AR226_3263

TRADE SECRET

Study Title

H-25231: One-Generation Reproduction Study in Rats

Volume 1 of 3

Laboratory Project ID: DuPont-9763

AUTHOR: Eve Mylchreest, Ph.D.

STUDY COMPLETED ON: January 31, 2003

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

WORK REQUEST NUMBER: [redacted]

SERVICE CODE NUMBER: [redacted]

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

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

The bulk test substance characterization and stability analyses were performed at DuPont Regional Analytical Services (RAS), a non-GLP laboratory. These analyses were in compliance with regulatory guidelines. None of the aforementioned analyses were performed under Good Laboratory Practice Standards; however, the analyses were conducted in compliance with ISO9002 regulations. All of the analyses are considered valid and sufficient for the purposes of this study.

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

Study Director: _____ 31-Jan-2003
Eve Mylchreest, Ph.D. Date
Senior Research Toxicologist

Applicant / Sponsor: _____ _____
DuPont Representative Date

QUALITY ASSURANCE STATEMENT

Haskell Sample Number(s):

25231

Dates of Inspections:

Protocol: February 25, 2002

Conduct: March 25, 2002; May 2, 2002; June 7,24, 2002; July 9,25, 2002; August 2,5,6,9, 2002

Records, Reports: August 23,25, 2002; September 30, 2002; October 1-4, 2002; December 10-13, 26,27,30,31, 2002; January 2,3, 2003

Dates Findings Reported to:

Study Director: January 7, 2003

Management: January 31, 2003

Reported by: Matthew Frentzel 31-JAN-2003

Matthew T. Frentzel, B.S. Date
Quality Assurance Auditor

CERTIFICATION

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

Analytical Evaluations by: Janet C. Maslanka — 30-JAN-2003
Janet C. Maslanka, B.S.
Senior Staff Chemist — Date

Clinical Pathology Evaluations by: Nancy E. Everds — 29-JAN-2003
Nancy E. Everds, D.V.M.
Diplomate A.C.V.P.
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Anatomic Pathology Evaluations by: John Hansen — 31-Jan-2003
John F. Hansen, D.V.M., Ph.D.
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Anatomic Pathology Evaluations Peer Review by: Steven A. Fitzgerald — 31-JAN-2003
G. Tracy Makovec, D.V.M.
Diplomate A.C.V.P.
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Approved by: Scott E. Loveless — 31-JAN-2003
Scott E. Loveless, Ph.D.
Research Manager and Director — Date

Issued by Study Director: Eve Mylchreest — 31-Jan-2003
Eve Mylchreest, Ph.D.
Senior Research Toxicologist — Date

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STUDY INFORMATION

Substance Tested: [redacted]

Synonyms/Codes: [redacted]
- H-25231

Submitter's Notebook Number(s): [redacted]

Haskell Number: 25231

Composition: [redacted]

Known Impurities: [redacted]

Physical Characteristics: Tan liquid

Stability: The test substance appeared to be stable under the conditions of the study; no evidence of instability was observed.

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

Study Initiated/Completed: March 15, 2002 / (see report cover page)

STUDY PERSONNEL

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SUMMARY

A one-generation reproduction study was conducted with H-25231 [redacted] involving the production of one set of litters. The test material was administered once daily by gavage to groups of male and female Crl:CD®(SD)IGS BR rats (20/group), the P_1 generation, at doses of 0, 75, 500, or 3500 mg/kg/day. Following at least 70 days of dosing, the P_1 generation rats were bred within their respective treatment groups, and allowed to deliver and rear their offspring until weaning (postpartum day 21). At weaning, 20 F_1 rats/sex/group were randomly selected to produce the next generation. Unselected weanling pups underwent a gross pathological examination. The F_1 generation rats were not exposed after weaning. The age of preputial separation and vaginal opening in the F_1 generation rats were evaluated. A clinical pathology evaluation (hematology, clinical chemistry, plasma and urine fluoride in P_1 males only) was conducted on week 10 on the first 10 P_1 rats/sex/group. Estrous cycle and sperm parameters were evaluated in the P_1 generation. At necropsy (P_1 females on postpartum day 21; P_1 males after siring litters [approximately 4 months of exposure], F_1 generation at postnatal day 60), reproductive and target organs were weighed and retained for histopathological examination.

Histopathological examination of reproductive organs (testes, epididymides, seminal vesicles, prostate, and uterus, ovaries, and vagina) was conducted only for P_1 males and females with impaired reproductive performance. Liver, kidney, and thyroid were processed and evaluated microscopically in 10 randomly selected control and high-dose P_1 males and females, and from all control and high-dose F_1 males. Thyroid, the only target tissue in P_1 females, was processed in all control and high-dose F_1 adult females. Target tissues from P_1 and F_1 animals were subsequently processed and evaluated in lower dose groups as needed to determine a no-adverse-effect level.

At 3500 mg/kg/day, effects considered to be related to H-25231 treatment include:

Adverse effects:

- Reductions in weekly mean body weights and body weight gains, overall mean body weight gain, weekly mean food consumption and food efficiency, overall food consumption, and overall food efficiency of P_1 male rats.
- Reductions in weekly mean body weight gain and food consumption of P_1 female rats during premating (test days 1-8) and on gestation days 0-7 and 7-14.
- Low incidences of clinical signs of toxicity in P_1 males (lung noise, salivation, stained fur) and females (salivation), which were generally sporadic.
- Reduction in mean pup weight throughout the entire lactation period for F_1 litters.
- Reductions in weekly mean body weights, body weight gains, and food consumption, overall body weight gain and food consumption of F_1 males.

- Reduction in weekly mean body weights and body weight gains (test days 1-8) of F_1 females.
- Increased mean age of preputial separation and vaginal opening in F_1 rats, which were considered due to reduced body weights and body weight gain during the post-weaning period.
- Potentially adverse, thyroid follicular hypertrophy in P_1 and F_1 males and females.
- Hepatocellular hypertrophy in the liver in P_1 males.
- Chronic progressive nephropathy in the kidney in P_1 males.

Non-adverse effects:

- Minimal decreases in red cell mass parameters (red cell count, hemoglobin, and/or hematocrit) and associated changes (red cell morphology and red cell distribution width) in P_1 males.
- Increased liver and kidney weights in P_1 males and females, and liver weights in F_1 females.
- Increased plasma and urine fluoride in P_1 males, indicating exposure to and metabolism of a fluoride-containing molecule.

At 500 mg/kg/day, effects considered to be related to H-25231 treatment include:

Adverse effects:

- Reductions in weekly mean body weight gains, overall weight gain and overall food consumption of P_1 males.
- Potentially adverse, thyroid follicular hypertrophy in P_1 and F_1 males, and P_1 females.
- Hepatocellular hypertrophy in the liver in P_1 males.
- Chronic progressive nephropathy in the kidney in P_1 males.

Non-adverse effects:

- Minimal decreases in red cell mass parameters (red cell count, hemoglobin, and/or hematocrit) and associated changes (red cell morphology and red cell distribution width) in P_1 males.
- Increased liver and kidney weights in P_1 males, and kidney weights in P_1 females.
- Increased plasma and urine fluoride in P_1 males, indicating exposure to and metabolism of a fluoride-containing molecule.

At 75 mg/kg/day, effects considered to be related to H-25231 treatment include:

Adverse effects:

- Potentially adverse, thyroid follicular hypertrophy in P_1 and F_1 males.

Non-adverse effects:

- Increased liver and kidney weights in P_1 males.
- Increased urine fluoride in P_1 males, indicating exposure to and metabolism of a fluoride-containing molecule.

Under the conditions of this study, a no-observed-effect level (NOEL)[a] was not determined for P_1 and F_1 rats, based on thyroid follicular hypertrophy in P_1 and F_1 adult males at $\geq$75 mg/kg/day. The NOEL for reproductive effects was 500 mg/kg/day, based on reductions in mean pup weights throughout the entire lactation period for F_1 litters at 3500 mg/kg/day.

[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

The test substance, H-25231, is a fluorosurfactant that contains [redacted] The dose levels for this study were selected based on the results from a range-finding study with H-25156[1] in which rats were dosed by oral gavage with 100 mg/kg/day (20 mg/kg/day active ingredient), 500 mg/kg/day (100 mg/kg/day active ingredient), or 2000 mg/kg/day (400 mg/kg/day active ingredient) for 49 days. No body weight effects or clinical signs of toxicity were observed in either males or females at any dose level. Therefore, males exposed to 2000 mg/kg/day had their dose increased to 5000 mg/kg/day (1000 mg/kg/day active) on test day 52. Over an approximate 2-week period, the males dosed with 5000 mg/kg/day had a 10% decrement in body weight compared to control and were subsequently sacrificed on test day 64. The remaining female and male test substance treated groups were sacrificed on test days 49 and 50, respectively, and liver, kidney, and blood were collected from the 100 and 500 mg/kg/day male dose groups. The livers were evaluated histopathologically, while liver enzymes were measured in the blood. No histopathological changes in the liver nor elevated liver enzymes were observed in the 100 or 500 mg/kg/day male dose groups. In addition, kidney weights were not altered, while liver weights in the 500 mg/kg/day male dose group appeared to be increased.

Data are also available from a 45-day range-finding[2] and 90-day gavage study[3] with a similar compound, H-24678, that contains the same active ingredient [redacted] In the range-finding study, rats were administered 10 mg/kg/day (3 mg/kg/day active ingredient), 100 mg/kg/day (30 mg/kg/day active ingredient), 1000 mg/kg/day (350 mg/kg/day active ingredient), or 3000 mg/kg/day (1000 mg/kg/day active ingredient) H-24678. Males exposed to 3000 mg/kg/day exhibited statistically significant lower body weights and reduced body weight gain after 4 weeks of dosing and therefore had their dose lowered to 2000 mg/kg/day (700 mg/kg/day active) for the remaining 2 weeks of the study. Reductions in body weight gain (15% – 20% lower than controls) were also observed in rats exposed to 100 and 1000 mg/kg/day. Liver weights were significantly higher (40%-45%) compared to control rats administered 1000 and 3000/2000 mg/kg/day H-24678. No compound-related effects on organ weight were observed in rats administered 10 or 100 mg/kg/day.

In the 90-day study with H-24678,[3] rats were administered 10 mg/kg/day (3 mg/kg/day active ingredient), 60 mg/kg/day (20 mg/kg/day active ingredient), or 300 mg/kg/day (100 mg/kg/day active ingredient). Small, but statistically significant decrements in body weight parameters, food consumption, and food efficiency occurred in males administered 300 mg/kg/day. Kidney weights were significantly increased in rats administered 60 mg/kg/day H-24678 or higher. Liver weights were also increased in the 300 mg/kg/day female group, while males in the 60 and 300 mg/kg/day groups had elevated liver enzymes.

The high-dose level of 3500 mg/kg/day (700 mg/kg/day active ingredient) was selected for this study and is expected to produce toxicity without excessive mortality. This was based on the results of the H-25156 range-finding study.[1] Rats in the high-dose level were able to tolerate 2000 mg/kg/day (400 mg/kg/day active) yet had a 10% decrement in body weight when compared with control when the dose was increased to 5000 mg/kg/day (1000 mg/kg/day active

ingredient). The low dose of 75 mg/kg/day (15 mg/kg/day active) was expected to be the no-observed-effect-level, while the 500 mg/kg/day (100 mg/kg/day active) dose was expected to induce some toxicity.

OBJECTIVE

The objective of this study was to evaluate the effect of the test substance on the gonadal function, conception, parturition, and growth, and development of male and female Crl:CD®(SD)IGS BR rats over one generation.

MATERIALS AND METHODS

A. Test Substance

The test substance was supplied by the sponsor as a tan liqui[redacted] The test substance appeared to be stable under the conditions of the study. No evidence of instability, such as a change in color or physical state, was observed.

B. Test Species

On March 5, 2002, 107 male and 109 female Crl:CD®(SD)IGS BR rats, with an assigned birth date of January 21, 2002 were received from Charles River Laboratories, Inc., Raleigh, North Carolina for use on this study. A subset of these animals (20 per sex) were used for a study of the time-course of blood fluorine, the results of which may be presented in a separate report.

The rat was selected for this study because it is a preferred species for reproductive toxicity testing as recommended by the guidelines. The Crl:CD®(SD)BR strain was chosen because extensive background information is available from the literature, the supplier, and previous studies with other compounds at DuPont Haskell Laboratory. This strain is also considered suitable relative to longevity, hardiness, and incidence of spontaneous disease.

C. Animal Husbandry

1. Housing

With the exception of the cohabitation periods, all rats were housed one per cage, sexes separate, in stainless steel, wire-mesh cages suspended above cage boards. Animal rooms were maintained on a 12-hour light/dark cycle (fluorescent light) and at a temperature of 22 ± 3°C and a relative humidity of 50% ± 20%. Occasional excursions outside the acceptable ranges were minor and did not affect the study.

Rats were housed as breeding pairs during the cohabitation period. During the gestation period, female rats were housed individually until gestation day 20. Beginning on gestation day 20 for mated females, or at the end of the cohabitation period for females without evidence of

copulation, female rats were housed individually in polycarbonate pans with bedding. During the lactation period, adult female rats were housed with their litters in polycarbonate pans.

2. Feed and Water

Tap water was provided *ad libitum*. All rats, except when fasted, were fed PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002 *ad libitum*.

3. Identification

Prior to assignment to groups, each rat was assigned a temporary cage identification. Subsequently, an individual identification number was tattooed on the tail of each rat. The information on the cage labels included the unique 6-digit Haskell animal number and the individual identification number assigned to each rat. F_1 generation rats retained after lactation were tattooed when they were approximately 21 days old.

4. 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.
- Feed samples are analyzed for total bacterial, spore and fungal counts.
- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

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

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

D. Quarantine and Pretest Period

Upon arrival at Haskell Laboratory, the rats were quarantined for 9 days. The rats were observed daily for any clinically apparent signs of disease or injury and weighed 3 times.

On the basis of acceptable body weight gains and clinical observations, all surviving rats were released from quarantine on test day –5 by the laboratory animal veterinarian designee.

E. Study Design

Treatment Groups and Daily Dosage

Group Number		Number/	Daily Dosage		Active Ingredient
P_1 Male	P_1 Female	Group	(mg/kg/day)[a]	Concentration	(mg/kg/day)
I-0	II-0	20	0	(Control)	0
III-0	IV-0	20	75	(Low)	15
V-0	VI-0	20	500	(Intermediate)	100
VII-0	VIII-0	20	3500	(High)	700

a Weight of test substance per kg of animal body weight.

Treatment Schedule

Generation	Approximate Age at Start of Dosing (days)	Approximate Number of Study Days Before Mating	Duration of Dosing
P_1	55	70	Until sacrifice
F_1	Not applicable	Not applicable	No treatment

Sacrifice Schedule

Animals	Schedule
Adult Males	After siring litters (at discretion of study director)
Pregnant Females	On day of weaning litters
Nonpregnant Females	With pregnant females
Weanlings	All unselected pups will be sacrificed on postnatal day 21
F_1 Adults	At approximately postnatal day 60

F. Assignment to Groups and Study Start

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 ($p > 0.05$).

G. Analytical Methods - Test Substance Administration, Preparation, and Sampling

1. Test substance Administration

The test substance was administered by gavage in order to ensure delivery of known concentrations of the test substance. Animals were dosed once daily for approximately 70 days prior to cohabitation and during the cohabitation period (up to 2 weeks). P_1 male 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 and lactation until their pups were weaned on postpartum day 21. Pregnant females in the process of delivery or showing signs of delivery were not dosed. From gestation day 18 until delivery, dose volumes were based on the gestation day 18 body weights. The volume of test substance or vehicle given to each rat was based on the most recently recorded body weight. Dose volumes were 5 mL/kg. Male and female control rats were similarly treated with deionized water at the same dose volume as used in the other groups.

2. Test Substance Preparation

The test substance was a suspension of active ingredient in vehicle (deionized water). The material was further diluted with vehicle to prepare 3 different concentrations for dosing. Solutions of the test substance in the vehicle were prepared daily and stored at room temperature until used. The method of mixing the test substance with the vehicle is documented in the study records.

3. Sampling

Samples containing H-25231 at the concentrations of 0, 15, 100, and 700 mg/mL were collected on Test Day 2 for uniformity/concentration verification and 5-hour room temperature stability. Since homogeneity and concentration results for the 15 mg/mL samples were not within acceptable ranges, samples containing H-25231 at the concentration of 15 mg/mL along with a 0 mg/mL control were collected on Test Day 9 for repeat analysis of uniformity/concentration verification and 5-hour room temperature stability. Samples at all concentrations were collected on Test Day 46 and Test Day 114 for concentration verification analysis.

All dosing solution samples were collected on the same day the solutions were prepared. The solution vehicle was deionized water.

4. Dosing Solution Treatment

Each 1 mL dosing sample was diluted in 100 mL volumetric with high performance liquid chromatography (HPLC) grade water. The samples were further diluted with 50:50 methanol/water to final concentrations of 0.00045, 0.00050, or 0.00056 mg/mL (0.45, 0.50, or 0.56 ppm) H-25231. Prior to this final dilution, each aliquot was corrected with HPLC grade water so that all samples to be analyzed contained an equivalent amount of water.

Samples submitted for analysis were analyzed the day the solutions were received.

5. Chromatographic Conditions

LC/MS Method

Method (Test Day 2/9)

HPLC Instrument:	Hewlett-Packard Model 1100 HPLC
MS Instrument	Micromass Quattro LC MS with "Z-spray" electrospray

LC parameters:

Column: XTerra®MS C18, 2.1mm x 30mm

Mobile Phase (Time Table), flow rate:

0.00 minutes: 50% methanol/50% 10 mM Ammonium Acetate, 0.25 mL/min.
10.00 minutes: 100% methanol/0% 10 mM Ammonium Acetate, 0.25 mL/min.
16.00 minutes: 100% methanol/0% 10 mM Ammonium Acetate, 0.25 mL/min.
16.01 minutes: 50% methanol/50% 10 mM Ammonium Acetate, 0.30 mL/min.
23.00 minutes: 50% methanol/50% 10 mM Ammonium Acetate, 0.30 mL/min.

Run Time: 23.0 minutes

Flow rate:	(noted above with mobile phase)
Injection Volume:	20 microliter
Oven Temperature:	35°C

MS parameters:

Ionization mode:	Electrospray (ESI), negative ions
Capillary voltage:	2.0 kV
Cone Voltage:	40 V
Source Temperature:	120°
Desolvation Temperature:	300°
Scan function:	SIR: 789, 889, 989, and 1089 m/z time: 0-16 minutes

LC/MS Method

Method (Test Day 47/114)

HPLC Instrument:	Waters Model 2790 HPLC
MS Instrument	Micromass Quattro Micro LC MS with "Z-spray" electrospray

LC parameters:

Columns: XTerra®MS C18, 2.1mm x 30mm and Phenomenex Mercury®MS Luna C18 (2), 2.0mm x 20mm

Mobile Phase (Time Table), flow rate:

0.00 minutes:	50% methanol/50% 10 mM Ammonium Acetate,	0.25 mL/min.
8.00 minutes:	100% methanol/0% 10 mM Ammonium Acetate,	0.25 mL/min.
9.00 minutes:	100% methanol/0% 10 mM Ammonium Acetate,	0.25 mL/min.
9.10 minutes:	100% methanol/0% 10 mM Ammonium Acetate,	0.40 mL/min.
12.00 minutes:	100% methanol/0% 10 mM Ammonium Acetate,	0.50 mL/min.
12.10 minutes:	50% methanol/50% 10 mM Ammonium Acetate,	0.40 mL/min.
18.00 minutes:	50% methanol/50% 10 mM Ammonium Acetate,	0.25 mL/min.

Run Time: 18.0 minutes

Flow rate:	(noted above with mobile phase)
Injection Volume:	20 microliter
Oven Temperature:	35°C

MS parameters:

Ionization mode:	Electrospray (ESI), negative ions
Capillary voltage:	3.5 kV
Cone Voltage:	40 V
Source Temperature:	150°
Desolvation Temperature:	300°
Scan function:	SIR: 789, 889, 989, and 1089 m/z time: 0-10 minutes

6. Calibration and Quantitation

A stock solution of the H-25231 test material (separate samples of H-25231, used as analytical reference) was made in HPLC grade water. Appropriate aliquots of the stock were diluted with 50:50 methanol/water after a correction with HPLC grade water so that an amount equivalent to the dosing samples would be maintained in each diluted standard. These solutions were used as calibration standards that bracketed the target concentration of the diluted dosing samples. Mass to charge ratio (m/z) from LC/MS analysis using negative ion electrospray ionization and selective ion monitoring of these standards over the mass range of 789 to 1089 (m/z = 789, 889, 989, 1089) were used to construct calibration curves by the appropriate regression (see Appendix A, Figure 1a – 1d for representative calibration curves). Measured concentrations for dosing solutions were determined by applying the peak area from replicate injections of the

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samples to each calibration curve. The mean result from the concentrations at all selected m/z (n = 4) is reported as the concentration for the sample.

Test substance uniformity in the vehicle was evaluated by calculating the coefficient of variation (C.V. = standard deviation/mean x 100) of the measured concentrations in duplicate samples for each dosing level. A coefficient of variation of less than or equal to 10% is the standard criterion at Haskell Laboratory for acceptable distribution of the test substance throughout the solution.

However, if the test substance has been shown to be difficult to disperse in the vehicle or the analysis has shown variability, a coefficient greater than 10 may be acceptable.

The mean result of the duplicate samples for each dosing level was used to determine the concentration of the test substance for the respective dosing levels.

Stability was evaluated by using the mean result of the duplicate samples from the concentration verification as the baseline for comparing the corresponding stability results.

H. Body Weights – P_1 Rats

1. Premating Feeding Period

All P_1 rats were weighed once per week.

2. Gestation and Lactation Periods

P_1 female rats were weighed on days 0, 7, 14, and 21 of each period.

Female rats without evidence of copulation, that copulated and did not deliver a litter, and male rats continued to be weighed on a weekly schedule.

I. Food Consumption and Food Efficiency – P_1 Rats

1. Premating and Cohabitation Dosing Periods

Individual food consumption was determined weekly throughout the period, ending test day 75 (reported up to test day 71). Each feeder was weighed at the beginning and end of the 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.

Food consumption was not determined during cohabitation.

2. Gestation and Lactation Periods

Individual food consumption of pregnant P_1 females was recorded on gestation days 0, 7, 14, and 21. Each feeder was weighed at the beginning and end of the 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.

Food consumption was not measured for females without evidence of copulation and for males. Food consumption was not measured during lactation.

J. Detailed Clinical Observations and Mortality – P_1 Rats

Cage-site examinations were conducted at least once daily throughout the study. At least once weekly throughout the premating feeding, gestation, and lactation periods, each of the P_1 parental rats were individually handled and carefully examined for abnormal behavior and/or appearance.

K. Estrous Cycle Evaluation

Vaginal lavage samples were collected daily from all P_1 female rats in order to determine the stages of the estrous cycle. Vaginal lavage samples were collected beginning 3 weeks prior to mating, and continuing until copulation was confirmed, or the cohabitation period ended. Vaginal lavage samples were collected from all P_1 parental female rats at the time of sacrifice. Vaginal lavage samples were examined microscopically for determination of the stage of the estrous cycle (diestrus, estrus, proestrus).

L. Breeding

1. Start of Cohabitation

After 2 weeks of exposure to the test substance

2. Duration of Cohabitation Period

Until evidence of copulation was observed (designated as day 0 of gestation), or 2 weeks had elapsed.

3. 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.

4. Evidence of Copulation

Intravaginal copulation plug or sperm in vaginal lavage sample. Vaginal lavage samples were collected daily from all P_1 female rats that did not have an intravaginal copulation plug in order to determine if there was sperm present in the vagina. Vaginal lavage samples were collected during cohabitation and continued until evidence of copulation was observed or the cohabitation period ended.

M. 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.

N. Lactation Procedures

The day when delivery was complete was designated day 0 postpartum. At each examination period, offspring were individually handled and examined for abnormal behavior and appearance; any dead, missing, or abnormal pups were recorded.

1. Day 0 Postpartum

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

2. Day 4 Postpartum

Litters were culled randomly to 8 (4/sex when possible). Extra offspring were euthanized (by decapitation) and discarded without pathological examination. Litters of 8 offspring or fewer were not reduced. Litter counts were determined prior to and after culling. Individual pup weights were determined prior to culling.

3. Days 7 and 14 Postpartum

Pups in each litter were counted by sex and individually weighed.

4. Day 21 Postpartum (Weaning)

Pups in each litter were counted by sex and individually weighed. Randomly selected weanlings (one/sex/litter) were placed in individual cages and monitored for attainment of developmental landmarks. All unselected pups were then sacrificed and subjected to a gross pathological examination.

O. F_1 Generation

1. Body Weight Measurements

All rats were weighed weekly until termination (approximately postnatal day 60). Rats were also weighed on the day of preputial separation or vaginal opening.

2. Food Consumption and Food Efficiency

Individual food consumption was determined weekly until termination (approximately postnatal day 60). Each feeder was weighed at the beginning and end of the 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 these determinations and body weight data, individual daily food consumption and food efficiency were calculated.

3. Clinical Observations

Cage-site examinations were conducted at least once daily. At least once weekly each rat was individually handled and carefully examined for abnormal behavior and/or appearance.

P. Developmental Landmarks

Developmental landmarks in the F_1 generation male and female rats (one/sex/litter) were monitored on a daily basis until criterion was achieved. Animals were also weighed on the day the developmental landmark was achieved.

1. Vaginal Patency

Female rats were examined once daily beginning on postnatal day 21 until achievement or postnatal day 43, whichever came first.

2. Preputial Separation

Male rats were examined beginning on postnatal day 35 until achievement or postnatal day 55, whichever came first.

Q. Clinical Pathology Evaluation

A clinical pathology evaluation was conducted on week 10 prior to cohabitation on the first 10 rats/sex/group designated for the reproductive evaluation. The day before collection of blood samples for the clinical pathology evaluation, the male rats were placed in metabolism cages. The male rats were fasted overnight (approximately 16 hours) and urine was collected from each rat. Females were fasted, but were not placed in metabolism cages, and urine was not collected. Blood samples for hematology and serum chemistry measurements were collected from the orbital sinus of each animal while the animal was under light carbon dioxide anesthesia. Blood samples for fluoride analysis were collected at sacrifice from the abdominal *vena cava* of male rats only while the animal was under carbon dioxide anesthesia.

1. Hematology

Blood samples were evaluated for quality by visual examination prior to analysis. Complete blood counts, including reticulocytes, were determined on a Bayer® Advia 120 hematology analyzer, or determined from microscopic evaluation of the blood smear. Wright-stained blood smears from all animals were examined microscopically for confirmation of automated results and evaluation of cellular morphology. Blood smears, stained with new methylene blue, were prepared from each animal undergoing a hematology evaluation, but were not needed for evaluation. Bone marrow smears were prepared at the final sacrifice from all surviving animals.

Bone marrow smears were stained with Wright's stain and coverslipped, but analysis was not necessary to support experimental findings.

The following hematology parameters were determined:

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

2. Serum Chemistry

Serum clinical chemistry parameters were measured on a Roche Diagnostics (BMC)/Hitachi® 717 clinical chemistry analyzer. Plasma fluorides were determined using a Φ12 pH meter and a fluoride-selective electrode.

The following serum and plasma clinical chemistry parameters were determined:

aspartate aminotransferase
alanine aminotransferase
sorbitol dehydrogenase
plasma fluoride

3. Urinalysis

Urine volume was measured. Urine fluorides were determined using a Φ12 pH meter and a fluoride-selective electrode.

The following urinalysis parameter was determined:

urine fluoride

R. Anatomic Pathology

1. P_1 Adults

All P_1 parental rats were sacrificed by carbon dioxide asphyxiation and exsanguination, and subjected to gross pathological examination, including those for which mating did not result in the production of offspring. The uteri of all cohabited females were examined for the presence and number of implantation sites.

The following table lists tissues that were weighed and/or collected from P_1 adults:

Tissues Weighed from P_1 Adults

Male	Female	Both Sexes
Testes	Uterus (with oviducts and cervix)	Thyroid Gland[a]
Epididymides	Ovaries	Liver
Seminal Vesicles (with Coagulating glands)		Brain
Prostate		Kidney

Tissues Collected from P_1 Adults

Male	Female	Both Sexes
Testes[b]	Ovaries	Thyroid Gland[a]
Epididymides[b]	Uterus (with cervix and oviducts)	Gross Observations[c]
Prostate		Pituitary Gland
Seminal Vesicles (with Coagulating Gland)	Vagina	Liver
		Kidney

a Thyroid glands were weighed after fixation.

b The right testis and epididymis collected from male rats were placed in Bouin's solution. The left testis and epididymis were frozen for sperm assessment. All other tissues (reproductive and non-reproductive) collected from male and female rats were placed in formalin.

c Gross lesions observed at necropsy for which histopathology was not appropriate or would not be additive were generally not collected.

2. Offspring

Offspring that were found dead during the lactation period underwent a gross pathological evaluation.

3. F_1 Weanlings

All unselected pups, litter size permitting, were sacrificed by carbon dioxide asphyxiation and underwent a gross pathological evaluation on postnatal day 21. Gross lesions were preserved.

4. F_1 Adults

All F_1 generation rats were sacrificed by carbon dioxide asphyxiation and exsanguination, and received a gross pathological examination, including F_1 rats that died (found dead, accidentally killed) or were sacrificed *in extremis* prior to postnatal day 60. Selected tissues and all gross lesions were preserved in appropriate fixative for possible future histopathological examination.

The following tables lists tissues that were collected and/or weighed from F_1 adults:

Tissues Weighed from F_1 Adults

Male	Female	Both Sexes
Testes	Uterus (with oviducts and cervix)	Thyroid Gland[a]
Epididymides	Ovaries	Liver
Seminal Vesicles (with Coagulating glands)		Brain
Prostate		Kidney

Tissues Collected from F_1 Adults

Male	Female	Both Sexes
Testes[b]	Ovaries	Thyroid Gland[a]
Epididymides[b]	Uterus (with cervix and oviducts)	Gross Observations[c]
Prostate		Pituitary Gland
Seminal Vesicles (with Coagulating Gland)	Vagina	Liver
		Kidney

a Thyroid glands were weighed after fixation.
b The testes and epididymides were placed in Bouin's solution. All other tissues (reproductive and non-reproductive) collected from male and female rats were placed in formalin.
c Gross lesions observed at necropsy for which histopathology was not appropriate or would not be additive were generally not collected.

5. Microscopic Evaluations – P_1 and F_1 Rats

Histopathological examination of reproductive organs (testes, epididymides, seminal vesicles, prostate, and uterus, ovaries, and vagina) was conducted only for P_1 males and females with impaired reproductive performance. Gross lesions were saved and evaluated microscopically if they might have been additive to the interpretations of the study. 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 pinnae) were saved, but not processed for microscopic evaluation.

Liver, kidney, and thyroid were processed and evaluated microscopically in 10 randomly selected control and high-dose male and female P_1 rats, and from all F_1 control and high-dose adult males. Thyroid, the only target tissue in P_1 females, was processed in all control and high-dose F_1 adult females. Target tissues from P_1 and F_1 animals were subsequently processed and evaluated in lower dose groups as needed to determine a no-adverse-effect level.

Selected tissues representing gross lesions from 3 F_1 Weanlings were also processed and evaluated microscopically.

S. Sperm Assessment

Sperm parameters for all P_1 parental males were evaluated. The right epididymis was removed and weighed. The right cauda epididymis was weighed, excised, and placed in 32°C phosphate buffered saline with 10 mg/mL bovine serum albumin, pricked with a needle to facilitate the release of sperm, and placed in an incubator at 32°C for 5 minutes. After incubation, an aliquot was placed in a sample chamber which was loaded into a Hamilton Thorne Integrated Visual Optical System (IVOS). The percentage of motile cells among at least 200 cells examined per animal were determined.

After removal of an aliquot of sampling for videotaping, the right cauda epididymis was further incubated for approximately 15 minutes. An aliquot was stained with eosin, and smears were prepared on microscope slides. Sperm smears were examined to determine the frequency of morphologically abnormal sperm, expressed as percentage of normal cells among at least 200 cells examined per animal. The specific types of abnormal morphologies, if any, were not categorized. The excised right cauda and the right caput and corpus epididymis were then placed in Bouin's solution.

The left epididymis and left testis, following removal, were flash frozen in liquid nitrogen and stored at –65° to –85°C until analyzed. After thawing, the cauda epididymis was excised, weighed, and homogenized. After thawing, the testis was weighed and homogenized. Sperm count per cauda epididymis and per gram cauda epididymis, and spermatid count per testis and per gram testis were determined using the IVOS.

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T. Statistical Analyses

The following table lists the indices of reproductive function that were calculated for the P_1 and F_1 adults.

Reproductive Function Calculations

Mating Index (%)	=	Number Copulated[a] / Number Cohabited	x 100
Fertility Index (%)	=	Number Pregnant[b] / Number Copulated[a]	x 100
Gestation Index (%)	=	Number of Litters with at Least One Live Pup / Number of Litters	x 100
Implantation Efficiency (%)[c]	=	Number of Pups Born / Number of Implantation Sites	x 100
Pups Born Alive (%)[c]	=	Number of Pups Born Alive / Number of Pups Born	x 100
Viability Index (%)[c,d]	=	Number of Pups Alive Day 4 Preculling / Number of pups born alive	x 100
Lactation Index (%)[c,d]	=	Number of pups alive at weaning (Day 21 postpartum) / Number of pups alive Day 4 Postculling	x 100
Litter Survival (%)[d]	=	Number of litters weaned / Number of viable litters delivered	x 100

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

Statistical Methods

Parameter	Preliminary Test	Method of Statistical Analysis: If preliminary test is not significant	Method of Statistical Analysis: If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Gestation Length Implantation Site Numbers Implantation Efficiency Mean Number of Pups Per Litter Percent Born Alive Precoital Interval Vaginal Patency Preputial Separation Litter Survival 0-4 Day Viability Lactation Index Organ Weight	Test for lack of trend[4]	Sequential application[5] of the Jonckheere-Terpstra trend test[6]	Preliminary tests for pairwise comparison
	OR[a]		
	Levene's test for homogeneity[7] and Shapiro-Wilk test[8] for normality[b]	One-way analysis of variance[9] and Dunnett's test[10]	Kruskall-Wallis test[11] and Dunn's test[12]
Food Efficiency	None	One-way Analysis of Variance[9] followed with Dunnett's test[10]	
Clinical Pathology	Levene's test for homogeneity[7] and Shapiro-Wilk test[8] for normality[b]	One-way analysis of variance[9] followed with Dunnett's test[10]	Kruskall-Wallis test[11] followed with Dunn's test[12]
Incidence of Clinical Observations Mating Index Fertility Index Gestation Index Viability Index	None	Cochran-Armitage test for trend[9]c	
Mean Pup Weights (Covariates: litter size, sex ratio) Sex Ratio	None	Linear contrast of least squares means[13]	Dunn's test[12]
Vaginal Patency (covariates: body weight) Preputial Separation (covariates: body weight)	Shapiro-Wilk test[8] for normality	Analysis of covariance[d][14]	Dunnett-Hsu[15]

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

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

c 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.

d A stepwise regression was used to determine which variables (body weight parameters) in addition to dose were significantly explanatory).[4]

For each parameter analyzed with a trend test, the test was applied to the data sequentially. If a significant dose-response was detected, data from the top dose group was excluded and the test repeated until no significant trend was detected.[5] For litter parameters, the proportion of affected fetuses per litter or the litter mean was used as the experimental unit for statistical evaluation.[17] The level of significance selected is $p < 0.05$. Additional statistical tests were used, and other parameters analyzed, as deemed necessary.

Where the data were tied and the standard large sample version of Jonckheere's test[6] was not applicable, exact p values were calculated using permutation methodology.[18]

RECORDS AND SAMPLE STORAGE

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.

A sample of the test substance was collected for archive purposes and retained at Haskell Laboratory. Specimens, raw data, and the final report will be retained at Haskell Laboratory, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware. Raw data will be retained at Haskell Laboratory, Newark, Delaware. Characterization data (percent purity, composition, and known impurities) will be stored at Regional Analytical Services (RAS), Jackson Laboratories, Deepwater, New Jersey. Characterization data used to support test substance stability will be retained at Haskell Laboratory, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware.

RESULTS AND DISCUSSION

ANALYTICAL

A. Chromatography
(Appendix A)

H-25231 eluted from the HPLC column as resolved peaks over mass to charge ratio (m/z) range of approximately 789 to 1089. For the purpose of quantitation, the m/z ratios of 789, 889, 989, 1089 for the "bis" substituted components [redacted] were determined to be representative of the H-25231 in the dosing matrix. Representative LC/MS chromatograms are shown in Appendix A, Figures 2(a - c). Test substance was not detected in the 0 mg/mL control.

B. Dosing Solution Analyses
(Table 1, Appendix A)

1. Concentration Verification and Stability Samples

Analytical results from dosing solutions prepared Test Day 2 and Test Day 9 (15.0 mg/mL, only) analyzed for uniformity/concentration verification and stability are shown in Summary Table 1 and Appendix A, Table I.

The following table summarizes the results for uniformity/concentration verification and stability analyses for the H-25231 sample preparation on Test Days 2 and 9.

Preparation Day	Nominal[a] mg/mL	Measured[b] mg/mL	Average % Nominal	CV %	Stability[c] % Nominal
Test Day 2	15	8.72[d], 12.8	72.0	27	72.0[d]
	100	91.6, 97.2	94.4	4	87.7
	700	715, 668[e]	98.8	5	108.4[e]
Test Day 9	15	12.7[d], 15.6[e]	94.7	14	110.0

a Dosing solution concentration mg H-25231/mL, based on 5 mL dose volume. H-25231 is approximately [redacted]
b Duplicate samples analyzed.
c Stability samples held for 5 hours at room temperature. Percent Nominal based on measured.
d Reported result based on all analysis from the original samples.
e Reported result based on duplicate reanalysis of the original sample.

The results for H-25231 samples prepared on Test Day 2, show that the test substance was adequately mixed (CV's less than 10) except at the 15 mg/mL level (CV = 27), at the targeted levels (target = ± 5.6% of nominal) except for the 15 mg/mL level (72% of nominal), and stable in the vehicle when held 5 hours at room temperature. An additional sample of the 15 mg/mL level was taken on Test Day 9 for repeat analysis since the results for the Test Day 2 sample did

not meet concentration and homogeneity acceptability criteria. The results for H-25231 sample prepared on Test Day 9 of the 15 mg/mL level, show that the test substance was adequately mixed (CV = 14), at the targeted levels (target = ± 5.3% of nominal), and stable in the vehicle when held 5 hours at room temperature. Test substance was not detected in the 0 mg/mL samples.

2. Concentration Verification Samples

Analytical results from dosing solutions prepared Test Day 46 and Test Day 114 and analyzed for concentration verification are shown in Summary Table 1 and Appendix A, Table II.

The following table summarizes the results for concentration verification analyses for the Test Days 46 and 114 of the H-25231 sample preparation.

Preparation Day	Nominal[a] mg/mL	Measured[b] mg/mL	Average % Nominal	CV %
Test Day 46	15	15.1, 16.6	106.0	7
	100	112, 113	113.0	1
	700	749, 666[c]	101.1	8
Test Day 114	15	16.5, 12.9[c]	98.0	17
	100	107, 120	114.0	8
	700	765, 681	103.3	8

a Dosing solution concentration mg H-25231/mL, based on 5 mL dose volume. H-25231 is approximately [redacted]
b Duplicate samples per level were analyzed. C.V. calculated to verify uniformity of mixture.
c Reported result based on duplicate reanalysis of the original sample.

The results for samples prepared on Test Days 46 and 114 indicate that the test substance was adequately mixed except for the 15 mg/mL level on Test Day 114 which was marginal and at the targeted levels (target = ± 14.0% of nominal) for all H-25231 samples. Test substance was not detected in the 0 mg/mL sample.

C. Analytical Conclusions

Results from the analysis of the test substance dosing solutions during the study indicate that the test substance was mixed properly except for the 15 mg/mL level on Test Day 2 but was acceptable on Test Day 9, 46, and marginally acceptable on Test Day 114, at the targeted levels except for the 15 mg/mL level on Test Day 2 and stable under the conditions of the study. Test substance was not found in the 0 mg/mL samples. The results obtained on Test Day 2 are not believed to have impacted the study since the repeat sampling on Test Day 9 and subsequent samplings showed acceptable results.

REPRODUCTIVE TOXICITY EVALUATIONS

IN-LIFE TOXICOLOGY

A. P_1 Rats - Mean Body Weights and Body Weight Gains

1. P_1 Males:
(Tables 2-3, Appendices B-C)

There were test substance-related reductions in body weights at 3500 mg/kg/day and body weight gains at ≥500 mg/kg/day. At 3500 mg/kg/day, mean body weight gain was reduced for much of the dosing period. As a result, weekly mean body weights were consistently reduced throughout the dosing period, and mean final body weight (test day 113) and overall weight gain (test days 1-113) were 80% and 64% of the control mean, respectively. At 500 mg/kg/day, there were transient reductions in body weight gain; the most evident of these occurred on test days 1-8, 15-22, 43-50, 85-92, and 92-99. As a result, mean final body weight (test day 113) and overall weight gain (test days 1-113) were 94% and 88% of the control mean, respectively.

2. P_1 Females:
(Tables 4-9, Appendices D-G)

There were test substance-related reductions in body weight gain at 3500 mg/kg/day. Mean body weight gain was reduced during premating, on test days 1-8 and 36-43, and on gestation days 0-7 and 7-14. These sporadic reductions in weight gain did not affect overall weight gain during premating (95% of control mean on test days 1-71) or gestation (95% of control mean on gestation days 0-21). Overall mean body weight gain during lactation was increased at 3500 mg/kg/day (226% of control mean on lactation days 0-21) and was mainly due to a mean body weight change that was 165% of control on lactation days 14-21. This finding was considered spurious and not biologically meaningful.

B. P_1 Rats - Food Consumption and Food Efficiency

1. P_1 Males:
(Tables 10-11, Appendix H)

There were test substance-related reductions in food consumption and food efficiency at 3500 mg/kg/day. Mean food consumption was reduced (89%-98% of the control mean) for much of the premating period. As a result, overall food consumption for this period (test days 1-71) was 93% of the control mean. Mean food efficiency was reduced (89%-98% of the control mean) for much of the premating period. As a result, overall food consumption for this period (test days 1-71) was 93% of the control mean.

2. P_1 Females:
(Tables 12-15, Appendices I-J)

There were test substance-related reductions in food consumption at 3500 mg/kg/day. Mean food consumption was reduced during premating, on test days 1-8, and on gestation days 0-7 and 7-14. These sporadic reductions in food consumption did not affect overall food consumption during premating (98% of control mean on test days 1-71) or gestation (93% of control mean on gestation days 0-21).

C. P_1 Rats - Clinical Observations and Mortality

1. P_1 Males:
(Table 16, Appendix K)

There was no test substance-related mortality. Two animals died as a result of gavage trauma; one in the 3500 mg/kg/day group on test day 42 and one in the 500 mg/kg/day group on test day 86. One animal in the 3500 mg/kg/day group was found dead on test day 66. This death was considered possibly due to gavage trauma since the lungs had red discoloration and congestion, and prior to sacrifice this animal did not display any significant reduction in body weight gain or food consumption, or show any overt signs of toxicity except for intermittent salivation. One animal in the control group was sacrificed *in extremis* on test day 60; prior to sacrifice this animal displayed reduced body weight gain and body weight loss as a result of a sore on shoulders/neck.

There were test substance-related clinical observations at 3500 mg/kg/day that consisted of low incidences of "lung noise," "salivation," "stained nose," and "stained perineum," which were generally sporadic. The salivation occurred after dosing and was not considered indicative of neurological effects since previous studies with this active ingredient showed no signs of neurotoxicity.

2. P_1 Females:
(Tables 17-19, Appendices L-N)

There was no mortality at any dose level. There were test substance-related clinical observations during premating at 3500 mg/kg/day that consisted of low incidences of sporadic salivation. There were no test substance-related clinical observations during gestation or lactation at any dose level. The salivation occurred after dosing and was not considered indicative of neurological effects since previous studies with this active ingredient showed no signs of neurotoxicity.

D. Sperm Parameters
(Table 20, Appendices O-Q)

There were no test substance-related effects on sperm motility, morphology, epididymal sperm or testicular spermatid numbers at any dose level. The percent normal sperm was statistically significantly reduced at 500 and 3500 mg/kg/day (98.3% and 98.3% vs. 99.1% for the control group). These changes were considered spurious due to their small magnitude and values were within the historical control range at Haskell Laboratory.

Historical Control Data for Haskell Laboratory 1999-2001

Study Start Date	Sperm Morphology (% Normal)
Mar-01	98.3
Dec-00	98.8
Sep-00	98.6
Jun-00	98.0
Jan-00	97.7
Mar-99	98.0
Apr-99	96.1
Jul-99	99.2
Mean	98.1
Standard Deviation	0.9
Minimum	96.1
Maximum	99.2

E. Estrous Cycle Parameters and Precoital Interval in P_1 Females
(Table 21, Appendices R-S)

There were no test substance-related effects on percent days in estrus, diestrus, or proestrus, mean cycle length, or precoital interval at any dose level.

F. Reproductive Indices
(Table 22, Appendices T-U)

There were no test substance-related effects on mating, fertility, gestation length, number of implantation sites, or implantation efficiency at any dose level. The P_1 generation fertility index was lower (not statistically significant) than the control group at 3500 mg/kg/day (75% vs. 90% for the control group). Implantation efficiency was statistically significantly reduced at 3500 mg/kg/day (93% vs. 96.9% for the control group). These changes were considered spurious due to the small magnitude, the unusually high implantation efficiency in the control group, and values were within the historical control range at Haskell Laboratory. These findings were not associated with any test substance-related change in other reproductive parameters in affected animals (implantations, litter size, pup viability, estrous cycle or sperm parameters, or reproductive organ histopathology).

Historical Control Data for Haskell Laboratory 1994-2002

Study Start Date	Fertility Index (%)	Implantation Efficiency(%)
Feb-02	100.0	93.8
Mar-01	85.0	90.0
Dec-00	72.2	96.6
Sep-00	90.0	91.2
Jan-00	87.5	92.1
Oct-98	75.0	84.4
Mar-97	90.0	93.4
Jul-95	93.3	90.2
Apr-94	93.1	90.7
Jan-94	82.1	86.3
Mean	86.8	90.9
Standard Deviation	8.5	3.5
Minimum	72.2	84.4
Maximum	100.0	96.6

G. F_1 Offspring Data

1. Litter Size, Sex Ratio and Pup Survival
(Table 23, Appendix V)

There were no test substance-related effects on the number of pups born, born alive, alive on day 4, 7, 14, or 21, nor were there any effects on sex ratio, or survival indices during the lactation period.

2. Pup Weights
(Table 24, Appendix W)

There was a test substance-related effect on pup weights at 3500 mg/kg/day. Mean pup weights were reduced during the lactation period and were 91%, 86%, 77%, and 76% of the control mean on lactation days 0, 7, 14, and 21, respectively. There was a test substance-related increase in the incidence of small whole body in F_1 pups that were sacrificed at weaning (5 vs. 0 pups in the control group) (see Gross Pathology Tables and Appendices for weanling rats).

3. Clinical Observations in F_1 Pups
(Table 25, Appendix X)

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

H. F_1 Rats - Mean Body Weights and Body Weight Gains
(Tables 26-29, Appendices Y-Z)

There were test substance-related reductions in body weights and body weight gain in males and females at 3500 mg/kg/day. Consistent with the reduction in pup weight at the end of lactation, mean body weights on the day of weaning (test day 1 or postnatal day 21) were also reduced (76% and 79% of control in males and females, respectively). Weekly mean body weight gains were reduced throughout much of the post-weaning period in males (76%-91% of control mean). As a result, weekly mean body weights were consistently reduced throughout the post-weaning period, and mean final body weight (test day 36) and overall weight gain (test days 1-36) were 87% and 89% of the control mean, respectively. Weekly mean body weight gain was reduced for the first week after weaning in females (86% of control mean on test days 1-8); however, mean final body weight and overall body weight gain were unaffected.

I. F_1 Rats - Food Consumption and Food Efficiency
(Tables 30-33, Appendix AA)

There were test substance-related reductions in food consumption in males at 3500 mg/kg/day. Mean food consumption was reduced (81%-91% of the control mean) for the first 3 weeks of the post-weaning period in males. As a result, overall food consumption for this period (test days 1-36) was 91% of the control mean. Mean food efficiency was not affected at any dose level.

J. F_1 Rats - Clinical Observations and Mortality
(Tables 34-35, Appendix BB)

There was no test substance-related mortality nor were there any clinical signs of toxicity in any group. One female in the 3500 mg/kg/day group was found dead on test day 7 (postnatal day 27); on the day prior to death this animal was weak and hunched over. One male in the 3500 mg/kg/day group was also weak and hunched over on test day 6. The mortality and clinical signs were considered spurious due to the low incidence.

K. F_1 Rats - Developmental Landmarks
(Table 36, Appendix BB)

There were no test substance-related effects on developmental landmarks. The mean age of preputial separation (45.333 days for the 3500 mg/kg/day group vs. 42.778 days for the control group) and vaginal opening (33.786 days for the 3500 mg/kg/day group vs. 31.772 days for the control group) were increased in the 3500 mg/kg/day groups. These changes were not considered to be due to the test substance but rather an indirect effect of the reduced body weights and body weight gain during the post weaning period.

L. Reproductive In-Life Toxicology Conclusions

The NOEL for reproductive toxicity in this study was 500 mg/kg/day, based on reductions in F_1 pup weights during lactation at 3500 mg/kg/day.

CLINICAL PATHOLOGY EVALUATIONS

A. Hematology
(Tables 37-38, Appendix CC)

There were no adverse changes in hematology parameters in rats dosed with the test substance. All statistically significant changes in hematology parameters were considered unrelated to treatment and/or non-adverse (not toxicologically significant). These changes are detailed below.

- Red cell mass parameters (red cell count, hemoglobin, hematocrit) were minimally decreased in males dosed with 75, 500, or 3500 mg/kg/day (variable statistical significance). There was a lack of a dose-response relationship in red cell mass effects despite the nearly 50-fold difference in dose between the low and high dose, and the presence of a clear dose-relationship in other parameters indicating exposure to the compound (plasma and urine fluoride). However, the changes at 500 and 3500 mg/kg/day were considered to be probably related to treatment because there was a minimal increase in red cell morphologic changes (anisocytosis, microcytosis, and hypochromasia) in males dosed with 500 or 3500 mg/kg/day, and mildly increased red cell distribution width at 3500 mg/kg/day, indicating a possible dose-related effect. The magnitude of change in all red cell parameters was small, and therefore, was considered to be non-adverse

- White cell counts were minimally increased in females dosed with 75, 500, or 3500 mg/kg/day (statistically significant only at 3500 mg/kg/day). Increased white cell counts were the result of statistically increased lymphocytes (females dosed with 75 or 3500 mg/kg/day only) and eosinophils (females dosed with 3500 mg/kg/day only). There was a lack of a dose-response relationship in white cell effects despite the nearly 50-fold difference in dose between the low and high dose. There were no other clinical pathology or histologic changes (e.g. inflammation) that correlated with these minimal changes. In addition, for those mean leukocyte counts (total and individual cell types) that were statistically significant, individual counts were generally within or just outside the reference range for individual control rats.[a] Therefore, these changes were considered unlikely to be related to treatment and non-adverse.

[a]The 2.5-97.5 percentile counts for female rats aged 19 weeks, reported as cells/uL, are WBC 4.92-13.25; ALYM 3.83-10.41; AEOS 0.06-0.22).[19]

B. Clinical Chemistry
(Tables 39-40, Appendix CC)

There were no adverse changes in serum clinical parameters in rats dosed with the test substance. Statistically significant changes in serum clinical chemistry parameters were considered unrelated to treatment and/or non-adverse (not toxicologically significant). These changes are detailed below.

- Alanine aminotransferase activity was minimally increased in males dosed with 75, 500 (not statistically significant), or 3500 mg/kg/day. There was a lack of a dose-response relationship in this effect despite the nearly 50-fold difference in dose between the low and high dose, and the presence of a clear dose-relationship in other parameters indicating exposure to the compound (plasma and urine fluoride, hepatocellular hypertrophy). In addition, the control mean is near the low end of the laboratory historical range for mean alanine aminotransferase activity in males of approximately the same age.[a] Therefore, although it is possible that the changes in alanine aminotransferase activity are related to treatment, it is more likely that the apparent increased activity in the treated group was due to the unusually low mean activity in the control group.

C. Plasma and Urine Fluoride
(Tables 39 and 41, Appendix CC)

Plasma and urine fluoride were measured in males only. Plasma fluoride was increased in males dosed with 500 or 3500 mg/kg/day, while urine fluoride was increased in males dosed with 75 (not statistically significant), 500, or 3500 mg/kg/day (Clinical Pathology Text Table 1). These changes occurred in a dose-related manner. Increases in plasma and urine fluoride indicate exposure and metabolism of a fluoride-containing molecule.

Clinical Pathology Text Table 1: Mean urine and plasma fluoride for males

Parameter (units)	Dose (mg/kg/day)			
	0	75	500	3500
PFLU (ug/mL)	0.1	0.1	***0.2***	***0.4***
% of control mean	NA	100%	***200%***	***400%***
UFLU (ug)	12.1	53.9	***176.1***	***512.4***
% of control mean	NA	445%	***1455%***	***4235%***

Statistical significance is indicated by bold italicized type.

[a] Means alanine aminotransferase activity for younger males (12-14 weeks old) is 28-50 U/L, while that for older males (30-65 weeks old) is 30-65 U/L.[20]

D. Clinical Pathology Conclusions

There were no adverse changes in clinical pathology parameters. Therefore, under the conditions of this study and for the clinical pathology parameters measured, the no-adverse-effect level was 3500 mg/kg/day for males and females, the highest dose administered, based on the lack of adverse findings at this dose.

Treatment related but non-adverse changes included minimally decreased red cell mass parameters, increased red cell distribution width (3500 mg/kg/day only), and increased red cell morphology in males dosed with 500 or 3500 mg/kg/day. In addition, increased plasma and urine fluoride measurements were observed in males dosed with 75 (urine fluoride only), 500, or 3500 mg/kg/day; the presence of fluoride in plasma and urine indicates exposure to and metabolism of a fluoride-containing molecule.

ANATOMICAL PATHOLOGY

A. Mortality
(P_1 Adult Rats - Appendices K, L-N, and FF)
(F_1 Adult Rats – Appendices BB and GG)

There were no test substance-related deaths in the study.

B. Organ Weight Data
(P_1 Adult Rats - Tables 42-43, Appendix DD)
(F_1 Adult Rats – Tables 44-45, Appendix EE)

There were statistically significant test substance-related higher mean liver and kidney weights in male and female P_1 rats as listed in the following table:

Test Substance-Related Organ Weight Effects In P_1 Males and Females

Dose Group:	75 mg/kg/day		500 mg/kg/day		3500 mg/kg/day	
Organ	Male	Female	Male	Female	Male	Female
Liver (absolute weight)	---	---	---	---	↑	↑
Liver (relative to body)	↑	---	↑	---	↑	↑
Liver (relative to brain)	---	---	↑	---	↑	↑
Kidneys (absolute)	---	---	---	---	↑	↑
Kidneys (relative to body)	↑	---	↑	↑	↑	↑
Kidneys (relative to brain)	↑	---	↑	---	↑	↑

Higher liver weights in P_1 rats correlated with microscopic hepatocellular hypertrophy and was considered non-adverse (see discussion in Microscopic Findings). There was no microscopic correlate for higher kidney weight. Higher kidney weight was most likely due to hypertrophy, which was below the threshold of microscopic detection, and was considered non-adverse. Other statistically significant organ weight changes (lower absolute, relative to brain and/or higher relative to body) in the epididymides, seminal vesicles, prostate and/or brain in P_1 males from the high dose group were interpreted to be the result of lower final body weight in that group and not test substance-related.

The mean relative (to body) liver weight was significantly higher than the control in the high dose female F_1 adults, and was considered a test substance-related effect. There was no microscopic correlate and the small weight increase was most likely due to hepatocellular hypertrophy that was below the threshold of microscopic detection. This weight change was considered a non-adverse finding (See discussion of hepatocellular hypertrophy in Microscopic findings section).

There were no other test substance-related organ weight effects in F_1 adult rats. Other significant organ weight changes (lower absolute, relative to brain and/or higher relative to body) in the testes, epididymides, and/or prostate in F_1 males from the high dose group were interpreted to be the result of lower final body weight in that group and not test substance related. Prostate weight from one high dose male rat (Animal No. 660638) was removed from the weight calculations due to a weighing error.

C. Gross Findings
(P_1 Adult Rats –Tables 46-47, Appendix FF)
(F_1 Adult Rats – Tables 48-49, Appendix GG)
(Weanlings – Table 50-51, Appendix HH and II)
(Pups – Tables 52-53, Appendix II)

There were no test substance-related gross observations in adult P_1, F_1, or in weanling rats. Gross observations occurred in low incidences and were randomly distributed across control and treatment groups.

Observations in pups of "lungs not expanded," and "no milk spot in the stomach," are nonspecific lesions that are commonly seen in all pups that are born dead, and thus are not considered to be compound-related. Pup viability and mortality are discussed elsewhere in this report.

D. Microscopic Findings
(P_1 Adult Rats – Tables 54-55; Appendix FF)
(F_1 Adult Rats – Tables 56-57, Appendix GG)
(Weanling Female Rats – Table 58, Appendix HH)

1. P_1 Adult Rats (P_1 Adult Rats – Tables 54-55; Appendix FF)

Hepatocellular hypertrophy in the liver and chronic progressive nephropathy in the kidney were increased in incidence in P_1 males from the 500 and 3500 mg/kg/day dose groups, and were interpreted to be test substance-related. Hepatocellular hypertrophy depicted hepatocytes with enlarged eosinophilic cytoplasm with intact hepatic cords and was interpreted to be an adaptive physiological response to exposure to a xenobiotic, and not biologically adverse. Chronic progressive nephropathy depicted basophilic staining of tubular epithelium, often with enlarged nuclei, sometimes accompanied by a minimal inflammatory component and minimal peritubular stromal thickening. Chronic progressive nephropathy occurs commonly as a spontaneous lesion in rats and the increased incidences noted in the current study represent a compound-related earlier onset of a typical age-related finding. The severity of this lesion was minimal in treated and in control animals and was unaccompanied by any correlative adverse clinical pathology findings (see Clinical Pathology portion of this report). Kidney changes in P_1 males administered 500 mg/kg/day and above were considered adverse findings.

Thyroid follicular hypertrophy was increased in incidence in all dose groups of P_1 males (75 mg/kg/day and higher) and in females in the intermediate and high (500 and 3500 mg/kg/day)

dose groups. Hypertrophy was generally minimal in severity with moderate severity diagnosed in 2 males (one 500 mg/kg/day and one 3500 mg/kg/day). Follicular hypertrophy was diagnosed when the follicular epithelium was tall columnar with a finely granular cytoplasm. Thyroid hypertrophy was considered test substance-related and potentially adverse.

Thyroid follicles containing altered colloid were found in thyroids from controls as well as treated animals. An increase in incidence and/or an increase in the number of affected follicles, and thus grade, was interpreted to be treatment-related. Altered colloid described as clumped or granular has been reported to occur spontaneously in Sprague-Dawley rats with increasing incidence with increasing age.[21] Thus, alterations in colloid are known to occur spontaneously in the Sprague-Dawley rat. In the present study, there was only a treatment-related increase in grade and not in incidence of the observation for P_1 males at all dose levels. There was an increase in the incidence of altered colloid in the 500 and 3500 mg/kg/day group P_1 females.

There was no consistent association between the presence or absence of altered colloid with follicles that were lined by hypertrophic or non-hypertrophic follicular cells.

Because altered colloid occurs spontaneously in healthy Sprague-Dawley rats, and because increases in its grading score did not correlate with degenerative morphologic observations, altered colloid was interpreted in the present study as not biological meaningful and not adverse.

2. F_1 Adult Rats (F_1 Adult Rats – Tables 56-57, Appendix GG)

Minimal hypertrophy of thyroid follicular epithelium was increased in incidence in F_1 adult males at all test substance dose groups and in one F_1 adult female from the 3500 mg/kg/day dose group. Altered colloid was detected in very few animals across dose groups and was not considered to be test substance-related in the F_1 adults. Thyroid hypertrophy was considered test substance-related and potentially adverse. The character and severity of thyroid hypertrophy was very similar between affected P_1 and F_1 animals. In females, the NOEL for thyroid changes was higher in the F_1 generation compared to the P_1 generation.

3. F_1 Weanlings (Weanling Female Rats – Table 58, Appendix HH)

There were no test substance-related findings in the weanlings examined. The few lesions present (hydronephrosis, bone fracture, urinary bladder inflammation with mucosal hyperplasia) are commonly observed spontaneous or incidental lesions in this age and strain of rat.

j. Anatomic Pathology Conclusions

The no-observed-adverse-effect level (NOEL) for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Under the conditions of this study, based on hypertrophy of thyroid epithelium, the NOEL for pathology was not determined in P_1 and F_1 adult males, was 75 mg/kg/day for P_1 adult females, and was 500 mg/kg/day for F_1 adult females.

CONCLUSIONS

Under the conditions of this study, a no-observed-effect level (NOEL)[a] was not determined for P_1 and F_1 rats, based on thyroid follicular hypertrophy in P_1 and F_1 adult males at $\geq$75 mg/kg/day. The NOEL for reproductive effects was 500 mg/kg/day, based on reductions in mean pup weights throughout the entire lactation period for F_1 litters at 3500 mg/kg/day.

[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 [22] and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union.[23]

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TABLES

TABLES

EXPLANATORY NOTES

Notes

Test Days 1-75 = Premating period
Test Days 76-90 = Cohabitation period

Abbreviations - Clinical Pathology

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 Serum and Plasma Chemistry Values

AST - aspartate aminotransferase
ALT - alanine aminotransferase
SDH - sorbitol dehydrogenase
PFLU - plasma fluoride

Summary of Urinalysis Values

UFLU - urine fluoride

TABLE 1

SUMMARY OF DOSING SOLUTION ANALYSES

Sample Type	Dosing Concentrations and Stability of H-25231 (mg/mL)[a]		
Test Day 2 Nominal:	15	100	700
Concentration Verification	8.72[b]	91.6	715
	(58.1)[c]	(91.6)	(102.1)
	12.8	97.2	668[d]
	(85.3)	(97.2)	(95.4)
Average Measured Conc.[e]	**10.8**	**94.4**	**691**
Average Percent Nominal[e]	**(72.0)**	**(94.4)**	**(98.8)**
Standard Deviation[e]	**± 2.9**	**± 4.0**	**± 33**
Coefficient of Variation[e]	**27%**	**4%**	**5%**
Stability			
0-Day Room Temperature[f]	**10.8**	**94.4**	**691**
	(72.0)	**(94.4)**	**(98.8)**
5-hour Room Temperature[g]	10.8	87.7	759
	(72.0)	(87.7)	(108.4)
Test Day 9			
Concentration Verification	12.7[b]	----[h]	----[h]
	(84.7)		
	15.6[d]	----[h]	----[h]
	(104.0)		
Average Measured Conc.[e]	**14.2**		
Average Percent Nominal[e]	**(94.7)**		
Standard Deviation[e]	**± 2.0**		
Coefficient of Variation[e]	**14%**		
Stability			
0-Day Room Temperature[f]	**14.2**		
	(94.7)		
5-hour Room Temperature[g]	16.5	----[h]	----[h]
	(110.0)		
Concentration Verification[i]			
Test Day 46	15.9	113	708[b]
	(106.0)	(113.0)	(101.1)
Test Day 114	14.7[b]	114	723
	(98.0)	(114.0)	(103.3)

a Dosing solution concentration mg H-25231/mL based on 5 mL dose volume. H-25231 is approximately [redacted]
b Mean result for all analysis on the original sample.
c Numbers in parentheses are the respective percent of nominal values.
d Mean result for duplicate reanalysis of the original sample.
e Mean, S.D. and C.V. for duplicate samples calculated to verify uniformity of mixture.
f Mean result for Test Day 2/9 concentration verification samples used for baseline for stability samples.
g Samples (Test Day 2/9) held at room temperature for 5 hours.
h Samples not submitted at 100 mg/mL and 700 mg/mL levels.
i Duplicate samples submitted. Mean result reported.

TABLE 2

MEAN BODY WEIGHTS (grams) OF P_1 MALE RATS

Group:	I-0	III-0	V-0	VII-0
Dose (mg/kg/day):	0	75	500	3500
Test Day				
1	280.705 11.038(19)	282.150 16.254(20)	280.095 17.039(20)	280.950 13.073(20)
8	328.795 15.689(19)	325.915 25.132(20)	320.525 22.059(20)	310.775# 22.865(20)
15	372.779 19.979(19)	370.265 33.315(20)	362.720 28.615(20)	344.930# 27.306(20)
22	413.263 23.642(19)	407.190 41.592(20)	396.845 34.923(20)	373.410# 36.048(20)
29	443.800 26.475(19)	441.255 46.750(20)	426.585 42.624(20)	398.090# 41.213(20)
36	469.489 29.543(19)	469.295 52.089(20)	453.710 48.275(20)	414.360# 41.010(20)
43	489.216 31.089(19)	491.340 58.499(20)	474.150 53.150(20)	425.484# 45.959(19)
50	513.721 35.429(19)	513.150 61.580(20)	489.045 55.908(20)	432.121# 44.357(19)
57	528.600 39.702(19)	529.720 67.382(20)	503.435 58.367(20)	448.100# 47.730(19)
64	545.063 42.339(19)	546.940 71.181(20)	519.430 59.740(20)	461.721# 54.438(19)
71[a]	555.321 43.764(19)	559.630 74.515(20)	530.605 60.329(20)	468.300# 57.872(18)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

a Day 71 = last weigh day of premating period.

TABLE 2 (Continued)

MEAN BODY WEIGHTS (grams) OF P_1 MALE RATS

Group:	I-0	III-0	V-0	VII-0
Dose (mg/kg/day):	0	75	500	3500
Test Day				
78	547.558 46.367(19)	553.160 74.282(20)	520.755 63.036(20)	456.039# 65.794(18)
85	564.232 48.458(19)	564.635 72.682(20)	532.850 63.070(20)	463.533# 62.448(18)
92	578.274 52.989(19)	576.615 75.452(20)	543.611 64.062(19)	470.222# 64.983(18)
99	591.011 55.185(19)	591.630 80.024(20)	552.537 66.185(19)	478.028# 63.958(18)
106	598.047 58.160(19)	602.035 83.343(20)	560.816 67.011(19)	479.383# 69.104(18)
113	607.016 62.443(19)	610.145 83.184(20)	567.916 70.567(19)	487.822# 69.251(18)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

a Day 71 = last weigh day of premating period.

TABLE 3

MEAN BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

Group:	I-0	III-0	V-0	VII-0
Dose (mg/kg/day):	0	75	500	3500
Test Day				
1- 8	48.089 7.967(19)	43.765 10.656(20)	40.430# 8.179(20)	29.825# 14.964(20)
8-15	43.984 8.906(19)	44.350 9.785(20)	42.195 8.538(20)	34.155# 12.675(20)
15-22	40.484 7.324(19)	36.925 9.346(20)	34.125# 8.605(20)	28.480# 14.058(20)
22-29	30.537 6.024(19)	34.065 7.000(20)	29.740 9.663(20)	24.680 10.372(20)
29-36	25.689 6.818(19)	28.040 7.232(20)	27.125 8.299(20)	16.270# 11.550(20)
36-43	19.726 6.921(19)	22.045 8.210(20)	20.440 8.060(20)	14.505 10.179(19)
43-50	24.505 6.326(19)	21.810 5.398(20)	14.895# 13.058(20)	6.637# 16.356(19)
50-57	14.879 6.263(19)	16.570 7.025(20)	14.390 8.331(20)	15.979 7.392(19)
57-64	16.463 4.380(19)	17.220 5.935(20)	12.995 5.464(20)	13.621 13.185(19)
64-71[a]	10.258 4.406(19)	12.690 7.114(20)	14.175@ 5.531(20)	5.894 14.734(18)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant difference at $p < 0.05$ by Jonckheere-Terpstra trend test.
@ Significant difference from control at $p < 0.05$ (Nonparametric comparison to control (Dunn's Test).

a Day 71 = last weigh day of premating period.

TABLE 3 (Continued)

MEAN BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

Group:	I-0	III-0	V-0	VII-0
Dose (mg/kg/day):	0	75	500	3500
Test Day				
71- 78	-7.763	-6.470	-9.850	-12.261
	8.408(19)	9.986(20)	12.715(20)	18.049(18)
78- 85	16.674	11.475	12.095	7.494
	8.621(19)	6.644(20)	7.849(20)	16.349(18)
85- 92	14.042	11.980	7.789#	6.689#
	6.456(19)	5.709(20)	5.763(19)	18.139(18)
92- 99	12.737	15.015	8.926#	7.806#
	6.001(19)	7.964(20)	4.684(19)	13.370(18)
99-106	7.037	10.405	8.279	1.356
	7.134(19)	7.792(20)	6.690(19)	16.965(18)
106-113	8.968	8.110	7.100	8.439
	6.536(19)	6.573(20)	7.016(19)	10.013(18)
1- 71[a]	274.616	277.480	250.510	188.122#
	40.730(19)	60.742(20)	47.575(20)	49.577(18)
1-113	326.311	327.995	287.584	207.644#
	59.368(19)	69.415(20)	57.687(19)	63.272(18)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

a Day 71 = last weigh day of premating period.

TABLE 4

MEAN BODY WEIGHTS (grams) OF P_1 FEMALE RATS DURING PREMATING

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day):	0	75	500	3500
Test Day				
1	190.645 11.679(20)	192.125 7.975(20)	193.240 13.359(20)	191.415 10.097(20)
8	202.980 15.412(20)	207.440 12.385(20)	205.760 15.346(20)	198.185 16.377(20)
15	218.500 20.790(20)	225.075 10.786(20)	220.025 19.231(20)	217.505 16.277(20)
22	232.910 17.997(20)	239.230 12.880(20)	236.390 21.861(20)	228.785 15.883(20)
29	240.970 20.965(20)	248.710 15.671(20)	244.290 23.601(20)	238.450 16.032(20)
36	248.045 27.027(20)	256.675 14.961(20)	249.475 18.756(20)	244.370 16.711(20)
43	253.980 25.693(20)	263.320 16.137(20)	253.155 23.097(20)	245.075 19.170(20)
50	263.255 24.699(20)	270.095 16.542(20)	263.680 24.975(20)	254.645 21.093(20)
57	267.210 24.368(20)	275.480 19.726(20)	269.725 28.046(20)	260.960 19.295(20)
64	269.360 25.755(20)	282.950 20.187(20)	273.760 25.351(20)	263.620 17.951(20)
71[a]	271.995 26.534(20)	284.265 17.044(20)	277.280 27.763(20)	268.875 21.619(20)

Data summarized as: Mean
Standard Deviation (n)

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

a Day 71 = last weigh day of premating period.

TABLE 5

MEAN BODY WEIGHT GAINS (grams) OF P_1 FEMALE RATS DURING PREMATING

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day):	0	75	500	3500
Test Day				
1- 8	12.335	15.315	12.520	6.770#
	8.862(20)	7.371(20)	7.395(20)	12.508(20)
8-15	15.520	17.635	14.265	19.320
	9.015(20)	3.898(20)	8.160(20)	9.604(20)
15-22	14.410	14.155	16.365	11.280
	6.897(20)	6.973(20)	7.878(20)	5.488(20)
22-29	8.060	9.480	7.900	9.665
	7.211(20)	6.791(20)	6.097(20)	7.050(20)
29-36	7.075	7.965	5.185	5.920
	10.654(20)	6.215(20)	7.037(20)	11.719(20)
36-43	5.935	6.645	3.680	0.705#
	7.448(20)	5.562(20)	7.416(20)	10.099(20)
43-50	9.275	6.775	10.525	9.570
	5.662(20)	3.803(20)	7.005(20)	11.353(20)
50-57	3.955	5.385	6.045	6.315
	6.646(20)	6.507(20)	6.258(20)	5.111(20)
57-64	2.150	7.470*	4.035	2.660
	7.222(20)	6.847(20)	6.109(20)	5.692(20)
64-71[a]	2.635	1.315	3.520	5.255
	6.379(20)	8.729(20)	6.552(20)	7.678(20)
1-71[a]	81.350	92.140	84.040	77.460
	19.056(20)	14.033(20)	20.207(20)	16.322(20)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

* Significant difference from control at $p < 0.05$ (Parametric comparison to control (Dunnett/Tamhane-Dunnett)

a Day 71 = last weigh day of premating period.

TABLE 6

MEAN BODY WEIGHTS (grams) OF P_1 FEMALE RATS DURING GESTATION

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day):	0	75	500	3500
Gestation Day				
0	274.439 25.755(18)	283.094 18.471(17)	279.818 32.087(17)	272.046 20.011(13)
7	309.156 27.639(18)	313.306 18.932(17)	310.253 31.104(17)	300.069 19.939(13)
14	339.844 28.876(18)	340.629 19.600(17)	337.506 31.107(17)	326.823 20.255(13)
21	414.767 39.163(18)	409.529 35.439(17)	415.344 33.925(16)	406.015 29.016(13)

Data summarized as: Mean
Standard Deviation (n)

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

TABLE 7

MEAN BODY WEIGHT GAINS (grams) OF P_1 FEMALE RATS DURING GESTATION

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day):	0	75	500	3500
Gestation Day				
0- 7	34.717 6.415(18)	30.212 5.374(17)	30.435 7.430(17)	28.023# 5.485(13)
7-14	30.689 6.823(18)	27.324 7.178(17)	27.253 5.010(17)	26.754# 4.861(13)
14-21	74.922 16.698(18)	68.900 24.377(17)	76.856 12.826(16)	79.192 16.018(13)
0-21	140.328 23.109(18)	126.435 31.681(17)	134.950 16.886(16)	133.969 16.292(13)

Data summarized as: Mean
Standard Deviation (n)
Statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 8

MEAN BODY WEIGHTS (grams) OF P_1 FEMALE RATS DURING LACTATION

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day):	0	75	500	3500
Lactation Day				
0	318.594 27.523(18)	311.437 20.333(19)	314.526 30.933(19)	301.613 25.254(15)
7	329.228 28.567(18)	331.405 19.893(19)	326.968 29.573(19)	324.627 20.497(15)
14	344.989 24.884(18)	341.879 19.219(19)	343.395 25.400(19)	331.780 17.720(15)
21	332.356 24.069(16)	332.521 19.168(19)	327.205 24.010(19)	329.240 19.590(15)

Data summarized as: Mean
Standard Deviation (n)

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

TABLE 9

MEAN BODY WEIGHT GAINS (grams) OF P_1 FEMALE RATS DURING LACTATION

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day):	0	75	500	3500
Lactation Day				
0- 7	10.633	19.968	12.442	23.013
	14.482(18)	20.495(19)	12.430(19)	11.723(15)
7-14	15.761	10.474	16.426	7.153
	10.754(18)	13.692(19)	11.047(19)	12.076(15)
14-21	-15.363	-9.358	-16.189	-2.540#
	12.145(16)	16.899(19)	12.214(19)	12.565(15)
0-21	12.206	21.084	12.679	27.627#
	10.412(16)	18.932(19)	19.667(19)	14.343(15)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 10

MEAN DAILY FOOD CONSUMPTION (grams/day) OF P_1 MALE RATS DURING PREMATING

Group:	I-0	III-0	V-0	VII-0
Dose (mg/kg/day):	0	75	500	3500
Test Day				
1- 8	25.805 1.886(19)	26.805 2.599(20)	25.060 2.164(20)	25.175 3.420(20)
8-15	25.884 2.121(19)	27.610 3.160(20)	25.370 2.669(20)	23.080# 3.871(20)
15-22	27.689 2.147(19)	28.550 3.107(20)	26.420 2.798(20)	25.685# 4.209(20)
22-29	27.774 2.407(19)	29.280 3.300(20)	26.870 3.402(20)	25.935# 4.137(20)
29-36	28.821 2.681(19)	30.605 3.936(20)	28.190 3.360(20)	26.575# 3.790(20)
36-43	28.216 3.281(19)	30.360 3.254(20)	27.745 3.445(20)	26.563# 3.298(19)
43-50	27.889 2.658(19)	29.330 3.305(20)	26.335 4.439(20)	24.900# 3.470(19)
50-57	28.368 2.947(19)	29.550 3.548(20)	26.580 3.495(20)	26.489# 3.482(19)
57-64	28.689 2.680(18)	30.325 3.750(20)	27.510 3.227(20)	27.895 5.070(19)
64-71[a]	27.695 2.956(19)	29.625 3.238(20)	27.045 3.225(20)	26.622 4.494(18)
1-71[a]	27.794 2.218(18)	29.215 3.124(20)	26.720 2.966(20)	25.894# 3.154(18)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

a Day 71 = last weigh day of premating period.

TABLE 11

MEAN DAILY FOOD EFFICIENCY (grams weight gain/grams food consumed) OF P_1 MALE RATS DURING PREMATING

Group:	I-0	III-0	V-0	VII-0
Dose (mg/kg/day):	0	75	500	3500
Test Day				
1- 8	0.265	0.231	0.229	0.163*
	0.031(19)	0.039(20)	0.034(20)	0.072(20)
8-15	0.242	0.228	0.236	0.199*
	0.040(19)	0.032(20)	0.029(20)	0.060(20)
15-22	0.208	0.183	0.182	0.153*
	0.029(19)	0.030(20)	0.031(20)	0.067(20)
22-29	0.157	0.165	0.155	0.134
	0.027(19)	0.021(20)	0.039(20)	0.049(20)
29-36	0.127	0.130	0.136	0.086*
	0.029(19)	0.028(20)	0.032(20)	0.061(20)
36-43	0.099	0.102	0.103	0.074
	0.034(19)	0.029(20)	0.042(20)	0.053(19)
43-50	0.124	0.106	0.069*	0.035*
	0.025(19)	0.020(20)	0.107(20)	0.090(19)
50-57	0.073	0.078	0.077	0.085
	0.026(19)	0.026(20)	0.043(20)	0.042(19)
57-64	0.080	0.080	0.067	0.061
	0.018(18)	0.023(20)	0.028(20)	0.062(19)
64-71[a]	0.053	0.060	0.075	0.022
	0.020(19)	0.033(20)	0.027(20)	0.104(18)
1-71[a]	0.141	0.134	0.133	0.103*
	0.012(18)	0.016(20)	0.014(20)	0.018(18)

Data summarized as: Mean
Standard Deviation (n)

* Statistically significant differences at $p < 0.05$ by One-way Analysis of Variance and Dunnett's tests.

a Day 71 = last weigh day of premating period.

TABLE 12

MEAN DAILY FOOD CONSUMPTION (grams) OF P_1 FEMALE RATS DURING PREMATING

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day):	0	75	500	3500
Test Day				
1- 8	16.945 1.750(20)	17.705 1.424(20)	17.230 2.193(20)	15.805# 1.984(20)
8-15	17.245 1.893(20)	18.470 2.081(20)	17.070 2.122(20)	16.365 2.502(20)
15-22	18.140 1.542(20)	18.805 1.596(20)	18.440 1.858(20)	16.790 3.408(20)
22-29	18.440 1.770(20)	19.110 1.751(20)	18.990 1.974(20)	18.560 2.098(20)
29-36	19.575 2.382(20)	19.790 1.920(20)	19.930 1.911(20)	18.725 1.972(20)
36-43	18.455 1.911(20)	18.660 1.377(20)	17.965 1.867(20)	18.510 2.722(20)
43-50	17.290 1.751(20)	17.930 1.383(20)	18.035 1.878(20)	17.325 1.599(20)
50-57	17.720 1.553(20)	18.450 1.210(20)	17.410 2.981(20)	17.975 1.226(20)
57-64	17.715 1.531(20)	18.935 1.982(20)	17.910 1.594(20)	17.015 1.949(20)
64-71[a]	17.660 1.509(20)	17.840 1.221(20)	17.565 2.125(20)	17.655 2.049(20)
1-71[a]	17.915 1.485(20)	18.570 1.156(20)	18.055 1.675(20)	17.485 1.097(20)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

a Day 71 = last weigh day of premating period.

TABLE 13

MEAN FOOD EFFICIENCY (grams weight gain/grams food consumed) OF P_1 FEMALE RATS DURING PREMATING

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day):	0	75	500	3500
Test Day				
1- 8	0.099 0.065(20)	0.122 0.054(20)	0.101 0.051(20)	0.052 0.104(20)
8-15	0.126 0.066(20)	0.138 0.033(20)	0.116 0.060(20)	0.178 0.120(20)
15-22	0.113 0.053(20)	0.105 0.045(20)	0.125 0.056(20)	0.100 0.048(20)
22-29	0.061 0.055(20)	0.070 0.047(20)	0.057 0.042(20)	0.073 0.055(20)
29-36	0.046 0.68(20)	0.057 0.044(20)	0.039 0.048(20)	0.043 0.091(20)
36-43	0.047 0.056(20)	0.050 0.041(20)	0.026 0.054(20)	0.002 0.082(20)
43-50	0.075 0.045(20)	0.053 0.028(20)	0.083 0.054(20)	0.078 0.088(20)
50-57	0.031 0.0.52(20)	0.041 0.048(20)	0.049 0.047(20)	0.051 0.041(20)
57-64	0.015 0.055(20)	0.054 0.048(20)	0.033 0.047(20)	0.018 0.050(20)
64-71[a]	0.021 0.052(20)	0.010 0.070(20)	0.026 0.049(20)	0.037 0.072(20)
1- 71[a]	0.064 0.012(20)	0.071 0.008(20)	0.066 0.012(20)	0.063 0.012(20)

Data summarized as: Mean
Standard Deviation (n)

There were no statistically significant differences at $p < 0.05$ by One-way Analysis of Variance and Dunnett's tests.

a Day 71 = last weigh day of premating period.

TABLE 14

MEAN DAILY FOOD CONSUMPTION (grams) OF P_1 FEMALE RATS DURING GESTATION

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day):	0	75	500	3500
Gestation Day				
0- 7	23.389 2.041(18)	27.319 2.739(16)	22.812 2.453(17)	20.992# 2.094(13)
7-14	24.872 2.219(18)	23.550 2.696(16)	23.894 2.677(17)	22.754# 2.219(13)
14-21	25.300 1.742(18)	24.618 3.590(17)	25.113 2.704(16)	24.769 2.412(13)
0-21	24.511 1.820(18)	23.863 2.608(16)	23.937 2.339(16)	22.838 2.073(13)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 15

MEAN FOOD EFFICIENCY (grams weight gain/grams food consumed) OF P_1 FEMALE RATS DURING GESTATION

Group:	II-0	IV-0	VI-0	VIII-0
Dose (mg/kg/day):	0	75	500	3500
Gestation Day				
0- 7	0.212 0.034(18)	0.189 0.026(16)	0.190 0.038(17)	0.192 0.039(13)
7-14	0.176 0.034(18)	0.165 0.039(16)	0.163 0.027(17)	0.168 0.021(13)
14-21	0.421 0.085(18)	0.393 0.127(17)	0.439 0.068(16)	0.457 0.094(13)
0-21	0.272 0.035(18)	0.252 0.060(16)	0.270 0.033(16)	0.280 0.032(13)

Data summarized as: Mean
Standard Deviation (n)

There were no statistically significant differences at $p < 0.05$ by One-way Analysis of Variance and Dunnett's tests.

TABLE 16

SUMMARY OF CLINICAL OBSERVATIONS IN P_1 MALE RATS

	Number of Rats with Observation			
GROUP:	I-0	III-0	V-0	VII-0
DOSE (mg/kg/day):	0	75	500	3500
N:	19	20	20	20
OBSERVATIONS				
Alopecia	3	4	4	4
Discharge Penis	0	0	0	1
Irregular Respiration	0	0	0	1
Lung Noise	0	0	0	2#
Salivation	0	0	0	5#
Sore	0	0	0	1
Stained Mouth	0	0	0	1
Stained Nose	0	0	0	2#
Stained Perineum	0	0	0	3#

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

TABLE 17

SUMMARY OF CLINICAL OBSERVATIONS IN P_1 FEMALE RATS DURING PREMATING AND COHABITATION

	Number of Rats with Observation			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSE (mg/kg/day):	0	75	500	3500
N:	20	20	20	20
OBSERVATIONS				
Alopecia	3	2	1	2
Hunched Over	0	0	0	1
Salivation	0	0	0	3#
Stained Perineum	0	0	0	1

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

TABLE 18

SUMMARY OF CLINICAL OBSERVATIONS IN P_1 FEMALE RATS DURING GESTATION

	Number of Rats with Observation			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSE (mg/kg/day):	0	75	500	3500
N:	20	17	17	18
OBSERVATIONS				
Alopecia	6	1	6	2
Sore Tail	0	0	0	1

Note: This table includes clinical observations from animals with evidence of copulation observed.

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

TABLE 19

SUMMARY OF CLINICAL OBSERVATIONS IN P_1 FEMALE RATS DURING LACTATION

	Number of Rats with Given Sign			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSE (mg/kg/day):	0	75	500	3500
N:	18	19	19	15
OBSERVATIONS				
Alopecia	5	4	5	3
Total No. of Rats with Masses	0	0	0	1
Site: 1 Mass Chest (2.0 cm)	0	0	0	1

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

TABLE 20

SUMMARY OF SPERM PARAMETERS IN P_1 MALE RATS

Group:	I-0	III-0	V-0	VII-0
Dose (mg/kg/day):	0	75	500	3500
MOTILITY				
Percent Motile	93.368	93.059	92.389	92.588
Standard Deviation	3.890 (19)[a]	2.331 (17))	7.594 (18)	4.124 (17))
MORPHOLOGY				
Percent Normal	99.053	99.105	98.316#	98.294#
Standard Deviation	0.685 (19)	0.636 (19)	1.030 (19)	1.251 (17)
EPIDIDYMAL SPERM (Millions)				
Per Cauda	305.558	291.165	287.716	286.956
Standard Deviation	27.539 (19)	70.283 (20)	69.512 (19)	46.468 (18)
Per gram Cauda	1059.553	1098.255	1118.147	1166.294
Standard Deviation	132.231 (19)	313.748 (20)	338.472 (19)	206.052 (18)
TESTICULAR SPERMATIDS (Millions)				
Per Testis	174.405	167.720	170.511	169.578
Standard Deviation	19.819 (19)	42.023 (20)	25.123 (19)	22.033 (18)
Per gram Testis	122.753	111.755	116.626	118.094
Standard Deviation	19.144 (19)	27.250 (20)	14.524 (19)	17.337 (18)

a Number in group is in parentheses.

Statistically significant trend by Jonckheere-Terpstra test; $p < 0.05$.

TABLE 21

MEAN ESTROUS CYCLE PARAMETERS AND PRECOITAL INTERVAL IN P_1 FEMALE RATS

Group	Dose (mg/kg/day)	N	Percent of Days in Estrus	Percent of Days in Diestrus	Percent of Days in Proestrus	Mean Cycle Length (days)	Mean Precoital Interval (days)
II-0	0	20	22	64	14	4.3(0.5)*a*	2.9(1.1)
IV-0	75	20	24	64	11	4.2(0.3)	3.2(1.8)*b*
VI-0	500	20	22	64	13	4.2(0.3)	3.2(1.8)*b*
VIII-0	3500	20	25	64	10	4.5(1.3)	4.0(3.6)

a Standard deviation is presented in parentheses.
b N=19.

There were no statistically significant trends in estrous cycle length or precoital interval by Jonckheere-Terpstra test ($p < 0.05$).

TABLE 22

SUMMARY OF REPRODUCTIVE INDICES: P_1 GENERATION

MATERNAL GROUP:	II-0	IV-0	VI-0	VIII-0
DOSE (mg/kg/day):	0	75	500	3500
MATING INDEX (%)	100	95	95	100
(No. copulated/cohoused)	(20/20)	(19/20)	(19/20)	(20/20)
FERTILITY INDEX (%)	90	100	100	75
(No. pregnant/copulated)	(18/20)	(19/19)	(19/19)	(15/20)
GESTATION LENGTH (days)	22.3	22.5	22.2	22.3
(No. in group)	(18)	(17)[a]	(17)[a]	(13)[a]
NUMBER OF IMPLANTATION SITES				
per pregnant female	13.3	11.8	13.3	13.9
Standard Deviation (No. in group)	3.09(18)	4.38(19)	2.13(19)	1.83(15)
IMPLANTATION EFFICIENCY (%)[b]	96.9	97.0	93.6	93.0*
Standard Deviation(No. in group)	5.16(18)	6.64(19)	8.34(19)	6.69(15)

a Gestation length could not be calculated for 2 females that were pregnant for which no evidence of copulation was observed.

b Number of pups born/number of implantation sites X 100.

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

There were no statistically significant differences from control in gestation length or number of implantation sites by Jonckheere-Terpstra test; $p < 0.05$.

* Statistically significant difference from control in implantation efficiency by Jonckheere-Terpstra test; $p < 0.05$.

TABLE 23

MEAN PUP NUMBERS AND SURVIVAL: F_1 GENERATION

MATERNAL GROUP:	II-0	IV-0	VI-0	VIII-0
DOSE (mg/kg/day):	0	75	500	3500
N:	18	19	19	15
MEAN NUMBER OF PUPS/LITTER				
Born	12.9	11.4	12.4	13.0
Born Alive	12.8	11.3	12.3	12.5
Day 4 Preculling	12.7	11.3	12.3	12.4
Day 4 Postculling	7.8	7.3	8.0	7.9
Day 7	7.8	7.3	8.0	7.9
Day 14	7.8	7.3	8.0	7.9
Day 21	7.8	7.3	8.0	7.9
MEAN NUMBER OF MALE PUPS/LITTER				
Born	6.8	6.6	6.2	6.0
Born Alive	6.7	6.6	6.2	5.9
Day 4 Preculling	6.7	6.5	6.2	5.9
Day 4 Postculling	4.0	3.9	3.9	3.9
Day 7	4.0	3.9	3.9	3.9
Day 14	4.0	3.9	3.9	3.9
Day 21	4.0	3.9	3.9	3.9
MEAN NUMBER OF FEMALE PUPS/LITTER				
Born	6.1	5.0[a]	6.1	7.0
Born Alive	6.1	5.0[a]	6.1	6.6
Day 4 Preculling	6.0	5.0[a]	6.1	6.5
Day 4 Postculling	3.8	3.6[a]	4.1	4.1
Day 7	3.8	3.6[a]	4.1	4.0
Day 14	3.8	3.6[a]	4.1	4.0
Day 21	3.8	3.6[a]	4.1	4.0
SURVIVAL (%)				
Sex Ratio (males)	0.53	0.59	0.50	0.46
Gestation Index[b]	100.0	100.0	100.0	100.0
Mean % Born Alive	99.1	99.7	99.6	96.4
0-4 Day Viability	99.5	99.7	99.5	98.8
Lactation Index[c]	100.0	100.0	100.0	99.2
Litter Survival[d]	100.0	100.0	100.0	100.0

a N = 18.
b Percent litters delivered having at least one live pup.
c Mean percent survival from Day 4 Postculling to Day 21.
d Percent litters born with at least one pup alive on Day 21.

There were no statistically significant trends in number of pups, sex ratio, mean percent born alive, 0-4 day viability, or lactation index by Jonckheere-Terpstra test; $p < 0.05$.

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

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

TABLE 24

MEAN PUP WEIGHTS: F_1 GENERATION

MATERNAL GROUP:	II-0	IV-0	VI-0	VIII-0
DOSE (mg/kg/day):	0	75	500	3500
N:	18	19	19	15
		MEAN PUP WEIGHTS (grams)		
Day 0	6.9 (0.5)[a]	7.1 (0.8)	6.8 (0.6)	6.3 (0.5)*
Day 4 Preculling	11.1 (1.1)	11.6 (1.6)[b]	11.5 (1.7)	10.1 (1.3)*
Day 4 Postculling	11.0 (1.2)	11.6 (1.6)[b]	11.4 (1.7)	10.1 (1.4)*
Day 7	17.4 (1.5)	17.9 (1.9)[b]	18.1 (2.2)	15.0 (2.5)*
Day 14	36.9 (2.2)	35.3 (3.5)[b]	35.7 (3.3)	28.4 (3.2)*
Day 21	58.8 (3.4)	58.4 (5.6)[b]	57.2 (5.8)	44.6 (6.9)*
		MEAN MALE PUP WEIGHTS (grams)		
Day 0	7.1 (0.4)[c]	7.2 (0.8)[c]	6.9 (0.6)	6.5 (0.5)
Day 4 Preculling	11.3 (1.1)	11.9 (1.7)[b]	11.6 (1.7)	10.3 (1.4)
Day 4 Postculling	11.3 (1.2)	11.9 (1.7)[b]	11.5 (1.7)	10.2 (1.5)
Day 7	17.9 (1.5)	18.2 (2.0)[b]	18.3 (2.3)	15.2 (2.7)
Day 14	37.7 (2.1	35.9 (3.8)[b]	36.1 (3.3)	28.7 (3.5)
Day 21	60.4 (3.0)	60.0 (5.7)[b]	58.3 (6.0)	45.2 (7.5)
		MEAN FEMALE PUP WEIGHTS (grams)		
Day 0	6.6 (0.4)[c]	6.8 (0.8)[d]	6.7 (0.6)	6.2 (0.5)
Day 4 Preculling	10.7 (1.1)	11.1 (1.4)[c]	11.3 (1.7)	9.9 (1.3)
Day 4 Postculling	10.7 (1.1)	11.1 (1.4)[c]	11.3 (1.7)	10.0 (1.3)
Day 7	16.9 (1.4)	17.2 (1.5)[c]	17.9 (2.3)	14.8 (2.3)
Day 14	36.0 (2.1)	34.3 (3.1)[c]	35.3 (3.3)	28.2 (2.9)
Day 21	57.0 (2.8)	55.9 (4.7)[c]	56.2 (5.6)	43.9 (6.5)

a Standard deviation is reported in parentheses.
b N = 18.
c N = 17.
d N = 16.

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

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

TABLE 25

SUMMARY OF PUP CLINICAL OBSERVATIONS: F_1 GENERATION

MATERNAL GROUP:	II-0	IV-0	VI-0	VIII-0
DOSE (mg/kg/day):	0	75	500	3500
OBSERVATIONS				
Discharge Right Rear Leg(s)	0	0	0	1 (1)
Small Whole Body	0	0	0	1 (1)
Sore	0	0	0	1 (1)
Subcutaneous Hemorrhage	0	0	0	1 (1)
Right Rear Paw Missing	0	0	0	1 (1)
TOTAL NUMBER OF SIGNS	0	0	0	4
NUMBER OF LITTERS AFFECTED	0	0	0	2
TOTAL NUMBER OF LITTERS	18	19	19	15

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

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

TABLE 26

MEAN BODY WEIGHTS (grams) OF F_1 MALE RATS

Group:	I-1	III-1	V-1	VII-1
Dose (mg/kg/day):	0	75	500	3500
Test Day[a]				
1	59.528 4.388(18)	60.653 5.361(19)	58.568 6.792(19)	45.493# 6.613(15)
8	102.144 7.927(18)	104.568 9.728(19)	99.274 10.356(19)	77.673# 15.459(15)
15	163.583 12.794(18)	164.237 13.475(19)	157.589 17.092(19)	131.320# 21.991(15)
22	227.311 18.988(18)	227.589 15.994(19)	219.937 22.982(19)	191.580# 26.782(15)
29	290.800 27.093(18)	288.821 19.655(19)	280.805 26.033(19)	249.587# 30.792(15)
36	357.761 35.355(18)	351.395 20.563(19)	340.242 27.868(19)	310.753# 36.626(15)

a Test Day 1 = Postnatal Day 21

Data summarized as: Mean
Standard Deviation (n)

Statistically significant trends by Jonckheere-Terpstra test ($p < 0.05$).

TABLE 27

MEAN BODY WEIGHTS GAINS (grams) OF F_1 MALE RATS

Group:	I-1	III-1	V-1	VII-1
Dose (mg/kg/day):	0	75	500	3500
Test Day[a]				
1- 8	42.617 5.165(18)	43.916 5.443(19)	40.705 6.299(19)	32.180# 11.494(15)
8-15	61.439 5.936(18)	59.668 5.371(19)	58.316 8.263(19)	53.647# 8.256(15)
15-22	63.728 7.552(18)	63.353 4.622(19)	62.347 7.757(19)	60.260 6.039(15)
22-29	63.489 9.149(18)	61.232 6.416(19)	60.868 6.133(19)	58.007# 5.824(15)
29-36	66.961 9.890(18)	62.574 6.790(19)	59.437# 6.183(19)	61.167# 7.837(15)
1-36	298.233 31.900(18)	290.742 16.712(19)	281.674 25.514(19)	265.260# 31.823(15)

a Test Day 1 = Postnatal Day 21

Data summarized as: Mean
Standard Deviation (n)

Statistically significant trends by Jonckheere-Terpstra test ($p < 0.05$).

TABLE 28

MEAN BODY WEIGHTS (grams) OF F_1 FEMALE RATS

Group:	II-1	IV-1	VI-1	VIII-1
Dose (mg/kg/day):	0	75	500	3500
Test Day[a]				
1	56.144 4.173(18)	55.278 5.510(18)	55.732 5.874(19)	44.593# 5.740(15)
8	93.661 8.359(18)	92.517 9.708(18)	90.416 9.718(19)	76.693# 12.012(14)
15	139.256 10.383(18)	136.717 12.549(18)	136.216 11.174(19)	119.514# 16.069(14)
22	174.733 16.426(18)	171.433 13.078(18)	172.453 11.987(19)	156.321# 15.933(14)
29	199.917 17.403(18)	193.094 15.963(18)	198.626 15.353(19)	183.486 16.387(14)
36	226.972 21.451(18)	217.950 19.548(18)	226.068 17.731(19)	212.507 18.594(14)

a Test Day 1 = Postnatal Day 21

Data summarized as: Mean
Standard Deviation (n)

Statistically significant trends by Jonckheere-Terpstra test ($p < 0.05$).

TABLE 29

MEAN BODY WEIGHTS GAINS (grams) OF F_1 FEMALE RATS

Group:	II-1	IV-1	VI-1	VIII-1
Dose (mg/kg/day):	0	75	500	3500
Test Day[a]				
1- 8	37.517 5.437(18)	37.239 5.004(18)	34.684 6.474(19)	32.443# 7.285(14)
8-15	45.594 6.136(18)	44.200 6.501(18)	45.800 4.359(19)	42.821 5.108(14)
15-22	35.478 9.288(18)	34.717 4.758(18)	36.237 6.683(19)	36.807 4.457(14)
22-29	25.183 6.349(18)	21.661 8.574(18)	26.174 6.923(19)	27.164 5.717(14)
29-36	27.056 7.717(18)	24.856 7.054(18)	27.442 5.171(19)	29.021 4.440(14)
1-36	170.828 20.951(18)	162.672 18.432(18)	170.337 16.088(19)	168.257 15.018(14)

a Test Day 1 = Postnatal Day 21

Data summarized as: Mean
Standard Deviation (n)

Statistically significant trends by Jonckheere-Terpstra test ($p < 0.05$).

TABLE 30

MEAN DAILY FOOD CONSUMPTION (grams) OF F_1 MALE RATS

Group:	I-1	III-1	V-1	VII-1
Dose (mg/kg/day):	0	75	500	3500
Test Day[a]				
1- 8	12.322 1.303(18)	13.389 2.070(19)	12.626 2.279(19)	10.020# 1.911(15)
8-15	19.622 1.711(18)	19.584 1.996(19)	19.111 1.957(19)	16.553# 2.166(15)
15-22	25.028 2.520(18)	25.174 1.912(19)	23.761 4.547(18)	22.733# 2.802(15)
22-29	27.383 2.981(18)	27.442 1.886(19)	27.400 1.958(18)	26.073 2.328(15)
29-36	30.872 3.872(18)	30.474 1.913(19)	30.068 2.031(19)	29.180 2.233(15)
1-36	23.044 2.288(18)	23.200 1.493(19)	22.744 1.483(18)	20.920# 2.096(15)

a Test Day 1 = Postnatal Day 21

Data summarized as: Mean
Standard Deviation (n)

Statistically significant trends by Jonckheere-Terpstra test ($p < 0.05$).

TABLE 31

MEAN DAILY FOOD EFFICIENCY (grams weight gain/grams food consumed) OF F_1 MALE RATS

Group:	I-1	III-1	V-1	VII-1
Dose (mg/kg/day):	0	75	500	3500
Test Day[a]				
1- 8	0.494 0.033(18)	0.475 0.026(19)	0.464 0.055(19)	0.435 0.161(15)
8-15	0.448 0.025(18)	0.436 0.026(19)	0.435 0.044(19)	0.464 0.042(15)
15-22	0.364 0.023(18)	0.360 0.025(19)	0.399 0.222(19)	0.381 0.029(15)
22-29	0.331 0.024(18)	0.319 0.024(19)	0.318 0.020(18)	0.319 0.026(15)
29-37	0.310 0.017(18)	0.294 0.028(19)	0.283* 0.025(19)	0.299 0.027(15)
1-36	0.370 0.009(18)	0.358 0.015(19)	0.360 0.020(18)	0.362 0.019(15)

a Test Day 1 = Postnatal Day 21

Data summarized as: Mean
Standard Deviation (n)

* Statistically significant difference from control at $p < 0.05$ by One-way Analysis of Variance and Dunnett's tests.

TABLE 32

MEAN DAILY FOOD CONSUMPTION (grams) OF F_1 FEMALE RATS

Group:	II-1	IV-1	VI-1	VIII-1
Dose (mg/kg/day):	0	75	500	3500
Test Day[a]				
1- 8	11.394 1.301(18)	11.667 1.209(18)	11.100 1.379(19)	10.293 1.666(14)
8-15	16.828 1.356(18)	17.150 1.996(18)	16.853 1.440(19)	15.521 1.763(14)
15-22	19.472 2.422(18)	19.550 1.908(18)	19.479 2.066(19)	18.421 1.878(14)
22-29	19.717 1.782(18)	19.378 3.024(18)	20.289 1.635(19)	19.707 2.129(14)
29-36	21.089 2.596(18)	21.078 5.463(18)	20.932 1.627(19)	21.229 2.024(14)
1-36	17.706 1.531(18)	17.772 1.905(18)	17.726 1.281(19)	17.029 1.721(14)

a Test Day 1 = Postnatal Day 21

Data summarized as: Mean
Standard Deviation (n)

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

TABLE 33

MEAN FOOD EFFICIENCY (grams weight gain/grams food consumed) OF F_1 FEMALE RATS

Group:	II-1	IV-1	VI-1	VIII-1
Dose (mg/kg/day):	0	75	500	3500
Test Day[a]				
1- 8	0.470 0.038(18)	0.455 0.033(18)	0.444 0.050(19)	0.446 0.060(14)
8-15	0.387 0.039(18)	0.369 0.039(18)	0.389 0.037(19)	0.395 0.025(14)
15-22	0.257 0.043(18)	0.255 0.035(18)	0.269 0.061(19)	0.288 0.042(14)
22-29	0.182 0.044(18)	0.160 0.054(18)	0.183 0.042(18)	0.197 0.040(14)
29-37	0.183 0.045(18)	0.173 0.046(18)	0.187 0.031(19)	0.195 0.025(14)
1-36	0.275 0.019(18)	0.262 0.021(18)	0.275 0.022(19)	0.283 0.013(14)

a Test Day 1 = Postnatal Day 21

Data summarized as: Mean
Standard Deviation (n)

There were no statistically significant differences at $p < 0.05$ by One-way Analysis of Variance and Dunnett's tests.

TABLE 34

SUMMARY OF CLINICAL OBSERVATIONS IN F_1 MALE RATS

	Number of Rats with Given Sign			
GROUP:	I-1	III-1	V-1	VII-1
DOSE (mg/kg/day):	0	75	500	3500
N:	18	19	19	15
OBSERVATION				
Alopecia	0	0	2	0
Hunched Over	0	0	0	1
Preputial Separation Complete	18	19	19	15
Stained Underbody	0	0	1	0
Weak	0	0	0	1

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

TABLE 35

SUMMARY OF CLINICAL OBSERVATIONS IN F_1 FEMALE RATS

	Number of Rats with Given Sign			
GROUP:	II-1	IV-1	VI-1	VIII-1
DOSE (mg/kg/day):	0	75	500	3500
N:	18	18	19	14
OBSERVATION				
Alopecia	1	0	1	0
Hunched Over	0	0	0	1
Swollen Left Front Paw(s)	1	0	0	0
Swollen Left Front Toe(s)	1	0	0	0
Vaginal Patency Complete	18	18	19	14
Weak	0	0	0	1

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

TABLE 36

SUMMARY OF DEVELOPMENTAL LANDMARKS IN F_1 RATS

PREPUTIAL SEPARATION - F_1 MALE RATS

	Number of Rats with Given Sign			
GROUP:	I-1	III-1	V-1	VII-1
DOSE (mg/kg/day):	0	75	500	3500
N:	18	19	19	15
OBSERVATIONS				
AGE (Days)[a]	42.778	41.947	43.632	45.333[b]
	1.833	1.224	2.891	2.795

VAGINAL PATENCY - F_1 FEMALE RATS

	Number of Rats with Given Sign			
GROUP:	II-1	IV-1	VI-1	VIII-1
DOSE (mg/kg/day):	0	75	500	3500
N:	18	18	19	14
OBSERVATIONS				
AGE (Days)[a]	31.722	32.722	33.316	33.786[c]
	1.227	3.392	2.626	3.068

Data summarized as: Mean
Standard Deviation (n)

a Age was calculated as follows using data presented in Appendix BB: Test day + 20 days = Age (days).
b Not significant by analysis of covariance (covariates: body weight on the day of achievement and body weight on postnatal day 35).
c Not significant by analysis of covariance (covariates: body weight on the day of achievement and body weight on postnatal day 28).

TABLE 37

SUMMARY OF HEMATOLOGY VALUES FOR P_1 MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 75 mg/kg/day	Group V 500 mg/kg/day	Group VII 3500 mg/kg/day
RBC ($x10^6/\mu L$)				
DAY 74	8.35	8.04*	8.04*	7.97*
	0.27(10)	0.28(10)	0.26(10)	0.18(10)
HGB (g/dL)				
DAY 74	15.8	15.3	15.2*	14.9*
	0.5(10)	0.7(10)	0.5(10)	0.6(10)
HCT (%)				
DAY 74	46.3	45.3	45.1	44.1*
	1.5(10)	2.0(10)	1.7(10)	1.5(10)
MCV (fl)				
DAY 74	55.4	56.3	56.1	55.4
	1.5(10)	1.4(10)	1.5(10)	1.9(10)
MCH (pg)				
DAY 74	19.0	19.1	18.9	18.7
	0.5(10)	0.5(10)	0.4(10)	0.7(10)
MCHC (g/dL)				
DAY 74	34.2	33.9	33.7	33.8
	0.3(10)	0.5(10)	0.4(10)	0.5(10)
RDW (%)				
DAY 74	12.8	12.5	12.9	14.0*
	0.5(10)	0.8(10)	0.7(10)	1.3(10)
ARET ($x10^3/\mu L$)				
DAY 74	204.2	194.2	181.0	188.2
	25.2(10)	30.2(10)	20.9(10)	47.7(10)
PLT ($x10^3/\mu L$)				
DAY 74	1251	1266	1224	1253
	178(10)	145(10)	86(9)	132(10)
WBC ($x10^3/\mu L$)				
DAY 74	14.65	14.20	15.66	16.39
	3.30(10)	3.56(10)	3.58(10)	3.03(10)
ANEU ($x10^3/\mu L$)				
DAY 74	2.07	1.68	1.76	2.28
	0.76(10)	0.62(10)	0.68(10)	0.70(10)
ALYM ($x10^3/\mu L$)				
DAY 74	11.99	12.01	13.37	13.51
	2.97(10)	2.89(10)	3.50(10)	2.92(10)

TABLE 37 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR P_1 MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 75 mg/kg/day	Group V 500 mg/kg/day	Group VII 3500 mg/kg/day
AMON ($x10^3/\mu L$)				
DAY 74	0.28	0.24	0.22	0.27
	0.13(10)	0.11(10)	0.09(10)	0.07(10)
AEOS ($x10^3/\mu L$)				
DAY 74	0.14	0.13	0.15	0.14
	0.06(10)	0.05(10)	0.09(10)	0.06(10)
ABAS ($x10^3/\mu L$)				
DAY 74	0.09	0.08	0.09	0.10
	0.06(10)	0.04(10)	0.03(10)	0.04(10)
ALUC ($x10^3/\mu L$)				
DAY 74	0.07	0.06	0.08	0.09
	0.02(10)	0.02(10)	0.03(10)	0.04(10)

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 38

SUMMARY OF HEMATOLOGY VALUES FOR P_1 FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 75 mg/kg/day	Group VI 500 mg/kg/day	Group VIII 3500 mg/kg/day
RBC ($x10^6/\mu L$)				
DAY 75	8.05	8.02	8.12	7.87
	0.32(10)	0.25(10)	0.44(10)	0.25(10)
HGB (g/dL)				
DAY 75	16.0	16.0	16.0	15.5
	0.6(10)	0.6(10)	0.6(10)	0.7(10)
HCT (%)				
DAY 75	45.4	45.3	45.9	44.2
	1.8(10)	1.6(10)	2.1(10)	1.6(10)
MCV (fl)				
DAY 75	56.4	56.5	56.6	56.2
	1.6(10)	1.3(10)	1.8(10)	1.2(10)
MCH (pg)				
DAY 75	19.9	19.9	19.7	19.7
	0.6(10)	0.3(10)	0.8(10)	0.6(10)
MCHC (g/dL)				
DAY 75	35.2	35.2	34.9	35.0
	0.4(10)	0.8(10)	0.6(10)	0.5(10)
RDW (%)				
DAY 75	11.1	11.0	11.1	11.5
	0.4(10)	0.3(10)	0.3(10)	0.4(10)
ARET ($x10^3/\mu L$)				
DAY 75	161.9	167.3	174.3	166.6
	29.5(10)	37.7(10)	28.5(10)	31.7(10)
PLT ($x10^3/\mu L$)				
DAY 75	1174	1136	1140	1109
	183(8)	100(8)	186(10)	168(10)
WBC ($x10^3/\mu L$)				
DAY 75	9.66	11.88	11.64	12.63*
	1.74(10)	1.56(10)	2.57(10)	2.48(10)
ANEU ($x10^3/\mu L$)				
DAY 75	0.97	0.85	1.77	1.45
	0.36(10)	0.46(10)	1.71(10)	0.35(10)
ALYM ($x10^3/\mu L$)				
DAY 75	8.29	10.59*	9.33	10.59*
	1.44(10)	1.53(10)	1.77(10)	2.23(10)

TABLE 38 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR P_1 FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 75 mg/kg/day	Group VI 500 mg/kg/day	Group VIII 3500 mg/kg/day
AMON ($x10^3/\mu L$)				
DAY 75	0.15	0.18	0.25	0.25
	0.05(10)	0.06(10)	0.15(10)	0.13(10)
AEOS ($x10^3/\mu L$)				
DAY 75	0.13	0.12	0.18	0.19*
	0.04(10)	0.03(10)	0.08(10)	0.06(10)
ABAS ($x10^3/\mu L$)				
DAY 75	0.06	0.08	0.07	0.08
	0.04(10)	0.03(10)	0.02(10)	0.04(10)
ALUC ($x10^3/\mu L$)				
DAY 75	0.06	0.07	0.05	0.06
	0.02(10)	0.02(10)	0.02(10)	0.03(10)

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

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR P_1 MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 75 mg/kg/day	Group V 500 mg/kg/day	Group VII 3500 mg/kg/day
AST (U/L)				
DAY 74	79	85	81	80
	10(10)	15(10)	19(10)	12(10)
ALT (U/L)				
DAY 74	31	39@	39	40@
	4(10)	7(10)	13(10)	6(10)
SDH (U/L)				
DAY 74	10.9	14.6	14.8	12.6
	4.3(10)	6.1(10)	5.5(10)	4.1(10)
PFLU (μg/mL)				
DAY 116	0.1	0.1	0.2@	0.4@
	0.0(10)	0.0(10)	0.0(10)	0.1(10)

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

@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

TABLE 40

SUMMARY OF SERUM AND PLASMA CHEMISTRY VALUES FOR P_1 FEMALE RATS

TEST/ PERIOD	Group II 0 mg/kg/day	Group IV 75 mg/kg/day	Group VI 500 mg/kg/day	Group VIII 3500 mg/kg/day
AST (U/L)				
DAY 75	91	83	79	102
	16(10)	17(10)	11(10)	45(10)
ALT (U/L)				
DAY 75	36	40	35	49
	10(10)	14(10)	6(10)	31(10)
SDH (U/L)				
DAY 75	13.2	14.5	15.3	19.3
	2.3(10)	3.1(10)	3.4(10)	14.7(10)

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

There were no statistically significant differences from control at $p < 0.05$.
\# Statistically significant difference from control at $p < 0.05$ by Jonckheere-Terpstra trend test.
* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

TABLE 41

SUMMARY OF URINALYSIS VALUES FOR P_1 MALE RATS

TEST/ PERIOD	Group I 0 mg/kg/day	Group III 75 mg/kg/day	Group V 500 mg/kg/day	Group VII 3500 mg/kg/day
UFLU (μg)				
DAY 116	12.1	53.9	176.1@	512.4@
	4.1(10)	9.3(10)	38.5(10)	109.5(10)

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

@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

TABLE 42

MEAN FINAL BODY AND ORGAN WEIGHTS FROM MALE RATS - P_1 ADULTS

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

Group:	I-0	III-0	V-0	VII-0
Dose(mg/kg/day):	0	75	500	3500
FINAL BODY WEIGHT	593.1	596.9	553.7	472.2*#
	64.5(19)	86.3(20)	72.6(19)	76.4(18)
LIVER	17.630	19.410	20.327	23.687@#
	3.591(19)	4.390(20)	4.448(19)	5.684(18)
KIDNEYS	3.898	4.145	4.233	4.323*#
	0.441(18)	0.432(20)	0.514(19)	0.483(18)
THYROID	0.026	0.026	0.023	0.023
	0.005(18)	0.007(20)	0.006(19)	0.007(18)
TESTES	3.637	3.624	3.685	3.592
	0.286(19)	0.658(20)	0.247(19)	0.353(18)
EPIDIDYMIDES	1.549	1.463	1.509	1.400@#
	0.332(19)	0.205(20)	0.104(19)	0.114(18)
SEMINAL VESICLES	2.661	2.834	2.589	2.380#
	0.429(19)	0.359(20)	0.370(19)	0.412(18)
PROSTATE	0.924	0.902	0.857	0.757@#
	0.204(19)	0.212(20)	0.149(19)	0.197(18)
BRAIN	2.216	2.180	2.185	2.117*#
	0.107(19)	0.122(20)	0.116(19)	0.120(18)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).
There were no statistically significant differences from control at $p < 0.05$.

TABLE 42 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS FROM MALE RATS - P_1 ADULTS

ORGAN WEIGHT RELATIVE TO FINAL BODY WEIGHT (grams)

Group:	I-0	III-0	V-0	VII-0
Dose(mg/kg/day):	0	75	500	3500
LIVER	2.9540	3.2329#	3.6486*#	4.9725*#
	0.3648(19)	0.4081(20)	0.5031(19)	0.5732(18)
KIDNEYS	0.6561	0.6998#	0.7678*#	0.9261*#
	0.0509(18)	0.0576(20)	0.0595(19)	0.1005(18)
THYROID	0.0043	0.0044	0.0042	0.0049
	0.0007(18)	0.0012(20)	0.0011(19)	0.0014(18)
TESTES	0.6186	0.6234	0.6761	0.7761@#
	0.0683(19)	0.1812(20)	0.0988(19)	0.1299(18)
EPIDIDYMIDES	0.2611	0.2489	0.2770	0.3017#
	0.0573(19)	0.0448(20)	0.0398(19)	0.0416(18)
SEMINAL VESICLES	0.4500	0.4816	0.4731	0.5122#
	0.0652(19)	0.0738(20)	0.0772(19)	0.0987(18)
PROSTATE	0.1557	0.1536	0.1571	0.1594
	0.0278(19)	0.0387(20)	0.0335(19)	0.0245(18)
BRAIN	0.3765	0.3713	0.3997	0.4581*#
	0.0312(19)	0.0485(20)	0.0463(19)	0.0692(18)

TABLE 42 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS FROM MALE RATS - P_1 ADULTS

ORGAN WEIGHT RELATIVE TO BRAIN (grams)

Group:	I-0	III-0	V-0	VII-0
Dosage (mg/kg/day):	0	75	500	3500
LIVER	793.3325	890.7778	927.0919#	1124.4798*#
	141.7064(19)	196.2618(20)	180.8646(19)	289.9338(18)
KIDNEYS	175.5338	190.1026*#	193.5102*#	204.3939*#
	15.1461(18)	16.4535(20)	18.4794(19)	21.6806(18)
THYROID	1.1454	1.2010	1.0685	1.1000
	0.1973(18)	0.3296(20)	0.2909(19)	0.3379(18)
TESTES	164.3347	167.3295	168.9197	169.9031
	13.4837(19)	36.0624(20)	11.8053(19)	16.3726(18)
EPIDIDYMIDES	69.8012	67.2511	69.2578	66.2537@#
	14.9033(19)	9.3190(20)	5.8373(19)	5.6720(18)
SEMINAL VESICLES	119.7666	129.8044	118.5087	113.0597
	16.1151(19)	12.6595(20)	15.6399(19)	22.4383(18)
PROSTATE	41.6833	41.4429	39.2501	35.7325@#
	8.5895(19)	9.7835(20)	6.6367(19)	9.0891(18)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).

Significant difference from control at $p < 0.05$ using Trend test (Jonckheere-Terpstra).
* Significant difference from control at $p < 0.05$ (Parametric comparison to control (Dunnett/Tamhane-Dunnett)
@ Significant difference from control at $p < 0.05$ by Dunn's nonparametric comparison to control.

TABLE 43

MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE RATS - P_1 ADULTS

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

Group:	II-0	IV-0	VI-0	VIII-0
Dose(mg/kg/day):	0	75	500	3500
FINAL BODY WEIGHT	326.8 27.9(18)	332.5 18.7(20)	325.8 24.2(19)	319.4 27.1(20)
LIVER	14.920 2.172(20)	15.110 2.141(20)	15.746 2.053(20)	16.678*# 2.292(20)
KIDNEYS	2.454 0.278(20)	2.608 0.365(20)	2.666 0.431(20)	2.651@# 0.256(20)
THYROID	0.024 0.006(19)	0.025 0.006(20)	0.024 0.006(19)	0.023 0.007(20)
UTERUS	0.553 0.152(20)	0.514 0.137(20)	0.564 0.122(20)	0.583 0.245(20)
OVARIES	1.145 0.045(20)	0.161 0.036(20)	0.144 0.033(20)	0.133 0.036(20)
BRAIN	1.929 0.125(20)	2.017 0.125(20)	1.976 0.119(20)	1.937 0.112(20)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).
There were no statistically significant differences from control at $p < 0.05$.

TABLE 43 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE RATS - P_1 ADULTS

ORGAN WEIGHT RELATIVE TO FINAL BODY WEIGHT (grams)

Group:	II-0	IV-0	VI-0	VIII-0
Dose(mg/kg/day):	0	75	500	3500
LIVER	4.5945	4.5350	4.8234	5.2045*#
	0.4607(18)	0.4991(20)	0.4319(20)	0.3877(20)
KIDNEYS	0.7550	0.7830	0.8156*#	0.8313*#
	0.0686(18)	0.0874(20)	0.0874(20)	0.0605(20)
THYROID	0.0071	0.0074	0.0074	0.0070
	0.0019(17)	0.0018(20)	0.0020(19)	0.0020(20)
UTERUS	0.1727	0.1553	0.1746	0.1873
	0.0520(18)	0.0431(20)	0.0423(20)	0.0982(20)
OVARIES	0.0431	0.0485	0.0444	0.0413
	0.0118(18)	0.0106(20)	0.0107(20)	0.0101(20)
BRAIN	0.5915	0.6075	0.6083	0.6099
	0.0342(18)	0.0363(20)	0.0413(20)	0.0536(20)

TABLE 43 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE RATS - P_1 ADULTS

ORGAN WEIGHT RELATIVE TO BRAIN (grams)

Group:	II-0	IV-0	VI-0	VIII-0
Dose(mg/kg/day):	0	75	500	3500
LIVER	771.5954	748.5316	796.6931	861.6516@#
	85.8678(20)	91.1277(20)	90.6247(20)	114.7512(20)
KIDNEYS	127.1357	129.0075	134.4536	137.0244@#
	10.5966(20)	14.1537(20)	15.4514(20)	12.9314(20)
THYROID	1.2254	1.2338	1.2193	1.1684
	0.3202(19)	0.3207(20)	0.2762(19)	0.3708(20)
UTERUS	28.8868	25.6838	28.5601	30.3206
	8.6820(20)	7.6432(20)	5.9830(20)	13.5387(20)
OVARIES	7.4390	7.9550	7.2392	6.8039
	2.0118(20)	1.5233(20)	1.3982(20)	1.6459(20)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).

Significant difference from control at $p < 0.05$ using Trend test (Jonckheere-Terpstra).
* Significant difference from control at $p < 0.05$ (Parametric comparison to control (Dunnett/Tamhane-Dunnett)
@ Significant difference from control at $p < 0.05$ by Dunn's nonparametric comparison to control.

TABLE 44

MEAN FINAL BODY AND ORGAN WEIGHTS FROM MALE RATS - F_1 ADULTS

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

Group:	I-1	III-1	V-1	VII-1
Dose(mg/kg/day):	0	75	500	3500
FINAL BODY WEIGHT	383.7	382.1	368.1	340.3*#
	43.5(18)	22.7(19)	31.3(19)	35.9(15)
LIVER	17.431	17.206	16.234	15.641#
	3.195(18)	1.590(19)	2.026(19)	1.701(15)
KIDNEYS	3.356	3.343	3.283	3.116#
	0.355(18)	0.274(19)	0.307(19)	0.347(15)
THYROID	0.022	0.023	0.022	0.021
	0.003(18)	0.006(19)	0.004(19)	0.003(14)
TESTES	3.140	3.211	3.079	2.848*#
	0.285(18)	0.244(19)	0.259(19)	0.386(15)
EPIDIDYMIDES	0.768	0.780	0.736	0.659*#
	0.098(18)	0.103(19)	0.112(19)	0.116(15)
SEMINAL VESICLES	1.286	1.378	1.304	1.229
	0.270(18)	0.213(19)	0.246(19)	0.258(15)
PROSTATE*	0.476	0.474	0.440	0.386@#
	0.102(18)	0.129(19)	0.107(19)	0.108(14)
BRAIN	1.990	2.027	1.979	1.913
	0.118(18)	0.112(19)	0.093(19)	0.121(15)

TABLE 44 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE RATS - F_1 ADULTS

ORGAN WEIGHT RELATIVE TO FINAL BODY WEIGHT (grams)

Group:	I-1	III-1	V-1	VII-1
Dosage(mg/kg/day):	0	75	500	3500
LIVER	4.513 0.394(18)	4.501 0.303(19)	4.413 0.416(19)	4.611 0.398(15)
KIDNEYS	0.878 0.071(18)	0.877 0.076(19)	0.894 0.073(19)	0.918 0.071(15)
THYORID	0.006 0.001(18)	0.006 0.002(19)	0.006 0.001(19)	0.006 0.001(14)
TESTES	0.828 0.108(18)	0.843 0.086(19)	0.840 0.077(19)	0.839 0.090(15)
EPIDIDYMIDES	0.202 0.030(18)	0.205 0.029(19)	0.200 0.027(19)	0.194 0.028(15)
SEMINAL VESICLES	0.337 0.073(18)	0.361 0.052(19)	0.353 0.056(19)	0.364 0.077(15)
PROSTATE*	0.124 0.023(18)	0.124 0.032(19)	0.119 0.026(19)	0.113 0.028(14)
BRAIN	0.524 0.062(18)	0.532 0.048(19)	0.540 0.041(19)	0.566# 0.044(15)

TABLE 44 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE RATS - F_1 ADULTS

ORGAN WEIGHT RELATIVE TO BRAIN (grams)

Group:	I-1	III-1	V-1	VII-1
Dosage (mg/kg/day):	0	75	500	3500
LIVER	877.435 164.736(18)	852.112 98.697(19)	819.154 83.370(19)	816.892 64.904(15)
KIDNEYS	168.825 16.790(18)	165.283 14.528(19)	165.848 12.951(19)	162.724 13.176(15)
THYROID	1.091 0.161(18)	1.157 0.303(19)	1.128 0.211(19)	1.108 0.194(14)
TESTES	157.948 12.537(18)	158.611 10.872(19)	155.731 13.511(19)	148.782 17.054(15)
EPIDIDYMIDES	38.549 4.131(18)	38.426 4.038(19)	37.123 5.029(19)	34.321*# 4.778(15)
SEMINAL VESICLES	64.500 12.144(18)	67.842 8.443(19)	65.856 12.253(19)	64.117 11.855(15)
PROSTATE[a]	23.854 4.499(18)	23.315 5.965(19)	22.175 5.055(19)	20.022@# 4.959(14)

Data summarized as: Mean
Standard Deviation (n)

a Prostate weight from animal 660638 was removed from calculation due to weighing error.

Statistical Methods: Trend test (Jonckheere-Terpstra).

Significant difference from control at $p < 0.05$ using Trend test (Jonckheere-Terpstra).

* Significant difference from control at $p < 0.05$ (Parametric comparison to control (Dunnett/Tamhane-Dunnett)

@ Significant difference from control at $p < 0.05$ by Dunn's nonparametric comparison to control.

TABLE 45

MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE RATS - F_1 ADULTS

MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)

Group:	II-1	IV-1	VI-1	VIII-1
Dosage(mg/kg/day):	0	75	500	3500
FINAL BODY WEIGHT	237.5	227.9	238.7	225.5
	22.9(18)	22.0(18)	20.3(19)	18.4(14)
LIVER	10.186	9.761	10.677	10.206
	1.710(18)	1.501(18)	1.468(19)	1.014(14)
KIDNEYS	2.148	2.068	2.206	2.080
	0.215(18)	0.204(18)	0.227(19)	0.261(14)
THYROID	0.020	0.018	0.019	0.018
	0.004(18)	0.006(18)	0.006(19)	0.003(14)
UTERUS	0.490	0.509	0.521	0.477
	0.123(18)	0.174(18)	0.177(19)	0.142(14)
OVARIES	0.247	0.120	0.149	0.136
	0.436(18)	0.017(18)	0.034(19)	0.027(14)
BRAIN	1.825	1.838	1.876	1.762
	0.112(18)	0.097(18)	0.109(19)	0.110(14)

TABLE 45 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE RATS - F_1 ADULTS

ORGAN WEIGHT RELATIVE TO FINAL BODY WEIGHT (grams)

Group:	II-1	IV-1	VI-1	VIII-1
Dosage(mg/kg/day):	0	75	500	3500
LIVER	4.271	4.274	4.464	4.528#
	0.391(18)	0.403(18)	0.387(19)	0.271(14)
KIDNEYS	0.906	0.911	0.926	0.923
	0.056(18)	0.076(18)	0.080(19)	0.093(14)
THYROID	0.008	0.008	0.008	0.008
	0.002(18)	0.003(18)	0.002(19)	0.001(14)
UTERUS	0.208	0.225	0.220	0.211
	0.058(18)	0.078(18)	0.079(19)	0.059(14)
OVARIES	0.102	0.053	0.063	0.060
	0.174(18)	0.008(18)	0.014(19)	0.011(14)
BRAIN	0.774	0.813	0.789	0.784
	0.074(18)	0.076(18)	0.056(19)	0.051(14)

TABLE 45 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS FROM FEMALE RATS - F_1 ADULTS

ORGAN WEIGHT RELATIVE TO BRAIN (grams)

Group:	II-1	IV-1	VI-1	VIII-1
Dosage(mg/kg/day):	0	75	500	3500
LIVER	559.636	531.860	568.963	578.696
	97.677(18)	84.213(18)	72.115(19)	36.327(14)
KIDNEYS	117.892	112.617	117.612	117.819
	11.783(18)	10.458(18)	10.588(19)	10.601(14)
THYROID	1.097	0.994	1.013	1.051
	0.217(18)	0.350(18)	0.297(19)	0.174(14)
UTERUS	26.805	27.787	27.897	27.158
	6.398(18)	9.727(18)	9.899(19)	8.184(14)
OVARIES	13.571	6.521@	7.897	7.736
	23.946(18)	0.797(18)	1.600(19)	1.520(14)

Data summarized as: Mean
Standard Deviation (n)

Statistical Methods: Trend test (Jonckheere-Terpstra).

Significant difference from control at p < 0.05 using Trend test (Jonckheere-Terpstra).

TABLE 46

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS - P_1 ADULTS

SITE/LESION:	GROUP DESIGNATION: I-0 DOSE (mg/kg/day): 0 NUMBER IN GROUP: 25	III-0 75 26	V-0 500 25	VII-0 3500 25
LIVER				
DILATATION	0	0	1	0
DISCOLORATION	0	0	0	1
ESOPHAGUS				
PERFORATION	0	0	0	1
RUPTURE	0	0	1	0
LUNGS				
DISCOLORATION	0	0	0	1
KIDNEYS				
MASS	1	0	0	0
DILATATION	0	1	0	0
EPIDIDYMIDES				
SMALL	0	1	0	0
TESTES				
SMALL	0	1	0	0
SOFT	0	0	0	1
SKIN				
ULCER/EROSION	1	0	0	0
STAIN	0	0	0	2
WET	0	0	0	1

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

TABLE 47

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS - P_1 ADULTS

SITE/LESION:	GROUP DESIGNATION: / DOSE (mg/kg/day): / NUMBER IN GROUP:	II-0 0 25	IV-0 75 25	VI-0 500 25	VIII-0 3500 25
KIDNEYS					
CYST		0	0	0	1
DILATATION		1	1	0	1
VAGINA					
FLUID		1	0	0	0
SKIN					
ALOPECIA		0	0	0	2
DISCOLORATION		1	0	0	0

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

TABLE 48

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS - F_1 ADULTS

SITE/LESION:	GROUP DESIGNATION:	I-1	III-1	V-1	VII-1
	DOSE (mg/kg/day):	0	75	500	3500
	NUMBER IN GROUP:	18	19	19	15
LIVER					
DISCOLORATION		1	0	0	0
URINARY BLADDER					
THICK		0	0	1	0
CALCULUS		0	0	1	0
KIDNEYS					
DILATATION		3	1	4	5
DISCOLORATION		0	0	1	0
THYMUS					
DISCOLORATION		0	0	0	1

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

TABLE 49

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS - F_1 ADULTS

SITE/LESION:	GROUP DESIGNATION: / DOSE (mg/kg/day): / NUMBER IN GROUP:	II-1 0 18	IV-1 75 18	VI-1 500 19	VIII-1 3500 15
URINARY BLADDER					
CALCULUS		0	0	1	0
KIDNEYS					
DILATATION		2	0	3	3
DEFORMITY		0	0	1	0

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

TABLE 50

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS - F_1 WEANLINGS

SITE/LESION:	GROUP DESIGNATION:	I-1	III-1	V-1	VII-1
	DOSE (mg/kg/day):	0	75	500	3500
	NUMBER IN GROUP:	54	55	56	43
WHOLE BODY					
SMALL		0	0	0	4

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

TABLE 51

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS - F_1 WEANLINGS

SITE/LESION:	GROUP DESIGNATION: / DOSE (mg/kg/day): / NUMBER IN GROUP:	II-1 0 50	IV-1 75 47	VI-1 500 58	VIII-1 3500 45
URINARY BLADDER					
CALCULUS		0	0	0	1
KIDNEYS					
DILATATION		0	1	0	0
LONG BONE					
MISSING		0	0	0	1
WHOLE BODY					
SMALL		0	0	0	1

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

TABLE 52

INCIDENCES OF GROSS OBSERVATIONS IN GENERATION F_1 MALE PUPS

SITE/LESION:	DAM GROUP DESIGNATION:	II-0	IV-0	VI-0	VIII-0
	DOSE (mg/kg/day):	0	75	500	3500
	NUMBER PUPS/LITTERS:	1/1	1/1	0/0	1/1
STOMACH					
NO MILK SPOT		1 (1)	1 (1)	0 (0)	1 (1)
LUNGS					
NOT EXPANDED		1 (1)	1 (1)	0 (0)	1 (1)
TOTAL LITTERS AFFECTED		1	1	0	1
TOTAL PUPS AFFECTED		1	1	0	1

For each group: The count of pups only includes those which underwent pathological examination.
The count of litters only includes those in which pups underwent pathological examination.

For each site/lesion: Numbers outside the parentheses are the number of pups affected.
Numbers in parentheses are the number of litters affected.

TABLE 53

INCIDENCES OF GROSS OBSERVATIONS IN GENERATION F_1 FEMALE PUPS

SITE/LESION:	DAM GROUP DESIGNATION:	II-0	IV-0	VI-0	VIII-0
	DOSE (mg/kg/day):	0	75	500	3500
	NUMBER PUPS/LITTERS:	1/1	0/0	0/0	6/4
STOMACH					
NO MILK SPOT		1 (1)	0 (0)	0 (0)	4 (2)
LUNGS					
NOT EXPANDED		1 (1)	0 (0)	0 (0)	3 (1)
TOTAL LITTERS AFFECTED		1	0	0	2
TOTAL PUPS AFFECTED		1	0	0	4

For each group: The count of pups only includes those which underwent pathological examination.
The count of litters only includes those in which pups underwent pathological examination.

For each site/lesion: Numbers outside the parentheses are the number of pups affected.
Numbers in parentheses are the number of litters affected.

TABLE 54

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS - P_1 ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	I-0	III-0	V-0	VII-0
		DOSE (mg/kg/day):	0	75	500	3500
		NUMBER IN GROUP:	20	20	20	20
LIVER			11	10	12	11
FATTY CHANGE, MEDIAN CLEFT			1 (-,-,1,-,-)	-	2 (-,1,1,-,-)	-
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR			-	-	10 (,1, , ,)	10 (, ,1, ,)
					(-,0,-,-,-)	(-,-,0,-,-)
INFLAMMATION, SUBACUTE/CHRONIC			11 (,1, , ,)	9 (, , , ,)	9 (, , , ,)	10 (, , , ,)
			(-,1,-,-,-)	(-,9,-,-,-)	(-,9,-,-,-)	(-,9,1,-,-)
NECROSIS, HEPATOCYTES, CENTRILOBULAR			-	-	-	1 (-,-,-,1,-)
KIDNEYS			12	10	11	10
*B: NEPHROBLASTOMA			1 (1,-,-,-,-)	-	-	-
INFARCT			-	-	-	1 (-,1,-,-,-)
NEPHROPATHY, CHRONIC PROGRESSIVE			4 (-,4,-,-,-)	2 (-,2,-,-,-)	8 (-,8,-,-,-)	9 (-,9,-,-,-)
PYELONEPHRITIS, UNILATERAL			-	-	-	1 (-,1,-,-,-)
THYROID GLAND			11	10	12	10
ALTERATION, COLLOID			9 (-,7,2,-,-)	10 (-,5,1,4,-)	11 (-,1,4,3,3)	10 (-,-,3,2,5)
HYPERTROPHY, FOLLICULAR CELL			-	2 (, , , ,)	11 (,1, , ,)	9 (, , , ,)
				(-,2,-,-,-)	(-,0,1,-,-)	(-,8,1,-,-)
INFLAMMATION, SUBACUTE/CHRONIC			1 (-,1,-,-,-)	-	-	1 (-,1,-,-,-)
TESTES			2	1	1	6
DEGENERATION/ATROPHY, SEMINIFEROUS TUBULES, UNILATERAL			-	1 (-,-,-,-,1)	-	1 (-,-,-,-,1)
EPIDIDYMIDES			2	1	1	5
OLIGOSPERMIA/GERM CELL DEBRIS, UNILATERAL			-	1 (-,-,-,-,1)	-	-
SEMINAL VESICLES WITH COA			2	1	1	5
PROSTATE GLAND			2	1	1	5
INFLAMMATION, SUBACUTE/CHRONIC			-	-	-	1 (-,1,-,-,-)

TABLE 50 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS - P_1 ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: DOSE (mg/kg/day): NUMBER IN GROUP:	I-0 0 20	III-0 75 20	V-0 500 20	VII-0 3500 20
OTHER						
ESOPHAGUS: INFLAMMATION/NECROSIS			1/-	0/-	1/-	2/1 (-,-,-,1,-)
ESOPHAGUS: NO ABNORMALITY DETECTED			-	-	1 (1,-,-,-,-)	-
LUNG: CONGESTION			-	-	-	1 (1,-,-,-,-)
SKIN: INFLAMMATION/ULCER			1 (-,-,-,1,-)	-	-	-
PITUITARY GLAND			0	0	0	0
TOTAL ANIMALS WITH PRIMARY TUMORS			1	0	0	0
TOTAL ANIMALS WITH BENIGN TUMORS			1	0	0	0
TOTAL ANIMALS WITH MALIGNANT TUMORS			0	0	0	0

NOTES:

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

TABLE 55

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS - P_1 ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: DOSE (mg/kg/day): NUMBER IN GROUP:	II-0 0 20	IV-0 75 20	VI-0 500 20	VIII-0 3500 20
LIVER			10	0	0	10
INFLAMMATION, SUBACUTE/CHRONIC			2 (-,2,-,-,-)	-	-	1 (-,1,-,-,-)
KIDNEYS			11	1	0	11
CYST			-	-	-	1 (-,1,-,-,-)
HYDRONEPHROSIS, BILATERAL			1 (-,-,-,1,-)	-	-	-
HYDRONEPHROSIS, UNILATERAL			-	1 (-,-,1,-,-)	-	1 (-,-,1,-,-)
INFARCT			-	-	-	1 (-,1,-,-,-)
NEPHROPATHY, CHRONIC PROGRESSIVE			1 (-,1,-,-,-)	-	-	1 (-,1,-,-,-)
PYELONEPHRITIS, BILATERAL			1 (-,-,1,-,-)	-	-	-
THYROID GLAND			10	10	10	10
ALTERATION, COLLOID			5 (-,4,1,-,-)	4 (-,4,-,-,-)	9 (-,3,5,1,-)	10 (-,4,1,5,-)
HYPERTROPHY, FOLLICULAR CELL			-	-	5 (-,5,-,-,-)	8 (-,8,-,-,-)
OVARIES WITH OVIDUCTS			2	1	1	5
UTERUS AND CERVIX			2	1	1	5
DILATATION, GLAND/LUMEN			1 (-,-,1,-,-)	-	-	1 (-,1,-,-,-)
VAGINA			2	1	1	5
OTHER			1	0	0	1
SKIN: NO ABNORMALITIES DETECTED			1 (1,-,-,-,-)	-	-	1 (1,-,-,-,-)
PITUITARY GLAND			0	0	0	0
TOTAL ANIMALS WITH PRIMARY TUMORS			0	0	0	0
TOTAL ANIMALS WITH BENIGN TUMORS			0	0	0	0
TOTAL ANIMALS WITH MALIGNANT TUMORS			0	0	0	0

TABLE 51 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS - P_1 ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	II-0	IV-0	VI-0	VIII-0
		DOSE (mg/kg/day):	0	75	500	3500
		NUMBER IN GROUP:	20	20	20	20

NOTES:

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

TABLE 56

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS - F_1 ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: I-1	III-1	V-1	VII-1
	DOSE (mg/kg/day):	0	75	500	3500
	NUMBER IN GROUP:	18	19	19	15
LIVER		18	0	0	15
INFLAMMATION, SUBACUTE/CHRONIC		9 (, , , ,) (-,9,-,-,-)	-	-	10 (,1, , ,) (-,0,-,-,-)
NECROSIS, FOCAL		-	-	-	1 (-,1,-,-,-)
KIDNEYS		18	1	5	15
CYST		-	-	-	2 (-,2,-,-,-)
HYDRONEPHROSIS, BILATERAL		1 (-,-,1,-,-)	-	-	1 (-,1,-,-,-)
HYDRONEPHROSIS, UNILATERAL		2 (-,1,1,-,-)	1 (-,-,1,-,-)	3 (-,2,-,1,-)	5 (-,4,1,-,-)
HYPERPLASIA, TRANSITIONAL CELL		-	-	1 (-,1,-,-,-)	-
INFARCT		1 (-,1,-,-,-)	-	-	-
NEPHROPATHY, CHRONIC PROGRESSIVE		11 (,1, , ,) (-,1,-,-,-)	1 (, , , ,) (-,1,-,-,-)	4 (, , , ,) (-,4,-,-,-)	10 (,1, , ,) (-,0,-,-,-)
PYELONEPHRITIS, BILATERAL		-	-	2 (-,1,-,1,-)	-
PYELONEPHRITIS, UNILATERAL		-	-	1 (-,1,-,-,-)	-
THYROID GLAND		17	19	19	15
ALTERATION, COLLOID		1 (-,1,-,-,-)	-	1 (-,1,-,-,-)	2 (-,2,-,-,-)
HYPERTROPHY, FOLLICULAR CELL		-	3 (-,3,-,-,-)	6 (-,6,-,-,-)	7 (-,7,-,-,-)
TESTES		0	0	0	0
EPIDIDYMIDES		0	0	0	0
SEMINAL VESICLES WITH COA		0	0	0	0
PROSTATE GLAND		0	0	0	0
OTHER		0	0	1	1
THYMUS: NO ABNORMALITY DETECTED		-	-	-	1 (1,-,-,-,-)
URINARY BLADDER: INFLAMMATION/HYPERPLASIA		-	-	1 (-,-,-,1,-)	-

TABLE 52 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS - F_1 ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	I-1	III-1	V-1	VII-1
		DOSE (mg/kg/day):	0	75	500	3500
		NUMBER IN GROUP:	18	19	19	15
PITUITARY GLAND			0	0	0	0
TOTAL ANIMALS WITH PRIMARY TUMORS			0	0	0	0
TOTAL ANIMALS WITH BENIGN TUMORS			0	0	0	0
TOTAL ANIMALS WITH MALIGNANT TUMORS			0	0	0	0

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

TABLE 57

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS - F_1 ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: II-1	IV-1	VI-1	VIII-1
		DOSE (mg/kg/day): 0	75	500	3500
		NUMBER IN GROUP: 18	18	19	15
LIVER		0	0	0	0
KIDNEYS		2	0	4	3
HYDRONEPHROSIS, BILATERAL		1 (-,-,1,-,-)	-	-	1 (-,-,1,-,-)
HYDRONEPHROSIS, UNILATERAL		1 (-,-,-,1,-)	-	3 (-,1,2,-,-)	2 (-,2,-,-,-)
HYPERPLASIA, TRANSITIONAL CELL		-	-	1 (-,1,-,-,-)	-
NEPHROPATHY, CHRONIC PROGRESSIVE		-	-	2 (-,2,-,-,-)	2 (-,2,-,-,-)
PYELONEPHRITIS, UNILATERAL		-	-	1 (-,-,-,1,-)	-
THYROID GLAND		18	0	19	14
HYPERTROPHY, FOLLICULAR CELL		-	-	-	1 (-,1,-,-,-)
OVARIES WITH OVIDUCTS		0	0	0	0
UTERUS AND CERVIX		0	0	0	0
VAGINA		0	0	0	0
OTHER		0	0	1	0
URINARY BLADDER: HYPERPLASIA, TRANSITIONAL CELL		-	-	1 (-,-,-,1,-)	-
URINARY BLADDER: INFLAMMATION, SUBACUTE/CHRONIC		-	-	1 (-,-,1,-,-)	-
PITUITARY GLAND		0	0	0	0
TOTAL ANIMALS WITH PRIMARY TUMORS		0	0	0	0
TOTAL ANIMALS WITH BENIGN TUMORS		0	0	0	0
TOTAL ANIMALS WITH MALIGNANT TUMORS		0	0	0	0

TABLE 53 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS - F_1 ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	II-1	IV-1	VI-1	VIII-1
		DOSE (mg/kg/day):	0	75	500	3500
		NUMBER IN GROUP:	18	18	19	15

NOTES:

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

TABLE 58

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS - F_1 WEANLINGS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: DOSE (mg/kg/day): NUMBER IN GROUP:	II-1 0 50	IV-1 75 47	VI-1 500 58	VIII-1 3500 45
LIVER			0	0	0	0
KIDNEYS			0	1	0	0
HYDRONEPHROSIS, UNILATERAL			-	1 (-,-,-,-,1)	-	-
THYROID GLAND			0	0	0	0
OVARIES WITH OVIDUCTS			0	0	0	0
UTERUS AND CERVIX			0	0	0	0
VAGINA			0	0	0	0
OTHER			0	0	0	2
LONG BONE: FRACTURE/CALLUS			-	-	-	1 (1,-,-,-,-)
LONG BONE: INFLAMMATION, SUBACUTE/CHRONIC			-	-	-	1 (-,-,-,1,-)
URINARY BLADDER: HYPERPLASIA, TRANSITIONAL CELL			-	-	-	1 (-,-,-,1,-)
URINARY BLADDER: INFLAMMATION, SUBACUTE/CHRONIC			-	-	-	1 (-,-,-,1,-)
PITUITARY GLAND			0	0	0	0
TOTAL ANIMALS WITH PRIMARY TUMORS			0	0	0	0
TOTAL ANIMALS WITH BENIGN TUMORS			0	0	0	0
TOTAL ANIMALS WITH MALIGNANT TUMORS			0	0	0	0

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

APPENDICES

APPENDIX A

ANALYTICAL DATA

Table I. Concentration Verification and Stability of H-25231 in Dosing Solutions

Preparation Day Sample Type	mg/mL H-25231(A) Nominal	 Measured	Percent Nominal
Test Day 2			
Concentration Verification(B)			
Control	0.0	ND(C)	----
	15-1	8.62	57.4
	15-1/1	9.36	62.4
	15-1/2	8.18	54.5
	Mean(D):	***8.72***	***(58.1)***
	15-2	12.8	85.3
	Mean(E):	10.8 ± 2.9 ***C.V. 27%***	(72.0)
	100-1	91.6	91.6
	100-2	97.2	97.2
	Mean(E):	***94.4 ± 4.0*** ***C.V. 4%***	***(94.4)***
	700-1	715	102.1
	700-2/1	698	99.6
	700-2/2	638	91.2
	Mean(F):	***668***	***(95.4)***
	Mean(E):	***691 ± 33*** ***C.V. 5%***	***(98.8)***
Stability			
	15	10.8(D)	72.0
	100	87.7	87.7
	700	759(F)	108.4
Test Day 9			
Concentration Verification(B)			
Control	0.0	ND(C)	----
	15-1	12.6	84.0
	15-1/1	12.8	85.3
	15-1/2	12.7	84.7
	Mean(D):	***12.7***	***(84.7)***
	15-2/1	16.0	106.7
	15-2/2	15.2	101.3
	Mean(F):	***15.6***	***(104.0)***
	Mean(E):	***14.2 ± 2.0*** ***C.V. 14%***	***(94.7)***
Stability			
5-Hour Room Temperature	15	16.5	110.0

(A) Dosing solution concentration mg H-25231/mL, based on 5 mL dose volume. H-25231 is approximately [redacted]
(B) Duplicate samples per level were analyzed. Mean, S.D. and C.V. calculated to verify uniformity of mixture.
(C) Denotes not detected.
(D) Mean result for all analyses on original sample.
(E) Mean result for analyses on duplicate samples.
(F) Mean result for duplicate reanalyzes of original sample. Original analysis not reported due to aliquot error.

Table II. Concentration Verification of H-25231 in Dosing Solutions

Preparation Day / Sample Type	mg/mL H-25231(A) Nominal	Measured	Percent Nominal
Test Day 46			
Concentration Verification(B)			
Control	0.0	ND(C)	----
	15-1	15.1	100.7
	15-2	16.6	110.7
	Mean:	***15.9 ± 1.1***	***(106.0)***
		C.V. 7%	
	100-1	112	112.0
	100-2	113	113.0
	Mean:	***113 ± 0.7***	***(113.0)***
		C.V. 1%	
	700-1	749	107.0
	700-2	666(D)	95.1
	Mean:	***708 ± 59***	***(101.1)***
		C.V. 8%	
Test Day 114			
Concentration Verification(B)			
Control	0.0	ND(C)	----
	15-1	16.5	110.0
	15-2	12.9(D)	86.2
	Mean:	***14.7 ± 2.5***	***(98.0)***
		C.V. 17%	
	100-1	107	107.0
	100-2	120	120.0
	Mean:	***114 ± 9.1***	***(114.0)***
		C.V. 8%	
	700-1	765	109.3
	700-2	681	97.3
	Mean:	***723 ± 59***	***(103.3)***
		C.V. 8%	

(A) Dosing solution concentration mg H-25231/mL based on 5 mL dose volume. H-25231 is approximately [redacted]

(B) Duplicate samples per level were analyzed. Mean, S.D. and C.V. calculated to verify uniformity of mixture.

(C) Denotes not detected.

(D) Mean result for duplicate reanalyzes of original sample. Original analysis not reported due to aliquot error.

Figure 1
Representative Analytical Calibration Curves

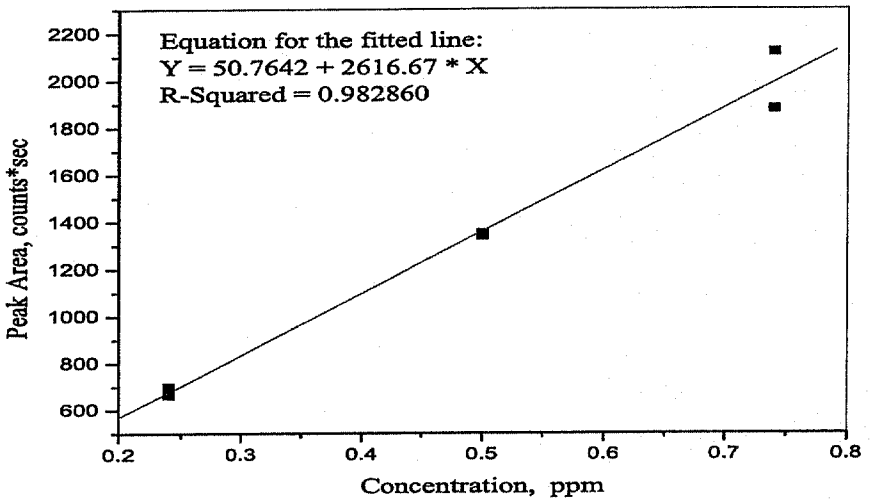

Figure 1a: Calibration curve (LC/MS - C6-C6/bis) showing linear fit (line) to replicate peak area measurements (squares) for calibration solutions of H-25231 diluted over a concentration range of 0.24 to 0.74 ppm (0.00024 to 0.00074 mg/mL).

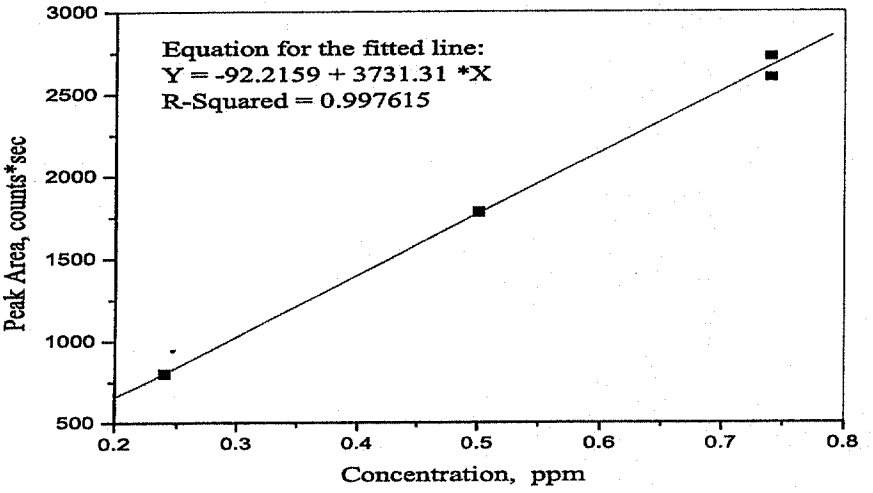

Figure 1b: Calibration curve (LC/MS – C6-C8 bis) showing linear fit (line) to replicate peak area measurements (squares) for calibration solutions of H-25231 diluted over a concentration range of 0.24 to 0.74 ppm (0.00024 to 0.00074 mg/mL).

Figure 1 (continued)
Representative Analytical Calibration Curve

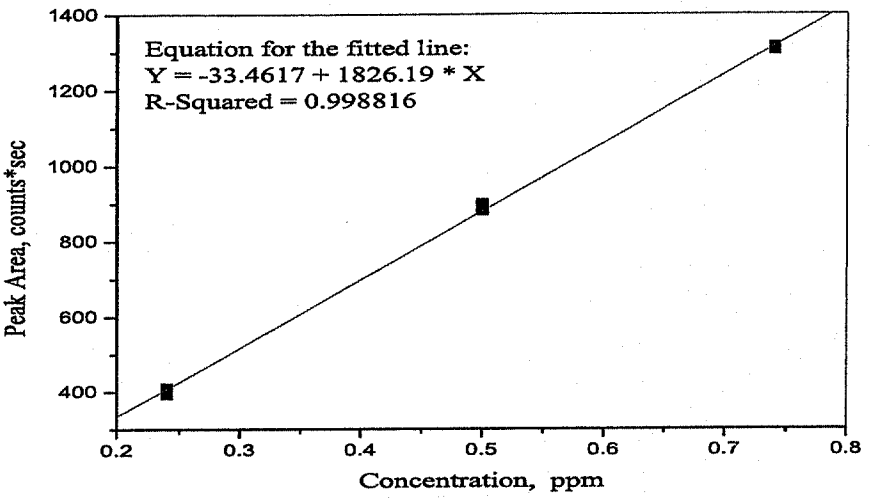

Figure 1c: Calibration curve (LC/MS – C8-C8 bis) showing non-linear fit (line) to replicate peak area measurements (squares) for calibration solutions of H-25231 diluted over a concentration range of 0.24 to 0.74 ppm (0.00024 to 0.00074 mg/mL).

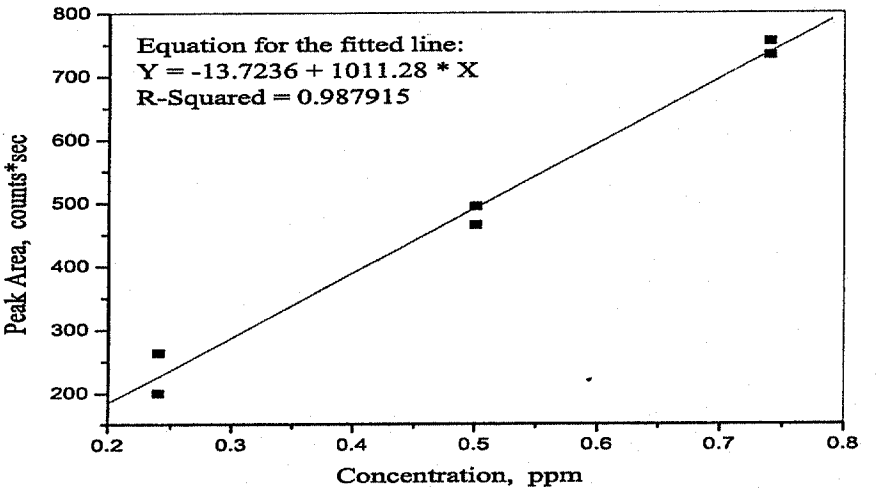

Figure 1d: Calibration curve (LC/MS – C10-C8 bis) showing non-linear fit (line) to replicate peak area measurements (squares) for calibration solutions of H-25231 diluted over a concentration range of 0.24 to 0.74 ppm (0.00024 to 0.00074 mg/mL).

Figure 2
Representative HPLC/MS Chromatography Chromatograms

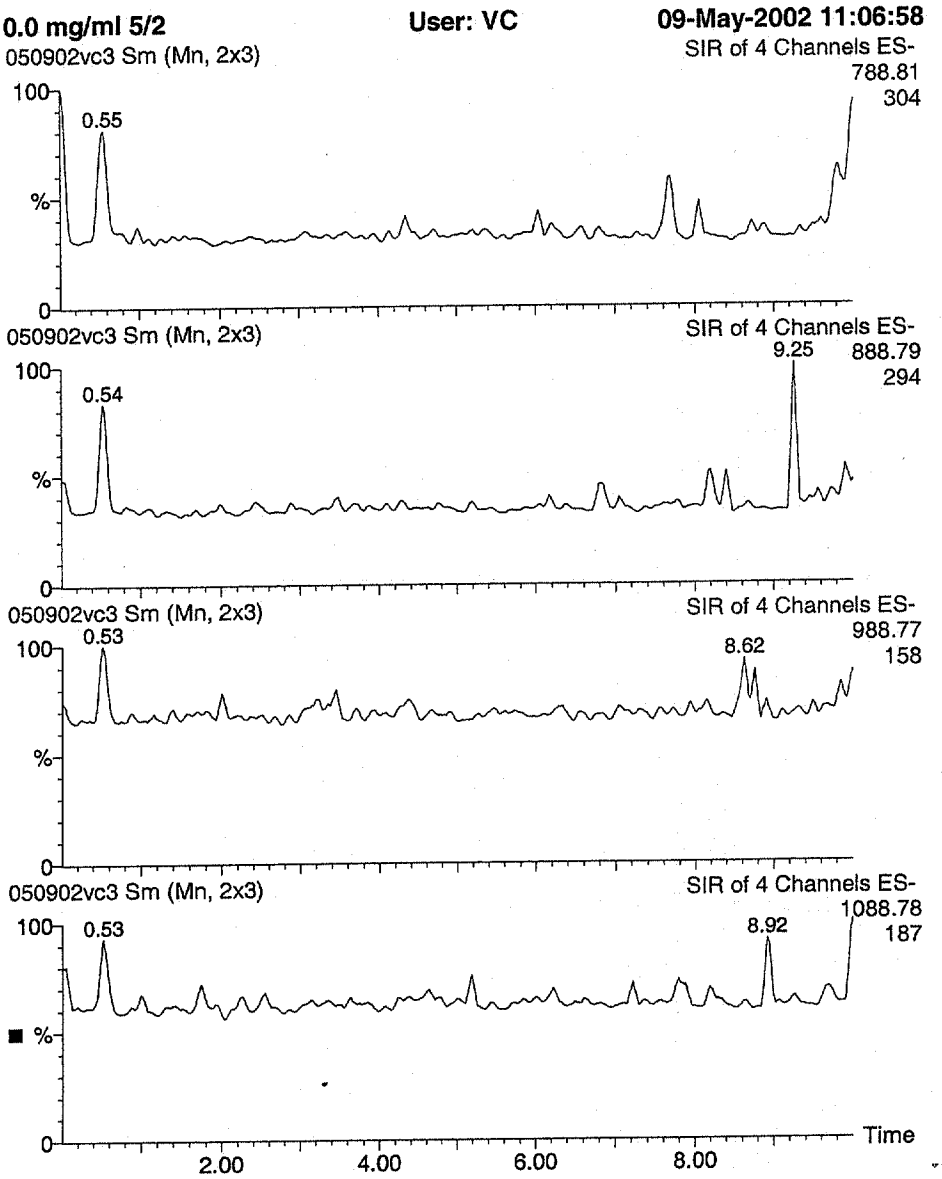

Figure 2a: Representative HPLC/MS chromatograms of 0.00 mg/mL dosing solution of H-25231.

Figure 2 (continued)
Representative HPLC/MS Chromatography Chromatograms

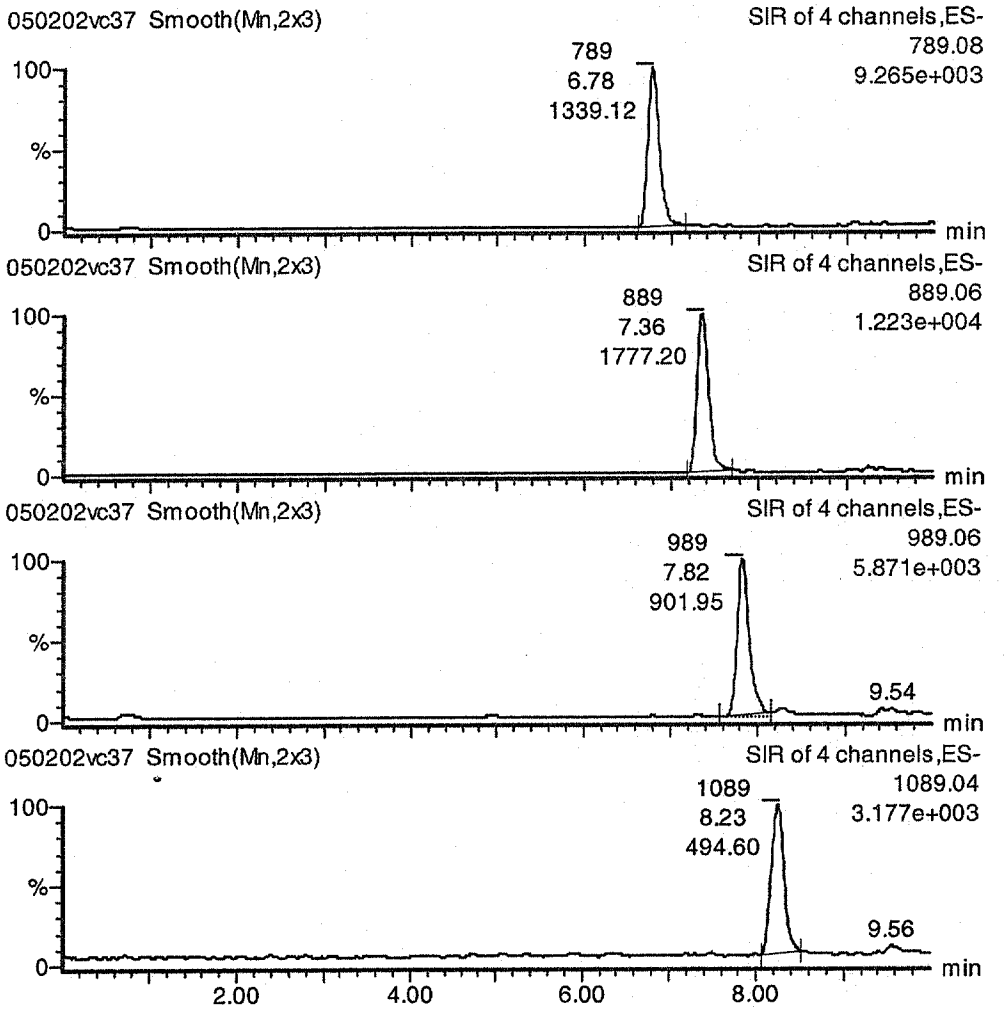

Figure 2b: Representative HPLC/MS chromatograms of 0.50 ppm (0.0005 mg/mL) analytical reference solution of H-25231.

Figure 2 (continued)
Representative HPLC/MS Chromatography Chromatograms

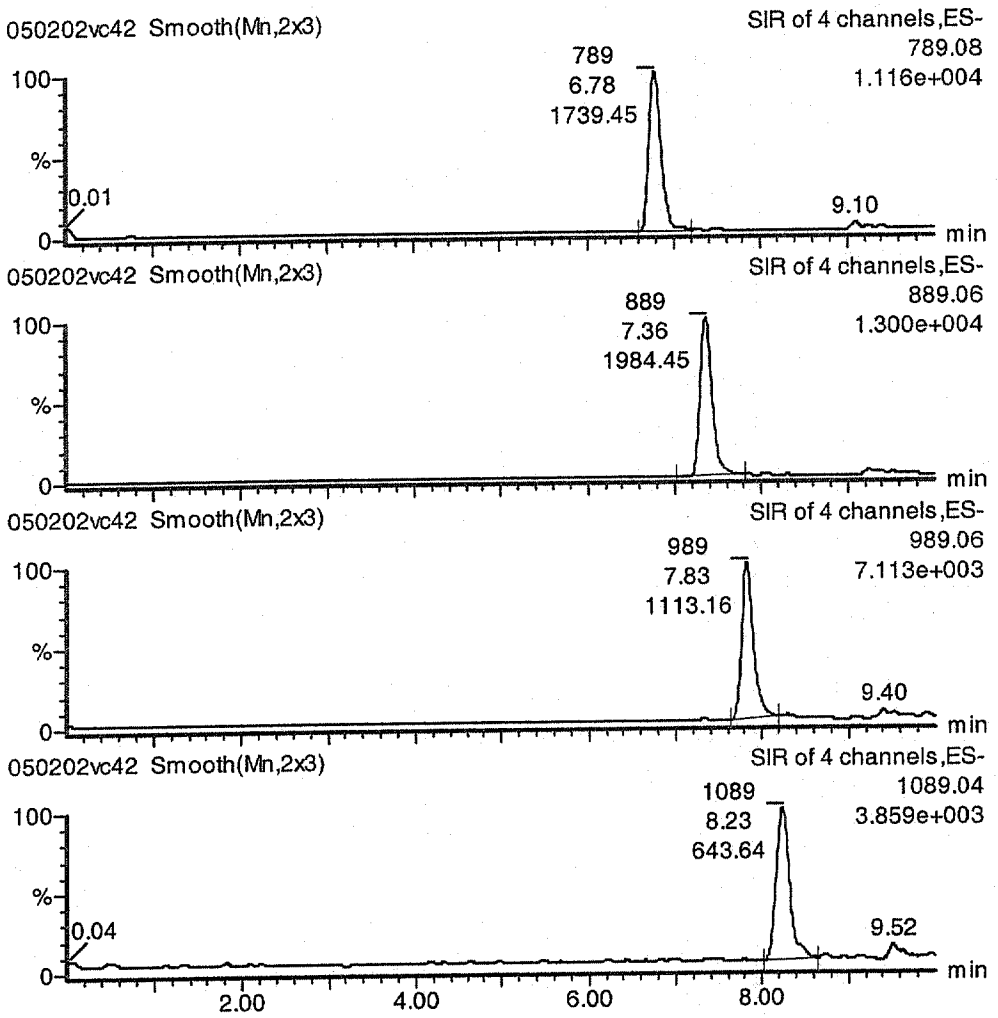

Figure 2c: Representative HPLC/MS chromatograms of 100 mg/mL dosing solution diluted to nominal concentration of 0.50 ppm (0.0005 mg/mL) of H-25231. The measured concentration of the representative solution is 112 mg/mL.

APPENDIX B

INDIVIDUAL BODY WEIGHTS OF P_1 MALE RATS

INDIVIDUAL BODY WEIGHTS OF P_1 MALE RATS

EXPLANATORY NOTES

Notes

Test Days 1-75 = Premating period
Test Days 76-90 = Cohabitation period

Abbreviations

AK = Accidentally Killed
FD = Found dead
SD = Sacrificed by design
SE = Sacrificed *in extremis*; data excluded from group means. (Group I-0, Animal No. 657409)
\- = No Data

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 MALE RATS

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

DAYS ON TEST:	1	8	15	22	29	36	43
ANIMAL NO.							
657391	279.5	333.8	374.7	421.1	453.2	470.1	495.3
657392	288.6	335.8	384.5	424.9	465.9	488.8	502.7
657393	302.5	361.0	403.7	438.9	465.7	485.3	495.5
657394	271.3	329.0	387.9	443.2	472.1	508.9	529.2
657395	274.3	322.2	362.2	403.7	431.0	458.3	487.7
657396	282.1	321.2	353.0	400.0	424.3	452.8	474.5
657397	280.9	321.1	348.2	382.3	396.0	414.6	436.9
657398	268.0	313.4	356.7	395.6	423.3	455.5	480.8
657399	275.9	326.4	370.3	402.2	438.9	460.0	479.6
657400	283.9	328.1	364.6	407.8	435.6	462.9	479.1
657401	299.4	337.2	374.7	410.6	445.6	471.5	490.3
657402	262.0	294.7	332.3	367.9	401.3	424.6	442.9
657403	274.4	319.0	366.4	404.1	437.3	449.8	448.9
657404	287.7	346.4	397.8	452.6	492.5	529.1	553.1
657405	295.4	351.5	410.1	454.6	485.5	513.2	535.4
657406	273.9	319.0	380.0	416.2	447.2	483.2	513.0
657407	288.4	349.6	392.8	435.5	468.6	496.9	516.6
657408	279.2	323.0	363.5	389.3	418.9	446.5	464.3
657409	295.3	345.1	390.5	433.9	481.4	501.2	525.7
657410	266.0	314.7	359.4	401.5	429.3	448.3	469.3

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 MALE RATS

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

DAYS ON TEST:	50	57	64	71	78	85	92
ANIMAL NO.							
657391	520.1	530.3	545.5	548.6	536.8	548.8	563.4
657392	532.6	554.9	573.9	581.7	564.0	592.3	603.1
657393	532.3	551.2	568.8	576.2	561.5	594.5	609.9
657394	559.9	581.5	598.1	602.7	598.0	610.9	627.5
657395	512.4	524.9	545.7	557.0	530.8	549.1	568.0
657396	497.4	504.9	525.5	537.5	517.2	542.2	551.2
657397	448.3	458.4	467.9	473.9	466.8	479.2	475.7
657398	511.9	532.9	549.7	560.3	546.0	568.4	584.9
657399	502.4	515.4	536.4	542.7	532.9	550.6	557.4
657400	492.6	511.6	527.2	539.0	530.0	538.3	547.1
657401	516.0	520.5	537.1	549.8	545.4	565.0	586.3
657402	468.5	484.0	494.0	504.7	498.6	517.3	533.7
657403	465.9	474.4	487.7	501.2	503.3	497.6	508.6
657404	582.9	611.7	628.7	651.1	655.2	671.1	695.4
657405	562.6	581.5	599.6	609.0	607.2	617.4	637.9
657406	540.1	557.8	581.9	592.8	594.6	621.1	643.0
657407	542.6	554.8	576.1	592.8	597.9	608.5	619.6
657408	482.5	490.5	502.1	511.6	503.6	521.5	533.7
657409	535.4	531.6	SE (DAY 60)	-	-	-	-
657410	489.7	502.2	510.3	518.5	513.8	526.6	540.8

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 MALE RATS

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

DAYS ON TEST:	99	106	113	
ANIMAL NO.				
657391	574.2	591.3	599.6	SD (DAY 114)
657392	620.5	634.6	640.8	SD (DAY 114)
657393	619.2	612.1	633.4	SD (DAY 114)
657394	642.0	655.9	665.7	SD (DAY 114)
657395	582.8	597.9	609.9	SD (DAY 114)
657396	572.2	576.3	584.3	SD (DAY 115)
657397	486.5	495.4	500.5	SD (DAY 115)
657398	600.0	601.8	613.6	SD (DAY 115)
657399	578.2	579.7	585.9	SD (DAY 115)
657400	566.2	567.2	579.3	SD (DAY 115)
657401	588.0	592.7	606.1	SD (DAY 116)
657402	537.8	549.1	549.5	SD (DAY 116)
657403	517.2	519.0	520.0	SD (DAY 116)
657404	709.6	727.9	749.1	SD (DAY 116)
657405	651.6	659.8	664.6	SD (DAY 116)
657406	661.5	671.5	682.7	SD (DAY 117)
657407	637.8	646.7	663.3	SD (DAY 117)
657408	536.0	530.7	534.9	SD (DAY 117)
657409	-	-	-	
657410	547.9	553.3	550.1	SD (DAY 117)

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 MALE RATS

GROUP: III-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	36	43
ANIMAL NO.							
657416	280.9	322.0	360.1	394.3	418.8	441.1	455.0
657417	288.4	329.9	359.6	391.0	425.3	439.2	459.6
657418	271.9	306.8	344.7	378.6	409.0	439.0	450.2
657419	274.5	310.5	356.6	394.6	427.0	457.7	481.9
657420	284.4	322.5	358.5	390.3	421.0	450.0	466.1
657421	296.6	335.9	380.7	413.8	448.5	481.2	514.5
657422	263.2	295.0	333.7	359.1	388.9	406.0	424.4
657423	280.1	327.1	366.3	408.5	440.0	473.2	496.6
657424	285.7	334.5	390.1	432.0	463.6	488.2	518.1
657425	317.4	375.0	441.5	498.7	539.6	577.6	621.1
657426	263.9	297.9	343.2	376.7	407.4	433.0	453.6
657427	282.9	331.6	379.0	409.0	445.2	479.5	501.6
657428	282.0	327.6	368.6	395.9	438.6	466.6	481.8
657429	299.9	362.0	416.6	472.8	512.7	542.9	561.1
657430	273.5	333.0	378.9	421.5	460.8	496.1	524.9
657431	290.7	331.1	384.5	426.4	471.5	508.1	532.1
657432	295.5	356.6	409.6	454.4	502.1	538.9	567.9
657433	302.2	353.1	406.4	449.7	483.2	509.5	534.5
657435	261.5	294.7	327.4	351.5	371.4	392.4	406.7
657596	247.8	271.5	299.3	325.0	350.5	365.7	375.1

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 MALE RATS

GROUP: III-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	50	57	64	71	78	85	92
ANIMAL NO.							
657416	477.8	487.2	502.1	514.9	504.9	515.2	526.6
657417	475.9	489.8	505.0	521.6	519.9	535.6	550.0
657418	470.3	480.5	488.2	496.1	490.7	497.3	502.5
657419	506.0	522.0	535.6	554.7	545.3	551.0	562.5
657420	478.3	484.1	510.2	510.6	509.4	530.3	542.4
657421	528.7	548.9	571.5	585.3	584.8	591.7	600.1
657422	446.6	465.2	473.0	496.1	464.5	485.3	502.6
657423	516.9	535.0	559.1	570.6	560.1	581.0	596.2
657424	540.0	558.8	569.8	591.9	561.2	572.8	589.6
657425	655.6	683.7	705.0	721.5	704.4	722.3	743.2
657426	481.0	487.7	502.0	511.0	509.1	524.4	540.7
657427	521.7	541.9	556.4	562.1	562.8	582.8	591.8
657428	501.4	520.2	541.7	542.4	545.0	553.2	570.0
657429	586.2	614.5	637.2	649.7	643.0	651.8	662.8
657430	544.1	557.0	579.4	599.6	605.9	612.1	617.9
657431	553.4	572.0	592.1	607.8	602.4	607.2	611.7
657432	600.2	629.6	653.4	673.5	674.5	671.2	691.8
657433	558.2	577.9	598.5	615.1	609.6	619.0	635.4
657435	429.2	438.4	449.3	459.0	459.7	475.3	475.9
657596	391.5	400.0	409.3	409.1	406.0	413.2	418.6

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 MALE RATS

GROUP: III-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	99	106	113	
ANIMAL NO.				
657416	536.1	546.4	552.6	SD (DAY 114)
657417	571.1	574.8	586.9	SD (DAY 114)
657418	516.1	527.2	530.2	SD (DAY 114)
657419	581.0	594.7	603.0	SD (DAY 114)
657420	538.5	538.7	557.3	SD (DAY 114)
657421	616.7	627.7	631.7	SD (DAY 115)
657422	512.5	516.7	529.6	SD (DAY 115)
657423	610.7	625.2	636.5	SD (DAY 115)
657424	601.0	593.6	594.1	SD (DAY 115)
657425	763.3	787.1	795.6	SD (DAY 115)
657426	552.0	559.4	559.9	SD (DAY 116)
657427	605.8	619.2	619.6	SD (DAY 116)
657428	586.4	593.5	609.2	SD (DAY 116)
657429	686.0	688.8	710.3	SD (DAY 116)
657430	623.3	637.3	649.5	SD (DAY 116)
657431	625.6	652.3	649.5	SD (DAY 117)
657432	725.3	741.7	750.8	SD (DAY 117)
657433	662.4	675.8	676.3	SD (DAY 117)
657435	491.1	505.9	514.7	SD (DAY 117)
657596	427.7	434.7	445.6	SD (DAY 117)

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 MALE RATS

GROUP: V-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	36	43
ANIMAL NO.							
657441	288.8	330.6	363.9	406.9	435.4	467.7	483.5
657442	249.2	278.3	308.3	330.6	348.5	359.7	355.6
657443	288.3	337.0	385.4	414.5	449.2	479.3	508.3
657444	280.6	327.4	373.2	416.2	444.3	489.9	510.6
657445	297.8	347.3	389.5	423.2	461.3	491.1	512.3
657446	256.2	289.2	322.4	347.0	366.6	384.6	399.5
657447	276.1	310.8	347.6	369.9	401.4	432.3	451.3
657448	274.8	313.8	347.6	381.5	415.9	442.2	467.7
657449	284.0	336.7	378.4	420.3	463.2	478.7	488.2
657450	258.6	303.3	354.9	389.6	418.7	443.0	462.7
657451	290.5	339.2	384.9	431.6	469.3	503.6	533.7
657452	288.8	338.2	390.9	428.4	469.7	494.2	518.5
657453	291.3	328.7	372.2	400.4	421.1	447.6	480.9
657454	269.7	317.5	362.4	399.2	430.4	461.6	482.9
657455	268.3	295.5	327.0	345.8	364.8	382.3	397.7
657456	293.8	323.5	376.8	408.9	435.2	462.4	488.8
657457	324.9	372.1	433.6	481.8	527.7	569.4	594.2
657458	264.6	300.1	341.4	382.8	420.3	441.3	463.5
657459	275.6	309.7	342.5	368.2	377.0	401.9	421.9
657460	280.0	311.6	351.5	390.1	411.7	441.4	461.2

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 MALE RATS

GROUP: V-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	50	57	64	71	78	85	92
ANIMAL NO.							
657441	503.4	510.2	522.9	534.7	520.9	535.7	539.5
657442	371.4	376.3	395.4	399.4	386.1	395.8	404.6
657443	521.5	533.4	538.4	555.6	529.6	559.2	569.2
657444	546.1	579.2	601.8	600.5	591.7	614.5	615.9
657445	530.6	543.4	551.2	561.7	549.3	547.7	566.0
657446	413.3	423.2	427.9	443.4	427.1	435.1	440.1
657447	469.1	484.9	499.6	514.2	513.7	522.5	533.1
657448	491.5	510.8	518.5	535.1	528.8	542.0	547.8
657449	503.0	511.0	524.7	543.0	527.2	542.5	548.0
657450	483.9	486.8	502.3	515.4	497.0	510.8	516.3
657451	551.8	575.1	591.4	612.7	616.6	618.8	636.6
657452	534.3	544.5	558.1	566.1	552.6	570.2	566.5
657453	446.7	479.3	501.5	516.0	527.8	536.8	546.0
657454	488.3	510.9	526.4	543.9	539.5	550.2	564.5
657455	415.2	428.0	432.9	445.3	447.7	456.4	466.0
657456	498.5	516.0	531.5	552.3	550.6	556.7	558.5
657457	617.2	630.9	646.5	663.2	659.2	667.2	679.5
657458	483.2	491.3	506.5	524.2	516.3	531.8	532.7
657459	433.9	447.8	459.7	476.4	473.3	476.4	AK (DAY 86)
657460	478.0	485.7	491.4	509.0	460.1	486.7	497.8

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 MALE RATS

GROUP: V-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	99	106	113	
ANIMAL NO.				
657441	538.8	545.7	553.6	SD (DAY 114)
657442	413.5	410.3	415.5	SD (DAY 114)
657443	580.7	586.3	585.7	SD (DAY 114)
657444	629.2	645.9	671.2	SD (DAY 114)
657445	580.6	578.3	572.7	SD (DAY 114)
657446	443.4	454.0	458.7	SD (DAY 115)
657447	540.7	548.7	557.9	SD (DAY 115)
657448	554.3	563.0	568.3	SD (DAY 115)
657449	558.9	570.5	572.4	SD (DAY 115)
657450	526.2	541.7	543.1	SD (DAY 115)
657451	640.2	642.4	653.0	SD (DAY 116)
657452	575.2	586.2	599.4	SD (DAY 116)
657453	555.9	574.0	581.0	SD (DAY 116)
657454	574.3	572.6	584.4	SD (DAY 116)
657455	471.1	481.1	488.5	SD (DAY 116)
657456	566.6	566.0	570.8	SD (DAY 117)
657457	699.6	710.4	729.1	SD (DAY 117)
657458	538.1	553.8	554.2	SD (DAY 117)
657459	-	-	-	
657460	510.9	524.6	530.9	SD (DAY 117)

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 MALE RATS

GROUP: VII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	36	43
ANIMAL NO.							
657466	267.4	271.4	316.0	360.6	377.5	393.8	424.2
657467	265.2	280.4	309.3	335.0	352.7	372.5	369.4
657468	286.3	283.8	324.1	324.2	365.6	406.0	433.8
657469	297.6	318.4	344.3	370.6	388.2	418.5	438.2
657470	255.1	287.0	315.2	337.4	349.3	373.2	377.0
657471	271.3	293.7	302.0	322.9	337.7	350.7	352.0
657472	290.9	322.9	372.1	408.2	439.9	452.0	468.4
657473	299.8	341.4	366.1	397.0	401.7	430.1	452.4
657474	270.5	314.7	336.0	365.7	389.1	409.7	424.5
657475	261.0	286.6	305.1	322.7	338.9	356.1	349.4
657476	288.8	330.0	355.2	350.8	383.7	388.5	400.1
657477	301.0	347.7	391.8	436.9	473.6	478.6	AK (DAY 42)
657478	279.0	326.6	369.2	408.2	441.5	469.9	488.7
657479	275.7	289.4	334.6	364.6	389.5	381.8	401.3
657480	287.8	318.8	362.6	388.4	418.1	422.2	435.1
657481	293.2	338.9	389.0	438.0	474.3	500.3	523.5
657482	274.8	295.0	333.5	355.1	376.2	383.7	394.5
657483	281.8	328.9	383.7	413.0	444.5	449.4	466.0
657484	287.8	313.2	334.0	383.6	421.6	431.4	457.1
657485	284.0	326.7	354.8	385.3	398.2	418.8	428.6

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 MALE RATS

GROUP: VII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	50	57	64	71	78	85	92
ANIMAL NO.							
657466	453.9	475.5	478.2	494.7	477.8	492.0	495.6
657467	384.4	393.1	390.0	396.0	359.8	391.1	391.9
657468	424.0	444.5	460.0	480.9	437.8	458.8	442.8
657469	463.1	485.1	503.0	511.5	492.4	470.3	482.0
657470	383.9	396.2	383.6	397.9	388.8	416.6	426.6
657471	351.7	362.2	368.9	374.5	315.0	337.6	366.4
657472	485.9	500.9	507.1	507.3	503.1	500.4	512.4
657473	478.5	493.4	516.4	530.0	515.1	520.9	531.1
657474	418.9	410.8	439.5	440.0	438.6	424.8	440.3
657475	371.9	391.1	396.5	409.6	403.3	402.7	399.8
657476	419.5	437.3	451.7	453.6	451.0	439.2	461.5
657477	-	-	-	-	-	-	-
657478	513.8	533.9	540.6	551.2	543.3	559.0	573.6
657479	397.4	411.2	414.9	412.8	409.7	429.5	419.6
657480	430.6	450.4	466.4	480.5	464.8	453.0	472.8
657481	497.3	525.0	565.7	590.0	590.2	606.1	627.5
657482	404.4	423.6	449.4	FD (DAY 66)	-	-	-
657483	462.5	477.4	497.7	454.1	460.2	481.0	494.3
657484	436.9	456.6	490.5	484.5	484.9	473.6	488.8
657485	431.7	445.7	452.6	460.3	472.9	487.0	437.0

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 MALE RATS

GROUP: VII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	99	106	113	
ANIMAL NO.				
657466	505.1	526.4	511.2	SD (DAY 114)
657467	408.8	399.8	412.5	SD (DAY 114)
657468	436.7	465.7	461.3	SD (DAY 114)
657469	504.1	490.0	497.6	SD (DAY 114)
657470	419.2	421.8	430.0	SD (DAY 114)
657471	379.7	375.5	383.2	SD (DAY 115)
657472	524.7	523.7	533.3	SD (DAY 115)
657473	520.5	495.9	497.2	SD (DAY 115)
657474	448.1	434.4	442.7	SD (DAY 115)
657475	406.7	422.4	428.6	SD (DAY 115)
657476	448.7	451.7	471.7	SD (DAY 116)
657477	-	-	-	
657478	568.0	590.9	604.8	SD (DAY 116)
657479	427.4	426.2	428.6	SD (DAY 116)
657480	482.9	451.4	475.4	SD (DAY 116)
657481	638.6	660.5	667.7	SD (DAY 117)
657482	-	-	-	
657483	501.1	492.1	492.3	SD (DAY 117)
657484	503.9	506.3	533.4	SD (DAY 117)
657485	480.3	494.2	509.3	SD (DAY 117)

APPENDIX C

INDIVIDUAL BODY WEIGHT GAINS OF P_1 MALE RATS

INDIVIDUAL BODY WEIGHT GAINS OF P_1 MALE RATS

EXPLANATORY NOTES

Notes

Test Days 1-75 = Premating period
Test Days 76-90 = Cohabitation period

Abbreviations

AK = Accidentally Killed
FD = Found dead
SD = Sacrificed by design
SE = Sacrificed *in extremis*; data excluded from group means. (Group I-0, Animal No. 657409)
\- = No Data

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

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

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657391	54.3	40.9	46.4	32.1	16.9	25.2	24.8
657392	47.2	48.7	40.4	41.0	22.9	13.9	29.9
657393	58.5	42.7	35.2	26.8	19.6	10.2	36.8
657394	57.7	58.9	55.3	28.9	36.8	20.3	30.7
657395	47.9	40.0	41.5	27.3	27.3	29.4	24.7
657396	39.1	31.8	47.0	24.3	28.5	21.7	22.9
657397	40.2	27.1	34.1	13.7	18.6	22.3	11.4
657398	45.4	43.3	38.9	27.7	32.2	25.3	31.1
657399	50.5	43.9	31.9	36.7	21.1	19.6	22.8
657400	44.2	36.5	43.2	27.8	27.3	16.2	13.5
657401	37.8	37.5	35.9	35.0	25.9	18.8	25.7
657402	32.7	37.6	35.6	33.4	23.3	18.3	25.6
657403	44.6	47.4	37.7	33.2	12.5	-0.9	17.0
657404	58.7	51.4	54.8	39.9	36.6	24.0	29.8
657405	56.1	58.6	44.5	30.9	27.7	22.2	27.2
657406	45.1	61.0	36.2	31.0	36.0	29.8	27.1
657407	61.2	43.2	42.7	33.1	28.3	19.7	26.0
657408	43.8	40.5	25.8	29.6	27.6	17.8	18.2
657409	49.8	45.4	43.4	47.5	19.8	24.5	9.7
657410	48.7	44.7	42.1	27.8	19.0	21.0	20.4

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

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

DAYS ON TEST:	50-57	57-64	64-71	71-78	78-85	85-92	92-99
ANIMAL NO.							
657391	10.2	15.2	3.1	-11.8	12.0	14.6	10.8
657392	22.3	19.0	7.8	-17.7	28.3	10.8	17.4
657393	18.9	17.6	7.4	-14.7	33.0	15.4	9.3
657394	21.6	16.6	4.6	-4.7	12.9	16.6	14.5
657395	12.5	20.8	11.3	-26.2	18.3	18.9	14.8
657396	7.5	20.6	12.0	-20.3	25.0	9.0	21.0
657397	10.1	9.5	6.0	-7.1	12.4	-3.5	10.8
657398	21.0	16.8	10.6	-14.3	22.4	16.5	15.1
657399	13.0	21.0	6.3	-9.8	17.7	6.8	20.8
657400	19.0	15.6	11.8	-9.0	8.3	8.8	19.1
657401	4.5	16.6	12.7	-4.4	19.6	21.3	1.7
657402	15.5	10.0	10.7	-6.1	18.7	16.4	4.1
657403	8.5	13.3	13.5	2.1	-5.7	11.0	8.6
657404	28.8	17.0	22.4	4.1	15.9	24.3	14.2
657405	18.9	18.1	9.4	-1.8	10.2	20.5	13.7
657406	17.7	24.1	10.9	1.8	26.5	21.9	18.5
657407	12.2	21.3	16.7	5.1	10.6	11.1	18.2
657408	8.0	11.6	9.5	-8.0	17.9	12.2	2.3
657409	-3.8	SE (DAY 60)	-	-	-	-	-
657410	12.5	8.1	8.2	-4.7	12.8	14.2	7.1

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

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

DAYS ON TEST:	99-106	106-113	1-71	1-113
ANIMAL NO.				
657391	17.1	8.3	269.1	320.1
657392	14.1	6.2	293.1	352.2
657393	-7.1	21.3	273.7	330.9
657394	13.9	9.8	331.4	394.4
657395	15.1	12.0	282.7	335.6
657396	4.1	8.0	255.4	302.2
657397	8.9	5.1	193.0	219.6
657398	1.8	11.8	292.3	345.6
657399	1.5	6.2	266.8	310.0
657400	1.0	12.1	255.1	295.4
657401	4.7	13.4	250.4	306.7
657402	11.3	0.4	242.7	287.5
657403	1.8	1.0	226.8	245.6
657404	18.3	21.2	363.4	461.4
657405	8.2	4.8	313.6	369.2
657406	10.0	11.2	318.9	408.8
657407	8.9	16.6	304.4	374.9
657408	-5.3	4.2	232.4	255.7
657409	-	-	-	-
657410	5.4	-3.2	252.5	284.1

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

GROUP: III-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657416	41.1	38.1	34.2	24.5	22.3	13.9	22.8
657417	41.5	29.7	31.4	34.3	13.9	20.4	16.3
657418	34.9	37.9	33.9	30.4	30.0	11.2	20.1
657419	36.0	46.1	38.0	32.4	30.7	24.2	24.1
657420	38.1	36.0	31.8	30.7	29.0	16.1	12.2
657421	39.3	44.8	33.1	34.7	32.7	33.3	14.2
657422	31.8	38.7	25.4	29.8	17.1	18.4	22.2
657423	47.0	39.2	42.2	31.5	33.2	23.4	20.3
657424	48.8	55.6	41.9	31.6	24.6	29.9	21.9
657425	57.6	66.5	57.2	40.9	38.0	43.5	34.5
657426	34.0	45.3	33.5	30.7	25.6	20.6	27.4
657427	48.7	47.4	30.0	36.2	34.3	22.1	20.1
657428	45.6	41.0	27.3	42.7	28.0	15.2	19.6
657429	62.1	54.6	56.2	39.9	30.2	18.2	25.1
657430	59.5	45.9	42.6	39.3	35.3	28.8	19.2
657431	40.4	53.4	41.9	45.1	36.6	24.0	21.3
657432	61.1	53.0	44.8	47.7	36.8	29.0	32.3
657433	50.9	53.3	43.3	33.5	26.3	25.0	23.7
657435	33.2	32.7	24.1	19.9	21.0	14.3	22.5
657596	23.7	27.8	25.7	25.5	15.2	9.4	16.4

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

GROUP: III-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	50-57	57-64	64-71	71-78	78-85	85-92	92-99
ANIMAL NO.							
657416	9.4	14.9	12.8	-10.0	10.3	11.4	9.5
657417	13.9	15.2	16.6	-1.7	15.7	14.4	21.1
657418	10.2	7.7	7.9	-5.4	6.6	5.2	13.6
657419	16.0	13.6	19.1	-9.4	5.7	11.5	18.5
657420	5.8	26.1	0.4	-1.2	20.9	12.1	-3.9
657421	20.2	22.6	13.8	-0.5	6.9	8.4	16.6
657422	18.6	7.8	23.1	-31.6	20.8	17.3	9.9
657423	18.1	24.1	11.5	-10.5	20.9	15.2	14.5
657424	18.8	11.0	22.1	-30.7	11.6	16.8	11.4
657425	28.1	21.3	16.5	-17.1	17.9	20.9	20.1
657426	6.7	14.3	9.0	-1.9	15.3	16.3	11.3
657427	20.2	14.5	5.7	0.7	20.0	9.0	14.0
657428	18.8	21.5	0.7	2.6	8.2	16.8	16.4
657429	28.3	22.7	12.5	-6.7	8.8	11.0	23.2
657430	12.9	22.4	20.2	6.3	6.2	5.8	5.4
657431	18.6	20.1	15.7	-5.4	4.8	4.5	13.9
657432	29.4	23.8	20.1	1.0	-3.3	20.6	33.5
657433	19.7	20.6	16.6	-5.5	9.4	16.4	27.0
657435	9.2	10.9	9.7	0.7	15.6	0.6	15.2
657596	8.5	9.3	-0.2	-3.1	7.2	5.4	9.1

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

GROUP: III-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	99-106	106-113	1-71	1-113
ANIMAL NO.				
657416	10.3	6.2	234.0	271.7
657417	3.7	12.1	233.2	298.5
657418	11.1	3.0	224.2	258.3
657419	13.7	8.3	280.2	328.5
657420	0.2	18.6	226.2	272.9
657421	11.0	4.0	288.7	335.1
657422	4.2	12.9	232.9	266.4
657423	14.5	11.3	290.5	356.4
657424	-7.4	0.5	306.2	308.4
657425	23.8	8.5	404.1	478.2
657426	7.4	0.5	247.1	296.0
657427	13.4	0.4	279.2	336.7
657428	7.1	15.7	260.4	327.2
657429	2.8	21.5	349.8	410.4
657430	14.0	12.2	326.1	376.0
657431	26.7	-2.8	317.1	358.8
657432	16.4	9.1	378.0	455.3
657433	13.4	0.5	312.9	374.1
657435	14.8	8.8	197.5	253.2
657596	7.0	10.9	161.3	197.8

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

GROUP: V-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657441	41.8	33.3	43.0	28.5	32.3	15.8	19.9
657442	29.1	30.0	22.3	17.9	11.2	-4.1	15.8
657443	48.7	48.4	29.1	34.7	30.1	29.0	13.2
657444	46.8	45.8	43.0	28.1	45.6	20.7	35.5
657445	49.5	42.2	33.7	38.1	29.8	21.2	18.3
657446	33.0	33.2	24.6	19.6	18.0	14.9	13.8
657447	34.7	36.8	22.3	31.5	30.9	19.0	17.8
657448	39.0	33.8	33.9	34.4	26.3	25.5	23.8
657449	52.7	41.7	41.9	42.9	15.5	9.5	14.8
657450	44.7	51.6	34.7	29.1	24.3	19.7	21.2
657451	48.7	45.7	46.7	37.7	34.3	30.1	18.1
657452	49.4	52.7	37.5	41.3	24.5	24.3	15.8
657453	37.4	43.5	28.2	20.7	26.5	33.3	-34.2
657454	47.8	44.9	36.8	31.2	31.2	21.3	5.4
657455	27.2	31.5	18.8	19.0	17.5	15.4	17.5
657456	29.7	53.3	32.1	26.3	27.2	26.4	9.7
657457	47.2	61.5	48.2	45.9	41.7	24.8	23.0
657458	35.5	41.3	41.4	37.5	21.0	22.2	19.7
657459	34.1	32.8	25.7	8.8	24.9	20.0	12.0
657460	31.6	39.9	38.6	21.6	29.7	19.8	16.8

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

GROUP: V-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	50-57	57-64	64-71	71-78	78-85	85-92	92-99
ANIMAL NO.							
657441	6.8	12.7	11.8	-13.8	14.8	3.8	-0.7
657442	4.9	19.1	4.0	-13.3	9.7	8.8	8.9
657443	11.9	5.0	17.2	-26.0	29.6	10.0	11.5
657444	33.1	22.6	-1.3	-8.8	22.8	1.4	13.3
657445	12.8	7.8	10.5	-12.4	-1.6	18.3	14.6
657446	9.9	4.7	15.5	-16.3	8.0	5.0	3.3
657447	15.8	14.7	14.6	-0.5	8.8	10.6	7.6
657448	19.3	7.7	16.6	-6.3	13.2	5.8	6.5
657449	8.0	13.7	18.3	-15.8	15.3	5.5	10.9
657450	2.9	15.5	13.1	-18.4	13.8	5.5	9.9
657451	23.3	16.3	21.3	3.9	2.2	17.8	3.6
657452	10.2	13.6	8.0	-13.5	17.6	-3.7	8.7
657453	32.6	22.2	14.5	11.8	9.0	9.2	9.9
657454	22.6	15.5	17.5	-4.4	10.7	14.3	9.8
657455	12.8	4.9	12.4	2.4	8.7	9.6	5.1
657456	17.5	15.5	20.8	-1.7	6.1	1.8	8.1
657457	13.7	15.6	16.7	-4.0	8.0	12.3	20.1
657458	8.1	15.2	17.7	-7.9	15.5	0.9	5.4
657459	13.9	11.9	16.7	-3.1	3.1	AK (DAY 86)	-
657460	7.7	5.7	17.6	-48.9	26.6	11.1	13.1

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

GROUP: V-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	99-106	106-113	1-71	1-113
ANIMAL NO.				
657441	6.9	7.9	245.9	264.8
657442	-3.2	5.2	150.2	166.3
657443	5.6	-0.6	267.3	297.4
657444	16.7	25.3	319.9	390.6
657445	-2.3	-5.6	263.9	274.9
657446	10.6	4.7	187.2	202.5
657447	8.0	9.2	238.1	281.8
657448	8.7	5.3	260.3	293.5
657449	11.6	1.9	259.0	288.4
657450	15.5	1.4	256.8	284.5
657451	2.2	10.6	322.2	362.5
657452	11.0	13.2	277.3	310.6
657453	18.1	7.0	224.7	289.7
657454	-1.7	11.8	274.2	314.7
657455	10.0	7.4	177.0	220.2
657456	-0.6	4.8	258.5	277.0
657457	10.8	18.7	338.3	404.2
657458	15.7	0.4	259.6	289.6
657459	-	-	200.8	-
657460	13.7	6.3	229.0	250.9

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

GROUP: VII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657466	4.0	44.6	44.6	16.9	16.3	30.4	29.7
657467	15.2	28.9	25.7	17.7	19.8	-3.1	15.0
657468	-2.5	40.3	0.1	41.4	40.4	27.8	-9.8
657469	20.8	25.9	26.3	17.6	30.3	19.7	24.9
657470	31.9	28.2	22.2	11.9	23.9	3.8	6.9
657471	22.4	8.3	20.9	14.8	13.0	1.3	-0.3
657472	32.0	49.2	36.1	31.7	12.1	16.4	17.5
657473	41.6	24.7	30.9	4.7	28.4	22.3	26.1
657474	44.2	21.3	29.7	23.4	20.6	14.8	-5.6
657475	25.6	18.5	17.6	16.2	17.2	-6.7	22.5
657476	41.2	25.2	-4.4	32.9	4.8	11.6	19.4
657477	46.7	44.1	45.1	36.7	5.0	AK (DAY 42)	-
657478	47.6	42.6	39.0	33.3	28.4	18.8	25.1
657479	13.7	45.2	30.0	24.9	-7.7	19.5	-3.9
657480	31.0	43.8	25.8	29.7	4.1	12.9	-4.5
657481	45.7	50.1	49.0	36.3	26.0	23.2	-26.2
657482	20.2	38.5	21.6	21.1	7.5	10.8	9.9
657483	47.1	54.8	29.3	31.5	4.9	16.6	-3.5
657484	25.4	20.8	49.6	38.0	9.8	25.7	-20.2
657485	42.7	28.1	30.5	12.9	20.6	9.8	3.1

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

GROUP: VII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	50-57	57-64	64-71	71-78	78-85	85-92	92-99
ANIMAL NO.							
657466	21.6	2.7	16.5	-16.9	14.2	3.6	9.5
657467	8.7	-3.1	6.0	-36.2	31.3	0.8	16.9
657468	20.5	15.5	20.9	-43.1	21.0	-16.0	-6.1
657469	22.0	17.9	8.5	-19.1	-22.1	11.7	22.1
657470	12.3	-12.6	14.3	-9.1	27.8	10.0	-7.4
657471	10.5	6.7	5.6	-59.5	22.6	28.8	13.3
657472	15.0	6.2	0.2	-4.2	-2.7	12.0	12.3
657473	14.9	23.0	13.6	-14.9	5.8	10.2	-10.6
657474	-8.1	28.7	0.5	-1.4	-13.8	15.5	7.8
657475	19.2	5.4	13.1	-6.3	-0.6	-2.9	6.9
657476	17.8	14.4	1.9	-2.6	-11.8	22.3	-12.8
657477	-	-	-	-	-	-	-
657478	20.1	6.7	10.6	-7.9	15.7	14.6	-5.6
657479	13.8	3.7	-2.1	-3.1	19.8	-9.9	7.8
657480	19.8	16.0	14.1	-15.7	-11.8	19.8	10.1
657481	27.7	40.7	24.3	0.2	15.9	21.4	11.1
657482	19.2	25.8	FD (DAY 66)	-	-	-	-
657483	14.9	20.3	-43.6	6.1	20.8	13.3	6.8
657484	19.7	33.9	-6.0	0.4	-11.3	15.2	15.1
657485	14.0	6.9	7.7	12.6	14.1	-50.0	43.3

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 MALE RATS

GROUP: VII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	99-106	106-113	1-71	1-113
ANIMAL NO.				
657466	21.3	-15.2	227.3	243.8
657467	-9.0	12.7	130.8	147.3
657468	29.0	-4.4	194.6	175.0
657469	-14.1	7.6	213.9	200.0
657470	2.6	8.2	142.8	174.9
657471	-4.2	7.7	103.2	111.9
657472	-1.0	9.6	216.4	242.4
657473	-24.6	1.3	230.2	197.4
657474	-13.7	8.3	169.5	172.2
657475	15.7	6.2	148.6	167.6
657476	3.0	20.0	164.8	182.9
657477	-	-	-	-
657478	22.9	13.9	272.2	325.8
657479	-1.2	2.4	137.1	152.9
657480	-31.5	24.0	192.7	187.6
657481	21.9	7.2	296.8	374.5
657482	-	-	-	-
657483	-9.0	0.2	172.3	210.5
657484	2.4	27.1	196.7	245.6
657485	13.9	15.1	176.3	225.3

APPENDIX D

INDIVIDUAL BODY WEIGHTS OF P_1 FEMALE RATS DURING PREMATING

INDIVIDUAL BODY WEIGHTS OF P_1 FEMALE RATS DURING PREMATING

EXPLANATORY NOTES

Notes

Test Days 1-75 = Premating period
Test Days 76-90 = Cohabitation period

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 FEMALE RATS DURING PREMATING

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

DAYS ON TEST:	1	8	15	22	29	36	43
ANIMAL NO.							
657491	159.1	179.7	180.0	197.3	197.9	209.0	207.4
657492	207.0	234.2	267.7	259.0	272.5	312.0	301.8
657493	182.8	196.4	220.0	237.5	237.7	246.2	253.8
657494	195.7	197.8	224.4	238.3	242.4	234.8	244.2
657495	196.6	200.3	213.5	227.0	231.9	227.2	242.9
657496	184.4	197.5	211.1	221.6	220.2	233.9	238.6
657497	193.8	208.0	212.0	238.5	247.8	256.0	256.9
657498	183.7	192.6	198.3	220.6	238.5	235.8	236.4
657499	194.6	217.7	239.2	250.8	253.9	272.4	282.4
657500	210.7	221.5	228.6	245.6	258.3	265.7	271.6
657501	186.2	192.1	206.6	217.6	229.8	232.0	234.4
657502	180.1	179.5	186.2	202.1	209.2	213.7	219.1
657503	197.8	218.2	234.7	251.7	254.0	268.1	291.4
657504	204.8	206.9	238.5	249.0	266.8	273.7	278.4
657505	178.6	190.3	208.1	224.3	222.4	222.0	239.1
657506	194.9	224.7	234.5	255.3	262.8	271.3	274.3
657507	195.3	211.9	233.6	250.3	268.4	268.7	268.6
657508	197.3	214.1	230.3	240.1	257.1	273.9	278.0
657509	182.5	187.3	196.6	212.8	229.7	232.0	234.5
657510	187.0	188.9	206.1	218.8	218.1	212.5	225.8

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 FEMALE RATS DURING PREMATING

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

DAYS ON TEST:	50	57	64	71
ANIMAL NO.				
657491	219.0	224.5	228.7	231.4
657492	298.2	285.2	310.3	312.3
657493	263.9	271.7	280.0	280.8
657494	252.4	254.7	253.6	259.4
657495	255.2	250.3	247.4	252.2
657496	250.0	250.8	256.3	257.0
657497	266.5	272.9	270.9	276.0
657498	253.3	252.0	260.8	251.2
657499	287.1	290.0	285.9	300.2
657500	288.9	292.2	297.4	293.7
657501	242.9	246.1	241.7	256.7
657502	233.8	242.4	248.0	241.7
657503	302.7	296.5	295.9	298.1
657504	288.9	306.1	301.8	314.3
657505	244.8	250.7	247.4	247.0
657506	280.1	290.5	295.8	294.8
657507	286.8	295.6	289.3	287.0
657508	280.2	287.7	294.7	296.1
657509	244.7	253.7	252.4	260.9
657510	225.7	230.6	228.9	229.1

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 FEMALE RATS DURING PREMATING

GROUP: IV-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	36	43
ANIMAL NO.							
657516	186.2	207.4	225.9	233.5	235.9	251.2	251.0
657517	176.4	182.8	199.7	214.3	224.2	228.9	233.7
657518	192.4	203.0	217.6	229.5	249.5	253.2	258.1
657519	197.1	205.1	225.2	246.3	262.7	265.2	282.1
657520	198.4	214.7	231.1	240.0	238.6	246.3	253.9
657521	185.6	197.3	218.7	232.6	241.2	247.7	261.0
657522	189.4	216.6	225.1	246.1	250.9	246.2	263.0
657523	199.2	215.0	232.9	237.7	247.1	250.8	253.9
657524	208.0	235.5	244.8	259.8	277.3	281.4	292.5
657525	185.1	201.7	222.0	228.8	237.0	255.5	254.9
657526	194.0	201.1	222.4	236.5	240.0	255.1	253.1
657527	191.0	204.1	216.8	225.6	228.4	241.2	250.9
657528	193.5	224.7	241.6	258.2	280.6	289.3	298.0
657529	178.9	184.8	207.0	217.8	230.4	233.0	241.6
657530	197.6	220.1	236.9	246.3	258.5	262.9	273.3
657531	198.3	208.0	229.7	234.6	251.6	261.4	264.0
657532	201.4	210.5	227.6	252.3	265.5	267.1	265.4
657533	185.5	200.0	220.9	236.2	237.6	256.4	262.2
657534	185.9	202.0	220.8	251.8	254.2	268.0	273.3
657535	198.6	214.4	234.8	256.7	263.0	272.7	280.5

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 FEMALE RATS DURING PREMATING

GROUP: IV-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	50	57	64	71
ANIMAL NO.				
657516	255.0	255.1	268.6	272.8
657517	240.0	247.0	253.3	247.2
657518	270.0	277.9	279.8	280.7
657519	293.5	312.7	325.3	303.1
657520	258.1	258.9	270.6	276.7
657521	266.0	278.7	277.1	285.6
657522	273.7	279.8	276.1	279.9
657523	254.3	263.9	272.5	270.7
657524	295.6	305.9	321.8	306.5
657525	264.1	266.4	273.8	282.1
657526	257.6	263.3	263.4	271.6
657527	255.0	256.7	266.8	279.3
657528	299.8	308.5	318.4	317.6
657529	246.6	243.9	256.3	256.0
657530	281.4	295.6	291.3	304.6
657531	271.6	271.8	283.0	284.6
657532	280.5	289.8	291.0	286.0
657533	273.2	276.7	286.1	284.5
657534	280.6	271.5	293.3	298.8
657535	285.3	285.5	290.5	297.0

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 FEMALE RATS DURING PREMATING

GROUP: VI-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	36	43
ANIMAL NO.							
657541	196.3	205.0	219.8	233.9	236.1	244.5	245.4
657542	193.1	207.7	226.1	243.0	255.6	254.1	263.4
657543	192.3	199.1	214.2	227.5	241.5	246.9	253.4
657544	211.8	213.3	238.5	263.0	269.0	275.4	277.2
657545	183.0	191.7	209.0	228.3	229.3	244.7	245.5
657546	206.2	211.5	215.3	231.1	229.0	235.0	236.8
657547	168.4	191.2	195.5	211.9	224.0	228.7	223.0
657548	210.1	232.4	254.6	267.4	269.5	269.8	273.8
657549	168.3	182.4	189.0	195.3	206.9	215.3	212.4
657550	189.0	200.4	225.4	241.2	247.8	256.8	253.6
657551	196.3	204.0	209.8	223.0	235.8	238.9	239.5
657552	203.8	215.3	227.3	253.7	256.4	263.1	272.8
657553	173.2	181.1	192.9	204.7	207.0	220.1	227.3
657554	185.1	197.0	213.4	215.6	224.1	233.5	241.8
657555	193.4	205.7	206.9	239.4	242.1	249.4	245.9
657556	214.3	236.2	257.4	263.3	277.4	280.2	288.2
657557	184.3	189.7	216.8	230.0	239.4	245.9	256.9
657558	195.3	209.4	220.5	232.8	245.7	251.4	252.7
657559	198.6	231.0	253.7	282.9	305.2	285.3	310.6
657560	202.0	211.1	214.4	239.8	244.0	250.5	242.9

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 FEMALE RATS DURING PREMATING

GROUP: VI-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	50	57	64	71
ANIMAL NO.				
657541	256.7	258.9	257.3	265.0
657542	277.6	282.6	286.0	295.7
657543	252.9	272.3	277.2	280.8
657544	292.8	299.0	297.4	314.4
657545	264.0	258.1	269.6	265.9
657546	249.8	256.8	264.4	265.8
657547	234.9	242.8	248.7	245.5
657548	300.5	316.7	327.4	341.7
657549	211.5	218.5	227.8	226.2
657550	260.9	267.1	276.5	277.6
657551	250.1	254.3	258.7	255.5
657552	280.1	288.7	291.3	295.4
657553	239.7	237.0	255.0	255.5
657554	241.0	242.7	245.5	255.0
657555	262.7	265.8	269.0	268.2
657556	293.8	300.4	301.0	304.1
657557	269.9	270.9	267.7	279.9
657558	256.9	259.6	261.8	269.2
657559	318.3	336.5	326.7	320.8
657560	259.5	265.8	266.2	263.4

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 FEMALE RATS DURING PREMATING

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29	36	43
ANIMAL NO.							
657566	187.2	187.9	204.9	223.1	237.0	264.9	242.4
657567	185.9	214.5	232.8	247.7	262.6	245.9	274.3
657568	196.7	197.6	221.8	233.1	244.2	225.9	227.0
657569	179.8	184.0	208.2	210.7	231.0	245.1	246.6
657570	180.7	200.8	216.7	222.9	240.9	245.2	242.6
657571	185.8	176.7	191.3	215.0	227.0	221.2	213.7
657572	204.7	213.7	234.7	247.3	266.5	267.8	271.6
657573	184.1	198.2	202.1	210.4	221.1	230.0	228.7
657574	194.2	227.9	231.9	240.9	233.6	253.6	257.7
657575	198.9	199.4	214.5	229.2	240.9	254.7	255.2
657576	210.7	227.2	244.7	250.5	257.3	257.2	270.3
657577	177.3	188.4	190.4	203.8	214.1	228.7	222.0
657578	191.1	195.0	216.7	228.8	240.3	245.8	248.4
657579	193.2	179.4	212.7	221.7	224.3	238.1	231.7
657580	200.9	212.0	244.0	247.4	256.9	267.2	263.8
657581	178.2	190.1	201.9	209.2	209.0	212.1	216.1
657582	188.5	182.7	216.9	235.4	245.3	240.4	247.2
657583	204.9	215.4	231.8	245.8	252.4	257.1	266.2
657584	204.0	203.1	231.0	246.2	244.1	264.0	253.3
657585	181.5	169.7	201.1	206.6	220.5	222.5	222.7

INDIVIDUAL BODY WEIGHTS (grams) OF P_1 FEMALE RATS DURING PREMATING

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	50	57	64	71
ANIMAL NO.				
657566	248.8	256.9	250.4	269.5
657567	283.8	289.5	283.8	289.3
657568	258.8	261.6	271.3	279.7
657569	225.1	238.6	242.7	242.8
657570	254.1	258.6	268.9	279.4
657571	229.2	241.5	235.2	244.3
657572	277.7	284.9	290.4	290.6
657573	235.5	245.3	246.0	229.4
657574	293.2	288.4	285.9	297.7
657575	267.6	277.0	279.7	292.8
657576	274.1	280.3	276.1	276.6
657577	225.5	235.8	244.8	245.5
657578	261.3	265.2	266.7	278.4
657579	245.3	240.6	251.9	258.1
657580	275.8	282.9	281.7	288.9
657581	223.8	230.1	237.8	240.1
657582	247.2	257.4	259.6	263.9
657583	270.6	270.5	273.6	283.7
657584	260.3	273.2	281.1	287.6
657585	235.2	240.9	244.8	239.2

APPENDIX E

INDIVIDUAL BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING PREMATING

INDIVIDUAL BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING PREMATING

EXPLANATORY NOTES

Notes

Test Days 1-75 = Premating period
Test Days 76-90 = Cohabitation period

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 FEMALE RATS DURING PREMATING

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

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657491	20.6	0.3	17.3	0.6	11.1	-1.6	11.6
657492	27.2	33.5	-8.7	13.5	39.5	-10.2	-3.6
657493	13.6	23.6	17.5	0.2	8.5	7.6	10.1
657494	2.1	26.6	13.9	4.1	-7.6	9.4	8.2
657495	3.7	13.2	13.5	4.9	-4.7	15.7	12.3
657496	13.1	13.6	10.5	-1.4	13.7	4.7	11.4
657497	14.2	4.0	26.5	9.3	8.2	0.9	9.6
657498	8.9	5.7	22.3	17.9	-2.7	0.6	16.9
657499	23.1	21.5	11.6	3.1	18.5	10.0	4.7
657500	10.8	7.1	17.0	12.7	7.4	5.9	17.3
657501	5.9	14.5	11.0	12.2	2.2	2.4	8.5
657502	-0.6	6.7	15.9	7.1	4.5	5.4	14.7
657503	20.4	16.5	17.0	2.3	14.1	23.3	11.3
657504	2.1	31.6	10.5	17.8	6.9	4.7	10.5
657505	11.7	17.8	16.2	-1.9	-0.4	17.1	5.7
657506	29.8	9.8	20.8	7.5	8.5	3.0	5.8
657507	16.6	21.7	16.7	18.1	0.3	-0.1	18.2
657508	16.8	16.2	9.8	17.0	16.8	4.1	2.2
657509	4.8	9.3	16.2	16.9	2.3	2.5	10.2
657510	1.9	17.2	12.7	-0.7	-5.6	13.3	-0.1

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 FEMALE RATS DURING PREMATING

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

DAYS ON TEST:	50-57	57-64	64-71	1-71
ANIMAL NO.				
657491	5.5	4.2	2.7	72.3
657492	-13.0	25.1	2.0	105.3
657493	7.8	8.3	0.8	98.0
657494	2.3	-1.1	5.8	63.7
657495	-4.9	-2.9	4.8	55.6
657496	0.8	5.5	0.7	72.6
657497	6.4	-2.0	5.1	82.2
657498	-1.3	8.8	-9.6	67.5
657499	2.9	-4.1	14.3	105.6
657500	3.3	5.2	-3.7	83.0
657501	3.2	-4.4	15.0	70.5
657502	8.6	5.6	-6.3	61.6
657503	-6.2	-0.6	2.2	100.3
657504	17.2	-4.3	12.5	109.5
657505	5.9	-3.3	-0.4	68.4
657506	10.4	5.3	-1.0	99.9
657507	8.8	-6.3	-2.3	91.7
657508	7.5	7.0	1.4	98.8
657509	9.0	-1.3	8.5	78.4
657510	4.9	-1.7	0.2	42.1

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 FEMALE RATS DURING PREMATING

GROUP: IV-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657516	21.2	18.5	7.6	2.4	15.3	-0.2	4.0
657517	6.4	16.9	14.6	9.9	4.7	4.8	6.3
657518	10.6	14.6	11.9	20.0	3.7	4.9	11.9
657519	8.0	20.1	21.1	16.4	2.5	16.9	11.4
657520	16.3	16.4	8.9	-1.4	7.7	7.6	4.2
657521	11.7	21.4	13.9	8.6	6.5	13.3	5.0
657522	27.2	8.5	21.0	4.8	-4.7	16.8	10.7
657523	15.8	17.9	4.8	9.4	3.7	3.1	0.4
657524	27.5	9.3	15.0	17.5	4.1	11.1	3.1
657525	16.6	20.3	6.8	8.2	18.5	-0.6	9.2
657526	7.1	21.3	14.1	3.5	15.1	-2.0	4.5
657527	13.1	12.7	8.8	2.8	12.8	9.7	4.1
657528	31.2	16.9	16.6	22.4	8.7	8.7	1.8
657529	5.9	22.2	10.8	12.6	2.6	8.6	5.0
657530	22.5	16.8	9.4	12.2	4.4	10.4	8.1
657531	9.7	21.7	4.9	17.0	9.8	2.6	7.6
657532	9.1	17.1	24.7	13.2	1.6	-1.7	15.1
657533	14.5	20.9	15.3	1.4	18.8	5.8	11.0
657534	16.1	18.8	31.0	2.4	13.8	5.3	7.3
657535	15.8	20.4	21.9	6.3	9.7	7.8	4.8

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 FEMALE RATS DURING PREMATING

GROUP: IV-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	50-57	57-64	64-71	1-71
ANIMAL NO.				
657516	0.1	13.5	4.2	86.6
657517	7.0	6.3	-6.1	70.8
657518	7.9	1.9	0.9	88.3
657519	19.2	12.6	-22.2	106.0
657520	0.8	11.7	6.1	78.3
657521	12.7	-1.6	8.5	100.0
657522	6.1	-3.7	3.8	90.5
657523	9.6	8.6	-1.8	71.5
657524	10.3	15.9	-15.3	98.5
657525	2.3	7.4	8.3	97.0
657526	5.7	0.1	8.2	77.6
657527	1.7	10.1	12.5	88.3
657528	8.7	9.9	-0.8	124.1
657529	-2.7	12.4	-0.3	77.1
657530	14.2	-4.3	13.3	107.0
657531	0.2	11.2	1.6	86.3
657532	9.3	1.2	-5.0	84.6
657533	3.5	9.4	-1.6	99.0
657534	-9.1	21.8	5.5	112.9
657535	0.2	5.0	6.5	98.4

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 FEMALE RATS DURING PREMATING

GROUP: VI-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657541	8.7	14.8	14.1	2.2	8.4	0.9	11.3
657542	14.6	18.4	16.9	12.6	-1.5	9.3	14.2
657543	6.8	15.1	13.3	14.0	5.4	6.5	-0.5
657544	1.5	25.2	24.5	6.0	6.4	1.8	15.6
657545	8.7	17.3	19.3	1.0	15.4	0.8	18.5
657546	5.3	3.8	15.8	-2.1	6.0	1.8	13.0
657547	22.8	4.3	16.4	12.1	4.7	-5.7	11.9
657548	22.3	22.2	12.8	2.1	0.3	4.0	26.7
657549	14.1	6.6	6.3	11.6	8.4	-2.9	-0.9
657550	11.4	25.0	15.8	6.6	9.0	-3.2	7.3
657551	7.7	5.8	13.2	12.8	3.1	0.6	10.6
657552	11.5	12.0	26.4	2.7	6.7	9.7	7.3
657553	7.9	11.8	11.8	2.3	13.1	7.2	12.4
657554	11.9	16.4	2.2	8.5	9.4	8.3	-0.8
657555	12.3	1.2	32.5	2.7	7.3	-3.5	16.8
657556	21.9	21.2	5.9	14.1	2.8	8.0	5.6
657557	5.4	27.1	13.2	9.4	6.5	11.0	13.0
657558	14.1	11.1	12.3	12.9	5.7	1.3	4.2
657559	32.4	22.7	29.2	22.3	-19.9	25.3	7.7
657560	9.1	3.3	25.4	4.2	6.5	-7.6	16.6

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 FEMALE RATS DURING PREMATING

GROUP: VI-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	50-57	57-64	64-71	1-71
ANIMAL NO.				
657541	2.2	-1.6	7.7	68.7
657542	5.0	3.4	9.7	102.6
657543	19.4	4.9	3.6	88.5
657544	6.2	-1.6	17.0	102.6
657545	-5.9	11.5	-3.7	82.9
657546	7.0	7.6	1.4	59.6
657547	7.9	5.9	-3.2	77.1
657548	16.2	10.7	14.3	131.6
657549	7.0	9.3	-1.6	57.9
657550	6.2	9.4	1.1	88.6
657551	4.2	4.4	-3.2	59.2
657552	8.6	2.6	4.1	91.6
657553	-2.7	18.0	0.5	82.3
657554	1.7	2.8	9.5	69.9
657555	3.1	3.2	-0.8	74.8
657556	6.6	0.6	3.1	89.8
657557	1.0	-3.2	12.2	95.6
657558	2.7	2.2	7.4	73.9
657559	18.2	-9.8	-5.9	122.2
657560	6.3	0.4	-2.8	61.4

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 FEMALE RATS DURING PREMATING

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657566	0.7	17.0	18.2	13.9	27.9	-22.5	6.4
657567	28.6	18.3	14.9	14.9	-16.7	28.4	9.5
657568	0.9	24.2	11.3	11.1	-18.3	1.1	31.8
657569	4.2	24.2	2.5	20.3	14.1	1.5	-21.5
657570	20.1	15.9	6.2	18.0	4.3	-2.6	11.5
657571	-9.1	14.6	23.7	12.0	-5.8	-7.5	15.5
657572	9.0	21.0	12.6	19.2	1.3	3.8	6.1
657573	14.1	3.9	8.3	10.7	8.9	-1.3	6.8
657574	33.7	4.0	9.0	-7.3	20.0	4.1	35.5
657575	0.5	15.1	14.7	11.7	13.8	0.5	12.4
657576	16.5	17.5	5.8	6.8	-0.1	13.1	3.8
657577	11.1	2.0	13.4	10.3	14.6	-6.7	3.5
657578	3.9	21.7	12.1	11.5	5.5	2.6	12.9
657579	-13.8	33.3	9.0	2.6	13.8	-6.4	13.6
657580	11.1	32.0	3.4	9.5	10.3	-3.4	12.0
657581	11.9	11.8	7.3	-0.2	3.1	4.0	7.7
657582	-5.8	34.2	18.5	9.9	-4.9	6.8	0.0
657583	10.5	16.4	14.0	6.6	4.7	9.1	4.4
657584	-0.9	27.9	15.2	-2.1	19.9	-10.7	7.0
657585	-11.8	31.4	5.5	13.9	2.0	0.2	12.5

INDIVIDUAL BODY WEIGHT GAINS (grams) OF P_1 FEMALE RATS DURING PREMATING

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	50-57	57-64	64-71	1-71
ANIMAL NO.				
657566	8.1	-6.5	19.1	82.3
657567	5.7	-5.7	5.5	103.4
657568	2.8	9.7	8.4	83.0
657569	13.5	4.1	0.1	63.0
657570	4.5	10.3	10.5	98.7
657571	12.3	-6.3	9.1	58.5
657572	7.2	5.5	0.2	85.9
657573	9.8	0.7	-16.6	45.3
657574	-4.8	-2.5	11.8	103.5
657575	9.4	2.7	13.1	93.9
657576	6.2	-4.2	0.5	65.9
657577	10.3	9.0	0.7	68.2
657578	3.9	1.5	11.7	87.3
657579	-4.7	11.3	6.2	64.9
657580	7.1	-1.2	7.2	88.0
657581	6.3	7.7	2.3	61.9
657582	10.2	2.2	4.3	75.4
657583	-0.1	3.1	10.1	78.8
657584	12.9	7.9	6.5	83.6
657585	5.7	3.9	-5.6	57.7

APPENDIX F

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING GESTATION

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING GESTATION

EXPLANATORY NOTES

Abbreviations

NP = No litter delivered; data excluded from statistical analysis.
- = No Data

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING GESTATION

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

GESTATION DAYS:	0	7	14	21
ANIMAL NO.	MEAN BODY WEIGHT (grams)			
657491	223.1	259.6	288.2	316.8
657492	303.1	351.1	395.8	490.4
657493	268.3	301.5	338.1	406.7
657494	264.8	300.1	336.3	426.5
657495	260.1	282.3	315.8	382.2
657496 (NP)	254.7	273.7	277.3	270.3
657497	278.6	314.7	346.8	436.2
657498	269.0	302.4	331.4	408.5
657499	288.7	316.2	336.0	413.2
657500	297.8	339.0	367.2	446.2
657501	258.2	293.0	323.4	405.2
657502	245.0	284.4	318.0	405.3
657503	303.4	334.5	359.7	401.8
657504	312.3	345.7	380.7	458.2
657505	248.4	290.6	319.5	398.6
657506	291.1	331.0	347.6	416.3
657507	294.1	330.3	355.0	438.6
657508	297.2	328.3	368.5	456.7
657509 (NP)	267.6	271.8	274.0	257.9
657510	236.7	260.1	289.2	358.4

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NO.	MEAN BODY WEIGHT GAINS (grams)			
657491	36.5	28.6	28.6	93.7
657492	48.0	44.7	94.6	187.3
657493	33.2	36.6	68.6	138.4
657494	35.3	36.2	90.2	161.7
657495	22.2	33.5	66.4	122.1
657496 (NP)	19.0	3.6	-7.0	15.6
657497	36.1	32.1	89.4	157.6
657498	33.4	29.0	77.1	139.5
657499	27.5	19.8	77.2	124.5
657500	41.2	28.2	79.0	148.4
657501	34.8	30.4	81.8	147.0
657502	39.4	33.6	87.3	160.3
657503	31.1	25.2	42.1	98.4
657504	33.4	35.0	77.5	145.9
657505	42.2	28.9	79.1	150.2
657506	39.9	16.6	68.7	125.2
657507	36.2	24.7	83.6	144.5
657508	31.1	40.2	88.2	159.5
657509 (NP)	4.2	2.2	-16.1	-9.7
657510	23.4	29.1	69.2	121.7

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING GESTATION

GROUP: IV-0 DOSE: 75 MG/KG/DAY

GESTATION DAYS:	0	7	14	21
ANIMAL NO.	MEAN BODY WEIGHT (grams)			
657516	266.9	309.8	345.0	427.7
657517	250.3	283.3	312.2	409.0
657518	287.7	309.9	337.2	403.8
657519 (NP)	-	-	-	-
657520	267.2	294.8	329.1	399.0
657521	289.5	310.5	337.5	415.0
657522	282.0	313.3	340.2	403.3
657523	277.1	298.9	311.3	336.7
657524	319.4	352.6	391.5	489.1
657525	268.0	297.1	333.3	399.3
657526	271.1	300.5	323.6	353.3
657527	270.4	303.7	339.8	449.3
657528	316.8	345.5	363.5	451.3
657529[a]	-	-	-	-
657530[a]	-	-	-	-
657531	295.1	328.6	354.8	413.2
657532	293.0	327.1	346.3	389.1
657533	269.5	297.1	322.5	398.1
657534	301.5	334.0	356.6	393.1
657535	287.1	319.5	346.3	431.7

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NO.	MEAN BODY WEIGHT GAINS (grams)			
657516	42.9	35.2	82.7	160.8
657517	33.0	28.9	96.8	158.7
657518	22.2	27.3	66.6	116.1
657519 (NP)	-	-	-	-
657520	27.6	34.3	69.9	131.8
657521	21.0	27.0	77.5	125.5
657522	31.3	26.9	63.1	121.3
657523	21.8	12.4	25.4	59.6
657524	33.2	38.9	97.6	169.7
657525	29.1	36.2	66.0	131.3
657526	29.4	23.1	29.7	82.2
657527	33.3	36.1	109.5	178.9
657528	28.7	18.0	87.8	134.5
657529[a]	-	-	-	-
657530[a]	-	-	-	-
657531	33.5	26.2	58.4	118.1
657532	34.1	19.2	42.8	96.1
657533	27.6	25.4	75.6	128.6
657534	32.5	22.6	36.5	91.6
657535	32.4	26.8	85.4	144.6

[a] Evidence of copulation was not observed; therefore, no gestation data were collected.

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING GESTATION

GROUP: VI-0 DOSE: 500 MG/KG/DAY

GESTATION DAYS:	0	7	14	21
ANIMAL NO.	MEAN BODY WEIGHT (grams)			
657541[a]	270.6	294.7	321.8	-
657542	295.1	317.8	345.2	422.2
657543	270.0	302.0	321.1	407.9
657544	309.4	343.4	374.9	444.9
657545	265.9	303.2	333.6	418.6
657546	268.9	291.1	328.4	413.9
657547	237.2	275.5	297.1	362.3
657548	346.0	363.5	385.7	447.8
657549	229.1	265.9	293.5	368.3
657550[b]	-	-	-	-
657551[b]	-	-	-	-
657552	293.4	320.1	339.9	432.4
657553	255.1	289.7	322.6	403.4
657554	251.8	282.7	310.0	365.7
657555	272.9	310.3	340.3	412.9
657556	312.4	343.8	374.0	473.7
657557 (NP)	-	-	-	-
657558	266.1	282.8	305.3	376.8
657559	336.5	376.8	401.8	460.6
657560	276.5	311.0	342.4	434.1

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NO.	MEAN BODY WEIGHT GAINS (grams)			
657541[a]	24.1	27.1	-	-
657542	22.7	27.4	77.0	127.1
657543	32.0	19.1	86.8	137.9
657544	34.0	31.5	70.0	135.5
657545	37.3	30.4	85.0	152.7
657546	22.2	37.3	85.5	145.0
657547	38.3	21.6	65.2	125.1
657548	17.5	22.2	62.1	101.8
657549	36.8	27.6	74.8	139.2
657550[b]	-	-	-	-
657551[b]	-	-	-	-
657552	26.7	19.8	92.5	139.0
657553	34.6	32.9	80.8	148.3
657554	30.9	27.3	55.7	113.9
657555	37.4	30.0	72.6	140.0
657556	31.4	30.2	99.7	161.3
657557 (NP)	-	-	-	-
657558	16.7	22.5	71.5	110.7
657559	40.3	25.0	58.8	124.1
657560	34.5	31.4	91.7	157.6

a Animal delivered prior to collection of Gestation Day 21 data.
b Evidence of copulation was not observed; therefore, no gestation data were collected.

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING GESTATION

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

GESTATION DAYS:	0	7	14	21
ANIMAL NO.	MEAN BODY WEIGHT (grams)			
657566[a]	-	-	-	-
657567 (NP)	327.6	338.9	340.6	325.9
657568	275.8	308.8	331.5	416.5
657569 (NP)	250.0	280.0	279.9	259.6
657570	281.7	298.4	323.3	422.6
657571[a]	-	-	-	-
657572	289.3	315.7	337.7	420.7
657573	252.2	285.2	312.3	364.6
657574	293.9	328.3	356.4	434.5
657575 (NP)	301.3	316.7	314.9	325.5
657576	281.9	316.9	356.8	450.9
657577	252.8	276.5	303.8	376.7
657578 (NP)	271.6	274.7	279.6	279.5
657579	257.6	288.6	315.6	359.6
657580	298.2	320.5	341.9	434.5
657581	247.7	272.4	304.0	386.6
657582 (NP)	268.8	294.4	270.1	280.8
657583	283.5	311.3	338.7	409.7
657584	285.5	310.5	334.3	419.2
657585	236.5	267.8	292.4	382.1

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NO.	MEAN BODY WEIGHT GAINS (grams)			
657566[a]	-	-	-	-
657567 (NP)	11.3	1.7	-14.7	-1.7
657568	33.0	22.7	85.0	140.7
657569 (NP)	30.0	-0.1	-20.3	9.6
657570	16.7	24.9	99.3	140.9
657571[a]	-	-	-	-
657572	26.4	22.0	83.0	131.4
657573	33.0	27.1	52.3	112.4
657574	34.4	28.1	78.1	140.6
657575 (NP)	15.4	-1.8	10.6	24.2
657576	35.0	39.9	94.1	169.0
657577	23.7	27.3	72.9	123.9
657578 (NP)	3.1	4.9	-0.1	7.9
657579	31.0	27.0	44.0	102.0
657580	22.3	21.4	92.6	136.3
657581	24.7	31.6	82.6	138.9
657582 (NP)	25.6	-24.3	10.7	12.0
657583	27.8	27.4	71.0	126.2
657584	25.0	23.8	84.9	133.7
657585	31.3	24.6	89.7	145.6

a Evidence of copulation was not observed; therefore, no gestation data were collected.

APPENDIX G

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING LACTATION

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING LACTATION

EXPLANATORY NOTES

Note

Test days for animal fates are determined from the initiation of test substance administration.

Abbreviations

-	=	No Data
NP	=	Not pregnant
SD	=	Sacrificed by design

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING LACTATION

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

LACTATION DAYS:	0	7	14	21	
ANIMAL NO.	MEAN BODY WEIGHT (grams)				
657491[a]	278.7	286.6	301.4	-	SD (DAY 121)
657492	362.1	373.7	394.5	381.6	SD (DAY 121)
657493[a]	333.6	321.3	344.9	-	SD (DAY 121)
657494	304.9	333.1	348.0	317.1	SD (DAY 123)
657495	298.8	320.7	330.6	315.6	SD (DAY 123)
657496 (NP)	-	-	-	-	SD (DAY 124)
657497	309.3	335.2	348.0	326.1	SD (DAY 124)
657498	300.3	301.6	322.4	301.6	SD (DAY 123)
657499	311.1	336.7	340.2	332.5	SD (DAY 122)
657500	351.9	364.6	364.0	356.0	SD (DAY 122)
657501	300.1	300.8	318.9	336.7	SD (DAY 123)
657502	300.3	287.7	312.1	310.1	SD (DAY 120)
657503	328.6	341.7	358.0	330.6	SD (DAY 122)
657504	359.4	385.1	376.1	352.6	SD (DAY 122)
657505	318.8	316.8	339.3	324.0	SD (DAY 123)
657506	346.3	351.6	367.6	357.9	SD (DAY 123)
657507	323.9	341.6	353.8	334.6	SD (DAY 122)
657508	343.9	332.6	372.7	354.0	SD (DAY 121)
657509 (NP)	-	-	-	-	SD (DAY 124)
657510	262.7	294.7	317.3	286.7	SD (DAY 126)

LACTATION DAYS:	0-7	7-14	14-21	0-21	
ANIMAL NO.	MEAN BODY WEIGHT GAINS (grams)				
657491[a]	7.9	14.8	-	-	SD (DAY 121)
657492	11.6	20.8	-12.9	19.5	SD (DAY 121)
657493[a]	-12.3	23.6	-	-	SD (DAY 121)
657494	28.2	14.9	-30.9	12.2	SD (DAY 123)
657495	21.9	9.9	-15.0	16.8	SD (DAY 123)
657496 (NP)	-	-	-	-	SD (DAY 124)
657497	25.9	12.8	-21.9	16.8	SD (DAY 124)
657498	1.3	20.8	-20.8	1.3	SD (DAY 123)
657499	25.6	3.5	-7.7	21.4	SD (DAY 122)
657500	12.7	-0.6	-8.0	4.1	SD (DAY 122)
657501	0.7	18.1	17.8	36.6	SD (DAY 123)
657502	-12.6	24.4	-2.0	9.8	SD (DAY 120)
657503	13.1	16.3	-27.4	2.0	SD (DAY 122)
657504	25.7	-9.0	-23.5	-6.8	SD (DAY 122)
657505	-2.0	22.5	-15.3	5.2	SD (DAY 123)
657506	5.3	16.0	-9.7	11.6	SD (DAY 123)
657507	17.7	12.2	-19.2	10.7	SD (DAY 122)
657508	-11.3	40.1	-18.7	10.1	SD (DAY 121)
657509 (NP)	-	-	-	-	SD (DAY 124)

[a] Lactation day 21 body weight inadvertently not recorded.

657510	32.0	22.6	-30.6	24.0 SD (DAY 126)

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING LACTATION

GROUP: IV-0 DOSE: 75 MG/KG/DAY

LACTATION DAYS:	0	7	14	21	
ANIMAL NO.	MEAN BODY WEIGHT (grams)				
657516	318.3	315.2	338.2	328.7	SD (DAY 120)
657517	290.6	298.2	321.4	300.0	SD (DAY 123)
657518	310.4	326.7	340.1	322.6	SD (DAY 122)
657519 (NP)	-	-	-	-	SD (DAY 124)
657520	288.4	325.2	330.0	323.4	SD (DAY 121)
657521	333.5	331.8	336.8	330.5	SD (DAY 123)
657522	331.8	344.3	312.4	348.4	SD (DAY 123)
657523	290.9	312.6	316.9	323.4	SD (DAY 123)
657524	290.4	379.6	389.2	368.9	SD (DAY 125)
657525	293.6	330.7	353.0	321.8	SD (DAY 121)
657526	304.3	330.9	341.4	341.1	SD (DAY 122)
657527	322.7	339.9	351.5	333.0	SD (DAY 120)
657528	345.8	348.3	336.1	351.6	SD (DAY 121)
657529	280.0	305.0	317.7	302.7	SD (DAY 122)
657530	309.7	327.3	347.3	355.3	SD (DAY 123)
657531	329.6	358.3	368.6	341.4	SD (DAY 127)
657532	321.8	343.1	354.6	343.3	SD (DAY 123)
657533	289.2	303.5	328.6	296.1	SD (DAY 121)
657534	340.9	343.3	355.1	343.4	SD (DAY 125)
657535	325.4	332.8	356.8	342.3	SD (DAY 123)

LACTATION DAYS:	0-7	7-14	14-21	0-21	
ANIMAL NO.	MEAN BODY WEIGHT GAINS (grams)				
657516	-3.1	23.0	-9.5	10.4	SD (DAY 120)
657517	7.6	23.2	-21.4	9.4	SD (DAY 123)
657518	16.3	13.4	-17.5	12.2	SD (DAY 122)
657519 (NP)	-	-	-	-	SD (DAY 124)
657520	36.8	4.8	-6.6	35.0	SD (DAY 121)
657521	-1.7	5.0	-6.3	-3.0	SD (DAY 123)
657522	12.5	-31.9	36.0	16.6	SD (DAY 123)
657523	21.7	4.3	6.5	32.5	SD (DAY 123)
657524	89.2	9.6	-20.3	78.5	SD (DAY 125)
657525	37.1	22.3	-31.2	28.2	SD (DAY 121)
657526	26.6	10.5	-0.3	36.8	SD (DAY 122)
657527	17.2	11.6	-18.5	10.3	SD (DAY 120)
657528	2.5	-12.2	15.5	5.8	SD (DAY 121)
657529	25.0	12.7	-15.0	22.7	SD (DAY 122)
657530	17.6	20.0	8.0	45.6	SD (DAY 123)
657531	28.7	10.3	-27.2	11.8	SD (DAY 127)
657532	21.3	11.5	-11.3	21.5	SD (DAY 123)
657533	14.3	25.1	-32.5	6.9	SD (DAY 121)
657534	2.4	11.8	-11.7	2.5	SD (DAY 125)
657535	7.4	24.0	-14.5	16.9	SD (DAY 123)

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING LACTATION

GROUP: VI-0 DOSE: 500 MG/KG/DAY

LACTATION DAYS:	0	7	14	21	
ANIMAL NO.	MEAN BODY WEIGHT (grams)				
657541	305.4	304.0	317.9	319.0	SD (DAY 122)
657542	322.8	316.7	343.8	327.2	SD (DAY 122)
657543	298.6	319.5	331.3	312.8	SD (DAY 121)
657544	349.2	370.8	353.5	308.0	SD (DAY 123)
657545	301.5	322.6	345.5	328.7	SD (DAY 120)
657546	306.6	304.7	331.6	326.1	SD (DAY 122)
657547	282.2	283.6	305.5	291.7	SD (DAY 123)
657548	380.7	378.9	379.2	359.1	SD (DAY 128)
657549	274.1	288.8	308.1	301.7	SD (DAY 121)
657550	307.2	341.1	349.4	310.9	SD (DAY 125)
657551	284.8	314.0	330.4	316.1	SD (DAY 122)
657552	309.7	331.3	347.5	351.6	SD (DAY 124)
657553	314.8	322.6	331.3	317.4	SD (DAY 123)
657554	274.8	304.7	323.8	306.6	SD (DAY 121)
657555	306.1	326.0	350.6	329.1	SD (DAY 123)
657556	355.8	369.5	385.9	378.6	SD (DAY 121)
657557 (NP)	-	-	-	-	SD (DAY 124)
657558	304.9	302.8	331.9	314.4	SD (DAY 121)
657559	376.9	384.3	404.9	374.3	SD (DAY 130)
657560	319.9	326.5	352.4	343.6	SD (DAY 122)

LACTATION DAYS:	0-7	7-14	14-21	0-21	
ANIMAL NO.	MEAN BODY WEIGHT GAINS (grams)				
657541	-1.4	13.9	1.1	13.6	SD (DAY 122)
657542	-6.1	27.1	-16.6	4.4	SD (DAY 122)
657543	20.9	11.8	-18.5	14.2	SD (DAY 121)
657544	21.6	-17.3	-45.5	-41.2	SD (DAY 123)
657545	21.1	22.9	-16.8	27.2	SD (DAY 120)
657546	-1.9	26.9	-5.5	19.5	SD (DAY 122)
657547	1.4	21.9	-13.8	9.5	SD (DAY 123)
657548	-1.8	0.3	-20.1	-21.6	SD (DAY 128)
657549	14.7	19.3	-6.4	27.6	SD (DAY 121)
657550	33.9	8.3	-38.5	3.7	SD (DAY 125)
657551	29.2	16.4	-14.3	31.3	SD (DAY 122)
657552	21.6	16.2	4.1	41.9	SD (DAY 124)
657553	7.8	8.7	-13.9	2.6	SD (DAY 123)
657554	29.9	19.1	-17.2	31.8	SD (DAY 121)
657555	19.9	24.6	-21.5	23.0	SD (DAY 123)
657556	13.7	16.4	-7.3	22.8	SD (DAY 121)
657557 (NP)	-	-	-	-	SD (DAY 124)
657558	-2.1	29.1	-17.5	9.5	SD (DAY 121)
657559	7.4	20.6	-30.6	-2.6	SD (DAY 130)
657560	6.6	25.9	-8.8	23.7	SD (DAY 122)

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS OF P_1 FEMALE RATS DURING LACTATION

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

LACTATION DAYS:	0	7	14	21	
ANIMAL NO.	MEAN BODY WEIGHT (grams)				
657566	287.6	306.8	314.8	321.6	SD (DAY 122)
657567 (NP)	-	-	-	-	SD (DAY 124)
657568	319.2	341.4	366.6	337.6	SD (DAY 120)
657569 (NP)	-	-	-	-	SD (DAY 124)
657570	302.9	325.7	338.8	325.7	SD (DAY 122)
657571	266.5	298.8	315.5	290.0	SD (DAY 123)
657572	318.0	348.5	343.1	343.4	SD (DAY 121)
657573	296.0	309.7	307.8	313.9	SD (DAY 122)
657574	335.3	341.0	328.8	340.3	SD (DAY 123)
657575 (NP)	-	-	-	-	SD (DAY 124)
657576	341.8	370.3	357.4	360.9	SD (DAY 121)
657577	283.8	318.6	333.8	333.4	SD (DAY 122)
657578 (NP)	-	-	-	-	SD (DAY 124)
657579	268.7	309.5	336.5	326.1	SD (DAY 121)
657580	326.2	322.0	333.7	340.3	SD (DAY 122)
657581	285.7	309.6	312.4	301.9	SD (DAY 123)
657582 (NP)	-	-	-	-	SD (DAY 124)
657583	316.0	336.4	336.1	347.7	SD (DAY 121)
657584	313.9	333.8	344.6	349.0	SD (DAY 125)
657585	262.6	297.3	306.8	306.8	SD (DAY 123)

LACTATION DAYS:	0-7	7-14	14-21	0-21	
ANIMAL NO.	MEAN BODY WEIGHT GAINS (grams)				
657566	19.2	8.0	6.8	34.0	SD (DAY 122)
657567 (NP)	-	-	-	-	SD (DAY 124)
657568	22.2	25.2	-29.0	18.4	SD (DAY 120)
657569 (NP)	-	-	-	-	SD (DAY 124)
657570	22.8	13.1	-13.1	22.8	SD (DAY 122)
657571	32.3	16.7	-25.5	23.5	SD (DAY 123)
657572	30.5	-5.4	0.3	25.4	SD (DAY 121)
657573	13.7	-1.9	6.1	17.9	SD (DAY 122)
657574	5.7	-12.2	11.5	5.0	SD (DAY 123)
657575 (NP)	-	-	-	-	SD (DAY 124)
657576	28.5	-12.9	3.5	19.1	SD (DAY 121)
657577	34.8	15.2	-0.4	49.6	SD (DAY 122)
657578 (NP)	-	-	-	-	SD (DAY 124)
657579	40.8	27.0	-10.4	57.4	SD (DAY 121)
657580	-4.2	11.7	6.6	14.1	SD (DAY 122)
657581	23.9	2.8	-10.5	16.2	SD (DAY 123)
657582 (NP)	-	-	-	-	SD (DAY 124)
657583	20.4	-0.3	11.6	31.7	SD (DAY 121)
657584	19.9	10.8	4.4	35.1	SD (DAY 125)
657585	34.7	9.5	0.0	44.2	SD (DAY 123)

APPENDIX H

INDIVIDUAL FOOD CONSUMPTION OF P_1 MALE RATS

INDIVIDUAL FOOD CONSUMPTION OF P_1 MALE RATS

EXPLANATORY NOTES

Notes

Test Days 1-75 = Premating period
Test Days 76-90 = Cohabitation period

Abbreviations

AK = Accidentally Killed
SE = Sacrificed *in extremis*; data excluded from group means. (Group I-0, Animal No. 657409)
- = No Data

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 MALE RATS

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

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657391	27.0	26.8	28.4	28.7	30.8	29.3	27.7
657392	26.0	26.8	29.2	29.2	28.6	27.6	28.8
657393	28.1	28.3	28.9	27.9	29.0	29.4	31.2
657394	27.5	28.0	31.1	32.2	33.4	31.3	32.0
657395	24.4	23.7	26.8	26.8	27.4	27.3	27.2
657396	23.8	25.1	25.8	24.9	26.2	26.5	26.3
657397	24.7	23.1	24.9	23.5	24.6	36.5	23.6
657398	24.3	26.2	27.4	28.0	28.9	29.0	29.4
657399	26.2	25.2	26.2	27.3	28.9	27.0	27.4
657400	25.4	23.4	26.0	26.1	27.6	25.4	24.1
657401	25.2	23.9	25.3	26.0	27.3	25.3	26.1
657402	22.4	22.7	25.6	25.4	25.6	26.5	25.5
657403	23.7	24.6	26.0	27.7	29.4	21.3	25.7
657404	30.3	30.1	32.7	33.2	34.4	32.9	32.7
657405	26.9	29.1	29.7	30.3	32.3	29.4	30.8
657406	26.1	26.0	28.7	27.8	30.1	30.7	30.8
657407	27.6	26.3	28.9	29.4	30.8	28.7	28.3
657408	26.6	27.8	25.7	25.8	26.4	26.1	25.9
657409	27.6	27.6	30.4	31.6	31.7	31.6	29.4
657410	24.1	24.7	28.8	27.5	25.9	25.9	26.4

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 MALE RATS

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

DAYS ON TEST:	50-57	57-64	64-71	1-71
ANIMAL NO.				
657391	28.5	29.5	27.8	28.5
657392	29.4	29.9	27.3	28.3
657393	31.1	30.8	29.6	29.5
657394	31.9	30.8	28.1	30.6
657395	27.0	28.1	27.9	26.7
657396	25.5	-a	26.1	-a
657397	24.4	24.0	22.5	25.2
657398	30.9	29.6	29.2	28.3
657399	28.2	29.0	27.9	27.3
657400	24.9	26.4	24.1	25.4
657401	26.2	26.6	25.6	25.8
657402	26.3	26.3	25.7	25.2
657403	24.5	25.2	24.9	25.3
657404	33.6	34.3	33.9	32.8
657405	30.8	30.7	29.9	30.0
657406	31.9	31.4	32.2	29.6
657407	31.4	30.7	32.1	29.4
657408	25.0	25.1	24.9	25.9
657409	26.4	SE (DAY 60)	-	-
657410	27.5	28.0	26.5	26.5

a No data due to weighing error on Test Day 64.

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 MALE RATS

GROUP: III-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657416	27.9	27.1	27.7	27.3	28.2	26.8	27.8
657417	28.6	25.2	26.1	28.1	26.1	28.4	28.0
657418	24.5	25.5	26.4	26.6	22.9	26.8	25.8
657419	24.2	25.4	26.5	27.5	29.9	29.8	29.5
657420	26.5	27.0	27.3	27.3	29.4	28.4	26.2
657421	29.5	28.7	29.4	28.7	31.5	30.9	29.4
657422	24.1	25.5	26.5	27.6	29.8	28.1	26.2
657423	26.6	29.6	31.1	30.5	32.6	31.6	31.0
657424	28.1	30.8	31.2	30.2	32.0	32.8	32.2
657425	31.0	33.5	35.4	35.4	38.1	39.0	36.3
657426	24.6	25.1	26.8	27.2	32.3	27.5	27.7
657427	25.9	26.8	28.3	28.8	31.9	29.3	28.6
657428	26.5	27.0	27.5	30.7	30.2	29.8	29.0
657429	29.9	30.5	32.5	33.2	35.8	32.5	33.0
657430	28.7	28.1	29.3	31.9	33.2	32.0	28.6
657431	26.7	29.1	27.9	32.2	32.6	33.2	31.3
657432	30.9	32.7	33.1	34.3	35.6	34.5	35.1
657433	27.3	30.8	31.1	31.8	31.0	32.3	31.8
657435	23.1	22.0	24.1	22.7	25.3	24.7	26.2

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 MALE RATS

GROUP: III-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	50-57	57-64	64-71	1-71
ANIMAL NO.				
657416	27.0	29.0	28.4	27.7
657417	28.2	30.4	30.7	28.0
657418	25.6	26.1	25.6	25.6
657419	29.1	30.8	29.2	28.2
657420	26.1	29.0	28.1	27.5
657421	30.2	31.0	30.8	30.0
657422	27.5	28.4	29.0	27.3
657423	30.6	32.0	31.1	30.7
657424	30.7	29.8	29.4	30.7
657425	38.1	37.8	36.3	36.1
657426	27.4	27.4	26.6	27.3
657427	29.5	29.6	29.0	28.8
657428	30.3	33.0	30.5	29.5
657429	33.1	33.3	32.7	32.6
657430	30.5	30.9	31.3	30.5
657431	32.4	31.4	31.2	30.8
657432	35.8	37.5	34.8	34.4
657433	30.4	32.5	30.6	31.0
657435	24.6	24.0	25.0	24.2

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 MALE RATS

GROUP: V-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657441	26.6	25.5	27.5	27.9	28.7	28.2	27.2
657442	22.0	20.3	21.4	21.7	21.2	18.5	21.1
657443	26.2	27.2	26.8	28.5	29.6	30.4	33.2
657444	25.6	27.2	28.9	29.3	32.1	33.0	32.9
657445	25.7	25.5	26.0	26.5	27.8	28.0	25.8
657446	21.1	21.6	21.7	21.5	24.2	24.2	22.7
657447	23.4	23.1	23.4	25.0	26.7	26.7	25.1
657448	23.8	22.8	24.6	24.9	26.7	26.4	25.9
657449	27.5	27.7	28.6	30.1	29.8	27.7	27.0
657450	26.2	26.6	27.4	28.1	28.0	28.1	27.7
657451	26.4	26.0	28.8	29.5	32.4	31.0	28.7
657452	26.9	28.4	28.8	29.4	28.7	28.7	28.0
657453	24.7	23.7	24.2	24.9	26.1	26.9	13.2
657454	25.9	26.1	27.8	27.5	29.6	29.4	26.3
657455	24.3	23.6	23.9	25.1	25.3	24.8	24.5
657456	24.7	26.1	26.9	27.9	29.3	27.3	26.9
657457	30.5	32.1	32.6	34.3	36.7	35.0	33.1
657458	22.2	24.7	27.5	28.2	28.6	28.3	26.8
657459	23.7	22.8	23.5	19.4	23.9	24.2	23.6
657460	23.8	26.4	28.1	27.7	28.4	28.1	27.0

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 MALE RATS

GROUP: V-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	50-57	57-64	64-71	1-71
ANIMAL NO.				
657441	27.0	27.1	26.9	27.3
657442	20.0	22.0	20.5	20.9
657443	27.2	27.6	28.7	28.5
657444	35.3	32.5	30.6	30.8
657445	26.3	27.0	25.3	26.4
657446	22.7	22.6	21.6	22.4
657447	25.7	25.8	24.2	24.9
657448	26.5	27.0	26.0	25.4
657449	26.1	27.1	28.3	28.0
657450	26.5	28.5	27.8	27.5
657451	31.1	31.5	31.5	29.7
657452	26.7	28.2	27.3	28.1
657453	23.4	26.7	26.3	24.0
657454	27.2	29.7	28.2	27.8
657455	24.3	23.0	24.2	24.3
657456	26.5	28.4	29.0	27.3
657457	32.6	35.6	34.0	33.7
657458	26.7	27.7	28.0	26.9
657459	21.9	25.3	23.9	23.2
657460	27.9	26.9	28.6	27.3

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 MALE RATS

GROUP: VII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657466	20.5	22.0	24.8	21.7	27.5	26.8	26.6
657467	20.6	19.1	21.1	24.7	24.1	23.7	21.9
657468	22.0	20.7	20.1	23.8	27.6	28.4	23.1
657469	24.2	23.4	24.3	25.5	27.6	26.6	27.9
657470	23.6	25.8	25.7	21.5	25.7	24.5	21.5
657471	21.8	17.7	19.9	21.2	23.2	22.2	19.6
657472	25.3	27.2	27.3	27.8	27.8	29.4	27.0
657473	27.2	22.8	29.6	22.4	26.2	28.0	29.9
657474	28.0	21.6	25.0	25.3	25.7	26.1	23.1
657475	21.2	18.5	18.8	19.3	20.8	20.0	20.7
657476	26.4	20.9	21.4	24.1	23.9	24.0	26.4
657477	27.6	28.4	32.3	34.2	32.5	AK (DAY 42)	-
657478	27.8	27.7	28.7	29.5	29.9	27.0	32.2
657479	20.9	24.2	23.4	25.0	20.9	25.2	20.8
657480	22.8	25.4	24.4	24.4	22.8	24.2	21.7
657481	29.4	30.6	32.6	33.0	33.2	33.4	26.2
657482	25.9	24.7	24.7	24.6	22.9	24.6	23.8
657483	32.5	31.2	29.1	29.7	27.2	30.9	26.9
657484	27.0	22.3	31.3	31.8	34.1	30.9	25.3
657485	28.8	27.4	29.2	29.2	27.9	28.8	28.5

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 MALE RATS

GROUP: VII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	50-57	57-64	64-71	1-71
ANIMAL NO.				
657466	29.0	26.7	26.7	25.2
657467	24.2	21.5	22.0	22.3
657468	28.0	29.3	28.8	25.2
657469	30.4	29.9	29.6	26.9
657470	23.9	18.4	25.0	23.6
657471	23.5	22.8	22.6	21.4
657472	27.3	27.3	26.4	27.3
657473	29.2	32.3	31.1	27.9
657474	20.4	27.5	25.1	24.8
657475	21.9	23.1	23.1	20.7
657476	26.0	29.6	26.6	24.9
657477	-	-	-	-
657478	32.6	29.2	32.3	29.7
657479	23.4	23.8	21.1	22.9
657480	25.1	27.1	25.5	24.3
657481	25.0	38.3	35.0	31.7
657482	25.0	27.1	FD (DAY 66)	-
657483	26.5	30.8	17.2	28.2
657484	33.6	38.6	29.9	30.5
657485	28.3	26.7	31.2	28.6

APPENDIX I

INDIVIDUAL FOOD CONSUMPTION OF P_1 FEMALE RATS DURING PREMATING

INDIVIDUAL FOOD CONSUMPTION OF P_1 FEMALE RATS DURING PREMATING

EXPLANATORY NOTES

Notes

Test Days 1-75 = Premating period
Test Days 76-90 = Cohabitation period

Abbreviation

- = No Data

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 FEMALE RATS DURING PREMATING

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

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657491	16.0	16.2	17.0	18.6	16.8	16.8	17.1
657492	19.1	22.4	18.2	18.7	25.2	22.8	15.8
657493	16.0	17.5	18.4	18.2	18.7	18.4	17.6
657494	16.6	17.4	18.7	19.1	19.1	19.2	17.9
657495	16.4	17.0	17.6	17.9	17.6	19.1	17.3
657496	17.8	16.0	16.8	17.0	18.9	19.1	17.2
657497	17.8	16.1	19.0	20.3	20.3	18.5	17.1
657498	16.4	15.7	19.0	18.3	18.4	17.6	18.7
657499	19.0	19.3	19.2	18.9	22.1	20.4	18.1
657500	17.3	17.8	20.1	18.6	21.7	19.6	19.2
657501	15.5	15.3	16.2	16.0	17.1	15.7	15.5
657502	14.7	14.0	15.4	15.6	16.0	15.8	15.3
657503	19.4	18.1	18.5	18.9	21.6	21.1	21.4
657504	15.6	17.8	17.9	18.0	20.2	18.9	16.6
657505	14.7	15.9	16.6	15.5	17.9	15.6	15.6
657506	20.8	18.7	20.2	22.0	21.8	19.5	17.8
657507	17.9	19.9	21.0	20.7	20.6	18.8	19.5
657508	17.9	17.3	19.2	21.3	21.7	18.9	18.0
657509	15.7	17.3	18.4	18.7	19.9	17.8	16.8
657510	14.3	15.2	15.4	16.5	15.9	15.5	13.3

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 FEMALE RATS DURING PREMATING

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

DAYS ON TEST:	50-57	57-64	64-71	1-71
ANIMAL NO.				
657491	16.8	16.2	16.8	16.8
657492	17.9	19.9	17.9	19.8
657493	18.6	18.2	18.3	18.0
657494	17.4	17.4	17.8	18.1
657495	16.1	19.5	17.5	17.6
657496	17.7	17.9	18.0	17.6
657497	18.4	18.8	19.1	18.5
657498	17.4	17.9	19.0	17.8
657499	18.9	17.5	18.4	19.2
657500	17.9	18.6	19.2	19.0
657501	15.6	15.3	15.9	15.8
657502	17.1	16.6	15.4	15.6
657503	17.5	18.7	19.7	19.5
657504	19.3	18.5	18.8	18.2
657505	16.1	15.3	15.2	15.8
657506	18.9	19.0	17.8	19.7
657507	19.5	18.3	18.7	19.5
657508	21.5	19.7	17.8	19.3
657509	17.3	16.4	18.0	17.6
657510	14.5	14.6	13.9	14.9

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 FEMALE RATS DURING PREMATING

GROUP: IV-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657516	19.0	17.8	16.9	19.8	19.7	17.2	17.3
657517	15.4	17.2	17.7	16.4	21.2	20.3	16.4
657518	17.5	17.4	18.1	19.7	19.1	18.4	17.9
657519	17.4	18.5	20.3	21.4	20.5	19.9	20.0
657520	18.9	17.9	18.5	20.2	18.4	19.7	17.3
657521	15.7	20.6	17.1	18.3	18.2	17.9	15.7
657522	17.6	25.0	17.7	16.5	19.3	20.0	18.1
657523	17.2	17.5	17.3	18.0	15.9	15.7	15.7
657524	20.8	17.1	18.6	23.1	21.7	19.8	18.6
657525	16.3	16.8	17.8	19.0	18.4	17.6	17.5
657526	16.6	18.0	18.9	18.2	18.9	18.1	15.9
657527	16.9	15.8	18.3	18.3	19.0	17.6	18.8
657528	18.4	20.0	21.3	21.8	21.8	21.4	19.5
657529	16.4	16.5	17.1	16.7	18.0	17.2	16.4
657530	18.4	18.0	18.6	18.0	17.5	17.8	18.2
657531	18.4	18.7	18.2	18.9	19.9	18.2	18.4
657532	19.6	20.4	21.5	19.4	20.4	19.7	19.7
657533	16.2	16.9	18.9	18.3	23.5	17.9	18.7
657534	17.9	18.4	21.7	20.6	23.2	19.7	20.0
657535	19.5	20.9	21.6	19.6	21.2	19.1	18.5

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 FEMALE RATS DURING PREMATING

GROUP: IV-0 DOSE: 75 MG/KG/DAY

DAYS ON TEST:	50-57	57-64	64-71	1-71
ANIMAL NO.				
657516	18.0	19.9	18.0	18.3
657517	17.0	17.1	16.6	17.5
657518	18.7	17.5	18.4	18.3
657519	20.7	23.5	17.1	19.9
657520	18.6	19.4	18.7	18.8
657521	17.8	16.6	17.1	17.5
657522	18.4	18.3	17.6	18.8
657523	16.3	15.4	15.1	16.4
657524	20.2	22.6	18.8	20.1
657525	17.7	18.2	17.2	17.6
657526	17.4	17.4	17.3	17.7
657527	17.5	19.1	18.4	18.0
657528	19.9	20.6	19.9	20.5
657529	16.8	17.7	16.2	16.9
657530	18.6	19.0	18.8	18.3
657531	18.0	20.4	18.7	18.8
657532	18.9	18.6	18.5	19.7
657533	19.4	17.5	16.5	18.4
657534	20.3	20.9	19.9	20.3
657535	18.8	19.0	18.0	19.6

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 FEMALE RATS DURING PREMATING

GROUP: VI-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657541	15.9	16.8	19.3	17.8	20.4	18.4	17.8
657542	17.1	16.3	17.3	18.3	20.1	17.4	17.2
657543	16.0	16.1	18.1	19.4	20.6	18.3	19.2
657544	16.1	17.2	20.6	20.5	20.2	18.6	20.6
657545	15.0	15.4	17.0	17.1	17.8	17.0	16.6
657546	15.8	16.0	17.3	16.8	18.1	16.3	16.8
657547	15.6	14.3	16.6	16.3	17.0	15.0	15.8
657548	17.6	19.9	21.1	19.0	20.8	21.1	20.3
657549	15.6	13.7	16.1	18.5	18.4	15.2	14.7
657550	16.5	18.1	18.6	19.3	18.7	15.5	16.1
657551	16.9	16.3	17.7	19.1	18.4	18.0	18.4
657552	16.0	15.4	18.3	17.3	16.8	17.3	18.1
657553	18.3	15.4	16.4	18.0	22.3	18.0	18.3
657554	18.9	16.5	16.3	21.6	21.2	18.6	16.7
657555	16.0	15.8	19.0	17.3	19.5	17.2	17.2
657556	21.1	20.5	21.0	23.0	22.5	20.3	20.1
657557	17.4	19.6	18.4	20.8	23.3	20.2	18.5
657558	16.8	18.4	16.9	18.2	18.9	16.5	16.3
657559	24.4	21.9	22.7	23.4	22.8	21.8	22.0
657560	17.6	17.8	20.1	18.1	20.8	18.6	20.0

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 FEMALE RATS DURING PREMATING

GROUP: VI-0 DOSE: 500 MG/KG/DAY

DAYS ON TEST:	50-57	57-64	64-71	1-71
ANIMAL NO.				
657541	18.3	18.3	18.7	18.2
657542	17.2	17.6	17.1	17.6
657543	18.7	19.1	18.4	18.4
657544	18.6	19.0	20.1	19.1
657545	15.7	16.3	15.7	16.4
657546	16.6	16.6	15.7	16.6
657547	16.2	16.3	15.9	15.9
657548	21.9	21.4	24.0	20.7
657549	16.3	16.3	14.7	15.9
657550	17.0	16.9	16.2	17.3
657551	17.1	18.2	16.4	17.6
657552	17.4	17.7	17.0	17.1
657553	18.5	19.2	15.9	18.0
657554	16.3	15.2	16.6	17.8
657555	15.3	16.9	16.6	17.1
657556	20.7	20.0	19.6	20.9
657557	17.9	18.8	19.0	19.4
657558	16.5	16.3	16.6	17.1
657559	23.6	20.1	19.1	22.2
657560	8.4	18.0	18.0	17.8

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 FEMALE RATS DURING PREMATING

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	29-36	36-43	43-50
ANIMAL NO.							
657566	13.0	14.7	16.6	17.8	17.0	15.9	16.2
657567	18.9	17.9	16.5	20.8	17.8	18.5	17.0
657568	14.0	16.8	16.4	19.7	19.0	19.5	16.3
657569	15.5	18.2	17.5	21.3	17.9	17.3	18.0
657570	16.8	16.5	19.2	16.2	18.8	17.4	16.9
657571	13.3	12.9	15.6	15.8	13.6	15.3	15.3
657572	15.4	17.0	17.8	21.0	18.9	17.7	17.3
657573	16.7	15.7	17.7	15.4	16.7	17.3	16.8
657574	20.0	18.6	18.1	16.4	18.2	17.2	22.7
657575	14.0	16.6	17.2	18.8	20.3	16.9	18.6
657576	19.3	18.4	18.1	17.6	19.4	19.1	17.6
657577	14.5	14.2	17.2	21.2	21.7	17.9	14.9
657578	15.1	16.2	17.7	18.9	20.2	22.5	17.5
657579	14.7	15.7	16.8	17.0	18.7	17.1	17.5
657580	16.1	17.8	3.0	21.8	18.8	19.8	17.4
657581	15.5	15.7	17.9	15.2	17.4	28.0	17.8
657582	15.4	8.4	18.3	20.2	18.7	19.2	16.9
657583	18.0	18.5	19.3	19.2	21.4	18.8	18.7
657584	16.1	19.5	19.1	18.5	22.5	17.7	17.3
657585	13.8	18.0	15.8	18.4	17.5	17.1	15.8

INDIVIDUAL FOOD CONSUMPTION (grams/day) OF P_1 FEMALE RATS DURING PREMATING

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

DAYS ON TEST:	50-57	57-64	64-71	1-71
ANIMAL NO.				
657566	15.8	11.6	17.6	15.6
657567	20.0	15.4	16.9	18.0
657568	17.7	19.5	18.8	17.8
657569	19.7	17.4	19.6	18.3
657570	18.9	19.1	18.8	17.9
657571	16.9	12.8	15.9	14.8
657572	17.4	16.4	16.2	17.5
657573	16.4	16.8	11.9	16.1
657574	19.8	17.1	19.5	18.8
657575	18.7	16.9	19.0	17.7
657576	17.8	18.2	17.2	18.3
657577	16.8	17.6	17.2	17.3
657578	18.3	18.3	18.4	18.3
657579	16.2	18.4	17.8	17.0
657580	18.8	17.0	20.4	17.1
657581	17.7	18.4	18.5	18.2
657582	18.0	17.6	17.3	17.0
657583	19.3	16.7	20.0	19.0
657584	18.2	18.8	18.2	18.6
657585	17.1	16.3	13.9	16.4

APPENDIX J

INDIVIDUAL FOOD CONSUMPTION OF P_1 FEMALE RATS DURING GESTATION

INDIVIDUAL FOOD CONSUMPTION OF P_1 FEMALE RATS DURING GESTATION

EXPLANATORY NOTES

Abbreviations

NP = No litter delivered; data excluded from statistical analysis.
- = No Data

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY P_1 FEMALE RATS DURING GESTATION

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

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NO.				
657491	21.7	23.1	22.0	22.2
657492	26.9	30.5	28.2	28.5
657493	23.0	25.7	24.8	24.5
657494	25.1	25.7	26.5	25.8
657495	20.7	24.8	22.6	22.7
657496 (NP)	20.7	20.2	15.9	18.9
657497	26.3	26.0	27.9	26.7
657498	23.9	25.6	25.6	25.0
657499	21.7	22.3	23.2	22.4
657500	26.5	25.7	26.2	26.1
657501	22.8	24.1	24.6	23.8
657502	22.2	23.0	25.2	23.5
657503	24.5	24.7	25.5	24.9
657504	22.8	26.2	24.9	24.6
657505	21.4	22.8	26.4	23.5
657506	22.7	25.8	27.3	25.3
657507	24.5	25.4	25.4	25.1
657508	24.6	26.4	26.0	25.7
657509 (NP)	17.0	17.4	16.8	17.1
657510	19.7	19.9	23.1	20.9

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY P_1 FEMALE RATS DURING GESTATION

GROUP: IV-0 DOSE: 75 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NO.				
657516	25.6	25.7	24.9	25.4
657517	21.7	21.9	24.1	22.6
657518	21.8	22.8	22.7	22.4
657519 (NP)	-	-	-	-
657520	23.3	23.7	24.8	23.9
657521[a]	96.9	-	22.9	-
657522	23.6	24.5	26.2	24.7
657523	20.1	19.3	20.8	20.1
657524	27.6	29.7	30.7	29.3
657525	20.6	23.3	23.2	22.4
657526	21.9	21.9	15.1	19.6
657527	21.9	24.8	27.3	24.7
657528	23.5	22.8	24.5	23.6
657529[b]	-	-	-	-
657530[b]	-	-	-	-
657531	29.0	21.6	25.6	25.4
657532	25.9	25.4	25.2	25.5
657533	19.7	18.7	23.3	20.6
657534	25.7	26.4	30.9	27.7
657535	21.2	24.3	26.3	23.9

a Due to error, food data were not recorded on 7G. Data for 0-7G excluded from the calculations.

b Evidence of copulation was not observed; therefore, no gestation data were collected.

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY P_1 FEMALE RATS DURING GESTATION

GROUP: VI-0 DOSE: 500 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NO.				
657541[a]	22.9	23.9	-	-
657542	20.8	20.7	23.2	21.6
657543	23.1	23.1	27.5	24.5
657544	24.2	26.1	24.3	24.9
657545	21.5	22.4	24.3	22.8
657546	19.9	24.0	24.6	22.8
657547	23.0	20.8	22.3	22.0
657548	23.5	25.2	29.0	25.9
657549	23.8	22.2	23.7	23.2
657550[b]	-	-	-	-
657551[b]	-	-	-	-
657552	21.5	21.1	22.5	21.7
657553	23.4	27.2	27.7	26.1
657554	21.3	22.6	21.4	21.8
657555	22.9	24.3	23.9	23.7
657556	25.3	27.2	29.4	27.3
657557 (NP)	-	-	-	-
657558	17.4	19.7	22.8	20.0
657559	28.8	28.9	25.5	27.7
657560	24.5	26.8	29.7	27.0

a Animal delivered prior to collection of Gestation Day 21 data.
b Evidence of copulation was not observed; therefore, no gestation data were collected.

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY P_1 FEMALE RATS DURING GESTATION

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

GESTATION DAYS:	0-7	7-14	14-21	0-21
ANIMAL NO.				
657566[a]	-	-	-	-
657567 (NP)	20.8	22.2	14.6	19.2
657568	21.3	23.4	27.3	24.0
657569 (NP)	29.1	18.7	20.5	22.7
657570	19.4	19.8	22.1	20.4
657571[a]	-	-	-	-
657572	20.2	19.5	22.7	20.8
657573	21.3	22.7	23.4	22.5
657574	24.0	25.2	27.0	25.4
657575 (NP)	19.7	20.8	20.6	20.4
657576	23.7	26.9	28.2	26.3
657577	18.5	21.9	23.9	21.4
657578 (NP)	17.1	16.6	16.2	16.6
657579	19.7	21.8	20.9	20.8
657580	22.2	24.5	24.9	23.9
657581	23.5	25.3	27.0	25.3
657582 (NP)	21.0	16.9	16.1	18.0
657583	20.6	22.4	24.6	22.5
657584	21.6	21.4	27.5	23.5
657585	16.9	21.0	22.5	20.1

a Evidence of copulation was not observed; therefore, no gestation data were collected.

APPENDIX K

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 MALE RATS

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 MALE RATS

EXPLANATORY NOTES

Notes

Test Days 1-75 = Premating period
Test Days 76-90 = Cohabitation period

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 MALE RATS

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

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
657391	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657392	ALOPECIA BOTH FRONT PAW(S) ALOPECIA LEFT FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 114	15 85	50 85
657393	ALOPECIA BOTH FRONT LEG(S) ALOPECIA BOTH FRONT PAW(S) ALOPECIA LEFT FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 114	29 29 85	78 78 85
657394	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657395	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657396	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 115		
657397	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 115		
657398	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 115		
657399	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 115		
657400	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 115		
657401	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 116		
657402	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 116		
657403	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 116	8 64	15 71
657404	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 116		
657405	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 116		
657406	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 117		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 MALE RATS

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

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
657407	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 117		
657408	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 117		
657409	SORE BOTH SHOULDER(S) SORE RIGHT SHOULDER(S) SORE NECK SACRIFICED IN EXTREMIS TEST DAY 60	10 43 43	36 60 60
657410	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 117		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 MALE RATS

GROUP: III-0 DOSE: 75 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
657416	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657417	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657418	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657419	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657420	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657421	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 115		
657422	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 115	36 36	115 115
657423	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 115	8 57	115 99
657424	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 115		
657425	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 115		
657426	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 116		
657427	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 116		
657428	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 116		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 MALE RATS

GROUP: III-0 DOSE: 75 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
657429	ALOPECIA BOTH FRONT PAW(S)	15	99
	ALOPECIA BOTH FRONT LEG(S)	29	116
	ALOPECIA RIGHT FRONT PAW(S)	106	116
	SACRIFICED BY DESIGN TEST DAY 116		
657430	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 116		
657431	ALOPECIA BOTH FRONT PAW(S)	117	117
	ALOPECIA BOTH FRONT LEG(S)	117	117
	SACRIFICED BY DESIGN TEST DAY 117		
657432	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 117		
657433	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 117		
657435	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 117		
657596	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 117		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 MALE RATS

GROUP: V-0 DOSE: 500 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
657441	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657442	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657443	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657444	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657445	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 114		
657446	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 115		
657447	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 115		
657448	ALOPECIA LEFT FRONT PAW(S) ALOPECIA BOTH FRONT PAW(S) ALOPECIA LEFT FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 115	99 106 106	99 115 115
657449	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 115		
657450	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) ALOPECIA LEFT FRONT PAW(S) ALOPECIA LEFT FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 115	50 50 106 106	78 78 115 115
657451	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 116		
657452	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 116		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 MALE RATS

GROUP: V-0 DOSE: 500 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
657453	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 116		
657454	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 116		
657455	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 116		
657456	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 117		
657457	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 117		
657458	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 117		
657459	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) ALOPECIA LEFT FRONT PAW(S) ACCIDENTLY KILLED TEST DAY 86	8 8 85	50 50 85
657460	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 117	29 29	117 117

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 MALE RATS

GROUP: VII-0 DOSE: 3500 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
657466	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 114		
657467	DISCHARGE PENIS RED	43	43
	LUNG NOISE	48	49
	SORE PENIS	92	92
	SACRIFICED BY DESIGN TEST DAY 114		
657468	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 114		
657469	STAINED PERINEUM YELLOW	80	92
	LUNG NOISE	80	80
	SACRIFICED BY DESIGN TEST DAY 114		
657470	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 114		
657471	ALOPECIA BOTH FRONT PAW(S)	8	16
	SALIVATION	16	16
	STAINED PERINEUM YELLOW	78	78
	SACRIFICED BY DESIGN TEST DAY 115		
657472	ALOPECIA BOTH FRONT LEG(S)	43	78
	SALIVATION	52	54
	ALOPECIA RIGHT FRONT LEG(S)	85	115
	ALOPECIA RIGHT FRONT PAW(S)	85	115
	SACRIFICED BY DESIGN TEST DAY 115		
657473	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 115		
657474	SALIVATION	54	54
	ALOPECIA BOTH FRONT PAW(S)	92	99
	ALOPECIA BOTH FRONT LEG(S)	92	99
	SACRIFICED BY DESIGN TEST DAY 115		
657475	STAINED NOSE RED	86	86
	SACRIFICED BY DESIGN TEST DAY 115		
657476	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 116		
657477	NO ABNORMALITIES DETECTED		
	ACCIDENTLY KILLED TEST DAY 42		
657478	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 116		
657479	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 116		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 MALE RATS

GROUP: VII-0 DOSE: 3500 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
657480	ALOPECIA RIGHT FRONT PAW(S)	22	29
	ALOPECIA BOTH FRONT PAW(S)	36	92
	SACRIFICED BY DESIGN TEST DAY 116		
657481	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 117		
657482	SALIVATION	10	22
	SALIVATION	31	31
	SALIVATION	52	52
	FOUND DEAD TEST DAY 66		
657483	STAINED MOUTH BROWN	66	69
	STAINED NOSE BROWN	66	69
	IRREGULAR RESPIRATION	66	66
	SACRIFICED BY DESIGN TEST DAY 117		
657484	SALIVATION	24	24
	SALIVATION	32	35
	SALIVATION	54	54
	SALIVATION	65	69
	STAINED PERINEUM YELLOW	85	85
	SACRIFICED BY DESIGN TEST DAY 117		
657485	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 117		

APPENDIX L

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING PREMATING AND COHABITATION

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING PREMATING AND COHABITATION[a]

EXPLANATORY NOTES

Notes

Test Days 1-75 = Premating period
Test Days 76-90 = Cohabitation period

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS
DURING PREMATING AND COHABITATION

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

ANIMAL NUMBER	OBSERVATION	TEST DAYS FIRST DAY OBSERVED	TEST DAYS LAST DAY OBSERVED
657491	NO ABNORMALITIES DETECTED		
657492	NO ABNORMALITIES DETECTED		
657493	NO ABNORMALITIES DETECTED		
657494	NO ABNORMALITIES DETECTED		
657495	NO ABNORMALITIES DETECTED		
657496	NO ABNORMALITIES DETECTED		
657497	ALOPECIA BOTH FRONT PAW(S)	8	71
	ALOPECIA BOTH FRONT LEG(S)	29	71
	ALOPECIA RIGHT SIDE(S)	57	71
657498	NO ABNORMALITIES DETECTED		
657499	NO ABNORMALITIES DETECTED		
657500	NO ABNORMALITIES DETECTED		
657501	NO ABNORMALITIES DETECTED		
657502	NO ABNORMALITIES DETECTED		
657503	NO ABNORMALITIES DETECTED		
657504	NO ABNORMALITIES DETECTED		
657505	ALOPECIA BOTH FRONT PAW(S)	8	36
	ALOPECIA BOTH FRONT PAW(S)	57	71
	ALOPECIA BOTH FRONT LEG(S)	57	71
657506	ALOPECIA BOTH FRONT PAW(S)	8	71
	ALOPECIA BOTH FRONT LEG(S)	8	57
	ALOPECIA ABDOMEN	8	36
657507	NO ABNORMALITIES DETECTED		
657508	NO ABNORMALITIES DETECTED		
657509	NO ABNORMALITIES DETECTED		
657510	NO ABNORMALITIES DETECTED		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS
DURING PREMATING AND COHABITATION

GROUP: IV-0 DOSE: 75 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	TEST DAYS FIRST DAY OBSERVED	TEST DAYS LAST DAY OBSERVED
657516	NO ABNORMALITIES DETECTED		
657517	NO ABNORMALITIES DETECTED		
657518	NO ABNORMALITIES DETECTED		
657519	NO ABNORMALITIES DETECTED		
657520	NO ABNORMALITIES DETECTED		
657521	NO ABNORMALITIES DETECTED		
657522	NO ABNORMALITIES DETECTED		
657523	NO ABNORMALITIES DETECTED		
657524	NO ABNORMALITIES DETECTED		
657525	ALOPECIA BOTH FRONT PAW(S)	8	8
657526	ALOPECIA BOTH FRONT PAW(S)	15	71
	ALOPECIA BOTH FRONT LEG(S)	22	71
657527	NO ABNORMALITIES DETECTED		
657528	NO ABNORMALITIES DETECTED		
657529	NO ABNORMALITIES DETECTED		
657530	NO ABNORMALITIES DETECTED		
657531	NO ABNORMALITIES DETECTED		
657532	NO ABNORMALITIES DETECTED		
657533	NO ABNORMALITIES DETECTED		
657534	NO ABNORMALITIES DETECTED		
657535	NO ABNORMALITIES DETECTED		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING PREMATING AND COHABITATION

GROUP: VI-0 DOSE: 500 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	TEST DAYS FIRST DAY OBSERVED	TEST DAYS LAST DAY OBSERVED
657541	NO ABNORMALITIES DETECTED		
657542	NO ABNORMALITIES DETECTED		
657543	NO ABNORMALITIES DETECTED		
657544	NO ABNORMALITIES DETECTED		
657545	ALOPECIA BOTH FRONT PAW(S)	29	71
	ALOPECIA BOTH FRONT LEG(S)	29	71
657546	NO ABNORMALITIES DETECTED		
657547	NO ABNORMALITIES DETECTED		
657548	NO ABNORMALITIES DETECTED		
657549	NO ABNORMALITIES DETECTED		
657550	NO ABNORMALITIES DETECTED		
657551	NO ABNORMALITIES DETECTED		
657552	NO ABNORMALITIES DETECTED		
657553	NO ABNORMALITIES DETECTED		
657554	NO ABNORMALITIES DETECTED		
657555	NO ABNORMALITIES DETECTED		
657556	NO ABNORMALITIES DETECTED		
657557	NO ABNORMALITIES DETECTED		
657558	NO ABNORMALITIES DETECTED		
657559	NO ABNORMALITIES DETECTED		
657560	NO ABNORMALITIES DETECTED		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING PREMATING AND COHABITATION

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	TEST DAYS FIRST DAY OBSERVED	TEST DAYS LAST DAY OBSERVED
657566	STAINED PERINEUM YELLOW	60	61
	HUNCHED OVER	60	61
657567	NO ABNORMALITIES DETECTED		
657568	NO ABNORMALITIES DETECTED		
657569	SALIVATION	16	16
657570	NO ABNORMALITIES DETECTED		
657571	NO ABNORMALITIES DETECTED		
657572	NO ABNORMALITIES DETECTED		
657573	NO ABNORMALITIES DETECTED		
657574	SALIVATION	51	51
657575	ALOPECIA BOTH FRONT LEG(S)	43	71
	ALOPECIA LEFT REAR LEG(S)	43	64
657576	ALOPECIA BOTH FRONT PAW(S)	57	71
	ALOPECIA BOTH FRONT LEG(S)	57	71
	ALOPECIA ABDOMEN	71	71
657577	SALIVATION	9	10
657578	NO ABNORMALITIES DETECTED		
657579	NO ABNORMALITIES DETECTED		
657580	NO ABNORMALITIES DETECTED		
657581	NO ABNORMALITIES DETECTED		
657582	NO ABNORMALITIES DETECTED		
657583	NO ABNORMALITIES DETECTED		
657584	NO ABNORMALITIES DETECTED		
657585	NO ABNORMALITIES DETECTED		

APPENDIX M

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING GESTATION

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING GESTATION

EXPLANATORY NOTES

Note

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

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING GESTATION

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

ANIMAL NUMBER	OBSERVATION	GESTATION DAYS FIRST DAY OBSERVED	GESTATION DAYS LAST DAY OBSERVED
657491	NO ABNORMALITIES DETECTED		
657492	NO ABNORMALITIES DETECTED		
657493	NO ABNORMALITIES DETECTED		
657494	NO ABNORMALITIES DETECTED		
657495	NO ABNORMALITIES DETECTED		
657496	NO ABNORMALITIES DETECTED		
657497	ALOPECIA BOTH FRONT PAW(S)	0	0
	ALOPECIA BOTH FRONT LEG(S)	0	21
	ALOPECIA RIGHT SIDE(S)	0	21
657498	NO ABNORMALITIES DETECTED		
657499	NO ABNORMALITIES DETECTED		
657500	NO ABNORMALITIES DETECTED		
657501	ALOPECIA LEFT SIDE(S)	14	14
	ALOPECIA RIGHT SIDE(S)	21	21
657502	NO ABNORMALITIES DETECTED		
657503	NO ABNORMALITIES DETECTED		
657504	NO ABNORMALITIES DETECTED		
657505	ALOPECIA BOTH FRONT PAW(S)	0	0
	ALOPECIA BOTH FRONT LEG(S)	0	0
	ALOPECIA BOTH FRONT PAW(S)	14	21
	ALOPECIA RIGHT FRONT LEG(S)	21	21
657506	ALOPECIA BOTH FRONT PAW(S)	0	21
657507	ALOPECIA LEFT FRONT LEG(S)	7	21
657508	NO ABNORMALITIES DETECTED		
657509	NO ABNORMALITIES DETECTED		
657510	ALOPECIA BOTH FRONT PAW(S)	0	0

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING GESTATION

GROUP: IV-0 DOSE: 75 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	GESTATION DAYS FIRST DAY OBSERVED	GESTATION DAYS LAST DAY OBSERVED
657516	NO ABNORMALITIES DETECTED		
657517	NO ABNORMALITIES DETECTED		
657518	NO ABNORMALITIES DETECTED		
657520	NO ABNORMALITIES DETECTED		
657521	NO ABNORMALITIES DETECTED		
657522	NO ABNORMALITIES DETECTED		
657523	NO ABNORMALITIES DETECTED		
657524	NO ABNORMALITIES DETECTED		
657525	NO ABNORMALITIES DETECTED		
657526	ALOPECIA BOTH FRONT PAW(S)	0	14
	ALOPECIA BOTH FRONT LEG(S)	0	14
	ALOPECIA RIGHT FRONT LEG(S)	21	21
657527	NO ABNORMALITIES DETECTED		
657528	NO ABNORMALITIES DETECTED		
657531	NO ABNORMALITIES DETECTED		
657532	NO ABNORMALITIES DETECTED		
657533	NO ABNORMALITIES DETECTED		
657534	NO ABNORMALITIES DETECTED		
657535	NO ABNORMALITIES DETECTED		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING GESTATION

GROUP: VI-0 DOSE: 500 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	GESTATION DAYS FIRST DAY OBSERVED	GESTATION DAYS LAST DAY OBSERVED
657541	NO ABNORMALITIES DETECTED		
657542	NO ABNORMALITIES DETECTED		
657543	NO ABNORMALITIES DETECTED		
657544	ALOPECIA LEFT FRONT LEG(S)	7	21
657545	ALOPECIA BOTH FRONT PAW(S)	0	21
	ALOPECIA BOTH FRONT LEG(S)	0	21
657546	NO ABNORMALITIES DETECTED		
657547	NO ABNORMALITIES DETECTED		
657548	NO ABNORMALITIES DETECTED		
657549	ALOPECIA LEFT FRONT PAW(S)	21	21
	ALOPECIA LEFT FRONT LEG(S)	21	21
657552	NO ABNORMALITIES DETECTED		
657553	NO ABNORMALITIES DETECTED		
657554	NO ABNORMALITIES DETECTED		
657555	NO ABNORMALITIES DETECTED		
657556	ALOPECIA BOTH FRONT PAW(S)	0	14
	ALOPECIA BOTH FRONT LEG(S)	0	21
657558	NO ABNORMALITIES DETECTED		
657559	ALOPECIA BOTH FRONT PAW(S)	0	21
	ALOPECIA BOTH FRONT LEG(S)	0	21
657560	ALOPECIA BOTH FRONT PAW(S)	7	21
	ALOPECIA BOTH FRONT LEG(S)	7	21

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING GESTATION

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	GESTATION DAYS FIRST DAY OBSERVED	GESTATION DAYS LAST DAY OBSERVED
657567	NO ABNORMALITIES DETECTED		
657568	NO ABNORMALITIES DETECTED		
657569	NO ABNORMALITIES DETECTED		
657570	NO ABNORMALITIES DETECTED		
657572	NO ABNORMALITIES DETECTED		
657573	NO ABNORMALITIES DETECTED		
657574	NO ABNORMALITIES DETECTED		
657575	ALOPECIA RIGHT SIDE(S)	14	21
	ALOPECIA RIGHT LEG(S)	21	21
657576	ALOPECIA BOTH FRONT PAW(S)	0	21
	ALOPECIA BOTH FRONT LEG(S)	0	21
	ALOPECIA ABDOMEN	0	21
657577	NO ABNORMALITIES DETECTED		
657578	NO ABNORMALITIES DETECTED		
657579	NO ABNORMALITIES DETECTED		
657580	NO ABNORMALITIES DETECTED		
657581	NO ABNORMALITIES DETECTED		
657582	SORE TAIL	0	21
657583	NO ABNORMALITIES DETECTED		
657584	NO ABNORMALITIES DETECTED		
657585	NO ABNORMALITIES DETECTED		

APPENDIX N

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING LACTATION

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING LACTATION

EXPLANATORY NOTES

Note

Test days for animal fates are determined from the initiation of test substance administration.

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING LACTATION

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

ANIMAL NUMBER	OBSERVATION	LACTATION DAYS FIRST DAY OBSERVED	LACTATION DAYS LAST DAY OBSERVED
657491	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 121		
657492	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 121		
657493	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 121		
657494	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 123		
657495	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 123		
657497	ALOPECIA BOTH FRONT LEG(S) ALOPECIA RIGHT SIDE(S) ALOPECIA RIGHT FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 124	0 0 21	14 21 21
657498	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 123		
657499	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		
657500	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		
657501	ALOPECIA RIGHT SIDE(S) SACRIFICED BY DESIGN TEST DAY 123	0	14
657502	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 120		
657503	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		
657504	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING LACTATION

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

ANIMAL NUMBER	OBSERVATION	LACTATION DAYS FIRST DAY OBSERVED	LACTATION DAYS LAST DAY OBSERVED
657505	ALOPECIA BOTH FRONT PAW(S)	0	7
	ALOPECIA RIGHT FRONT LEG(S)	0	21
	SACRIFICED BY DESIGN TEST DAY 123		
657506	ALOPECIA BOTH FRONT PAW(S)	0	21
	SACRIFICED BY DESIGN TEST DAY 123		
657507	ALOPECIA LEFT FRONT LEG(S)	0	0
	ALOPECIA BOTH FRONT LEG(S)	7	21
	ALOPECIA BOTH FRONT PAW(S)	21	21
	SACRIFICED BY DESIGN TEST DAY 122		
657508	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 121		
657510	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 126		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING LACTATION

GROUP: IV-0 DOSE: 75 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	LACTATION DAYS FIRST DAY OBSERVED	LACTATION DAYS LAST DAY OBSERVED
657516	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 120		
657517	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 123		
657518	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		
657520	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 121		
657521	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 123		
657522	ALOPECIA RIGHT FRONT LEG(S) ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 123	14 21	21 21
657523	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 123	0 0	21 21
657524	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 125		
657525	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 121		
657526	ALOPECIA RIGHT FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 122	0	14
657527	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 120		
657528	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 121		
657529	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING LACTATION

GROUP: IV-0 DOSE: 75 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	LACTATION DAYS FIRST DAY OBSERVED	LACTATION DAYS LAST DAY OBSERVED
657530	ALOPECIA BOTH FRONT PAW(S)	14	21
	ALOPECIA BOTH FRONT LEG(S)	14	21
	SACRIFICED BY DESIGN TEST DAY 123		
657531	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 127		
657532	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 123		
657533	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 121		
657534	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 125		
657535	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 123		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING LACTATION

GROUP: VI-0 DOSE: 500 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	LACTATION DAYS FIRST DAY OBSERVED	LACTATION DAYS LAST DAY OBSERVED
657541	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		
657542	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		
657543	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 121		
657544	ALOPECIA LEFT FRONT LEG(S) ALOPECIA RIGHT FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 123	0 7	0 21
657545	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 120	0 0	21 21
657546	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		
657547	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 123		
657548	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 128		
657549	ALOPECIA LEFT FRONT PAW(S) ALOPECIA LEFT FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 121	0 0	14 14
657550	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 125		
657551	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		
657552	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 124		
657553	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 123		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING LACTATION

GROUP: VI-0 DOSE: 500 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	LACTATION DAYS FIRST DAY OBSERVED	LACTATION DAYS LAST DAY OBSERVED
657554	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 121		
657555	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 123		
657556	ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 121	0	21
657558	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 121		
657559	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 130		
657560	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) SACRIFICED BY DESIGN TEST DAY 122	0 0	21 21

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING LACTATION

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	LACTATION DAYS FIRST DAY OBSERVED	LACTATION DAYS LAST DAY OBSERVED
657566	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		
657568	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 120		
657570	MASS 1 2.0 cm CHEST SACRIFICED BY DESIGN TEST DAY 122	14	14
657571	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 123		
657572	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 121		
657573	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		
657574	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 123		
657576	ALOPECIA BOTH FRONT PAW(S) ALOPECIA BOTH FRONT LEG(S) ALOPECIA ABDOMEN ALOPECIA CHEST SACRIFICED BY DESIGN TEST DAY 121	0 0 0 14	21 21 21 21
657577	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		
657579	ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 121	7	21
657580	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 122		
657581	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 123		
657583	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 121		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA IN P_1 FEMALE RATS DURING LACTATION

GROUP: VIII-0 DOSE: 3500 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	LACTATION DAYS FIRST DAY OBSERVED	LACTATION DAYS LAST DAY OBSERVED
657584	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 125		
657585	ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 123	21	21