.678	0.2244	33.383	0.292	0.0967	14.377	
830	0.599	0.2181	35.132	0.191	0.0695	11.202	
834							
835							
836							
Mean	0.667	0.2196	35.175	0.230	0.0758	12.093	
S.D.	0.172	0.0466	7.9329	0.052	0.0146	2.1194	

Group : VIII-0 Treatment : 200 mg/kgVIII-0 Sex : FEMALES

ANIMAL	SPLEEN (Gms)	%FBW	%BRAIN	(Gms)	THYMUS (Gms)	%FBW	%BRAIN
805	0.496	0.1630	26.695	0.155	0.0509	8.3423	
811	0.571	0.1911	30.848	0.208	0.0696	11.237	
816	0.694	0.2095	36.354	0.285	0.0861	14.929	
822	0.421	0.1458	21.780	0.104	0.0360	5.3802	
824	0.590	0.1934	31.020	0.201	0.0659	10.568	
Mean	0.554	0.1806	29.339	0.191	0.0617	10.091	
S.D.	0.103	0.0257	5.4417	0.067	0.0190	3.5426	

*** Listing Complete ***

FBW - Final Body Weight

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APPENDIX II

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC OBSERVATIONS

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

1
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : I-0 Treatment: 0 mg/kg I-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

748 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
 FATTY CHANGE, HEPATOCELLULAR, CENTRILOBULAR, mild.
HEART :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
PROSTATE :
 AGGREGATES, LYMPHOID, moderate.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

748 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

2
Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : I-0 Treatment: 0 mg/kg I-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

748 Continued from previous page

Histopathology :

No Microscopic Abnormality Observed :
KIDNEYS, LUNGS, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS, ADRENAL GLANDS,
SCIATIC NERVE, THYROID GLAND, TRACHEA, SEMINAL VESICLES,
URINARY BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
BONE MARROW, COAGULATING GLANDS, PEYER'S PATCH

749 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.

749 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

3
Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : I-0 Treatment: 0 mg/kg I-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

749 Continued from previous page

Histopathology :

LIVER :
 FATTY CHANGE, MEDIAN CLEFT, minimal.
KIDNEYS :
 AGGREGATES, LYMPHOID, minimal.
THYMUS :
 HEMORRHAGE, minimal.
PROSTATE :
 AGGREGATES, LYMPHOID, minimal.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, SCIATIC
NERVE, THYROID GLAND, TRACHEA, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT, BONE
MARROW, COAGULATING GLANDS, PEYER'S PATCH

756 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

756 Continued on the next page

4
Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : I-0 Treatment: 0 mg/kg I-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

756 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYIMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
KIDNEYS :
 AGGREGATES, LYMPHOID, minimal.
 CHRONIC PROGRESSIVE NEPHROPATHY, minimal.
THYMUS :
 HEMORRHAGE, minimal.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, SCIATIC
NERVE, THYROID GLAND, TRACHEA, PROSTATE, SEMINAL VESICLES,
URINARY BLADDER, TESTES, EPIDIDYIMIDES, FEMUR/KNEE JOINT,
BONE MARROW, COAGULATING GLANDS, PEYER'S PATCH

5
Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : I-0 Treatment: 0 mg/kg I-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

760 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
 FATTY CHANGE, HEPATOCELLULAR, CENTRILOBULAR, minimal.
KIDNEYS :
 AGGREGATES, LYMPHOID, minimal.
LUNGS :
 INFLAMMATION, ALVEOLAR, ACUTE, minimal.
PROSTATE :
 AGGREGATES, LYMPHOID, mild.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

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6
Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : I-0 Treatment: 0 mg/kg I-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

760 Continued from previous page

Histopathology :

No Microscopic Abnormality Observed :

HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH, DUODENUM,
JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, TRACHEA,
SEMINAL VESICLES, URINARY BLADDER, TESTES, EPIDIDYMIDES,
FEMUR/KNEE JOINT, BONE MARROW, COAGULATING GLANDS, PEYER'S
PATCH

762

Terminal Sacrifice

Killed on Day : 34

Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :

LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

762 Continued on the next page

7
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : I-0 Treatment: 0 mg/kg I-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

762 Continued from previous page

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
KIDNEYS :
 AGGREGATES, LYMPHOID, minimal.
LUNGS :
 INFLAMMATION, PERIVASCULAR, minimal.
MESENTERIC LYMPH NODE :
 ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, minimal.
PROSTATE :
 AGGREGATES, LYMPHOID, minimal.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH, DUODENUM,
JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MANDIBULAR LYMPH NODE, THYMUS, ADRENAL GLANDS, SCIATIC
NERVE, THYROID GLAND, TRACHEA, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT, BONE
MARROW, COAGULATING GLANDS, PEYER'S PATCH

767 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

767 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

8
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : I-0 Treatment: 0 mg/kg I-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

767 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.

PROSTATE :
AGGREGATES, LYMPHOID, minimal.

CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
STOMACH, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

777 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

777 Continued on the next page

9
Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : I-0 Treatment: 0 mg/kg I-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

777 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

PROSTATE :
AGGREGATES, LYMPHOID, moderate.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LIVER, STOMACH, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

780 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

780 Continued on the next page

10
Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : I-0 Treatment: 0 mg/kg I-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

780 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LIVER, STOMACH, PROSTATE, SEMINAL VESICLES, TESTES,
EPIDIDYMIDES, COAGULATING GLANDS

782 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

782 Continued on the next page

11
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : I-0 Treatment: 0 mg/kg I-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

782 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
PROSTATE :
AGGREGATES, LYMPHOID, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
STOMACH, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

786 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

786 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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12
Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : I-0 Treatment: 0 mg/kg I-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

786 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
PROSTATE :
 AGGREGATES, LYMPHOID, minimal.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
STOMACH, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

13
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : III-0 Treatment: 15 mg/kg III-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

750 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, PROSTATE, SEMINAL VESICLES, TESTES,
EPIDIDYMIDES, COAGULATING GLANDS

752 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

14
Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : III-0 Treatment: 15 mg/kg III-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

752 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

PROSTATE :
AGGREGATES, LYMPHOID, mild.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LIVER, THYROID GLAND, SEMINAL VESICLES, TESTES,
EPIDIDYMIDES, COAGULATING GLANDS

757 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

15
Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : III-0 Treatment: 15 mg/kg III-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

757 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
PROSTATE :
 AGGREGATES, LYMPHOID, minimal.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

759 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

759 Continued on the next page

16
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : III-0 Treatment: 15 mg/kg III-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

759 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
PROSTATE :
AGGREGATES, LYMPHOID, mild.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

769 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

769 Continued on the next page

17
Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : III-0 Treatment: 15 mg/kg III-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

769 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.
COAGULATING GLANDS :
ONE OF A PAIR PRESENT.

No Microscopic Abnormality Observed :
THYROID GLAND, PROSTATE, SEMINAL VESICLES, TESTES,
EPIDIDYMIDES, COAGULATING GLANDS

770 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

770 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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18
Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : III-0 Treatment: 15 mg/kg III-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

770 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
TESTES :
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, UNILATERAL,
minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
PROSTATE, SEMINAL VESICLES, EPIDIDYMIDES,
COAGULATING GLANDS

773 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED
773 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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19
Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : III-0 Treatment: 15 mg/kg III-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

773 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
PROSTATE, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

776 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

776 Continued on the next page

20
Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : III-0 Treatment: 15 mg/kg III-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

776 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
FATTY CHANGE, HEPATOCELLULAR, CENTRILOBULAR, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
PROSTATE, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

790 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

790 Continued on the next page

21
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : III-0 Treatment: 15 mg/kg III-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

790 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
PROSTATE, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

791 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

791 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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22
Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : III-0 Treatment: 15 mg/kg III-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

791 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
PROSTATE :
AGGREGATES, LYMPHOID, moderate.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.
COAGULATING GLANDS :
ONE OF A PAIR PRESENT.

No Microscopic Abnormality Observed :
SEMINAL VESICLES, TESTES, EPIDIDYMIDES, COAGULATING GLANDS

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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23
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : V-0 Treatment: 50 mg/kg V-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

747 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
HYPERTROPHY, HEPATOCELLULAR, CENTRIOBULAR, minimal.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, PROSTATE, SEMINAL VESICLES, TESTES,
EPIDIDYMIDES, COAGULATING GLANDS

751 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

751 Continued on the next page

24
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : V-0 Treatment: 50 mg/kg V-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

751 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
HYPERTROPHY, HEPATOCELLULAR, CENTRIOBULAR, minimal.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.

CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, PROSTATE, SEMINAL VESICLES, TESTES,
EPIDIDYMIDES, COAGULATING GLANDS

755 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

755 Continued on the next page

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With the Reproduction/Developmental Toxicity Screening Test in Rats

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25
Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : V-0 Treatment: 50 mg/kg V-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

755 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
PROSTATE :
 AGGREGATES, LYMPHOID, moderate.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

764 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

764 Continued on the next page

26
Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : V-0 Treatment: 50 mg/kg V-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

764 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
HYPERTROPHY, HEPATOCELLULAR, CENTRIOBULAR, minimal.
PROSTATE :
AGGREGATES, LYMPHOID, moderate.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

766 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED
766 Continued on the next page

27
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : V-0 Treatment: 50 mg/kg V-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

766 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, PROSTATE, SEMINAL VESICLES, TESTES,
EPIDIDYMIDES, COAGULATING GLANDS

772 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

772 Continued on the next page

28
Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : V-0 Treatment: 50 mg/kg V-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

772 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
PROSTATE :
AGGREGATES, LYMPHOID, mild.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
SEMINAL VESICLES, TESTES, EPIDIDYMIDES, COAGULATING GLANDS

774 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

774 Continued on the next page

29
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : V-0 Treatment: 50 mg/kg V-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

774 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
PROSTATE :
 AGGREGATES, LYMPHOID, minimal.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
SEMINAL VESICLES, TESTES, EPIDIDYMIDES, COAGULATING GLANDS

778 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

778 Continued on the next page

30
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : V-0 Treatment: 50 mg/kg V-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

778 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

PROSTATE :
AGGREGATES, LYMPHOID, minimal.
TESTES :
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, UNILATERAL,
minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LIVER, SEMINAL VESICLES, EPIDIDYMIDES, COAGULATING GLANDS

783 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

783 Continued on the next page

31
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : V-0 Treatment: 50 mg/kg V-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

783 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
PROSTATE :
AGGREGATES, LYMPHOID, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
SEMINAL VESICLES, TESTES, EPIDIDYMIDES, COAGULATING GLANDS

784 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

784 Continued on the next page

32
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : V-0 Treatment: 50 mg/kg V-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

784 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LIVER, PROSTATE, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

33
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

753 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
 HYPERTROPHY, HEPATOCELLULAR, CENTRILOBULAR, minimal.
COLON :
 Minimal, LYMPHATIC CONGESTION.
THYMUS :
 HEMORRHAGE, minimal.
THYROID GLAND :
 HYPERTROPHY, FOLLICULAR CELL, minimal.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

753 Continued on the next page

34
Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

753 Continued from previous page

Histopathology :

No Microscopic Abnormality Observed :
KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, RECTUM, MESENTERIC LYMPH
NODE, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, SCIATIC NERVE,
TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY BLADDER,
TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT, BONE MARROW,
COAGULATING GLANDS, PEYER'S PATCH

754 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.

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With the Reproduction/Developmental Toxicity Screening Test in Rats

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35
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

754 Continued from previous page

Histopathology :

LIVER :
 HYPERTROPHY, HEPATOCELLULAR, CENTRIOLOBULAR, minimal.
KIDNEYS :
 AGGREGATES, LYMPHOID, minimal.
 CHRONIC PROGRESSIVE NEPHROPATHY, minimal.
THYMUS :
 HEMORRHAGE, minimal.
PROSTATE :
 AGGREGATES, LYMPHOID, minimal.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
 LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
 DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
 LYMPH NODE, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, SCIATIC
 NERVE, THYROID GLAND, TRACHEA, SEMINAL VESICLES, URINARY
 BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT, BONE
 MARROW, COAGULATING GLANDS, PEYER'S PATCH

758 Found Dead
 Duration of dosing-days: 3
 Exposure Group : Unscheduled death
 Animal is signed off from necropsy

Gross Pathology :

LUNGS :
 DISCOLORATION, DARK, RED.

758 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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36
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

758 Continued from previous page

Gross Pathology :

LUNGS :
 EXPANDED.
TRACHEA :
 FLUID, CLEAR.

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS, ADRENAL GLANDS,
SCIATIC NERVE, THYROID GLAND, PARATHYROID GLANDS, PROSTATE,
SEMINAL VESICLES, URINARY BLADDER, TESTES, EPIDIDYMIDES,
FEMUR/KNEE JOINT, COAGULATING GLANDS

Histopathology :

LUNGS :
 HEMORRHAGE, mild.
THYMUS :
 HEMORRHAGE, mild.
TRACHEA :
 INFLAMMATION, ACUTE, MUCOSAL, moderate.
 EXUDATE, moderate, purulent.
CAUSE OF DEATH :
 ACCIDENTALLY KILLED, (Dosing Accident).

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

No Microscopic Abnormality Observed :

LIVER, KIDNEYS, HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, SCIATIC
NERVE, THYROID GLAND, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT, BONE
Marrow, COAGULATING GLANDS, PEYER'S PATCH

765

Terminal Sacrifice

Killed on Day : 34

Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :

LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :

HYPERTROPHY, HEPATOCELLULAR, CENTRIOBULAR, minimal.

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

KIDNEYS :
 AGGREGATES, LYMPHOID, minimal.
 CHRONIC PROGRESSIVE NEPHROPATHY, minimal.
THYMUS :
 HEMORRHAGE, minimal.
THYROID GLAND :
 HYPERTROPHY, FOLLICULAR CELL, minimal.
PROSTATE :
 AGGREGATES, LYMPHOID, minimal.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
 LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
 DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
 LYMPH NODE, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, SCIATIC
 NERVE, TRACHEA, SEMINAL VESICLES, URINARY BLADDER, TESTES,
 EPIDIDYMIDES, FEMUR/KNEE JOINT, BONE MARROW,
 COAGULATING GLANDS, PEYER'S PATCH

775 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

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39
Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

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Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
KIDNEYS :
 HYDRONEPHROSIS, UNILATERAL, minimal.
MANDIBULAR LYMPH NODE :
 ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, minimal.
THYROID GLAND :
 HYPERTROPHY, FOLLICULAR CELL, minimal.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, THYMUS, ADRENAL GLANDS, SCIATIC NERVE, TRACHEA,
PROSTATE, SEMINAL VESICLES, URINARY BLADDER, TESTES,
EPIDIDYMIDES, FEMUR/KNEE JOINT, BONE MARROW,
COAGULATING GLANDS, PEYER'S PATCH

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With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

779 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
LUNGS :
 INFLAMMATION, PERIVASCULAR, minimal.
 INFLAMMATION, ALVEOLAR, ACUTE, mild.
MESENTERIC LYMPH NODE :
 ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, minimal.
THYROID GLAND :
 HYPERTROPHY, FOLLICULAR CELL, minimal.
PROSTATE :
 AGGREGATES, LYMPHOID, minimal.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

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Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

No Microscopic Abnormality Observed :
KIDNEYS, HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MANDIBULAR
LYMPH NODE, THYMUS, ADRENAL GLANDS, SCIATIC NERVE, TRACHEA,
SEMINAL VESICLES, URINARY BLADDER, TESTES, EPIDIDYMIDES,
FEMUR/KNEE JOINT, BONE MARROW, COAGULATING GLANDS,
PEYER'S PATCH

781 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

LIVER :

 HYPERTROPHY, HEPATOCELLULAR, CENTRILOBULAR, minimal.

PROSTATE :

 AGGREGATES, LYMPHOID, minimal.

CAUSE OF DEATH :

 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :

 STOMACH, SEMINAL VESICLES, TESTES, EPIDIDYMITES,
 COAGULATING GLANDS

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 Terminal Sacrifice

 Killed on Day : 34

 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :

 LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
 STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
 MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
 ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
 GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
 BLADDER, TESTES, EPIDIDYMITES, FEMUR/KNEE JOINT,
 COAGULATING GLANDS

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

LIVER :
 HYPERTROPHY, HEPATOCELLULAR, CENTRILOBULAR, minimal.
PROSTATE :
 AGGREGATES, LYMPHOID, mild.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
 STOMACH, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
 COAGULATING GLANDS

787 Terminal Sacrifice
 Killed on Day : 34
 Animal is signed off from necropsy

Gross Pathology :

PROSTATE :
 SMALL.
SEMINAL VESICLES :
 SMALL, BILATERAL.
TESTES :
 DEFORMITY, SOFT, BILATERAL.
EPIDIDYMIDES :
 SMALL, BILATERAL.

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With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

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Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, URINARY BLADDER, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
STOMACH, PROSTATE, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

788 Terminal Sacrifice
Killed on Day : 34
Animal is signed off from necropsy

NO ABNORMALITY DETECTED

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VII-0 Treatment: 200 mg/kg VII-0 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

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Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, PROSTATE, SEMINAL VESICLES, URINARY
BLADDER, TESTES, EPIDIDYMIDES, FEMUR/KNEE JOINT,
COAGULATING GLANDS

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
HYPERTROPHY, HEPATOCELLULAR, CENTRIOLOBULAR, minimal.
PROSTATE :
AGGREGATES, LYMPHOID, mild.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
STOMACH, SEMINAL VESICLES, TESTES, EPIDIDYMIDES,
COAGULATING GLANDS

Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

793 Terminal Sacrifice
 Killed on Day : 43
 Animal is signed off from necropsy

COMMENT: , 14 IMPLANT SITES, 15 CORPORA LUTEA.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
 HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
 FATTY CHANGE, HEPATOCELLULAR, PERIportal, minimal.
KIDNEYS :
 CHRONIC PROGRESSIVE NEPHROPATHY, minimal.
LUNGS :
 INFLAMMATION, PERIVASCULAR, minimal.
SPLEEN :
 HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, mild.
THYMUS :
 DEPLETION/ATROPHY, LYMPHOID, minimal.
UTERUS :
 IMPLANTATION SITES.

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

VAGINA :

 Diestrus/Anestrus.

BONE MARROW :

 HEMATOPOIESIS, INCREASED, mild.

CAUSE OF DEATH :

 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :

 HEART, BRAIN, SPINAL CORD, STOMACH, DUODENUM, JEJUNUM,
 ILEUM, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE,
 MANDIBULAR LYMPH NODE, ADRENAL GLANDS, SCIATIC NERVE,
 THYROID GLAND, TRACHEA, OVARIES, URINARY BLADDER,
 FEMUR/KNEE JOINT, PEYER'S PATCH, CERVIX

794

Terminal Sacrifice

Killed on Day : 46

Animal is signed off from necropsy

COMMENT:, IMPLANT SITES = 12 / CORPORA LUTEA = 12.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :

 LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
 STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
 MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
 ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
 GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Gross Pathology :

No Macroscopic Abnormality Observed :
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
THYMUS :
 HEMORRHAGE, minimal.
UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, SCIATIC
NERVE, THYROID GLAND, TRACHEA, OVARIES, URINARY BLADDER,
FEMUR/KNEE JOINT, BONE MARROW, PEYER'S PATCH, CERVIX

796 Terminal Sacrifice
 Killed on Day : 45
 Animal is signed off from necropsy

COMMENT:, 15 IMPLANT SITES, 15 CORPORA LUTEA.
NO ABNORMALITY DETECTED

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
SPLEEN :
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, mild.
MANDIBULAR LYMPH NODE :
HYPERPLASIA, PLASMA CELL, mild.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
BONE MARROW :
HEMATOPOIESIS, INCREASED, minimal.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

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A-1846: Combined Repeated Dose Toxicity Study
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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

No Microscopic Abnormality Observed :

KIDNEYS, LUNGS, HEART, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, THYMUS, ADRENAL GLANDS, SCIATIC NERVE, THYROID
GLAND, TRACHEA, OVARIES, URINARY BLADDER, FEMUR/KNEE JOINT,
PEYER'S PATCH, CERVIX

797

Terminal Sacrifice

Killed on Day : 45

Animal is signed off from necropsy

COMMENT:., 14 IMPLANT SITES, 14 CORPORA LUTEA.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :

LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :

INFLAMMATION, SUBACUTE/CHRONIC, minimal.

HEMATOPOIESIS, EXTRAMEDULLARY, minimal.

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Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

KIDNEYS :
 AGGREGATES, LYMPHOID, minimal.
SPLEEN :
 HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, minimal.
UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LUNGS, HEART, BRAIN, SPINAL CORD, STOMACH, DUODENUM,
JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, TRACHEA,
OVARIES, URINARY BLADDER, FEMUR/KNEE JOINT, BONE MARROW,
PEYER'S PATCH, CERVIX

798 Terminal Sacrifice
 Killed on Day : 44
 Animal is signed off from necropsy

COMMENT: , 15 IMPLANT SITES, 15 CORPORA LUTEA.
NO ABNORMALITY DETECTED

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
SPLEEN :
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, minimal.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, mild.
ADRENAL GLANDS :
ONE OF A PAIR PRESENT.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
BONE MARROW :
HEMATOPOIESIS, INCREASED, mild.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

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Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

No Microscopic Abnormality Observed :
KIDNEYS, LUNGS, HEART, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, SCIATIC
NERVE, THYROID GLAND, TRACHEA, OVARIES, URINARY BLADDER,
FEMUR/KNEE JOINT, PEYER'S PATCH, CERVIX

806 Terminal Sacrifice
 Killed on Day : 43
 Animal is signed off from necropsy

COMMENT:, 14 IMPLANT SITES, 14 CORPORA LUTEA.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

806 Continued from previous page

Histopathology :

UTERUS :
 IMPLANTATION SITES.

VAGINA :
 Diestrus/Anestrus.

CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
 STOMACH, OVARIES, CERVIX

809 Terminal Sacrifice
 Killed on Day : 45
 Animal is signed off from necropsy

COMMENT:, 13 IMPLANT SITES, 15 CORPORA LUTEA.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

809 Continued from previous page

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
 HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
 STOMACH, OVARIES, CERVIX

814 Terminal Sacrifice
 Killed on Day : 45
 Animal is signed off from necropsy

COMMENT:, 14 IMPLANT SITES, 14 CORPORA LUTEA.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

814 Continued from previous page

Histopathology :

VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LIVER, STOMACH, OVARIES, UTERUS, CERVIX

819 Terminal Sacrifice
Killed on Day : 45
Animal is signed off from necropsy

COMMENT:, 14 IMPLANT SITES, 14 CORPORA LUTEA.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.

819 Continued on the next page

57
Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

819 Continued from previous page

Histopathology :

UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
 STOMACH, OVARIES, CERVIX

829 Terminal Sacrifice
 Killed on Day : 44
 Animal is signed off from necropsy

COMMENT:., IMPLANT SITES 14, CORPORA LUTEA 16.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

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58
Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : II-0 Treatment: 0 mg/kg II-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

829 Continued from previous page

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
STOMACH, OVARIES, CERVIX

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : IV-0 Treatment: 15 mg/kg IV-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

800 Terminal Sacrifice
 Killed on Day : 45
 Animal is signed off from necropsy

COMMENT:, 13 IMPLANT SITES, 13 CORPORA LUTEA.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
 THYROID GLAND, OVARIES, CERVIX

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Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : IV-0 Treatment: 15 mg/kg IV-0 Sex: Females

Animal Ref	Microscopic & Macroscopic Findings
807	Terminal Sacrifice Killed on Day : 44 Animal is signed off from necropsy

COMMENT: , IMPLANT SITES 13, CORPORA LUTEA 13.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, OVARIES, CERVIX

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : IV-0 Treatment: 15 mg/kg IV-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

808 Terminal Sacrifice
 Killed on Day : 45
 Animal is signed off from necropsy

COMMENT: , 12 IMPLANT SITES, 16 CORPORA LUTEA.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, OVARIES, CERVIX

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Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : IV-0 Treatment: 15 mg/kg IV-0 Sex: Females

Animal Ref	Microscopic & Macroscopic Findings
812	Terminal Sacrifice Killed on Day : 45 Animal is signed off from necropsy

COMMENT: , 15 IMPLANT SITES, 15 CORPORA LUTEA.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LIVER, THYROID GLAND, OVARIES, CERVIX

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : IV-0 Treatment: 15 mg/kg IV-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

820 Unscheduled Sacrifice
 Duration of dosing-days: 39
 Exposure Group : Unscheduled death
 Animal is signed off from necropsy

COMMENT:, 3 PUPS IN RIGHT UTERINE HORN.
COMMENT:, 13 IMPLANT SITES.
COMMENT:, 13 CORPORA LUTEA.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
 FATTY CHANGE, HEPATOCELLULAR, MIDZONAL, minimal.
KIDNEYS :
 FATTY CHANGE, TUBULAR, DIFFUSE, mild.
SPLEEN :
 DEPLETION/ATROPHY, LYMPHOID, mild.
THYMUS :
 NECROSIS, ACUTE, LYMPHOID, moderate.
 DEPLETION/ATROPHY, LYMPHOID, mild.
UTERUS :
 IMPLANTATION SITES.

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : IV-0 Treatment: 15 mg/kg IV-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

820 Continued from previous page

Histopathology :

VAGINA :

Diestrus/Anestrus.

INFLAMMATION, MUCOSAL, moderate, with ulceration.

CAUSE OF DEATH :

DYSTOCIA.

No Microscopic Abnormality Observed :

LUNGS, HEART, BRAIN, SPINAL CORD, STOMACH, DUODENUM,
JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, ADRENAL
GLANDS, SCIATIC NERVE, THYROID GLAND, TRACHEA, OVARIES,
URINARY BLADDER, FEMUR/KNEE JOINT, BONE MARROW,
PEYER'S PATCH, CERVIX

821

Terminal Sacrifice

Killed on Day : 45

Animal is signed off from necropsy

COMMENT: , 14 IMPLANT SITES, 14 CORPORA LUTEA.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :

LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,

821 Continued on the next page

65
Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : IV-0 Treatment: 15 mg/kg IV-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

821 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, OVARIES, CERVIX

823 Terminal Sacrifice
 Killed on Day : 43
 Animal is signed off from necropsy

COMMENT: , 15 IMPLANT SITES, 17 CORPORA LUTEA.
NO ABNORMALITY DETECTED

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : IV-0 Treatment: 15 mg/kg IV-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

823 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
 OVARIES, CERVIX

825 Terminal Sacrifice
 Killed on Day : 44
 Animal is signed off from necropsy

COMMENT:., IMPLANT SITES 15, CORPORA LUTEA 16.
NO ABNORMALITY DETECTED

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : IV-0 Treatment: 15 mg/kg IV-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

825 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
OVARIES, CERVIX

831 Terminal Sacrifice
Killed on Day : 42
Animal is signed off from necropsy

COMMENT:, 15 IMPLANT SITES, 15 CORPORA LUTEA.
NO ABNORMALITY DETECTED

831 Continued on the next page

Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : IV-0 Treatment: 15 mg/kg IV-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

831 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
OVARIES, CERVIX

832 Terminal Sacrifice
 Killed on Day : 40
 Animal is signed off from necropsy

COMMENT: , 14 IMPLANT SITES, 14 CORPORA LUTEA.

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With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : IV-0 Treatment: 15 mg/kg IV-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

832 Continued from previous page

Gross Pathology :

UTERUS :
THICK, BILATERAL, HORNS.

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, VAGINA,
URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
FATTY CHANGE, HEPATOCELLULAR, MIDZONAL, minimal.
UTERUS :
IMPLANTATION SITES.
INFLAMMATION, SUBACUTE/CHRONIC, MUCOSAL, moderate, with
hemorrhage.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, OVARIES, CERVIX

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VI-0 Treatment: 50 mg/kg VI-0 Sex: Females

Animal Ref	Microscopic & Macroscopic Findings
795	Found Dead Duration of dosing-days: 39 Exposure Group : Unscheduled death Animal is signed off from necropsy

COMMENT:, 15 PUPS IN UTERINE HORNS.
COMMENT:, 15 IMPLANT SITES.
COMMENT:, 15 CORPORA LUTEA.

Gross Pathology :

STOMACH :
DISTENDED WITH FLUID, BROWN, severe.
PITUITARY GLAND :
DISCOLORATION, DARK.

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS, ADRENAL GLANDS,
SCIATIC NERVE, THYROID GLAND, PARATHYROID GLANDS, TRACHEA,
MAMMARY GLAND (FEMALE), OVARIES, UTERUS, VAGINA,
URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

SPLEEN :
DEPLETION/ATROPHY, LYMPHOID, mild.
MESENTERIC LYMPH NODE :
NECROSIS, ACUTE, LYMPHOID, mild.
MANDIBULAR LYMPH NODE :
INFLAMMATION, ACUTE, mild.
NECROSIS, ACUTE, LYMPHOID, minimal.

795 Continued on the next page

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VI-0 Treatment: 50 mg/kg VI-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

795 Continued from previous page

Histopathology :

THYMUS :
 NECROSIS, ACUTE, LYMPHOID, severe.
PITUITARY GLAND :
 CONGESTION, mild.
TRACHEA :
 INFLAMMATION, ACUTE, MUCOSAL, mild.
 AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, mild.
UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 DYSTOCIA.

No Microscopic Abnormality Observed :
 LIVER, KIDNEYS, LUNGS, HEART, BRAIN, SPINAL CORD, STOMACH,
 DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, ADRENAL
 GLANDS, SCIATIC NERVE, THYROID GLAND, OVARIES, URINARY
 BLADDER, FEMUR/KNEE JOINT, BONE MARROW, PEYER'S PATCH,
 CERVIX

799 Terminal Sacrifice
 Killed on Day : 45
 Animal is signed off from necropsy

 COMMENT: , 13 IMPLANT SITES, 13 CORPORA LUTEA.
 NO ABNORMALITY DETECTED

799 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VI-0 Treatment: 50 mg/kg VI-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

799 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.

UTERUS :
IMPLANTATION SITES.

VAGINA :
Diestrus/Anestrus.

CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, OVARIES, CERVIX

801 Terminal Sacrifice
Killed on Day : 44
Animal is signed off from necropsy

COMMENT:, IMPLANT SITES 14, CORPORA LUTEA 14.
NO ABNORMALITY DETECTED

801 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VI-0 Treatment: 50 mg/kg VI-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

801 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LIVER, THYROID GLAND, OVARIES, CERVIX

815 Terminal Sacrifice
 Killed on Day : 45
 Animal is signed off from necropsy

COMMENT:, 15 IMPLANT SITES, 15 CORPORA LUTEA.
NO ABNORMALITY DETECTED

815 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VI-0 Treatment: 50 mg/kg VI-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

815 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
THYROID GLAND, OVARIES, CERVIX

826 Unscheduled Sacrifice
Duration of dosing-days: 40
Exposure Group : Unscheduled death
Animal is signed off from necropsy

COMMENT: , 16 PUPS IN UTERUS.
826 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VI-0 Treatment: 50 mg/kg VI-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

826 Continued from previous page

COMMENT: , 16 IMPLANT SITES, 17 CORPORA LUTEA.

Gross Pathology :

UTERUS :
FETUS IN BIRTH CANAL.

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, VAGINA,
URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
FATTY CHANGE, HEPATOCELLULAR, MIDZONAL, minimal.
KIDNEYS :
FATTY CHANGE, TUBULAR, DIFFUSE, moderate.
DEGENERATION/NECROSIS, TUBULAR, EPITHELIAL, mild.
DILATATION, TUBULAR, DIFFUSE, mild, with protein casts.
SPLEEN :
DEPLETION/ATROPHY, LYMPHOID, moderate.
MESENTERIC LYMPH NODE :
DEPLETION/ATROPHY, LYMPHOID, mild.
MANDIBULAR LYMPH NODE :
DEPLETION/ATROPHY, LYMPHOID, mild.
THYMUS :
NECROSIS, ACUTE, LYMPHOID, severe.

826 Continued on the next page

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VI-0 Treatment: 50 mg/kg VI-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

826 Continued from previous page

Histopathology :

THYMUS :
 DEPLETION/ATROPHY, LYMPHOID, mild.
TRACHEA :
 INFLAMMATION, ACUTE, MUCOSAL, minimal.
UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
 DILATATION, moderate.
FEMUR/KNEE JOINT :
 FIBROUS OSTEODYSTROPHY, minimal.
CAUSE OF DEATH :
 DYSTOCIA.

No Microscopic Abnormality Observed :
LUNGS, HEART, BRAIN, SPINAL CORD, STOMACH, DUODENUM,
JEJUNUM, ILEUM, CECUM, COLON, RECTUM, ADRENAL GLANDS,
SCIATIC NERVE, THYROID GLAND, OVARIES, URINARY BLADDER,
BONE MARROW, PEYER'S PATCH, CERVIX

828 Terminal Sacrifice
 Killed on Day : 45
 Animal is signed off from necropsy

COMMENT:, 14 IMPLANT SITES, 16 CORPORA LUTEA.
NO ABNORMALITY DETECTED

828 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VI-0 Treatment: 50 mg/kg VI-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

828 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
 THYROID GLAND, OVARIES, CERVIX

830 Terminal Sacrifice
 Killed on Day : 49
 Animal is signed off from necropsy

COMMENT:, 13 CORPORA LUTEA.
COMMENT:, 12 IMPLANT SITES.
NO ABNORMALITY DETECTED

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VI-0 Treatment: 50 mg/kg VI-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

830 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
 THYROID GLAND, OVARIES, CERVIX

834 Terminal Sacrifice
 Killed on Day : 44
 Animal is signed off from necropsy

COMMENT: , IMPLANT SITES 16, CORPORA LUTEA 16.
NO ABNORMALITY DETECTED

834 Continued on the next page

Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VI-0 Treatment: 50 mg/kg VI-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

834 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
OVARIES, CERVIX

835 Terminal Sacrifice
Killed on Day : 44
Animal is signed off from necropsy

COMMENT:, IMPLANT SITES 15, CORPORA LUTEA 15.
NO ABNORMALITY DETECTED

835 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VI-0 Treatment: 50 mg/kg VI-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

835 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
OVARIES, CERVIX

836 Terminal Sacrifice
Killed on Day : 45
Animal is signed off from necropsy

COMMENT:, 14 IMPLANT SITES, 15 CORPORA LUTEA.
NO ABNORMALITY DETECTED

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VI-0 Treatment: 50 mg/kg VI-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

836 Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
 OVARIES, CERVIX

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Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

792 Found Dead
 Duration of dosing-days: 16
 Exposure Group : Unscheduled death
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
 HYPERTROPHY, HEPATOCELLULAR, CENTRIOLOBULAR, minimal.
 NECROSIS, FOCAL, minimal, subcapsular.
KIDNEYS :
 AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, mild.
LUNGS :
 INFLAMMATION, ALVEOLAR, ACUTE, minimal.
SPLEEN :
 DEPLETION/ATROPHY, LYMPHOID, mild.
 PIGMENT INCREASED, mild.
STOMACH :
 AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, mild.
JEJUNUM :
 AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, mild.
792 Continued on the next page

A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

ILEUM :
 AUTOLYSIS: NO MICROSCOPIC EXAMINATION, severe.
CECUM :
 AUTOLYSIS: NO MICROSCOPIC EXAMINATION, severe.
COLON :
 AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, mild.
RECTUM :
 AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, mild.
MESENTERIC LYMPH NODE :
 DEPLETION/ATROPHY, LYMPHOID, minimal.
MANDIBULAR LYMPH NODE :
 DEPLETION/ATROPHY, LYMPHOID, minimal.
THYMUS :
 NECROSIS, ACUTE, LYMPHOID, severe.
THYROID GLAND :
 AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, mild.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 UNDETERMINED.

No Microscopic Abnormality Observed :
HEART, BRAIN, SPINAL CORD, STOMACH, DUODENUM, JEJUNUM,
COLON, RECTUM, ADRENAL GLANDS, SCIATIC NERVE,
THYROID GLAND, TRACHEA, OVARIES, UTERUS, URINARY BLADDER,
FEMUR/KNEE JOINT, BONE MARROW, PEYER'S PATCH, CERVIX

ORGANS NOT EXAMINED:
ILEUM, CECUM

Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref	Microscopic & Macroscopic Findings
805	Terminal Sacrifice Killed on Day : 49 Animal is signed off from necropsy

12 IMPLANT SITES.
COMMENT: , 12 CORPORA LUTEA .
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HYPERTROPHY, HEPATOCELLULAR, CENTRILOBULAR, minimal.
KIDNEYS :
DILATATION, TUBULAR, FOCAL, minimal.
SPLEEN :
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, minimal.
STOMACH :
EROSION/ULCER, NONGLANDULAR, mild, with inflammation.
THYMUS :
HEMORRHAGE, minimal.
THYROID GLAND :
HYPERTROPHY, FOLLICULAR CELL, minimal.

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

805 Continued from previous page

Histopathology :

UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
LUNGS, HEART, BRAIN, SPINAL CORD, DUODENUM, JEJUNUM, ILEUM,
CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, MANDIBULAR
LYMPH NODE, ADRENAL GLANDS, SCIATIC NERVE, TRACHEA,
OVARIES, URINARY BLADDER, FEMUR/KNEE JOINT, BONE MARROW,
PEYER'S PATCH, CERVIX

810 Unscheduled Sacrifice
 Duration of dosing-days: 17
 Exposure Group : Unscheduled death
 Animal is signed off from necropsy

NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Gross Pathology :

No Macroscopic Abnormality Observed :
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
 HYPERTROPHY, HEPATOCELLULAR, CENTRIOBULAR, minimal.
 NECROSIS, FOCAL, mild, subcapsular.
KIDNEYS :
 HYDRONEPHROSIS, UNILATERAL, minimal.
SPLEEN :
 HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, minimal.
 HYPERPLASIA, LYMPHOID, mild.
THYMUS :
 NECROSIS, ACUTE, LYMPHOID, minimal.
TRACHEA :
 INFLAMMATION, ACUTE, MUCOSAL, severe.
 EXUDATE, severe, purulent.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 DOSING ACCIDENT.

No Microscopic Abnormality Observed :
LUNGS, HEART, BRAIN, SPINAL CORD, STOMACH, DUODENUM,
JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, ADRENAL
GLANDS, SCIATIC NERVE, THYROID GLAND, OVARIES, UTERUS,
URINARY BLADDER, FEMUR/KNEE JOINT, BONE MARROW,

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Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

810 Continued from previous page

Histopathology :

No Microscopic Abnormality Observed :
PEYER'S PATCH, CERVIX

811 Terminal Sacrifice
 Killed on Day : 44
 Animal is signed off from necropsy

COMMENT:, IMPLANT SITES 10, CORPORA LUTEA 9.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
 HYPERTROPHY, HEPATOCELLULAR, CENTRILOBULAR, minimal.
 INFLAMMATION, SUBACUTE/CHRONIC, minimal.
SPLEEN :
 HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, mild.
UTERUS :
 IMPLANTATION SITES.

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Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
KIDNEYS, LUNGS, HEART, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS, ADRENAL GLANDS,
SCIATIC NERVE, THYROID GLAND, TRACHEA, OVARIES, URINARY
BLADDER, FEMUR/KNEE JOINT, BONE MARROW, PEYER'S PATCH,
CERVIX

813 Found Dead
Duration of dosing-days: 37
Exposure Group : Unscheduled death
Animal is signed off from necropsy

COMMENT:, 10 IMPLANT SITES.
COMMENT:, 10 PUPS IN UTERUS.
COMMENT:, 12 CORPORA LUTEA .

Gross Pathology :

LUNGS :
EXPANDED.

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Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS, ADRENAL GLANDS,
SCIATIC NERVE, THYROID GLAND, PARATHYROID GLANDS, TRACHEA,
MAMMARY GLAND (FEMALE), OVARIES, UTERUS, VAGINA,
URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
 HYPERTROPHY, HEPATOCELLULAR, CENTRILOBULAR, minimal.
KIDNEYS :
 AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, mild.
SPLEEN :
 DEPLETION/ATROPHY, LYMPHOID, minimal.
STOMACH :
 AUTOLYSIS: NO MICROSCOPIC EXAMINATION.
CECUM :
 AUTOLYSIS: NO MICROSCOPIC EXAMINATION, severe.
COLON :
 AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, mild.
RECTUM :
 AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, mild.
THYROID GLAND :
 AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, moderate.
TRACHEA :
 INFLAMMATION, ACUTE, MUCOSAL, mild.
 EXUDATE, mild, purulent.

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

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Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
URINARY BLADDER :
 AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, minimal.
BONE MARROW :
 HEMATOPOIESIS, INCREASED, minimal.
CAUSE OF DEATH :
 DYSTOCIA.

No Microscopic Abnormality Observed :
LUNGS, HEART, BRAIN, SPINAL CORD, DUODENUM, JEJUNUM, ILEUM,
COLON, RECTUM, MESENTERIC LYMPH NODE,
MANDIBULAR LYMPH NODE, THYMUS, ADRENAL GLANDS, SCIATIC
NERVE, THYROID GLAND, OVARIES, URINARY BLADDER, FEMUR/KNEE
JOINT, PEYER'S PATCH, CERVIX

ORGANS NOT EXAMINED:
STOMACH, CECUM

816 Terminal Sacrifice
 Killed on Day : 45
 Animal is signed off from necropsy

COMMENT: , 15 IMPLANT SITES, 15 CORPORA LUTEA.
NO ABNORMALITY DETECTED

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A-1846: Combined Repeated Dose Toxicity Study
With the Reproduction/Developmental Toxicity Screening Test in Rats

DuPont-14109

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
NECROSIS, FOCAL, minimal, subcapsular.
HYPERTROPHY, HEPATOCELLULAR, CENTRIOLOBULAR, minimal.
KIDNEYS :
DILATATION, TUBULAR, FOCAL, minimal.
SPLEEN :
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, mild.
MANDIBULAR LYMPH NODE :
HYPERPLASIA, PLASMA CELL, mild.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
BONE MARROW :
HEMATOPOIESIS, INCREASED, mild.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

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A-1846: Combined Repeated Dose Toxicity Study
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Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

No Microscopic Abnormality Observed :
LUNGS, HEART, BRAIN, SPINAL CORD, STOMACH, DUODENUM,
JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, THYMUS, ADRENAL GLANDS, SCIATIC
NERVE, THYROID GLAND, TRACHEA, OVARIES, URINARY BLADDER,
FEMUR/KNEE JOINT, PEYER'S PATCH, CERVIX

817 Unscheduled Sacrifice
Duration of dosing-days: 38
Exposure Group : Unscheduled death
Animal is signed off from necropsy

COMMENT:, ONE MORIBUND PUP FOUND IN REPRO PAN AT NECROPSY.
COMMENT:, 11 PUPS IN UTERUS.
COMMENT:, 12 IMPLANT SITES.
COMMENT:, 13 CORPORA LUTEA.

Gross Pathology :

TRACHEA :
FLUID, FOAMY.

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, MAMMARY GLAND (FEMALE), OVARIES, UTERUS, VAGINA,
URINARY BLADDER, FEMUR/KNEE JOINT

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

LIVER :
 HYPERTROPHY, HEPATOCELLULAR, CENTRIOBULAR, minimal.
SPLEEN :
 DEPLETION/ATROPHY, LYMPHOID, mild.
 PIGMENT INCREASED, minimal.
THYMUS :
 NECROSIS, ACUTE, LYMPHOID, severe.
 DEPLETION/ATROPHY, LYMPHOID, mild.
 HEMORRHAGE, minimal.
UTERUS :
 IMPLANTATION SITES.
VAGINA :
 Diestrus/Anestrus.
CAUSE OF DEATH :
 DYSTOCIA.

No Microscopic Abnormality Observed :
 KIDNEYS, LUNGS, HEART, BRAIN, SPINAL CORD, STOMACH,
 DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
 LYMPH NODE, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, SCIATIC
 NERVE, THYROID GLAND, TRACHEA, OVARIES, URINARY BLADDER,
 FEMUR/KNEE JOINT, BONE MARROW, PEYER'S PATCH, CERVIX

818 Found Dead
 Duration of dosing-days: 39
 Exposure Group : Unscheduled death
 Animal is signed off from necropsy

 COMMENT: , 14 IMPLANT SITES.
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Date:19-JUL-04

Individual Animal Listing

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STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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COMMENT:, 14 CORPORA LUTEA.

COMMENT:, 14 PUPS IN UTERINE HORNS.

Gross Pathology :

CECUM :

DISTENDED WITH FLUID, BROWN, severe.

PITUITARY GLAND :

DISCOLORATION, DARK.

No Macroscopic Abnormality Observed :

LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :

NECROSIS, CENTRIOBULAR, mild.

HYPERTROPHY, HEPATOCELLULAR, CENTRIOBULAR, minimal.

KIDNEYS :

HYDRONEPHROSIS, UNILATERAL, minimal.

AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, mild.

SPLEEN :

DEPLETION/ATROPHY, LYMPHOID, mild.

CECUM :

AUTOLYSIS: NO MICROSCOPIC EXAMINATION, severe.

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Date:19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Histopathology :

COLON :
AUTOLYSIS: NECROPSY AND HISTOLOGY PERFORMED, mild.
THYMUS :
NECROSIS, ACUTE, LYMPHOID, severe.
HEMORRHAGE, mild.
PEYER'S PATCH :
NOT PRESENT.
PITUITARY GLAND :
CONGESTION, mild.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
DYSTOCIA.

No Microscopic Abnormality Observed :
LUNGS, HEART, BRAIN, SPINAL CORD, STOMACH, DUODENUM,
JEJUNUM, ILEUM, COLON, RECTUM, MESENTERIC LYMPH NODE,
MANDIBULAR LYMPH NODE, ADRENAL GLANDS, SCIATIC NERVE,
THYROID GLAND, TRACHEA, OVARIES, URINARY BLADDER,
FEMUR/KNEE JOINT, BONE MARROW, CERVIX

ORGANS NOT EXAMINED:
CECUM

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Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref	Microscopic & Macroscopic Findings
822	Terminal Sacrifice Killed on Day : 57 Animal is signed off from necropsy

COMMENT:, IMPLANT SITES = 15 / CORPORA LUTEA = 15.
NO ABNORMALITY DETECTED

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
HYPERTROPHY, HEPATOCELLULAR, CENTRILOBULAR, minimal.
KIDNEYS :
CHRONIC PROGRESSIVE NEPHROPATHY, minimal.
AGGREGATES, LYMPHOID, minimal.
DILATATION, TUBULAR, FOCAL, minimal.
LUNGS :
INFLAMMATION, ALVEOLAR, SUBACUTE/CHRONIC, minimal.
SPLEEN :
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, mild.
CECUM :
INFLAMMATION, MUCOSAL, minimal.

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Date: 19-JUL-04

Individual Animal Listing
Showing animal data for individual animals
STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)
Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

822 Continued from previous page

Histopathology :

MESENTERIC LYMPH NODE :
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS, minimal.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, moderate.
VAGINA :
Diestrus/Anestrus.
BONE MARROW :
HEMATOPOIESIS, INCREASED, mild.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

No Microscopic Abnormality Observed :
HEART, BRAIN, SPINAL CORD, STOMACH, DUODENUM, JEJUNUM,
ILEUM, COLON, RECTUM, MANDIBULAR LYMPH NODE,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, TRACHEA,
OVARIES, UTERUS, URINARY BLADDER, FEMUR/KNEE JOINT, PEYER'S
PATCH, CERVIX

824 Terminal Sacrifice
Killed on Day : 46
Animal is signed off from necropsy

COMMENT: , IMPLANT SITES = 16 / COPORA LUTEA = 16.
NO ABNORMALITY DETECTED

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Date: 19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

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Gross Pathology :

No Macroscopic Abnormality Observed :

LIVER, KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD,
STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM,
MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODE, THYMUS,
ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND, PARATHYROID
GLANDS, TRACHEA, MAMMARY GLAND (FEMALE), OVARIES, UTERUS,
VAGINA, URINARY BLADDER, FEMUR/KNEE JOINT

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
HYPERTROPHY, HEPATOCELLULAR, CENTRIOBULAR, minimal.
MANDIBULAR LYMPH NODE :
HYPERPLASIA, PLASMA CELL, mild.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, minimal.
UTERUS :
IMPLANTATION SITES.
VAGINA :
Diestrus/Anestrus.
CAUSE OF DEATH :
TERMINAL SACRIFICE.

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Date:19-JUL-04

Individual Animal Listing

Showing animal data for individual animals

STUDY : 15031/26200/1422 (* APPROVED PROTOCOL *)

Dose Group : VIII-0 Treatment: 200 mg/kgVIII-0 Sex: Females

Animal Ref Microscopic & Macroscopic Findings

824 Continued from previous page

Histopathology :

No Microscopic Abnormality Observed :
KIDNEYS, LUNGS, HEART, SPLEEN, BRAIN, SPINAL CORD, STOMACH,
DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC
LYMPH NODE, ADRENAL GLANDS, SCIATIC NERVE, THYROID GLAND,
TRACHEA, OVARIES, URINARY BLADDER, FEMUR/KNEE JOINT, BONE
Marrow, PEYER'S PATCH, CERVIX

*** Listing Complete ***