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RE: TSCA 8(E) SUBSTANTIAL RISK NOTICE ON: 1-Butanesulfonamide,
1,1,2,2,3,3,4,4,4-nonafluoro-N-(2-hydroxyethyl)-N-methyl, (CAS 34454-97-2)

Dear Sirs:

3M has received data for a subchronic oral toxicity study in rats conducted with a chemical intermediate 1-butanesulfonamide, 1,1,2,2,3,3,4,4,4-nonafluoro-N-(2-hydroxyethyl)-N-methyl, (CAS 34454-97-2) (fluorochemical alcohol) indicating developmental effects.

The study was conducted by Argus Research; a copy of the final report is enclosed. Male rats were administered the fluorochemical alcohol at doses of 0, 10, 50 or 250 mg/kg/day beginning fourteen days before cohabitation and continuing until after cohabitation, for a minimum of 28 days of dosage. Female rats were administered the substance at the same dosage levels beginning fourteen days before cohabitation and continuing until day 5 of lactation.

In the 250 mg/kg/day dosage group, several significant effects were observed. The number of liveborn pups was significantly decreased and the number of stillborn pups was significantly increased. The number of pups found dead or presumed cannibalized on days 1 and 2 to day 5 postpartum was significantly increased. The viability index and number of pups surviving per litter on postpartum day 5 were significantly reduced. These effects at the highest dosage level (250 mg/kg/day) were not observed in the lower dosage groups.

Additionally, some rats in the 50 and 250 mg/kg/day dosage groups were observed to have significantly increased liver weights and microscopic changes in the liver, thymus and/or stomach.

3M uses the fluorochemical alcohol as a chemical intermediate to manufacture polymeric materials. In the manufacturing setting and as administered during toxicity testing, it contains approximately 93-94% of CAS 34454-97-2 and 4-5% functionally

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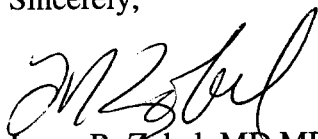
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related branched isomers and monohydrides. The fluorochemical alcohol is present in final products at trace amounts.

Please contact James Zappia (651-733-5180) if you have any questions or if we can provide additional information.

Once a docket number has been assigned for this submittal, please send the docket number postal card to Cheri Kedrowski, 3M Center Bldg. 220-2E-02, St. Paul, MN 55144.

Sincerely,

A handwritten signature in black ink, appearing to read 'L. Zobel', written in a cursive style.

Larry R. Zobel, MD MPH
Staff Vice President and Medical Director

Enclosure

FINAL REPORT

PROTOCOL 418-027

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST

SPONSOR'S STUDY NUMBER: T-7599

FINAL REPORT DATE: 25 MARCH 2003

PROTOCOL 418-027 - ORAL (GAVAGE) COMBINED REPEATED DOSE
TOXICITY STUDY OF T 7599.7 WITH THE
REPRODUCTION/DEVELOPMENTAL TOXICITY
SCREENING TEST

SPONSOR'S STUDY NUMBER: T-7599

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TITLE: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST

ARGUS RESEARCH PROTOCOL NUMBER: 418-027
SPONSOR'S STUDY NUMBER: T-7599

1. SUMMARY AND CONCLUSION

1.1. Methods^a

Sixty male and sixty female Crl:CD®(SD)IGS VAF/Plus® rats were assigned to four dosage groups (Groups I through IV), 15 rats per sex per group. The test substance was T 7599.7 and the vehicle was aqueous 0.5% or 1.0% carboxymethylcellulose (CMC). The 0.5% CMC was used for the first four days of the study and the 1.0% CMC was used for the remainder of the study. The test substance or vehicle was administered to the male rats beginning 14 days before cohabitation and continuing until sacrifice, after completion of the cohabitation period, after a minimum of 28 days of dosage and to the female rats beginning 14 days before cohabitation and continuing until day 5 of lactation (DL 5). Dosages were 0 (Vehicle), 10, 50 and 250 mg/kg/day. The dosage volume was adjusted daily.

Within each dosage group, consecutive order was used to assign the first five male and the first five female rats to a functional observational battery (FOB) and motor activity assessment. The next five rats per sex in each group were assigned to hematology and clinical biochemistry evaluations. The last five rats per sex in each group were assigned to metabolite analysis. Histological evaluations were performed on the last ten rats per sex in each group. Rats were observed for viability at least twice each day of the study. Observations for clinical signs of effects of the test substance, abortions, premature deliveries and deaths were made daily before dosage. Postdosage observations were recorded approximately 60 ± 10 minutes after dosage administration and on the day of sacrifice. Once before the first dosage and at least once weekly thereafter, detailed clinical observations were conducted for all male and female rats. Body weights for male and female rats were recorded daily during the dosage period and at sacrifice. Feed consumption values for male rats were recorded weekly during the dosage period. Feed consumption values for female rats were recorded weekly to cohabitation and on gestation days (DGs) 0, 7, 10, 12, 15, 18, 20 and 25 (if necessary) and on lactation days (DLs) 1 and 5.

a. Detailed descriptions of all procedures used in the conduct of this study are provided in the appropriate sections of this report and in APPENDIX D (PROTOCOL AND AMENDMENTS).

Estrous cycling was evaluated by examination of vaginal cytology beginning with the day after the first administration and then until spermatozoa were observed in a smear of the vaginal contents and/or a copulatory plug was observed *in situ* during the cohabitation period. Female rats were evaluated for adverse clinical signs observed during parturition, duration of gestation, litter sizes and pup viability at birth. Maternal behavior was evaluated on DLs 1 and 5.

Motor activity was evaluated on five male and five female rats per group once during the course of the study, before scheduled sacrifice. Day 1 of lactation was defined as the day of birth and was also the first day on which all pups in a litter were individually weighed. Each litter was evaluated for viability at least twice daily. The pups in each litter were counted twice daily. Clinical observations were recorded once daily. Pup body weights were recorded on DLs 1 and 5. After 36 days of dosage, all male rats were sacrificed and on DL 6, all surviving female rats were sacrificed. A gross necropsy was performed. The testes and epididymides of all male rats were weighed, and the testes, epididymides, seminal vesicles with coagulating gland and prostate were retained. The ovaries and the uterus with cervix of each female rat were weighed, and ovaries, uterus, vagina and a mammary gland were retained.

The following organs were individually weighed: liver, kidneys, adrenals, thymus, testes, epididymides, spleen, brain, heart, ovaries and uterus. The following tissues or representative samples were retained: brain, small and large intestines, lungs, lymph nodes, peripheral nerve, stomach, kidneys, spleen, thymus, trachea, urinary bladder, testes, epididymides, seminal vesicles, prostate, spinal cord, liver, adrenals, heart, thyroid/parathyroid, uterus, bone marrow, ovaries, uterus, vagina, mammary gland (female rats only) and gross lesions. Histological examination was conducted for the assigned ten rats per sex from the control and high dosage groups. Histological evaluations were performed on the livers of ten male and ten female rats, the thymuses of ten female rats and the stomachs of ten male rats in the 10 and 50 mg/kg/day dosage groups.

At scheduled sacrifice, blood was collected from the five male and five female rats per group assigned to hematology and clinical chemistry sample collection. One aliquot was analyzed for hematologic parameters. Two blood smear slides were prepared for each sample for measurements of differential leukocyte count. Plasma from another aliquot was measured for prothrombin time and activated partial thromboplastin time. Serum from a third aliquot was analyzed for clinical chemistry parameters. Blood samples were collected from the five rats per sex per group assigned to metabolite analysis. The liver was excised and the organ weight recorded.

On DL 5, pups were sacrificed and examined for gross lesions. Pups found dead on DLs 2 to 4 were examined for gross lesions and for possible cause of death.

1.2. Results - Males

All male rats survived to scheduled sacrifice. Significant increases in excess salivation, perioral substance and urine-stained abdominal fur occurred in the 250 mg/kg/day dosage group. All other clinical observations and all necropsy observations were considered unrelated to the test substance.

Body weight gains were significantly reduced in the 250 mg/kg/day dosage group on DSs 1 to 8, 1 to 15 and 1 to 36. Body weight gains were also significantly decreased in the 50 mg/kg/day dosage group on DSs 1 to 36. Body weights were significantly reduced on DS 29 and 36 in the 250 mg/kg/day dosage group. Absolute feed consumption values were significantly reduced in the 50 and 250 mg/kg/day dosage groups on DSs 1 to 8 and significantly reduced in the 250 mg/kg/day dosage groups on DSs 1 to 15 and 1 to 36. Relative feed consumption values were significantly reduced on DSs 1 to 8 in the 50 and 250 mg/kg/day dosage groups.

Terminal body weights of the male rats were significantly reduced in the 250 mg/kg/day dosage group. Absolute weights of the left and right kidneys were significantly increased in the 50 and 250 mg/kg/day dosage groups and the absolute weight of the liver was significantly increased in the 250 mg/kg/day dosage group. The ratios of the weights of these organs to terminal body weights were significantly increased in the 50 and 250 mg/kg/day dosage groups. Relative to the brain weight, only the liver weight in the 250 mg/kg/day dosage group was significantly increased. Treatment-related microscopic changes were observed in the liver of male rats in the 50 and 250 mg/kg/day dosage groups and in the stomach of male rats in the 250 mg/kg/day dosage group. Dosages of the test substance as high as 250 mg/kg/day did not affect any hematology or clinical chemistry values evaluated. All mating and fertility parameters were unaffected by dosages of the test substance as high as 250 mg/kg/day.

There were no statistically significant or biologically important differences among the four dosage groups in the measures of the functional observational battery (FOB). Body weights recorded during the functional operational battery for the treated groups were not significantly different than the control group for the male rats. There were no statistically significant or biologically important differences among the four dosage groups in the measures of motor activity on DS 86.

1.3. Results - Females

All female rats survived to scheduled sacrifice. All clinical and necropsy observations were considered unrelated to the test substance. Body weight gains were significantly reduced during the prehabitation period in the 250 mg/kg/day dosage group on DSs 1 to 8 and 1 to 15. Body weights and body weight gains were not significantly affected by dosages of the test substance during gestation or lactation.

Terminal body weights of the female rats were reduced in the 250 mg/kg/day dosage group. Absolute liver weight was significantly increased in the 250 mg/kg/day dosage group. The ratios of the weight of this organ and the weight of the right kidney to

terminal body weights were significantly increased in the 250 mg/kg/day dosage group. Only the ratio of the liver weight to brain weight in the 250 mg/kg/day dosage group was significantly increased. Treatment-related microscopic changes were observed in the liver and thymus of female rats in the 250 mg/kg/day dosage group.

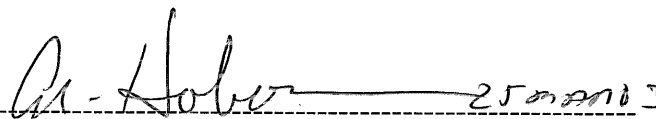
Dosages as high as 250 mg/kg/day did not affect any hematology or clinical chemistry values evaluated. Absolute and relative feed consumption values were not significantly affected by dosages of the test substance during the prehabitation, gestation or lactation periods. All estrous, mating and fertility parameters were unaffected by dosages of the test substance as high as 250 mg/kg/day. There were no statistically significant or biologically important differences among the four dosage groups in the measures of the FOB. Body weights recorded during the functional operational battery for the treated groups were not significantly different than the control group for the female rats. There were no statistically significant or biologically important differences among the four dosage groups in the measures of motor activity on DS 86.

The number of liveborn pups was significantly reduced and number of stillborn pups was significantly increased in the 250 mg/kg/day dosage group. The number of pups found dead or presumed cannibalized on day 1 and days 2 to 5 postpartum was significantly increased in the 250 mg/kg/day dosage groups. The viability index and number of pups surviving per litter on postpartum day 5 were significantly reduced in the 250 mg/kg/day dosage group. Pup body weights per litter were also reduced in the 250 mg/kg/day dosage group on postpartum days 1 and 5.

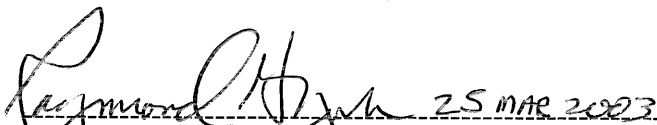
Values for the numbers of dams delivering litters, duration of gestation, averages for implantation sites per delivered litter, gestation index, numbers of dams with stillborn pups, dams with all pups dying, stillborn pups, surviving pups per litter on postpartum day 1 and pup sex ratios were comparable among the four dosage groups. No clinical or necropsy observations in the F1 generation pups were attributable to dosages of the test substance as high as 250 mg/kg/day.

1.4. Conclusion

On the basis of these data, the paternal no-observable-adverse-effect-level (NOAEL) for T 7599.7 is 10 mg/kg/day (the 50 mg/kg/day dosage caused reduced weight gain during prehabitation, reduced absolute and relative feed consumption values, increased absolute and relative liver and kidney weight, and liver histopathology). The maternal NOAEL is 50 mg/kg/day (the 250 mg/kg/day dosage caused reduced weight gain during prehabitation, reduced terminal body weights, increased absolute and relative liver weight, and histopathology of the liver and thymus). The reproductive NOAEL is greater than 250 mg/kg/day (all estrous, mating and fertility parameters were unaffected by dosages of the test substance as high as 250 mg/kg/day). The NOAEL for viability and growth in the offspring is 50 mg/kg/day (dosages of 250 mg/kg/day caused postnatal mortality and decreased pup body weights).

 25 MAR 2003

Alan M. Hoberman, Ph.D., DABT Date
Director of Research

 25 MAR 2003

Raymond G. York, Ph.D., DABT Date
Associate Director of Research
Study Director

2. DESCRIPTION OF TEST PROCEDURES

2.1. Conduct of Study

2.1.1. Sponsor

3M Corporate Toxicology, 3M Center, Building 220-2E-02, St. Paul, Minnesota
55144-1000

2.1.2. Testing Facility

Argus Research, 905 Sheehy Drive, Building A, Horsham, Pennsylvania 19044-1297

2.1.3. Study Number

418-027

2.1.4. Sponsor's Study Number

T-7599

2.1.5. Purpose of the Study

The purpose of this study was to provide information on the possible health hazards that may result from repeated exposure of CrI:CD®(SD)IGS BR VAF/Plus® male and female rats to a test substance beginning before cohabitation, through mating and continuing for at least 28 days (male rats) or through parturition until day 5 of lactation (female rats). This repeated dose study incorporated a reproduction/developmental toxicity screening test to provide initial information on possible effects on male and female reproductive performance (e.g., gonadal function, mating behavior, conception, development of the conceptus and parturition). The study also placed emphasis on neurological effects as a specific endpoint and was designed to identify the neurotoxic potential of a test substance, which may warrant further in-depth investigation.

2.1.6. Study Design

The requirements of the Organisation for Economic Co-operation and Development (OECD)⁽¹⁾ were used as the basis for study design.

2.1.7. Regulatory Compliance

This study was conducted in compliance with Good Laboratory Practice (GLP) regulations of the Organisation for Economic Co-operation and Development (OECD)⁽²⁾, U.S. Food and Drug Administration (FDA)⁽³⁾ and the Japanese Ministry of Health and Welfare (MHW)⁽⁴⁾. There were no deviations from the GLP regulations that affected the quality or integrity of the study. Quality Assurance Unit findings derived from the inspections during the conduct of this study are documented and have been provided to the Study Director and the Testing Facility Management.

2.1.8. Ownership of the Study

The Sponsor owns the study. All raw data, analyses, reports and preserved tissues are the property of the Sponsor.

2.1.9. Study Monitor

Paul H. Lieder, Ph.D., DABT

2.1.10. Study Director

Raymond G. York, Ph.D., DABT, Associate Director of Research
Address as cited above for Testing Facility

2.1.11. Technical Performance

John F. Barnett, B.S. (Director of Laboratory Operations)
Christine A. O'Brien (Research Associate)
Lorna A. Sinotte, B.S. (Laboratory Technician)
Stephanie M. Dorizio, B.A. (Necropsy Laboratory Technician)
Christopher K. Ruppert, B.S. (Formulation Laboratory Technician)

2.1.12. Report Preparation

Raymond G. York, Ph.D., DABT
Jo Ann Frazee, M.S. (Study Coordinator)
JoAnne M. Conklin, B.S. (Data Management Specialist)
Jennifer M. Hughes (Report Administrator)

2.1.13. Report Review

Mildred S. Christian, Ph.D., Fellow, ATS (Executive Director of Research)
Alan M. Hoberman, Ph.D., DABT (Director of Research)

2.1.14. Date Protocol Signed

15 February 2002

2.1.15. Dates of Technical Performance**2.1.15.1. Male Rats**

| | |
|---|-----------------------|
| Rat Arrival | 12 FEB 02 |
| Dosage Period (14 days before cohabitation and through a 14-day cohabitation period until sacrifice after at least 28 days of dosage) | 18 FEB 02 - 25 MAR 02 |
| FOB and Motor Activity Evaluation | 19 MAR 02 - 20 MAR 02 |
| Scheduled Sacrifice | 26 MAR 02 |

2.1.15.2. Female Rats

| | |
|---|-----------------------------|
| Rat Arrival | 12 FEB 02 |
| Dosage Period (14 days before cohabitation through DL ^a 5) | 18 FEB 02 - 12 APR 02 |
| Dosage Period Estrous Cycle Evaluation | 19 FEB 02 - 04 MAR 02 |
| Cohabitation Period | |
| Male 1 | 04 MAR 02 PM - 11 MAR 02 AM |
| Male 2 | 11 MAR 02 PM - 18 MAR 02 AM |
| DG ^b 0 | 05 MAR 02 - 17 MAR 02 |
| Delivery Period ^c (DL 1) | 27 MAR 02 - 08 APR 02 |
| DG 25 Sacrifice (Rats that did not deliver a litter) | 30 MAR 02 - 12 APR 02 |
| FOB Evaluation and Motor Activity Evaluation | 31 MAR 02 - 12 APR 02 |
| Pup Sacrifice (DL 5) | 31 MAR 02 - 12 APR 02 |
| Scheduled Sacrifice (DL 6) | 01 APR 02 - 13 APR 02 |

2.1.16. Records Maintained

The original report, raw data and reserve samples of each lot of bulk test substance and bulk vehicle components are retained in the archives of Argus Research. Any preserved tissues are retained in the archives of the Testing Facility for one year after the mailing of the draft final report, after which time the Sponsor will decide their final disposition. All unused prepared formulations were discarded at the Testing Facility. Unused bulk test substance will be returned to the Sponsor.

2.2. Test Substance Information**2.2.1. Description**

T 7599.7 - amber waxy solid

-
- DL is an abbreviation for day of lactation.
 - DG is an abbreviation used for day of (presumed) gestation.
 - The day of birth is designated lactation day 0 (postpartum day 0) in the Health Effects Test Guidelines - Reproduction and Fertility Effects (Office of Prevention, Pesticides and Toxic Substances 870.3800, August, 1998) and in the OECD Guideline for the Testing of Chemicals - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (Section 4, No. 422, 22 March 1966). This same day is designated day 1 postpartum (day 1 of lactation) in the Standard Operating Procedures of the Testing Facility. Throughout this study, the day of birth was designated day 1 postpartum (day 1 of lactation) and all subsequent ages of the F1 generation rats and days of the lactation period were determined and cited accordingly.

2.2.2. Lot Number

6

2.2.3. Date Received and Storage Conditions

The test substance was received on 18 February 2002 and stored at room temperature, protected from light.

2.2.4. Special Handling Instructions

Standard safety precautions (use of protective clothing, gloves, dust-mist/HEPA-filtered mask, safety goggles or safety glasses and a face-shield) were worn during formulation preparation and dosage. A half-face respirator was worn when the bulk test substance was not being used in a chemical fume hood.

2.2.5. Analysis of Purity

Information to document or certify the identity, composition, method of synthesis, strength and purity of the test substance was provided by the Sponsor to the Testing Facility. A Certificate of Analysis is available in APPENDIX F.

2.3. Vehicle Information**2.3.1. Description**

Aqueous 0.5% or 1.0% carboxymethylcellulose (CMC) (medium viscosity) prepared carboxymethylcellulose, an off-white powder, and reverse osmosis membrane processed water.

The 0.5% CMC was used for the first four days of the study. Beginning 22 February 2002, the 1.0% CMC was used for the remainder of the study.

2.3.2. Lot Number

120K0252

2.3.3. Date Received and Storage Conditions

The carboxymethylcellulose was received on 11 September 2001 from Sigma Chemical Co., St. Louis, Missouri, and stored at room temperature. R.O. deionized water is available from a continuous source at the Testing Facility and is maintained at room temperature.

2.3.4. Special Handling Instructions

Standard safety precautions (use of protective clothing, gloves, dust-mist/HEPA-filtered mask, safety goggles or safety glasses and a face-shield) were taken when handling the vehicle components and prepared vehicle.

2.3.5. Analysis of Purity

Neither the Sponsor nor the Study Director was aware of any potential contaminants likely to have been present in the vehicle that would have interfered with the results of this study. The expiration date of the carboxymethylcellulose is September 2005.

2.4. Test Substance Preparation and Storage Conditions

Formulations were prepared weekly at the Testing Facility. Prepared test substance and vehicle formulations were stored refrigerated, protected from light.

2.4.1. Sample Information

| Sample Type | Size | Date Retained | Storage/Shipping Conditions | Shipped To | Date Shipped |
|--|--------------|--|---|---------------------------|------------------------|
| Bulk Test Substance | 5 g 1 g | 26 FEB 02 ^a 12 APR 02 ^b | Room temperature, protected from light | SRI ^c | 26 FEB 02 15 APR 02 |
| Concentration ^d (all levels) | 2 mL 2 mL | 03 APR 02 ^e 04 APR 02 ^f | Refrigerated, protected from light | SRI ^c | 03 APR 02 04 APR 02 |
| Homogeneity ^g (all levels) | 2 mL 2 mL | 18 FEB 02 28 FEB 02 | Refrigerated, protected from light | SRI ^c | 18 FEB 02 28 FEB 02 |
| Stability ^h | 2 mL 2 mL | 18 FEB 02 ⁱ 28 FEB 02 ^j | Refrigerated, protected from light | SRI ^c | 18 FEB 02 28 FEB 02 |
| Bulk Test Substance Reserve | 1 g | 22 APR 02 | Room temperature, protected from light | Testing Facility Archives | 23 APR 02 |
| Vehicle Components Reserve | | | Room temperature | Testing Facility Archives | |
| Carboxymethylcellulose | 1 g | 22 APR 02 | | | 23 APR 02 |
| R.O. Deionized Water | 1 g | 22 APR 02 | | | 23 APR 02 |

- a. A sample of the bulk test substance was retained for use in the preparation of analytical standards and for possible spectrophotometric analysis.
- b. A sample of the bulk test article was retained on the last day of dosage administration and shipped for analysis.
- c. Southern Research Institute, Birmingham, Alabama.
- d. Quadruplicate samples were taken from each concentration on the last day of preparation. Two samples from each quadruplicate set were shipped for analysis. The remaining samples were retained at the Testing Facility as backup samples.
- e. Sample for 1 mg/mL.
- f. Samples for 0, 5 and 25 mg/mL
- g. Quadruplicate samples were taken from the top, middle and bottom of each concentration on the first day of preparation. Two samples of each quadruplicate set were shipped for analysis. The remaining samples were retained at the Testing Facility as backup samples.
- h. Two sets of duplicate samples from each concentration were taken on the first day of preparation. One sample of each duplicate set was shipped for analysis. These samples were analyzed as soon after preparation as possible and ten days after the first analysis. The remaining samples were retained at the Testing Facility as backup samples.
- i. Prepared using 0.5% carboxymethylcellulose.
- j. Prepared using 1.0% carboxymethylcellulose.

2.4.2. Analytical Results

Results of the analytical analyses are available in APPENDIX G.

2.5. Test System

2.5.1. Species

Rat

2.5.2. Strain

CrI:CD®(SD)IGS BR VAF/Plus®

2.5.3. Supplier (Source)

Charles River Laboratories, Inc., Raleigh, North Carolina

2.5.4. Sex

Male and Female

2.5.5. Rationale for Test System

The CrI:CD®(SD)IGS BR VAF/Plus® rat was selected as the Test System because: 1) it is one mammalian species accepted for use in toxicity studies and it has been widely used throughout industry; 2) this strain of rat has been demonstrated to be sensitive to reproductive and developmental toxins; and 3) historical data and experience exist at the Testing Facility⁽⁵⁻⁷⁾.

2.5.6. Test System Data**2.5.6.1. Male Rats**

| | |
|----------------------------------|-----------|
| Number of Rats | 70 |
| Approximate Date of Birth | 04 DEC 01 |
| Approximate Age at Arrival | 71 days |
| Weight (g) the Day after Arrival | 282 - 333 |
| Weight (g) at Study Assignment | 303 - 354 |

2.5.6.2. Female Rats

| | |
|----------------------------------|-----------|
| Number of Rats | 70 |
| Approximate Date of Birth | 10 DEC 01 |
| Approximate Age at Arrival | 65 days |
| Weight (g) the Day after Arrival | 185 - 226 |
| Weight (g) at Study Assignment | 210 - 230 |

2.5.7. Method of Randomization

Upon arrival, the male and female rats were assigned to individual housing on the basis of computer-generated random units. After an acclimation period of at least five days, male and female rats were selected for study on the basis of physical appearance and body weights recorded during acclimation. The rats were assigned to four dosage groups (Groups I through IV), 15 rats per sex per group, using a computer-generated (weight-ordered) randomization procedure.

Within each dosage group, consecutive order was used to assign the first five male and the first five female rats to a functional observational battery (FOB) and motor activity assessment. The next five rats per sex in each group were assigned to hematology and clinical biochemistry evaluations. The last five rats per sex in each group were assigned

to metabolite analysis. Histological evaluations were performed on the last ten rats per sex in each group.

2.5.8. System of Identification

Male and female rats assigned temporary numbers at receipt and given unique permanent identification numbers when assigned to the study. Rats were permanently identified using Monel® self piercing ear tags (Gey Band and Tag Co., Inc., No. MSPT 20101). Cage tags were marked with the study number, permanent rat number, sex, test substance identification, generation and dosage level.

Pups were not individually identified during lactation; all parameters were evaluated in terms of the litter.

2.6. Husbandry

2.6.1. Research Facility Registration

USDA Registration No. 14-R-0144 under the Animal Welfare Act, 7 U.S.C. 2131 *et seq.*

2.6.2. Study Room

The study room was maintained under conditions of positive airflow relative to a hallway and independently supplied with a minimum of ten changes per hour of 100% fresh air that had been passed through 99.97% HEPA filters. Room temperature and humidity were monitored constantly throughout the study. Room temperature was targeted at 66°F to 77°F (19°C to 25°C); relative humidity was targeted at 30% to 70%^a.

2.6.3. Housing

Fo generation rats were individually housed in stainless steel wire-bottomed cages except during cohabitation period and postpartum periods. During cohabitation, each pair of male and female rats was housed in the male rat's cage. Beginning no later than DG 20, Fo generation female rats were individually housed in nesting boxes. Each dam and delivered litter was housed in a common nesting box during the postpartum period. All cage sizes and housing conditions were in compliance with the *Guide for the Care and Use of Laboratory Animals*⁽⁸⁾.

2.6.4. Lighting

An automatically-controlled fluorescent light cycle was maintained at 12-hours light: 12-hours dark, with each dark period beginning at 1900 hours EST.

a. See APPENDIX H (TEMPERATURE AND RELATIVE HUMIDITY REPORT).

2.6.5. Sanitization

Cage pan liners were changed at least three times weekly. Cages were changed approximately every other week. Bedding was changed as often as necessary to keep the rats dry and clean.

2.6.6. Feed

Rats were given *ad libitum* access to Certified Rodent Diet®#5002 (PMI Nutrition International, Inc., St. Louis, Missouri) in individual feeders. Rats were fasted overnight before sacrifice.

2.6.7. Feed Analysis

Analyses were routinely performed by the feed supplier. No contaminants at levels exceeding the maximum concentration for certified feed or deviations from expected nutritional requirements were detected by these analyses. Copies of the results of the feed analyses are available in the raw data.

Neither the Sponsor nor the Study Director was aware of any potential contaminants likely to have been present in the feed that would have interfered with the results of this study.

2.6.8. Water

Local water that had been processed by passage through a reverse osmosis membrane (R.O. water) was available to the rats *ad libitum* from an automatic watering access system and/or individual water bottles attached to the cages. Chlorine was added to the processed water as a bacteriostat.

2.6.9. Water Analysis

The processed water is analyzed twice annually for possible chemical contamination (Lancaster Laboratories, Lancaster, Pennsylvania) and monthly for possible bacterial contamination (Analytical Laboratories, Inc., Chalfont, Pennsylvania). Copies of the results of the water analyses are available in the raw data.

Neither the Sponsor nor the Study Director was aware of any potential contaminants likely to have been present in the water that would have interfered with the results of this study.

2.6.10. Bedding Material

Bed-o'cobs® bedding (The Andersons Industrial Products Group, Maumee, Ohio) was used as the nesting material.

2.6.11. Bedding Analysis

Analyses for possible contamination are conducted semi-annually. Copies of the results of the bedding analyses are available in the raw data.

Neither the Sponsor nor the Study Director was aware of any potential contaminants likely to have been present in the bedding that would have interfered with the results of this study.

2.7. Methods

2.7.1. Dosage Administration

| Dosage Group | Dosage ^a (mg/kg/day) | Concentration (mg/mL) | Dosage Volume (mL/kg) | Number of Rats per Sex | Assigned Numbers | |
|--------------|---------------------------------|-----------------------|-----------------------|------------------------|---|---|
| | | | | | Male Rats | Female Rats |
| I | 0 (Vehicle) | 0 | 10 | 15 | 17601, 17602, 17603, 17604, 17607, 17608, 17618, 17630, 17631, 17639, 17648, 17652, 17656, 17658, 17660 | 17662, 17672, 17673, 17674, 17680, 17681, 17690, 17694, 17695, 17703, 17713, 17715, 17716, 17717, 17719 |
| II | 10 | 1 | 10 | 15 | 17615, 17616, 17624, 17626, 17632, 17634, 17635, 17638, 17642, 17643, 17645, 17649, 17651, 17653, 17655 | 17663, 17665, 17666, 17668, 17671, 17675, 17679, 17684, 17688, 17698, 17702, 17704, 17707, 17708, 17710 |
| III | 50 | 5 | 10 | 15 | 17605, 17610, 17611, 17613, 17619, 17620, 17623, 17627, 17628, 17633, 17640, 17646, 17650, 17657, 17659 | 17661, 17667, 17669, 17670, 17676, 17687, 17693, 17697, 17700, 17701, 17705, 17706, 17709, 17718, 17720 |
| IV | 250 | 25 | 10 | 15 | 17606, 17609, 17612, 17614, 17617, 17621, 17622, 17625, 17629, 17636, 17637, 17641, 17644, 17647, 17654 | 17664, 17677, 17678, 17682, 17683, 17685, 17686, 17689, 17691, 17692, 17696, 17699, 17711, 17712, 17714 |

a. The test substance was considered 100% pure for the purpose of dosage calculations.

2.7.2. Rationale for Dosage Selection

Dosages were selected by the Sponsor based on previous studies conducted with the test substance, taking into account possible differences in sensitivity between pregnant and nonpregnant rats. The highest dosage was expected to cause toxic effects but not mortality or obvious suffering. The descending sequence of the lower dosage levels were selected for the purpose of demonstrating any dosage-related response, with no adverse effects expected at the lowest level.

2.7.3. Route and Rationale for Route of Administration

The oral (gavage) route was selected for use because: 1) in comparison with the dietary route, the exact dosage can be accurately administered; and 2) it is one possible route of human exposure.

2.7.4. Method and Frequency of Administration

2.7.4.1. Fo Generation Rats

Male rats were administered the test substance and/or the vehicle once daily beginning 14 days before cohabitation (maximum 14 days) and continuing until sacrifice, after completion of the cohabitation period, after a minimum of 28 days of dosage. Female rats were administered the test substance and/or the vehicle once daily beginning 14 days before cohabitation (maximum 14 days) and continuing until DL 5. The dosage volume was adjusted daily on the basis of the individual body weights recorded before intubation^a. The rats were intubated once daily at approximately the same time each day.

2.7.4.2. F1 Generation Pups

F1 generation pups were not directly administered the test substance and/or vehicle, but may have been possibly exposed to test substance and/or vehicle during maternal gestation (*in utero* exposure) or via maternal milk during the lactation period.

2.7.5. Method of Study Performance

2.7.5.1. Fo Generation Rats

Within each dosage group, consecutive order was used to assign rats to cohabitation, one male rat per female rat. The cohabitation period consisted of a maximum of 14 days. Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug *in situ* were considered to be DG 0 and assigned to individual housing. Female rats that were not mated with a male rat within the first seven days of cohabitation were assigned an alternate male rat that had mated (same dosage group) and remained in cohabitation for a maximum of seven additional days.

Rats were observed for viability at least twice each day of the study. Rats were examined for clinical observations and general appearance weekly during the acclimation period. Observations for clinical signs of effects of the test substance, abortions, premature deliveries and deaths were made daily before dosage. On the first day of dosage, postdosage observations were recorded at approximately hourly intervals for the first four hours after administration. The observation at four hours after administration was at the end of the normal working day. Postdosage observations for subsequent days of dosage were recorded approximately 60 ± 10 minutes after dosage administration and on the day of sacrifice^b.

Once before the first dosage and at least once weekly thereafter, detailed clinical observations were conducted for all male and female rats. These observations were made

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- a. See APPENDIX E (DEVIATIONS FROM THE PROTOCOL AND THE STANDARD OPERATING PROCEDURES OF THE TESTING FACILITY), item 1.
- b. See APPENDIX E, items 2 and 3.

outside the cage in a standard arena at the same time each day of conduct. Effort was made to ensure that variations in the test conditions were minimal and that observations were conducted by observers unaware of treatment groups. Signs noted included, but were not limited to: changes in skin, fur, eyes, mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g., lacrimation, piloerection, pupil size, unusual respiratory pattern). Changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypic behavior (e.g., excessive grooming, repetitive circling), difficult or prolonged parturition or bizarre behavior (e.g., self-mutilation, walking backwards) were also recorded.

Body weights for male and female rats were recorded weekly during the acclimation period, daily during the dosage period and at sacrifice. Feed consumption values for male rats were recorded weekly during the dosage period. Feed left was recorded on the day before sacrifice. Feed consumption values for female rats were recorded weekly to cohabitation and on DGs 0, 7, 10, 12, 15, 18, 20 and 25 (if necessary) and on DLs 1 and 5. Feed left was recorded on the day before sacrifice. During cohabitation, when two rats occupied the same cage with one feed jar, replenishment of feed jars was documented but individual values were not recorded or tabulated. Male and female rats were fasted overnight before sacrifice.

Estrous cycling was evaluated by examination of vaginal cytology beginning with the day after the first administration and then until spermatozoa were observed in a smear of the vaginal contents and/or a copulatory plug was observed *in situ* during the cohabitation period.

Female rats were evaluated for adverse clinical signs observed during parturition, duration of gestation (DG 0 to the day the first pup was observed), litter sizes (all pups delivered) and pup viability at birth. Maternal behavior was evaluated on DLs 1 and 5. Variations from expected maternal behavior were recorded, if and when present, on all other days of the postpartum period.

On one occasion during the course of the study, shortly before scheduled sacrifice, a functional observational battery (FOB)⁽⁹⁻¹²⁾ was conducted on five male and five female rats per group. For male rats, this assessment was conducted approximately one week before scheduled sacrifice. Female rats were tested during the lactation period, the day before scheduled sacrifice. To avoid hyperthermia of pups, dams were separated from their litters for no longer than 30 to 40 minutes.

The FOB evaluation was conducted by an observer unaware of the group assignment of the rat. The following parameters were assessed:

1. Lacrimation, salivation, palpebral closure, prominence of the eye, pupillary reaction to light, piloerection, respiration, and urination and defecation (autonomic functions).

2. Sensorimotor responses to visual, auditory, tactile and painful stimuli (reactivity and sensitivity).
3. Reactions to handling and behavior in the open field (excitability).
4. Gait pattern in the open field, severity of gait abnormalities, air righting reaction, visual placing response and landing foot splay (gait and sensorimotor coordination).
5. Forelimb and hindlimb grip strength.
6. Abnormal clinical signs including but not limited to convulsions, tremors and other unusual behavior, hypotonia or hypertonia, emaciation, dehydration, unkempt appearance and deposits around the eyes, nose or mouth.

The ability of this battery to detect the effects of positive control substances has been established (Testing Facility Positive Control Data) and is available in APPENDIX I.

Motor activity was evaluated on five male and five female rats per group once during the course of the study. For male rats, this assessment was conducted approximately one week before scheduled sacrifice. Female rats were tested during the lactation period, the day before scheduled sacrifice.

The movements of each rat were monitored by a passive infrared sensor mounted outside a stainless steel, wire-bottomed cage (40.6 x 25.4 x 17.8 cm). Each test session was 1.5 hours in duration with the number of movements and time spent in movement tabulated at each five-minute interval. The apparatus monitored a rack of up to 32 cages and sensors during each session, with each rat tested in the same location on the rack across test sessions. Groups were counterbalanced across testing sessions and cages. Data demonstrating that the test system is capable of detecting increases in activity produced by positive control substances (Testing Facility Positive Control Data) is available in APPENDIX I.

2.7.5.2. F1 Generation Pups

Day 1 of lactation (postpartum) was defined as the day of birth and was also the first day on which all pups in a litter were individually weighed (pup body weights were recorded after all pups in a litter were delivered and groomed by the dam).

Each litter was evaluated for viability at least twice daily. The pups in each litter were counted once daily. Clinical observations were recorded once daily. Pup body weights were recorded on DLs 1 and 5 (terminal weight).

2.7.6. Gross Necropsy

2.7.6.1. Fo Generation Rats

After 36 days of dosage, all male rats were sacrificed on the day following the last dosage, day 37 of study (DS 37) and on DL 6, all surviving female rats were sacrificed. Rats were sacrificed by carbon dioxide asphyxiation, and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Gross necropsy of all male and female rats included an initial physical examination of external surfaces and all orifices, as well as the cranial, thoracic and abdominal cavities and their contents. Special attention was paid to the organs of the reproductive system. The number of implantation sites and corpora lutea were recorded. Tissue trimming and histopathology was performed under the supervision of or by a Board-Certified Veterinary Pathologist. Gross lesions were retained in neutral buffered 10% formalin and examined histologically. Representative photographs of gross lesions are available in the raw data.

The testes and epididymides of all male rats were weighed, and the testes, epididymides, seminal vesicles with coagulating gland and prostate were retained in neutral buffered 10% formalin. The testes were fixed in Bouin's solution for 48 to 96 hours before being retained in neutral buffered 10% formalin. The ovaries and the uterus with cervix of each female rat were weighed, and ovaries, uterus, vagina and a mammary gland were retained in neutral buffered 10% formalin. Uteri of apparently nonpregnant rats were examined after being pressed between glass plates to confirm the absence of implantation sites, and retained in neutral buffered 10% formalin.

Ten rats per sex per group not assigned to functional observational battery and motor activity tests were assigned to histological evaluations. The following organs were excised, trimmed and individually weighed as soon as possible after excision to avoid drying: liver, kidneys, adrenals, thymus, testes, epididymides, spleen, brain, heart, ovaries and uterus (with cervix)^a. The following tissues or representative samples were retained in neutral buffered 10% formalin: brain (representative regions including cerebrum, cerebellum, pons), small and large intestines (including Peyer's patches), lungs (perfused with neutral buffered 10% formalin), lymph nodes (submandibular and mediastinal), peripheral nerve (sciatic), stomach, kidneys, spleen, thymus, trachea, urinary bladder, testes (fixed in Bouin's solution for 48 to 96 hours before being retained in neutral buffered 10% formalin), epididymides, seminal vesicles (with coagulating gland), prostate, spinal cord (cervical, thoracic and lumbar), liver, adrenals, heart, thyroid/parathyroid, uterus, bone marrow, ovaries, uterus, vagina, mammary gland (female rats only) and gross lesions. Histological examination of retained tissues, including reproductive organs, was conducted for the assigned ten rats per sex from the control and high dosage groups. Histological evaluations were performed on the livers of ten male and ten female rats, the thymuses of ten female rats and the stomachs of ten male rats in the 10 and 50 mg/kg/day dosage groups. Tissues to be examined

a. See APPENDIX E, item 4.

histologically were shipped to Research Pathology Services, Inc., New Britain, Pennsylvania for evaluation. Results of the histological evaluation are available in APPENDIX J.

At scheduled sacrifice, the five male and five female rats per group assigned to hematology and clinical chemistry sample collection were exsanguinated from the inferior vena cava following sacrifice. Rats were fasted overnight before sacrifice. Approximately 5 mL of blood was collected. The tubes containing the samples were labeled with the protocol number, Sponsor study number, animal number, group number, dosage level, day of study, collection interval, date of collection, species, generation and storage conditions.

Approximately 1 mL of blood was collected into EDTA-coated tubes and maintained on wet ice or refrigerated until shipment for analysis of the following hematologic parameters: erythrocyte count (RBC), hematocrit (HCT), hemoglobin (HGB), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), total leukocyte count (WBC), differential leukocyte count, platelet count (PLAT), mean platelet volume (MPV) and cell morphology. Two blood smear slides were prepared at the Testing Facility for each sample for measurements of differential leukocyte count.

Approximately 1.8 mL of blood was added to a tube containing 0.2 mL of sodium citrate (0.129 M). The contents were mixed and maintained on wet ice until the tubes were centrifuged (within 30 minutes of the collection time). The resulting plasma was transferred to a transport tube and immediately frozen^a. Plasma samples were maintained on dry ice or in a freezer ($\leq -70^{\circ}\text{C}$) until shipped for measurement of prothrombin time (PT) and activated partial thromboplastin time (APTT).

Approximately 2 mL of blood was collected into serum separator tubes and centrifuged. The resulting sera samples were immediately frozen on dry ice and maintained frozen ($\leq -70^{\circ}\text{C}$) until shipment for analysis of the following parameters: total protein (TP), triglycerides (TRI), albumin (A), globulin (G), albumin/globulin Ratio (A/G), glucose (GLU), cholesterol (CHOL), total bilirubin (TBILI), urea nitrogen (BUN), creatinine (CREAT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALK), calcium (CA), phosphorus (PHOS), sodium (NA), potassium (K) and chloride (CL)^a.

Samples for hematology and clinical chemistry analyses were shipped to Redfield Laboratories, A Division of CRL-DDS, Redfield, Arkansas. Results of these analyses are available in APPENDIX K.

Blood samples (approximately 3 mL) were collected from the five rats per sex per group assigned to metabolite analysis. Blood was collected from the vena cava. Each sample was divided into two aliquots. One aliquot of 2 mL was transferred into an EDTA-coated (purple top) tube and refrigerated. The second aliquot (approximately 1 mL) was

a. See APPENDIX E, item 5.

transferred into a serum tube, allowed to clot and spun in a centrifuge. The resulting serum was transferred into polypropylene tubes labeled with the protocol number, Sponsor study number, animal number, group number, dosage level, day of study, collection interval, date of collection, species, generation and storage conditions. All samples were immediately frozen on dry ice and maintained frozen ($\leq -70^{\circ}\text{C}$) until shipment for analysis.

The liver was excised and the organ weight recorded. One lobe (right lateral) was placed in a conical tube and flash frozen in an ice/alcohol bath. Liver samples were maintained frozen ($\leq -70^{\circ}\text{C}$) until shipment for analysis.

Liver and serum samples were shipped on dry ice and whole blood will be shipped on ice packs. Samples to be analyzed were shipped to Southern Research Institute, Birmingham, Alabama, for analysis. Results of these analyses are available in APPENDIX K.

Female rats that did not deliver a litter were sacrificed on DG 25. Gross necropsy, examination and tissue retention were conducted as described above for rats at scheduled sacrifice.

Dams with no surviving pups were sacrificed after the last pup was found dead, missing or presumed cannibalized. Gross necropsy, examination and tissue retention was conducted as described above for rats at scheduled sacrifice. Gross lesions were preserved in neutral buffered 10% formalin for possible future evaluation. Representative photographs of gross lesions are available in the raw data.

2.7.6.2. F1 Generation Pups

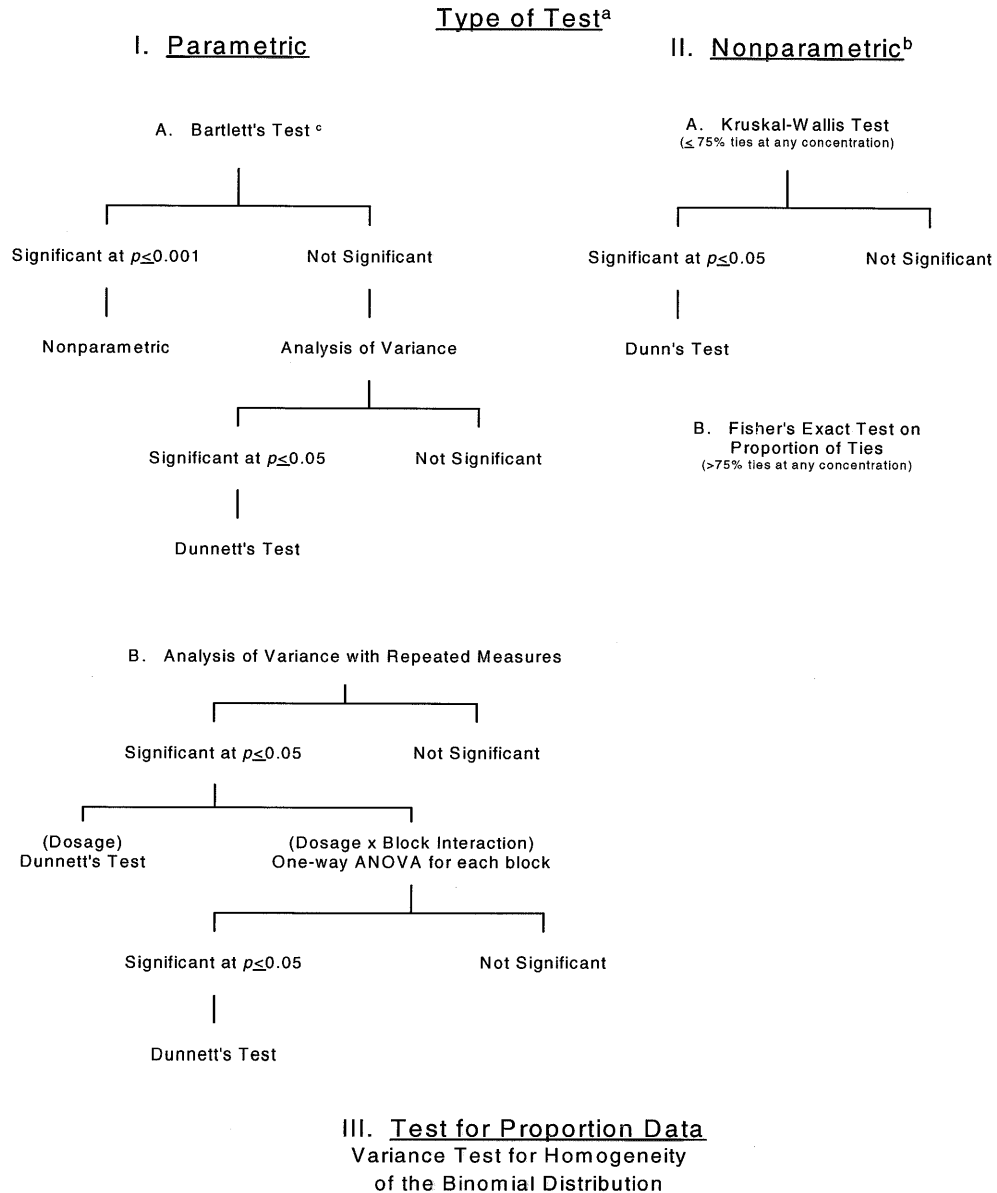
On DL 5, pups were sacrificed by carbon dioxide asphyxiation and examined for gross lesions. Necropsy included a single cross-section of the head at the level of the frontal-parietal suture and examination of the cross-sectioned brain for apparent hydrocephaly. Gross lesions were preserved in neutral buffered 10% formalin for possible future evaluation. Representative photographs of gross lesions are available in the raw data.

Pups that died before initial examination of the litter for pup viability were evaluated for vital status at birth. The lungs were removed and immersed in water. Pups with lungs that sank were identified as stillborn; pups with lungs that floated were identified as liveborn, and to have died shortly after birth. Pups found dead on DLs 2 to 4 were examined for gross lesions and for the cause of death.

2.7.7. Data Collection and Statistical Analyses

Data generated during the course of this study were recorded either by hand or using the *Argus Automated Data Collection and Management System*, the *Vivarium Temperature and Relative Humidity Monitoring System*, the *Coulbourn Instruments Passive Infrared Motor Activity System*, the *Coulbourn Instruments Auditory Startle System*, the *Coulbourn Instruments Spatial Delayed Alternation System*, and/or the passive avoidance software. All data were tabulated, summarized and/or statistically analyzed using the *Argus Automated Data Collection and Management System*, the *Vivarium Temperature and Relative Humidity Monitoring System*, *Microsoft Excel* [part of Microsoft Office 97 (version SR-2)] and/or *The SAS System* (version 6.12).

Averages and percentages were calculated. Litter values were used where appropriate. The following schematic represents the statistical analyses of the data:



-
- a. Statistically significant probabilities are reported as either $p \leq 0.05$ or $p \leq 0.001$.
- b. Proportion data are not included in this category.
- c. Test for homogeneity of variance.

Adult data was evaluated with the individual rat as the unit measured. Litter values were used in evaluation of pup data, as appropriate.

Variables with interval or ratio scales of measurement, such as body weights, feed consumption values, latency and errors per trial scores in behavioral tests and percent mortality per litter were analyzed as described under the Parametric heading of the schematic. Bartlett's Test of Homogeneity of Variances⁽¹³⁾ was used to estimate the probability that the dosage groups have different variances. A non-significant result ($p > 0.001$) indicated that an assumption of homogeneity of variance was not inappropriate, and the data was compared using the Analysis of Variance⁽¹⁴⁾. If that test was significant ($p \leq 0.05$), the groups given the test substance were compared with the control group using Dunnett's Test⁽¹⁵⁾. If Bartlett's Test was significant ($p \leq 0.001$), the Analysis of Variance Test was not appropriate, and the data was analyzed as described under the Nonparametric heading of the schematic. When 75% or fewer of the scores in all the groups were tied, the Kruskal-Wallis Test⁽¹⁶⁾ was used to analyze the data, and in the event of a significant result ($p \leq 0.05$), Dunn's Test⁽¹⁷⁾ was used to compare the groups given the test substance with the control group. When more than 75% of the scores in any dosage group were tied, Fisher's Exact Test⁽¹⁸⁾ was used to compare the proportion of ties in the groups.

Data from the motor activity test, with measurements recorded at intervals (Blocks) throughout each test session, were analyzed using an Analysis of Variance with Repeated Measures⁽¹⁹⁾, as described under that heading in the schematic. A significant result ($p \leq 0.05$) in that test could have appeared as effect of Dosage (differences among dosage groups in the totals of all measurements in a session) or as an interaction between Dosage and Block (differences in the patterns of dosage group values across the measurement periods). If the Dosage effect was significant, the totals for the control group and the groups given the test substance were compared using Dunnett's Test⁽¹⁵⁾. If the Dosage x Block interaction was significant, an Analysis of Variance⁽¹⁴⁾ was used to evaluate the data at each measurement period, and a significant result ($p \leq 0.05$) was followed by a comparison of the dosage groups using Dunnett's test⁽¹⁵⁾.

Variables that had graded or count scores, such as litter size, the number of trials to a criterion in a behavioral test or the day a developmental landmark appeared, were analyzed using the procedures described under the Nonparametric heading of the schematic.

Clinical observation incidence data were analyzed using the Variance Test for Homogeneity of the Binomial Distribution⁽²⁰⁾.

3. RESULTS - MALE RATS

3.1. Mortality, Clinical and Necropsy Observations (Summaries - Tables B1 and B2; Individual Data - Tables B15 and B16)

3.1.1. Mortality

All male rats survived to scheduled sacrifice.

3.1.2. Clinical Observations

Significant increases ($p \leq 0.01$) in the incidences of excess salivation, perioral substance and urine-stained abdominal fur occurred in the 250 mg/kg/day dosage group.

All other clinical observations were considered unrelated to the test substance because: 1) the incidences were not dosage-dependent; and/or 2) the observation occurred in only one or two male rats in any dosage group. These observations included chromorhinorea, soft or liquid feces, missing/broken incisors, chromodacryorrhea, scabs on right forelimb, red substance on the penis and ulceration on right forelimb.

3.1.3. Necropsy Observations

All necropsy observations were considered unrelated to the test substance because: 1) the incidences were not dosage-dependent; and/or 2) the observation occurred in only one male rat (17636) in the 250 mg/kg/day dosage group. These observations included a tan, firm, lobular mass (2.8 cm x 0.9 cm x 0.7 cm) on the right hemisphere of the prostate and a red ventral side of the same prostate gland. A cut surface of the mass revealed a tan smooth surface. Histomorphologic diagnosis was suppurative prostatitis.

3.1.4. Histopathology

Treatment-related microscopic changes were observed in the liver of male rats in the 50 and 250 mg/kg/day dosage groups and in the stomach of male rats in the 250 mg/kg/day dosage group.

The treatment-related microscopic changes in the liver consisted of minimal or mild enlargement (hypertrophy) of centrilobular hepatocytes in most of the male rats in the 250 mg/kg/day dosage group and 4 out of 10 in the 50 mg/kg/day dosage group. The enlargement was due to an increased amount of finely granular, dense eosinophilic cytoplasm. Also, in three of the affected rats in the 250 mg/kg/day dosage group, necrosis of individual enlarged hepatocytes was seen in the centrilobular areas.

Microscopic examination of the stomach revealed focal erosions in the pyloric glandular mucosa of two rats in the 250 mg/kg/day dosage group.

No treatment-related microscopic changes were observed in any of the male rats given 10 mg/kg/day of the test substance.

3.2. Terminal Body Weights and Organ Weights and Ratios (%) of Organ Weight to Terminal Body Weight and Brain Weight (Summaries - Tables B3 through B5; Individual Data - Tables B17 and B18)

Terminal body weights of the male rats were significantly reduced ($p \leq 0.01$) in the 250 mg/kg/day dosage group, as compared with control group values.

Absolute weights of the left and right kidneys were significantly increased ($p \leq 0.05$ or $p \leq 0.01$) in the 50 and 250 mg/kg/day dosage groups and the absolute weight of the liver was significantly increased ($p \leq 0.01$) in the 250 mg/kg/day dosage group, as compared with the control group value. The ratios of the weights of these organs to terminal body weights were significantly increased ($p \leq 0.05$ or $p \leq 0.01$) in the 50 and 250 mg/kg/day dosage groups. Relative to the brain weight, only the liver weight in the 250 mg/kg/day dosage group was significantly increased ($p \leq 0.01$).

3.3. Hematology and Clinical Chemistry (Summaries - Tables B6 through B7)

Dosages of the test substance as high as 250 mg/kg/day did not affect any hematology or clinical chemistry values evaluated. Average values for red blood cells (RBC), white blood cells (WBC), hemoglobin concentration (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, volume, prothrombin and activated partial thromboplastin time (PT and APTT), mean platelet volume (MPV), nucleated red blood cell count (NRBC), lymphocytes, segmented neutrophils, bands, monocytes, eosinophils, basophils and abnormal lymphocytes in male rats were comparable among the four dosage groups and did not differ significantly.

Average values for total protein (TP), albumin (A), glucose (GLU), cholesterol (CHOL), total bilirubin (TBILI), blood urea nitrogen (BUN), creatinine (CREAT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALK), calcium (CA), phosphorus (PHOS), triglycerides (TRIG), sodium (NA), potassium (K), chloride (CL), globulin (G) and albumin/globulin ratio (A/G) in male rats were comparable among the four dosage groups and did not differ significantly.

3.4. Body Weights and Body Weight Changes (Figure 1; Summaries - Tables B8 and B9; Individual Data - Table B19)

Body weight gains were significantly reduced ($p \leq 0.01$) in the 250 mg/kg/day dosage group on study days (DSs) 1 to 8, 1 to 15 and 1 to 36. Body weight gains were also significantly decreased ($p \leq 0.05$) in the 50 mg/kg/day dosage group on DSs 1 to 36.

Body weights were significantly reduced ($p \leq 0.01$) on DS 29 and 36 in the 250 mg/kg/day dosage group. Body weights and body weight gains of the male rats were unaffected by dosages of the test substance as high as 10 mg/kg/day.

3.5. Absolute (g/day) and Relative (g/kg/day) Feed Consumption Values (Summaries - Tables B10 and B11; Individual Data - Table B20)

Absolute (g/day) feed consumption values were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) in the 50 and 250 mg/kg/day dosage groups on DSs 1 to 8 and significantly reduced ($p \leq 0.01$) in the 250 mg/kg/day dosage groups on DSs 1 to 15 and 1 to 36. Absolute feed consumption values during the recovery period were comparable between the 0 (Vehicle) and 10 mg/kg/day dosage groups.

Relative (g/kg/day) feed consumption values were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) on DSs 1 to 8 in the 50 and 250 mg/kg/day dosage groups. Relative feed consumption values of the male rats were unaffected by dosages of the test substance as high as 10 mg/kg/day.

3.6. Mating and Fertility (Summary - Table B12; Individual Data - Table B21)

All mating and fertility parameters (numbers of days in cohabitation, rats that mated, fertility index, rats with confirmed mating dates during the first and second week of cohabitation, rats pregnant per rats in cohabitation and the number of pregnant rats per number of rats in cohabitation) were unaffected by dosages of the test substance as high as 250 mg/kg/day.

3.7. Functional Observational Battery (Summary - Table B13; Individual Data - Table B22)

There were no statistically significant or biologically important differences among the four dosage groups in the measures of the functional observational battery (FOB). There were no alterations in home cage behavior, autonomic functions (lacrimation, salivation, palpebral closure, prominence of the eye, pupillary reaction to light, piloerection, respiration, defecation and urination), sensorimotor functions [responses to visual, auditory, tactile and painful stimuli (reactivity and sensitivity)], excitability (reactions to handling and behavior in the open field), gait and sensorimotor coordination (gait pattern in the open field, severity of gait abnormalities, air righting reaction and landing foot splay) and forelimb and hindlimb grip strength and abnormal clinical observations including but not limited to: convulsions, tremors, unusual behavior, hypotonia or hypertonia, emaciation, dehydration, unkempt appearance and deposits around the eyes, nose or mouth.

Body weights recorded during the functional operational battery for the treated groups were not significantly different than the control group for the male rats.

3.8. Motor Activity (Figure 3 and 4; Summary - Table B14; Individual Data - Table B23)

There were no statistically significant or biologically important differences among the four dosage groups in the measures of motor activity on DS 8.

4. RESULTS - Female Rats

4.1. Mortality, Clinical and Necropsy Observations (Summaries - Tables C1 and C2; Individual Data - Tables C27 and C28)

4.1.1. Mortality

All female rats survived to scheduled sacrifice.

4.1.2. Clinical Observations

All clinical observations were considered unrelated to the test substance because: 1) the incidences were not dosage-dependent; and/or 2) the observation occurred in only one or two female rats in any dosage group. These observations included perioral substance, excess salivation, bent tail, chromodacryorrhea, corneal opacity of right eye, localized alopecia on the limbs, underside or head, urine-stained abdominal fur, red perivaginal substance, soft or liquid feces, missing/broken incisors and dehydration.

4.1.3. Necropsy Observations

All necropsy observations were considered unrelated to the test substance because: 1) the incidences were not dosage-dependent; and/or 2) the observation occurred in only one female rat in the 50 mg/kg/day dosage group and one female rat in the 250 mg/kg/day dosage group. These observations included an absent right kidney in one 50 mg/kg/day dosage group female rat (17706) and a small thymus in one 250 mg/kg/day dosage group female rat (17696). The small thymus was not available for histomorphologic diagnosis.

4.1.4. Histopathology

Treatment-related microscopic changes were observed in the liver and thymus of female rats in the 250 mg/kg/day dosage group.

The treatment-related microscopic changes in the liver consisted of minimal or mild enlargement (hypertrophy) of centrilobular hepatocytes in most of the female rats in the 250 mg/kg/day dosage group. The enlargement was due to an increased amount of finely granular, dense eosinophilic cytoplasm.

Microscopic examination of the thymus revealed an increased incidence and severity of atrophy of the thymic lobules in female rats in the 250 mg/kg/day dosage group.

No treatment-related microscopic changes were observed in any of the female rats given 10 mg/kg/day of the test substance.

4.2. Terminal Body Weights and Organ Weights and Ratios (%) of Organ Weight to Terminal Body Weight and Brain Weight (Summaries - Tables C3 through C5; Individual Data - Tables C29 and C30)

Terminal body weights of the female rats were reduced (-4.8%), albeit not significantly, in the 250 mg/kg/day dosage group, as compared with control group values.

Absolute weights of the liver was significantly increased ($p \leq 0.01$) in the 250 mg/kg/day dosage group, as compared with the control group value. The ratios of the weight of this organ and the weight of the right kidney to terminal body weights were significantly increased ($p \leq 0.01$) in the 250 mg/kg/day dosage group. Only the ratio of the liver weight to brain weight in the 250 mg/kg/day dosage group was significantly increased ($p \leq 0.01$) was considered treatment-related; the significantly increased ($p \leq 0.05$) ratio of the liver weight to brain weight in the 10 mg/kg/day dosage group was not considered treatment-related because it was not dosage dependent.

4.3. Hematology and Clinical Chemistry (Summaries - Tables C6 and C7)

Dosages as high as 250 mg/kg/day did not affect any hematology or clinical chemistry values evaluated. Average values for red blood cells (RBC), white blood cells (WBC), hemoglobin concentration (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, prothrombin and activated partial thromboplastin time (PT and APTT), mean platelet volume (MPV), nucleated red blood cell count (NRBC), lymphocytes, segmented neutrophils, bands, monocytes, eosinophils, basophils, abnormal lymphocytes in female rats were comparable among the four dosage groups and did not differ significantly.

Average values for total protein (TP), albumin (A), glucose (GLU), cholesterol (CHOL), total bilirubin (TBILI), blood urea nitrogen (BUN), creatinine (CREAT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALK), calcium (CA), phosphorus (PHOS), triglycerides (TRIG), sodium (NA), potassium (K), chloride (CL), globulin (G) and albumin/globulin ratio (A/G) in female rats were comparable among the four dosage groups and did not differ significantly.

4.4. Body Weights and Body Weight Changes (Figure 1; Summaries - Tables C8 through C13; Individual Data - Tables C31 through C33)

4.4.1. Precohabitation

Body weight gains were significantly reduced ($p \leq 0.05$) during the precohabitation period in the 250 mg/kg/day dosage group on DSs 1 to 8 and 1 to 15. Body weights were not significantly affected by dosages of the test substance on any weight day during precohabitation.

4.4.2. Gestation

Body weights and body weight gains were not significantly affected by dosages of the test substance during gestation.

Body weights gains were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) during gestation on days of gestation (DGs) 0 to 3 and 12 to 15 in the 50 mg/kg/day dosage group and on DGs 12 to 15 in the 10 mg/kg/day dosage group. These significant reductions in body weight gain were not considered treatment-related because they were not dosage-dependent.

4.4.3. Lactation

Body weight gains were not significantly affected by dosages of the test substance during lactation. Body weights were significantly reduced ($p \leq 0.05$) during lactation on day of lactation (DL) 1 in the 250 mg/kg/day dosage group but was not considered treatment-related because it did not persist.

4.5. Absolute (g/day) and Relative (g/kg/day) Feed Consumption Values (Summaries - Tables C14 through C19; Individual Data - Tables C34 through C36)

4.5.1. Precohabitation

Absolute (g/day) and relative (g/kg/day) feed consumption values were not significantly affected by dosages of the test substance during the precohabitation period.

4.5.2. Gestation

Absolute (g/day) feed consumption values were not significantly affected by dosages of the test substance during the gestation period.

Relative (g/kg/day) feed consumption values were significantly increased ($p \leq 0.01$) during gestation on DGs 15 to 18 in the 250 mg/kg/day dosage group but was not considered treatment-related because it did not persist.

4.5.3. Lactation

Absolute and relative feed consumption values were not significantly affected by dosages of the test substance during lactation.

4.6. Estrous Cycling, Mating and Fertility (Summary - Table C20; Individual Data - Table C37)

The average numbers of estrous stages per 14 days were comparable among the four dosage groups and did not significantly differ. The number of rats with six or more consecutive days of diestrus or estrus did not differ significantly.

All mating and fertility parameters (numbers of days in cohabitation, rats that mated, Fertility Index, rats with confirmed mating dates during the first and second week of cohabitation, rats pregnant per rats in cohabitation and the number of pregnant rats per number of rats in cohabitation) were unaffected by dosages of the test substance as high as 250 mg/kg/day.

4.7. Functional Observational Battery (Summary - Table C21; Individual Data - Table C38)

There were no statistically significant or biologically important differences among the four dosage groups in the measures of the functional observational battery (FOB). There were no alterations in home cage behavior, autonomic functions (lacrimation, salivation, palpebral closure, prominence of the eye, pupillary reaction to light, piloerection, respiration, defecation and urination), sensorimotor functions [responses to visual, auditory, tactile and painful stimuli (reactivity and sensitivity)], excitability (reactions to handling and behavior in the open field), gait and sensorimotor coordination (gait pattern in the open field, severity of gait abnormalities, air righting reaction and landing foot splay) and forelimb and hindlimb grip strength and abnormal clinical observations including but not limited to: convulsions, tremors, unusual behavior, hypotonia or hypertonia, emaciation, dehydration, unkempt appearance and deposits around the eyes, nose or mouth.

Body weights recorded during the functional operational battery for the treated groups were not significantly different than the control group for the female rats.

4.8. Motor Activity (Figures 5 and 6; Summary - Table C22; Individual Data - Table C39)

There were no statistically significant or biologically important differences among the four dosage groups in the measures of motor activity on DS 86.

4.9. Natural Delivery and Litter Observations (Summary - Tables C23 and C24; Individual Data - Tables C40 through C43)

Pregnancy occurred in all 15 (100%) rats assigned to the 0 (Vehicle) and 50 mg/kg/day dosage groups, 14 (93.3%) of the rats assigned to the 10 mg/kg/day dosage group and 13 (86.7%) of the rats assigned to the 250 mg/kg/day dosage group. All pregnant dams delivered a litter of one or more liveborn pups. The number of liveborn pups was significantly reduced ($p \leq 0.01$) in the 250 mg/kg/day dosage group. The number of stillborn pups was significantly increased ($p \leq 0.01$) in the 250 mg/kg/day dosage group. The number of pups found dead or presumed cannibalized on day 1 and days 2 to 5 postpartum was significantly increased ($p \leq 0.01$) in the 250 mg/kg/day dosage groups. The viability index (81.5%) was significantly reduced ($p \leq 0.01$) in the 250 mg/kg/day dosage group, compared to the control group value (99.1%). The number of pups surviving per litter on postpartum day 5 was significantly reduced ($p \leq 0.05$) in the 250 mg/kg/day dosage group. Pup body weights per litter were also reduced, albeit not significantly, in the 250 mg/kg/day dosage group on postpartum days 1 and 5. These

findings at 250 mg/kg/day were considered related to the test substance because they were dosage dependent.

Values for the numbers of dams delivering litters, the duration of gestation, averages for implantation sites per delivered litter, the gestation index (number of dams with one or more liveborn pups/number of pregnant rats), the numbers of dams with stillborn pups, dams with all pups dying, stillborn pups, surviving pups per litter on postpartum day 1 and pup sex ratios were comparable among the four dosage groups and did not significantly differ.

4.10. Pup Clinical and Necropsy Observations (Summary - Tables C25 and C26; Individual Data - Tables C44 and C45)

No clinical or necropsy observations in the F1 generation pups were attributable to dosages of the test substance as high as 250 mg/kg/day because: 1) the incidences were not dosage-dependent; and 2) the observation occurred in only one to three litters. These clinical observations included: not nursing, not nesting, pale and bruise on head, back, mouth, lower midline, chest and/or neck. Necropsy observations on postpartum day 5 was limited to slight dilation of the renal pelvis of one pup from a 10 mg/kg/day dosage group litter.

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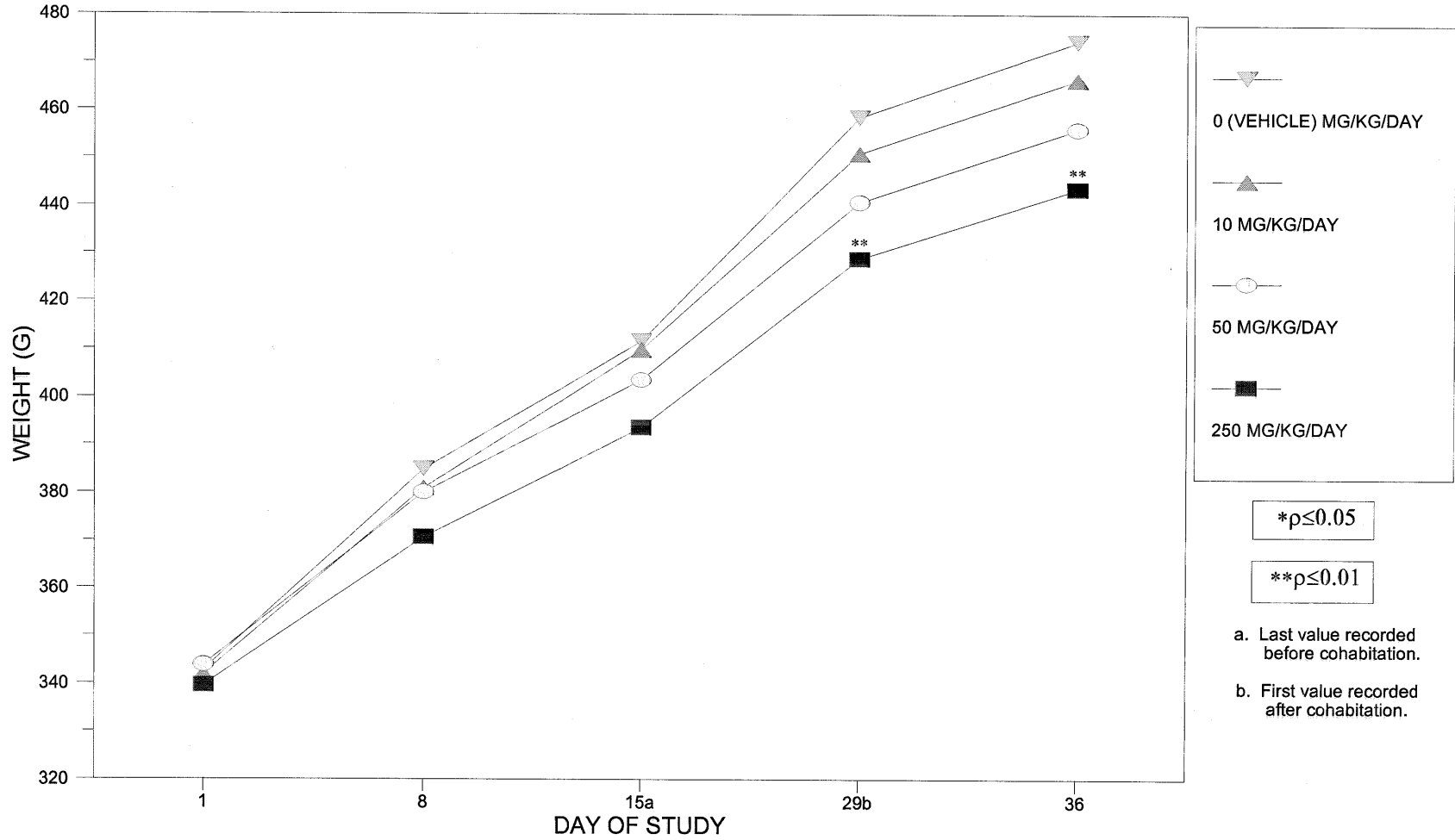
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APPENDIX A
REPORT FIGURES

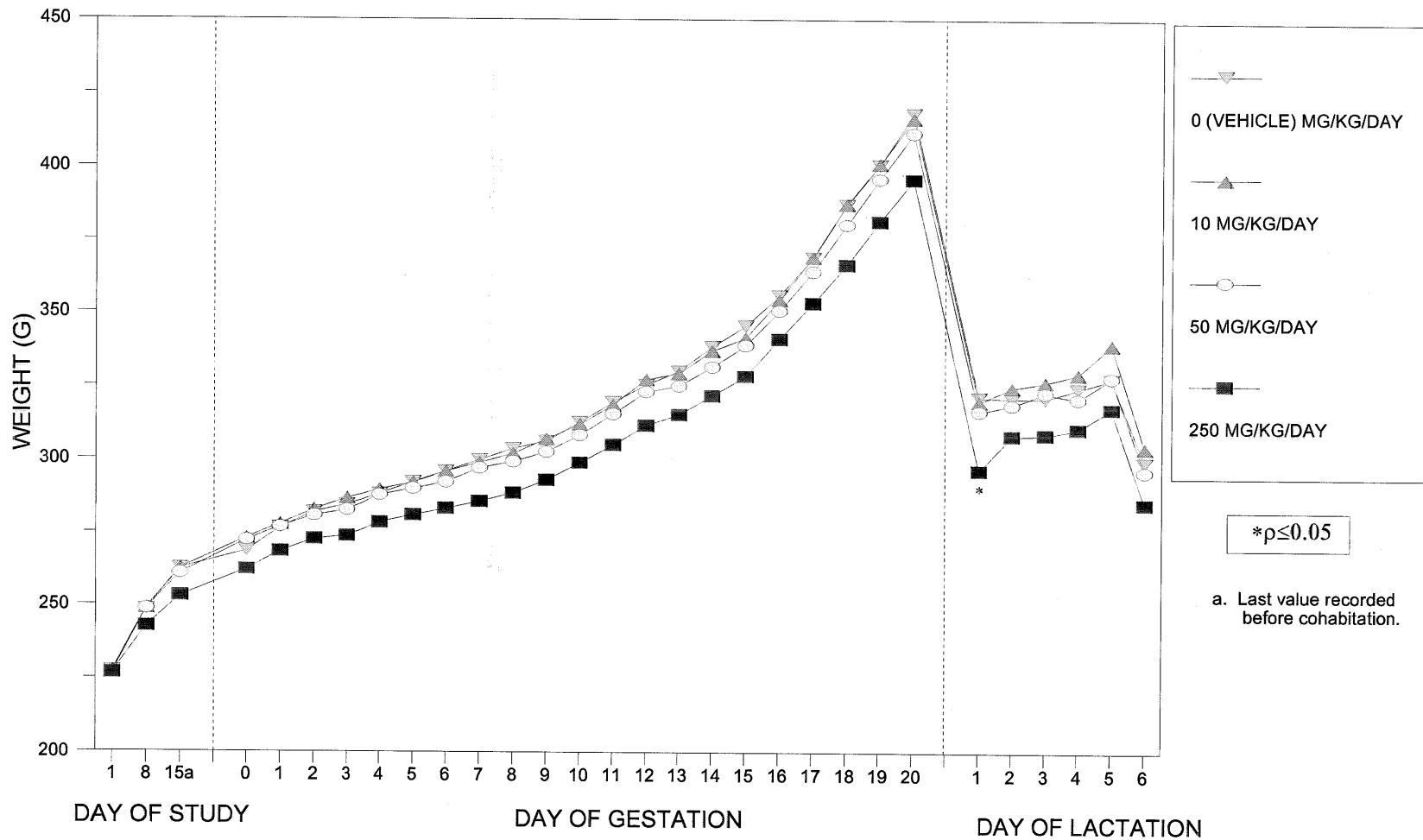
BODY WEIGHTS - MALE RATS

Figure 1



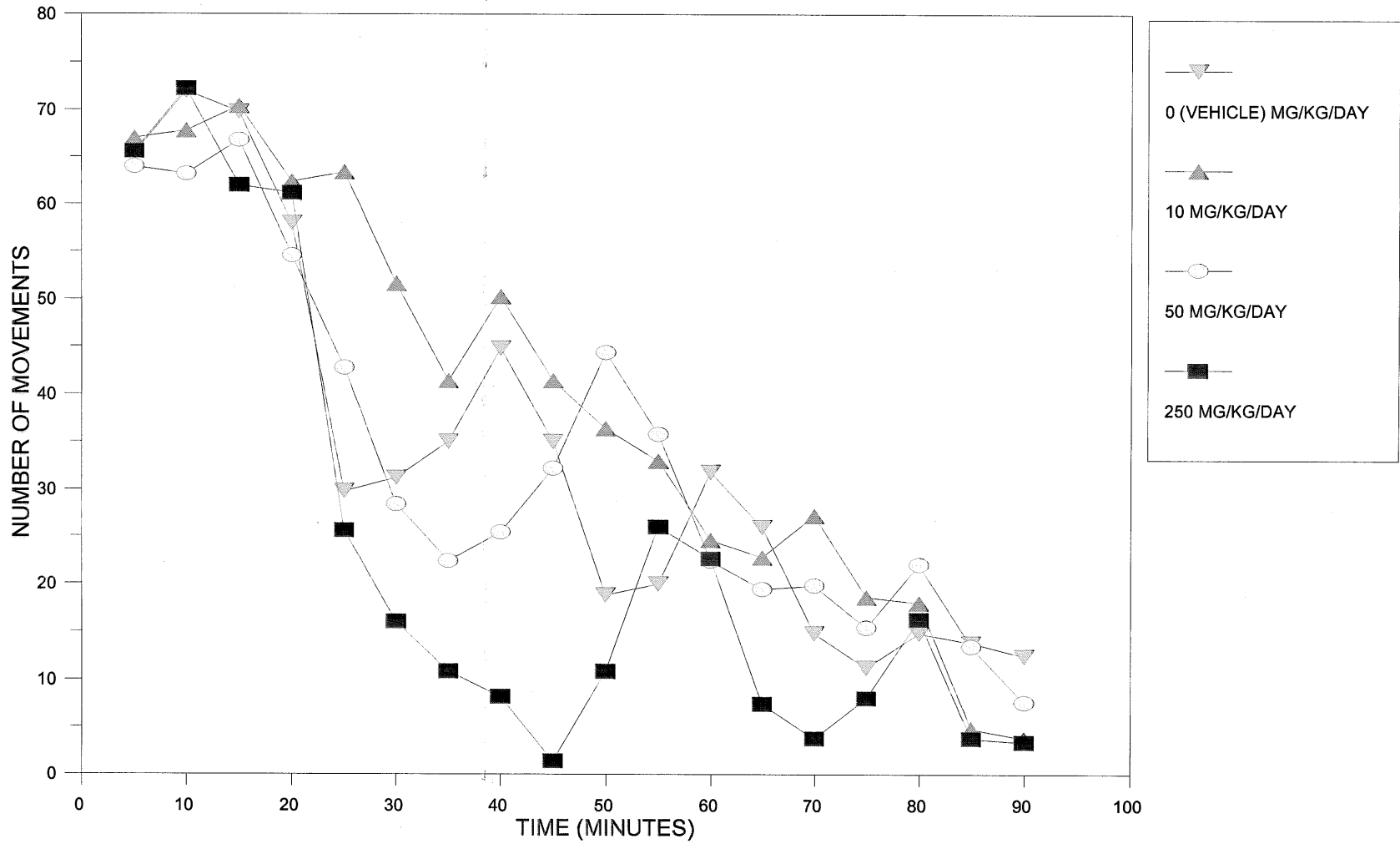
BODY WEIGHTS - FEMALE RATS

Figure 2



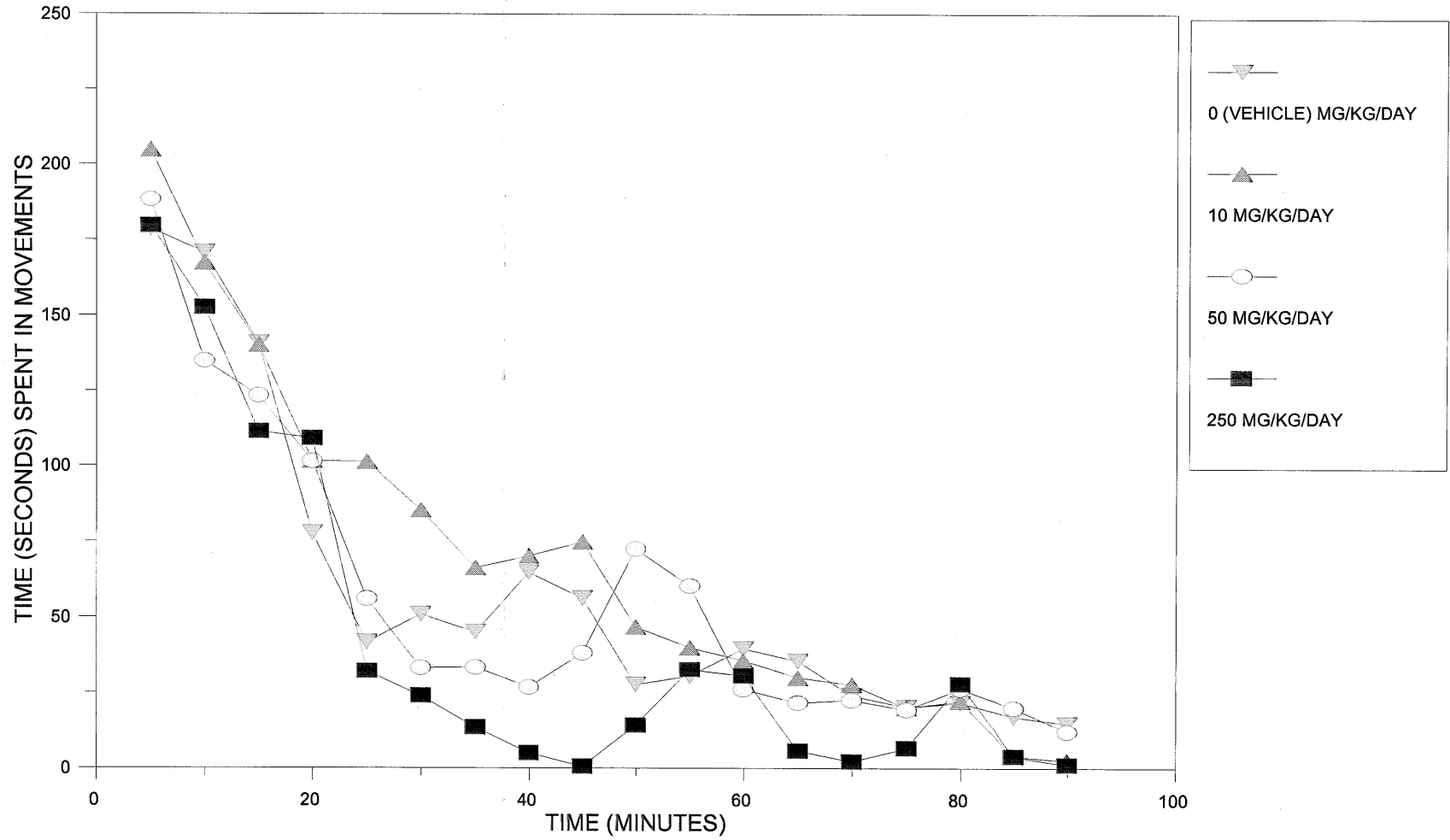
MOTOR ACTIVITY - NUMBER OF MOVEMENTS - MALE RATS

Figure 3



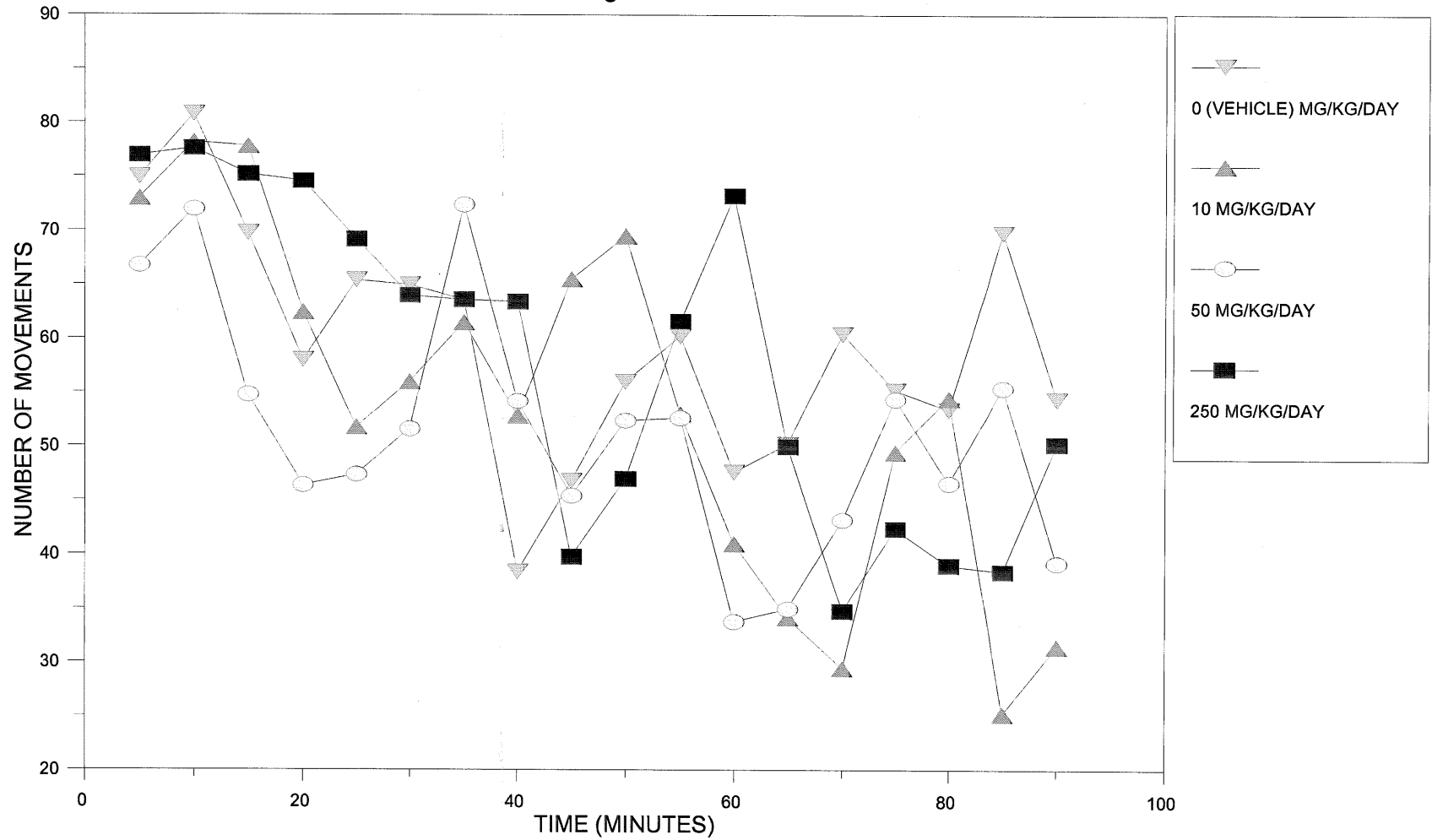
MOTOR ACTIVITY - TIME SPENT IN MOVEMENT - MALE RATS

Figure 4



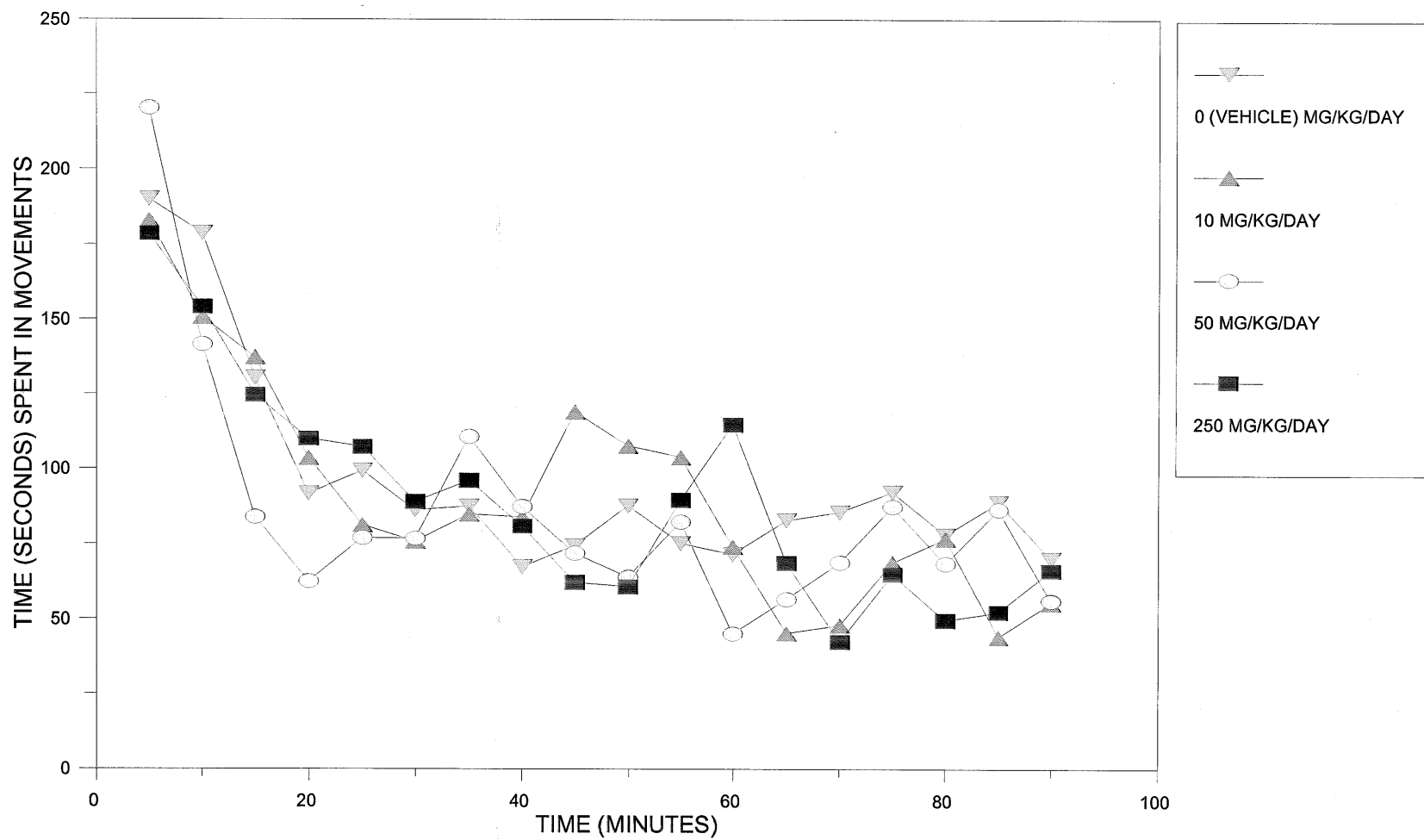
MOTOR ACTIVITY - NUMBER OF MOVEMENTS - FEMALE RATS

Figure 5



MOTOR ACTIVITY - TIME SPENT IN MOVEMENT - FEMALE RATS

Figure 6



APPENDIX B

REPORT TABLES - F₀ GENERATION MALE RATS

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - F0 GENERATION MALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | I 0 (VEHICLE) | II 10 | III 50 | IV 250 |
|------------------------------------|------------------|----------|-----------|-----------|
| MAXIMUM POSSIBLE INCIDENCE | 555/ 15 | 555/ 15 | 555/ 15 | 555/ 15 |
| MORTALITY | 0 | 0 | 0 | 0 |
| EXCESS SALIVATION | 0/ 0 | 0/ 0 | 0/ 0 | 24/ 10** |
| RED, SLIGHT PERIORAL SUBSTANCE | 0/ 0 | 0/ 0 | 0/ 0 | 15/ 10** |
| URINE-STAINED ABDOMINAL FUR | 0/ 0 | 0/ 0 | 1/ 1 | 14/ 4** |
| CHROMORHINORRHEA | 4/ 3 | 6/ 4 | 2/ 1 | 6/ 3 |
| LOCALIZED ALOPECIA: LIMBS | 0/ 0 | 0/ 0 | 6/ 1 | 16/ 2 |
| CHROMODACRYORRHEA | 0/ 0 | 0/ 0 | 1/ 1 | 5/ 2 |
| SOFT OR LIQUID FECES | 3/ 2 | 3/ 2 | 0/ 0 | 2/ 2 |
| RIGHT FORELIMB: SCAB(S) | 0/ 0 | 0/ 0 | 0/ 0 | 14/ 1 |
| INCISORS: MISSING/BROKEN | 0/ 0 | 0/ 0 | 1/ 1 | 9/ 1 |
| PENIS: RED SUBSTANCE | 0/ 0 | 1/ 1 | 1/ 1 | 1/ 1 |
| RIGHT FORELIMB: ULCERATION | 0/ 0 | 0/ 0 | 0/ 0 | 1/ 1 |

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.

N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.

** Significantly different from the vehicle control group value ($p < 0.01$).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B2 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F₀ GENERATION MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|---|---|-------------|----|-----|-----|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS EXAMINED a | N | 15 | 15 | 15 | 15 |
| MORTALITY | N | 0 | 0 | 0 | 0 |
| APPEARED NORMAL | N | 15 | 15 | 15 | 14 |
| PROSTATE: | | | | | |
| RIGHT HEMISPHERE, TAN, FIRM, LOBULAR MASS | N | 0 | 0 | 0 | 1 |
| VENTRAL RIGHT SIDE, RED | N | 0 | 0 | 0 | 1 |

a. Refer to the individual clinical observations table (Table B15) for external observations confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B3 (PAGE 1): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS - SUMMARY - F0 GENERATION MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------|-----------|---------------|---------------|---------------|----------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | | 15 | 15 | 15 | 15 |
| TERMINAL BODY WEIGHT | MEAN±S.D. | 447.1 ± 34.7 | 439.0 ± 21.3 | 428.6 ± 32.2 | 412.3 ± 16.0** |
| EPIDIDYMIS LEFT | MEAN±S.D. | 0.74 ± 0.06 | 0.72 ± 0.09 | 0.72 ± 0.08 | 0.71 ± 0.06 |
| TESTIS LEFT | MEAN±S.D. | 1.76 ± 0.14 | 1.64 ± 0.29 | 1.73 ± 0.15 | 1.74 ± 0.13 |
| EPIDIDYMIS RIGHT | MEAN±S.D. | 0.76 ± 0.06 | 0.74 ± 0.10 | 0.73 ± 0.09 | 0.70 ± 0.06 |
| TESTIS RIGHT | MEAN±S.D. | 1.74 ± 0.14 | 1.72 ± 0.12 | 1.74 ± 0.15 | 1.75 ± 0.14 |
| BRAIN | MEAN±S.D. | 2.31 ± 0.10 | 2.25 ± 0.12 | 2.36 ± 0.09 | 2.32 ± 0.16 |
| LIVER | MEAN±S.D. | 13.61 ± 1.26 | 13.79 ± 1.74 | 14.06 ± 1.51 | 18.31 ± 2.27** |
| KIDNEY LEFT | MEAN±S.D. | 1.94 ± 0.16 | 1.96 ± 0.16 | 2.12 ± 0.18* | 2.16 ± 0.13** |
| KIDNEY RIGHT | MEAN±S.D. | 2.00 ± 0.09 | 2.02 ± 0.21 | 2.16 ± 0.18* | 2.18 ± 0.13* |
| ADRENAL LEFT | MEAN±S.D. | 0.030 ± 0.003 | 0.030 ± 0.005 | 0.029 ± 0.006 | 0.030 ± 0.007 |
| ADRENAL RIGHT | MEAN±S.D. | 0.028 ± 0.004 | 0.032 ± 0.005 | 0.029 ± 0.002 | 0.028 ± 0.004 |
| SPLEEN | MEAN±S.D. | 0.89 ± 0.09 | 0.79 ± 0.12 | 0.85 ± 0.12 | 0.83 ± 0.10 |
| THYMUS | MEAN±S.D. | 0.54 ± 0.14 | 0.43 ± 0.13 | 0.43 ± 0.14 | 0.40 ± 0.12 |
| HEART | MEAN±S.D. | 1.51 ± 0.13 | 1.49 ± 0.20 | 1.46 ± 0.16 | 1.45 ± 0.17 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

[] = NUMBER OF VALUES AVERAGED.

a. Results did not warrant examination of the five additional rats.

b. Excludes a value for rat 17660, which had an organ damaged (weight affected).

* Significantly different from the vehicle control group value (p<0.05).

** Significantly different from the vehicle control group value (p<0.01).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B4 (PAGE 1): RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - SUMMARY - F₀ GENERATION MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|--------------------|-----------|---------------|---------------|-----------------|-----------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | | 15 | 15 | 15 | 15 |
| EPIDIDYMIS LEFT | MEAN±S.D. | 0.165 ± 0.016 | 0.165 ± 0.019 | 0.167 ± 0.023 | 0.173 ± 0.018 |
| TESTIS LEFT | MEAN±S.D. | 0.395 ± 0.050 | 0.373 ± 0.066 | 0.406 ± 0.048 | 0.422 ± 0.038 |
| EPIDIDYMIS RIGHT | MEAN±S.D. | 0.169 ± 0.019 | 0.167 ± 0.025 | 0.171 ± 0.026 | 0.171 ± 0.017 |
| TESTIS RIGHT | MEAN±S.D. | 0.392 ± 0.046 | 0.393 ± 0.027 | 0.409 ± 0.047 | 0.425 ± 0.041 |
| BRAIN | MEAN±S.D. | 0.521 ± 0.039 | 0.512 ± 0.032 | 0.547 ± 0.033 | 0.555 ± 0.050 |
| LIVER | MEAN±S.D. | 3.043 ± 0.144 | 3.133 ± 0.278 | 3.275 ± 0.166** | 4.434 ± 0.450** |
| KIDNEY LEFT | MEAN±S.D. | 0.436 ± 0.046 | 0.448 ± 0.043 | 0.493 ± 0.056* | 0.517 ± 0.033** |
| KIDNEY RIGHT | MEAN±S.D. | 0.451 ± 0.037 | 0.462 ± 0.051 | 0.501 ± 0.056* | 0.521 ± 0.031** |
| ADRENAL LEFT b | MEAN±S.D. | 6.562 ± 0.570 | 6.737 ± 1.213 | 6.690 ± 1.451 | 7.069 ± 1.568 |
| ADRENAL RIGHT b | MEAN±S.D. | 6.325 ± 0.938 | 7.215 ± 1.194 | 6.826 ± 0.724 | 6.598 ± 1.005 |
| SPLEEN | MEAN±S.D. | 0.200 ± 0.027 | 0.178 ± 0.026 | 0.197 ± 0.033 | 0.197 ± 0.021 |
| THYMUS | MEAN±S.D. | 0.122 ± 0.032 | 0.099 ± 0.030 | 0.099 ± 0.033 | 0.096 ± 0.029 |
| HEART | MEAN±S.D. | 0.341 ± 0.027 | 0.341 ± 0.038 | 0.338 ± 0.039 | 0.348 ± 0.042 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

RATIOS (%) = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

[] = NUMBER OF VALUES AVERAGED.

a. Results did not warrant examination of the five additional rats.

b. Value was multiplied by 1000.

c. Excludes a value for rat 17660, which had an organ damaged (weight affected).

* Significantly different from the vehicle control group value (p<0.05).

** Significantly different from the vehicle control group value (p<0.01).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B5 (PAGE 1): RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - SUMMARY - F₀ GENERATION MALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | | I 0 (VEHICLE) | II 10 | III 50 | IV 250 |
|------------------------------------|-----------|----------------------|----------------|----------------|-------------------|
| RATS TESTED | N | 10a | 10a | 10a | 10a |
| BRAIN WEIGHT | MEAN±S.D. | 2.31 ± 0.10 | 2.25 ± 0.12 | 2.36 ± 0.09 | 2.32 ± 0.16 |
| EPIDIDYMIS LEFT | MEAN±S.D. | 31.28 ± 2.24 | 32.08 ± 3.44 | 29.98 ± 3.37 | 29.86 ± 2.87 |
| TESTIS LEFT | MEAN±S.D. | 75.14 ± 6.24 | 75.90 ± 4.98 | 73.00 ± 8.32 | 73.95 ± 10.60 |
| EPIDIDYMIS RIGHT | MEAN±S.D. | 31.97 ± 2.81 | 32.63 ± 3.73 | 30.38 ± 3.16 | 29.72 ± 3.60 |
| TESTIS RIGHT | MEAN±S.D. | 74.42 ± 5.96 | 76.90 ± 3.34 | 72.98 ± 6.85 | 73.87 ± 9.89 |
| LIVER | MEAN±S.D. | 594.63 ± 42.79 | 620.48 ± 81.18 | 603.91 ± 53.24 | 807.37 ± 123.75** |
| KIDNEY LEFT | MEAN±S.D. | 83.88 ± 7.32 | 87.59 ± 7.45 | 90.39 ± 9.47 | 93.84 ± 9.85 |
| KIDNEY RIGHT | MEAN±S.D. | 86.77 ± 5.89 | 90.12 ± 9.43 | 91.76 ± 8.79 | 94.73 ± 10.17 |
| ADRENAL LEFT | MEAN±S.D. | 1.18 ± 0.30 [9]b | 1.32 ± 0.27 | 1.22 ± 0.25 | 1.29 ± 0.38 |
| ADRENAL RIGHT | MEAN±S.D. | 1.22 ± 0.16 | 1.42 ± 0.29 | 1.25 ± 0.11 | 1.19 ± 0.18 |
| SPLEEN | MEAN±S.D. | 38.72 ± 5.38 | 35.15 ± 4.75 | 36.13 ± 5.76 | 35.99 ± 6.32 |
| THYMUS | MEAN±S.D. | 23.66 ± 7.02 | 19.20 ± 5.21 | 18.19 ± 5.94 | 17.22 ± 4.88 |
| HEART | MEAN±S.D. | 65.48 ± 7.01 | 66.42 ± 7.27 | 61.92 ± 6.70 | 63.19 ± 9.74 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

RATIOS (%) = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.

a. Results did not warrant examination of the five additional rats.

b. Excludes a value for rat 17660, which had an organ damaged (weight affected).

** Significantly different from the vehicle control group value (p<0.01).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B6 (PAGE 1): HEMATOLOGY - SUMMARY - F₀ GENERATION MALE RATS
(See last page of this table for abbreviations)

| DOSAGE GROUP | | I | II | III | IV |
|--------------------|-----------|--------------|--------------|--------------|--------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 5 | 5 | 5 | 5 |
| WBC (THSN/CU MM) | MEAN±S.D. | 14.7 ± 3.61 | 18.9 ± 2.96 | 15.3 ± 3.36 | 19.3 ± 7.90 |
| RBC (MILL/CU MM) | MEAN±S.D. | 7.55 ± 0.493 | 7.56 ± 0.448 | 7.27 ± 0.291 | 7.17 ± 0.270 |
| HGB (GRAMS/DL) | MEAN±S.D. | 15.8 ± 0.26 | 15.6 ± 0.71 | 15.2 ± 0.40 | 15.1 ± 0.65 |
| HCT (%) | MEAN±S.D. | 43.7 ± 1.82 | 42.5 ± 2.12 | 41.4 ± 1.30 | 40.5 ± 1.88 |
| MCV (CU MICRONS) | MEAN±S.D. | 57.9 ± 2.09 | 56.3 ± 0.84 | 56.9 ± 1.94 | 56.5 ± 1.44 |
| MCH (PICO GRAMS) | MEAN±S.D. | 21.0 ± 1.15 | 20.7 ± 0.42 | 20.9 ± 0.70 | 21.1 ± 0.88 |
| MCHC (%) | MEAN±S.D. | 36.3 ± 0.97 | 36.8 ± 0.35 | 36.6 ± 1.17 | 37.4 ± 1.25 |
| PLT (THSN/CU MM) | MEAN±S.D. | 1197 ± 122.5 | 1172 ± 54.0 | 1218 ± 190.7 | 1283 ± 138.9 |
| PT (SECONDS) | MEAN±S.D. | 14.4 ± 0.66 | 13.7 ± 0.39 | 14.7 ± 0.70 | 14.6 ± 0.96 |
| APTT (SECONDS) | MEAN±S.D. | 25.4 ± 1.89 | 25.9 ± 2.33 | 26.2 ± 2.18 | 26.7 ± 2.51 |

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B6 (PAGE 2): HEMATOLOGY - SUMMARY - F0 GENERATION MALE RATS
(See the page of this table for abbreviations)

| DOSAGE GROUP | | I | II | III | IV |
|-------------------------|-----------|-------------|-------------|-------------|-------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 5 | 5 | 5 | 5 |
| MPV (CU MICRONS) | MEAN±S.D. | 9.2 ± 0.32 | 9.7 ± 0.79 | 9.5 ± 1.03 | 9.1 ± 0.67 |
| NRBC COUNT | MEAN±S.D. | 0 ± 0.0 | 0 ± 0.0 | 0 ± 0.0 | 0 ± 0.0 |
| Lymphocyte (THSN/CU MM) | MEAN±S.D. | 12.6 ± 3.67 | 15.8 ± 3.21 | 13.3 ± 3.24 | 14.1 ± 4.01 |
| Segmented (THSN/CU MM) | MEAN±S.D. | 1.9 ± 0.26 | 2.8 ± 0.87 | 1.8 ± 0.41 | 5.0 ± 7.38 |
| Bands (THSN/CU MM) | MEAN±S.D. | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 |
| Monocytes (THSN/CU MM) | MEAN±S.D. | 0.1 ± 0.07 | 0.2 ± 0.20 | 0.1 ± 0.09 | 0.1 ± 0.13 |
| Eosinophil (THSN/CU MM) | MEAN±S.D. | 0.1 ± 0.05 | 0.2 ± 0.11 | 0.2 ± 0.15 | 0.1 ± 0.14 |
| Basophils (THSN/CU MM) | MEAN±S.D. | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 |
| Abnormal L (THSN/CU MM) | MEAN±S.D. | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 |
| Other (THSN/CU MM) | MEAN±S.D. | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 |

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B6 (PAGE 3): HEMATOLOGY - SUMMARY - Fo GENERATION MALE RATS

| KEY TO HEMATOLOGY TABLE | |
|-------------------------|---|
| ABBREVIATION | TERMINOLOGY |
| WBC | White Blood Cells (Leukocytes) |
| RBC | Red Blood Cells (Erythrocytes) |
| HGB | Hemoglobin |
| HCT | Hematocrit (Packed Cell Volume) |
| MCV | Mean Corpuscular Volume |
| MCH | Mean Corpuscular Hemoglobin |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| PLAT | Platelets |
| MPV | Mean Platelet Volume |
| PT | Prothrombin Time |
| APTT | Activated Partial Thromboplastin |
| NRBC | Nucleated Red Blood Cell Count |
| Segmented | Segmented Neutrophils |
| Abnormal L | Abnormal Lymphocytes |
| Other | Other Cells |

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B7 (PAGE 1): CLINICAL CHEMISTRY - SUMMARY - Fo GENERATION MALE RATS
(See last page of this table for abbreviations)

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | | I 0 (VEHICLE) | II 10 | III 50 | IV 250 |
|------------------------------------|-----------|------------------|------------|------------|------------|
| RATS TESTED | N | 5 | 5 | 5 | 5 |
| TP (G/DL) | MEAN±S.D. | 6.3 ± 0.29 | 6.3 ± 0.34 | 6.2 ± 0.29 | 6.3 ± 0.16 |
| A (G/DL) | MEAN±S.D. | 4.0 ± 0.16 | 4.1 ± 0.15 | 4.1 ± 0.21 | 4.2 ± 0.43 |
| GLU (MG/DL) | MEAN±S.D. | 159 ± 11.0 | 184 ± 23.9 | 156 ± 12.7 | 108 ± 11.5 |
| CHOL (MG/DL) | MEAN±S.D. | 56 ± 11.9 | 52 ± 5.3 | 49 ± 5.5 | 29 ± 8.2 |
| TBILI (MG/DL) | MEAN±S.D. | 0.1 ± 0.00 | 0.1 ± 0.00 | 0.1 ± 0.00 | 0.1 ± 0.00 |
| BUN (MG/DL) | MEAN±S.D. | 12 ± 1.6 | 14 ± 2.3 | 13 ± 1.3 | 17 ± 5.9 |
| CREAT (MG/DL) | MEAN±S.D. | 0.3 ± 0.05 | 0.3 ± 0.04 | 0.3 ± 0.04 | 0.4 ± 0.09 |
| ALT (U/L) | MEAN±S.D. | 38 ± 2.3 | 43 ± 1.6 | 47 ± 4.2 | 48 ± 6.5 |
| AST (U/L) | MEAN±S.D. | 88 ± 3.4 | 86 ± 10.2 | 96 ± 5.7 | 102 ± 8.3 |

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B7 (PAGE 2): CLINICAL CHEMISTRY - SUMMARY - Fo GENERATION MALE RATS
(See last page of this table for abbreviations)

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | | I 0 (VEHICLE) | II 10 | III 50 | IV 250 |
|------------------------------------|-----------|------------------|-------------|-------------|-------------|
| RATS TESTED | N | 5 | 5 | 5 | 5 |
| ALK (U/L) | MEAN±S.D. | 107 ± 27.4 | 108 ± 28.6 | 116 ± 23.4 | 123 ± 20.0 |
| CA (MG/DL) | MEAN±S.D. | 11.1 ± 0.37 | 11.4 ± 0.38 | 11.4 ± 0.29 | 11.3 ± 0.14 |
| PHOS (MG/DL) | MEAN±S.D. | 8.5 ± 0.87 | 9.7 ± 2.45 | 9.4 ± 0.90 | 10.0 ± 1.51 |
| TRI (MG/DL) | MEAN±S.D. | 72 ± 22.2 | 59 ± 13.1 | 66 ± 23.2 | 31 ± 9.5 |
| NA (MMOL/L) | MEAN±S.D. | 148 ± 1.5 | 147 ± 2.9 | 148 ± 0.8 | 148 ± 2.8 |
| K (MMOL/L) | MEAN±S.D. | 5.7 ± 0.51 | 6.2 ± 1.01 | 6.5 ± 0.49 | 6.5 ± 0.80 |
| CL (MMOL/L) | MEAN±S.D. | 96 ± 1.8 | 98 ± 2.9 | 100 ± 2.2 | 99 ± 2.9 |
| G (G/DL) | MEAN±S.D. | 2.2 ± 0.18 | 2.3 ± 0.26 | 2.1 ± 0.20 | 2.1 ± 0.41 |
| A/G | MEAN±S.D. | 1.8 ± 0.15 | 1.8 ± 0.21 | 2.0 ± 0.22 | 2.0 ± 0.49 |

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B7 (PAGE 3): CLINICAL CHEMISTRY - SUMMARY - F0 GENERATION MALE RATS

| KEY TO CLINICAL CHEMISTRY TABLE | |
|---------------------------------|----------------------------|
| ABBREVIATION | TERMINOLOGY |
| TP | Total Protein |
| A | Albumin |
| GLU | Glucose |
| CHOL | Cholesterol |
| TBILI | Total Bilirubin |
| BUN | Blood Urea Nitrogen |
| CREAT | Creatinine |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| ALK | Alkaline Phosphatase |
| CA | Calcium |
| PHOS | Phosphorus (inorganic) |
| TRI | Triglycerides |
| NA | Sodium |
| K | Potassium |
| CL | Chloride |
| G | Globulin |
| A/G | Albumin/Globulin Ratio |

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B8 (PAGE 1): BODY WEIGHTS - SUMMARY - F₀ GENERATION MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|--------------------|-----------|--------------|--------------|--------------|----------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| BODY WEIGHT (G) | | | | | |
| DAY 1 | MEAN±S.D. | 342.7 ± 9.4 | 341.9 ± 9.4 | 343.8 ± 13.1 | 339.5 ± 9.4 |
| DAY 8 | MEAN±S.D. | 384.8 ± 16.3 | 380.9 ± 13.0 | 380.0 ± 20.1 | 370.6 ± 11.4 |
| DAY 15a | MEAN±S.D. | 411.6 ± 24.8 | 409.8 ± 16.5 | 403.4 ± 24.4 | 393.5 ± 13.9 |
| DAY 29b | MEAN±S.D. | 458.3 ± 32.5 | 450.8 ± 20.8 | 440.7 ± 31.7 | 428.8 ± 13.9** |
| DAY 36 | MEAN±S.D. | 474.2 ± 36.0 | 466.3 ± 22.5 | 455.9 ± 32.2 | 443.5 ± 14.9** |

DAY = DAY OF STUDY

a. Last value recorded before cohabitation.

b. First value recorded after cohabitation.

** Significantly different from the vehicle control group value ($p \leq 0.01$).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B9 (PAGE 1): BODY WEIGHT CHANGES - SUMMARY - F0 GENERATION MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|------------------------|-----------|--------------|--------------|---------------|----------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| BODY WEIGHT CHANGE (G) | | | | | |
| DAYS 1 - 8 | MEAN±S.D. | +42.1 ± 9.1 | +39.0 ± 7.5 | +36.2 ± 9.8 | +31.1 ± 5.2** |
| DAYS 8 - 15a | MEAN±S.D. | +26.8 ± 10.1 | +28.9 ± 7.6 | +23.4 ± 6.8 | +22.9 ± 6.8 |
| DAYS 1 - 15a | MEAN±S.D. | +68.9 ± 17.8 | +67.9 ± 12.8 | +59.6 ± 12.5 | +53.9 ± 9.9** |
| DAYS 29b- 36 | MEAN±S.D. | +15.9 ± 6.0 | +15.5 ± 5.4 | +15.2 ± 7.1 | +14.7 ± 3.7 |
| DAYS 1 - 36 | MEAN±S.D. | +131.5± 29.6 | +124.4± 21.8 | +112.1± 21.2* | +103.9± 13.8** |

DAYS = DAYS OF STUDY

a. Last value recorded before cohabitation.

b. First value recorded after cohabitation.

* Significantly different from the vehicle control group value ($p \leq 0.05$).

** Significantly different from the vehicle control group value ($p \leq 0.01$).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B10 (PAGE 1): ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - SUMMARY - F₀ GENERATION MALE RATS

| DOSAGE GROUP | | I | II | III | IV | |
|----------------------|-----------|-------------|----------------------|-------------|--------------|----|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 | |
| RATS TESTED | | N | 15 | 15 | 15 | 15 |
| FEED CONSUMPTION (G) | | | | | | |
| DAYS 1 - 8 | MEAN±S.D. | 27.4 ± 2.0 | 26.2 ± 1.6 | 25.9 ± 2.4* | 24.7 ± 1.4** | |
| DAYS 8 - 15a | MEAN±S.D. | 26.3 ± 2.8 | 25.8 ± 1.6 | 25.5 ± 2.6 | 24.9 ± 1.9 | |
| DAYS 1 - 15a | MEAN±S.D. | 26.9 ± 2.4 | [14]b 26.1 ± 1.4 | 25.7 ± 2.3 | 24.8 ± 1.4** | |
| DAYS 29c- 36 | MEAN±S.D. | 28.3 ± 2.8 | [14]b 27.2 ± 1.9 | 26.8 ± 2.8 | 26.0 ± 1.6 | |
| DAYS 1 - 36 | MEAN±S.D. | 27.3 ± 2.4 | 26.4 ± 1.5 | 26.1 ± 2.3 | 25.2 ± 1.3** | |

DAYS = DAYS OF STUDY

[] = NUMBER OF VALUES AVERAGED

- a. Last value recorded before cohabitation.
- b. Excludes values that were associated with spillage.
- c. First value recorded after cohabitation.

* Significantly different from the vehicle control group value ($p \leq 0.05$).

** Significantly different from the vehicle control group value ($p \leq 0.01$).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B11 (PAGE 1): RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - SUMMARY - F0 GENERATION MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------|-----------|-------------|----------------------|-------------|--------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| FEED CONSUMPTION (G) | | | | | |
| DAYS 1 - 8 | MEAN±S.D. | 75.1 ± 3.8 | 72.4 ± 3.2 | 71.4 ± 4.9* | 70.0 ± 3.1** |
| DAYS 8 - 15a | MEAN±S.D. | 66.0 ± 4.5 | 65.1 ± 3.4 | 65.2 ± 4.4 | 65.2 ± 3.7 |
| DAYS 1 - 15a | MEAN±S.D. | 70.4 ± 3.9 | 68.6 ± 2.7 [14]b | 68.2 ± 3.6 | 67.5 ± 2.7 |
| DAYS 29c- 36 | MEAN±S.D. | 60.6 ± 3.2 | 59.5 ± 2.8 [14]b | 59.9 ± 4.3 | 59.8 ± 2.6 |
| DAYS 1 - 36 | MEAN±S.D. | 65.3 ± 2.7 | 63.9 ± 2.2 | 64.0 ± 3.3 | 63.5 ± 2.1 |

DAYS = DAYS OF STUDY

[] = NUMBER OF VALUES AVERAGED

- a. Last value recorded before cohabitation.
- b. Excludes values that were associated with spillage.
- c. First value recorded after cohabitation.

* Significantly different from the vehicle control group value ($p \leq 0.05$).

** Significantly different from the vehicle control group value ($p \leq 0.01$).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B12 (PAGE 1): MATING AND FERTILITY - SUMMARY - F₀ GENERATION MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|--------------------------------------|------------|------------------|------------------|------------------|------------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS IN COHABITATION | N | 15 | 15 | 15 | 15 |
| DAYS IN COHABITATION a | MEAN±S.D. | 2.9 ± 1.6 | 2.7 ± 1.0 | 3.5 ± 1.7 | 2.8 ± 2.1 |
| RATS THAT MATED b | N(%) | 14 (93.3) | 15 (100.0) | 13 (86.7) | 13 (86.7) |
| FERTILITY INDEX c,d | N/N (%) | 14/14 (100.0) | 14/15 (93.3) | 13/13 (100.0) | 12/13 (92.3) |
| RATS WITH CONFIRMED MATING DATES | N | 14 | 15 | 13 | 13 |
| MATED WITH FEMALE e | | | | | |
| DAYS 1- 7 | N(%) | 14 (100.0) | 15 (100.0) | 13 (100.0) | 13 (100.0) |
| DAYS 8-14 | N(%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| RATS PREGNANT/RATS IN COHABITATION d | N/N (%) | 14/15 (93.3) | 14/15 (93.3) | 13/15 (86.7) | 12/15 (80.0) |

- a. Restricted to rats with a confirmed mating date and rats that did not mate.
b. Includes only one mating for each male rat.
c. Number of pregnancies/number of rats that mated.
d. Includes only one pregnancy for each rat that impregnated more than one female rat.
e. Restricted to rats with a confirmed mating date.

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TABLE B13 (PAGE 1): FUNCTIONAL OBSERVATIONAL BATTERY - SUMMARY - MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------------|------------|-------------|-----|-----|-----|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS | N | 5 | 5 | 5 | 5 |
| HOME CAGE BEHAVIOR | | | | | |
| 1: Sleeping | N | 0 | 0 | 0 | 0 |
| 2: Awake, Immobile | N | 5 | 5 | 5 | 5 |
| 3: Normal movement | N | 0 | 0 | 0 | 0 |
| 4: Unusual posture | N | 0 | 0 | 0 | 0 |
| 5: Unusual behavior | N | 0 | 0 | 0 | 0 |
| ALTERATIONS (HOME CAGE) | | | | | |
| 1: None | N | 5 | 5 | 5 | 5 |
| 2: Stereotyped behavior | N | 0 | 0 | 0 | 0 |
| 3: Bizarre behavior | N | 0 | 0 | 0 | 0 |
| 4: Limb twitches/tremor | N | 0 | 0 | 0 | 0 |
| 5: Whole body tremor/spasm | N | 0 | 0 | 0 | 0 |
| 6: Unusual posture | N | 0 | 0 | 0 | 0 |
| 7: Tonic-clonic seizure | N | 0 | 0 | 0 | 0 |
| REACTION TO REMOVAL | | | | | |
| (1) Sits quietly | N | 5 | 5 | 5 | 5 |
| (2) Vocalization | N | 0 | 0 | 0 | 0 |
| (3) Runs or freezes | N | 0 | 0 | 0 | 0 |
| (4) Tail or throat rattles | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| REACTION TO HANDLING | | | | | |
| (1) No resistance | N | 5 | 5 | 5 | 5 |
| (2) Vocalization | N | 0 | 0 | 0 | 0 |
| (3) Tense | N | 0 | 0 | 0 | 0 |
| (4) Squirming | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B13 (PAGE 2): FUNCTIONAL OBSERVATIONAL BATTERY - SUMMARY - MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------------|------------|-------------|-----------|-----------|------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS | N | 5 | 5 | 5 | 5 |
| REARS IN OPEN FIELD | MEAN±S.D. | 7.2 ± 2.9 | 7.2 ± 3.1 | 7.2 ± 4.2 | 10.6 ± 6.9 |
| DEFECATION IN OPEN FIELD | | | | | |
| 1: None | N | 2 | 1 | 5 | 3 |
| 2: Feces normal | N | 2 | 4 | 0 | 1 |
| 3: Soft or liquid feces | N | 1 | 0 | 0 | 1 |
| URINATION IN OPEN FIELD | | | | | |
| (1) None | N | 1 | 0 | 3 | 3 |
| (2) Normal urination | N | 4 | 5 | 2 | 2 |
| (3) Excess urination | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.8 | 2.0 | 1.4 | 1.4 |
| LEVEL OF AROUSAL | | | | | |
| (1) Stuporous | N | 0 | 0 | 0 | 0 |
| (2) Sluggish | N | 0 | 0 | 0 | 0 |
| (3) Apparently normal | N | 5 | 5 | 5 | 5 |
| (4) Sudden darting | N | 0 | 0 | 0 | 0 |
| (5) Freezing, vocalization | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 3.0 | 3.0 | 3.0 |
| ALTERATIONS (OPEN FIELD) | | | | | |
| 1: None | N | 5 | 5 | 5 | 5 |
| 2: Stereotyped behavior | N | 0 | 0 | 0 | 0 |
| 3: Bizarre behavior | N | 0 | 0 | 0 | 0 |
| 4: Limb twitches/tremor | N | 0 | 0 | 0 | 0 |
| 5: Whole body tremor/spasm | N | 0 | 0 | 0 | 0 |
| 6: Unusual posture | N | 0 | 0 | 0 | 0 |
| 7: Tonic-clonic seizure | N | 0 | 0 | 0 | 0 |

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

a. Excludes a value that was incorrectly recorded.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B13 (PAGE 3): FUNCTIONAL OBSERVATIONAL BATTERY - SUMMARY - MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------------|------------|-------------|-----|-----|-----|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS | N | 5 | 5 | 5 | 5 |
| GAIT PATTERN | | | | | |
| 1: Apparently normal | N | 5 | 5 | 5 | 5 |
| 2: Ataxic | N | 0 | 0 | 0 | 0 |
| 3: Limbs splay or drag | N | 0 | 0 | 0 | 0 |
| 4: Spastic, tip-toe | N | 0 | 0 | 0 | 0 |
| 5: Duck-walk | N | 0 | 0 | 0 | 0 |
| 6: Scissors gait | N | 0 | 0 | 0 | 0 |
| GAIT ABNORMALITY, SEVERITY | | | | | |
| (1) Normal gait | N | 5 | 5 | 5 | 5 |
| (2) Slight | N | 0 | 0 | 0 | 0 |
| (3) Moderate | N | 0 | 0 | 0 | 0 |
| (4) Extreme | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| PALPEBRAL CLOSURE | | | | | |
| (1) Wide open | N | 5 | 5 | 5 | 5 |
| (2) Slightly drooping | N | 0 | 0 | 0 | 0 |
| (3) Half-closed | N | 0 | 0 | 0 | 0 |
| (4) Completely shut | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| PROMINENCE OF THE EYE | | | | | |
| 1: Normal | N | 5 | 5 | 5 | 5 |
| 2: Exophthalmos | N | 0 | 0 | 0 | 0 |
| 3: Enophthalmos | N | 0 | 0 | 0 | 0 |

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B13 (PAGE 4): FUNCTIONAL OBSERVATIONAL BATTERY - SUMMARY - MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|------------------------------|------------|-------------|-----|-----|-----|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS | N | 5 | 5 | 5 | 5 |
| LACRIMATION | | | | | |
| (1) No excess | N | 5 | 5 | 5 | 5 |
| (2) Excess at eyelid margin | N | 0 | 0 | 0 | 0 |
| (3) Margin persistently damp | N | 0 | 0 | 0 | 0 |
| (4) Extends beyond margin | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| SALIVATION | | | | | |
| (1) No excess | N | 5 | 5 | 5 | 5 |
| (2) Margin of mouth wet | N | 0 | 0 | 0 | 0 |
| (3) 1/4 to 1/2 submandibular | N | 0 | 0 | 0 | 0 |
| (4) Entire submandibular | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| PILOERECTOR | N | 0 | 0 | 0 | 0 |
| ABNORMAL RESPIRATION | N | 0 | 0 | 0 | 0 |
| APPEARANCE | | | | | |
| (1) Clean and groomed | N | 5 | 5 | 5 | 5 |
| (2) Unkempt | N | 0 | 0 | 0 | 0 |
| (3) Urine and/or fecal stain | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| VISUAL REACTION | | | | | |
| (1) None | N | 0 | 0 | 0 | 0 |
| (2) Orienting | N | 5 | 5 | 5 | 5 |
| (3) Startle | N | 0 | 0 | 0 | 0 |
| (4) More energetic reaction | N | 0 | 0 | 0 | 0 |
| (5) Attacks | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 2.0 | 2.0 | 2.0 | 2.0 |

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B13 (PAGE 5): FUNCTIONAL OBSERVATIONAL BATTERY - SUMMARY - MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|-----------------------------|------------|-------------|-----|-----|-----|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS | N | 5 | 5 | 5 | 5 |
| TACTILE REACTION | | | | | |
| (1) None | N | 0 | 0 | 0 | 0 |
| (2) Orienting | N | 5 | 5 | 5 | 5 |
| (3) Startle | N | 0 | 0 | 0 | 0 |
| (4) More energetic reaction | N | 0 | 0 | 0 | 0 |
| (5) Attacks | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 2.0 | 2.0 | 2.0 | 2.0 |
| AUDITORY REACTION | | | | | |
| (1) None | N | 0 | 0 | 0 | 0 |
| (2) Orienting | N | 0 | 0 | 0 | 0 |
| (3) Startle | N | 5 | 5 | 5 | 5 |
| (4) More energetic reaction | N | 0 | 0 | 0 | 0 |
| (5) Intense vocalization | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 3.0 | 3.0 | 3.0 | 3.0 |
| TAIL-PINCH REACTION | | | | | |
| (1) None | N | 0 | 0 | 0 | 0 |
| (2) Orienting | N | 5 | 5 | 5 | 5 |
| (3) Startle | N | 0 | 0 | 0 | 0 |
| (4) More energetic reaction | N | 0 | 0 | 0 | 0 |
| (5) Attacks | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 2.0 | 2.0 | 2.0 | 2.0 |
| VISUAL PLACING RESPONSE | | | | | |
| (1) Early extension | N | 5 | 5 | 5 | 5 |
| (2) Extension after contact | N | 0 | 0 | 0 | 0 |
| (3) No extension | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B13 (PAGE 6): FUNCTIONAL OBSERVATIONAL BATTERY - SUMMARY - MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|-----------------------------|------------|---------------|--------------|---------------|---------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS | N | 5 | 5 | 5 | 5 |
| AIR RIGHTING RESPONSE | | | | | |
| (1) All feet land on ground | N | 5 | 5 | 5 | 5 |
| (2) Lands on side | N | 0 | 0 | 0 | 0 |
| (3) Lands on back | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| PUPIL RESPONSE TO LIGHT | N | 5 | 5 | 5 | 5 |
| FORELIMB GRIP TEST | | | | | |
| Maximum (G) | MEAN±S.D. | 375.0 ± 120.9 | 423.0 ± 55.0 | 404.0 ± 110.4 | 293.0 ± 114.2 |
| Average (G) | MEAN±S.D. | 337.6 ± 112.8 | 393.4 ± 50.4 | 329.0 ± 98.1 | 276.4 ± 105.8 |
| HINDLIMB GRIP TEST | | | | | |
| Maximum (G) | MEAN±S.D. | 387.0 ± 123.0 | 341.0 ± 66.8 | 420.0 ± 99.7 | 354.0 ± 104.0 |
| Average (G) | MEAN±S.D. | 355.0 ± 105.3 | 309.0 ± 55.1 | 382.8 ± 96.0 | 315.0 ± 97.8 |
| LANDING FOOT SPLAY | | | | | |
| Average (CM) | MEAN±S.D. | 8.6 ± 1.5 | 9.6 ± 2.2 | 8.0 ± 1.3 | 7.9 ± 1.3 |
| BODY WEIGHT (G) | N | 464.6 ± 37.3 | 457.5 ± 19.9 | 438.6 ± 28.4 | 422.4 ± 12.3 |

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B14 (PAGE 1): MOTOR ACTIVITY - SUMMARY - F0 GENERATION MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|---------------------|-------------|---------------|---------------|---------------|--------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| DAY 86 | | | | | |
| NUMBER OF RATS | N | 5 | 5 | 5 | 5 |
| NUMBER OF MOVEMENTS | | | | | |
| BLOCK 1 | MEAN ± S.D. | 65.4 ± 9.9 | 67.0 ± 10.0 | 64.0 ± 4.1 | 65.6 ± 5.3 |
| BLOCK 2 | MEAN ± S.D. | 72.0 ± 7.6 | 67.8 ± 9.0 | 63.2 ± 15.3 | 72.2 ± 12.2 |
| BLOCK 3 | MEAN ± S.D. | 69.8 ± 4.1 | 70.4 ± 15.1 | 66.8 ± 11.6 | 62.0 ± 9.0 |
| BLOCK 4 | MEAN ± S.D. | 58.0 ± 18.9 | 62.4 ± 14.6 | 54.6 ± 14.5 | 61.2 ± 10.8 |
| BLOCK 5 | MEAN ± S.D. | 29.8 ± 29.2 | 63.4 ± 19.9 | 42.8 ± 30.9 | 25.6 ± 29.2 |
| BLOCK 6 | MEAN ± S.D. | 31.2 ± 28.8 | 51.6 ± 30.9 | 28.4 ± 24.5 | 16.0 ± 22.4 |
| BLOCK 7 | MEAN ± S.D. | 35.0 ± 35.3 | 41.4 ± 28.8 | 22.4 ± 29.7 | 10.8 ± 21.4 |
| BLOCK 8 | MEAN ± S.D. | 44.8 ± 27.6 | 50.2 ± 31.9 | 25.4 ± 22.4 | 8.2 ± 13.1 |
| BLOCK 9 | MEAN ± S.D. | 35.0 ± 34.2 | 41.4 ± 23.7 | 32.2 ± 31.3 | 1.4 ± 1.7 |
| BLOCK 10 | MEAN ± S.D. | 18.8 ± 23.7 | 36.4 ± 30.2 | 44.4 ± 27.2 | 10.8 ± 20.9 |
| BLOCK 11 | MEAN ± S.D. | 20.0 ± 27.0 | 33.0 ± 22.8 | 35.8 ± 31.7 | 26.0 ± 24.2 |
| BLOCK 12 | MEAN ± S.D. | 31.8 ± 38.6 | 24.6 ± 19.5 | 22.4 ± 22.3 | 22.6 ± 27.8 |
| BLOCK 13 | MEAN ± S.D. | 26.0 ± 31.5 | 22.8 ± 29.9 | 19.4 ± 27.6 | 7.4 ± 7.7 |
| BLOCK 14 | MEAN ± S.D. | 14.8 ± 25.5 | 27.2 ± 26.2 | 19.8 ± 24.1 | 3.8 ± 6.8 |
| BLOCK 15 | MEAN ± S.D. | 11.2 ± 21.8 | 18.6 ± 24.3 | 15.4 ± 23.9 | 8.0 ± 12.5 |
| BLOCK 16 | MEAN ± S.D. | 14.8 ± 22.6 | 18.0 ± 21.1 | 22.0 ± 21.0 | 16.2 ± 24.2 |
| BLOCK 17 | MEAN ± S.D. | 13.8 ± 25.9 | 4.8 ± 5.3 | 13.4 ± 23.0 | 3.8 ± 6.9 |
| BLOCK 18 | MEAN ± S.D. | 12.4 ± 23.9 | 3.8 ± 5.0 | 7.6 ± 14.8 | 3.4 ± 4.7 |
| TOTAL | MEAN ± S.D. | 604.6 ± 292.0 | 704.8 ± 280.9 | 600.0 ± 120.2 | 425.0 ± 91.8 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B14 (PAGE 2): MOTOR ACTIVITY - SUMMARY - F₀ GENERATION MALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------------------|-------------|----------------|----------------|----------------|---------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| DAY 86 | | | | | |
| NUMBER OF RATS | N | 5 | 5 | 5 | 5 |
| TIME (SECONDS) SPENT IN MOVEMENT | | | | | |
| BLOCK 1 | MEAN ± S.D. | 178.6 ± 20.7 | 204.8 ± 16.2 | 188.4 ± 19.3 | 179.6 ± 22.4 |
| BLOCK 2 | MEAN ± S.D. | 170.8 ± 18.0 | 167.4 ± 10.1 | 135.0 ± 31.2 | 152.6 ± 29.4 |
| BLOCK 3 | MEAN ± S.D. | 140.8 ± 42.6 | 140.2 ± 23.4 | 123.4 ± 20.5 | 111.6 ± 23.8 |
| BLOCK 4 | MEAN ± S.D. | 77.8 ± 18.5 | 101.8 ± 22.4 | 101.6 ± 30.8 | 109.2 ± 52.2 |
| BLOCK 5 | MEAN ± S.D. | 41.8 ± 54.5 | 101.4 ± 39.2 | 56.2 ± 43.7 | 32.2 ± 38.2 |
| BLOCK 6 | MEAN ± S.D. | 51.0 ± 62.5 | 85.4 ± 50.9 | 33.2 ± 28.1 | 24.0 ± 45.5 |
| BLOCK 7 | MEAN ± S.D. | 45.2 ± 49.3 | 66.4 ± 61.9 | 33.4 ± 50.3 | 13.6 ± 30.4 |
| BLOCK 8 | MEAN ± S.D. | 64.8 ± 43.6 | 70.4 ± 48.2 | 26.8 ± 31.0 | 5.0 ± 9.1 |
| BLOCK 9 | MEAN ± S.D. | 56.4 ± 59.5 | 75.0 ± 46.2 | 38.2 ± 39.3 | 0.6 ± 0.9 |
| BLOCK 10 | MEAN ± S.D. | 27.8 ± 47.1 | 47.0 ± 39.9 | 72.6 ± 55.4 | 14.2 ± 28.0 |
| BLOCK 11 | MEAN ± S.D. | 30.6 ± 42.4 | 40.0 ± 36.4 | 60.4 ± 64.3 | 32.8 ± 34.1 |
| BLOCK 12 | MEAN ± S.D. | 39.6 ± 52.6 | 35.8 ± 35.6 | 26.2 ± 27.9 | 30.6 ± 43.0 |
| BLOCK 13 | MEAN ± S.D. | 35.6 ± 47.6 | 30.0 ± 39.9 | 21.8 ± 31.0 | 5.8 ± 8.0 |
| BLOCK 14 | MEAN ± S.D. | 24.2 ± 49.7 | 27.8 ± 28.4 | 22.6 ± 30.9 | 2.2 ± 4.9 |
| BLOCK 15 | MEAN ± S.D. | 20.4 ± 45.6 | 20.2 ± 29.9 | 19.4 ± 34.8 | 6.6 ± 11.3 |
| BLOCK 16 | MEAN ± S.D. | 21.8 ± 43.8 | 22.2 ± 30.4 | 26.4 ± 28.4 | 28.0 ± 40.6 |
| BLOCK 17 | MEAN ± S.D. | 17.2 ± 37.4 | 4.0 ± 6.2 | 20.0 ± 36.4 | 4.0 ± 8.9 |
| BLOCK 18 | MEAN ± S.D. | 14.8 ± 32.0 | 2.6 ± 4.3 | 12.2 ± 26.2 | 1.2 ± 2.7 |
| TOTAL | MEAN ± S.D. | 1059.2 ± 547.0 | 1242.4 ± 381.5 | 1017.8 ± 181.4 | 753.8 ± 146.0 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B15 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP I | VEHICLE | 0 (VEHICLE) MG/KG/DAY |
|----------------|-------------|-----------------------|
| RAT # | DESCRIPTION | |
| 17601 | | NO ADVERSE FINDINGS |
| 17602 | | NO ADVERSE FINDINGS |
| 17603 | DS(35) | CHROMORHINORRHEA |
| 17604 | | NO ADVERSE FINDINGS |
| 17607 | | NO ADVERSE FINDINGS |
| 17608 | | NO ADVERSE FINDINGS |
| 17618 | | NO ADVERSE FINDINGS |
| 17630 | | NO ADVERSE FINDINGS |
| 17631 | DS(11) | SOFT OR LIQUID FECES |
| 17639 | DS(14- 15) | SOFT OR LIQUID FECES |
| | DS(34) | CHROMORHINORRHEA |
| 17648 | | NO ADVERSE FINDINGS |
| 17652 | | NO ADVERSE FINDINGS |
| 17656 | | NO ADVERSE FINDINGS |
| 17658 | | NO ADVERSE FINDINGS |
| 17660 | DS(34- 35) | CHROMORHINORRHEA |

DS = DAY OF STUDY

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B15 (PAGE 2): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP II | | LOW DOSAGE | 10 MG/KG/DAY |
|-----------------|-------------|----------------------|--------------|
| RAT # | | DESCRIPTION | |
| 17615 | DS(34) | PENIS: RED SUBSTANCE | |
| 17616 | DS(34- 35) | CHROMORHINORRHEA | |
| 17624 | | NO ADVERSE FINDINGS | |
| 17626 | | NO ADVERSE FINDINGS | |
| 17632 | | NO ADVERSE FINDINGS | |
| 17634 | DS(14) | CHROMORHINORRHEA | |
| | DS(35) | CHROMORHINORRHEA | |
| 17635 | | NO ADVERSE FINDINGS | |
| 17638 | | NO ADVERSE FINDINGS | |
| 17642 | | NO ADVERSE FINDINGS | |
| 17643 | DS(14) | CHROMORHINORRHEA | |
| 17645 | DS(10) | SOFT OR LIQUID FECES | |
| | DS(14) | SOFT OR LIQUID FECES | |
| 17649 | | NO ADVERSE FINDINGS | |
| 17651 | DS(15) | SOFT OR LIQUID FECES | |
| 17653 | DS(14) | CHROMORHINORRHEA | |
| 17655 | | NO ADVERSE FINDINGS | |

DS = DAY OF STUDY

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B15 (PAGE 3): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP III | | MIDDLE DOSAGE | 50 MG/KG/DAY |
|------------------|-------------|-----------------------------|--------------|
| RAT # | | DESCRIPTION | |
| 17605 | | NO ADVERSE FINDINGS | |
| 17610 | DS(14) | CHROMORHINORRHEA | |
| | DS(16) | URINE-STAINED ABDOMINAL FUR | |
| | DS(27) | CHROMORHINORRHEA | |
| 17611 | | NO ADVERSE FINDINGS | |
| 17613 | | NO ADVERSE FINDINGS | |
| 17619 | | NO ADVERSE FINDINGS | |
| 17620 | | NO ADVERSE FINDINGS | |
| 17623 | | NO ADVERSE FINDINGS | |
| 17627 | DS(23) | CHROMODACRYORRHEA | |
| | DS(23) | INCISORS: MISSING/BROKEN | |
| 17628 | DS(10) | PENIS: RED SUBSTANCE | |
| 17633 | | NO ADVERSE FINDINGS | |
| 17640 | | NO ADVERSE FINDINGS | |
| 17646 | DS(32- 37) | LOCALIZED ALOPECIA: LIMBS a | |
| 17650 | | NO ADVERSE FINDINGS | |
| 17657 | | NO ADVERSE FINDINGS | |
| 17659 | | NO ADVERSE FINDINGS | |

DS = DAY OF STUDY

a. Observation confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B15 (PAGE 4): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP IV | | HIGH DOSAGE | 250 MG/KG/DAY |
|-----------------|-------------|--------------------------------|---------------|
| RAT # | | DESCRIPTION | |
| 17606 | DS(10) | EXCESS SALIVATION | |
| | DS(12- 13) | EXCESS SALIVATION | |
| | DS(17) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DS(23) | EXCESS SALIVATION | |
| | DS(30- 31) | EXCESS SALIVATION | |
| 17609 | DS(33) | EXCESS SALIVATION | |
| | DS(12) | CHROMORHINORRHEA | |
| | DS(12- 13) | CHROMODACRYORRHEA | |
| | DS(14) | CHROMORHINORRHEA | |
| | DS(14- 22) | INCISORS: MISSING/BROKEN | |
| 17612 | DS(16- 17) | CHROMODACRYORRHEA | |
| | DS(32) | EXCESS SALIVATION | |
| | DS(30) | RED, SLIGHT PERIORAL SUBSTANCE | |
| 17614 | DS(35) | PENIS: RED SUBSTANCE | |
| | DS(14- 15) | CHROMORHINORRHEA | |
| 17617 | DS(29) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DS(1) | EXCESS SALIVATION | |
| | DS(14) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DS(14) | URINE-STAINED ABDOMINAL FUR | |
| | DS(16) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DS(29) | EXCESS SALIVATION | |
| | DS(32) | EXCESS SALIVATION | |
| | DS(37) | URINE-STAINED ABDOMINAL FUR | |

DS = DAY OF STUDY

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B15 (PAGE 5): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP IV | | HIGH DOSAGE | 250 MG/KG/DAY |
|-----------------|-------------|--|---------------|
| RAT # | | DESCRIPTION | |
| 17621 | DS(25) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DS(30) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DS(31) | EXCESS SALIVATION | |
| | DS(35) | EXCESS SALIVATION | |
| 17622 | DS(16- 17) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DS(23- 31) | RIGHT FORELIMB: SCAB(S) (DID NOT EXCEED 2.5 CM X 0.5 CM) | |
| | DS(32) | RIGHT FORELIMB: ULCERATION (1.0 CM IN DIAMETER) | |
| | DS(32) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DS(33- 37) | RIGHT FORELIMB: SCAB(S) (DID NOT EXCEED 1.0 CM IN DIAMETER)a | |
| | DS(37) | CHROMODACRYORRHEA a | |
| | DS(37) | LOCALIZED ALOPECIA: LIMBS a | |
| 17625 | DS(32) | RED, SLIGHT PERIORAL SUBSTANCE | |
| 17629 | DS(6- 7) | CHROMORHINORRHEA | |
| | DS(14) | URINE-STAINED ABDOMINAL FUR | |
| | DS(19) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DS(24) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DS(30) | EXCESS SALIVATION | |
| | DS(31- 35) | URINE-STAINED ABDOMINAL FUR | |
| | DS(37) | URINE-STAINED ABDOMINAL FUR | |
| 17636 | DS(14) | EXCESS SALIVATION | |
| | DS(37) | URINE-STAINED ABDOMINAL FUR | |
| 17637 | DS(15) | EXCESS SALIVATION | |
| 17641 | DS(11) | EXCESS SALIVATION | |
| | DS(15) | EXCESS SALIVATION | |
| | DS(23- 37) | LOCALIZED ALOPECIA: LIMBS a | |
| | DS(31) | EXCESS SALIVATION | |
| | DS(33- 34) | EXCESS SALIVATION | |
| 17644 | DS(17) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DS(32- 35) | URINE-STAINED ABDOMINAL FUR | |
| 17647 | DS(3) | SOFT OR LIQUID FECES | |
| | DS(10) | EXCESS SALIVATION | |
| | DS(13) | EXCESS SALIVATION | |
| 17654 | DS(3) | SOFT OR LIQUID FECES | |
| | DS(11) | EXCESS SALIVATION | |
| | DS(29) | RED, SLIGHT PERIORAL SUBSTANCE | |

DS = DAY OF STUDY

a. Observation confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B16 (PAGE 1): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION MALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | RAT NUMBER | DAY OF NECROPSY | DOSES ADMINISTERED | OBSERVATIONS a |
|------------------------------------|---------------|--------------------|-----------------------|------------------------------|
| I 0 (VEHICLE) | 17601 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17602 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17603 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17604 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17607 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17608 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17618 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17630 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17631 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17639 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17648 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17652 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17656 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17658 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17660 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B15) for external observations confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B16 (PAGE 2): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | RAT NUMBER | DAY OF NECROPSY | DOSES ADMINISTERED | OBSERVATIONS a |
|------------------------------------|---------------|--------------------|-----------------------|------------------------------|
| II | | | | |
| 10 | 17615 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17616 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17624 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17626 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17632 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17634 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17635 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17638 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17642 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17643 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17645 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17649 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17651 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17653 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17655 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B15) for external observations confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B16 (PAGE 3): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION MALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | RAT NUMBER | DAY OF NECROPSY | DOSES ADMINISTERED | OBSERVATIONS a |
|------------------------------------|---------------|--------------------|-----------------------|------------------------------|
| III | | | | |
| 50 | 17605 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17610 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17611 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17613 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17619 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17620 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17623 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17627 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17628 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17633 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17640 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17646 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17650 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17657 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17659 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B15) for external observations confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B16 (PAGE 4): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION MALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | RAT NUMBER | DAY OF NECROPSY | DOSES ADMINISTERED | OBSERVATIONS a |
|------------------------------------|---------------|--------------------|-----------------------|--|
| IV 250 | 17606 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17609 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17612 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17614 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17617 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17621 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17622 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17625 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17629 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17636 | DS 37 | 36 | PROSTATE: RIGHT HEMISPHERE, TAN, FIRM, LOBULAR MASS (2.8 CM X 0.9 CM X 0.7 CM), CUT SURFACE REVEALED A TAN, SMOOTH SURFACE; VENTRAL RIGHT SIDE, RED. ALL OTHER TISSUES APPEARED NORMAL. |
| | 17637 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17641 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17644 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17647 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |
| | 17654 | DS 37 | 36 | ALL TISSUES APPEARED NORMAL. |

DS = DAY OF STUDY

a. Refer to the individual clinical observations table (Table B15) for external observations confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B17 (PAGE 1): TERMINAL BODY WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP I | | VEHICLE | | | | | | | | 0 (VEHICLE) MG/KG/DAY | | | |
|----------------|----------------------|------------------|------------|-------------|------------|-------------------|------------|--------------|------------|-----------------------|------------|----------|------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | EPIDIDYMISS LEFT | | TESTIS LEFT | | EPIDIDYMISS RIGHT | | TESTIS RIGHT | | BRAIN | | LIVER | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW |
| 17601 | 439. | 0.82 | 0.19 | 1.70 | 0.39 | 0.79 | 0.18 | 1.73 | 0.39 | | | 12.36 | 2.82 |
| 17602 | 512. | 0.80 | 0.16 | 1.76 | 0.34 | 0.82 | 0.16 | 1.78 | 0.35 | | | 15.56 | 3.04 |
| 17603 | 446. | 0.74 | 0.16 | 1.80 | 0.40 | 0.76 | 0.17 | 1.71 | 0.38 | | | 13.86 | 3.11 |
| 17604 | 433. | 0.80 | 0.18 | 1.96 | 0.45 | 0.82 | 0.19 | 1.99 | 0.46 | | | 11.86 | 2.74 |
| 17607 | 418. | 0.73 | 0.17 | 1.78 | 0.42 | 0.81 | 0.19 | 1.73 | 0.41 | | | 12.97 | 3.10 |
| 17608 | 469. | 0.84 | 0.18 | 1.77 | 0.38 | 0.88 | 0.19 | 1.72 | 0.37 | 2.42 | 0.52 | 14.64 | 3.12 |
| 17618 | 422. | 0.71 | 0.17 | 1.69 | 0.40 | 0.76 | 0.18 | 1.61 | 0.38 | 2.32 | 0.55 | 13.24 | 3.14 |
| 17630 | 448. | 0.75 | 0.17 | 1.80 | 0.40 | 0.78 | 0.17 | 1.79 | 0.40 | 2.39 | 0.53 | 13.82 | 3.08 |
| 17631 | 439. | 0.67 | 0.15 | 1.68 | 0.38 | 0.64 | 0.14 | 1.78 | 0.40 | 2.28 | 0.52 | 13.55 | 3.09 |
| 17639 | 483. | 0.69 | 0.14 | 1.51 | 0.31 | 0.70 | 0.14 | 1.50 | 0.31 | 2.12 | 0.44 | 14.04 | 2.91 |
| 17648 | 415. | 0.77 | 0.18 | 1.87 | 0.45 | 0.81 | 0.20 | 1.90 | 0.46 | 2.23 | 0.54 | 11.97 | 2.88 |
| 17652 | 520. | 0.72 | 0.14 | 1.68 | 0.32 | 0.75 | 0.14 | 1.71 | 0.33 | 2.46 | 0.47 | 16.55 | 3.18 |
| 17656 | 428. | 0.71 | 0.16 | 2.02 | 0.47 | 0.69 | 0.16 | 1.92 | 0.45 | 2.36 | 0.55 | 13.25 | 3.10 |
| 17658 | 433. | 0.63 | 0.14 | 1.51 | 0.35 | 0.70 | 0.16 | 1.50 | 0.35 | 2.25 | 0.52 | 13.27 | 3.06 |
| 17660 | 401. | 0.74 | 0.18 | 1.84 | 0.46 | 0.68 | 0.17 | 1.77 | 0.44 | 2.29 | 0.57 | 13.17 | 3.28 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B17 (PAGE 2): TERMINAL BODY WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - P₀ GENERATION MALE RATS

| DOSAGE GROUP I | | VEHICLE | | | | | | | | | | | |
|----------------|----------------------|-----------------------|------------|--------------|------------|--------------|-------------------------|---------------|-------------------------|----------|------------|----------|------------|
| | | 0 (VEHICLE) MG/KG/DAY | | | | | | | | | | | |
| RAT NUMBER | TERMINAL BODY WEIGHT | KIDNEY LEFT | | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | SPLEEN | | THYMUS | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW ^a | ABS. WT. | REL. % TBW ^a | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW |
| 17608 | 469. | 2.06 | 0.44 | 2.11 | 0.45 | 0.033 | 7.04 | 0.032 | 6.82 | 0.77 | 0.16 | 0.53 | 0.11 |
| 17618 | 422. | 2.09 | 0.50 | 2.02 | 0.48 | 0.031 | 7.34 | 0.034 | 8.06 | 0.87 | 0.21 | 0.49 | 0.12 |
| 17630 | 448. | 1.98 | 0.44 | 2.03 | 0.45 | 0.032 | 7.14 | 0.026 | 5.80 | 0.81 | 0.18 | 0.34 | 0.08 |
| 17631 | 439. | 1.81 | 0.41 | 1.92 | 0.44 | 0.027 | 6.15 | 0.029 | 6.60 | 1.01 | 0.23 | 0.59 | 0.13 |
| 17639 | 483. | 2.02 | 0.42 | 2.10 | 0.43 | 0.027 | 5.59 | 0.026 | 5.38 | 1.02 | 0.21 | 0.71 | 0.15 |
| 17648 | 415. | 1.89 | 0.46 | 2.00 | 0.48 | 0.025 | 6.02 | 0.030 | 7.23 | 0.84 | 0.20 | 0.50 | 0.12 |
| 17652 | 520. | 2.04 | 0.39 | 1.97 | 0.38 | 0.034 | 6.54 | 0.029 | 5.58 | 0.85 | 0.16 | 0.56 | 0.11 |
| 17656 | 428. | 1.69 | 0.39 | 1.84 | 0.43 | 0.028 | 6.54 | 0.024 | 5.61 | 0.86 | 0.20 | 0.35 | 0.08 |
| 17658 | 433. | 1.69 | 0.39 | 1.94 | 0.45 | 0.029 | 6.70 | 0.030 | 6.93 | 1.02 | 0.24 | 0.82 | 0.19 |
| 17660 | 401. | 2.10 | 0.52 | 2.09 | 0.52 | 0.008b | 2.00b | 0.021 | 5.24 | 0.86 | 0.21 | 0.54 | 0.13 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

a. Value was multiplied by 1000.

b. Damaged during processing (weight affected); values excluded from group averages and statistical analyses.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B17 (PAGE 3): TERMINAL BODY WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP I | | VEHICLE | | 0 (VEHICLE) MG/KG/DAY | |
|----------------|----------------------|----------|------------|-----------------------|------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | HEART | | ABS. WT. | REL. % TBW |
| | | ABS. WT. | REL. % TBW | | |
| 17608 | 469. | 1.46 | 0.31 | | |
| 17618 | 422. | 1.43 | 0.34 | | |
| 17630 | 448. | 1.51 | 0.34 | | |
| 17631 | 439. | 1.61 | 0.37 | | |
| 17639 | 483. | 1.63 | 0.34 | | |
| 17648 | 415. | 1.66 | 0.40 | | |
| 17652 | 520. | 1.64 | 0.32 | | |
| 17656 | 428. | 1.36 | 0.32 | | |
| 17658 | 433. | 1.52 | 0.35 | | |
| 17660 | 401. | 1.28 | 0.32 | | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B17 (PAGE 4): TERMINAL BODY WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP II | | LOW DOSAGE | | | | | | 10 MG/KG/DAY | | | | | |
|-----------------|----------------------|------------------|------------|-------------|------------|-------------------|------------|--------------|------------|----------|------------|----------|------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | EPIDIDYMISS LEFT | | TESTIS LEFT | | EPIDIDYMISS RIGHT | | TESTIS RIGHT | | BRAIN | | LIVER | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW |
| 17615 | 424. | 0.66 | 0.16 | 1.76 | 0.42 | 0.70 | 0.16 | 1.75 | 0.41 | | | 12.66 | 2.98 |
| 17616 | 437. | 0.83 | 0.19 | 1.71 | 0.39 | 0.91 | 0.21 | 1.73 | 0.40 | | | 14.57 | 3.33 |
| 17624 | 417. | 0.65 | 0.16 | 0.69 | 0.16 | 0.68 | 0.16 | 1.57 | 0.38 | | | 12.06 | 2.89 |
| 17626 | 456. | 0.74 | 0.16 | 1.68 | 0.37 | 0.69 | 0.15 | 1.67 | 0.37 | | | 14.49 | 3.18 |
| 17632 | 457. | 0.68 | 0.15 | 1.76 | 0.38 | 0.71 | 0.16 | 1.83 | 0.40 | | | 13.60 | 2.98 |
| 17634 | 433. | 0.64 | 0.15 | 1.51 | 0.35 | 0.70 | 0.16 | 1.60 | 0.37 | 2.29 | 0.53 | 13.01 | 3.00 |
| 17635 | 440. | 0.83 | 0.19 | 1.69 | 0.38 | 0.87 | 0.20 | 1.80 | 0.41 | 2.31 | 0.52 | 14.06 | 3.20 |
| 17638 | 452. | 0.80 | 0.18 | 1.88 | 0.42 | 0.79 | 0.17 | 1.88 | 0.42 | 2.45 | 0.54 | 14.20 | 3.14 |
| 17642 | 413. | 0.72 | 0.17 | 1.70 | 0.41 | 0.76 | 0.18 | 1.72 | 0.42 | 2.21 | 0.54 | 12.00 | 2.90 |
| 17643 | 494. | 0.79 | 0.16 | 1.86 | 0.38 | 0.80 | 0.16 | 1.84 | 0.37 | 2.26 | 0.46 | 18.47 | 3.74 |
| 17645 | 440. | 0.90 | 0.20 | 1.91 | 0.43 | 0.86 | 0.20 | 1.91 | 0.43 | 2.40 | 0.54 | 16.04 | 3.64 |
| 17649 | 440. | 0.57 | 0.13 | 1.47 | 0.33 | 0.59 | 0.13 | 1.47 | 0.33 | 2.02 | 0.46 | 12.55 | 2.85 |
| 17651 | 434. | 0.69 | 0.16 | 1.58 | 0.36 | 0.68 | 0.16 | 1.68 | 0.39 | 2.20 | 0.51 | 11.98 | 2.76 |
| 17653 | 442. | 0.60 | 0.14 | 1.76 | 0.40 | 0.55 | 0.12 | 1.70 | 0.38 | 2.18 | 0.49 | 14.34 | 3.24 |
| 17655 | 406. | 0.69 | 0.17 | 1.70 | 0.42 | 0.75 | 0.18 | 1.69 | 0.42 | 2.15 | 0.53 | 12.82 | 3.16 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B17 (PAGE 5): TERMINAL BODY WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP II | | LOW DOSAGE | | | | | | 10 MG/KG/DAY | | | | | |
|-----------------|----------------------|-------------|------------|--------------|------------|--------------|--------------|---------------|--------------|----------|------------|----------|------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | KIDNEY LEFT | | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | SPLEEN | | THYMUS | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW |
| 17634 | 433. | 1.97 | 0.45 | 1.89 | 0.44 | 0.027 | 6.24 | 0.029 | 6.70 | 0.69 | 0.16 | 0.53 | 0.12 |
| 17635 | 440. | 2.10 | 0.48 | 2.21 | 0.50 | 0.031 | 7.04 | 0.029 | 6.59 | 0.84 | 0.19 | 0.61 | 0.14 |
| 17638 | 452. | 1.87 | 0.41 | 1.97 | 0.44 | 0.029 | 6.42 | 0.032 | 7.08 | 0.75 | 0.16 | 0.53 | 0.12 |
| 17642 | 413. | 1.82 | 0.44 | 1.89 | 0.46 | 0.026 | 6.30 | 0.032 | 7.75 | 0.85 | 0.20 | 0.48 | 0.12 |
| 17643 | 494. | 2.10 | 0.42 | 2.26 | 0.46 | 0.028 | 5.67 | 0.034 | 6.88 | 0.94 | 0.19 | 0.53 | 0.11 |
| 17645 | 440. | 2.14 | 0.49 | 2.14 | 0.49 | 0.026 | 5.91 | 0.029 | 6.59 | 0.99 | 0.22 | 0.37 | 0.08 |
| 17649 | 440. | 1.83 | 0.42 | 1.81 | 0.41 | 0.037 | 8.41 | 0.041 | 9.32 | 0.58 | 0.13 | 0.24 | 0.05 |
| 17651 | 434. | 1.72 | 0.40 | 1.78 | 0.41 | 0.038 | 8.76 | 0.040 | 9.22 | 0.70 | 0.16 | 0.24 | 0.06 |
| 17653 | 442. | 1.91 | 0.43 | 1.90 | 0.43 | 0.022 | 4.98 | 0.027 | 6.11 | 0.74 | 0.17 | 0.36 | 0.08 |
| 17655 | 406. | 2.19 | 0.54 | 2.37 | 0.58 | 0.031 | 7.64 | 0.024 | 5.91 | 0.83 | 0.20 | 0.45 | 0.11 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.
a. Value was multiplied by 1000.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B17 (PAGE 6): TERMINAL BODY WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP II | | LOW DOSAGE | | 10 MG/KG/DAY | |
|-----------------|----------------------|------------|------------|--------------|--|
| | | HEART | | | |
| RAT NUMBER | TERMINAL BODY WEIGHT | ABS. WT. | REL. % TBW | | |
| 17634 | 433. | 1.59 | 0.37 | | |
| 17635 | 440. | 1.40 | 0.32 | | |
| 17638 | 452. | 1.57 | 0.35 | | |
| 17642 | 413. | 1.37 | 0.33 | | |
| 17643 | 494. | 1.82 | 0.37 | | |
| 17645 | 440. | 1.72 | 0.39 | | |
| 17649 | 440. | 1.28 | 0.29 | | |
| 17651 | 434. | 1.56 | 0.36 | | |
| 17653 | 442. | 1.18 | 0.27 | | |
| 17655 | 406. | 1.45 | 0.36 | | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B17 (PAGE 7): TERMINAL BODY WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - P₀ GENERATION MALE RATS

| DOSAGE GROUP III | | MIDDLE DOSAGE | | | | | | 50 MG/KG/DAY | | | | | |
|------------------|----------------------|------------------|------------|-------------|------------|-------------------|------------|--------------|------------|----------|------------|----------|------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | EPIDIDYMISS LEFT | | TESTIS LEFT | | EPIDIDYMISS RIGHT | | TESTIS RIGHT | | BRAIN | | LIVER | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW |
| 17605 | 392. | 0.73 | 0.19 | 1.66 | 0.42 | 0.75 | 0.19 | 1.62 | 0.41 | | | 12.49 | 3.19 |
| 17610 | 467. | 0.74 | 0.16 | 1.73 | 0.37 | 0.71 | 0.15 | 1.77 | 0.38 | | | 15.99 | 3.42 |
| 17611 | 422. | 0.64 | 0.15 | 1.65 | 0.39 | 0.64 | 0.15 | 1.67 | 0.40 | | | 12.49 | 2.96 |
| 17613 | 411. | 0.92 | 0.22 | 1.94 | 0.47 | 0.97 | 0.24 | 2.09 | 0.51 | | | 13.00 | 3.16 |
| 17619 | 410. | 0.70 | 0.17 | 1.88 | 0.46 | 0.76 | 0.18 | 1.82 | 0.44 | | | 14.61 | 3.56 |
| 17620 | 475. | 0.70 | 0.15 | 1.63 | 0.34 | 0.65 | 0.14 | 1.67 | 0.35 | 2.48 | 0.52 | 16.22 | 3.41 |
| 17623 | 426. | 0.70 | 0.16 | 1.64 | 0.38 | 0.71 | 0.17 | 1.64 | 0.38 | 2.46 | 0.58 | 13.91 | 3.26 |
| 17627 | 415. | 0.67 | 0.16 | 1.61 | 0.39 | 0.71 | 0.17 | 1.68 | 0.40 | 2.39 | 0.58 | 12.79 | 3.08 |
| 17628 | 389. | 0.80 | 0.20 | 1.86 | 0.48 | 0.80 | 0.20 | 1.77 | 0.46 | 2.24 | 0.58 | 12.94 | 3.33 |
| 17633 | 484. | 0.74 | 0.15 | 1.94 | 0.40 | 0.74 | 0.15 | 1.92 | 0.40 | 2.38 | 0.49 | 16.89 | 3.49 |
| 17640 | 398. | 0.69 | 0.17 | 1.76 | 0.44 | 0.72 | 0.18 | 1.82 | 0.46 | 2.21 | 0.56 | 12.58 | 3.16 |
| 17646 | 423. | 0.64 | 0.15 | 1.66 | 0.39 | 0.64 | 0.15 | 1.64 | 0.39 | 2.29 | 0.54 | 13.15 | 3.11 |
| 17650 | 482. | 0.73 | 0.15 | 1.58 | 0.33 | 0.75 | 0.16 | 1.59 | 0.33 | 2.42 | 0.50 | 15.87 | 3.29 |
| 17657 | 417. | 0.57 | 0.14 | 1.49 | 0.36 | 0.62 | 0.15 | 1.54 | 0.37 | 2.34 | 0.56 | 13.85 | 3.32 |
| 17659 | 418. | 0.81 | 0.19 | 1.98 | 0.47 | 0.80 | 0.19 | 1.88 | 0.45 | 2.34 | 0.56 | 14.18 | 3.39 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B17 (PAGE 8): TERMINAL BODY WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - P0 GENERATION MALE RATS

| DOSAGE GROUP III | | MIDDLE DOSAGE | | | | | | 50 MG/KG/DAY | | | | | |
|------------------|----------------------|---------------|------------|--------------|------------|--------------|--------------|---------------|--------------|----------|------------|----------|------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | KIDNEY LEFT | | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | SPLEEN | | THYMUS | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW |
| 17620 | 475. | 2.30 | 0.48 | 2.37 | 0.50 | 0.027 | 5.68 | 0.026 | 5.47 | 0.83 | 0.17 | 0.24 | 0.05 |
| 17623 | 426. | 2.00 | 0.47 | 2.09 | 0.49 | 0.029 | 6.81 | 0.031 | 7.28 | 0.68 | 0.16 | 0.62 | 0.14 |
| 17627 | 415. | 1.82 | 0.44 | 1.92 | 0.46 | 0.035 | 8.43 | 0.033 | 7.95 | 0.77 | 0.18 | 0.49 | 0.12 |
| 17628 | 389. | 2.30 | 0.59 | 2.29 | 0.59 | 0.032 | 8.23 | 0.030 | 7.71 | 1.05 | 0.27 | 0.23 | 0.06 |
| 17633 | 484. | 2.36 | 0.49 | 2.37 | 0.49 | 0.033 | 6.82 | 0.031 | 6.40 | 1.02 | 0.21 | 0.55 | 0.11 |
| 17640 | 398. | 2.26 | 0.57 | 2.29 | 0.58 | 0.030 | 7.54 | 0.028 | 7.04 | 0.70 | 0.18 | 0.31 | 0.08 |
| 17646 | 423. | 2.08 | 0.49 | 2.00 | 0.47 | 0.014 | 3.31 | 0.028 | 6.62 | 0.83 | 0.20 | 0.62 | 0.15 |
| 17650 | 482. | 1.93 | 0.40 | 1.92 | 0.40 | 0.031 | 6.43 | 0.033 | 6.85 | 0.85 | 0.18 | 0.40 | 0.08 |
| 17657 | 417. | 2.00 | 0.48 | 2.09 | 0.50 | 0.027 | 6.47 | 0.026 | 6.24 | 0.81 | 0.19 | 0.45 | 0.11 |
| 17659 | 418. | 2.19 | 0.52 | 2.23 | 0.53 | 0.030 | 7.18 | 0.028 | 6.70 | 0.95 | 0.23 | 0.38 | 0.09 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ABS. WT. = ORGAN WEIGHT.

REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

a. Value was multiplied by 1000.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B17 (PAGE 9): TERMINAL BODY WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP III | | MIDDLE DOSAGE | | 50 MG/KG/DAY | |
|------------------|----------------------|---------------|------------|--------------|--|
| | | HEART | | | |
| RAT NUMBER | TERMINAL BODY WEIGHT | ABS. WT. | REL. % TBW | | |
| 17620 | 475. | 1.62 | 0.34 | | |
| 17623 | 426. | 1.46 | 0.34 | | |
| 17627 | 415. | 1.08 | 0.26 | | |
| 17628 | 389. | 1.43 | 0.37 | | |
| 17633 | 484. | 1.54 | 0.32 | | |
| 17640 | 398. | 1.37 | 0.34 | | |
| 17646 | 423. | 1.52 | 0.36 | | |
| 17650 | 482. | 1.40 | 0.29 | | |
| 17657 | 417. | 1.57 | 0.38 | | |
| 17659 | 418. | 1.58 | 0.38 | | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B17 (PAGE 10): TERMINAL BODY WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP IV | | HIGH DOSAGE | | | | | | 250 MG/KG/DAY | | | | | |
|-----------------|----------------------|------------------|------------|-------------|------------|-------------------|------------|---------------|------------|----------|------------|----------|------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | EPIDIDYMISS LEFT | | TESTIS LEFT | | EPIDIDYMISS RIGHT | | TESTIS RIGHT | | BRAIN | | LIVER | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW |
| 17606 | 390. | 0.71 | 0.18 | 1.81 | 0.46 | 0.71 | 0.18 | 1.81 | 0.46 | | | 14.69 | 3.77 |
| 17609 | 407. | 0.84 | 0.21 | 1.80 | 0.44 | 0.77 | 0.19 | 1.92 | 0.47 | | | 15.67 | 3.85 |
| 17612 | 388. | 0.76 | 0.20 | 1.88 | 0.48 | 0.78 | 0.20 | 1.89 | 0.49 | | | 16.48 | 4.25 |
| 17614 | 428. | 0.76 | 0.18 | 1.80 | 0.42 | 0.74 | 0.17 | 1.80 | 0.42 | | | 23.34 | 5.45 |
| 17617 | 394. | 0.67 | 0.17 | 1.80 | 0.46 | 0.69 | 0.18 | 1.87 | 0.47 | | | 19.20 | 4.87 |
| 17621 | 417. | 0.70 | 0.17 | 1.80 | 0.43 | 0.67 | 0.16 | 1.81 | 0.43 | 2.52 | 0.60 | 16.80 | 4.03 |
| 17622 | 407. | 0.66 | 0.16 | 1.66 | 0.41 | 0.76 | 0.19 | 1.72 | 0.42 | 2.47 | 0.61 | 18.75 | 4.61 |
| 17625 | 431. | 0.69 | 0.16 | 1.53 | 0.35 | 0.64 | 0.15 | 1.48 | 0.34 | 2.20 | 0.51 | 18.98 | 4.40 |
| 17629 | 414. | 0.73 | 0.18 | 1.66 | 0.40 | 0.67 | 0.16 | 1.70 | 0.41 | 2.44 | 0.59 | 18.26 | 4.41 |
| 17636 | 445. | 0.67 | 0.15 | 1.96 | 0.44 | 0.72 | 0.16 | 1.96 | 0.44 | 2.01 | 0.45 | 21.64 | 4.86 |
| 17637 | 427. | 0.64 | 0.15 | 1.63 | 0.38 | 0.65 | 0.15 | 1.65 | 0.39 | 2.23 | 0.52 | 19.80 | 4.64 |
| 17641 | 416. | 0.73 | 0.18 | 1.56 | 0.38 | 0.73 | 0.18 | 1.54 | 0.37 | 2.33 | 0.56 | 18.99 | 4.56 |
| 17644 | 407. | 0.70 | 0.17 | 1.67 | 0.41 | 0.71 | 0.17 | 1.64 | 0.40 | 2.27 | 0.56 | 17.54 | 4.31 |
| 17647 | 400. | 0.74 | 0.18 | 1.93 | 0.48 | 0.72 | 0.18 | 1.85 | 0.46 | 2.19 | 0.55 | 18.47 | 4.62 |
| 17654 | 413. | 0.62 | 0.15 | 1.60 | 0.39 | 0.57 | 0.14 | 1.65 | 0.40 | 2.50 | 0.60 | 16.03 | 3.88 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B17 (PAGE 11): TERMINAL BODY WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP IV | | HIGH DOSAGE | | | | | | 250 MG/KG/DAY | | | | | |
|-----------------|----------------------|-------------|------------|--------------|------------|--------------|--------------|---------------|--------------|----------|------------|----------|------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | KIDNEY LEFT | | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | SPLEEN | | THYMUS | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW |
| 17621 | 417. | 2.09 | 0.50 | 2.29 | 0.55 | 0.030 | 7.19 | 0.029 | 6.95 | 0.75 | 0.18 | 0.51 | 0.12 |
| 17622 | 407. | 2.17 | 0.53 | 2.05 | 0.50 | 0.031 | 7.62 | 0.028 | 6.88 | 0.70 | 0.17 | 0.43 | 0.10 |
| 17625 | 431. | 2.15 | 0.50 | 2.12 | 0.49 | 0.020 | 4.64 | 0.018 | 4.18 | 1.05 | 0.24 | 0.60 | 0.14 |
| 17629 | 414. | 1.94 | 0.47 | 2.02 | 0.49 | 0.023 | 5.56 | 0.027 | 6.52 | 0.80 | 0.19 | 0.36 | 0.09 |
| 17636 | 445. | 2.21 | 0.50 | 2.29 | 0.51 | 0.045 | 10.11 | 0.027 | 6.07 | 0.89 | 0.20 | 0.20 | 0.04 |
| 17637 | 427. | 2.11 | 0.49 | 2.19 | 0.51 | 0.032 | 7.49 | 0.029 | 6.79 | 0.84 | 0.20 | 0.37 | 0.09 |
| 17641 | 416. | 2.39 | 0.57 | 2.34 | 0.56 | 0.034 | 8.17 | 0.034 | 8.17 | 0.70 | 0.17 | 0.40 | 0.10 |
| 17644 | 407. | 2.34 | 0.57 | 2.35 | 0.58 | 0.022 | 5.40 | 0.028 | 6.88 | 0.82 | 0.20 | 0.25 | 0.06 |
| 17647 | 400. | 2.08 | 0.52 | 2.09 | 0.52 | 0.028 | 7.00 | 0.028 | 7.00 | 0.84 | 0.21 | 0.40 | 0.10 |
| 17654 | 413. | 2.13 | 0.52 | 2.07 | 0.50 | 0.031 | 7.51 | 0.027 | 6.54 | 0.87 | 0.21 | 0.49 | 0.12 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

ABS. WT. = ORGAN WEIGHT.

REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

a. Value was multiplied by 1000.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B17 (PAGE 12): TERMINAL BODY WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP IV | | HIGH DOSAGE | | 250 MG/KG/DAY | |
|-----------------|----------------------|-------------|------------|---------------|--|
| | | HEART | | | |
| RAT NUMBER | TERMINAL BODY WEIGHT | ABS. WT. | REL. % TBW | | |
| 17621 | 417. | 1.35 | 0.32 | | |
| 17622 | 407. | 1.41 | 0.35 | | |
| 17625 | 431. | 1.88 | 0.44 | | |
| 17629 | 414. | 1.29 | 0.31 | | |
| 17636 | 445. | 1.37 | 0.31 | | |
| 17637 | 427. | 1.37 | 0.32 | | |
| 17641 | 416. | 1.39 | 0.33 | | |
| 17644 | 407. | 1.38 | 0.34 | | |
| 17647 | 400. | 1.57 | 0.39 | | |
| 17654 | 413. | 1.53 | 0.37 | | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B18 (PAGE 1): BRAIN WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - INDIVIDUAL DATA - Fo GENERATION MALE RATS

| DOSAGE GROUP I | | VEHICLE | | | | | | | | 0 (VEHICLE) MG/KG/DAY | | | |
|----------------|--------------|------------------|------------|-------------|------------|-------------------|------------|--------------|------------|-----------------------|------------|-------------|------------|
| RAT NUMBER | BRAIN WEIGHT | EPIDIDYMISS LEFT | | TESTIS LEFT | | EPIDIDYMISS RIGHT | | TESTIS RIGHT | | LIVER | | KIDNEY LEFT | |
| | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17608 | 2.42 | 0.84 | 34.71 | 1.77 | 73.14 | 0.88 | 36.36 | 1.72 | 71.07 | 14.64 | 604.96 | 2.06 | 85.12 |
| 17618 | 2.32 | 0.71 | 30.60 | 1.69 | 72.84 | 0.76 | 32.76 | 1.61 | 69.40 | 13.24 | 570.69 | 2.09 | 90.09 |
| 17630 | 2.39 | 0.75 | 31.38 | 1.80 | 75.31 | 0.78 | 32.64 | 1.79 | 74.90 | 13.82 | 578.24 | 1.98 | 82.84 |
| 17631 | 2.28 | 0.67 | 29.38 | 1.68 | 73.68 | 0.64 | 28.07 | 1.78 | 78.07 | 13.55 | 594.30 | 1.81 | 79.38 |
| 17639 | 2.12 | 0.69 | 32.55 | 1.51 | 71.23 | 0.70 | 33.02 | 1.50 | 70.75 | 14.04 | 662.26 | 2.02 | 95.28 |
| 17648 | 2.23 | 0.77 | 34.53 | 1.87 | 83.86 | 0.81 | 36.32 | 1.90 | 85.20 | 11.97 | 536.77 | 1.89 | 84.75 |
| 17652 | 2.46 | 0.72 | 29.27 | 1.68 | 68.29 | 0.75 | 30.49 | 1.71 | 69.51 | 16.55 | 672.76 | 2.04 | 82.93 |
| 17656 | 2.36 | 0.71 | 30.08 | 2.02 | 85.59 | 0.69 | 29.24 | 1.92 | 81.36 | 13.25 | 561.44 | 1.69 | 71.61 |
| 17658 | 2.25 | 0.63 | 28.00 | 1.51 | 67.11 | 0.70 | 31.11 | 1.50 | 66.67 | 13.27 | 589.78 | 1.69 | 75.11 |
| 17660 | 2.29 | 0.74 | 32.31 | 1.84 | 80.35 | 0.68 | 29.69 | 1.77 | 77.29 | 13.17 | 575.11 | 2.10 | 91.70 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B18 (PAGE 2): BRAIN WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP I | | VEHICLE | | | | | | | | | | | |
|----------------|--------------|-----------------------|------------|--------------|------------|---------------|------------|----------|------------|----------|------------|----------|------------|
| | | 0 (VEHICLE) MG/KG/DAY | | | | | | | | | | | |
| RAT NUMBER | BRAIN WEIGHT | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | SPLEEN | | THYMUS | | HEART | |
| | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17608 | 2.42 | 2.11 | 87.19 | 0.033 | 1.36 | 0.032 | 1.32 | 0.77 | 31.82 | 0.53 | 21.90 | 1.46 | 60.33 |
| 17618 | 2.32 | 2.02 | 87.07 | 0.031 | 1.34 | 0.034 | 1.46 | 0.87 | 37.50 | 0.49 | 21.12 | 1.43 | 61.64 |
| 17630 | 2.39 | 2.03 | 84.94 | 0.032 | 1.34 | 0.026 | 1.09 | 0.81 | 33.89 | 0.34 | 14.22 | 1.51 | 63.18 |
| 17631 | 2.28 | 1.92 | 84.21 | 0.027 | 1.18 | 0.029 | 1.27 | 1.01 | 44.30 | 0.59 | 25.88 | 1.61 | 70.61 |
| 17639 | 2.12 | 2.10 | 99.06 | 0.027 | 1.27 | 0.026 | 1.23 | 1.02 | 48.11 | 0.71 | 33.49 | 1.63 | 76.89 |
| 17648 | 2.23 | 2.00 | 89.69 | 0.025 | 1.12 | 0.030 | 1.34 | 0.84 | 37.67 | 0.50 | 22.42 | 1.66 | 74.44 |
| 17652 | 2.46 | 1.97 | 80.08 | 0.034 | 1.38 | 0.029 | 1.18 | 0.85 | 34.55 | 0.56 | 22.76 | 1.64 | 66.67 |
| 17656 | 2.36 | 1.84 | 77.97 | 0.028 | 1.19 | 0.024 | 1.02 | 0.86 | 36.44 | 0.35 | 14.83 | 1.36 | 57.63 |
| 17658 | 2.25 | 1.94 | 86.22 | 0.029 | 1.29 | 0.030 | 1.33 | 1.02 | 45.33 | 0.82 | 36.44 | 1.52 | 67.56 |
| 17660 | 2.29 | 2.09 | 91.27 | 0.008a | 0.35a | 0.021 | 0.92 | 0.86 | 37.55 | 0.54 | 23.58 | 1.28 | 55.90 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.

a. Damaged during processing (weight affected); values excluded from group averages and statistical analyses.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B18 (PAGE 3): BRAIN WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP II | | LOW DOSAGE | | | | | | 10 MG/KG/DAY | | | | | |
|-----------------|--------------|-----------------|------------|-------------|------------|------------------|------------|--------------|------------|----------|------------|-------------|------------|
| RAT NUMBER | BRAIN WEIGHT | EPIDIDYMIS LEFT | | TESTIS LEFT | | EPIDIDYMIS RIGHT | | TESTIS RIGHT | | LIVER | | KIDNEY LEFT | |
| | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17634 | 2.29 | 0.64 | 27.95 | 1.51 | 65.94 | 0.70 | 30.57 | 1.60 | 69.87 | 13.01 | 568.12 | 1.97 | 86.03 |
| 17635 | 2.31 | 0.83 | 35.93 | 1.69 | 73.16 | 0.87 | 37.66 | 1.80 | 77.92 | 14.06 | 608.66 | 2.10 | 90.91 |
| 17638 | 2.45 | 0.80 | 32.65 | 1.88 | 76.73 | 0.79 | 32.24 | 1.88 | 76.73 | 14.20 | 579.59 | 1.87 | 76.33 |
| 17642 | 2.21 | 0.72 | 32.58 | 1.70 | 76.92 | 0.76 | 34.39 | 1.72 | 77.83 | 12.00 | 542.99 | 1.82 | 82.35 |
| 17643 | 2.26 | 0.79 | 34.96 | 1.86 | 82.30 | 0.80 | 35.40 | 1.84 | 81.42 | 18.47 | 817.26 | 2.10 | 92.92 |
| 17645 | 2.40 | 0.90 | 37.50 | 1.91 | 79.58 | 0.86 | 35.83 | 1.91 | 79.58 | 16.04 | 668.33 | 2.14 | 89.17 |
| 17649 | 2.02 | 0.57 | 28.22 | 1.47 | 72.77 | 0.59 | 29.21 | 1.47 | 72.77 | 12.55 | 621.29 | 1.83 | 90.59 |
| 17651 | 2.20 | 0.69 | 31.36 | 1.58 | 71.82 | 0.68 | 30.91 | 1.68 | 76.36 | 11.98 | 544.54 | 1.72 | 78.18 |
| 17653 | 2.18 | 0.60 | 27.52 | 1.76 | 80.73 | 0.55 | 25.23 | 1.70 | 77.98 | 14.34 | 657.80 | 1.91 | 87.61 |
| 17655 | 2.15 | 0.69 | 32.09 | 1.70 | 79.07 | 0.75 | 34.88 | 1.69 | 78.60 | 12.82 | 596.28 | 2.19 | 101.86 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B18 (PAGE 4): BRAIN WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP II | | LOW DOSAGE | | | | | | 10 MG/KG/DAY | | | | | |
|-----------------|--------------|--------------|------------|--------------|------------|---------------|------------|--------------|------------|----------|------------|----------|------------|
| RAT NUMBER | BRAIN WEIGHT | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | SPLEEN | | THYMUS | | HEART | |
| | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17634 | 2.29 | 1.89 | 82.53 | 0.027 | 1.18 | 0.029 | 1.27 | 0.69 | 30.13 | 0.53 | 23.14 | 1.59 | 69.43 |
| 17635 | 2.31 | 2.21 | 95.67 | 0.031 | 1.34 | 0.029 | 1.26 | 0.84 | 36.36 | 0.61 | 26.41 | 1.40 | 60.61 |
| 17638 | 2.45 | 1.97 | 80.41 | 0.029 | 1.18 | 0.032 | 1.31 | 0.75 | 30.61 | 0.53 | 21.63 | 1.57 | 64.08 |
| 17642 | 2.21 | 1.89 | 85.52 | 0.026 | 1.18 | 0.032 | 1.45 | 0.85 | 38.46 | 0.48 | 21.72 | 1.37 | 61.99 |
| 17643 | 2.26 | 2.26 | 100.00 | 0.028 | 1.24 | 0.034 | 1.50 | 0.94 | 41.59 | 0.53 | 23.45 | 1.82 | 80.53 |
| 17645 | 2.40 | 2.14 | 89.17 | 0.026 | 1.08 | 0.029 | 1.21 | 0.99 | 41.25 | 0.37 | 15.42 | 1.72 | 71.67 |
| 17649 | 2.02 | 1.81 | 89.60 | 0.037 | 1.83 | 0.041 | 2.03 | 0.58 | 28.71 | 0.24 | 11.88 | 1.28 | 63.37 |
| 17651 | 2.20 | 1.78 | 80.91 | 0.038 | 1.73 | 0.040 | 1.82 | 0.70 | 31.82 | 0.24 | 10.91 | 1.56 | 70.91 |
| 17653 | 2.18 | 1.90 | 87.16 | 0.022 | 1.01 | 0.027 | 1.24 | 0.74 | 33.94 | 0.36 | 16.51 | 1.18 | 54.13 |
| 17655 | 2.15 | 2.37 | 110.23 | 0.031 | 1.44 | 0.024 | 1.12 | 0.83 | 38.60 | 0.45 | 20.93 | 1.45 | 67.44 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B18 (PAGE 5): BRAIN WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP III | | MIDDLE DOSAGE | | | | 50 MG/KG/DAY | | | | | | | |
|------------------|--------------|------------------|------------|-------------|------------|-------------------|------------|--------------|------------|----------|------------|-------------|------------|
| RAT NUMBER | BRAIN WEIGHT | EPIDIDYMISS LEFT | | TESTIS LEFT | | EPIDIDYMISS RIGHT | | TESTIS RIGHT | | LIVER | | KIDNEY LEFT | |
| | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17620 | 2.48 | 0.70 | 28.22 | 1.63 | 65.72 | 0.65 | 26.21 | 1.67 | 67.34 | 16.22 | 654.03 | 2.30 | 92.74 |
| 17623 | 2.46 | 0.70 | 28.46 | 1.64 | 66.67 | 0.71 | 28.86 | 1.64 | 66.67 | 13.91 | 565.45 | 2.00 | 81.30 |
| 17627 | 2.39 | 0.67 | 28.03 | 1.61 | 67.36 | 0.71 | 29.71 | 1.68 | 70.29 | 12.79 | 535.15 | 1.82 | 76.15 |
| 17628 | 2.24 | 0.80 | 35.71 | 1.86 | 83.04 | 0.80 | 35.71 | 1.77 | 79.02 | 12.94 | 577.68 | 2.30 | 102.68 |
| 17633 | 2.38 | 0.74 | 31.09 | 1.94 | 81.51 | 0.74 | 31.09 | 1.92 | 80.67 | 16.89 | 709.66 | 2.36 | 99.16 |
| 17640 | 2.21 | 0.69 | 31.22 | 1.76 | 79.64 | 0.72 | 32.58 | 1.82 | 82.35 | 12.58 | 569.23 | 2.26 | 102.26 |
| 17646 | 2.29 | 0.64 | 27.95 | 1.66 | 72.49 | 0.64 | 27.95 | 1.64 | 71.62 | 13.15 | 574.24 | 2.08 | 90.83 |
| 17650 | 2.42 | 0.73 | 30.16 | 1.58 | 65.29 | 0.75 | 30.99 | 1.59 | 65.70 | 15.87 | 655.78 | 1.93 | 79.75 |
| 17657 | 2.34 | 0.57 | 24.36 | 1.49 | 63.68 | 0.62 | 26.50 | 1.54 | 65.81 | 13.85 | 591.88 | 2.00 | 85.47 |
| 17659 | 2.34 | 0.81 | 34.62 | 1.98 | 84.62 | 0.80 | 34.19 | 1.88 | 80.34 | 14.18 | 605.98 | 2.19 | 93.59 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B18 (PAGE 6): BRAIN WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP III | | MIDDLE DOSAGE | | | | | | 50 MG/KG/DAY | | | | | |
|------------------|--------------|---------------|------------|--------------|------------|---------------|------------|--------------|------------|----------|------------|----------|------------|
| RAT NUMBER | BRAIN WEIGHT | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | SPLEEN | | THYMUS | | HEART | |
| | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17620 | 2.48 | 2.37 | 95.56 | 0.027 | 1.09 | 0.026 | 1.05 | 0.83 | 33.47 | 0.24 | 9.68 | 1.62 | 65.32 |
| 17623 | 2.46 | 2.09 | 84.96 | 0.029 | 1.18 | 0.031 | 1.26 | 0.68 | 27.64 | 0.62 | 25.20 | 1.46 | 59.35 |
| 17627 | 2.39 | 1.92 | 80.33 | 0.035 | 1.46 | 0.033 | 1.38 | 0.77 | 32.22 | 0.49 | 20.50 | 1.08 | 45.19 |
| 17628 | 2.24 | 2.29 | 102.23 | 0.032 | 1.43 | 0.030 | 1.34 | 1.05 | 46.87 | 0.23 | 10.27 | 1.43 | 63.84 |
| 17633 | 2.38 | 2.37 | 99.58 | 0.033 | 1.39 | 0.031 | 1.30 | 1.02 | 42.86 | 0.55 | 23.11 | 1.54 | 64.70 |
| 17640 | 2.21 | 2.29 | 103.62 | 0.030 | 1.36 | 0.028 | 1.27 | 0.70 | 31.67 | 0.31 | 14.03 | 1.37 | 61.99 |
| 17646 | 2.29 | 2.00 | 87.34 | 0.014 | 0.61 | 0.028 | 1.22 | 0.83 | 36.24 | 0.62 | 27.07 | 1.52 | 66.38 |
| 17650 | 2.42 | 1.92 | 79.34 | 0.031 | 1.28 | 0.033 | 1.36 | 0.85 | 35.12 | 0.40 | 16.53 | 1.40 | 57.85 |
| 17657 | 2.34 | 2.09 | 89.32 | 0.027 | 1.15 | 0.026 | 1.11 | 0.81 | 34.62 | 0.45 | 19.23 | 1.57 | 67.09 |
| 17659 | 2.34 | 2.23 | 95.30 | 0.030 | 1.28 | 0.028 | 1.20 | 0.95 | 40.60 | 0.38 | 16.24 | 1.58 | 67.52 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B18 (PAGE 7): BRAIN WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP IV | | HIGH DOSAGE | | | | | | 250 MG/KG/DAY | | | | | |
|-----------------|--------------|-----------------|------------|-------------|------------|------------------|------------|---------------|------------|----------|------------|-------------|------------|
| RAT NUMBER | BRAIN WEIGHT | EPIDIDYMIS LEFT | | TESTIS LEFT | | EPIDIDYMIS RIGHT | | TESTIS RIGHT | | LIVER | | KIDNEY LEFT | |
| | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17621 | 2.52 | 0.70 | 27.78 | 1.80 | 71.43 | 0.67 | 26.59 | 1.81 | 71.82 | 16.80 | 666.67 | 2.09 | 82.94 |
| 17622 | 2.47 | 0.66 | 26.72 | 1.66 | 67.21 | 0.76 | 30.77 | 1.72 | 69.64 | 18.75 | 759.11 | 2.17 | 87.85 |
| 17625 | 2.20 | 0.69 | 31.36 | 1.53 | 69.54 | 0.64 | 29.09 | 1.48 | 67.27 | 18.98 | 862.73 | 2.15 | 97.73 |
| 17629 | 2.44 | 0.73 | 29.92 | 1.66 | 68.03 | 0.67 | 27.46 | 1.70 | 69.67 | 18.26 | 748.36 | 1.94 | 79.51 |
| 17636 | 2.01 | 0.67 | 33.33 | 1.96 | 97.51 | 0.72 | 35.82 | 1.96 | 97.51 | 21.64 | 1076.62 | 2.21 | 109.95 |
| 17637 | 2.23 | 0.64 | 28.70 | 1.63 | 73.09 | 0.65 | 29.15 | 1.65 | 73.99 | 19.80 | 887.89 | 2.11 | 94.62 |
| 17641 | 2.33 | 0.73 | 31.33 | 1.56 | 66.95 | 0.73 | 31.33 | 1.54 | 66.09 | 18.99 | 815.02 | 2.39 | 102.58 |
| 17644 | 2.27 | 0.70 | 30.84 | 1.67 | 73.57 | 0.71 | 31.28 | 1.64 | 72.25 | 17.54 | 772.69 | 2.34 | 103.08 |
| 17647 | 2.19 | 0.74 | 33.79 | 1.93 | 88.13 | 0.72 | 32.88 | 1.85 | 84.47 | 18.47 | 843.38 | 2.08 | 94.98 |
| 17654 | 2.50 | 0.62 | 24.80 | 1.60 | 64.00 | 0.57 | 22.80 | 1.65 | 66.00 | 16.03 | 641.20 | 2.13 | 85.20 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B18 (PAGE 8): BRAIN WEIGHTS, ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - INDIVIDUAL DATA - P0 GENERATION MALE RATS

| DOSAGE GROUP IV | | HIGH DOSAGE | | | | | | 250 MG/KG/DAY | | | | | |
|-----------------|--------------|--------------|------------|--------------|------------|---------------|------------|---------------|------------|----------|------------|----------|------------|
| RAT NUMBER | BRAIN WEIGHT | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | SPLEEN | | THYMUS | | HEART | |
| | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17621 | 2.52 | 2.29 | 90.87 | 0.030 | 1.19 | 0.029 | 1.15 | 0.75 | 29.76 | 0.51 | 20.24 | 1.35 | 53.57 |
| 17622 | 2.47 | 2.05 | 83.00 | 0.031 | 1.26 | 0.028 | 1.13 | 0.70 | 28.34 | 0.43 | 17.41 | 1.41 | 57.08 |
| 17625 | 2.20 | 2.12 | 96.36 | 0.020 | 0.91 | 0.018 | 0.82 | 1.05 | 47.73 | 0.60 | 27.27 | 1.88 | 85.45 |
| 17629 | 2.44 | 2.02 | 82.79 | 0.023 | 0.94 | 0.027 | 1.11 | 0.80 | 32.79 | 0.36 | 14.75 | 1.29 | 52.87 |
| 17636 | 2.01 | 2.29 | 113.93 | 0.045 | 2.24 | 0.027 | 1.34 | 0.89 | 44.28 | 0.20 | 9.95 | 1.37 | 68.16 |
| 17637 | 2.23 | 2.19 | 98.21 | 0.032 | 1.43 | 0.029 | 1.30 | 0.84 | 37.67 | 0.37 | 16.59 | 1.37 | 61.43 |
| 17641 | 2.33 | 2.34 | 100.43 | 0.034 | 1.46 | 0.034 | 1.46 | 0.70 | 30.04 | 0.40 | 17.17 | 1.39 | 59.66 |
| 17644 | 2.27 | 2.35 | 103.52 | 0.022 | 0.97 | 0.028 | 1.23 | 0.82 | 36.12 | 0.25 | 11.01 | 1.38 | 60.79 |
| 17647 | 2.19 | 2.09 | 95.43 | 0.028 | 1.28 | 0.028 | 1.28 | 0.84 | 38.36 | 0.40 | 18.26 | 1.57 | 71.69 |
| 17654 | 2.50 | 2.07 | 82.80 | 0.031 | 1.24 | 0.027 | 1.08 | 0.87 | 34.80 | 0.49 | 19.60 | 1.53 | 61.20 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B19 (PAGE 1): BODY WEIGHTS - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| RAT # | DOSAGE GROUP I | | | VEHICLE | | | | | | | | 0 (VEHICLE) MG/KG/DAY | | | | | |
|-------|----------------|------|------|---------|------|------|------|------|------|------|------|-----------------------|------|------|------|------|----|
| | DAY | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15a | 16 |
| 17601 | 333. | 331. | 340. | 348. | 367. | 365. | 375. | 383. | 380. | 388. | 384. | 396. | 398. | 401. | 409. | 403. | |
| 17602 | 362. | 371. | 380. | 389. | 400. | 401. | 410. | 419. | 425. | 431. | 436. | 441. | 449. | 458. | 463. | 458. | |
| 17603 | 342. | 350. | 357. | 364. | 369. | 373. | 379. | 383. | 391. | 395. | 398. | 406. | 408. | 413. | 417. | 412. | |
| 17604 | 349. | 353. | 363. | 368. | 377. | 376. | 386. | 389. | 399. | 396. | 402. | 403. | 412. | 414. | 418. | 413. | |
| 17607 | 330. | 333. | 341. | 348. | 354. | 358. | 360. | 364. | 365. | 369. | 372. | 377. | 379. | 382. | 385. | 382. | |
| 17608 | 353. | 364. | 367. | 379. | 379. | 388. | 393. | 396. | 402. | 404. | 410. | 412. | 421. | 423. | 428. | 433. | |
| 17618 | 343. | 347. | 351. | 361. | 366. | 374. | 376. | 383. | 379. | 384. | 390. | 396. | 394. | 394. | 398. | 404. | |
| 17630 | 347. | 352. | 357. | 366. | 374. | 381. | 384. | 387. | 395. | 402. | 408. | 412. | 416. | 424. | 421. | 418. | |
| 17631 | 332. | 337. | 346. | 355. | 360. | 364. | 370. | 376. | 374. | 380. | 372. | 389. | 393. | 394. | 394. | 398. | |
| 17639 | 350. | 356. | 358. | 364. | 371. | 380. | 385. | 395. | 397. | 404. | 407. | 414. | 421. | 425. | 425. | 427. | |
| 17648 | 333. | 340. | 350. | 354. | 359. | 363. | 374. | 372. | 370. | 381. | 384. | 389. | 390. | 390. | 395. | 391. | |
| 17652 | 349. | 362. | 370. | 380. | 386. | 391. | 399. | 410. | 415. | 425. | 430. | 438. | 445. | 450. | 456. | 454. | |
| 17656 | 342. | 348. | 352. | 359. | 364. | 371. | 373. | 380. | 379. | 380. | 388. | 386. | 391. | 393. | 398. | 392. | |
| 17658 | 345. | 356. | 360. | 363. | 368. | 372. | 374. | 381. | 378. | 384. | 384. | 387. | 391. | 392. | 393. | 390. | |
| 17660 | 331. | 338. | 344. | 343. | 350. | 353. | 355. | 354. | 362. | 360. | 363. | 367. | 368. | 374. | 374. | 375. | |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Last value recorded before cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B19 (PAGE 2): BODY WEIGHTS - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| RAT # | DOSAGE GROUP I | | | VEHICLE | | | | | | | | | | | | | |
|-------|----------------|------|------|---------|------|------|------|------|------|------|------|------|------|------|------|------|----|
| | DAY | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29a | 30 | 31 | 32 |
| 17601 | 414. | 416. | 421. | 416. | 418. | 427. | 428. | 433. | 434. | 444. | 438. | 444. | 455. | 453. | 466. | 460. | |
| 17602 | 464. | 468. | 476. | 479. | 479. | 484. | 490. | 493. | 496. | 504. | 514. | 514. | 522. | 516. | 532. | 533. | |
| 17603 | 424. | 428. | 432. | 434. | 439. | 444. | 448. | 447. | 453. | 458. | 459. | 468. | 471. | 473. | 465. | 470. | |
| 17604 | 418. | 417. | 421. | 423. | 420. | 427. | 433. | 436. | 430. | 435. | 438. | 438. | 449. | 450. | 447. | 457. | |
| 17607 | 388. | 395. | 398. | 402. | 401. | 405. | 407. | 410. | 408. | 415. | 417. | 418. | 427. | 425. | 424. | 429. | |
| 17608 | 436. | 438. | 442. | 445. | 444. | 448. | 454. | 452. | 456. | 458. | 463. | 467. | 474. | 474. | 477. | 480. | |
| 17618 | 408. | 405. | 413. | 414. | 413. | 420. | 416. | 424. | 428. | 430. | 428. | 436. | 439. | 434. | 439. | 440. | |
| 17630 | 423. | 429. | 434. | 436. | 439. | 441. | 446. | 446. | 451. | 454. | 456. | 459. | 459. | 464. | 468. | 469. | |
| 17631 | 401. | 406. | 413. | 418. | 423. | 428. | 426. | 433. | 436. | 440. | 437. | 449. | 454. | 454. | 457. | 467. | |
| 17639 | 431. | 432. | 438. | 440. | 446. | 446. | 452. | 452. | 462. | 463. | 465. | 475. | 481. | 482. | 489. | 490. | |
| 17648 | 397. | 391. | 396. | 397. | 404. | 410. | 405. | 412. | 412. | 416. | 413. | 422. | 426. | 426. | 432. | 438. | |
| 17652 | 459. | 464. | 475. | 473. | 479. | 485. | 487. | 497. | 497. | 506. | 509. | 511. | 524. | 526. | 531. | 540. | |
| 17656 | 394. | 400. | 401. | 406. | 409. | 412. | 411. | 416. | 418. | 423. | 427. | 429. | 435. | 438. | 440. | 444. | |
| 17658 | 400. | 400. | 402. | 408. | 414. | 413. | 418. | 429. | 425. | 434. | 440. | 444. | 448. | 448. | 449. | 451. | |
| 17660 | 379. | 379. | 382. | 379. | 382. | 388. | 393. | 394. | 392. | 399. | 399. | 402. | 410. | 404. | 409. | 414. | |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. First value recorded after cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B19 (PAGE 3): BODY WEIGHTS - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| RAT # | DOSAGE GROUP I | | | | | VEHICLE 0 (VEHICLE) MG/KG/DAY |
|-------|----------------|------|------|------|------|----------------------------------|
| | DAY | 33 | 34 | 35 | 36 | |
| 17601 | | 458. | 467. | 465. | 473. | 439. |
| 17602 | | 533. | 541. | 545. | 544. | 512. |
| 17603 | | 473. | 471. | 471. | 476. | 446. |
| 17604 | | 450. | 459. | 462. | 461. | 433. |
| 17607 | | 433. | 438. | 439. | 436. | 418. |
| 17608 | | 484. | 490. | 495. | 493. | 469. |
| 17618 | | 443. | 443. | 446. | 446. | 422. |
| 17630 | | 475. | 475. | 476. | 474. | 448. |
| 17631 | | 458. | 466. | 467. | 469. | 439. |
| 17639 | | 495. | 496. | 503. | 504. | 483. |
| 17648 | | 436. | 436. | 437. | 440. | 415. |
| 17652 | | 537. | 540. | 547. | 550. | 520. |
| 17656 | | 446. | 451. | 454. | 457. | 428. |
| 17658 | | 449. | 457. | 462. | 463. | 433. |
| 17660 | | 417. | 420. | 426. | 427. | 401. |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B19 (PAGE 4): BODY WEIGHTS - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| RAT # | DOSAGE GROUP II | | | | | | | | | | | | | | | |
|-------|-------------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| | LOW DOSAGE 10 MG/KG/DAY | | | | | | | | | | | | | | | |
| DAY | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15a | 16 |
| 17615 | 328. | 332. | 334. | 342. | 339. | 350. | 348. | 354. | 363. | 362. | 367. | 368. | 381. | 383. | 389. | 391. |
| 17616 | 354. | 361. | 365. | 374. | 380. | 385. | 390. | 396. | 403. | 403. | 409. | 410. | 413. | 416. | 420. | 419. |
| 17624 | 336. | 339. | 343. | 352. | 358. | 360. | 370. | 374. | 375. | 381. | 378. | 382. | 385. | 388. | 394. | 387. |
| 17626 | 344. | 350. | 360. | 370. | 376. | 382. | 391. | 390. | 390. | 394. | 403. | 404. | 407. | 409. | 415. | 414. |
| 17632 | 334. | 341. | 348. | 356. | 364. | 373. | 381. | 387. | 391. | 399. | 401. | 414. | 416. | 422. | 428. | 422. |
| 17634 | 357. | 362. | 366. | 371. | 378. | 380. | 386. | 390. | 392. | 398. | 399. | 402. | 407. | 410. | 416. | 406. |
| 17635 | 337. | 341. | 350. | 353. | 360. | 368. | 374. | 373. | 373. | 385. | 381. | 387. | 392. | 396. | 404. | 397. |
| 17638 | 347. | 350. | 358. | 368. | 373. | 376. | 385. | 390. | 393. | 398. | 400. | 405. | 405. | 406. | 417. | 409. |
| 17642 | 328. | 331. | 336. | 342. | 339. | 351. | 352. | 360. | 364. | 363. | 370. | 375. | 376. | 380. | 386. | 386. |
| 17643 | 350. | 358. | 362. | 374. | 385. | 392. | 399. | 402. | 410. | 419. | 422. | 435. | 436. | 432. | 449. | 446. |
| 17645 | 336. | 339. | 342. | 352. | 362. | 366. | 372. | 376. | 384. | 382. | 384. | 388. | 400. | 392. | 401. | 391. |
| 17649 | 340. | 348. | 353. | 360. | 364. | 369. | 372. | 378. | 383. | 393. | 396. | 398. | 401. | 408. | 411. | 406. |
| 17651 | 336. | 341. | 344. | 348. | 367. | 370. | 376. | 375. | 370. | 381. | 381. | 388. | 392. | 394. | 395. | 397. |
| 17653 | 353. | 356. | 363. | 368. | 374. | 378. | 385. | 390. | 393. | 404. | 404. | 408. | 413. | 420. | 420. | 415. |
| 17655 | 349. | 348. | 355. | 361. | 370. | 365. | 377. | 379. | 380. | 388. | 390. | 393. | 395. | 396. | 402. | 386. |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Last value recorded before cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B19 (PAGE 5): BODY WEIGHTS - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| RAT # | DOSAGE GROUP II | | | LOW DOSAGE | | | | | | | | 10 MG/KG/DAY | | | | | |
|-------|-----------------|------|------|------------|------|------|------|------|------|------|------|--------------|------|------|------|------|----|
| | DAY | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29a | 30 | 31 | 32 |
| 17615 | 393. | 399. | 399. | 406. | 411. | 414. | 408. | 414. | 415. | 417. | 423. | 424. | 430. | 425. | 435. | 438. | |
| 17616 | 427. | 422. | 424. | 424. | 428. | 427. | 428. | 432. | 436. | 436. | 445. | 443. | 447. | 447. | 450. | 454. | |
| 17624 | 396. | 405. | 403. | 409. | 413. | 412. | 419. | 420. | 423. | 423. | 426. | 432. | 432. | 431. | 430. | 441. | |
| 17626 | 414. | 415. | 424. | 429. | 434. | 438. | 446. | 445. | 443. | 451. | 456. | 462. | 463. | 471. | 469. | 473. | |
| 17632 | 435. | 425. | 434. | 434. | 436. | 443. | 444. | 451. | 450. | 457. | 461. | 464. | 471. | 473. | 470. | 484. | |
| 17634 | 415. | 415. | 420. | 425. | 421. | 430. | 429. | 438. | 440. | 445. | 440. | 443. | 454. | 449. | 456. | 460. | |
| 17635 | 401. | 404. | 408. | 411. | 416. | 419. | 419. | 429. | 428. | 436. | 438. | 447. | 451. | 445. | 456. | 453. | |
| 17638 | 407. | 416. | 409. | 423. | 427. | 429. | 429. | 432. | 436. | 442. | 447. | 446. | 455. | 457. | 467. | 473. | |
| 17642 | 388. | 393. | 399. | 403. | 408. | 410. | 410. | 416. | 417. | 420. | 424. | 423. | 427. | 424. | 423. | 425. | |
| 17643 | 456. | 451. | 455. | 459. | 466. | 472. | 476. | 486. | 484. | 489. | 496. | 502. | 506. | 511. | 512. | 516. | |
| 17645 | 401. | 402. | 410. | 415. | 416. | 419. | 417. | 426. | 424. | 431. | 440. | 441. | 453. | 452. | 450. | 458. | |
| 17649 | 407. | 410. | 414. | 410. | 416. | 424. | 425. | 430. | 430. | 433. | 439. | 441. | 452. | 446. | 451. | 455. | |
| 17651 | 406. | 410. | 409. | 412. | 413. | 417. | 417. | 425. | 430. | 434. | 441. | 440. | 447. | 450. | 455. | 456. | |
| 17653 | 426. | 425. | 427. | 432. | 431. | 430. | 437. | 442. | 443. | 447. | 452. | 455. | 455. | 460. | 461. | 465. | |
| 17655 | 397. | 386. | 398. | 400. | 400. | 403. | 409. | 413. | 416. | 408. | 418. | 415. | 419. | 423. | 422. | 426. | |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. First value recorded after cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B19 (PAGE 6): BODY WEIGHTS - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| RAT # | DOSAGE GROUP II | | | | | LOW DOSAGE | 10 MG/KG/DAY |
|-------|-----------------|------|------|------|------|------------|--------------|
| | DAY | 33 | 34 | 35 | 36 | 37 | |
| 17615 | | 440. | 444. | 448. | 452. | 424. | |
| 17616 | | 458. | 460. | 461. | 461. | 437. | |
| 17624 | | 440. | 436. | 444. | 443. | 417. | |
| 17626 | | 473. | 467. | 478. | 476. | 456. | |
| 17632 | | 484. | 484. | 486. | 488. | 457. | |
| 17634 | | 455. | 453. | 460. | 460. | 433. | |
| 17635 | | 457. | 456. | 459. | 466. | 440. | |
| 17638 | | 470. | 475. | 479. | 482. | 452. | |
| 17642 | | 423. | 431. | 438. | 440. | 413. | |
| 17643 | | 513. | 522. | 521. | 529. | 494. | |
| 17645 | | 454. | 463. | 465. | 464. | 440. | |
| 17649 | | 452. | 455. | 463. | 464. | 440. | |
| 17651 | | 453. | 461. | 459. | 464. | 434. | |
| 17653 | | 464. | 464. | 466. | 468. | 442. | |
| 17655 | | 420. | 430. | 431. | 438. | 406. | |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B19 (PAGE 7): BODY WEIGHTS - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| RAT # | DOSAGE GROUP III | | | MIDDLE DOSAGE | | | | 50 MG/KG/DAY | | | | | | | | |
|-------|------------------|------|------|---------------|------|------|------|--------------|------|------|------|------|------|------|------|------|
| | DAY | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15a |
| 17605 | 325. | 324. | 330. | 334. | 339. | 342. | 346. | 353. | 356. | 353. | 352. | 360. | 359. | 365. | 367. | 364. |
| 17610 | 363. | 373. | 381. | 385. | 388. | 394. | 401. | 406. | 416. | 419. | 416. | 423. | 425. | 432. | 438. | 431. |
| 17611 | 339. | 346. | 354. | 363. | 367. | 375. | 377. | 386. | 386. | 390. | 394. | 398. | 398. | 401. | 405. | 396. |
| 17613 | 346. | 350. | 353. | 366. | 374. | 377. | 385. | 396. | 392. | 396. | 396. | 406. | 407. | 412. | 415. | 412. |
| 17619 | 330. | 334. | 336. | 343. | 348. | 350. | 355. | 357. | 360. | 362. | 367. | 368. | 373. | 378. | 380. | 374. |
| 17620 | 358. | 364. | 373. | 379. | 386. | 395. | 404. | 412. | 416. | 417. | 424. | 429. | 430. | 436. | 435. | 441. |
| 17623 | 342. | 346. | 356. | 356. | 368. | 372. | 373. | 380. | 381. | 388. | 389. | 393. | 397. | 402. | 409. | 407. |
| 17627 | 340. | 337. | 342. | 345. | 347. | 352. | 358. | 363. | 363. | 370. | 373. | 375. | 386. | 388. | 391. | 396. |
| 17628 | 328. | 332. | 341. | 345. | 342. | 350. | 353. | 356. | 352. | 359. | 362. | 366. | 365. | 371. | 369. | 371. |
| 17633 | 356. | 366. | 374. | 382. | 393. | 402. | 408. | 404. | 400. | 415. | 418. | 422. | 425. | 427. | 435. | 435. |
| 17640 | 338. | 344. | 345. | 352. | 358. | 361. | 367. | 371. | 371. | 375. | 376. | 382. | 380. | 384. | 388. | 388. |
| 17646 | 349. | 354. | 363. | 368. | 373. | 379. | 381. | 384. | 386. | 376. | 386. | 387. | 395. | 395. | 402. | 387. |
| 17650 | 370. | 369. | 376. | 386. | 389. | 389. | 398. | 401. | 408. | 414. | 418. | 422. | 425. | 431. | 437. | 431. |
| 17657 | 337. | 338. | 349. | 359. | 362. | 367. | 368. | 365. | 373. | 374. | 382. | 389. | 378. | 380. | 388. | 386. |
| 17659 | 336. | 344. | 346. | 349. | 359. | 359. | 362. | 366. | 370. | 373. | 376. | 383. | 384. | 389. | 392. | 391. |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Last value recorded before cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B19 (PAGE 8): BODY WEIGHTS - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| RAT # | DOSAGE GROUP III | | | MIDDLE DOSAGE | | | | 50 MG/KG/DAY | | | | | | | | |
|-------|------------------|------|------|---------------|------|------|------|--------------|------|------|------|------|------|------|------|------|
| | DAY | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29a | 30 | 31 |
| 17605 | 367. | 376. | 381. | 381. | 385. | 389. | 390. | 394. | 391. | 399. | 403. | 406. | 407. | 406. | 408. | 415. |
| 17610 | 435. | 439. | 444. | 448. | 450. | 457. | 462. | 465. | 464. | 465. | 471. | 473. | 484. | 482. | 490. | 489. |
| 17611 | 403. | 400. | 411. | 408. | 407. | 408. | 410. | 415. | 415. | 415. | 420. | 424. | 433. | 429. | 432. | 434. |
| 17613 | 417. | 418. | 420. | 419. | 419. | 417. | 421. | 422. | 419. | 418. | 422. | 422. | 432. | 433. | 426. | 435. |
| 17619 | 384. | 388. | 389. | 390. | 394. | 398. | 401. | 399. | 404. | 411. | 416. | 413. | 425. | 420. | 420. | 430. |
| 17620 | 443. | 446. | 452. | 455. | 451. | 457. | 464. | 466. | 471. | 473. | 481. | 481. | 485. | 487. | 489. | 491. |
| 17623 | 411. | 411. | 413. | 413. | 415. | 414. | 422. | 423. | 421. | 426. | 430. | 432. | 438. | 440. | 444. | 446. |
| 17627 | 402. | 400. | 409. | 406. | 406. | 408. | 402. | 415. | 413. | 418. | 418. | 421. | 421. | 424. | 424. | 430. |
| 17628 | 378. | 374. | 379. | 384. | 385. | 386. | 389. | 392. | 391. | 393. | 390. | 397. | 388. | 399. | 401. | 403. |
| 17633 | 445. | 443. | 442. | 450. | 456. | 460. | 462. | 468. | 467. | 472. | 478. | 484. | 488. | 489. | 492. | 502. |
| 17640 | 387. | 388. | 391. | 391. | 395. | 395. | 399. | 402. | 402. | 405. | 407. | 408. | 416. | 412. | 416. | 420. |
| 17646 | 399. | 400. | 402. | 408. | 410. | 414. | 407. | 417. | 422. | 420. | 430. | 432. | 437. | 437. | 437. | 444. |
| 17650 | 448. | 452. | 459. | 460. | 459. | 462. | 464. | 472. | 469. | 478. | 480. | 480. | 491. | 496. | 496. | 504. |
| 17657 | 391. | 393. | 396. | 403. | 400. | 402. | 405. | 410. | 412. | 418. | 419. | 422. | 433. | 431. | 435. | 439. |
| 17659 | 397. | 402. | 399. | 405. | 406. | 412. | 412. | 416. | 422. | 424. | 422. | 423. | 432. | 431. | 436. | 442. |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. First value recorded after cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B19 (PAGE 9): BODY WEIGHTS - INDIVIDUAL DATA - P0 GENERATION MALE RATS

| RAT # | DOSAGE GROUP III | | | MIDDLE DOSAGE | | 50 MG/KG/DAY |
|-------|------------------|------|------|---------------|------|--------------|
| | DAY | 33 | 34 | 35 | 36 | |
| 17605 | | 412. | 414. | 421. | 423. | 392. |
| 17610 | | 484. | 487. | 490. | 488. | 467. |
| 17611 | | 437. | 441. | 439. | 445. | 422. |
| 17613 | | 431. | 427. | 434. | 433. | 411. |
| 17619 | | 428. | 434. | 433. | 435. | 410. |
| 17620 | | 496. | 503. | 505. | 498. | 475. |
| 17623 | | 444. | 446. | 447. | 454. | 426. |
| 17627 | | 429. | 430. | 434. | 438. | 415. |
| 17628 | | 400. | 404. | 409. | 413. | 389. |
| 17633 | | 499. | 505. | 509. | 510. | 484. |
| 17640 | | 417. | 420. | 420. | 426. | 398. |
| 17646 | | 446. | 452. | 454. | 454. | 423. |
| 17650 | | 498. | 504. | 509. | 515. | 482. |
| 17657 | | 440. | 446. | 452. | 457. | 417. |
| 17659 | | 437. | 443. | 443. | 449. | 418. |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B19 (PAGE 10): BODY WEIGHTS - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| RAT # | DOSAGE GROUP IV | | | | HIGH DOSAGE | | | | | | | | 250 MG/KG/DAY | | | | |
|-------|-----------------|------|------|------|-------------|------|------|------|------|------|------|------|---------------|------|------|------|------|
| | DAY | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15a | 16 |
| 17606 | | 321. | 328. | 321. | 332. | 338. | 343. | 348. | 351. | 355. | 358. | 365. | 365. | 366. | 369. | 373. | 370. |
| 17609 | | 358. | 358. | 360. | 373. | 375. | 382. | 383. | 388. | 392. | 394. | 397. | 400. | 398. | 392. | 400. | 409. |
| 17612 | | 340. | 340. | 345. | 349. | 354. | 356. | 357. | 365. | 369. | 369. | 374. | 374. | 374. | 378. | 379. | 384. |
| 17614 | | 348. | 343. | 338. | 355. | 360. | 371. | 376. | 382. | 389. | 396. | 394. | 398. | 404. | 408. | 413. | 403. |
| 17617 | | 330. | 329. | 332. | 340. | 344. | 354. | 352. | 354. | 358. | 359. | 362. | 366. | 365. | 367. | 370. | 363. |
| 17621 | | 347. | 349. | 351. | 361. | 370. | 373. | 380. | 387. | 386. | 392. | 392. | 395. | 398. | 401. | 403. | 394. |
| 17622 | | 336. | 336. | 327. | 349. | 353. | 364. | 367. | 370. | 380. | 379. | 385. | 389. | 389. | 392. | 394. | 380. |
| 17625 | | 338. | 342. | 338. | 350. | 357. | 366. | 369. | 376. | 389. | 388. | 390. | 392. | 398. | 405. | 408. | 393. |
| 17629 | | 332. | 336. | 341. | 348. | 349. | 361. | 361. | 368. | 372. | 380. | 379. | 380. | 387. | 390. | 396. | 388. |
| 17636 | | 350. | 350. | 350. | 357. | 366. | 368. | 377. | 380. | 386. | 396. | 402. | 401. | 407. | 411. | 414. | 403. |
| 17637 | | 342. | 346. | 352. | 358. | 362. | 367. | 370. | 377. | 374. | 382. | 382. | 387. | 389. | 393. | 402. | 390. |
| 17641 | | 342. | 340. | 344. | 350. | 354. | 362. | 365. | 369. | 368. | 373. | 378. | 381. | 383. | 392. | 396. | 392. |
| 17644 | | 328. | 320. | 316. | 328. | 331. | 341. | 346. | 355. | 353. | 360. | 363. | 367. | 368. | 373. | 380. | 376. |
| 17647 | | 343. | 349. | 345. | 354. | 360. | 362. | 361. | 366. | 363. | 370. | 371. | 375. | 378. | 377. | 384. | 381. |
| 17654 | | 338. | 345. | 341. | 352. | 360. | 364. | 370. | 371. | 381. | 374. | 379. | 379. | 382. | 385. | 390. | 388. |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Last value recorded before cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B19 (PAGE 11): BODY WEIGHTS - INDIVIDUAL DATA - P0 GENERATION MALE RATS

| RAT # | DOSAGE GROUP IV | | | HIGH DOSAGE | | | | | | | | 250 MG/KG/DAY | | | | | |
|-------|-----------------|------|------|-------------|------|------|------|------|------|------|------|---------------|------|------|------|------|------|
| | DAY | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29a | 30 | 31 | 32 |
| 17606 | | 379. | 384. | 385. | 391. | 388. | 394. | 396. | 395. | 399. | 398. | 404. | 403. | 405. | 402. | 410. | 408. |
| 17609 | | 395. | 407. | 401. | 416. | 414. | 416. | 417. | 421. | 427. | 424. | 422. | 432. | 427. | 426. | 432. | 433. |
| 17612 | | 385. | 384. | 389. | 390. | 390. | 393. | 398. | 399. | 401. | 401. | 406. | 406. | 408. | 406. | 411. | 410. |
| 17614 | | 415. | 418. | 418. | 420. | 426. | 425. | 430. | 432. | 436. | 434. | 432. | 431. | 442. | 437. | 430. | 449. |
| 17617 | | 363. | 363. | 368. | 371. | 380. | 379. | 384. | 381. | 389. | 392. | 400. | 404. | 409. | 412. | 412. | 411. |
| 17621 | | 401. | 402. | 403. | 408. | 411. | 407. | 416. | 417. | 413. | 423. | 424. | 421. | 428. | 432. | 432. | 437. |
| 17622 | | 389. | 393. | 399. | 410. | 410. | 411. | 405. | 412. | 411. | 418. | 418. | 421. | 424. | 423. | 424. | 423. |
| 17625 | | 407. | 411. | 413. | 418. | 422. | 424. | 426. | 430. | 430. | 438. | 447. | 453. | 450. | 442. | 445. | 456. |
| 17629 | | 402. | 405. | 406. | 416. | 412. | 412. | 421. | 423. | 426. | 425. | 426. | 432. | 430. | 436. | 436. | 436. |
| 17636 | | 412. | 408. | 417. | 422. | 425. | 429. | 429. | 432. | 437. | 439. | 442. | 445. | 443. | 446. | 463. | 466. |
| 17637 | | 409. | 400. | 403. | 406. | 413. | 416. | 415. | 424. | 430. | 428. | 437. | 435. | 442. | 446. | 447. | 449. |
| 17641 | | 396. | 395. | 402. | 401. | 404. | 409. | 412. | 423. | 412. | 420. | 426. | 430. | 442. | 435. | 438. | 442. |
| 17644 | | 376. | 386. | 385. | 389. | 390. | 399. | 396. | 406. | 400. | 405. | 407. | 418. | 421. | 420. | 427. | 428. |
| 17647 | | 384. | 390. | 394. | 392. | 396. | 403. | 398. | 404. | 408. | 408. | 412. | 419. | 425. | 422. | 420. | 430. |
| 17654 | | 391. | 392. | 398. | 404. | 414. | 409. | 407. | 415. | 418. | 419. | 426. | 431. | 436. | 433. | 438. | 439. |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. First value recorded after cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B19 (PAGE 12): BODY WEIGHTS - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| RAT # | DOSAGE GROUP IV | | | | | HIGH DOSAGE | 250 MG/KG/DAY |
|-------|-----------------|------|------|------|------|-------------|---------------|
| | DAY | 33 | 34 | 35 | 36 | 37 | |
| 17606 | | 413. | 415. | 416. | 421. | 390. | |
| 17609 | | 430. | 433. | 438. | 438. | 407. | |
| 17612 | | 412. | 414. | 413. | 418. | 388. | |
| 17614 | | 447. | 452. | 449. | 453. | 428. | |
| 17617 | | 412. | 416. | 422. | 427. | 394. | |
| 17621 | | 437. | 436. | 442. | 449. | 417. | |
| 17622 | | 428. | 436. | 433. | 438. | 407. | |
| 17625 | | 447. | 462. | 466. | 469. | 431. | |
| 17629 | | 437. | 440. | 440. | 444. | 414. | |
| 17636 | | 460. | 460. | 470. | 462. | 445. | |
| 17637 | | 452. | 452. | 459. | 458. | 427. | |
| 17641 | | 439. | 445. | 449. | 453. | 416. | |
| 17644 | | 422. | 430. | 431. | 436. | 407. | |
| 17647 | | 425. | 428. | 436. | 434. | 400. | |
| 17654 | | 446. | 445. | 455. | 452. | 413. | |

DAY = DAY OF STUDY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B20 (PAGE 1): FEED CONSUMPTION VALUES - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| RAT # | DOSAGE GROUP I | | | VEHICLE | 0 (VEHICLE) MG/KG/DAY |
|-------|----------------|------|---------------|---------|-----------------------|
| | DAYS | 1- 8 | 8- 15a 29b-36 | | |
| 17601 | 192. | 189. | 194. | | |
| 17602 | 220. | 219. | 230. | | |
| 17603 | 201. | 200. | 196. | | |
| 17604 | 195. | 193. | 202. | | |
| 17607 | 181. | 167. | 170. | | |
| 17608 | 196. | 190. | 205. | | |
| 17618 | 183. | 176. | 175. | | |
| 17630 | 206. | 201. | 190. | | |
| 17631 | 189. | 177. | 207. | | |
| 17639 | 194. | 184. | 220. | | |
| 17648 | 184. | 164. | 186. | | |
| 17652 | 216. | 218. | 240. | | |
| 17656 | 177. | 159. | 180. | | |
| 17658 | 178. | 156. | 180. | | |
| 17660 | 169. | 172. | 194. | | |

DAYS = DAYS OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

- a. Last value recorded before cohabitation.
- b. First value recorded after cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B20 (PAGE 2): FEED CONSUMPTION VALUES - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| RAT # | DOSAGE GROUP II | | | LOW DOSAGE | 10 MG/KG/DAY |
|-------|-----------------|------|--------|------------|--------------|
| | DAYS | 1- 8 | 8- 15a | 29b-36 | |
| 17615 | | 158. | 183. | 189. | |
| 17616 | | 190. | 184. | 186. | |
| 17624 | | 177. | 165. | 178. | |
| 17626 | | 189. | 176. | 188. | |
| 17632 | | 200. | 208. | 209. | |
| 17634 | | 186. | 180. | 196. | |
| 17635 | | 191. | 184. | 196. | |
| 17638 | | 181. | 169. | 201. | |
| 17642 | | 171. | c | 168. | |
| 17643 | | 202. | 196. | 220. | |
| 17645 | | 181. | 172. | 190. | |
| 17649 | | 173. | 179. | 191. | |
| 17651 | | 181. | 172. | 169. | |
| 17653 | | 188. | 183. | 188. | |
| 17655 | | 186. | 180. | 192. | |

DAYS = DAYS OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

- Last value recorded before cohabitation.
- First value recorded after cohabitation.
- Spilled feed precluded the calculation of this value.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B20 (PAGE 3): FEED CONSUMPTION VALUES - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| RAT # | DOSAGE GROUP III | | | MIDDLE DOSAGE | 50 MG/KG/DAY |
|-------|------------------|------|--------|---------------|--------------|
| | DAYS | 1- 8 | 8- 15a | 29b-36 | |
| 17605 | | 184. | 169. | 187. | |
| 17610 | | 195. | 207. | 199. | |
| 17611 | | 184. | 170. | 169. | |
| 17613 | | 198. | 183. | 169. | |
| 17619 | | 154. | 157. | 166. | |
| 17620 | | 214. | 215. | 229. | |
| 17623 | | 184. | 168. | 179. | |
| 17627 | | 164. | 177. | 165. | |
| 17628 | | 165. | 181. | 197. | |
| 17633 | | 207. | 200. | 216. | |
| 17640 | | 175. | 162. | 171. | |
| 17646 | | 186. | 155. | 187. | |
| 17650 | | 173. | 196. | 210. | |
| 17657 | | 170. | 171. | 191. | |
| 17659 | | 167. | 171. | 182. | |

DAYS = DAYS OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

- a. Last value recorded before cohabitation.
- b. First value recorded after cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B20 (PAGE 4): FEED CONSUMPTION VALUES - INDIVIDUAL DATA - P0 GENERATION MALE RATS

| RAT # | DOSAGE GROUP IV | | | HIGH DOSAGE | 200 MG/KG/DAY |
|-------|-----------------|------|--------|-------------|---------------|
| | DAYS | 1- 8 | 8- 15a | 29b-36 | |
| 17606 | | 163. | 165. | 157. | |
| 17609 | | 179. | 171. | 177. | |
| 17612 | | 163. | 157. | 164. | |
| 17614 | | 186. | 209. | 190. | |
| 17617 | | 165. | 162. | 178. | |
| 17621 | | 195. | 179. | 188. | |
| 17622 | | 168. | 185. | 179. | |
| 17625 | | 178. | 187. | 192. | |
| 17629 | | 180. | 167. | 176. | |
| 17636 | | 164. | 190. | 189. | |
| 17637 | | 178. | 167. | 185. | |
| 17641 | | 178. | 170. | 186. | |
| 17644 | | 164. | 165. | 180. | |
| 17647 | | 169. | 176. | 197. | |
| 17654 | | 166. | 169. | 194. | |

DAYS = DAYS OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

- a. Last value recorded before cohabitation.
- b. First value recorded after cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B21 (PAGE 1): MATING AND FERTILITY - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP I | | VEHICLE | | 0 (VEHICLE) MG/KG/DAY | |
|----------------|----------------------|---------------|-------------|-------------------------|--|
| RAT # | DAYS IN COHABITATION | MATING STATUS | MATING DATE | FEMALE PREGNANCY STATUS | |
| 17601 | 3 | M | C | P(17662) | |
| 17602 | 4 | M | C | P(17672) | |
| 17603 | 1 | M | C | P(17673) | |
| 17604 | 1 | M | C | P(17674) | |
| 17607 | 3 | M | C | P(17680) | |
| 17608 | 3 | M | C | P(17681) | |
| 17618 | 3 | M | C | P(17690) | |
| 17630 | 1 | M | C | P(17694) | |
| 17631 | 2 | M | C | P(17695) | |
| 17639 | 3 | M | C | P(17703) | |
| 17648 | 3 | M | C | P(17713) | |
| 17652a | 4 | M | C | P(17715) | |
| 17652b | 2 | M | C | P(17719) | |
| 17656 | 4 | M | C | P(17716) | |
| 17658 | 1 | M | C | P(17717) | |
| 17660 | 7 | DID NOT MATE | - | -(17719) | |

M = MATED () = FEMALE RAT NUMBER

C = CONFIRMED

P = PREGNANT NP = NOT PREGNANT

a. Result of first cohabitation period.

b. Male rat mated early in the first cohabitation period and was cohabited with a second female rat.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B21 (PAGE 2): MATING AND FERTILITY - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP II | | LOW DOSAGE | 10 MG/KG/DAY | | |
|-----------------|----------------------|---------------|--------------|-------------------------|--|
| RAT # | DAYS IN COHABITATION | MATING STATUS | MATING DATE | FEMALE PREGNANCY STATUS | |
| 17615 | 3 | M | C | NP(17663) | |
| 17616 | 3 | M | C | P(17665) | |
| 17624 | 1 | M | C | P(17666) | |
| 17626 | 3 | M | C | P(17668) | |
| 17632 | 3 | M | C | P(17671) | |
| 17634 | 2 | M | C | P(17675) | |
| 17635 | 3 | M | C | P(17679) | |
| 17638 | 4 | M | C | P(17684) | |
| 17642 | 3 | M | C | P(17688) | |
| 17643 | 3 | M | C | P(17698) | |
| 17645 | 1 | M | C | P(17702) | |
| 17649 | 2 | M | C | P(17704) | |
| 17651 | 4 | M | C | P(17707) | |
| 17653 | 1 | M | C | P(17708) | |
| 17655 | 4 | M | C | P(17710) | |

M = MATED () = FEMALE RAT NUMBER
 C = CONFIRMED
 P = PREGNANT NP = NOT PREGNANT

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B21 (PAGE 3): MATING AND FERTILITY - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP III | | MIDDLE DOSAGE | | 50 MG/KG/DAY |
|------------------|----------------------|---------------|-------------|-------------------------|
| RAT # | DAYS IN COHABITATION | MATING STATUS | MATING DATE | FEMALE PREGNANCY STATUS |
| 17605 | 2 | M | C | P(17661) |
| 17610 | 2 | M | C | P(17667) |
| 17611 | 3 | M | C | P(17669) |
| 17613 | 4 | M | C | P(17670) |
| 17619 | 2 | M | C | P(17676) |
| 17620 | 4 | M | C | P(17687) |
| 17623 | 1 | M | C | P(17693) |
| 17627 | 3 | M | C | P(17697) |
| 17628a | 3 | M | C | P(17700) |
| 17628b | 6 | M | C | P(17709) |
| 17633 | 3 | M | C | P(17701) |
| 17640 | 3 | M | C | P(17705) |
| 17646 | 4 | M | C | P(17706) |
| 17650 | 7 | DID NOT MATE | - | -(17709) |
| 17657 | 7 | DID NOT MATE | - | -(17718) |
| 17659a | 4 | M | C | P(17720) |
| 17659b | 6 | M | C | P(17718) |

M = MATED () = FEMALE RAT NUMBER

C = CONFIRMED

P = PREGNANT NP = NOT PREGNANT

a. Result of first cohabitation period.

b. Male rat mated early in the first cohabitation period and was cohabited with a second female rat.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B21 (PAGE 4): MATING AND FERTILITY - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP IV | | HIGH DOSAGE | | 250 MG/KG/DAY |
|-----------------|----------------------|---------------|-------------|-------------------------|
| RAT # | DAYS IN COHABITATION | MATING STATUS | MATING DATE | FEMALE PREGNANCY STATUS |
| 17606 | 7 | DID NOT MATE | - | -(17664) |
| 17609a | 4 | M | C | P(17677) |
| 17609b | 6 | M | C | P(17682) |
| 17612 | 4 | M | C | P(17678) |
| 17614 | 7 | DID NOT MATE | - | -(17682) |
| 17617 | 3 | M | C | P(17683) |
| 17621 | 1 | M | C | P(17685) |
| 17622 | 1 | M | C | NP(17686) |
| 17625 | 1 | M | C | P(17689) |
| 17629 | 4 | M | C | P(17691) |
| 17636 | 1 | M | C | P(17692) |
| 17637 | 1 | M | C | P(17696) |
| 17641a | 3 | M | C | P(17699) |
| 17641b | 7 | DID NOT MATE | - | -(17664) |
| 17644 | 1 | M | C | P(17711) |
| 17647 | 1 | M | C | P(17712) |
| 17654 | 3 | M | C | P(17714) |

M = MATED () = FEMALE RAT NUMBER

C = CONFIRMED

P = PREGNANT NP = NOT PREGNANT

a. Result of first cohabitation period.

b. Male rat mated early in the first cohabitation period and was cohabited with a second female rat.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B22 (PAGE 1): FUNCTIONAL OBSERVATIONAL BATTERY - INDIVIDUAL DATA - MALE RATS

| DOSAGE GROUP I | | | | | | 0 (VEHICLE) MG/KG/DAY |
|----------------------------|-------|-------|-------|-------|-------|-----------------------|
| RAT # | 17601 | 17602 | 17603 | 17604 | 17607 | |
| HOME CAGE BEHAVIOR | 2 | 2 | 2 | 2 | 2 | |
| ALTERATIONS (HOME CAGE) | 1 | 1 | 1 | 1 | 1 | |
| REACTION TO REMOVAL | 1 | 1 | 1 | 1 | 1 | |
| REACTION TO HANDLING | 1 | 1 | 1 | 1 | 1 | |
| REARS IN OPEN FIELD | 8 | 9 | 9 | 2 | 8 | |
| DEFECATION IN OPEN FIELD | 1 | 2 | 3 | 2 | 1 | |
| URINATION IN OPEN FIELD | 2 | 2 | 2 | 1 | 2 | |
| LEVEL OF AROUSAL | 3 | 3 | 3 | 3 | 3 | |
| ALTERATIONS (OPEN FIELD) | 1 | 1 | 1 | 1 | 1 | |
| GAIT PATTERN | 1 | 1 | 1 | 1 | 1 | |
| GAIT ABNORMALITY, SEVERITY | 1 | 1 | 1 | 1 | 1 | |
| PALPEBRAL CLOSURE | 1 | 1 | 1 | 1 | 1 | |
| PROMINENCE OF THE EYE | 1 | 1 | 1 | 1 | 1 | |
| LACRIMATION | 1 | 1 | 1 | 1 | 1 | |
| SALIVATION | 1 | 1 | 1 | 1 | 1 | |
| PILOERECTION | 0 | 0 | 0 | 0 | 0 | |
| ABNORMAL RESPIRATION | 0 | 0 | 0 | 0 | 0 | |
| APPEARANCE | 1 | 1 | 1 | 1 | 1 | |
| VISUAL REACTION | 2 | 2 | 2 | 2 | 2 | |
| TACTILE REACTION | 2 | 2 | 2 | 2 | 2 | |
| AUDITORY REACTION | 3 | 3 | 3 | 3 | 3 | |
| TAIL-PINCH REACTION | 2 | 2 | 2 | 2 | 2 | |
| VISUAL PLACING RESPONSE | 1 | 1 | 1 | 1 | 1 | |
| AIR RIGHTING RESPONSE | 1 | 1 | 1 | 1 | 1 | |
| PUPIL RESPONSE TO LIGHT | 1 | 1 | 1 | 1 | 1 | |
| FORELIMB GRIP TEST #1 | 345 | 510 | 190 | 355 | 370 | |
| FORELIMB GRIP TEST #2 | 450 | 405 | 125 | 350 | 275 | |
| HINDLIMB GRIP TEST #1 | 445 | 375 | 310 | 200 | 360 | |
| HINDLIMB GRIP TEST #2 | 555 | 375 | 430 | 215 | 285 | |
| LANDING FOOT SPLAY #1 | 8.7 | 7.5 | 9.5 | 7.7 | 7.5a | |
| LANDING FOOT SPLAY #2 | 8.9 | 7.6 | 12.6 | 9.6 | 6.9 | |
| BODY WEIGHT (G) | 455 | 525 | 469 | 449 | 425 | |

VALUES ARE THE QUANTITY, CATEGORY NUMBER, QUANTAL RESPONSE OR SCORE RECORDED FOR EACH ITEM IN THE BATTERY.

a. Soft or liquid feces were observed during during landing foot splay testing.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B22 (PAGE 2): FUNCTIONAL OBSERVATIONAL BATTERY - INDIVIDUAL DATA - MALE RATS

| DOSAGE GROUP II | | 10 MG/KG/DAY | | | | |
|----------------------------|-------|--------------|-------|-------|-------|--|
| RAT # | 17615 | 17616 | 17624 | 17626 | 17632 | |
| HOME CAGE BEHAVIOR | 2 | 2 | 2 | 2 | 2 | |
| ALTERATIONS (HOME CAGE) | 1 | 1 | 1 | 1 | 1 | |
| REACTION TO REMOVAL | 1 | 1 | 1 | 1 | 1 | |
| REACTION TO HANDLING | 1 | 1 | 1 | 1 | 1 | |
| REARS IN OPEN FIELD | 8 | 7 | 9 | 10 | 2 | |
| DEFECATION IN OPEN FIELD | 2 | 2 | 2 | 2 | 1 | |
| URINATION IN OPEN FIELD | 2 | 2 | 2 | 2 | 2 | |
| LEVEL OF AROUSAL | 3 | 3 | 3 | 3 | 3 | |
| ALTERATIONS (OPEN FIELD) | 1 | 1 | 1 | 1 | 1 | |
| GAIT PATTERN | 1 | 1 | 1 | 1 | 1 | |
| GAIT ABNORMALITY, SEVERITY | 1 | 1 | 1 | 1 | 1 | |
| PALPEBRAL CLOSURE | 1 | 1 | 1 | 1 | 1 | |
| PROMINENCE OF THE EYE | 1 | 1 | 1 | 1 | 1 | |
| LACRIMATION | 1 | 1 | 1 | 1 | 1 | |
| SALIVATION | 1 | 1 | 1 | 1 | 1 | |
| PILOERECTION | 0 | 0 | 0 | 0 | 0 | |
| ABNORMAL RESPIRATION | 0 | 0 | 0 | 0 | 0 | |
| APPEARANCE | 1 | 1 | 1 | 1 | 1 | |
| VISUAL REACTION | 2 | 2 | 2 | 2 | 2 | |
| TACTILE REACTION | 2 | 2 | 2 | 2 | 2 | |
| AUDITORY REACTION | 3 | 3 | 3 | 3 | 3 | |
| TAIL-PINCH REACTION | 2 | 2 | 2 | 2 | 2 | |
| VISUAL PLACING RESPONSE | 1 | 1 | 1 | 1 | 1 | |
| AIR RIGHTING RESPONSE | 1 | 1 | 1 | 1 | 1 | |
| PUPIL RESPONSE TO LIGHT | 1 | 1 | 1 | 1 | 1 | |
| FORELIMB GRIP TEST #1 | 330 | 425 | 420 | 405 | 445 | |
| FORELIMB GRIP TEST #2 | 325 | 470 | 290 | 450 | 370 | |
| HINDLIMB GRIP TEST #1 | 410 | 335 | 345 | 205 | 365 | |
| HINDLIMB GRIP TEST #2 | 275 | 355 | 245 | 230 | 325 | |
| LANDING FOOT SPLAY #1 | 7.0 | 8.1 | 11.2 | 12.5 | 7.8 | |
| LANDING FOOT SPLAY #2 | 9.8 | 8.5 | 11.3 | 12.7 | 7.2 | |
| BODY WEIGHT (G) | 433 | 450 | 441a | 470 | 477 | |

VALUES ARE THE QUANTITY, CATEGORY NUMBER, QUANTAL RESPONSE OR SCORE RECORDED FOR EACH ITEM IN THE BATTERY.

a. Value appeared incorrectly recorded and was excluded from group averages and statistical analyses.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B22 (PAGE 3): FUNCTIONAL OBSERVATIONAL BATTERY - INDIVIDUAL DATA - MALE RATS

| DOSAGE GROUP III | | | | | | 50 MG/KG/DAY |
|----------------------------|-------|-------|-------|-------|-------|--------------|
| RAT # | 17605 | 17610 | 17611 | 17613 | 17619 | |
| HOME CAGE BEHAVIOR | 2 | 2 | 2 | 2 | 2 | |
| ALTERATIONS (HOME CAGE) | 1 | 1 | 1 | 1 | 1 | |
| REACTION TO REMOVAL | 1 | 1 | 1 | 1 | 1 | |
| REACTION TO HANDLING | 1 | 1 | 1 | 1 | 1 | |
| REARS IN OPEN FIELD | 10 | 10 | 7 | 9 | 0 | |
| DEFECATION IN OPEN FIELD | 1 | 1 | 1 | 1 | 1 | |
| URINATION IN OPEN FIELD | 1 | 1 | 2 | 2 | 1 | |
| LEVEL OF AROUSAL | 3 | 3 | 3 | 3 | 3 | |
| ALTERATIONS (OPEN FIELD) | 1 | 1 | 1 | 1 | 1 | |
| GAIT PATTERN | 1 | 1 | 1 | 1 | 1 | |
| GAIT ABNORMALITY, SEVERITY | 1 | 1 | 1 | 1 | 1 | |
| PALPEBRAL CLOSURE | 1 | 1 | 1 | 1 | 1 | |
| PROMINENCE OF THE EYE | 1 | 1 | 1 | 1 | 1 | |
| LACRIMATION | 1 | 1 | 1 | 1 | 1 | |
| SALIVATION | 1 | 1 | 1 | 1 | 1 | |
| PILOERECTION | 0 | 0 | 0 | 0 | 0 | |
| ABNORMAL RESPIRATION | 0 | 0 | 0 | 0 | 0 | |
| APPEARANCE | 1 | 1 | 1 | 1 | 1 | |
| VISUAL REACTION | 2 | 2 | 2 | 2 | 2 | |
| TACTILE REACTION | 2 | 2 | 2 | 2 | 2 | |
| AUDITORY REACTION | 3 | 3 | 3 | 3 | 3 | |
| TAIL-PINCH REACTION | 2 | 2 | 2 | 2 | 2 | |
| VISUAL PLACING RESPONSE | 1 | 1 | 1 | 1 | 1 | |
| AIR RIGHTING RESPONSE | 1 | 1 | 1 | 1 | 1 | |
| PUPIL RESPONSE TO LIGHT | 1 | 1 | 1 | 1 | 1 | |
| FORELIMB GRIP TEST #1 | 205 | 395 | 315 | 380 | 195 | |
| FORELIMB GRIP TEST #2 | 270 | 575 | 410 | 400 | 365 | |
| HINDLIMB GRIP TEST #1 | 285 | 560 | 405 | 390 | 310 | |
| HINDLIMB GRIP TEST #2 | 360 | 465 | 480 | 345 | 230 | |
| LANDING FOOT SPLAY #1 | 7.2 | 7.2 | 9.9 | 7.0 | 8.1 | |
| LANDING FOOT SPLAY #2 | 7.1 | 7.4 | 9.7 | 6.5 | 9.3 | |
| BODY WEIGHT (G) | 415 | 488 | 432 | 430 | 428 | |

VALUES ARE THE QUANTITY, CATEGORY NUMBER, QUANTAL RESPONSE OR SCORE RECORDED FOR EACH ITEM IN THE BATTERY.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B22 (PAGE 4): FUNCTIONAL OBSERVATIONAL BATTERY - INDIVIDUAL DATA - MALE RATS

| DOSAGE GROUP IV | | 250 MG/KG/DAY | | | | |
|----------------------------|-------|---------------|-------|-------|-------|--|
| RAT # | 17606 | 17609 | 17612 | 17614 | 17617 | |
| HOME CAGE BEHAVIOR | 2 | 2 | 2 | 2 | 2 | |
| ALTERATIONS (HOME CAGE) | 1 | 1 | 1 | 1 | 1 | |
| REACTION TO REMOVAL | 1 | 1 | 1 | 1 | 1 | |
| REACTION TO HANDLING | 1 | 1 | 1 | 1 | 1 | |
| REARS IN OPEN FIELD | 13 | 19 | 12 | 9 | 0 | |
| DEFECATION IN OPEN FIELD | 1 | 2 | 1 | 1 | 3 | |
| URINATION IN OPEN FIELD | 2 | 1 | 1 | 1 | 2 | |
| LEVEL OF AROUSAL | 3 | 3 | 3 | 3 | 3 | |
| ALTERATIONS (OPEN FIELD) | 1 | 1 | 1 | 1 | 1 | |
| GAIT PATTERN | 1 | 1 | 1 | 1 | 1 | |
| GAIT ABNORMALITY, SEVERITY | 1 | 1 | 1 | 1 | 1 | |
| PALPEBRAL CLOSURE | 1 | 1 | 1 | 1 | 1 | |
| PROMINENCE OF THE EYE | 1 | 1 | 1 | 1 | 1 | |
| LACRIMATION | 1 | 1 | 1 | 1 | 1 | |
| SALIVATION | 1 | 1 | 1 | 1 | 1 | |
| PILOERECTION | 0 | 0 | 0 | 0 | 0 | |
| ABNORMAL RESPIRATION | 0 | 0 | 0 | 0 | 0 | |
| APPEARANCE | 1 | 1 | 1 | 1a | 1 | |
| VISUAL REACTION | 2 | 2 | 2 | 2 | 2 | |
| TACTILE REACTION | 2 | 2 | 2 | 2 | 2 | |
| AUDITORY REACTION | 3 | 3 | 3 | 3 | 3 | |
| TAIL-PINCH REACTION | 2 | 2 | 2 | 2 | 2 | |
| VISUAL PLACING RESPONSE | 1 | 1 | 1 | 1 | 1 | |
| AIR RIGHTING RESPONSE | 1 | 1 | 1 | 1 | 1 | |
| PUPIL RESPONSE TO LIGHT | 1 | 1 | 1 | 1 | 1 | |
| FORELIMB GRIP TEST #1 | 210 | 275 | 400 | 170 | 285 | |
| FORELIMB GRIP TEST #2 | 200 | 310 | 465 | 140 | 310 | |
| HINDLIMB GRIP TEST #1 | 190 | 385 | 400 | 180 | 290 | |
| HINDLIMB GRIP TEST #2 | 410 | 405 | 460 | 205 | 225 | |
| LANDING FOOT SPLAY #1 | 8.0 | 7.6 | 6.6 | 6.9 | 8.7 | |
| LANDING FOOT SPLAY #2 | 10.2 | 7.8 | 6.5 | 6.7 | 10.0 | |
| BODY WEIGHT (G) | 410 | 434 | 411 | 436 | 421 | |

VALUES ARE THE QUANTITY, CATEGORY NUMBER, QUANTAL RESPONSE OR SCORE RECORDED FOR EACH ITEM IN THE BATTERY.

a. Chromorhinorrhea.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B23 (PAGE 1): MOTOR ACTIVITY - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP I | 0 (VEHICLE) MG/KG/DAY | | | | |
|---------------------|-----------------------|-------|-------|-------|-------|
| RAT NUMBER | 17601 | 17602 | 17603 | 17604 | 17607 |
| DAY 86 | | | | | |
| NUMBER OF MOVEMENTS | | | | | |
| BLOCK 1 | 76 | 58 | 75 | 54 | 64 |
| BLOCK 2 | 79 | 70 | 81 | 65 | 65 |
| BLOCK 3 | 72 | 63 | 70 | 70 | 74 |
| BLOCK 4 | 63 | 33 | 76 | 74 | 44 |
| BLOCK 5 | 36 | 0 | 7 | 74 | 32 |
| BLOCK 6 | 1 | 6 | 41 | 72 | 36 |
| BLOCK 7 | 0 | 2 | 79 | 62 | 32 |
| BLOCK 8 | 2 | 55 | 72 | 61 | 34 |
| BLOCK 9 | 0 | 81 | 6 | 57 | 31 |
| BLOCK 10 | 0 | 26 | 9 | 57 | 2 |
| BLOCK 11 | 28 | 4 | 3 | 64 | 1 |
| BLOCK 12 | 77 | 1 | 6 | 71 | 4 |
| BLOCK 13 | 67 | 3 | 7 | 53 | 0 |
| BLOCK 14 | 9 | 2 | 3 | 60 | 0 |
| BLOCK 15 | 0 | 0 | 6 | 50 | 0 |
| BLOCK 16 | 4 | 2 | 14 | 54 | 0 |
| BLOCK 17 | 3 | 1 | 5 | 60 | 0 |
| BLOCK 18 | 1 | 0 | 6 | 55 | 0 |
| TOTAL | 518 | 407 | 566 | 1113 | 419 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B23 (PAGE 2): MOTOR ACTIVITY - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP I | 0 (VEHICLE) MG/KG/DAY | | | | |
|----------------------------------|-----------------------|-------|-------|-------|-------|
| RAT NUMBER | 17601 | 17602 | 17603 | 17604 | 17607 |
| DAY 86 | | | | | |
| TIME (SECONDS) SPENT IN MOVEMENT | | | | | |
| BLOCK 1 | 186 | 196 | 147 | 169 | 195 |
| BLOCK 2 | 161 | 149 | 180 | 168 | 196 |
| BLOCK 3 | 79 | 146 | 120 | 180 | 179 |
| BLOCK 4 | 84 | 54 | 104 | 78 | 69 |
| BLOCK 5 | 33 | 0 | 9 | 136 | 31 |
| BLOCK 6 | 0 | 2 | 53 | 154 | 46 |
| BLOCK 7 | 0 | 0 | 107 | 86 | 33 |
| BLOCK 8 | 0 | 85 | 88 | 109 | 42 |
| BLOCK 9 | 0 | 123 | 1 | 114 | 44 |
| BLOCK 10 | 0 | 25 | 3 | 110 | 1 |
| BLOCK 11 | 45 | 8 | 1 | 99 | 0 |
| BLOCK 12 | 103 | 0 | 2 | 91 | 2 |
| BLOCK 13 | 101 | 0 | 5 | 72 | 0 |
| BLOCK 14 | 7 | 1 | 0 | 113 | 0 |
| BLOCK 15 | 0 | 0 | 0 | 102 | 0 |
| BLOCK 16 | 2 | 0 | 7 | 100 | 0 |
| BLOCK 17 | 0 | 0 | 2 | 84 | 0 |
| BLOCK 18 | 0 | 0 | 2 | 72 | 0 |
| TOTAL | 801 | 789 | 831 | 2037 | 838 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B23 (PAGE 3): MOTOR ACTIVITY - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP II | 10 MG/KG/DAY | | | | |
|---------------------|--------------|-------|-------|-------|-------|
| RAT NUMBER | 17615 | 17616 | 17624 | 17626 | 17632 |
| DAY 86 | | | | | |
| NUMBER OF MOVEMENTS | | | | | |
| BLOCK 1 | 52 | 66 | 78 | 65 | 74 |
| BLOCK 2 | 59 | 76 | 77 | 58 | 69 |
| BLOCK 3 | 57 | 91 | 75 | 54 | 75 |
| BLOCK 4 | 48 | 74 | 73 | 45 | 72 |
| BLOCK 5 | 31 | 85 | 70 | 63 | 68 |
| BLOCK 6 | 0 | 81 | 59 | 67 | 51 |
| BLOCK 7 | 0 | 71 | 27 | 64 | 45 |
| BLOCK 8 | 0 | 64 | 50 | 50 | 87 |
| BLOCK 9 | 0 | 43 | 55 | 55 | 54 |
| BLOCK 10 | 1 | 72 | 9 | 48 | 52 |
| BLOCK 11 | 0 | 27 | 30 | 60 | 48 |
| BLOCK 12 | 2 | 44 | 17 | 14 | 46 |
| BLOCK 13 | 0 | 65 | 0 | 5 | 44 |
| BLOCK 14 | 0 | 58 | 0 | 44 | 34 |
| BLOCK 15 | 0 | 37 | 0 | 52 | 4 |
| BLOCK 16 | 2 | 6 | 0 | 41 | 41 |
| BLOCK 17 | 1 | 3 | 0 | 13 | 7 |
| BLOCK 18 | 0 | 5 | 12 | 0 | 2 |
| TOTAL | 253 | 968 | 632 | 798 | 873 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B23 (PAGE 4): MOTOR ACTIVITY - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP II | | 10 MG/KG/DAY | | | | |
|----------------------------------|-------|--------------|-------|-------|-------|--|
| RAT NUMBER | 17615 | 17616 | 17624 | 17626 | 17632 | |
| DAY 86 | | | | | | |
| TIME (SECONDS) SPENT IN MOVEMENT | | | | | | |
| BLOCK 1 | 233 | 196 | 195 | 196 | 204 | |
| BLOCK 2 | 182 | 154 | 164 | 170 | 167 | |
| BLOCK 3 | 135 | 169 | 160 | 120 | 117 | |
| BLOCK 4 | 85 | 122 | 94 | 79 | 129 | |
| BLOCK 5 | 45 | 136 | 127 | 123 | 76 | |
| BLOCK 6 | 0 | 107 | 78 | 119 | 123 | |
| BLOCK 7 | 0 | 143 | 12 | 112 | 65 | |
| BLOCK 8 | 0 | 94 | 55 | 73 | 130 | |
| BLOCK 9 | 0 | 86 | 77 | 127 | 85 | |
| BLOCK 10 | 0 | 74 | 7 | 74 | 80 | |
| BLOCK 11 | 0 | 28 | 20 | 93 | 59 | |
| BLOCK 12 | 1 | 68 | 15 | 15 | 80 | |
| BLOCK 13 | 0 | 91 | 0 | 9 | 50 | |
| BLOCK 14 | 0 | 66 | 0 | 42 | 31 | |
| BLOCK 15 | 0 | 29 | 0 | 69 | 3 | |
| BLOCK 16 | 1 | 5 | 0 | 70 | 35 | |
| BLOCK 17 | 0 | 0 | 0 | 14 | 6 | |
| BLOCK 18 | 0 | 3 | 10 | 0 | 0 | |
| TOTAL | 682 | 1571 | 1014 | 1505 | 1440 | |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B23 (PAGE 5): MOTOR ACTIVITY - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP III | 50 MG/KG/DAY | | | | |
|---------------------|--------------|-------|-------|-------|-------|
| RAT NUMBER | 17605 | 17610 | 17611 | 17613 | 17619 |
| DAY 86 | | | | | |
| NUMBER OF MOVEMENTS | | | | | |
| BLOCK 1 | 66 | 64 | 63 | 69 | 58 |
| BLOCK 2 | 67 | 37 | 64 | 75 | 73 |
| BLOCK 3 | 64 | 51 | 81 | 63 | 75 |
| BLOCK 4 | 70 | 40 | 43 | 50 | 70 |
| BLOCK 5 | 69 | 22 | 0 | 52 | 71 |
| BLOCK 6 | 41 | 0 | 11 | 28 | 62 |
| BLOCK 7 | 41 | 2 | 1 | 2 | 66 |
| BLOCK 8 | 2 | 52 | 29 | 3 | 41 |
| BLOCK 9 | 4 | 34 | 43 | 2 | 78 |
| BLOCK 10 | 1 | 68 | 66 | 48 | 39 |
| BLOCK 11 | 0 | 40 | 80 | 48 | 11 |
| BLOCK 12 | 0 | 37 | 51 | 1 | 23 |
| BLOCK 13 | 1 | 31 | 63 | 0 | 2 |
| BLOCK 14 | 0 | 55 | 34 | 0 | 10 |
| BLOCK 15 | 5 | 57 | 14 | 1 | 0 |
| BLOCK 16 | 54 | 31 | 11 | 0 | 14 |
| BLOCK 17 | 14 | 53 | 0 | 0 | 0 |
| BLOCK 18 | 1 | 34 | 0 | 2 | 1 |
| TOTAL | 500 | 708 | 654 | 444 | 694 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B23 (PAGE 6): MOTOR ACTIVITY - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP III | | 50 MG/KG/DAY | | | | |
|----------------------------------|-------|--------------|-------|-------|-------|--|
| RAT NUMBER | 17605 | 17610 | 17611 | 17613 | 17619 | |
| DAY 86 | | | | | | |
| TIME (SECONDS) SPENT IN MOVEMENT | | | | | | |
| BLOCK 1 | 177 | 181 | 221 | 190 | 173 | |
| BLOCK 2 | 119 | 134 | 166 | 164 | 92 | |
| BLOCK 3 | 144 | 98 | 135 | 135 | 105 | |
| BLOCK 4 | 145 | 88 | 67 | 88 | 120 | |
| BLOCK 5 | 108 | 25 | 0 | 64 | 84 | |
| BLOCK 6 | 59 | 0 | 8 | 39 | 60 | |
| BLOCK 7 | 54 | 0 | 0 | 0 | 113 | |
| BLOCK 8 | 0 | 71 | 17 | 0 | 46 | |
| BLOCK 9 | 6 | 35 | 53 | 0 | 97 | |
| BLOCK 10 | 0 | 112 | 137 | 77 | 37 | |
| BLOCK 11 | 0 | 71 | 160 | 64 | 7 | |
| BLOCK 12 | 0 | 66 | 39 | 0 | 26 | |
| BLOCK 13 | 0 | 40 | 68 | 0 | 1 | |
| BLOCK 14 | 0 | 71 | 36 | 0 | 6 | |
| BLOCK 15 | 4 | 81 | 12 | 0 | 0 | |
| BLOCK 16 | 58 | 56 | 4 | 0 | 14 | |
| BLOCK 17 | 16 | 84 | 0 | 0 | 0 | |
| BLOCK 18 | 0 | 59 | 0 | 1 | 1 | |
| TOTAL | 890 | 1272 | 1123 | 822 | 982 | |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B23 (PAGE 7): MOTOR ACTIVITY - INDIVIDUAL DATA - F0 GENERATION MALE RATS

| DOSAGE GROUP IV | 250 MG/KG/DAY | | | | |
|---------------------|---------------|-------|-------|-------|-------|
| RAT NUMBER | 17606 | 17609 | 17612 | 17614 | 17617 |
| DAY 86 | | | | | |
| NUMBER OF MOVEMENTS | | | | | |
| BLOCK 1 | 61 | 60 | 65 | 72 | 70 |
| BLOCK 2 | 70 | 54 | 76 | 88 | 73 |
| BLOCK 3 | 48 | 64 | 63 | 73 | 62 |
| BLOCK 4 | 54 | 60 | 48 | 73 | 71 |
| BLOCK 5 | 1 | 52 | 1 | 12 | 62 |
| BLOCK 6 | 2 | 6 | 0 | 18 | 54 |
| BLOCK 7 | 3 | 1 | 0 | 1 | 49 |
| BLOCK 8 | 1 | 8 | 1 | 0 | 31 |
| BLOCK 9 | 0 | 2 | 0 | 1 | 4 |
| BLOCK 10 | 2 | 0 | 48 | 0 | 4 |
| BLOCK 11 | 1 | 32 | 47 | 50 | 0 |
| BLOCK 12 | 3 | 56 | 1 | 50 | 3 |
| BLOCK 13 | 4 | 20 | 0 | 9 | 4 |
| BLOCK 14 | 1 | 1 | 1 | 16 | 0 |
| BLOCK 15 | 10 | 0 | 1 | 29 | 0 |
| BLOCK 16 | 57 | 2 | 0 | 20 | 2 |
| BLOCK 17 | 1 | 0 | 0 | 16 | 2 |
| BLOCK 18 | 1 | 5 | 0 | 11 | 0 |
| TOTAL | 320 | 423 | 352 | 539 | 491 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE B23 (PAGE 8): MOTOR ACTIVITY - INDIVIDUAL DATA - F₀ GENERATION MALE RATS

| DOSAGE GROUP IV | 250 MG/KG/DAY | | | | |
|----------------------------------|---------------|-------|-------|-------|-------|
| RAT NUMBER | 17606 | 17609 | 17612 | 17614 | 17617 |
| DAY 86 | | | | | |
| TIME (SECONDS) SPENT IN MOVEMENT | | | | | |
| BLOCK 1 | 192 | 197 | 181 | 187 | 141 |
| BLOCK 2 | 163 | 173 | 108 | 180 | 139 |
| BLOCK 3 | 82 | 114 | 95 | 142 | 125 |
| BLOCK 4 | 122 | 146 | 44 | 167 | 67 |
| BLOCK 5 | 0 | 70 | 0 | 14 | 77 |
| BLOCK 6 | 0 | 5 | 0 | 10 | 105 |
| BLOCK 7 | 0 | 0 | 0 | 0 | 68 |
| BLOCK 8 | 0 | 4 | 0 | 0 | 21 |
| BLOCK 9 | 0 | 1 | 0 | 0 | 2 |
| BLOCK 10 | 0 | 0 | 64 | 0 | 7 |
| BLOCK 11 | 0 | 33 | 79 | 52 | 0 |
| BLOCK 12 | 1 | 92 | 0 | 60 | 0 |
| BLOCK 13 | 1 | 19 | 0 | 8 | 1 |
| BLOCK 14 | 0 | 0 | 0 | 11 | 0 |
| BLOCK 15 | 7 | 0 | 0 | 26 | 0 |
| BLOCK 16 | 89 | 0 | 0 | 51 | 0 |
| BLOCK 17 | 0 | 0 | 0 | 20 | 0 |
| BLOCK 18 | 0 | 0 | 0 | 6 | 0 |
| TOTAL | 657 | 854 | 571 | 934 | 753 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

APPENDIX C

REPORT TABLES - F₀ GENERATION FEMALE RATS

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP | I | II | III | IV |
|---|-------------|---------|---------|---------|
| DOSAGE (MG/KG/DAY) | 0 (VEHICLE) | 10 | 50 | 250 |
| MORTALITY | 0 | 0 | 0 | 0 |
| <u>PRECOHABITATION (DAY 1 OF STUDY TO THE DAY OF COHABITATION):</u> | | | | |
| MAXIMUM POSSIBLE INCIDENCE | 225/ 15 | 225/ 15 | 225/ 15 | 225/ 15 |
| RED, SLIGHT PERIORAL SUBSTANCE | 1/ 1 | 0/ 0 | 0/ 0 | 3/ 3 |
| EXCESS SALIVATION | 1/ 1 | 0/ 0 | 0/ 0 | 4/ 2 |
| TAIL BENT | 0/ 0 | 0/ 0 | 0/ 0 | 13/ 1 |
| CHROMODACRYORRHEA | 1/ 1 | 0/ 0 | 0/ 0 | 1/ 1 |
| RIGHT EYE: CORNEAL OPACITY | 0/ 0 | 0/ 0 | 12/ 1 | 0/ 0 |
| LOCALIZED ALOPECIA: LIMBS | 9/ 2 | 1/ 1 | 0/ 0 | 0/ 0 |

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
 MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
 N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C1 (PAGE 2): CLINICAL OBSERVATIONS - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | I 0 (VEHICLE) | II 10 | III 50 | IV 250 |
|--|------------------|----------|-----------|-----------|
| MORTALITY | 0 | 0 | 0 | 0 |
| <u>PRESUMED GESTATION: a</u> | | | | |
| MAXIMUM POSSIBLE INCIDENCE | 330/ 15 | 335/ 15 | 331/ 15 | 316/ 14 |
| EXCESS SALIVATION | 0/ 0 | 0/ 0 | 0/ 0 | 25/ 7** |
| RED, SLIGHT OR MODERATE PERIORAL SUBSTANCE | 0/ 0 | 0/ 0 | 0/ 0 | 16/ 6** |
| LOCALIZED ALOPECIA: TOTAL | 43/ 2 | 40/ 3 | 26/ 2 | 41/ 3 |
| LIMBS | 43/ 2 | 40/ 3 | 26/ 2 | 38/ 2 |
| UNDERSIDE | 0/ 0 | 0/ 0 | 0/ 0 | 4/ 1 |
| HEAD | 0/ 0 | 0/ 0 | 0/ 0 | 3/ 1 |
| URINE-STAINED ABDOMINAL FUR | 0/ 0 | 0/ 0 | 0/ 0 | 12/ 2 |
| TAIL BENT | 0/ 0 | 0/ 0 | 0/ 0 | 22/ 1 |
| RED PERIVAGINAL SUBSTANCE | 0/ 0 | 0/ 0 | 0/ 0 | 1/ 1 |
| CHROMODACRYORRHEA | 0/ 0 | 0/ 0 | 2/ 1 | 0/ 0 |
| INCISORS: MISSING/BROKEN | 0/ 0 | 1/ 1 | 0/ 0 | 0/ 0 |
| SOFT OR LIQUID FECES | 0/ 0 | 1/ 1 | 0/ 0 | 0/ 0 |

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
 MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
 N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.

a. Restricted to rats with a confirmed mating date.

** Significantly different from the vehicle control group value ($p \leq 0.01$).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C1 (PAGE 3): CLINICAL OBSERVATIONS - SUMMARY - P₀ GENERATION FEMALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | I 0 (VEHICLE) | II 10 | III 50 | IV 250 |
|------------------------------------|------------------|----------|-----------|-----------|
| MORTALITY | 0 | 0 | 0 | 0 |
| <u>LACTATION:</u> | | | | |
| MAXIMUM POSSIBLE INCIDENCE | 90/ 15 | 84/ 14 | 90/ 15 | 70/ 13 |
| LOCALIZED ALOPECIA: TOTAL | 12/ 2 | 13/ 3 | 12/ 2 | 7/ 2 |
| LIMBS | 12/ 2 | 13/ 3 | 12/ 2 | 7/ 2 |
| UNDERSIDE | 0/ 0 | 0/ 0 | 0/ 0 | 6/ 1 |
| EXCESS SALIVATION | 0/ 0 | 0/ 0 | 0/ 0 | 4/ 2 |
| TAIL BENT | 0/ 0 | 0/ 0 | 0/ 0 | 6/ 1 |
| DEHYDRATION | 0/ 0 | 0/ 0 | 0/ 0 | 1/ 1 |

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RATS WITH OBSERVATIONS.
 MAXIMUM POSSIBLE INCIDENCE = (DAYS x RATS)/NUMBER OF RATS EXAMINED PER GROUP.
 N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RATS WITH OBSERVATION.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C2 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|------------------------|---|-------------|----|-----|-----|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS EXAMINED a | N | 15 | 15 | 15 | 15 |
| MORTALITY | N | 0 | 0 | 0 | 0 |
| APPEARED NORMAL | N | 15 | 15 | 14 | 14 |
| KIDNEYS: RIGHT, ABSENT | N | 0 | 0 | 1 | 0 |
| THYMUS: SMALL | N | 0 | 0 | 0 | 1 |

a. Refer to the individual clinical observations table (Table C27) for external observations confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C3 (PAGE 1): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS - SUMMARY - F0 GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------|-----------|---------------|---------------|---------------|----------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| PREGNANT | N | 15 | 14 | 15 | 13 |
| INCLUDED IN ANALYSES | N | 15 | 14 | 15 | 11a |
| TERMINAL BODY WEIGHT | MEAN±S.D. | 299.1 ± 24.7 | 304.0 ± 18.9 | 296.0 ± 25.0 | 284.8 ± 11.1 |
| BRAIN | MEAN±S.D. | 2.20 ± 0.08 | 2.19 ± 0.07 | 2.19 ± 0.07 | 2.20 ± 0.08 |
| | | [10]b | [10]b | [10]b | [9]b |
| LIVER | MEAN±S.D. | 11.22 ± 1.26 | 11.81 ± 1.50 | 11.66 ± 1.28 | 13.56 ± 0.89** |
| KIDNEY LEFT | MEAN±S.D. | 1.20 ± 0.13 | 1.29 ± 0.14 | 1.31 ± 0.32 | 1.23 ± 0.08 |
| | | [10]b | [10]b | [10]b | [9]b |
| KIDNEY RIGHT | MEAN±S.D. | 1.20 ± 0.13 | 1.31 ± 0.10 | 1.27 ± 0.14 | 1.27 ± 0.08 |
| | | [10]b | [10]b | [9]b,c | [9]b |
| ADRENAL LEFT | MEAN±S.D. | 0.042 ± 0.004 | 0.046 ± 0.008 | 0.041 ± 0.008 | 0.045 ± 0.008 |
| | | [10]b | [10]b | [10]b | [9]b |
| ADRENAL RIGHT | MEAN±S.D. | 0.041 ± 0.006 | 0.043 ± 0.006 | 0.038 ± 0.008 | 0.040 ± 0.006 |
| | | [10]b | [10]b | [10]b | [9]b |
| SPLEEN | MEAN±S.D. | 0.70 ± 0.06 | 0.74 ± 0.14 | 0.76 ± 0.10 | 0.64 ± 0.09 |
| | | [10]b | [10]b | [10]b | [9]b |
| THYMUS | MEAN±S.D. | 0.27 ± 0.07 | 0.34 ± 0.07 | 0.29 ± 0.07 | 0.22 ± 0.05 |
| | | [10]b | [10]b | [10]b | [9]b |
| OVARY LEFT | MEAN±S.D. | 0.080 ± 0.017 | 0.079 ± 0.012 | 0.079 ± 0.015 | 0.076 ± 0.010 |
| OVARY RIGHT | MEAN±S.D. | 0.081 ± 0.014 | 0.083 ± 0.013 | 0.084 ± 0.015 | 0.080 ± 0.014 |
| UTERUS WITH CERVIX | MEAN±S.D. | 0.80 ± 0.11 | 0.79 ± 0.10 | 0.78 ± 0.09 | 0.70 ± 0.06 |
| HEART | MEAN±S.D. | 1.08 ± 0.11 | 1.15 ± 0.08 | 1.11 ± 0.14 | 1.00 ± 0.12 |
| | | [10]b | [10]b | [10]b | [9]b |

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dams that were sacrificed due to no surviving pups.

b. Results did not warrant examination of the five additional rats.

c. Excludes rat 17706, which had an absent right kidney.

** Significantly different from the vehicle control group value ($p \leq 0.01$).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C4 (PAGE 1): RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - SUMMARY - F0 GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------|-----------|----------------|----------------|----------------|-----------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| PREGNANT | N | 15 | 14 | 15 | 13 |
| INCLUDED IN ANALYSES | N | 15 | 14 | 15 | 11a |
| TERMINAL BODY WEIGHT | MEAN±S.D. | 299.1 ± 24.7 | 304.0 ± 18.9 | 296.0 ± 25.0 | 284.8 ± 11.1 |
| BRAIN | MEAN±S.D. | 0.733 ± 0.059 | 0.706 ± 0.029 | 0.728 ± 0.065 | 0.778 ± 0.040 |
| | | [10]b | [10]b | [10]b | [9]b |
| LIVER | MEAN±S.D. | 3.753 ± 0.336 | 3.871 ± 0.318 | 3.935 ± 0.233 | 4.763 ± 0.284** |
| KIDNEY LEFT | MEAN±S.D. | 0.397 ± 0.029 | 0.416 ± 0.042 | 0.432 ± 0.096 | 0.434 ± 0.034 |
| | | [10]b | [10]b | [10]b | [9]b |
| KIDNEY RIGHT | MEAN±S.D. | 0.400 ± 0.036 | 0.421 ± 0.031 | 0.421 ± 0.042 | 0.449 ± 0.035** |
| | | [10]b | [10]b | [9]b,d | [9]b |
| ADRENAL LEFT c | MEAN±S.D. | 13.994 ± 2.004 | 14.906 ± 2.273 | 13.476 ± 1.549 | 15.943 ± 3.030 |
| | | [10]b | [10]b | [10]b | [9]b |
| ADRENAL RIGHT c | MEAN±S.D. | 13.767 ± 2.449 | 13.951 ± 1.699 | 12.481 ± 1.930 | 14.297 ± 2.379 |
| | | [10]b | [10]b | [10]b | [9]b |
| SPLEEN | MEAN±S.D. | 0.234 ± 0.021 | 0.236 ± 0.037 | 0.255 ± 0.047 | 0.227 ± 0.031 |
| | | [10]b | [10]b | [10]b | [9]b |
| THYMUS | MEAN±S.D. | 0.092 ± 0.019 | 0.107 ± 0.019 | 0.094 ± 0.020 | 0.076 ± 0.019 |
| | | [10]b | [10]b | [10]b | [9]b |
| OVARY LEFT c | MEAN±S.D. | 26.915 ± 6.046 | 25.976 ± 4.034 | 26.551 ± 3.476 | 26.802 ± 3.440 |
| OVARY RIGHT c | MEAN±S.D. | 27.215 ± 4.339 | 27.123 ± 3.255 | 28.301 ± 4.894 | 28.246 ± 4.797 |
| UTERUS WITH CERVIX | MEAN±S.D. | 0.267 ± 0.034 | 0.258 ± 0.035 | 0.263 ± 0.028 | 0.246 ± 0.025 |
| HEART | MEAN±S.D. | 0.361 ± 0.019 | 0.371 ± 0.026 | 0.366 ± 0.036 | 0.354 ± 0.034 |
| | | [10]b | [10]b | [10]b | [9]b |

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

RATIOS (%) = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dams that were sacrificed due to no surviving pups.

b. Results did not warrant examination of the five additional rats.

c. Value was multiplied by 1000.

d. Excludes rat 17706, which had an absent right kidney.

** Significantly different from the vehicle control group value (p<0.01).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C5 (PAGE 1): RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------|-----------|----------------|-----------------|-----------------------|------------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 10 | 10 | 10 | 12 |
| PREGNANT | N | 10 | 10 | 10 | 11 |
| INCLUDED IN ANALYSES | N | 10 | 10 | 10 | 9a |
| BRAIN WEIGHT | MEAN±S.D. | 2.20 ± 0.08 | 2.19 ± 0.07 | 2.19 ± 0.07 | 2.20 ± 0.08 |
| LIVER | MEAN±S.D. | 521.53 ± 59.00 | 564.65 ± 40.68* | 547.24 ± 48.14 | 616.82 ± 35.48** |
| KIDNEY LEFT | MEAN±S.D. | 54.44 ± 5.35 | 59.07 ± 5.87 | 59.77 ± 14.09 | 55.99 ± 2.45 |
| KIDNEY RIGHT | MEAN±S.D. | 54.59 ± 5.44 | 59.89 ± 4.34 | 58.08 ± 6.21 [9]b | 57.96 ± 3.10 |
| ADRENAL LEFT | MEAN±S.D. | 1.90 ± 0.20 | 2.11 ± 0.34 | 1.88 ± 0.36 | 2.04 ± 0.34 |
| ADRENAL RIGHT | MEAN±S.D. | 1.88 ± 0.29 | 1.98 ± 0.28 | 1.74 ± 0.38 | 1.83 ± 0.27 |
| SPLEEN | MEAN±S.D. | 32.11 ± 3.12 | 33.76 ± 6.06 | 34.92 ± 4.73 | 29.17 ± 3.90 |
| THYMUS | MEAN±S.D. | 12.42 ± 3.30 | 15.40 ± 2.84 | 13.18 ± 3.13 | 9.85 ± 2.66 |
| OVARY LEFT | MEAN±S.D. | 3.69 ± 0.86 | 3.66 ± 0.59 | 3.82 ± 0.73 | 3.42 ± 0.44 |
| OVARY RIGHT | MEAN±S.D. | 3.75 ± 0.77 | 3.94 ± 0.42 | 3.95 ± 0.67 | 3.63 ± 0.73 |
| UTERUS WITH CERVIX | MEAN±S.D. | 36.63 ± 5.32 | 36.42 ± 4.93 | 36.07 ± 2.57 | 32.66 ± 2.24 |
| HEART | MEAN±S.D. | 49.34 ± 4.16 | 52.51 ± 3.48 | 50.74 ± 6.49 | 45.77 ± 5.51 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

RATIOS (%) = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dams that were sacrificed due to no surviving pups.

b. Excludes rat 17706, which had an absent right kidney.

* Significantly different from the vehicle control group value ($p \leq 0.05$).

** Significantly different from the vehicle control group value ($p \leq 0.01$).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C6 (PAGE 1): HEMATOLOGY - SUMMARY - F0 GENERATION FEMALE RATS
(See last page of this table for abbreviations)

| DOSAGE GROUP | | I | II | III | IV |
|----------------------|-----------|--------------|----------------------|----------------------|--------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 5 | 5 | 6 | 4 |
| INCLUDED IN ANALYSES | N | 4a | 5 | 6 | 4 |
| WBC (THSN/CU MM) | MEAN±S.D. | 20.2 ± 2.70 | 14.9 ± 1.92 | 20.2 ± 2.71 | 21.6 ± 2.83 |
| RBC (MILL/CU MM) | MEAN±S.D. | 5.86 ± 0.466 | 6.00 ± 0.246 | 5.77 ± 0.578 | 5.76 ± 0.371 |
| HGB (GRAMS/DL) | MEAN±S.D. | 13.9 ± 0.61 | 14.3 ± 0.46 | 13.7 ± 0.78 | 13.2 ± 0.68 |
| HCT (%) | MEAN±S.D. | 36.8 ± 1.61 | 38.2 ± 1.08 | 36.3 ± 2.88 | 34.1 ± 2.46 |
| MCV (CU MICRONS) | MEAN±S.D. | 63.0 ± 2.88 | 63.6 ± 2.77 | 63.0 ± 1.87 | 59.2 ± 1.38 |
| MCH (PICO GRAMS) | MEAN±S.D. | 23.8 ± 1.21 | 23.8 ± 1.08 | 23.8 ± 1.26 | 22.9 ± 0.46 |
| MCHC (%) | MEAN±S.D. | 37.8 ± 0.72 | 37.4 ± 0.17 | 37.8 ± 1.01 | 38.7 ± 1.36 |
| PLAT (THSN/CU MM) | MEAN±S.D. | 1534 ± 140.4 | 947 ± 531.0 | 1598 ± 423.9 | 1547 ± 236.6 |
| PT (SECONDS) | MEAN±S.D. | 13.3 ± 0.40 | 13.3 ± 0.34 [4]a | 13.2 ± 0.16 [5]a | 13.2 ± 0.22 |
| APTT (SECONDS) | MEAN±S.D. | 21.2 ± 2.32 | 18.2 ± 1.95 | 22.0 ± 3.70 | 19.8 ± 4.39 |

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for rats that had clotted samples.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C6 (PAGE 2): HEMATOLOGY - SUMMARY - Fo GENERATION FEMALE RATS
(See last page of this table for abbreviations)

| DOSAGE GROUP | | I | II | III | IV |
|-------------------------|-----------|-------------|---------------------|---------------------|-------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 5 | 5 | 6 | 4 |
| INCLUDED IN ANALYSES | N | 4a | 5 | 6 | 4 |
| MPV (CU MICRONS) | MEAN±S.D. | 7.7 ± 0.91 | 8.8 ± 2.08 [4]a | 8.0 ± 1.02 [5]a | 8.2 ± 0.58 |
| NRBC COUNT | MEAN±S.D. | 0 ± 0.0 | 0 ± 0.0 | 0 ± 0.0 | 0 ± 0.0 |
| Lymphocyte (THSN/CU MM) | MEAN±S.D. | 15.9 ± 1.81 | 12.6 ± 2.28 | 15.5 ± 2.48 | 16.4 ± 4.17 |
| Segmented (THSN/CU MM) | MEAN±S.D. | 3.9 ± 1.38 | 2.0 ± 0.76 | 4.4 ± 1.54 | 4.1 ± 1.95 |
| Bands (THSN/CU MM) | MEAN±S.D. | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.1 ± 0.12 |
| Monocytes (THSN/CU MM) | MEAN±S.D. | 0.3 ± 0.34 | 0.2 ± 0.16 | 0.2 ± 0.27 | 0.9 ± 0.56 |
| Eosinophil (THSN/CU MM) | MEAN±S.D. | 0.1 ± 0.12 | 0.0 ± 0.00 | 0.1 ± 0.17 | 0.0 ± 0.00 |
| Basophils (THSN/CU MM) | MEAN±S.D. | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 |
| Abnormal L (THSN/CU MM) | MEAN±S.D. | 0.1 ± 0.10 | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.1 ± 0.15 |
| Other (THSN/CU MM) | MEAN±S.D. | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 | 0.0 ± 0.00 |

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for rats that had clotted samples.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C6 (PAGE 3): HEMATOLOGY - SUMMARY - Fo GENERATION FEMALE RATS

| KEY TO HEMATOLOGY TABLE | |
|-------------------------|---|
| ABBREVIATION | TERMINOLOGY |
| WBC | White Blood Cells (Leukocytes) |
| RBC | Red Blood Cells (Erythrocytes) |
| HGB | Hemoglobin |
| HCT | Hematocrit (Packed Cell Volume) |
| MCV | Mean Corpuscular Volume |
| MCH | Mean Corpuscular Hemoglobin |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| PLAT | Platelets |
| MPV | Mean Platelet Volume |
| PT | Prothrombin Time |
| APTT | Activated Partial Thromboplastin |
| NRBC | Nucleated Red Blood Cell Count |
| Segmented | Segmented Neutrophils |
| Abnormal L | Abnormal Lymphocytes |
| Other | Other Cells |

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TABLE C7 (PAGE 1): CLINICAL CHEMISTRY - SUMMARY - Fo GENERATION FEMALE RATS
(See last page of this table for abbreviations)

| DOSAGE GROUP | | I | II | III | IV |
|--------------------|-----------|-------------|------------|------------|------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 5 | 5 | 6 | 4 |
| TP (G/DL) | MEAN±S.D. | 6.5 ± 0.45 | 6.5 ± 0.61 | 6.2 ± 0.44 | 6.3 ± 0.59 |
| A (G/DL) | MEAN±S.D. | 4.2 ± 0.30 | 4.2 ± 0.25 | 4.1 ± 0.33 | 4.1 ± 0.14 |
| GLU (MG/DL) | MEAN±S.D. | 125 ± 26.9 | 138 ± 6.6 | 124 ± 27.4 | 114 ± 28.1 |
| CHOL (MG/DL) | MEAN±S.D. | 52 ± 11.8 | 61 ± 7.5 | 58 ± 14.5 | 57 ± 12.9 |
| TBILI (MG/DL) | MEAN±S.D. | 0.1 ± 0.05 | 0.1 ± 0.04 | 0.1 ± 0.00 | 0.1 ± 0.05 |
| BUN (MG/DL) | MEAN±S.D. | 20 ± 3.6 | 18 ± 3.3 | 19 ± 3.3 | 21 ± 2.5 |
| CREAT (MG/DL) | MEAN±S.D. | 0.4 ± 0.04 | 0.3 ± 0.09 | 0.3 ± 0.04 | 0.4 ± 0.08 |
| ALT (U/L) | MEAN±S.D. | 60 ± 7.4 | 57 ± 13.0 | 62 ± 13.3 | 94 ± 7.4 |
| AST (U/L) | MEAN±S.D. | 100 ± 9.1 | 94 ± 18.8 | 117 ± 20.0 | 120 ± 23.8 |

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C7 (PAGE 2): CLINICAL CHEMISTRY - SUMMARY - Fo GENERATION FEMALE RATS
(See last page of this table for abbreviations)

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | | I 0 (VEHICLE) | II 10 | III 50 | IV 250 |
|------------------------------------|-----------|------------------|-------------|-------------|-------------|
| RATS TESTED | N | 5 | 5 | 6 | 4 |
| ALK (U/L) | MEAN±S.D. | 63 ± 19.5 | 51 ± 9.5 | 54 ± 23.0 | 87 ± 28.5 |
| CA (MG/DL) | MEAN±S.D. | 11.8 ± 0.37 | 11.7 ± 0.54 | 11.5 ± 0.31 | 11.9 ± 0.66 |
| PHOS (MG/DL) | MEAN±S.D. | 9.3 ± 0.13 | 8.1 ± 0.85 | 8.8 ± 1.54 | 9.5 ± 0.50 |
| TRI (MG/DL) | MEAN±S.D. | 56 ± 12.5 | 57 ± 22.2 | 48 ± 22.2 | 66 ± 10.6 |
| NA (MMOL/L) | MEAN±S.D. | 143 ± 2.1 | 142 ± 1.1 | 143 ± 1.0 | 140 ± 2.1 |
| K (MMOL/L) | MEAN±S.D. | 6.7 ± 0.37 | 6.4 ± 0.74 | 6.7 ± 0.51 | 6.7 ± 0.22 |
| CL (MMOL/L) | MEAN±S.D. | 97 ± 3.0 | 98 ± 1.2 | 101 ± 1.8 | 98 ± 2.9 |
| G (G/DL) | MEAN±S.D. | 2.3 ± 0.19 | 2.4 ± 0.38 | 2.2 ± 0.13 | 2.2 ± 0.46 |
| A/G | MEAN±S.D. | 1.8 ± 0.11 | 1.8 ± 0.20 | 1.9 ± 0.12 | 2.0 ± 0.44 |

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C7 (PAGE 3): CLINICAL CHEMISTRY - SUMMARY - F0 GENERATION FEMALE RATS

KEY TO CLINICAL CHEMISTRY TABLE

| ABBREVIATION | TERMINOLOGY |
|--------------|----------------------------|
| TP | Total Protein |
| A | Albumin |
| GLU | Glucose |
| CHOL | Cholesterol |
| TBILI | Total Bilirubin |
| BUN | Blood Urea Nitrogen |
| CREAT | Creatinine |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| ALK | Alkaline Phosphatase |
| CA | Calcium |
| PHOS | Phosphorus (inorganic) |
| TRI | Triglycerides |
| NA | Sodium |
| K | Potassium |
| CL | Chloride |
| G | Globulin |
| A/G | Albumin/Globulin Ratio |

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C8 (PAGE 1): BODY WEIGHTS - PRECOHABITATION - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|--------------------|-----------|--------------|--------------|--------------|--------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| BODY WEIGHT (G) | | | | | |
| DAY 1 | MEAN±S.D. | 227.2 ± 7.9 | 227.3 ± 7.5 | 226.5 ± 5.9 | 226.5 ± 5.7 |
| DAY 8 | MEAN±S.D. | 248.2 ± 11.8 | 248.8 ± 9.1 | 248.5 ± 12.1 | 242.5 ± 10.0 |
| DAY 15a | MEAN±S.D. | 262.3 ± 14.7 | 262.3 ± 13.5 | 260.7 ± 14.6 | 252.9 ± 12.8 |

DAY = DAY OF STUDY

a. Last value recorded before cohabitation.

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TABLE C9 (PAGE 1): BODY WEIGHT CHANGES - PRECOHABITATION - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|------------------------|-----------|--------------|-------------|--------------|--------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| BODY WEIGHT CHANGE (G) | | | | | |
| DAYS 1 - 8 | MEAN±S.D. | +21.0 ± 6.2 | +21.5 ± 4.4 | +21.9 ± 7.5 | +16.0 ± 6.5* |
| DAYS 8 - 15a | MEAN±S.D. | +14.1 ± 5.2 | +13.5 ± 6.0 | +12.2 ± 5.3 | +10.3 ± 4.1 |
| DAYS 1 - 15a | MEAN±S.D. | +35.1 ± 10.0 | +34.9 ± 8.4 | +34.1 ± 10.4 | +26.3 ± 8.9* |

DAYS = DAYS OF STUDY

a. Last value recorded before cohabitation.

* Significantly different from the vehicle control group value ($p < 0.05$).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C10 (PAGE 1): MATERNAL BODY WEIGHTS - GESTATION - SUMMARY - F0 GENERATION FEMALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | | I 0 (VEHICLE) | II 10 | III 50 | IV 250 |
|------------------------------------|-----------|------------------|--------------|--------------|--------------|
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| PREGNANT | N | 15 | 14 | 15 | 13 |
| MATERNAL BODY WEIGHT (G) | | | | | |
| DAY 0 | MEAN±S.D. | 268.5 ± 13.4 | 272.9 ± 13.0 | 272.1 ± 17.0 | 262.0 ± 16.2 |
| DAY 1 | MEAN±S.D. | 276.3 ± 14.5 | 277.6 ± 14.8 | 276.8 ± 16.8 | 268.2 ± 13.1 |
| DAY 2 | MEAN±S.D. | 281.8 ± 15.5 | 282.7 ± 15.0 | 280.6 ± 17.7 | 272.5 ± 14.2 |
| DAY 3 | MEAN±S.D. | 284.4 ± 15.6 | 286.5 ± 17.4 | 282.5 ± 17.6 | 273.7 ± 14.8 |
| DAY 4 | MEAN±S.D. | 288.0 ± 15.0 | 289.4 ± 15.9 | 287.6 ± 19.0 | 278.3 ± 16.6 |
| DAY 5 | MEAN±S.D. | 292.1 ± 16.4 | 291.9 ± 17.3 | 289.8 ± 18.5 | 280.9 ± 16.4 |
| DAY 6 | MEAN±S.D. | 295.8 ± 17.9 | 295.8 ± 17.7 | 292.0 ± 18.4 | 283.1 ± 15.7 |
| DAY 7 | MEAN±S.D. | 299.7 ± 18.4 | 298.7 ± 16.5 | 296.8 ± 19.3 | 285.5 ± 17.2 |
| DAY 8 | MEAN±S.D. | 303.5 ± 18.9 | 301.9 ± 17.4 | 299.0 ± 20.6 | 288.3 ± 17.5 |
| DAY 9 | MEAN±S.D. | 306.0 ± 20.0 | 306.8 ± 19.2 | 302.4 ± 21.2 | 292.8 ± 18.0 |
| DAY 10 | MEAN±S.D. | 312.5 ± 20.6 | 311.8 ± 20.1 | 308.1 ± 21.9 | 298.7 ± 17.1 |
| DAY 11 | MEAN±S.D. | 319.3 ± 21.8 | 318.4 ± 19.6 | 315.3 ± 22.2 | 304.8 ± 17.3 |
| DAY 12 | MEAN±S.D. | 325.3 ± 22.7 | 327.1 ± 21.6 | 322.9 ± 24.1 | 311.5 ± 16.7 |
| DAY 13 | MEAN±S.D. | 329.8 ± 24.6 | 329.2 ± 21.8 | 324.9 ± 24.1 | 315.2 ± 16.7 |
| DAY 14 | MEAN±S.D. | 338.3 ± 26.4 | 336.9 ± 23.8 | 331.3 ± 23.6 | 321.5 ± 17.2 |

DAY = DAY OF GESTATION

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TABLE C10 (PAGE 2): MATERNAL BODY WEIGHTS - GESTATION - SUMMARY - F0 GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|--------------------------|-----------|--------------|--------------|--------------|--------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| PREGNANT | N | 15 | 14 | 15 | 13 |
| MATERNAL BODY WEIGHT (G) | | | | | |
| DAY 15 | MEAN±S.D. | 345.4 ± 25.9 | 341.4 ± 24.5 | 338.8 ± 24.0 | 328.3 ± 17.0 |
| DAY 16 | MEAN±S.D. | 355.7 ± 25.5 | 354.2 ± 25.9 | 350.5 ± 23.4 | 340.9 ± 16.5 |
| DAY 17 | MEAN±S.D. | 368.6 ± 27.4 | 368.8 ± 26.5 | 363.9 ± 24.5 | 353.2 ± 16.4 |
| DAY 18 | MEAN±S.D. | 386.9 ± 29.4 | 387.1 ± 29.6 | 380.1 ± 24.1 | 366.2 ± 17.6 |
| DAY 19 | MEAN±S.D. | 400.6 ± 29.7 | 400.9 ± 30.7 | 395.7 ± 24.2 | 381.2 ± 15.9 |
| DAY 20 | MEAN±S.D. | 418.1 ± 34.5 | 416.5 ± 32.8 | 411.4 ± 26.7 | 395.6 ± 17.0 |

DAY = DAY OF GESTATION

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C11 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - GESTATION - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | | I 0 (VEHICLE) | II 10 | III 50 | IV 250 |
|------------------------------------|-----------|------------------|---------------|--------------|--------------|
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| PREGNANT | N | 15 | 14 | 15 | 13 |
| MATERNAL BODY WEIGHT CHANGE (G) | | | | | |
| DAYS 0 - 3 | MEAN±S.D. | +15.9 ± 4.8 | +13.6 ± 5.7 | +10.4 ± 5.7* | +11.7 ± 5.4 |
| DAYS 3 - 6 | MEAN±S.D. | +11.4 ± 5.5 | +9.4 ± 4.9 | +9.5 ± 4.2 | +9.4 ± 3.7 |
| DAYS 6 - 9 | MEAN±S.D. | +10.2 ± 4.5 | +11.0 ± 3.8 | +10.4 ± 5.2 | +9.7 ± 4.3 |
| DAYS 9 - 12 | MEAN±S.D. | +19.3 ± 4.9 | +20.3 ± 5.3 | +20.5 ± 4.2 | +18.7 ± 6.5 |
| DAYS 12 - 15 | MEAN±S.D. | +20.1 ± 4.6 | +14.3 ± 6.2** | +15.9 ± 5.2* | +16.8 ± 4.1 |
| DAYS 15 - 18 | MEAN±S.D. | +41.5 ± 6.2 | +45.7 ± 9.2 | +41.3 ± 5.5 | +37.9 ± 6.0 |
| DAYS 18 - 20 | MEAN±S.D. | +31.2 ± 8.6 | +29.4 ± 6.7 | +31.3 ± 6.3 | +29.4 ± 5.6 |
| DAYS 0 - 20 | MEAN±S.D. | +149.6± 24.8 | +143.6± 23.0 | +139.3± 17.1 | +133.6± 12.8 |

DAYS = DAYS OF GESTATION

* Significantly different from the vehicle control group value ($p \leq 0.05$).

** Significantly different from the vehicle control group value ($p \leq 0.01$).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C12 (PAGE 1): MATERNAL BODY WEIGHTS - LACTATION - SUMMARY - F0 GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|--------------------------|-----------|--------------|--------------|--------------|------------------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| PREGNANT | N | 15 | 14 | 15 | 13 |
| DELIVERED A LITTER | N | 15 | 14 | 15 | 13 |
| MATERNAL BODY WEIGHT (G) | | | | | |
| DAY 1 | MEAN±S.D. | 321.2 ± 24.7 | 319.8 ± 20.8 | 316.5 ± 25.0 | 296.3 ± 25.7* |
| DAY 2 | MEAN±S.D. | 320.9 ± 27.2 | 324.6 ± 25.7 | 318.7 ± 26.1 | 308.2 ± 14.1 [11]a |
| DAY 3 | MEAN±S.D. | 320.9 ± 26.5 | 326.4 ± 24.7 | 322.7 ± 25.9 | 308.4 ± 15.0 [11]a |
| DAY 4 | MEAN±S.D. | 324.1 ± 27.6 | 329.1 ± 25.0 | 320.6 ± 25.8 | 310.6 ± 14.6 [11]a |
| DAY 5 | MEAN±S.D. | 327.5 ± 29.4 | 339.1 ± 21.6 | 327.9 ± 27.5 | 317.4 ± 12.3 [11]a |
| DAY 6 | MEAN±S.D. | 299.1 ± 24.7 | 304.0 ± 18.9 | 296.0 ± 25.0 | 284.8 ± 11.1 [11]a |

DAY = DAY OF LACTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dams that were sacrificed due to no surviving pups.

* Significantly different from the vehicle control group value ($p \leq 0.05$).

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TABLE C13 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - LACTATION - SUMMARY - F0 GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|---------------------------------|-----------|-------------|-------------|-------------|------------------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| PREGNANT | N | 15 | 14 | 15 | 13 |
| DELIVERED A LITTER | N | 15 | 14 | 15 | 13 |
| MATERNAL BODY WEIGHT CHANGE (G) | | | | | |
| DAYS 1 - 2 | MEAN±S.D. | -0.3 ± 9.3 | +4.7 ± 8.2 | +2.2 ± 7.2 | +3.1 ± 4.6 [11]a |
| DAYS 2 - 3 | MEAN±S.D. | -0.1 ± 8.0 | +1.8 ± 6.5 | +3.9 ± 5.9 | +0.3 ± 6.3 [11]a |
| DAYS 3 - 4 | MEAN±S.D. | +3.3 ± 6.4 | +2.7 ± 8.3 | -2.1 ± 6.0 | +2.2 ± 4.3 [11]a |
| DAYS 4 - 5 | MEAN±S.D. | +3.4 ± 9.0 | +10.0 ± 6.9 | +7.3 ± 4.3 | +6.8 ± 7.7 [11]a |
| DAYS 5 - 6 | MEAN±S.D. | -28.4 ± 8.6 | -35.1 ± 8.5 | -31.9 ± 5.8 | -32.6 ± 8.0 [11]a |
| DAYS 1 - 6 | MEAN±S.D. | -22.1 ± 9.6 | -15.8 ± 6.5 | -20.5 ± 9.7 | -20.3 ± 13.3 [11]a |

DAYS = DAYS OF LACTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dams that were sacrificed due to no surviving pups.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C14 (PAGE 1): ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - PRECOHABITATION - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|--------------------------|-----------|-------------|------------|------------|----------------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| FEED CONSUMPTION (G/DAY) | | | | | |
| DAYS 1 - 8 | MEAN±S.D. | 19.4 ± 2.8 | 19.4 ± 1.7 | 19.8 ± 2.8 | 18.5 ± 2.6 |
| DAYS 8 - 15a | MEAN±S.D. | 20.3 ± 2.5 | 20.7 ± 2.1 | 20.3 ± 2.8 | 19.2 ± 1.6 [14]b |
| DAYS 1 - 15a | MEAN±S.D. | 19.8 ± 2.6 | 20.0 ± 1.8 | 20.0 ± 2.7 | 18.6 ± 1.6 [14]b |

DAYS = DAYS OF STUDY

[] = NUMBER OF VALUES AVERAGED

a. Last value recorded before cohabitation.

b. Excludes values that were associated with spillage.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C15 (PAGE 1): RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - PRECOHABITATION - SUMMARY - F0 GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|-----------------------------|-----------|-------------|------------|------------|----------------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| FEED CONSUMPTION (G/KG/DAY) | | | | | |
| DAYS 1 - 8 | MEAN±S.D. | 82.2 ± 12.7 | 81.6 ± 5.4 | 83.4 ± 9.3 | 79.0 ± 9.4 |
| DAYS 8 - 15a | MEAN±S.D. | 79.6 ± 10.7 | 80.7 ± 5.3 | 79.5 ± 7.3 | 77.3 ± 3.9 [14]b |
| DAYS 1 - 15a | MEAN±S.D. | 80.9 ± 11.6 | 81.3 ± 4.6 | 81.5 ± 7.9 | 77.2 ± 4.0 [14]b |

DAYS = DAYS OF STUDY

[] = NUMBER OF VALUES AVERAGED

a. Last value recorded before cohabitation.

b. Excludes values that were associated with spillage.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C16 (PAGE 1): MATERNAL ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - GESTATION - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|-----------------------------------|-----------|-------------|------------|------------|----------------------------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| PREGNANT | N | 15 | 14 | 15 | 13 |
| MATERNAL FEED CONSUMPTION (G/DAY) | | | | | |
| DAYS 0 - 7 | MEAN±S.D. | 23.3 ± 1.9 | 23.3 ± 2.7 | 22.6 ± 3.2 | 22.2 ± 2.3 [12] ^a |
| DAYS 7 - 10 | MEAN±S.D. | 25.1 ± 2.4 | 25.2 ± 2.7 | 23.7 ± 3.6 | 24.2 ± 2.7 |
| DAYS 10 - 12 | MEAN±S.D. | 25.4 ± 2.9 | 25.6 ± 4.0 | 25.0 ± 3.2 | 26.5 ± 3.4 |
| DAYS 12 - 15 | MEAN±S.D. | 26.4 ± 2.9 | 26.5 ± 3.8 | 25.7 ± 4.2 | 26.4 ± 2.3 |
| DAYS 15 - 18 | MEAN±S.D. | 26.8 ± 3.1 | 28.3 ± 3.2 | 26.9 ± 3.7 | 28.1 ± 3.2 |
| DAYS 18 - 20 | MEAN±S.D. | 25.7 ± 3.7 | 25.3 ± 3.4 | 25.8 ± 2.8 | 25.0 ± 2.8 |
| DAYS 0 - 20 | MEAN±S.D. | 25.0 ± 2.3 | 25.2 ± 2.7 | 24.4 ± 3.0 | 24.8 ± 1.8 |

DAYS = DAYS OF GESTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values that were associated with spillage.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C17 (PAGE 1): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - GESTATION - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|--------------------------------------|-----------|-------------|------------|-------------|----------------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| PREGNANT | N | 15 | 14 | 15 | 13 |
| MATERNAL FEED CONSUMPTION (G/KG/DAY) | | | | | |
| DAYS 0 - 7 | MEAN±S.D. | 81.6 ± 4.0 | 80.9 ± 5.7 | 79.0 ± 7.1 | 80.8 ± 6.6 [12]a |
| DAYS 7 - 10 | MEAN±S.D. | 82.1 ± 5.0 | 82.4 ± 6.2 | 78.4 ± 8.3 | 83.2 ± 8.1 |
| DAYS 10 - 12 | MEAN±S.D. | 79.5 ± 5.7 | 80.0 ± 9.5 | 79.3 ± 8.9 | 86.8 ± 10.3 |
| DAYS 12 - 15 | MEAN±S.D. | 78.8 ± 4.9 | 79.1 ± 7.2 | 77.7 ± 10.1 | 82.8 ± 5.9 |
| DAYS 15 - 18 | MEAN±S.D. | 73.6 ± 5.5 | 77.9 ± 5.1 | 75.0 ± 8.1 | 81.2 ± 9.1** |
| DAYS 18 - 20 | MEAN±S.D. | 64.0 ± 7.4 | 62.9 ± 6.2 | 65.1 ± 4.7 | 65.8 ± 7.5 |
| DAYS 0 - 20 | MEAN±S.D. | 77.3 ± 3.7 | 77.8 ± 4.4 | 76.1 ± 6.0 | 80.2 ± 4.8 |

DAYS = DAYS OF GESTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values that were associated with spillage.

** Significantly different from the vehicle control group value (p<0.01).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C18 (PAGE 1): MATERNAL ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - LACTATION - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|-----------------------------------|-----------|-------------|----------------------|----------------------|----------------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| PREGNANT | N | 15 | 14 | 15 | 13 |
| DELIVERED A LITTER | N | 15 | 14 | 15 | 13 |
| MATERNAL FEED CONSUMPTION (G/DAY) | | | | | |
| DAYS 1 - 5 | MEAN±S.D. | 31.4 ± 5.6 | 36.4 ± 4.2 [13]a | 33.0 ± 5.6 [14]a | 30.8 ± 7.4 [11]b |

DAYS = DAYS OF LACTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values that were associated with spillage.

b. Excludes values for dams that were sacrificed due to no surviving pups.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C19 (PAGE 1): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - LACTATION - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|--------------------------------------|-----------|-------------|-----------------------|------------------------|-----------------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS TESTED | N | 15 | 15 | 15 | 15 |
| PREGNANT | N | 15 | 14 | 15 | 13 |
| DELIVERED A LITTER | N | 15 | 14 | 15 | 13 |
| MATERNAL FEED CONSUMPTION (G/KG/DAY) | | | | | |
| DAYS 1 - 5 | MEAN±S.D. | 97.0 ± 13.4 | 110.9 ± 8.4 [13]a | 103.3 ± 13.2 [14]a | 99.2 ± 22.8 [11]b |

DAYS = DAYS OF LACTATION

[] = NUMBER OF VALUES AVERAGED

a. Excludes values that were associated with spillage.

b. Excludes values for dams that were sacrificed due to no surviving pups.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C20 (PAGE 1): MATING AND FERTILITY, ESTROUS CYCLING AND DAYS IN COHABITATION - SUMMARY - F0 GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|--|-----------|-------------|-----------|-----------|-----------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| <u>ESTROUS CYCLING OBSERVATIONS</u> | | | | | |
| RATS EVALUATED | N | 15 | 15 | 15 | 15 |
| PRECOHABITATION ESTROUS CYCLING | | | | | |
| ESTROUS STAGES/ 14 DAYS | MEAN±S.D. | 3.1 ± 1.1 | 3.4 ± 0.8 | 3.2 ± 1.0 | 3.4 ± 0.6 |
| RATS WITH 6 OR MORE CONSECUTIVE DAYS OF DIESTRUS | N | 1 | 0 | 1 | 0 |
| RATS WITH 6 OR MORE CONSECUTIVE DAYS OF ESTRUS | N | 0 | 0 | 0 | 0 |

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C20 (PAGE 2): MATING AND FERTILITY, ESTROUS CYCLING AND DAYS IN COHABITATION - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|-------------------------------------|------------|-------------------|-------------------|-------------------|-------------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| <u>MATING OBSERVATIONS</u> | | | | | |
| RATS IN COHABITATION | N | 15 | 15 | 15 | 15 |
| DAYS IN COHABITATION a | MEAN+S.D. | 3.0 ± 2.0 | 2.7 ± 1.0 | 4.3 ± 3.6 | 3.7 ± 4.2 |
| RATS THAT MATED | N(%) | 15(100.0) | 15(100.0) | 15(100.0) | 14(93.3) |
| FERTILITY INDEX b | N/N (%) | 15/ 15 (100.0) | 14/ 15 (93.3) | 15/ 15 (100.0) | 13/ 14 (92.8) |
| RATS WITH CONFIRMED MATING DATES | N | 15 | 15 | 15 | 14 |
| MATED BY FIRST MALE c DAYS 1-7 | N(%) | 14(93.3) | 15(100.0) | 13(86.7) | 13(92.8) |
| MATED BY SECOND MALE c DAYS 7-14 | N(%) | 1(6.7) | 0(0.0) | 2(13.3) | 1(7.1) |
| RATS PREGNANT/RATS IN COHABITATION | N/N (%) | 15/ 15 (100.0) | 14/ 15 (93.3) | 15/ 15 (100.0) | 13/ 15 (86.7) |

- a. Restricted to rats with a confirmed mating date and rats that did not mate.
b. Number of pregnancies/number of rats that mated.
c. Restricted to rats with a confirmed mating date.

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TABLE C21 (PAGE 1): FUNCTIONAL OBSERVATIONAL BATTERY - SUMMARY - FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------------|------------|-------------|-----|-----|-----|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS | N | 5 | 4 | 5 | 5 |
| HOME CAGE BEHAVIOR | | | | | |
| 1: Sleeping | N | 3 | 2 | 0 | 2 |
| 2: Awake, Immobile | N | 2 | 2 | 5 | 3 |
| 3: Normal movement | N | 0 | 0 | 0 | 0 |
| 4: Unusual posture | N | 0 | 0 | 0 | 0 |
| 5: Unusual behavior | N | 0 | 0 | 0 | 0 |
| ALTERATIONS (HOME CAGE) | | | | | |
| 1: None | N | 5 | 4 | 5 | 5 |
| 2: Stereotyped behavior | N | 0 | 0 | 0 | 0 |
| 3: Bizarre behavior | N | 0 | 0 | 0 | 0 |
| 4: Limb twitches/tremor | N | 0 | 0 | 0 | 0 |
| 5: Whole body tremor/spasm | N | 0 | 0 | 0 | 0 |
| 6: Unusual posture | N | 0 | 0 | 0 | 0 |
| 7: Tonic-clonic seizure | N | 0 | 0 | 0 | 0 |
| REACTION TO REMOVAL | | | | | |
| (1) Sits quietly | N | 5 | 4 | 5 | 5 |
| (2) Vocalization | N | 0 | 0 | 0 | 0 |
| (3) Runs or freezes | N | 0 | 0 | 0 | 0 |
| (4) Tail or throat rattles | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| REACTION TO HANDLING | | | | | |
| (1) No resistance | N | 5 | 4 | 5 | 5 |
| (2) Vocalization | N | 0 | 0 | 0 | 0 |
| (3) Tense | N | 0 | 0 | 0 | 0 |
| (4) Squirming | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C21 (PAGE 2): FUNCTIONAL OBSERVATIONAL BATTERY - SUMMARY - FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------------|------------|-------------|------------|------------|-----------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS | N | 5 | 4 | 5 | 5 |
| REARS IN OPEN FIELD | MEAN±S.D. | 7.8 ± 1.8 | 10.3 ± 1.7 | 10.0 ± 2.8 | 9.0 ± 2.2 |
| DEFECATION IN OPEN FIELD | | | | | |
| 1: None | N | 5 | 3 | 5 | 5 |
| 2: Feces normal | N | 0 | 1 | 0 | 0 |
| 3: Soft or liquid feces | N | 0 | 0 | 0 | 0 |
| URINATION IN OPEN FIELD | | | | | |
| (1) None | N | 5 | 3 | 5 | 5 |
| (2) Normal urination | N | 0 | 1 | 0 | 0 |
| (3) Excess urination | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.3 | 1.0 | 1.0 |
| LEVEL OF AROUSAL | | | | | |
| (1) Stuporous | N | 0 | 0 | 0 | 0 |
| (2) Sluggish | N | 0 | 0 | 0 | 0 |
| (3) Apparently normal | N | 5 | 4 | 5 | 5 |
| (4) Sudden darting | N | 0 | 0 | 0 | 0 |
| (5) Freezing, vocalization | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 3.0 | 3.0 | 3.0 | 3.0 |
| ALTERATIONS (OPEN FIELD) | | | | | |
| 1: None | N | 4 | 4 | 5 | 5 |
| 2: Stereotyped behavior | N | 0 | 0 | 0 | 0 |
| 3: Bizarre behavior | N | 0 | 0 | 0 | 0 |
| 4: Limb twitches/tremor | N | 0 | 0 | 0 | 0 |
| 5: Whole body tremor/spasm | N | 0 | 0 | 0 | 0 |
| 6: Unusual posture | N | 0 | 0 | 0 | 0 |
| 7: Tonic-clonic seizure | N | 0 | 0 | 0 | 0 |

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C21 (PAGE 3): FUNCTIONAL OBSERVATIONAL BATTERY - SUMMARY - FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------------|------------|-------------|-----|-----|-----|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS | N | 5 | 4 | 5 | 5 |
| GAIT PATTERN | | | | | |
| 1: Apparently normal | N | 5 | 4 | 5 | 5 |
| 2: Ataxic | N | 0 | 0 | 0 | 0 |
| 3: Limbs splay or drag | N | 0 | 0 | 0 | 0 |
| 4: Spastic, tip-toe | N | 0 | 0 | 0 | 0 |
| 5: Duck-walk | N | 0 | 0 | 0 | 0 |
| 6: Scissors gait | N | 0 | 0 | 0 | 0 |
| GAIT ABNORMALITY, SEVERITY | | | | | |
| (1) Normal gait | N | 5 | 4 | 5 | 5 |
| (2) Slight | N | 0 | 0 | 0 | 0 |
| (3) Moderate | N | 0 | 0 | 0 | 0 |
| (4) Extreme | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| PALPEBRAL CLOSURE | | | | | |
| (1) Wide open | N | 5 | 4 | 5 | 5 |
| (2) Slightly drooping | N | 0 | 0 | 0 | 0 |
| (3) Half-closed | N | 0 | 0 | 0 | 0 |
| (4) Completely shut | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| PROMINENCE OF THE EYE | | | | | |
| 1: Normal | N | 5 | 4 | 5 | 5 |
| 2: Exophthalmos | N | 0 | 0 | 0 | 0 |
| 3: Enophthalmos | N | 0 | 0 | 0 | 0 |

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

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TABLE C21 (PAGE 4): FUNCTIONAL OBSERVATIONAL BATTERY - SUMMARY - FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|------------------------------|------------|-------------|-----|-----|-----|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS | N | 5 | 4 | 5 | 5 |
| LACRIMATION | | | | | |
| (1) No excess | N | 5 | 4 | 5 | 5 |
| (2) Excess at eyelid margin | N | 0 | 0 | 0 | 0 |
| (3) Margin persistently damp | N | 0 | 0 | 0 | 0 |
| (4) Extends beyond margin | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| SALIVATION | | | | | |
| (1) No excess | N | 5 | 4 | 4 | 5 |
| (2) Margin of mouth wet | N | 0 | 0 | 1 | 0 |
| (3) 1/4 to 1/2 submandibular | N | 0 | 0 | 0 | 0 |
| (4) Entire submandibular | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.2 | 1.0 |
| PILOERECTION | N | 0 | 0 | 0 | 0 |
| ABNORMAL RESPIRATION | N | 0 | 0 | 0 | 0 |
| APPEARANCE | | | | | |
| (1) Clean and groomed | N | 5 | 4 | 5 | 5 |
| (2) Unkempt | N | 0 | 0 | 0 | 0 |
| (3) Urine and/or fecal stain | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| VISUAL REACTION | | | | | |
| (1) None | N | 0 | 0 | 0 | 0 |
| (2) Orienting | N | 5 | 4 | 5 | 5 |
| (3) Startle | N | 0 | 0 | 0 | 0 |
| (4) More energetic reaction | N | 0 | 0 | 0 | 0 |
| (5) Attacks | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 2.0 | 2.0 | 2.0 | 2.0 |

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

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TABLE C21 (PAGE 5): FUNCTIONAL OBSERVATIONAL BATTERY - SUMMARY - FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|-----------------------------|------------|-------------|-----|-----|-----|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS | N | 5 | 4 | 5 | 5 |
| TACTILE REACTION | | | | | |
| (1) None | N | 0 | 0 | 0 | 0 |
| (2) Orienting | N | 5 | 4 | 5 | 5 |
| (3) Startle | N | 0 | 0 | 0 | 0 |
| (4) More energetic reaction | N | 0 | 0 | 0 | 0 |
| (5) Attacks | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 2.0 | 2.0 | 2.0 | 2.0 |
| AUDITORY REACTION | | | | | |
| (1) None | N | 0 | 0 | 0 | 0 |
| (2) Orienting | N | 0 | 0 | 0 | 0 |
| (3) Startle | N | 5 | 4 | 5 | 5 |
| (4) More energetic reaction | N | 0 | 0 | 0 | 0 |
| (5) Intense vocalization | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 3.0 | 3.0 | 3.0 | 3.0 |
| TAIL-PINCH REACTION | | | | | |
| (1) None | N | 0 | 0 | 0 | 0 |
| (2) Orienting | N | 5 | 4 | 5 | 5 |
| (3) Startle | N | 0 | 0 | 0 | 0 |
| (4) More energetic reaction | N | 0 | 0 | 0 | 0 |
| (5) Attacks | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 2.0 | 2.0 | 2.0 | 2.0 |
| VISUAL PLACING RESPONSE | | | | | |
| (1) Early extension | N | 5 | 4 | 5 | 5 |
| (2) Extension after contact | N | 0 | 0 | 0 | 0 |
| (3) No extension | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

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TABLE C21 (PAGE 6): FUNCTIONAL OBSERVATIONAL BATTERY - SUMMARY - FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|-----------------------------|------------|--------------|---------------|--------------|---------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| RATS | N | 5 | 4 | 5 | 5 |
| AIR RIGHTING RESPONSE | | | | | |
| (1) All feet land on ground | N | 5 | 4 | 5 | 5 |
| (2) Lands on side | N | 0 | 0 | 0 | 0 |
| (3) Lands on back | N | 0 | 0 | 0 | 0 |
| | MEAN SCORE | 1.0 | 1.0 | 1.0 | 1.0 |
| PUPIL RESPONSE TO LIGHT | N | 5 | 4 | 5 | 5 |
| FORELIMB GRIP TEST | | | | | |
| Maximum (G) | MEAN±S.D. | 316.0 ± 53.4 | 303.8 ± 105.5 | 260.0 ± 40.8 | 381.0 ± 114.9 |
| Average (G) | MEAN±S.D. | 296.2 ± 43.2 | 276.8 ± 101.7 | 240.6 ± 23.2 | 358.0 ± 108.7 |
| HINDLIMB GRIP TEST | | | | | |
| Maximum (G) | MEAN±S.D. | 298.0 ± 90.7 | 321.3 ± 65.4 | 258.0 ± 44.2 | 359.0 ± 106.5 |
| Average (G) | MEAN±S.D. | 274.0 ± 85.3 | 306.0 ± 58.2 | 221.2 ± 38.6 | 328.8 ± 119.0 |
| LANDING FOOT SPLAY | | | | | |
| Average (CM) | MEAN±S.D. | 6.7 ± 0.3 | 6.3 ± 1.6 | 6.7 ± 0.7 | 6.8 ± 0.9 |
| BODY WEIGHT (G) | MEAN±S.D. | 332.8 ± 24.7 | 322.5 ± 26.9 | 321.2 ± 23.8 | 313.8 ± 25.9 |

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

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TABLE C22 (PAGE 1): MOTOR ACTIVITY - SUMMARY - F0 GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|---------------------|-------------|----------------|---------------|---------------|----------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| DAY 86 | | | | | |
| NUMBER OF RATS | N | 5 | 4 | 5 | 5 |
| NUMBER OF MOVEMENTS | | | | | |
| BLOCK 1 | MEAN ± S.D. | 75.0 ± 8.5 | 73.0 ± 4.7 | 66.8 ± 12.8 | 77.0 ± 13.0 |
| BLOCK 2 | MEAN ± S.D. | 80.8 ± 12.8 | 78.2 ± 6.7 | 72.0 ± 16.8 | 77.6 ± 23.7 |
| BLOCK 3 | MEAN ± S.D. | 69.8 ± 17.3 | 77.8 ± 9.1 | 54.8 ± 38.4 | 75.2 ± 13.7 |
| BLOCK 4 | MEAN ± S.D. | 58.0 ± 29.8 | 62.5 ± 33.3 | 46.4 ± 41.6 | 74.6 ± 16.5 |
| BLOCK 5 | MEAN ± S.D. | 65.4 ± 30.3 | 51.8 ± 27.7 | 47.4 ± 37.8 | 69.2 ± 20.8 |
| BLOCK 6 | MEAN ± S.D. | 65.0 ± 33.3 | 56.0 ± 39.0 | 51.6 ± 29.8 | 64.0 ± 16.8 |
| BLOCK 7 | MEAN ± S.D. | 63.6 ± 28.6 | 61.5 ± 44.4 | 72.4 ± 8.2 | 63.6 ± 23.8 |
| BLOCK 8 | MEAN ± S.D. | 38.4 ± 30.4 | 52.8 ± 35.0 | 54.2 ± 10.1 | 63.4 ± 31.0 |
| BLOCK 9 | MEAN ± S.D. | 46.8 ± 32.4 | 65.5 ± 9.1 | 45.4 ± 39.6 | 39.8 ± 30.4 |
| BLOCK 10 | MEAN ± S.D. | 56.0 ± 30.4 | 69.5 ± 12.9 | 52.4 ± 13.0 | 47.0 ± 32.1 |
| BLOCK 11 | MEAN ± S.D. | 60.2 ± 39.1 | 53.0 ± 11.0 | 52.6 ± 23.6 | 61.6 ± 23.4 |
| BLOCK 12 | MEAN ± S.D. | 47.6 ± 36.6 | 41.0 ± 32.3 | 33.8 ± 25.0 | 73.2 ± 17.7 |
| BLOCK 13 | MEAN ± S.D. | 50.2 ± 25.2 | 34.2 ± 23.3 | 35.0 ± 27.1 | 50.0 ± 27.4 |
| BLOCK 14 | MEAN ± S.D. | 60.4 ± 17.9 | 29.5 ± 28.5 | 43.2 ± 25.8 | 34.8 ± 27.6 |
| BLOCK 15 | MEAN ± S.D. | 55.2 ± 10.1 | 49.5 ± 32.3 | 54.4 ± 30.2 | 42.4 ± 37.8 |
| BLOCK 16 | MEAN ± S.D. | 53.4 ± 14.3 | 54.5 ± 35.9 | 46.6 ± 29.1 | 39.0 ± 27.3 |
| BLOCK 17 | MEAN ± S.D. | 69.8 ± 28.0 | 25.2 ± 32.6 | 55.4 ± 29.1 | 38.4 ± 32.9 |
| BLOCK 18 | MEAN ± S.D. | 54.4 ± 13.4 | 31.5 ± 30.6 | 39.2 ± 29.7 | 50.2 ± 27.7 |
| TOTAL | MEAN ± S.D. | 1070.0 ± 277.2 | 967.0 ± 219.2 | 923.6 ± 256.7 | 1041.0 ± 192.9 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

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TABLE C22 (PAGE 2): MOTOR ACTIVITY - SUMMARY - Fo GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV |
|----------------------------------|-------------|----------------|----------------|----------------|----------------|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| DAY 86 | | | | | |
| NUMBER OF RATS | N | 5 | 4 | 5 | 5 |
| TIME (SECONDS) SPENT IN MOVEMENT | | | | | |
| BLOCK 1 | MEAN ± S.D. | 190.2 ± 37.2 | 183.2 ± 29.5 | 220.4 ± 29.9 | 178.6 ± 28.4 |
| BLOCK 2 | MEAN ± S.D. | 178.8 ± 47.1 | 150.8 ± 22.8 | 141.6 ± 54.2 | 154.2 ± 29.9 |
| BLOCK 3 | MEAN ± S.D. | 130.4 ± 61.0 | 137.2 ± 43.1 | 84.2 ± 72.6 | 124.6 ± 33.6 |
| BLOCK 4 | MEAN ± S.D. | 91.8 ± 61.6 | 103.8 ± 71.5 | 62.8 ± 62.9 | 110.0 ± 38.5 |
| BLOCK 5 | MEAN ± S.D. | 99.4 ± 51.8 | 81.5 ± 62.8 | 77.2 ± 80.6 | 107.4 ± 40.2 |
| BLOCK 6 | MEAN ± S.D. | 86.4 ± 49.0 | 76.0 ± 50.8 | 77.0 ± 48.4 | 89.2 ± 30.8 |
| BLOCK 7 | MEAN ± S.D. | 87.8 ± 42.3 | 85.0 ± 57.7 | 110.8 ± 17.4 | 96.2 ± 35.6 |
| BLOCK 8 | MEAN ± S.D. | 67.6 ± 55.4 | 84.2 ± 64.3 | 87.6 ± 49.7 | 81.0 ± 43.6 |
| BLOCK 9 | MEAN ± S.D. | 74.6 ± 57.8 | 119.0 ± 23.8 | 72.0 ± 71.9 | 62.4 ± 56.7 |
| BLOCK 10 | MEAN ± S.D. | 88.0 ± 55.3 | 107.8 ± 20.2 | 64.2 ± 36.6 | 61.0 ± 43.3 |
| BLOCK 11 | MEAN ± S.D. | 75.4 ± 54.6 | 104.0 ± 73.8 | 82.6 ± 46.8 | 89.8 ± 46.8 |
| BLOCK 12 | MEAN ± S.D. | 71.8 ± 56.4 | 74.2 ± 80.8 | 45.2 ± 39.6 | 114.8 ± 15.0 |
| BLOCK 13 | MEAN ± S.D. | 83.0 ± 54.6 | 45.5 ± 40.1 | 56.8 ± 48.8 | 68.8 ± 44.3 |
| BLOCK 14 | MEAN ± S.D. | 85.8 ± 21.9 | 48.2 ± 65.4 | 69.0 ± 39.3 | 42.6 ± 38.6 |
| BLOCK 15 | MEAN ± S.D. | 92.4 ± 17.7 | 69.0 ± 53.1 | 87.6 ± 48.4 | 65.0 ± 62.0 |
| BLOCK 16 | MEAN ± S.D. | 78.2 ± 32.9 | 77.0 ± 54.6 | 68.6 ± 52.8 | 49.8 ± 39.2 |
| BLOCK 17 | MEAN ± S.D. | 89.0 ± 46.3 | 44.2 ± 74.1 | 86.6 ± 47.4 | 52.4 ± 47.0 |
| BLOCK 18 | MEAN ± S.D. | 70.2 ± 27.2 | 55.5 ± 69.8 | 56.2 ± 50.4 | 66.4 ± 40.0 |
| TOTAL | MEAN ± S.D. | 1740.8 ± 585.8 | 1646.2 ± 621.4 | 1550.4 ± 528.7 | 1614.2 ± 357.2 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C23 (PAGE 1): NATURAL DELIVERY OBSERVATIONS - SUMMARY - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP | | I | II | III | IV | |
|--|----------------|-------------------|-------------------|-------------------|-------------------|----|
| DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 | |
| RATS ASSIGNED TO NATURAL DELIVERY | | N | 15 | 15 | 15 | 15 |
| PREGNANT | N(%) | 15(100.0) | 14(93.3) | 15(100.0) | 13(86.7) | |
| DELIVERED A LITTER | N(%) | 15(100.0) | 14(100.0) | 15(100.0) | 13(100.0) | |
| DURATION OF GESTATION a | MEAN±S.D. | 22.7 ± 0.4 | 22.5 ± 0.5 | 22.8 ± 0.4 | 22.9 ± 0.3 | |
| IMPLANTATION SITES PER DELIVERED LITTER | N MEAN±S.D. | 251 16.7 ± 2.4 | 226 16.1 ± 2.5 | 247 16.5 ± 1.1 | 204 15.7 ± 1.5 | |
| DAMS WITH STILLBORN PUPS | N(%) | 1(6.7) | 0(0.0) | 2(13.3) | 4(30.8) | |
| DAMS WITH NO LIVEBORN PUPS | N | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | |
| GESTATION INDEX b | % N/N | 100.0 15/ 15 | 100.0 14/ 14 | 100.0 15/ 15 | 100.0 13/ 13 | |
| DAMS WITH ALL PUPS DYING DAYS 1-5 POSTPARTUM | N(%) | 0(0.0) | 0(0.0) | 0(0.0) | 3(23.1)** | |

a. Calculated as the time (in days) elapsed between confirmed mating (arbitrarily defined as day 0) and the time (in days) the first pup was delivered.

b. Number of rats with live offspring/number of pregnant rats.

** Significantly different from the vehicle control group value ($p \leq 0.01$).

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TABLE C24 (PAGE 1): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F1 GENERATION LITTERS

| MATERNAL DOSAGE GROUP | | I | II | III | IV |
|--|-----------|-------------|-------------|-------------|-----------------|
| MATERNAL DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 |
| DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS | | N 15 | 14 | 15 | 13 |
| PUPS DELIVERED (TOTAL) | | N 236 | 215 | 231 | 183 |
| | MEAN±S.D. | 15.7 ± 2.3 | 15.4 ± 2.6 | 15.4 ± 1.2 | 14.1 ± 2.8 |
| LIVEBORN | MEAN±S.D. | 15.7 ± 2.2 | 15.4 ± 2.6 | 15.1 ± 0.9 | 13.3 ± 3.3 |
| | N(%) | 235 (99.6) | 215 (100.0) | 227 (98.3) | 173 (94.5)** |
| STILLBORN | MEAN±S.D. | 0.1 ± 0.2 | 0.0 ± 0.0 | 0.3 ± 0.7 | 0.5 ± 0.8 |
| | N(%) | 1 (0.4) | 0 (0.0) | 4 (1.7) | 6 (3.3)** |
| UNKNOWN VITAL STATUS | N | 0 | 0 | 0 | 4 |
| PUPS FOUND DEAD OR PRESUMED CANNIBALIZED | | | | | |
| DAY 1 | N/N(%) | 2/235 (0.8) | 0/215 (0.0) | 0/227 (0.0) | 4/173 (2.3)** |
| DAYS 2- 5 | N/N(%) | 0/233 (0.0) | 2/215 (0.9) | 2/227 (0.9) | 28/169 (16.6)** |
| VIABILITY INDEX a | % | 99.1 | 99.1 | 99.1 | 81.5** |
| | N/N | 233/235 | 213/215 | 225/227 | 141/173 |

DAY(S) = DAY(S) POSTPARTUM

a. Number of live pups on day 5 postpartum/number of liveborn pups on day 1 postpartum.

** Significantly different from the vehicle control group value ($p \leq 0.01$).

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TABLE C24 (PAGE 2): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F1 GENERATION LITTERS

| MATERNAL DOSAGE GROUP | | I | II | III | IV | |
|--|-----------|-------------|-------------|-------------|-----------------------|----|
| MATERNAL DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 | |
| DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS | | N | 15 | 14 | 15 | 13 |
| SURVIVING PUPS/LITTER a | | | | | | |
| DAY 1b | MEAN±S.D. | 15.7 ± 2.2 | 15.4 ± 2.6 | 15.1 ± 0.9 | 13.3 ± 3.3 | |
| DAY 5 | MEAN±S.D. | 15.5 ± 2.1 | 15.2 ± 2.4 | 15.0 ± 1.0 | 10.8 ± 6.3* | |
| PERCENT MALE PUPS PER NUMBER OF PUPS SEXED | | | | | | |
| DAY 1b | MEAN±S.D. | 53.0 ± 9.2 | 52.7 ± 12.2 | 52.2 ± 17.0 | 44.2 ± 16.2 | |
| DAY 5 | MEAN±S.D. | 53.1 ± 9.7 | 52.9 ± 12.2 | 52.8 ± 17.4 | 47.0 ± 17.4 [10]c | |

DAY = DAY POSTPARTUM

[] = NUMBER OF VALUES AVERAGED

a. Average number of live pups per litter, including litters with no surviving pups.

b. Includes pups born alive, found dead day 1 postpartum.

c. Excludes values for dams that were sacrificed due to no surviving pups.

* Significantly different from the vehicle control group value ($p \leq 0.05$).

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TABLE C24 (PAGE 3): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F1 GENERATION LITTERS

| MATERNAL DOSAGE GROUP | | I | II | III | IV | |
|--|-----------|-------------|------------|------------|------------|--------|
| MATERNAL DOSAGE (MG/KG/DAY) | | 0 (VEHICLE) | 10 | 50 | 250 | |
| DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS | | N | 15 | 14 | 15 | 13 |
| LIVE LITTER SIZE AT WEIGHING | | | | | | |
| DAY 1 | MEAN±S.D. | 15.5 ± 2.1 | 15.4 ± 2.6 | 15.1 ± 0.9 | 14.1 ± 1.8 | [12]a |
| DAY 5 | MEAN±S.D. | 15.5 ± 2.1 | 15.2 ± 2.4 | 15.0 ± 1.0 | 14.1 ± 1.7 | [10]a |
| PUP WEIGHT/LITTER (GRAMS) | | | | | | |
| DAY 1 | MEAN±S.D. | 6.4 ± 0.7 | 6.3 ± 0.4 | 6.5 ± 0.3 | 5.9 ± 0.8 | [12]a |
| DAY 5 | MEAN±S.D. | 9.6 ± 1.0 | 10.0 ± 0.8 | 10.0 ± 1.0 | 9.3 ± 1.3 | [10]a |

DAY = DAY POSTPARTUM

[] = NUMBER OF VALUES AVERAGED

a. Excludes values for dams that were sacrificed due to no surviving pups.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C25 (PAGE 1): CLINICAL OBSERVATIONS FROM BIRTH TO DAY 5 POSTPARTUM - SUMMARY - F1 GENERATION PUPS

| MATERNAL DOSAGE GROUP | I | II | III | IV |
|------------------------------------|-------------|---|-----|-----|
| MATERNAL DOSAGE (MG/KG/DAY) | 0 (VEHICLE) | 10 | 50 | 250 |
| LITTERS EXAMINED (N) | 15 | 14 | 15 | 13 |
| TRANSIENT CLINICAL OBSERVATIONS: a | | TOTAL FREQUENCY (DAYS x PUPS)/LITTERS WITH OBSERVATIONS | | |
| COLD TO TOUCH | N/N 0/0 | 0/0 | 0/0 | 2/1 |
| NOT NESTING | N/N 0/0 | 0/0 | 0/0 | 2/1 |
| NOT NURSING | N/N 0/0 | 0/0 | 0/0 | 2/1 |
| PALE | N/N 0/0 | 2/1 | 0/0 | 0/0 |
| BRUISE b | N/N 2/1 | 9/1 | 2/1 | 9/3 |

STATISTICAL ANALYSES WERE RESTRICTED TO THE NUMBER OF LITTERS WITH OBSERVATIONS.

a. Tabulation restricted to adverse observations; all other pups appeared normal.

b. Head, back, mouth, lower midline, chest, and/or neck.

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TABLE C26 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F1 GENERATION PUPS

| MATERNAL DOSAGE GROUP | I | II | III | IV |
|--|-----------------|------------|------------|------------|
| MATERNAL DOSAGE (MG/KG/DAY) | 0 (VEHICLE) | 10 | 50 | 250 |
| LITTERS EXAMINED (N) | 15 | 14 | 15 | 13 |
| TOTAL PUPS STILLBORN | | | | |
| OR FOUND DEAD a,b | N 2 | 0 | 4 | 5 |
| STILLBORN | N 1 | 0 | 4 | 3 |
| FOUND DEAD | N 1 | 0 | 0 | 2 |
| NO MILK IN STOMACH c | N(%) 1(100.0) | 0(0.0) | 0(0.0) | 1(50.0) |
| PUPS SACRIFICED AND NECROPSIED ON DAY 5 POSTPARTUM b | | | | |
| LITTERS EVALUATED | N 15 | 14 | 15 | 10 |
| PUPS EVALUATED | N 233 | 213 | 225 | 141 |
| APPEARED NORMAL | | | | |
| LITTER INCIDENCE | N(%) 15(100.0) | 14(100.0) | 15(100.0) | 10(100.0) |
| PUP INCIDENCE | N(%) 233(100.0) | 212(99.5) | 225(100.0) | 141(100.0) |
| KIDNEYS: | | | | |
| BILATERAL, PELVIS, SLIGHT DILATION | | | | |
| LITTER INCIDENCE | N(%) 0(0.0) | 1(7.1) | 0(0.0) | 0(0.0) |
| PUP INCIDENCE | N(%) 0(0.0) | 1(0.5) | 0(0.0) | 0(0.0) |

- a. Restricted to pups in which complete necropsies were performed. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation.
- b. Refer to the individual pup clinical observations table (Table C44) for external clinical observations confirmed at necropsy.
- c. Analysis restricted to pups found dead and necropsied.

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TABLE C27 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| DOSAGE GROUP I | | VEHICLE | 0 (VEHICLE) MG/KG/DAY |
|----------------|-------------|--------------------------------|-----------------------|
| RAT # | | DESCRIPTION | |
| 17662 | | NO ADVERSE FINDINGS | |
| 17672 | DS(14) | EXCESS SALIVATION | |
| 17673 | | NO ADVERSE FINDINGS | |
| 17674 | DS(3) | CHROMODACRYORRHEA | |
| 17680 | DS(14) | RED, SLIGHT PERIORAL SUBSTANCE | |
| 17681 | | NO ADVERSE FINDINGS | |
| 17690 | | NO ADVERSE FINDINGS | |
| 17694 | | NO ADVERSE FINDINGS | |
| 17695 | DS(11- 16) | LOCALIZED ALOPECIA: LIMBS | |
| | DG(0- 20) | LOCALIZED ALOPECIA: LIMBS | |
| | DL(1- 6) | LOCALIZED ALOPECIA: LIMBS a | |
| 17703 | | NO ADVERSE FINDINGS | |
| 17713 | | NO ADVERSE FINDINGS | |
| 17715 | | NO ADVERSE FINDINGS | |
| 17716 | | NO ADVERSE FINDINGS | |
| 17717 | DS(12- 15) | LOCALIZED ALOPECIA: LIMBS | |
| | DG(0- 21) | LOCALIZED ALOPECIA: LIMBS | |
| | DL(1- 6) | LOCALIZED ALOPECIA: LIMBS a | |
| 17719 | | NO ADVERSE FINDINGS | |

DS = DAY OF STUDY DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION

a. Observation confirmed at necropsy.

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TABLE C27 (PAGE 2): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP II | | LOW DOSAGE | 10 MG/KG/DAY |
|-----------------|-------------|-----------------------------|--------------|
| RAT # | | DESCRIPTION | |
| 17663 | DG(0) | SOFT OR LIQUID FECES | |
| 17665 | | NO ADVERSE FINDINGS | |
| 17666 | | NO ADVERSE FINDINGS | |
| 17668 | | NO ADVERSE FINDINGS | |
| 17671 | DG(9- 21) | LOCALIZED ALOPECIA: LIMBS | |
| | DL(1- 6) | LOCALIZED ALOPECIA: LIMBS a | |
| 17675 | | NO ADVERSE FINDINGS | |
| 17679 | DG(14) | INCISORS: MISSING/BROKEN | |
| 17684 | | NO ADVERSE FINDINGS | |
| 17688 | | NO ADVERSE FINDINGS | |
| 17698 | DS(13) | LOCALIZED ALOPECIA: LIMBS | |
| | DG(12- 19) | LOCALIZED ALOPECIA: LIMBS | |
| 17702 | | NO ADVERSE FINDINGS | |
| 17704 | | NO ADVERSE FINDINGS | |
| 17707 | DG(3- 21) | LOCALIZED ALOPECIA: LIMBS | |
| | DL(1- 5) | LOCALIZED ALOPECIA: LIMBS | |
| 17708 | DL(5- 6) | LOCALIZED ALOPECIA: LIMBS a | |
| 17710 | | NO ADVERSE FINDINGS | |

DS = DAY OF STUDY DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION

a. Observation confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C27 (PAGE 3): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP III | | MIDDLE DOSAGE | 50 MG/KG/DAY |
|------------------|-------------|-----------------------------|--------------|
| RAT # | | DESCRIPTION | |
| 17661 | DG(20- 21) | CHROMODACRYORRHEA | |
| 17667 | | NO ADVERSE FINDINGS | |
| 17669 | DG(18- 21) | LOCALIZED ALOPECIA: LIMBS | |
| | DL(1- 6) | LOCALIZED ALOPECIA: LIMBS a | |
| 17670 | DS(16) | URINE-STAINED ABDOMINAL FUR | |
| 17676 | | NO ADVERSE FINDINGS | |
| 17687 | DS(3- 13) | RIGHT EYE: CORNEAL OPACITY | |
| | DS(15- 16) | RIGHT EYE: CORNEAL OPACITY | |
| 17693 | | NO ADVERSE FINDINGS | |
| 17697 | | NO ADVERSE FINDINGS | |
| 17700 | | NO ADVERSE FINDINGS | |
| 17701 | | NO ADVERSE FINDINGS | |
| 17705 | | NO ADVERSE FINDINGS | |
| 17706 | | NO ADVERSE FINDINGS | |
| 17709 | DS(17- 27) | LOCALIZED ALOPECIA: LIMBS | |
| | DG(0- 21) | LOCALIZED ALOPECIA: LIMBS | |
| | DL(1- 6) | LOCALIZED ALOPECIA: LIMBS a | |
| 17718 | | NO ADVERSE FINDINGS | |
| 17720 | DS(16) | URINE-STAINED ABDOMINAL FUR | |

DS = DAY OF STUDY DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION

a. Observation confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C27 (PAGE 4): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP IV | | HIGH DOSAGE | 250 MG/KG/DAY |
|-----------------|--------------|---------------------------------|---------------|
| RAT # | | DESCRIPTION | |
| 17664 | DS(21- 28) | INCISORS: MISSING/BROKEN | |
| | DS(50) | RED, SLIGHT PERIORAL SUBSTANCE | |
| 17677 | DS(16- 18) | URINE-STAINED ABDOMINAL FUR | |
| | DG(0- 2) | URINE-STAINED ABDOMINAL FUR | |
| 17678 | DS(17) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(1) | EXCESS SALIVATION | |
| | DG(13) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(20) | EXCESS SALIVATION | |
| 17682 | DS(23- 25) | EXCESS SALIVATION | |
| | DG(3) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(15) | RED, SLIGHT PERIORAL SUBSTANCE | |
| 17683 | DG(5- 21) | LOCALIZED ALOPECIA: LIMBS | |
| | DG(18- 21) | LOCALIZED ALOPECIA: UNDERSIDE | |
| | DL(1- 6) | LOCALIZED ALOPECIA: LIMBS a | |
| | DL(1- 6) | LOCALIZED ALOPECIA: UNDERSIDE a | |
| 17685 | DS(12) | EXCESS SALIVATION | |
| | DS(14- 15) | EXCESS SALIVATION | |
| | DG(0- 7) | EXCESS SALIVATION | |
| | DG(13- 16) | EXCESS SALIVATION | |
| | DG(19- 20) | EXCESS SALIVATION | |
| | DL(1) | EXCESS SALIVATION | |
| | DL(3) | EXCESS SALIVATION | |
| | DL(5) | EXCESS SALIVATION | |
| 17686 | DS(15) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(0) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(3) | URINE-STAINED ABDOMINAL FUR | |
| | DG(6) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(7- 14) | URINE-STAINED ABDOMINAL FUR | |
| | DG(8- 9) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(15) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(16) | EXCESS SALIVATION | |
| | DG(20- 22) | LOCALIZED ALOPECIA: HEAD | |
| | DG(21) | EXCESS SALIVATION | |

DS = DAY OF STUDY DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C27 (PAGE 5): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP IV | | HIGH DOSAGE | 250 MG/KG/DAY |
|-----------------|------------|-------------------------------------|---------------|
| RAT # | | DESCRIPTION | |
| 17689 | | NO ADVERSE FINDINGS | |
| 17691 | DS(3) | CHROMODACRYORRHEA | |
| | DG(11) | EXCESS SALIVATION | |
| 17692 | DG(3) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(7) | RED, SLIGHT PERIORAL SUBSTANCE | |
| 17696 | DS(13) | EXCESS SALIVATION | |
| | DG(1) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(5) | EXCESS SALIVATION | |
| | DG(9) | EXCESS SALIVATION | |
| | DG(13) | EXCESS SALIVATION | |
| | DG(16) | EXCESS SALIVATION | |
| | DL(2) | SACRIFICED DUE TO NO SURVIVING PUPS | |
| 17699 | | NO ADVERSE FINDINGS | |
| 17711 | DS(14) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(0) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(4) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(6) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(9) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(14) | RED PERIVAGINAL SUBSTANCE | |
| | DG(15) | RED, MODERATE PERIORAL SUBSTANCE | |
| | DG(17) | EXCESS SALIVATION | |
| | DL(1) | DEHYDRATION a | |
| | DL(2) | SACRIFICED DUE TO NO SURVIVING PUPS | |
| 17712 | DS(3- 15) | TAIL BENT | |
| | DS(15) | RED, SLIGHT PERIORAL SUBSTANCE | |
| | DG(0- 21) | TAIL BENT | |
| | DG(1- 21) | LOCALIZED ALOPECIA: LIMBS | |
| | DG(14) | EXCESS SALIVATION | |
| | DL(1) | EXCESS SALIVATION | |
| | DL(1) | LOCALIZED ALOPECIA: LIMBS | |
| | DL(1- 6) | TAIL BENT a | |
| 17714 | DS(17) | RED, SLIGHT PERIORAL SUBSTANCE | |

DS = DAY OF STUDY DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION
a. Observation confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C28 (PAGE 1): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | RAT NUMBER | DAY OF NECROPSY | PREGNANCY STATUS | DOSES ADMINISTERED | OBSERVATIONS a |
|------------------------------------|---------------|--------------------|---------------------|-----------------------|------------------------------|
| I | | | | | |
| 0 (VEHICLE) | 17662 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17672 | DL 6 | P | 45 | ALL TISSUES APPEARED NORMAL. |
| | 17673 | DL 6 | P | 42 | ALL TISSUES APPEARED NORMAL. |
| | 17674 | DL 6 | P | 42 | ALL TISSUES APPEARED NORMAL. |
| | 17680 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17681 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17690 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17694 | DL 6 | P | 42 | ALL TISSUES APPEARED NORMAL. |
| | 17695 | DL 6 | P | 41 | ALL TISSUES APPEARED NORMAL. |
| | 17703 | DL 6 | P | 42 | ALL TISSUES APPEARED NORMAL. |
| | 17713 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17715 | DL 6 | P | 45 | ALL TISSUES APPEARED NORMAL. |
| | 17716 | DL 6 | P | 45 | ALL TISSUES APPEARED NORMAL. |
| | 17717 | DL 6 | P | 42 | ALL TISSUES APPEARED NORMAL. |
| | 17719 | DL 6 | P | 49 | ALL TISSUES APPEARED NORMAL. |
| II | | | | | |
| 10 | 17663 | DG 25 | NP | 42 | ALL TISSUES APPEARED NORMAL. |
| | 17665 | DL 6 | P | 43 | ALL TISSUES APPEARED NORMAL. |
| | 17666 | DL 6 | P | 42 | ALL TISSUES APPEARED NORMAL. |
| | 17668 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17671 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17675 | DL 6 | P | 43 | ALL TISSUES APPEARED NORMAL. |
| | 17679 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17684 | DL 6 | P | 45 | ALL TISSUES APPEARED NORMAL. |
| | 17688 | DL 6 | P | 43 | ALL TISSUES APPEARED NORMAL. |
| | 17698 | DL 6 | P | 43 | ALL TISSUES APPEARED NORMAL. |
| | 17702 | DL 6 | P | 42 | ALL TISSUES APPEARED NORMAL. |
| | 17704 | DL 6 | P | 43 | ALL TISSUES APPEARED NORMAL. |
| | 17707 | DL 6 | P | 45 | ALL TISSUES APPEARED NORMAL. |
| | 17708 | DL 6 | P | 42 | ALL TISSUES APPEARED NORMAL. |
| | 17710 | DL 6 | P | 45 | ALL TISSUES APPEARED NORMAL. |

DS = DAY OF STUDY DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION

P = PREGNANT NP = NOT PREGNANT

a. Refer to the individual clinical observations table (Table C27) for external observations confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C28 (PAGE 2): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | RAT NUMBER | DAY OF NECROPSY | PREGNANCY STATUS | DOSES ADMINISTERED | OBSERVATIONS a |
|------------------------------------|---------------|--------------------|---------------------|-----------------------|---|
| III | | | | | |
| 50 | 17661 | DL 6 | P | 43 | ALL TISSUES APPEARED NORMAL. |
| | 17667 | DL 6 | P | 43 | ALL TISSUES APPEARED NORMAL. |
| | 17669 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17670 | DL 6 | P | 45 | ALL TISSUES APPEARED NORMAL. |
| | 17676 | DL 6 | P | 43 | ALL TISSUES APPEARED NORMAL. |
| | 17687 | DL 6 | P | 45 | ALL TISSUES APPEARED NORMAL. |
| | 17693 | DL 6 | P | 42 | ALL TISSUES APPEARED NORMAL. |
| | 17697 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17700 | DL 6 | P | 43 | ALL TISSUES APPEARED NORMAL. |
| | 17701 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17705 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17706 | DL 6 | P | 45 | KIDNEYS: RIGHT, ABSENT. ALL OTHER TISSUES APPEARED NORMAL. |
| | 17709 | DL 6 | P | 53 | ALL TISSUES APPEARED NORMAL. |
| | 17718 | DL 6 | P | 53 | ALL TISSUES APPEARED NORMAL. |
| | 17720 | DL 6 | P | 45 | ALL TISSUES APPEARED NORMAL. |
| IV | | | | | |
| 250 | 17664 | DS 54 | NP | 53 | ALL TISSUES APPEARED NORMAL. |
| | 17677 | DL 6 | P | 46 | ALL TISSUES APPEARED NORMAL. |
| | 17678 | DL 6 | P | 45 | ALL TISSUES APPEARED NORMAL. |
| | 17682 | DL 6 | P | 53 | ALL TISSUES APPEARED NORMAL. |
| | 17683 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17685 | DL 6 | P | 42 | ALL TISSUES APPEARED NORMAL. |
| | 17686 | DG 25 | NP | 40 | ALL TISSUES APPEARED NORMAL. |
| | 17689 | DL 6 | P | 41 | ALL TISSUES APPEARED NORMAL. |
| | 17691 | DL 6 | P | 45 | ALL TISSUES APPEARED NORMAL. |
| | 17692 | DL 6 | P | 42 | ALL TISSUES APPEARED NORMAL. |

DS = DAY OF STUDY DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION

P = PREGNANT NP = NOT PREGNANT

a. Refer to the individual clinical observations table (Table C27) for external observations confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C28 (PAGE 3): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS

| DOSAGE GROUP DOSAGE (MG/KG/DAY) | RAT NUMBER | DAY OF NECROPSY | PREGNANCY STATUS | DOSES ADMINISTERED | OBSERVATIONS a |
|------------------------------------|---------------|--------------------|---------------------|-----------------------|--|
| IV 250 cont. | 17696 | DL 2 | P | 39 | SACRIFICED DUE TO NO SURVIVING PUPS ON DAY 2 OF LACTATION. THYMUS: SMALL. ALL OTHER TISSUES APPEARED NORMAL. |
| | 17699 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |
| | 17711 | DL 2 | P | 39 | SACRIFICED DUE TO NO SURVIVING PUPS ON DAY 2 OF LACTATION. ALL TISSUES APPEARED NORMAL. |
| | 17712 | DL 6 | P | 42 | ALL TISSUES APPEARED NORMAL. |
| | 17714 | DL 6 | P | 44 | ALL TISSUES APPEARED NORMAL. |

DS = DAY OF STUDY DG = DAY OF PRESUMED GESTATION DL = DAY OF LACTATION

P = PREGNANT NP = NOT PREGNANT

a. Refer to the individual clinical observations table (Table C27) for external observations confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C29 (PAGE 1): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP I | | VEHICLE 0 (VEHICLE) MG/KG/DAY | | | | | | | | | | | |
|----------------|----------------------|-------------------------------|------------|----------|------------|-------------|------------|--------------|------------|--------------|--------------|---------------|--------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | BRAIN | | LIVER | | KIDNEY LEFT | | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW a |
| 17662 P | 303. | | | 9.58 | 3.16 | | | | | | | | |
| 17672 P | 319. | | | 12.34 | 3.87 | | | | | | | | |
| 17673 P | 271. | | | 10.17 | 3.75 | | | | | | | | |
| 17674 P | 282. | | | 10.10 | 3.58 | | | | | | | | |
| 17680 P | 303. | | | 11.66 | 3.85 | | | | | | | | |
| 17681 P | 303. | 2.04 | 0.67 | 11.10 | 3.66 | 1.13 | 0.37 | 1.19 | 0.39 | 0.034 | 11.22 | 0.034 | 11.22 |
| 17690 P | 345. | 2.27 | 0.66 | 12.40 | 3.59 | 1.28 | 0.37 | 1.31 | 0.38 | 0.047 | 13.62 | 0.047 | 13.62 |
| 17694 P | 291. | 2.28 | 0.78 | 11.10 | 3.81 | 1.21 | 0.42 | 1.33 | 0.46 | 0.041 | 14.09 | 0.042 | 14.43 |
| 17695 P | 271. | 2.16 | 0.80 | 10.63 | 3.92 | 1.08 | 0.40 | 1.00 | 0.37 | 0.039 | 14.39 | 0.033 | 12.18 |
| 17703 P | 339. | 2.27 | 0.67 | 13.19 | 3.89 | 1.51 | 0.44 | 1.43 | 0.42 | 0.042 | 12.39 | 0.044 | 12.98 |
| 17713 P | 292. | 2.26 | 0.77 | 9.91 | 3.39 | 1.03 | 0.35 | 1.03 | 0.35 | 0.037 | 12.67 | 0.034 | 11.64 |
| 17715 P | 328. | 2.22 | 0.68 | 11.72 | 3.57 | 1.24 | 0.38 | 1.17 | 0.36 | 0.041 | 12.50 | 0.041 | 12.50 |
| 17716 P | 298. | 2.15 | 0.72 | 13.55 | 4.55 | 1.19 | 0.40 | 1.21 | 0.41 | 0.044 | 14.76 | 0.042 | 14.09 |
| 17717 P | 274. | 2.15 | 0.78 | 9.57 | 3.49 | 1.15 | 0.42 | 1.15 | 0.42 | 0.049 | 17.88 | 0.054 | 19.71 |
| 17719 P | 268. | 2.16 | 0.80 | 11.30 | 4.22 | 1.14 | 0.42 | 1.17 | 0.44 | 0.044 | 16.42 | 0.041 | 15.30 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.
P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
a. Value was multiplied by 1000.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C29 (PAGE 2): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP I | | VEHICLE 0 (VEHICLE) MG/KG/DAY | | | | | | | | | | | |
|----------------|----------------------|-------------------------------|------------|----------|------------|------------|--------------|-------------|--------------|--------------------|------------|----------|------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | SPLEEN | | THYMUS | | OVARY LEFT | | OVARY RIGHT | | UTERUS WITH CERVIX | | HEART | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW |
| 17662 P | 303. | | | | | 0.089 | 29.37 | 0.075 | 24.75 | 0.71 | 0.23 | | |
| 17672 P | 319. | | | | | 0.070 | 21.94 | 0.080 | 25.08 | 0.82 | 0.26 | | |
| 17673 P | 271. | | | | | 0.098 | 36.16 | 0.068 | 25.09 | 0.71 | 0.26 | | |
| 17674 P | 282. | | | | | 0.067 | 23.76 | 0.095 | 33.69 | 0.77 | 0.27 | | |
| 17680 P | 303. | | | | | 0.068 | 22.44 | 0.081 | 26.73 | 0.93 | 0.31 | | |
| 17681 P | 303. | 0.76 | 0.25 | 0.33 | 0.11 | 0.080 | 26.40 | 0.096 | 31.68 | 0.74 | 0.24 | 1.04 | 0.34 |
| 17690 P | 345. | 0.70 | 0.20 | 0.38 | 0.11 | 0.094 | 27.25 | 0.078 | 22.61 | 0.84 | 0.24 | 1.17 | 0.34 |
| 17694 P | 291. | 0.66 | 0.23 | 0.23 | 0.08 | 0.081 | 27.84 | 0.070 | 24.05 | 0.77 | 0.26 | 1.11 | 0.38 |
| 17695 P | 271. | 0.70 | 0.26 | 0.24 | 0.09 | 0.103 | 38.01 | 0.090 | 33.21 | 0.96 | 0.35 | 0.94 | 0.35 |
| 17703 P | 339. | 0.79 | 0.23 | 0.37 | 0.11 | 0.111 | 32.74 | 0.113 | 33.33 | 0.95 | 0.28 | 1.25 | 0.37 |
| 17713 P | 292. | 0.65 | 0.22 | 0.31 | 0.11 | 0.044 | 15.07 | 0.057 | 19.52 | 0.74 | 0.25 | 1.02 | 0.35 |
| 17715 P | 328. | 0.76 | 0.23 | 0.25 | 0.08 | 0.066 | 20.12 | 0.096 | 29.27 | 0.98 | 0.30 | 1.24 | 0.38 |
| 17716 P | 298. | 0.70 | 0.23 | 0.20 | 0.07 | 0.080 | 26.84 | 0.071 | 23.82 | 0.68 | 0.23 | 1.00 | 0.34 |
| 17717 P | 274. | 0.73 | 0.27 | 0.27 | 0.10 | 0.068 | 24.82 | 0.071 | 25.91 | 0.62 | 0.23 | 1.08 | 0.39 |
| 17719 P | 268. | 0.59 | 0.22 | 0.15 | 0.06 | 0.083 | 30.97 | 0.079 | 29.48 | 0.77b | 0.29 | 0.99 | 0.37 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

a. Value was multiplied by 1000.

b. Damaged during processing (weight not affected).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C29 (PAGE 3): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP II | | | LOW DOSAGE | | | | 10 MG/KG/DAY | | | | | | |
|-----------------|----------------------|----------|------------|----------|------------|-------------|--------------|--------------|------------|--------------|-------------------------|---------------|-------------------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | BRAIN | | LIVER | | KIDNEY LEFT | | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW ^a | ABS. WT. | REL. % TBW ^a |
| 17663 | NP 267. | | | 7.49 | 2.80 | | | | | | | | |
| 17665 | P 308. | | | 10.81 | 3.51 | | | | | | | | |
| 17666 | P 289. | | | 12.16 | 4.21 | | | | | | | | |
| 17668 | P 299. | | | 10.54 | 3.52 | | | | | | | | |
| 17671 | P 256. | | | 8.16 | 3.19 | | | | | | | | |
| 17675 | P 297. | 2.18 | 0.73 | 12.27 | 4.13 | 1.31 | 0.44 | 1.34 | 0.45 | 0.044 | 14.81 | 0.039 | 13.13 |
| 17679 | P 295. | 2.13 | 0.72 | 11.54 | 3.91 | 1.35 | 0.46 | 1.30 | 0.44 | 0.037 | 12.54 | 0.036 | 12.20 |
| 17684 | P 317. | 2.15 | 0.68 | 12.17 | 3.84 | 1.30 | 0.41 | 1.37 | 0.43 | 0.042 | 13.25 | 0.042 | 13.25 |
| 17688 | P 311. | 2.21 | 0.71 | 11.60 | 3.73 | 1.02 | 0.33 | 1.20 | 0.38 | 0.054 | 17.36 | 0.049 | 15.76 |
| 17698 | P 299. | 2.24 | 0.75 | 11.43 | 3.82 | 1.38 | 0.46 | 1.41 | 0.47 | 0.047 | 15.72 | 0.036 | 12.04 |
| 17702 | P 307. | 2.05 | 0.67 | 11.83 | 3.85 | 1.14 | 0.37 | 1.23 | 0.40 | 0.041 | 13.36 | 0.040 | 13.03 |
| 17704 | P 327. | 2.26 | 0.69 | 13.36 | 4.08 | 1.41 | 0.43 | 1.41 | 0.43 | 0.049 | 14.98 | 0.049 | 14.98 |
| 17707 | P 296. | 2.18 | 0.74 | 11.40 | 3.85 | 1.15 | 0.39 | 1.10 | 0.37 | 0.047 | 15.88 | 0.045 | 15.20 |
| 17708 | P 328. | 2.29 | 0.70 | 14.27 | 4.35 | 1.49 | 0.45 | 1.35 | 0.41 | 0.039 | 11.89 | 0.042 | 12.80 |
| 17710 | P 327. | 2.20 | 0.67 | 13.78 | 4.21 | 1.39 | 0.42 | 1.40 | 0.43 | 0.063 | 19.27 | 0.056 | 17.12 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

a. Value was multiplied by 1000.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C29 (PAGE 4): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP II | | | LOW DOSAGE | | | | | | | | 10 MG/KG/DAY | | | |
|-----------------|----------------------|----------|------------|----------|------------|------------|--------------|-------------|--------------|--------------------|--------------|----------|------------|--|
| RAT NUMBER | TERMINAL BODY WEIGHT | SPLEEN | | THYMUS | | OVARY LEFT | | OVARY RIGHT | | UTERUS WITH CERVIX | | HEART | | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | |
| 17663 NP | 267. | | | | | 0.053 | 19.85 | 0.062 | 23.22 | 0.48 | 0.18 | | | |
| 17665 P | 308. | | | | | 0.078 | 25.32 | 0.094 | 30.52 | 0.62 | 0.20 | | | |
| 17666 P | 289. | | | | | 0.067 | 23.18 | 0.076 | 26.30 | 0.91 | 0.31 | | | |
| 17668 P | 299. | | | | | 0.082 | 27.42 | 0.073 | 24.41 | 0.80 | 0.27 | | | |
| 17671 P | 256. | | | | | 0.073 | 28.52 | 0.053 | 20.70 | 0.74 | 0.29 | | | |
| 17675 P | 297. | 0.75 | 0.25 | 0.36 | 0.12 | 0.078 | 26.26 | 0.086 | 28.96 | 0.89 | 0.30 | 1.13 | 0.38 | |
| 17679 P | 295. | 0.55 | 0.19 | 0.29 | 0.10 | 0.063 | 21.36 | 0.071 | 24.07 | 0.71 | 0.24 | 1.00 | 0.34 | |
| 17684 P | 317. | 0.74 | 0.23 | 0.36 | 0.11 | 0.080 | 25.24 | 0.090 | 28.39 | 0.84 | 0.26 | 1.19 | 0.38 | |
| 17688 P | 311. | 0.64 | 0.20 | 0.26 | 0.08 | 0.090 | 28.94 | 0.086 | 27.65 | 0.76 | 0.24 | 1.23 | 0.40 | |
| 17698 P | 299. | 0.66 | 0.22 | 0.30 | 0.10 | 0.110 | 36.79 | 0.092 | 30.77 | 0.70 | 0.23 | 1.26 | 0.42 | |
| 17702 P | 307. | 0.71 | 0.23 | 0.29 | 0.09 | 0.071 | 23.13 | 0.082 | 26.71 | 0.92 | 0.30 | 1.16 | 0.38 | |
| 17704 P | 327. | 0.98 | 0.30 | 0.37 | 0.11 | 0.074 | 22.63 | 0.100 | 30.58 | 0.95 | 0.29 | 1.18 | 0.36 | |
| 17707 P | 296. | 0.60 | 0.20 | 0.29 | 0.10 | 0.077 | 26.01 | 0.086 | 29.05 | 0.66 | 0.22 | 1.08 | 0.36 | |
| 17708 P | 328. | 0.82 | 0.25 | 0.50 | 0.15 | 0.069 | 21.04 | 0.072 | 21.95 | 0.78 | 0.24 | 1.10 | 0.34 | |
| 17710 P | 327. | 0.95 | 0.29 | 0.36 | 0.11 | 0.091 | 27.83 | 0.097 | 29.66 | 0.75 | 0.23 | 1.16 | 0.35 | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

a. Value was multiplied by 1000.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C29 (PAGE 5): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP III | | | MIDDLE DOSAGE | | | | 50 MG/KG/DAY | | | | | | | |
|------------------|----------------------|----------|---------------|----------|------------|-------------|--------------|--------------|------------|--------------|--------------|---------------|--------------|--|
| RAT NUMBER | TERMINAL BODY WEIGHT | BRAIN | | LIVER | | KIDNEY LEFT | | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW a | |
| 17661 P | 280. | | | 10.84 | 3.87 | | | | | | | | | |
| 17667 P | 311. | | | 13.45 | 4.32 | | | | | | | | | |
| 17669 P | 296. | | | 10.92 | 3.69 | | | | | | | | | |
| 17670 P | 268. | | | 10.80 | 4.03 | | | | | | | | | |
| 17676 P | 265. | | | 9.21 | 3.48 | | | | | | | | | |
| 17687 P | 337. | 2.13 | 0.63 | 13.22 | 3.92 | 1.25 | 0.37 | 1.33 | 0.39 | 0.045 | 13.35 | 0.042 | 12.46 | |
| 17693 P | 274. | 2.15 | 0.78 | 10.76 | 3.93 | 1.05 | 0.38 | 1.16 | 0.42 | 0.033 | 12.04 | 0.033 | 12.04 | |
| 17697 P | 268. | 2.17 | 0.81 | 10.23 | 3.82 | 1.11 | 0.41 | 1.10 | 0.41 | 0.030 | 11.19 | 0.026 | 9.70 | |
| 17700 P | 310. | 2.13 | 0.69 | 10.96 | 3.54 | 1.35 | 0.44 | 1.46 | 0.47 | 0.043 | 13.87 | 0.043 | 13.87 | |
| 17701 P | 311. | 2.26 | 0.73 | 12.74 | 4.10 | 1.12 | 0.36 | 1.19 | 0.38 | 0.047 | 15.11 | 0.042 | 13.50 | |
| 17705 P | 330. | 2.11 | 0.64 | 12.94 | 3.92 | 1.19 | 0.36 | 1.19 | 0.36 | 0.053 | 16.06 | 0.047 | 14.24 | |
| 17706 P | 315. | 2.22 | 0.70 | 12.79 | 4.06 | 2.15 | 0.68 | b | b | 0.043 | 13.65 | 0.039 | 12.38 | |
| 17709 P | 262. | 2.13 | 0.81 | 11.06 | 4.22 | 1.12 | 0.43 | 1.12 | 0.43 | 0.031 | 11.83 | 0.029 | 11.07 | |
| 17718 P | 295. | 2.27 | 0.77 | 12.17 | 4.12 | 1.46 | 0.49 | 1.45 | 0.49 | 0.038 | 12.88 | 0.029 | 9.83 | |
| 17720 P | 318. | 2.29 | 0.72 | 12.75 | 4.01 | 1.28 | 0.40 | 1.41 | 0.44 | 0.047 | 14.78 | 0.050 | 15.72 | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

a. Value was multiplied by 1000.

b. Dam 17706 had an absent right kidney. See the individual necropsy observations table (Table C28).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C29 (PAGE 6): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP III | | MIDDLE DOSAGE 50 MG/KG/DAY | | | | | | | | | | | |
|------------------|-------------------------|-------------------------------|---------------|-------------|---------------|---------------|----------------------------|----------------|----------------------------|-----------------------|---------------|-------------|---------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | SPLEEN | | THYMUS | | OVARY LEFT | | OVARY RIGHT | | UTERUS WITH CERVIX | | HEART | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW ^a | ABS. WT. | REL. % TBW ^a | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW |
| 17661 P | 280. | | | | | 0.073 | 26.07 | 0.088 | 31.43 | 0.63 | 0.22 | | |
| 17667 P | 311. | | | | | 0.067 | 21.54 | 0.097 | 31.19 | 0.94b | 0.30 | | |
| 17669 P | 296. | | | | | 0.072 | 24.32 | 0.080 | 27.03 | 0.89 | 0.30 | | |
| 17670 P | 268. | | | | | 0.078 | 29.10 | 0.054 | 20.15 | 0.67 | 0.25 | | |
| 17676 P | 265. | | | | | 0.060 | 22.64 | 0.072 | 27.17 | 0.67 | 0.25 | | |
| 17687 P | 337. | 0.78 | 0.23 | 0.37 | 0.11 | 0.101 | 29.97 | 0.101 | 29.97 | 0.74 | 0.22 | 1.05 | 0.31 |
| 17693 P | 274. | 0.79 | 0.29 | 0.18 | 0.06 | 0.062 | 22.63 | 0.081 | 29.56 | 0.72b | 0.26 | 0.99 | 0.36 |
| 17697 P | 268. | 0.66 | 0.25 | 0.19 | 0.07 | 0.071 | 26.49 | 0.093 | 34.70 | 0.85 | 0.32 | 0.98 | 0.36 |
| 17700 P | 310. | 0.62 | 0.20 | 0.35 | 0.11 | 0.082 | 26.45 | 0.077 | 24.84 | 0.82 | 0.26 | 1.12 | 0.36 |
| 17701 P | 311. | 0.74 | 0.24 | 0.32 | 0.10 | 0.072 | 23.15 | 0.064 | 20.58 | 0.86 | 0.28 | 1.17 | 0.38 |
| 17705 P | 330. | 0.73 | 0.22 | 0.27 | 0.08 | 0.097 | 29.39 | 0.075 | 22.73 | 0.83 | 0.25 | 1.38 | 0.42 |
| 17706 P | 315. | 0.84 | 0.27 | 0.31 | 0.10 | 0.108 | 34.28 | 0.111 | 35.24 | 0.82 | 0.26 | 1.11 | 0.35 |
| 17709 P | 262. | 0.90 | 0.34 | 0.31 | 0.12 | 0.066 | 25.19 | 0.090 | 34.35 | 0.72 | 0.27 | 0.91 | 0.35 |
| 17718 P | 295. | 0.92 | 0.31 | 0.23 | 0.08 | 0.082 | 27.80 | 0.074 | 25.08 | 0.76 | 0.26 | 1.28 | 0.43 |
| 17720 P | 318. | 0.65 | 0.20 | 0.35 | 0.11 | 0.093 | 29.24 | 0.097 | 30.50 | 0.76 | 0.24 | 1.10 | 0.34 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

a. Value was multiplied by 1000.

b. Damaged during processing (weight not affected).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C29 (PAGE 7): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| DOSAGE GROUP IV | | | HIGH DOSAGE | | | | 250 MG/KG/DAY | | | | | | |
|-----------------|----------------------|-------------------|-------------|----------|------------|-------------|---------------|--------------|------------|--------------|-------------------------|---------------|-------------------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | BRAIN | | LIVER | | KIDNEY LEFT | | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW ^a | ABS. WT. | REL. % TBW ^a |
| 17664 | NP --- | ---- | ---- | 11.51 | ---- | ---- | ---- | ---- | ---- | ---- | ---- | ---- | ---- |
| 17677 | P 287. | | | 13.06 | 4.55 | | | | | | | | |
| 17678 | P 293. | 2.23 | 0.76 | 13.68 | 4.67 | 1.23 | 0.42 | 1.25 | 0.43 | 0.050 | 17.06 | 0.038 | 12.97 |
| 17682 | P 300. | | | 14.07 | 4.69 | | | | | | | | |
| 17683 | P 259. | 2.19 | 0.84 | 12.48 | 4.82 | 1.17 | 0.45 | 1.28 | 0.49 | 0.054 | 20.85 | 0.048 | 18.53 |
| 17685 | P 277. | 2.31 ^b | 0.83 | 13.29 | 4.80 | 1.37 | 0.49 | 1.40 | 0.50 | 0.043 | 15.52 | 0.034 | 12.27 |
| 17686 | NP 284. | 2.10 | 0.74 | 12.31 | 4.33 | 1.30 | 0.46 | 1.31 | 0.46 | 0.037 | 13.03 | 0.036 | 12.68 |
| 17689 | P 285. | 2.27 | 0.80 | 14.32 | 5.02 | 1.30 | 0.46 | 1.27 | 0.44 | 0.045 | 15.79 | 0.043 | 15.09 |
| 17691 | P 286. | 2.02 | 0.71 | 11.62 | 4.06 | 1.12 | 0.39 | 1.21 | 0.42 | 0.037 | 12.94 | 0.036 | 12.59 |
| 17692 | P 277. | 2.17 | 0.78 | 13.67 | 4.94 | 1.22 | 0.44 | 1.21 | 0.44 | 0.031 | 11.19 | 0.033 | 11.91 |
| 17696 | P ^c --- | 2.17 | ---- | 14.77 | ---- | 1.28 | ---- | 1.24 | ---- | 0.053 | ---- | 0.041 | ---- |
| 17699 | P 283. | 2.18 | 0.77 | 14.51 | 5.13 | 1.30 | 0.46 | 1.40 | 0.49 | 0.055 | 19.43 | 0.050 | 17.67 |
| 17711 | P ^c --- | 2.10 | ---- | 12.56 | ---- | 1.38 | ---- | 1.38 | ---- | 0.059 | ---- | 0.052 | ---- |
| 17712 | P 292. | 2.19 | 0.75 | 14.14 | 4.84 | 1.21 | 0.41 | 1.22 | 0.42 | 0.041 | 14.04 | 0.039 | 13.36 |
| 17714 | P 294. | 2.22 | 0.76 | 14.33 | 4.87 | 1.16 | 0.39 | 1.22 | 0.41 | 0.049 | 16.67 | 0.042 | 14.28 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

a. Value was multiplied by 1000.

b. Damaged during processing (weight not affected).

c. Dam was sacrificed due to no surviving pups on day 2 of lactation; values excluded from group averages and statistical analyses.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C29 (PAGE 8): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP IV | | | HIGH DOSAGE | | | | 250 MG/KG/DAY | | | | | | |
|-----------------|----------------------|----------|-------------|----------|------------|------------|---------------|-------------|--------------|--------------------|------------|----------|------------|
| RAT NUMBER | TERMINAL BODY WEIGHT | SPLEEN | | THYMUS | | OVARY LEFT | | OVARY RIGHT | | UTERUS WITH CERVIX | | HEART | |
| | | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW a | ABS. WT. | REL. % TBW | ABS. WT. | REL. % TBW |
| 17664 NP | --- | ---- | ---- | ---- | ---- | 0.068 | ----- | 0.081 | ----- | 0.51b | ---- | ---- | ---- |
| 17677 P | 287. | | | | | 0.072 | 25.09 | 0.083 | 28.92 | 0.68 | 0.24 | | |
| 17678 P | 293. | 0.81 | 0.28 | 0.30 | 0.10 | 0.074 | 25.26 | 0.100 | 34.13 | 0.76 | 0.26 | 1.21 | 0.41 |
| 17682 P | 300. | | | | | 0.092 | 30.67 | 0.086 | 28.67 | 0.58 | 0.19 | | |
| 17683 P | 259. | 0.60 | 0.23 | 0.23 | 0.09 | 0.074 | 28.57 | 0.074 | 28.57 | 0.68 | 0.26 | 0.90 | 0.35 |
| 17685 P | 277. | 0.54 | 0.19 | 0.20 | 0.07 | 0.079 | 28.52 | 0.072 | 25.99 | 0.70 | 0.25 | 0.94 | 0.34 |
| 17686 NP | 284. | 0.48 | 0.17 | 0.43 | 0.15 | 0.058 | 20.42 | 0.053 | 18.66 | 0.42 | 0.15 | 1.09 | 0.38 |
| 17689 P | 285. | 0.70 | 0.24 | 0.19 | 0.07 | 0.072 | 25.26 | 0.066 | 23.16 | 0.82 | 0.29 | 0.99 | 0.35 |
| 17691 P | 286. | 0.54 | 0.19 | 0.29 | 0.10 | 0.066 | 23.08 | 0.074 | 25.87 | 0.67 | 0.23 | 0.94 | 0.33 |
| 17692 P | 277. | 0.66 | 0.24 | 0.15 | 0.05 | 0.057 | 20.58 | 0.076 | 27.44 | 0.71 | 0.26 | 0.84 | 0.30 |
| 17696 P c | --- | 0.49 | ---- | 0.06d | ---- | 0.070 | ----- | 0.083 | ----- | 1.71 | ---- | 0.85 | ---- |
| 17699 P | 283. | 0.67 | 0.24 | 0.23 | 0.08 | 0.090 | 31.80 | 0.102 | 36.04 | 0.64 | 0.23 | 1.00 | 0.35 |
| 17711 P c | --- | 0.39 | ---- | 0.23 | ---- | 0.062 | ----- | 0.086 | ----- | 2.15 | ---- | 1.04 | ---- |
| 17712 P | 292. | 0.69 | 0.24 | 0.20 | 0.07 | 0.088 | 30.14 | 0.095 | 32.53 | 0.77 | 0.26 | 1.18 | 0.40 |
| 17714 P | 294. | 0.56 | 0.19 | 0.15 | 0.05 | 0.076 | 25.85 | 0.057 | 19.39 | 0.71 | 0.24 | 1.05 | 0.36 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

a. Value was multiplied by 1000.

b. Damaged during processing (weight not affected).

c. Dam was sacrificed due to no surviving pups on day 2 of lactation; values excluded from group averages and statistical analyses.

d. Dam 17696 had a small thymus. See the individual necropsy observations table (Table C28).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C30 (PAGE 1): ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| DOSAGE GROUP I | | | VEHICLE 0 (VEHICLE) MG/KG/DAY | | | | | | | | | | | |
|----------------|--------------|------|-------------------------------|------------|-------------|------------|--------------|------------|--------------|------------|---------------|------------|----------|------------|
| RAT NUMBER | BRAIN WEIGHT | | LIVER | | KIDNEY LEFT | | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | SPLEEN | |
| | | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17681 | P | 2.04 | 11.10 | 544.12 | 1.13 | 55.39 | 1.19 | 58.33 | 0.034 | 1.67 | 0.034 | 1.67 | 0.76 | 37.25 |
| 17690 | P | 2.27 | 12.40 | 546.26 | 1.28 | 56.39 | 1.31 | 57.71 | 0.047 | 2.07 | 0.047 | 2.07 | 0.70 | 30.84 |
| 17694 | P | 2.28 | 11.10 | 486.84 | 1.21 | 53.07 | 1.33 | 58.33 | 0.041 | 1.80 | 0.042 | 1.84 | 0.66 | 28.95 |
| 17695 | P | 2.16 | 10.63 | 492.13 | 1.08 | 50.00 | 1.00 | 46.30 | 0.039 | 1.80 | 0.033 | 1.53 | 0.70 | 32.41 |
| 17703 | P | 2.27 | 13.19 | 581.06 | 1.51 | 66.52 | 1.43 | 63.00 | 0.042 | 1.85 | 0.044 | 1.94 | 0.79 | 34.80 |
| 17713 | P | 2.26 | 9.91 | 438.50 | 1.03 | 45.58 | 1.03 | 45.58 | 0.037 | 1.64 | 0.034 | 1.50 | 0.65 | 28.76 |
| 17715 | P | 2.22 | 11.72 | 527.93 | 1.24 | 55.86 | 1.17 | 52.70 | 0.041 | 1.85 | 0.041 | 1.85 | 0.76 | 34.23 |
| 17716 | P | 2.15 | 13.55 | 630.23 | 1.19 | 55.35 | 1.21 | 56.28 | 0.044 | 2.05 | 0.042 | 1.95 | 0.70 | 32.56 |
| 17717 | P | 2.15 | 9.57 | 445.12 | 1.15 | 53.49 | 1.15 | 53.49 | 0.049 | 2.28 | 0.054 | 2.51 | 0.73 | 33.95 |
| 17719 | P | 2.16 | 11.30 | 523.15 | 1.14 | 52.78 | 1.17 | 54.17 | 0.044 | 2.04 | 0.041 | 1.90 | 0.59 | 27.31 |

| RAT NUMBER | BRAIN WEIGHT | | THYMUS | | OVARY LEFT | | OVARY RIGHT | | UTERUS WITH CERVIX | | HEART | |
|------------|--------------|------|----------|------------|------------|------------|-------------|------------|--------------------|------------|----------|------------|
| | | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17681 | P | 2.04 | 0.33 | 16.18 | 0.080 | 3.92 | 0.096 | 4.70 | 0.74 | 36.27 | 1.04 | 50.98 |
| 17690 | P | 2.27 | 0.38 | 16.74 | 0.094 | 4.14 | 0.078 | 3.44 | 0.84 | 37.00 | 1.17 | 51.54 |
| 17694 | P | 2.28 | 0.23 | 10.09 | 0.081 | 3.55 | 0.070 | 3.07 | 0.77 | 33.77 | 1.11 | 48.68 |
| 17695 | P | 2.16 | 0.24 | 11.11 | 0.103 | 4.77 | 0.090 | 4.17 | 0.96 | 44.44 | 0.94 | 43.52 |
| 17703 | P | 2.27 | 0.37 | 16.30 | 0.111 | 4.89 | 0.113 | 4.98 | 0.95 | 41.85 | 1.25 | 55.07 |
| 17713 | P | 2.26 | 0.31 | 13.72 | 0.044 | 1.95 | 0.057 | 2.52 | 0.74 | 32.74 | 1.02 | 45.13 |
| 17715 | P | 2.22 | 0.25 | 11.26 | 0.066 | 2.97 | 0.096 | 4.32 | 0.98 | 44.14 | 1.24 | 55.86 |
| 17716 | P | 2.15 | 0.20 | 9.30 | 0.080 | 3.72 | 0.071 | 3.30 | 0.68 | 31.63 | 1.00 | 46.51 |
| 17717 | P | 2.15 | 0.27 | 12.56 | 0.068 | 3.16 | 0.071 | 3.30 | 0.62 | 28.84 | 1.08 | 50.23 |
| 17719 | P | 2.16 | 0.15 | 6.94 | 0.083 | 3.84 | 0.079 | 3.66 | 0.77a | 35.65 | 0.99 | 45.83 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.
P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
a. Damaged during processing (weight not affected).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C30 (PAGE 2): ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP II | | | LOW DOSAGE | | | | 10 MG/KG/DAY | | | | | | | |
|-----------------|--------------|------|------------|------------|-------------|------------|--------------|------------|--------------|------------|---------------|------------|----------|------------|
| RAT NUMBER | BRAIN WEIGHT | | LIVER | | KIDNEY LEFT | | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | SPLEEN | |
| | | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17675 | P | 2.18 | 12.27 | 562.84 | 1.31 | 60.09 | 1.34 | 61.47 | 0.044 | 2.02 | 0.039 | 1.79 | 0.75 | 34.40 |
| 17679 | P | 2.13 | 11.54 | 541.78 | 1.35 | 63.38 | 1.30 | 61.03 | 0.037 | 1.74 | 0.036 | 1.69 | 0.55 | 25.82 |
| 17684 | P | 2.15 | 12.17 | 566.05 | 1.30 | 60.46 | 1.37 | 63.72 | 0.042 | 1.95 | 0.042 | 1.95 | 0.74 | 34.42 |
| 17688 | P | 2.21 | 11.60 | 524.89 | 1.02 | 46.15 | 1.20 | 54.30 | 0.054 | 2.44 | 0.049 | 2.22 | 0.64 | 28.96 |
| 17698 | P | 2.24 | 11.43 | 510.27 | 1.38 | 61.61 | 1.41 | 62.95 | 0.047 | 2.10 | 0.036 | 1.61 | 0.66 | 29.46 |
| 17702 | P | 2.05 | 11.83 | 577.07 | 1.14 | 55.61 | 1.23 | 60.00 | 0.041 | 2.00 | 0.040 | 1.95 | 0.71 | 34.63 |
| 17704 | P | 2.26 | 13.36 | 591.15 | 1.41 | 62.39 | 1.41 | 62.39 | 0.049 | 2.17 | 0.049 | 2.17 | 0.98 | 43.36 |
| 17707 | P | 2.18 | 11.40 | 522.94 | 1.15 | 52.75 | 1.10 | 50.46 | 0.047 | 2.16 | 0.045 | 2.06 | 0.60 | 27.52 |
| 17708 | P | 2.29 | 14.27 | 623.14 | 1.49 | 65.06 | 1.35 | 58.95 | 0.039 | 1.70 | 0.042 | 1.83 | 0.82 | 35.81 |
| 17710 | P | 2.20 | 13.78 | 626.36 | 1.39 | 63.18 | 1.40 | 63.64 | 0.063 | 2.86 | 0.056 | 2.54 | 0.95 | 43.18 |

| RAT NUMBER | BRAIN WEIGHT | | THYMUS | | OVARY LEFT | | OVARY RIGHT | | UTERUS WITH CERVIX | | HEART | |
|------------|--------------|------|----------|------------|------------|------------|-------------|------------|--------------------|------------|----------|------------|
| | | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17675 | P | 2.18 | 0.36 | 16.51 | 0.078 | 3.58 | 0.086 | 3.94 | 0.89 | 40.82 | 1.13 | 51.83 |
| 17679 | P | 2.13 | 0.29 | 13.62 | 0.063 | 2.96 | 0.071 | 3.33 | 0.71 | 33.33 | 1.00 | 46.95 |
| 17684 | P | 2.15 | 0.36 | 16.74 | 0.080 | 3.72 | 0.090 | 4.19 | 0.84 | 39.07 | 1.19 | 55.35 |
| 17688 | P | 2.21 | 0.26 | 11.76 | 0.090 | 4.07 | 0.086 | 3.89 | 0.76 | 34.39 | 1.23 | 55.66 |
| 17698 | P | 2.24 | 0.30 | 13.39 | 0.110 | 4.91 | 0.092 | 4.11 | 0.70 | 31.25 | 1.26 | 56.25 |
| 17702 | P | 2.05 | 0.29 | 14.15 | 0.071 | 3.46 | 0.082 | 4.00 | 0.92 | 44.88 | 1.16 | 56.58 |
| 17704 | P | 2.26 | 0.37 | 16.37 | 0.074 | 3.27 | 0.100 | 4.42 | 0.95 | 42.04 | 1.18 | 52.21 |
| 17707 | P | 2.18 | 0.29 | 13.30 | 0.077 | 3.53 | 0.086 | 3.94 | 0.66 | 30.28 | 1.08 | 49.54 |
| 17708 | P | 2.29 | 0.50 | 21.83 | 0.069 | 3.01 | 0.072 | 3.14 | 0.78 | 34.06 | 1.10 | 48.03 |
| 17710 | P | 2.20 | 0.36 | 16.36 | 0.091 | 4.14 | 0.097 | 4.41 | 0.75 | 34.09 | 1.16 | 52.73 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.
P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C30 (PAGE 3): ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP III | | | MIDDLE DOSAGE | | | | 50 MG/KG/DAY | | | | | | | |
|------------------|--------------|----------|---------------|-------------|------------|--------------|--------------|--------------|------------|---------------|------------|----------|------------|--|
| RAT NUMBER | BRAIN WEIGHT | LIVER | | KIDNEY LEFT | | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | SPLEEN | | |
| | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | |
| 17687 | P 2.13 | 13.22 | 620.66 | 1.25 | 58.68 | 1.33 | 62.44 | 0.045 | 2.11 | 0.042 | 1.97 | 0.78 | 36.62 | |
| 17693 | P 2.15 | 10.76 | 500.46 | 1.05 | 48.84 | 1.16 | 53.95 | 0.033 | 1.53 | 0.033 | 1.53 | 0.79 | 36.74 | |
| 17697 | P 2.17 | 10.23 | 471.43 | 1.11 | 51.15 | 1.10 | 50.69 | 0.030 | 1.38 | 0.026 | 1.20 | 0.66 | 30.41 | |
| 17700 | P 2.13 | 10.96 | 514.55 | 1.35 | 63.38 | 1.46 | 68.54 | 0.043 | 2.02 | 0.043 | 2.02 | 0.62 | 29.11 | |
| 17701 | P 2.26 | 12.74 | 563.72 | 1.12 | 49.56 | 1.19 | 52.65 | 0.047 | 2.08 | 0.042 | 1.86 | 0.74 | 32.74 | |
| 17705 | P 2.11 | 12.94 | 613.27 | 1.19 | 56.40 | 1.19 | 56.40 | 0.053 | 2.51 | 0.047 | 2.23 | 0.73 | 34.60 | |
| 17706 | P 2.22 | 12.79 | 576.13 | 2.15 | 96.85 | a | a | 0.043 | 1.94 | 0.039 | 1.76 | 0.84 | 37.84 | |
| 17709 | P 2.13 | 11.06 | 519.25 | 1.12 | 52.58 | 1.12 | 52.58 | 0.031 | 1.46 | 0.029 | 1.36 | 0.90 | 42.25 | |
| 17718 | P 2.27 | 12.17 | 536.12 | 1.46 | 64.32 | 1.45 | 63.88 | 0.038 | 1.67 | 0.029 | 1.28 | 0.92 | 40.53 | |
| 17720 | P 2.29 | 12.75 | 556.77 | 1.28 | 55.90 | 1.41 | 61.57 | 0.047 | 2.05 | 0.050 | 2.18 | 0.65 | 28.38 | |

| RAT NUMBER | BRAIN WEIGHT | THYMUS | | OVARY LEFT | | OVARY RIGHT | | UTERUS WITH CERVIX | | HEART | |
|------------|--------------|----------|------------|------------|------------|-------------|------------|--------------------|------------|----------|------------|
| | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW |
| 17687 | P 2.13 | 0.37 | 17.37 | 0.101 | 4.74 | 0.101 | 4.74 | 0.74 | 34.74 | 1.05 | 49.30 |
| 17693 | P 2.15 | 0.18 | 8.37 | 0.062 | 2.88 | 0.081 | 3.77 | 0.72b | 33.49 | 0.99 | 46.05 |
| 17697 | P 2.17 | 0.19 | 8.76 | 0.071 | 3.27 | 0.093 | 4.28 | 0.85 | 39.17 | 0.98 | 45.16 |
| 17700 | P 2.13 | 0.35 | 16.43 | 0.082 | 3.85 | 0.077 | 3.62 | 0.82 | 38.50 | 1.12 | 52.58 |
| 17701 | P 2.26 | 0.32 | 14.16 | 0.072 | 3.18 | 0.064 | 2.83 | 0.86 | 38.05 | 1.17 | 51.77 |
| 17705 | P 2.11 | 0.27 | 12.80 | 0.097 | 4.60 | 0.075 | 3.55 | 0.83 | 39.34 | 1.38 | 65.40 |
| 17706 | P 2.22 | 0.31 | 13.96 | 0.108 | 4.86 | 0.111 | 5.00 | 0.82 | 36.94 | 1.11 | 50.00 |
| 17709 | P 2.13 | 0.31 | 14.55 | 0.066 | 3.10 | 0.090 | 4.22 | 0.72 | 33.80 | 0.91 | 42.72 |
| 17718 | P 2.27 | 0.23 | 10.13 | 0.082 | 3.61 | 0.074 | 3.26 | 0.76 | 33.48 | 1.28 | 56.39 |
| 17720 | P 2.29 | 0.35 | 15.28 | 0.093 | 4.06 | 0.097 | 4.24 | 0.76 | 33.19 | 1.10 | 48.03 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

a. Dam 17706 had an absent right kidney. See the individual necropsy observations table (Table C28).

b. Damaged during processing (weight not affected).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C30 (PAGE 4): ORGAN WEIGHTS AND RATIOS (%) OF ORGAN WEIGHT TO BRAIN WEIGHT - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP IV | | HIGH DOSAGE | | | | | | | | | | 250 MG/KG/DAY | | | |
|-----------------|--------------|-------------|------------|-------------|------------|--------------|------------|--------------|------------|---------------|------------|---------------|------------|-------|--|
| RAT NUMBER | BRAIN WEIGHT | LIVER | | KIDNEY LEFT | | KIDNEY RIGHT | | ADRENAL LEFT | | ADRENAL RIGHT | | SPLEEN | | | |
| | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | | |
| 17678 | P | 2.23 | 13.68 | 613.45 | 1.23 | 55.16 | 1.25 | 56.05 | 0.050 | 2.24 | 0.038 | 1.70 | 0.81 | 36.32 | |
| 17683 | P | 2.19 | 12.48 | 569.86 | 1.17 | 53.42 | 1.28 | 58.45 | 0.054 | 2.46 | 0.048 | 2.19 | 0.60 | 27.40 | |
| 17685 | P | 2.31a | 13.29 | 575.32 | 1.37 | 59.31 | 1.40 | 60.61 | 0.043 | 1.86 | 0.034 | 1.47 | 0.54 | 23.38 | |
| 17686 | NP | 2.10 | 12.31 | 586.19 | 1.30 | 61.90 | 1.31 | 62.38 | 0.037 | 1.76 | 0.036 | 1.71 | 0.48 | 22.86 | |
| 17689 | P | 2.27 | 14.32 | 630.84 | 1.30 | 57.27 | 1.27 | 55.95 | 0.045 | 1.98 | 0.043 | 1.89 | 0.70 | 30.84 | |
| 17691 | P | 2.02 | 11.62 | 575.25 | 1.12 | 55.44 | 1.21 | 59.90 | 0.037 | 1.83 | 0.036 | 1.78 | 0.54 | 26.73 | |
| 17692 | P | 2.17 | 13.67 | 629.95 | 1.22 | 56.22 | 1.21 | 55.76 | 0.031 | 1.43 | 0.033 | 1.52 | 0.66 | 30.41 | |
| 17696b | P | 2.17 | 14.77 | 680.64 | 1.28 | 58.99 | 1.24 | 57.14 | 0.053 | 2.44 | 0.041 | 1.89 | 0.49 | 22.58 | |
| 17699 | P | 2.18 | 14.51 | 665.60 | 1.30 | 59.63 | 1.40 | 64.22 | 0.055 | 2.52 | 0.050 | 2.29 | 0.67 | 30.73 | |
| 17711b | P | 2.10 | 12.56 | 598.10 | 1.38 | 65.71 | 1.38 | 65.71 | 0.059 | 2.81 | 0.052 | 2.48 | 0.39 | 18.57 | |
| 17712 | P | 2.19 | 14.14 | 645.66 | 1.21 | 55.25 | 1.22 | 55.71 | 0.041 | 1.87 | 0.039 | 1.78 | 0.69 | 31.51 | |
| 17714 | P | 2.22 | 14.33 | 645.50 | 1.16 | 52.25 | 1.22 | 54.95 | 0.049 | 2.21 | 0.042 | 1.89 | 0.56 | 25.22 | |

| RAT NUMBER | BRAIN WEIGHT | THYMUS | | OVARY LEFT | | OVARY RIGHT | | UTERUS WITH CERVIX | | HEART | | |
|------------|--------------|----------|------------|------------|------------|-------------|------------|--------------------|------------|----------|------------|-------|
| | | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | ABS. WT. | REL. % BRW | |
| 17678 | P | 2.23 | 0.30 | 13.45 | 0.074 | 3.32 | 0.100 | 4.48 | 0.76 | 34.08 | 1.21 | 54.26 |
| 17683 | P | 2.19 | 0.23 | 10.50 | 0.074 | 3.38 | 0.074 | 3.38 | 0.68 | 31.05 | 0.90 | 41.10 |
| 17685 | P | 2.31a | 0.20 | 8.66 | 0.079 | 3.42 | 0.072 | 3.12 | 0.70 | 30.30 | 0.94 | 40.69 |
| 17686 | NP | 2.10 | 0.43 | 20.48 | 0.058 | 2.76 | 0.053 | 2.52 | 0.42 | 20.00 | 1.09 | 51.90 |
| 17689 | P | 2.27 | 0.19 | 8.37 | 0.072 | 3.17 | 0.066 | 2.91 | 0.82 | 36.12 | 0.99 | 43.61 |
| 17691 | P | 2.02 | 0.29 | 14.36 | 0.066 | 3.27 | 0.074 | 3.66 | 0.67 | 33.17 | 0.94 | 46.53 |
| 17692 | P | 2.17 | 0.15 | 6.91 | 0.057 | 2.63 | 0.076 | 3.50 | 0.71 | 32.72 | 0.84 | 38.71 |
| 17696b | P | 2.17 | 0.06c | 2.76 | 0.070 | 3.22 | 0.083 | 3.82 | 1.71 | 78.80 | 0.85 | 39.17 |
| 17699 | P | 2.18 | 0.23 | 10.55 | 0.090 | 4.13 | 0.102 | 4.68 | 0.64 | 29.36 | 1.00 | 45.87 |
| 17711b | P | 2.10 | 0.23 | 10.95 | 0.062 | 2.95 | 0.086 | 4.10 | 2.15 | 102.38 | 1.04 | 49.52 |
| 17712 | P | 2.19 | 0.20 | 9.13 | 0.088 | 4.02 | 0.095 | 4.34 | 0.77 | 35.16 | 1.18 | 53.88 |
| 17714 | P | 2.22 | 0.15 | 6.76 | 0.076 | 3.42 | 0.057 | 2.57 | 0.71 | 31.98 | 1.05 | 47.30 |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/BRAIN WEIGHT) X 100.

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

a. Damaged during processing (weight not affected).

b. Dam was sacrificed due to no surviving pups on day 2 of lactation; values excluded from group averages and statistical analyses.

c. Dam 17696 had a small thymus. See the individual necropsy observations table (Table C28).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C31 (PAGE 1): BODY WEIGHTS - PRECOHABITATION - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP I | | | | | VEHICLE | | | | | 0 (VEHICLE) MG/KG/DAY | | | | |
|-------|----------------|------|------|------|------|---------|------|------|------|------|-----------------------|------|------|------|------|
| | DAY | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 17662 | 222. | 221. | 229. | 231. | 234. | 234. | 238. | 241. | 243. | 239. | 246. | 247. | 249. | 247. | 252. |
| 17672 | 237. | 241. | 240. | 243. | 254. | 250. | 253. | 262. | 266. | 264. | 267. | 276. | 279. | 279. | 275. |
| 17673 | 225. | 225. | 224. | 229. | 232. | 234. | 228. | 239. | 237. | 241. | 236. | 238. | 245. | 247. | 246. |
| 17674 | 229. | 230. | 237. | 240. | 242. | 243. | 251. | 254. | 261. | 264. | 261. | 270. | 271. | 277. | 270. |
| 17680 | 222. | 220. | 229. | 232. | 233. | 229. | 235. | 245. | 246. | 243. | 247. | 251. | 256. | 250. | 257. |
| 17681 | 239. | 235. | 242. | 245. | 244. | 247. | 252. | 257. | 253. | 256. | 260. | 262. | 265. | 263. | 267. |
| 17690 | 224. | 226. | 234. | 237. | 242. | 242. | 248. | 258. | 253. | 261. | 262. | 262. | 269. | 271. | 275. |
| 17694 | 226. | 226. | 230. | 232. | 237. | 243. | 245. | 243. | 249. | 251. | 253. | 251. | 257. | 264. | 265. |
| 17695 | 216. | 220. | 227. | 224. | 226. | 231. | 237. | 234. | 233. | 241. | 244. | 239. | 244. | 254. | 250. |
| 17703 | 240. | 238. | 248. | 248. | 256. | 252. | 260. | 268. | 266. | 266. | 273. | 279. | 283. | 278. | 292. |
| 17713 | 230. | 229. | 239. | 239. | 240. | 237. | 245. | 252. | 249. | 249. | 253. | 257. | 252. | 254. | 260. |
| 17715 | 237. | 238. | 247. | 249. | 246. | 247. | 258. | 259. | 261. | 262. | 270. | 273. | 271. | 269. | 274. |
| 17716 | 221. | 222. | 224. | 227. | 227. | 229. | 231. | 233. | 238. | 235. | 233. | 240. | 242. | 242. | 244. |
| 17717 | 224. | 227. | 232. | 229. | 234. | 240. | 246. | 250. | 256. | 262. | 260. | 264. | 270. | 270. | 271. |
| 17719 | 216. | 217. | 221. | 219. | 219. | 224. | 228. | 228. | 227. | 230. | 233. | 238. | 238. | 234. | 237. |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Last value recorded before cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C31 (PAGE 2): BODY WEIGHTS - PRECOHABITATION - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP II | | | | | LOW DOSAGE | | | | | 10 MG/KG/DAY | | | | |
|-------|-----------------|------|------|------|------|------------|------|------|------|------|--------------|------|------|------|------|
| | DAY | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 17663 | 221. | 220. | 224. | 222. | 229. | 223. | 235. | 235. | 237. | 237. | 240. | 243. | 246. | 247. | 247. |
| 17665 | 234. | 232. | 238. | 244. | 242. | 238. | 245. | 250. | 247. | 247. | 251. | 256. | 256. | 257. | 262. |
| 17666 | 223. | 226. | 233. | 234. | 240. | 244. | 248. | 248. | 256. | 259. | 259. | 259. | 263. | 269. | 268. |
| 17668 | 224. | 225. | 231. | 235. | 233. | 233. | 236. | 240. | 241. | 240. | 244. | 247. | 248. | 246. | 252. |
| 17671 | 215. | 215. | 222. | 222. | 224. | 220. | 224. | 236. | 230. | 226. | 231. | 235. | 235. | 232. | 235. |
| 17675 | 233. | 236. | 238. | 238. | 238. | 241. | 246. | 250. | 248. | 256. | 254. | 253. | 253. | 259. | 260. |
| 17679 | 221. | 225. | 231. | 234. | 236. | 236. | 240. | 249. | 246. | 248. | 254. | 257. | 257. | 260. | 262. |
| 17684 | 228. | 234. | 236. | 239. | 243. | 245. | 247. | 251. | 259. | 260. | 261. | 264. | 266. | 268. | 264. |
| 17688 | 225. | 226. | 229. | 232. | 234. | 235. | 240. | 246. | 246. | 250. | 255. | 258. | 256. | 261. | 265. |
| 17698 | 237. | 230. | 239. | 246. | 246. | 242. | 250. | 258. | 258. | 255. | 262. | 264. | 267. | 266. | 272. |
| 17702 | 223. | 230. | 227. | 233. | 240. | 246. | 244. | 250. | 263. | 263. | 254. | 259. | 270. | 269. | 261. |
| 17704 | 233. | 232. | 236. | 240. | 246. | 248. | 250. | 255. | 261. | 268. | 271. | 267. | 273. | 278. | 280. |
| 17707 | 218. | 224. | 220. | 226. | 227. | 230. | 232. | 237. | 235. | 234. | 236. | 238. | 243. | 242. | 245. |
| 17708 | 239. | 238. | 245. | 252. | 254. | 254. | 260. | 266. | 270. | 272. | 271. | 278. | 283. | 286. | 285. |
| 17710 | 236. | 238. | 239. | 249. | 246. | 251. | 256. | 261. | 264. | 265. | 265. | 272. | 280. | 278. | 276. |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Last value recorded before cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C31 (PAGE 3): BODY WEIGHTS - PRECOHABITATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP III | | | | MIDDLE DOSAGE | | | | | 50 MG/KG/DAY | | | | | |
|-------|------------------|------|------|------|---------------|------|------|------|------|--------------|------|------|------|------|------|
| | DAY | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 17661 | 218. | 220. | 226. | 222. | 222. | 229. | 230. | 226. | 228. | 234. | 235. | 233. | 232. | 237. | 239. |
| 17667 | 232. | 240. | 247. | 249. | 244. | 252. | 258. | 257. | 256. | 263. | 268. | 264. | 262. | 270. | 272. |
| 17669 | 231. | 231. | 241. | 242. | 244. | 242. | 253. | 257. | 258. | 258. | 265. | 268. | 267. | 267. | 271. |
| 17670 | 228. | 226. | 229. | 234. | 238. | 238. | 238. | 249. | 247. | 245. | 247. | 249. | 258. | 254. | 249. |
| 17676 | 217. | 218. | 218. | 223. | 226. | 227. | 225. | 231. | 232. | 235. | 236. | 234. | 238. | 243. | 246. |
| 17687 | 238. | 238. | 248. | 252. | 255. | 256. | 262. | 270. | 268. | 276. | 281. | 288. | 289. | 287. | 289. |
| 17693 | 222. | 226. | 230. | 234. | 237. | 237. | 238. | 249. | 249. | 250. | 248. | 246. | 256. | 255. | 253. |
| 17697 | 225. | 225. | 230. | 235. | 233. | 232. | 237. | 243. | 241. | 240. | 244. | 250. | 249. | 253. | 252. |
| 17700 | 225. | 229. | 233. | 238. | 242. | 244. | 249. | 256. | 254. | 255. | 261. | 263. | 266. | 266. | 273. |
| 17701 | 236. | 235. | 244. | 248. | 249. | 249. | 255. | 261. | 262. | 264. | 269. | 269. | 271. | 272. | 278. |
| 17705 | 225. | 225. | 230. | 235. | 239. | 240. | 242. | 255. | 253. | 248. | 263. | 262. | 268. | 261. | 271. |
| 17706 | 227. | 231. | 234. | 238. | 243. | 244. | 246. | 253. | 257. | 259. | 259. | 266. | 266. | 262. | 266. |
| 17709 | 222. | 220. | 223. | 224. | 228. | 223. | 229. | 232. | 233. | 230. | 236. | 240. | 243. | 240. | 245. |
| 17718 | 228. | 231. | 230. | 234. | 235. | 237. | 236. | 243. | 244. | 248. | 246. | 250. | 254. | 253. | 249. |
| 17720 | 224. | 226. | 222. | 229. | 233. | 235. | 245. | 245. | 253. | 258. | 259. | 264. | 278. | 269. | 257. |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Last value recorded before cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C31 (PAGE 4): BODY WEIGHTS - PRECOHABITATION - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP IV | | | | | HIGH DOSAGE | | | | | 250 MG/KG/DAY | | | | |
|-------|-----------------|------|------|------|------|-------------|------|------|------|------|---------------|------|------|------|------|
| | DAY | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 17664 | 217. | 219. | 214. | 219. | 225. | 227. | 223. | 232. | 233. | 235. | 232. | 241. | 244. | 244. | 242. |
| 17677 | 236. | 239. | 244. | 240. | 249. | 255. | 257. | 256. | 251. | 263. | 264. | 273. | 271. | 270. | 268. |
| 17678 | 228. | 227. | 229. | 231. | 236. | 238. | 234. | 244. | 243. | 246. | 242. | 249. | 251. | 248. | 250. |
| 17682 | 224. | 233. | 234. | 235. | 237. | 242. | 247. | 248. | 252. | 253. | 256. | 256. | 256. | 256. | 260. |
| 17683 | 222. | 220. | 226. | 226. | 228. | 226. | 228. | 234. | 233. | 236. | 240. | 241. | 240. | 241. | 243. |
| 17685 | 233. | 233. | 235. | 230. | 236. | 241. | 239. | 241. | 246. | 251. | 250. | 246. | 253. | 257. | 258. |
| 17686 | 227. | 225. | 227. | 228. | 229. | 230. | 228. | 237. | 237. | 235. | 235. | 242. | 241. | 243. | 244. |
| 17689 | 226. | 226. | 229. | 235. | 238. | 238. | 241. | 247. | 248. | 250. | 252. | 256. | 256. | 256. | 260. |
| 17691 | 229. | 222. | 215. | 223. | 233. | 234. | 235. | 243. | 244. | 245. | 243. | 249. | 248. | 253. | 252. |
| 17692 | 222. | 224. | 225. | 224. | 231. | 235. | 235. | 236. | 241. | 244. | 243. | 241. | 246. | 247. | 246. |
| 17696 | 218. | 219. | 218. | 225. | 228. | 225. | 223. | 232. | 233. | 236. | 234. | 236. | 241. | 235. | 234. |
| 17699 | 232. | 234. | 239. | 243. | 247. | 248. | 254. | 256. | 257. | 256. | 260. | 260. | 264. | 260. | 267. |
| 17711 | 223. | 222. | 223. | 224. | 232. | 234. | 233. | 234. | 239. | 239. | 238. | 240. | 243. | 243. | 241. |
| 17712 | 227. | 228. | 221. | 228. | 234. | 237. | 226. | 234. | 238. | 239. | 236. | 235. | 243. | 244. | 246. |
| 17714 | 234. | 235. | 242. | 248. | 252. | 252. | 258. | 264. | 264. | 264. | 270. | 278. | 280. | 278. | 282. |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Last value recorded before cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C32 (PAGE 1): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP I | VEHICLE | O (VEHICLE) MG/KG/DAY | | | | | | | | | | | | |
|-------|----------------|---------|-----------------------|-------|------|------|------|------|------|------|------|------|------|------|------|
| | | | PREGNANCY STATUS | DAY 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 17662 | P | | 255. | 263. | 270. | 270. | 276. | 281. | 287. | 288. | 293. | 300. | 303. | 310. | 315. |
| 17672 | P | | 289. | 298. | 299. | 301. | 304. | 312. | 316. | 323. | 326. | 324. | 336. | 348. | 346. |
| 17673 | P | | 248. | 253. | 261. | 265. | 267. | 269. | 275. | 276. | 283. | 284. | 286. | 296. | 300. |
| 17674 | P | | 272. | 284. | 290. | 293. | 294. | 302. | 304. | 308. | 315. | 316. | 321. | 329. | 338. |
| 17680 | P | | 268. | 272. | 286. | 281. | 285. | 288. | 289. | 297. | 300. | 304. | 312. | 320. | 328. |
| 17681 | P | | 277. | 284. | 286. | 287. | 292. | 298. | 301. | 306. | 309. | 312. | 320. | 328. | 334. |
| 17690 | P | | 281. | 289. | 301. | 300. | 307. | 312. | 324. | 328. | 330. | 340. | 343. | 351. | 361. |
| 17694 | P | | 265. | 274. | 277. | 278. | 284. | 286. | 295. | 292. | 299. | 300. | 309. | 312. | 319. |
| 17695 | P | | 254. | 259. | 262. | 268. | 270. | 278. | 280. | 284. | 280. | 281. | 292. | 293. | 305. |
| 17703 | P | | 286. | 296. | 309. | 313. | 316. | 319. | 327. | 331. | 336. | 341. | 347. | 354. | 362. |
| 17713 | P | | 260. | 269. | 274. | 276. | 283. | 279. | 281. | 292. | 293. | 293. | 302. | 304. | 317. |
| 17715 | P | | 288. | 298. | 300. | 310. | 308. | 316. | 316. | 320. | 327. | 328. | 337. | 344. | 352. |
| 17716 | P | | 253. | 264. | 265. | 271. | 276. | 280. | 277. | 283. | 285. | 292. | 295. | 303. | 307. |
| 17717 | P | | 269. | 276. | 279. | 282. | 284. | 286. | 288. | 285. | 291. | 292. | 297. | 306. | 305. |
| 17719 | P | | 262. | 266. | 268. | 271. | 274. | 275. | 277. | 282. | 286. | 283. | 287. | 291. | 291. |
| | | | DAY 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
| 17662 | P | | 316. | 323. | 329. | 342. | 354. | 367. | 380. | 392. | 406. | | | | |
| 17672 | P | | 354. | 360. | 372. | 380. | 394. | 408. | 424. | 442. | 464. | | | | |
| 17673 | P | | 304. | 308. | 316. | 326. | 336. | 351. | 364. | 380. | 393. | | | | |
| 17674 | P | | 341. | 352. | 360. | 371. | 385. | 407. | 429. | 453. | 461. | | | | |
| 17680 | P | | 332. | 341. | 352. | 360. | 377. | 397. | 412. | 438. | 458. | | | | |
| 17681 | P | | 334. | 346. | 348. | 358. | 370. | 391. | 403. | 414. | 427. | | | | |
| 17690 | P | | 371. | 380. | 386. | 400. | 413. | 440. | 454. | 476. | 512. | | | | |
| 17694 | P | | 325. | 338. | 344. | 354. | 367. | 383. | 399. | 417. | 437. | | | | |
| 17695 | P | | 299. | 307. | 319. | 332. | 341. | 362. | 372. | 380. | | | | | |
| 17703 | P | | 370. | 387. | 389. | 400. | 419. | 439. | 448. | 477. | | | | | |
| 17713 | P | | 318. | 331. | 333. | 345. | 355. | 376. | 380. | 392. | 413. | | | | |
| 17715 | P | | 360. | 364. | 373. | 377. | 392. | 410. | 423. | 444. | 469. | | | | |
| 17716 | P | | 313. | 316. | 327. | 337. | 352. | 361. | 379. | 392. | 410. | | | | |
| 17717 | P | | 310. | 318. | 324. | 332. | 339. | 357. | 367. | 381. | 387. | | | | |
| 17719 | P | | 300. | 304. | 309. | 321. | 335. | 354. | 375. | 393. | 415. | | | | |

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
 DAY = DAY OF PRESUMED GESTATION
 ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C32 (PAGE 2): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP II | LOW DOSAGE | | | | | | | | | | | | |
|------------------|-----------------|--------------|------|------|------|------|------|------|------|------|------|------|------|----|
| | | 10 MG/KG/DAY | | | | | | | | | | | | |
| PREGNANCY STATUS | DAY | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| 17663 NP | 258. | 253. | 250. | 256. | 261. | 261. | 259. | 260. | 262. | 267. | 271. | 268. | 266. | |
| 17665 P | 267. | 271. | 274. | 280. | 284. | 286. | 295. | 296. | 297. | 300. | 308. | 315. | 324. | |
| 17666 P | 272. | 275. | 279. | 284. | 286. | 278. | 283. | 288. | 289. | 292. | 298. | 298. | 303. | |
| 17668 P | 263. | 261. | 269. | 276. | 280. | 279. | 291. | 290. | 294. | 298. | 306. | 314. | 324. | |
| 17671 P | 244. | 251. | 255. | 249. | 258. | 260. | 263. | 265. | 271. | 273. | 280. | 281. | 292. | |
| 17675 P | 266. | 267. | 272. | 277. | 278. | 282. | 283. | 291. | 291. | 298. | 299. | 306. | 313. | |
| 17679 P | 271. | 277. | 282. | 279. | 284. | 284. | 286. | 291. | 290. | 298. | 298. | 306. | 316. | |
| 17684 P | 283. | 286. | 294. | 294. | 298. | 304. | 303. | 309. | 311. | 314. | 324. | 333. | 339. | |
| 17688 P | 275. | 281. | 285. | 288. | 293. | 298. | 303. | 305. | 310. | 316. | 324. | 329. | 336. | |
| 17698 P | 278. | 284. | 298. | 300. | 305. | 309. | 314. | 309. | 317. | 321. | 334. | 336. | 342. | |
| 17702 P | 273. | 284. | 286. | 291. | 292. | 289. | 296. | 299. | 300. | 309. | 306. | 316. | 319. | |
| 17704 P | 277. | 291. | 294. | 299. | 298. | 304. | 306. | 313. | 316. | 324. | 329. | 336. | 348. | |
| 17707 P | 264. | 261. | 265. | 270. | 271. | 278. | 275. | 279. | 283. | 283. | 286. | 299. | 304. | |
| 17708 P | 288. | 290. | 294. | 301. | 303. | 310. | 312. | 320. | 323. | 328. | 332. | 334. | 349. | |
| 17710 P | 300. | 308. | 311. | 323. | 322. | 326. | 332. | 327. | 335. | 345. | 347. | 354. | 371. | |
| | DAY 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | |
| 17663 NP | 268. | 269. | 270. | 272. | 269. | 268. | 267. | 269. | 277. | 279. | 281. | 279. | 267. | |
| 17665 P | 326. | 336. | 339. | 354. | 368. | 390. | 396. | 417. | 434. | | | | | |
| 17666 P | 307. | 309. | 314. | 326. | 339. | 355. | 371. | 387. | 400. | | | | | |
| 17668 P | 322. | 338. | 337. | 353. | 373. | 382. | 391. | 405. | 426. | | | | | |
| 17671 P | 289. | 294. | 300. | 310. | 322. | 334. | 346. | 359. | 371. | | | | | |
| 17675 P | 317. | 317. | 321. | 335. | 353. | 377. | 395. | 411. | 434. | | | | | |
| 17679 P | 313. | 323. | 323. | 330. | 343. | 348. | 362. | 375. | 383. | | | | | |
| 17684 P | 348. | 351. | 361. | 373. | 388. | 404. | 425. | 441. | 468. | | | | | |
| 17688 P | 332. | 351. | 344. | 366. | 387. | 406. | 419. | 432. | | | | | | |
| 17698 P | 340. | 356. | 353. | 364. | 376. | 397. | 402. | 413. | | | | | | |
| 17702 P | 329. | 332. | 345. | 357. | 370. | 389. | 404. | 416. | 436. | | | | | |
| 17704 P | 349. | 356. | 372. | 382. | 399. | 425. | 445. | 459. | 468. | | | | | |
| 17707 P | 313. | 315. | 320. | 328. | 340. | 363. | 377. | 389. | 408. | | | | | |
| 17708 P | 350. | 355. | 363. | 378. | 389. | 414. | 431. | 456. | 472. | | | | | |
| 17710 P | 374. | 384. | 388. | 403. | 416. | 436. | 449. | 471. | 498. | | | | | |

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
 DAY = DAY OF PRESUMED GESTATION
 ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C32 (PAGE 3): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP III | | | MIDDLE DOSAGE | | | | 50 MG/KG/DAY | | | | | | |
|---------|------------------|-------|------|---------------|------|------|------|--------------|------|------|------|------|------|------|
| | PREGNANCY STATUS | DAY 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| 17661 P | | 243. | 251. | 248. | 253. | 259. | 258. | 265. | 276. | 275. | 279. | 286. | 293. | 302. |
| 17667 P | | 273. | 287. | 290. | 296. | 295. | 299. | 301. | 308. | 313. | 316. | 321. | 327. | 335. |
| 17669 P | | 282. | 288. | 290. | 290. | 294. | 295. | 293. | 301. | 305. | 307. | 309. | 317. | 325. |
| 17670 P | | 262. | 262. | 265. | 262. | 269. | 275. | 274. | 275. | 279. | 287. | 292. | 295. | 305. |
| 17676 P | | 247. | 250. | 253. | 253. | 255. | 260. | 261. | 265. | 262. | 265. | 270. | 274. | 282. |
| 17687 P | | 305. | 305. | 311. | 313. | 322. | 326. | 333. | 336. | 337. | 348. | 356. | 366. | |
| 17693 P | | 255. | 262. | 265. | 268. | 272. | 275. | 279. | 281. | 283. | 279. | 288. | 298. | 302. |
| 17697 P | | 258. | 262. | 274. | 274. | 271. | 274. | 275. | 275. | 277. | 280. | 286. | 297. | 298. |
| 17700 P | | 277. | 280. | 285. | 288. | 293. | 296. | 297. | 300. | 305. | 310. | 312. | 321. | 328. |
| 17701 P | | 293. | 298. | 299. | 301. | 311. | 311. | 312. | 322. | 324. | 331. | 341. | 346. | 354. |
| 17705 P | | 280. | 288. | 297. | 297. | 303. | 299. | 311. | 316. | 320. | 325. | 330. | 338. | 352. |
| 17706 P | | 276. | 282. | 283. | 286. | 294. | 301. | 302. | 301. | 306. | 314. | 317. | 324. | 337. |
| 17709 P | | 273. | 272. | 276. | 278. | 284. | 286. | 286. | 293. | 291. | 287. | 296. | 301. | 300. |
| 17718 P | | 288. | 292. | 297. | 294. | 299. | 298. | 301. | 304. | 305. | 306. | 311. | 320. | 324. |
| 17720 P | | 269. | 273. | 276. | 284. | 293. | 294. | 297. | 302. | 304. | 309. | 314. | 323. | 333. |
| | DAY 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | |
| 17661 P | | 306. | 312. | 326. | 340. | 355. | 376. | 391. | 402. | 424. | | | | |
| 17667 P | | 337. | 342. | 353. | 361. | 378. | 395. | 412. | 419. | 440. | | | | |
| 17669 P | | 325. | 330. | 338. | 348. | 367. | 386. | 403. | 416. | 436. | | | | |
| 17670 P | | 306. | 315. | 320. | 337. | 346. | 362. | 380. | 394. | 416. | | | | |
| 17676 P | | 284. | 291. | 298. | 308. | 324. | 334. | 350. | 358. | 373. | | | | |
| 17687 P | | 370. | 370. | 376. | 388. | 403. | 417. | 434. | 450. | 476. | | | | |
| 17693 P | | 301. | 306. | 312. | 327. | 330. | 351. | 369. | 385. | 405. | | | | |
| 17697 P | | 300. | 310. | 318. | 326. | 344. | 361. | 373. | 386. | 405. | | | | |
| 17700 P | | 333. | 341. | 352. | 361. | 375. | 390. | 405. | 416. | | | | | |
| 17701 P | | 355. | 365. | 366. | 383. | 388. | 410. | 423. | 442. | 466. | | | | |
| 17705 P | | 350. | 359. | 367. | 377. | 394. | 407. | 418. | 443. | 467. | | | | |
| 17706 P | | 340. | 339. | 351. | 359. | 377. | 377. | 401. | 423. | 443. | | | | |
| 17709 P | | 304. | 308. | 307. | 324. | 331. | 352. | 362. | 379. | 391. | | | | |
| 17718 P | | 326. | 335. | 344. | 352. | 367. | 386. | 402. | 423. | | | | | |
| 17720 P | | 336. | 346. | 354. | 366. | 380. | 397. | 413. | 435. | 454. | | | | |

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C32 (PAGE 4): MATERNAL BODY WEIGHTS - PRESUMED GESTATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP IV | | | HIGH DOSAGE | | | | 250 MG/KG/DAY | | | | | | |
|----------|----------------------|-------|------|-------------|------|------|------|---------------|------|------|------|------|------|----|
| | PREGNANCY STATUS | DAY 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| 17664 NP | MATING NOT CONFIRMED | | | | | | | | | | | | | |
| 17677 P | 268. | 276. | 278. | 281. | 288. | 290. | 286. | 289. | 296. | 297. | 303. | 313. | 317. | |
| 17678 P | 263. | 269. | 274. | 283. | 284. | 289. | 292. | 297. | 299. | 303. | 309. | 320. | 327. | |
| 17682 P | 288. | 284. | 288. | 290. | 293. | 292. | 293. | 299. | 299. | 303. | 308. | 310. | 319. | |
| 17683 P | 250. | 264. | 265. | 261. | 264. | 267. | 270. | 266. | 278. | 279. | 293. | 304. | 315. | |
| 17685 P | 262. | 268. | 270. | 275. | 280. | 282. | 288. | 289. | 290. | 295. | 299. | 302. | 305. | |
| 17686 NP | 243. | 251. | 259. | 265. | 267. | 268. | 272. | 271. | 278. | 284. | 286. | 302. | 293. | |
| 17689 P | 264. | 268. | 267. | 268. | 270. | 272. | 276. | 282. | 288. | 290. | 293. | 302. | 305. | |
| 17691 P | 264. | 268. | 274. | 277. | 281. | 288. | 287. | 295. | 296. | 304. | 309. | 316. | 317. | |
| 17692 P | 254. | 260. | 262. | 264. | 269. | 269. | 274. | 278. | 276. | 283. | 284. | 291. | 299. | |
| 17696 P | 231. | 244. | 252. | 252. | 252. | 255. | 257. | 256. | 259. | 261. | 272. | 274. | 282. | |
| 17699 P | 272. | 275. | 283. | 282. | 289. | 292. | 299. | 295. | 296. | 302. | 309. | 312. | 321. | |
| 17711 P | 249. | 254. | 256. | 256. | 261. | 264. | 266. | 268. | 264. | 271. | 278. | 282. | 293. | |
| 17712 P | 250. | 261. | 267. | 264. | 271. | 274. | 276. | 276. | 280. | 285. | 288. | 295. | 301. | |
| 17714 P | 291. | 296. | 306. | 305. | 316. | 318. | 317. | 322. | 327. | 333. | 338. | 341. | 348. | |
| | DAY 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | |
| 17664 NP | MATING NOT CONFIRMED | | | | | | | | | | | | | |
| 17677 P | 319. | 325. | 332. | 341. | 358. | 363. | 373. | 386. | 398. | 381. | | | | |
| 17678 P | 330. | 332. | 338. | 347. | 364. | 373. | 385. | 405. | 422. | | | | | |
| 17682 P | 324. | 331. | 341. | 355. | 367. | 371. | 389. | 401. | | | | | | |
| 17683 P | 318. | 328. | 326. | 339. | 348. | 369. | 380. | 396. | 417. | | | | | |
| 17685 P | 313. | 319. | 328. | 340. | 351. | 373. | 389. | 403. | 409. | | | | | |
| 17686 NP | 272. | 277. | 275. | 266. | 270. | 278. | 284. | 294. | 290. | 296. | 299. | 298. | 284. | |
| 17689 P | 316. | 324. | 327. | 350. | 355. | 369. | 389. | 409. | 420. | | | | | |
| 17691 P | 324. | 324. | 331. | 340. | 351. | 359. | 374. | 381. | 391. | | | | | |
| 17692 P | 298. | 307. | 315. | 329. | 340. | 357. | 371. | 395. | 409. | | | | | |
| 17696 P | 284. | 290. | 299. | 311. | 323. | 338. | 356. | 369. | 377. | 370. | | | | |
| 17699 P | 326. | 333. | 340. | 352. | 366. | 380. | 396. | 403. | 415. | | | | | |
| 17711 P | 295. | 300. | 305. | 319. | 332. | 337. | 355. | 366. | 364. | 354. | | | | |
| 17712 P | 304. | 309. | 320. | 333. | 350. | 366. | 385. | 399. | 408. | | | | | |
| 17714 P | 347. | 358. | 366. | 376. | 387. | 406. | 414. | 430. | 443. | | | | | |

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAY = DAY OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C33 (PAGE 1): MATERNAL BODY WEIGHTS - LACTATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP I | | VEHICLE | | | | 0 (VEHICLE) MG/KG/DAY |
|-------|----------------|------|---------|------|------|------|-----------------------|
| | DAY 1 | 2 | 3 | 4 | 5 | 6 | |
| 17662 | 304. | 315. | 321. | 328. | 328. | 303. | |
| 17672 | 339. | 329. | 350. | 354. | 361. | 319. | |
| 17673 | 304. | 287. | 290. | 301. | 295. | 271. | |
| 17674 | 321. | 326. | 321. | 318. | 306. | 282. | |
| 17680 | 331. | 331. | 332. | 339. | 338. | 303. | |
| 17681 | 326. | 329. | 327. | 331. | 337. | 303. | |
| 17690 | 360. | 381. | 366. | 372. | 388. | 345. | |
| 17694 | 315. | 317. | 322. | 328. | 317. | 291. | |
| 17695 | 294. | 293. | 286. | 298. | 299. | 271. | |
| 17703 | 366. | 354. | 354. | 362. | 371. | 339. | |
| 17713 | 312. | 305. | 311. | 302. | 321. | 292. | |
| 17715 | 356. | 357. | 353. | 353. | 350. | 328. | |
| 17716 | 305. | 306. | 302. | 298. | 307. | 298. | |
| 17717 | 291. | 294. | 293. | 286. | 295. | 274. | |
| 17719 | 294. | 290. | 285. | 292. | 300. | 268. | |

DAY = DAY OF LACTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C33 (PAGE 2): MATERNAL BODY WEIGHTS - LACTATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP II | | LOW DOSAGE | | | | 10 MG/KG/DAY |
|-------|-----------------|------|------------|------|------|------|--------------|
| | DAY 1 | 2 | 3 | 4 | 5 | 6 | |
| 17663 | NOT PREGNANT | | | | | | |
| 17665 | 325. | 324. | 327. | 326. | 335. | 308. | |
| 17666 | 297. | 304. | 299. | 301. | 309. | 289. | |
| 17668 | 308. | 312. | 323. | 329. | 342. | 299. | |
| 17671 | 276. | 273. | 270. | 262. | 290. | 256. | |
| 17675 | 307. | 313. | 323. | 325. | 335. | 297. | |
| 17679 | 322. | 313. | 307. | 319. | 328. | 295. | |
| 17684 | 332. | 345. | 344. | 339. | 348. | 317. | |
| 17688 | 332. | 339. | 337. | 352. | 355. | 311. | |
| 17698 | 315. | 318. | 328. | 339. | 341. | 299. | |
| 17702 | 328. | 327. | 333. | 340. | 344. | 307. | |
| 17704 | 342. | 350. | 346. | 349. | 351. | 327. | |
| 17707 | 299. | 299. | 309. | 319. | 330. | 296. | |
| 17708 | 351. | 357. | 359. | 344. | 360. | 328. | |
| 17710 | 344. | 370. | 364. | 363. | 379. | 327. | |

DAY = DAY OF LACTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C33 (PAGE 3): MATERNAL BODY WEIGHTS - LACTATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP III | | | MIDDLE DOSAGE | | | 50 MG/KG/DAY |
|-------|------------------|------|------|---------------|------|------|--------------|
| | DAY 1 | 2 | 3 | 4 | 5 | 6 | |
| 17661 | 311. | 299. | 306. | 297. | 306. | 280. | |
| 17667 | 331. | 329. | 332. | 329. | 341. | 311. | |
| 17669 | 321. | 322. | 319. | 325. | 336. | 296. | |
| 17670 | 294. | 297. | 294. | 292. | 294. | 268. | |
| 17676 | 269. | 276. | 287. | 289. | 294. | 265. | |
| 17687 | 351. | 354. | 359. | 354. | 364. | 337. | |
| 17693 | 294. | 286. | 295. | 299. | 302. | 274. | |
| 17697 | 295. | 297. | 311. | 295. | 304. | 268. | |
| 17700 | 334. | 343. | 344. | 335. | 348. | 310. | |
| 17701 | 351. | 348. | 350. | 345. | 348. | 311. | |
| 17705 | 331. | 349. | 361. | 362. | 374. | 330. | |
| 17706 | 337. | 337. | 337. | 341. | 340. | 315. | |
| 17709 | 282. | 287. | 284. | 286. | 290. | 262. | |
| 17718 | 314. | 323. | 320. | 318. | 326. | 295. | |
| 17720 | 333. | 334. | 341. | 342. | 351. | 318. | |

DAY = DAY OF LACTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C33 (PAGE 4): MATERNAL BODY WEIGHTS - LACTATION - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP IV | | HIGH DOSAGE | | | | 250 MG/KG/DAY |
|-------|------------------------------------|---|-------------|------|------|------|---------------|
| | DAY 1 | 2 | 3 | 4 | 5 | 6 | |
| 17664 | NOT PREGNANT; MATING NOT CONFIRMED | | | | | | |
| 17677 | 304. | 298. | 304. | 304. | 304. | 287. | |
| 17678 | 327. | 324. | 332. | 328. | 330. | 293. | |
| 17682 | 306. | 310. | 317. | 321. | 338. | 300. | |
| 17683 | 298. | 302. | 296. | 294. | 304. | 259. | |
| 17685 | 293. | 304. | 295. | 294. | 307. | 277. | |
| 17686 | NOT PREGNANT | | | | | | |
| 17689 | 301. | 302. | 307. | 312. | 324. | 285. | |
| 17691 | 303. | 308. | 310. | 307. | 315. | 286. | |
| 17692 | 273. | 279. | 282. | 291. | 300. | 277. | |
| 17696 | 248. | SACRIFICED DUE TO NO SURVIVING PUPS ON DAY 2 OF LACTATION | | | | | |
| 17699 | 314. | 318. | 315. | 320. | 322. | 283. | |
| 17711 | 248. | SACRIFICED DUE TO NO SURVIVING PUPS ON DAY 2 OF LACTATION | | | | | |
| 17712 | 307. | 313. | 304. | 310. | 322. | 292. | |
| 17714 | 330. | 332. | 331. | 336. | 326. | 294. | |

DAY = DAY OF LACTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C34 (PAGE 1): FEED CONSUMPTION VALUES - PRECOHABITATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP I | | VEHICLE | 0 (VEHICLE) MG/KG/DAY |
|-------|----------------|------|---------|-----------------------|
| | DAYS | 1- 8 | | |
| 17662 | | 138. | 132. | |
| 17672 | | 141. | 150. | |
| 17673 | | 103. | 110. | |
| 17674 | | 145. | 150. | |
| 17680 | | 133. | 145. | |
| 17681 | | 134. | 141. | |
| 17690 | | 127. | 146. | |
| 17694 | | 128. | 141. | |
| 17695 | | 141. | 139. | |
| 17703 | | 136. | 147. | |
| 17713 | | 129. | 130. | |
| 17715 | | 136. | 136. | |
| 17716 | | 196. | 192. | |
| 17717 | | 129. | 148. | |
| 17719 | | 123. | 124. | |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Last value recorded before cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C34 (PAGE 2): FEED CONSUMPTION VALUES - PRECOHABITATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP II | | LOW DOSAGE | 10 MG/KG/DAY |
|-------|-----------------|------|------------|--------------|
| | DAYS | 1- 8 | 8- 15a | |
| 17663 | | 117. | 139. | |
| 17665 | | 156. | 149. | |
| 17666 | | 134. | 141. | |
| 17668 | | 126. | 131. | |
| 17671 | | 115. | 112. | |
| 17675 | | 128. | 143. | |
| 17679 | | 145. | 151. | |
| 17684 | | 140. | 156. | |
| 17688 | | 128. | 153. | |
| 17698 | | 142. | 141. | |
| 17702 | | 143. | 150. | |
| 17704 | | 139. | 162. | |
| 17707 | | 124. | 122. | |
| 17708 | | 151. | 160. | |
| 17710 | | 145. | 164. | |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Last value recorded before cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C34 (PAGE 3): FEED CONSUMPTION VALUES - PRECOHABITATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP III | | MIDDLE DOSAGE | 50 MG/KG/DAY |
|-------|------------------|------|---------------|--------------|
| | DAYS | 1- 8 | | |
| 17661 | | 123. | 117. | |
| 17667 | | 130. | 132. | |
| 17669 | | 150. | 146. | |
| 17670 | | 138. | 132. | |
| 17676 | | 119. | 125. | |
| 17687 | | 187. | 191. | |
| 17693 | | 140. | 133. | |
| 17697 | | 129. | 136. | |
| 17700 | | 157. | 153. | |
| 17701 | | 160. | 167. | |
| 17705 | | 124. | 150. | |
| 17706 | | 140. | 146. | |
| 17709 | | 110. | 118. | |
| 17718 | | 124. | 133. | |
| 17720 | | 144. | 158. | |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Last value recorded before cohabitation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C34 (PAGE 4): FEED CONSUMPTION VALUES - PRECOHABITATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP IV | | HIGH DOSAGE | 250 MG/KG/DAY |
|-------|-----------------|------|-------------|---------------|
| | DAYS | 1- 8 | 8- 15a | |
| 17664 | | 125. | 134. | |
| 17677 | | 147. | 145. | |
| 17678 | | 123. | 129. | |
| 17682 | | 178. | b | |
| 17683 | | 118. | 122. | |
| 17685 | | 133. | 149. | |
| 17686 | | 121. | 122. | |
| 17689 | | 135. | 139. | |
| 17691 | | 113. | 141. | |
| 17692 | | 126. | 137. | |
| 17696 | | 108. | 124. | |
| 17699 | | 138. | 141. | |
| 17711 | | 119. | 122. | |
| 17712 | | 109. | 122. | |
| 17714 | | 147. | 153. | |

DAY = DAY OF STUDY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

- a. Last value recorded before cohabitation.
- b. Spilled feed precluded the calculation of this value.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C35 (PAGE 1): MATERNAL FEED CONSUMPTION VALUES - PRESUMED GESTATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP I | | VEHICLE | | | | 0 (VEHICLE) MG/KG/DAY |
|-----------|----------------|--------|---------|---------|---------|---------|-----------------------|
| | 0 - 7 | 7 - 10 | 10 - 12 | 12 - 15 | 15 - 18 | 18 - 20 | |
| PREGNANCY | | | | | | | |
| STATUS | DAYS | | | | | | |
| 17662 P | 159. | 80. | 50. | 74. | 78. | 42. | |
| 17672 P | 171. | 75. | 55. | 85. | 85. | 54. | |
| 17673 P | 138. | 64. | 45. | 67. | 67. | 50. | |
| 17674 P | 171. | 83. | 53. | 85. | 92. | 68. | |
| 17680 P | 165. | 79. | 55. | 85. | 91. | 56. | |
| 17681 P | 159. | 77. | 53. | 82. | 78. | 49. | |
| 17690 P | 190. | 89. | 61. | 94. | 99. | 62. | |
| 17694 P | 168. | 76. | 44. | 80. | 83. | 52. | |
| 17695 P | 161. | 72. | 52. | 81. | 80. | 51. | |
| 17703 P | 183. | 84. | 55. | 85. | 91. | 47. | |
| 17713 P | 154. | 74. | 49. | 75. | 71. | 39. | |
| 17715 P | 176. | 77. | 58. | 90. | 75. | 56. | |
| 17716 P | 159. | 66. | 48. | 75. | 69. | 52. | |
| 17717 P | 148. | 66. | 41. | 65. | 75. | 44. | |
| 17719 P | 149. | 67. | 43. | 66. | 74. | 50. | |

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAYS = DAYS OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C35 (PAGE 2): MATERNAL FEED CONSUMPTION VALUES - PRESUMED GESTATION - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP II | | | | | | LOW DOSAGE | 10 MG/KG/DAY |
|----------|------------------|--------|---------|---------|---------|---------|------------|--------------|
| | PREGNANCY STATUS | | | | | | | |
| DAYS | 0 - 7 | 7 - 10 | 10 - 12 | 12 - 15 | 15 - 18 | 18 - 20 | | |
| 17663 NP | 139. | 63. | 39. | 57. | 56. | 31. | | |
| 17665 P | 168. | 75. | 56. | 78. | 83. | 45. | | |
| 17666 P | 135. | 59. | 39. | 61. | 71. | 46. | | |
| 17668 P | 157. | 83. | 55. | 81. | 88. | 44. | | |
| 17671 P | 139. | 69. | 41. | 62. | 72. | 41. | | |
| 17675 P | 152. | 71. | 47. | 69. | 76. | 51. | | |
| 17679 P | 164. | 75. | 52. | 82. | 83. | 49. | | |
| 17684 P | 170. | 76. | 57. | 87. | 86. | 58. | | |
| 17688 P | 165. | 80. | 43. | 74. | 101. | 55. | | |
| 17698 P | 168. | 81. | 55. | 83. | 85. | 40. | | |
| 17702 P | 166. | 71. | 42. | 81. | 84. | 58. | | |
| 17704 P | 179. | 82. | 60. | 98. | 99. | 57. | | |
| 17707 P | 139. | 63. | 51. | 73. | 74. | 48. | | |
| 17708 P | 172. | 87. | 52. | 83. | 95. | 61. | | |
| 17710 P | 207. | 84. | 67. | 101. | 92. | 55. | | |

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
 DAYS = DAYS OF PRESUMED GESTATION
 ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C35 (PAGE 3): MATERNAL FEED CONSUMPTION VALUES - PRESUMED GESTATION - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP III | | MIDDLE DOSAGE | | | | 50 MG/KG/DAY | |
|---------|------------------|------|---------------|--------|---------|---------|--------------|---------|
| | PREGNANCY STATUS | DAYS | 0 - 7 | 7 - 10 | 10 - 12 | 12 - 15 | 15 - 18 | 18 - 20 |
| 17661 P | | | 140. | 71. | 58. | 86. | 90. | 58. |
| 17667 P | | | 154. | 73. | 47. | 74. | 80. | 50. |
| 17669 P | | | 155. | 70. | 52. | 76. | 89. | 48. |
| 17670 P | | | 129. | 60. | 44. | 73. | 70. | 50. |
| 17676 P | | | 126. | 58. | 47. | 66. | 65. | 41. |
| 17687 P | | | 207. | 87. | 58. | 92. | 81. | 61. |
| 17693 P | | | 146. | 65. | 40. | 54. | 68. | 52. |
| 17697 P | | | 146. | 64. | 48. | 77. | 86. | 44. |
| 17700 P | | | 169. | 81. | 54. | 91. | 98. | 52. |
| 17701 P | | | 188. | 83. | 53. | 88. | 94. | 58. |
| 17705 P | | | 167. | 84. | 56. | 85. | 94. | 54. |
| 17706 P | | | 178. | 78. | 53. | 83. | 75. | 52. |
| 17709 P | | | 143. | 52. | 38. | 53. | 65. | 45. |
| 17718 P | | | 152. | 62. | 45. | 67. | 72. | 51. |
| 17720 P | | | 172. | 79. | 57. | 91. | 84. | 58. |

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)
 DAYS = DAYS OF PRESUMED GESTATION
 ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C35 (PAGE 4): MATERNAL FEED CONSUMPTION VALUES - PRESUMED GESTATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP IV | | HIGH DOSAGE | | | | 250 MG/KG/DAY |
|--------|-----------------|----------------------|-------------|---------|---------|---------|---------------|
| | PREGNANCY | | | | | | |
| STATUS | DAYS | 0 - 7 | 7 - 10 | 10 - 12 | 12 - 15 | 15 - 18 | 18 - 20 |
| 17664 | NP | MATING NOT CONFIRMED | | | | | |
| 17677 | P | 153. | 73. | 52. | 82. | 72. | 45. |
| 17678 | P | 175. | 73. | 58. | 79. | 79. | 55. |
| 17682 | P | 170. | 72. | 68. | 77. | 80. | 52. |
| 17683 | P | 136. | 82. | 57. | 85. | 93. | 46. |
| 17685 | P | 174. | 76. | 42. | 69. | 86. | 51. |
| 17686 | NP | 148. | 63. | 34. | 50. | 48. | 44. |
| 17689 | P | 140. | 78. | 50. | 76. | 82. | 51. |
| 17691 | P | a | 74. | 46. | 76. | 76. | 42. |
| 17692 | P | 152. | 67. | 47. | 77. | 84. | 51. |
| 17696 | P | 136. | 60. | 53. | 72. | 79. | 47. |
| 17699 | P | 162. | 72. | 58. | 87. | 97. | 49. |
| 17711 | P | 136. | 55. | 47. | 71. | 75. | 50. |
| 17712 | P | 174. | 82. | 54. | 89. | 106. | 65. |
| 17714 | P | 164. | 82. | 56. | 90. | 89. | 47. |

P = PREGNANT NP = NOT PREGNANT (VALUES EXCLUDED FROM AVERAGES)

DAYS = DAYS OF PRESUMED GESTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Spilled feed precluded the calculation of this value.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C36 (PAGE 1): MATERNAL FEED CONSUMPTION VALUES - LACTATION - INDIVIDUAL DATA - Fo GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP I | VEHICLE | 0 (VEHICLE) MG/KG/DAY |
|-----------|----------------|---------|-----------------------|
| DAY 1 - 5 | | | |
| 17662 | 144. | | |
| 17672 | 143. | | |
| 17673 | 93. | | |
| 17674 | 97. | | |
| 17680 | 150. | | |
| 17681 | 129. | | |
| 17690 | 168. | | |
| 17694 | 126. | | |
| 17695 | 118. | | |
| 17703 | 127. | | |
| 17713 | 100. | | |
| 17715 | 138. | | |
| 17716 | 138. | | |
| 17717 | 94. | | |
| 17719 | 121. | | |

DAY = DAY OF LACTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C36 (PAGE 2): MATERNAL FEED CONSUMPTION VALUES - LACTATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP II | LOW DOSAGE | 10 MG/KG/DAY |
|-----------|-----------------|------------|--------------|
| DAY 1 - 5 | | | |
| 17663 | NOT PREGNANT | | |
| 17665 | | 133. | |
| 17666 | | 131. | |
| 17668 | | 158. | |
| 17671 | | 117. | |
| 17675 | | 153. | |
| 17679 | | 118. | |
| 17684 | | 156. | |
| 17688 | | 147. | |
| 17698 | a | | |
| 17702 | | 139. | |
| 17704 | | 164. | |
| 17707 | | 147. | |
| 17708 | | 166. | |
| 17710 | | 163. | |

DAY = DAY OF LACTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Spilled feed precluded the calculation of this value.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C36 (PAGE 3): MATERNAL FEED CONSUMPTION VALUES - LACTATION - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP III | MIDDLE DOSAGE | 50 MG/KG/DAY |
|-----------|------------------|---------------|--------------|
| DAY 1 - 5 | | | |
| 17661 | 116. | | |
| 17667 | 110. | | |
| 17669 | 141. | | |
| 17670 | 109. | | |
| 17676 | 130. | | |
| 17687 | 154. | | |
| 17693 | 119. | | |
| 17697 | 110. | | |
| 17700 | 167. | | |
| 17701 | 126. | | |
| 17705 | a | | |
| 17706 | 150. | | |
| 17709 | 105. | | |
| 17718 | 141. | | |
| 17720 | 173. | | |

DAY = DAY OF LACTATION

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Spilled feed precluded the calculation of this value.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C36 (PAGE 4): MATERNAL FEED CONSUMPTION VALUES - LACTATION - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| RAT # | DOSAGE GROUP IV | HIGH DOSAGE | 250 MG/KG/DAY |
|-----------|---|-------------|---------------|
| DAY 1 - 5 | | | |
| 17664 | NOT PREGNANT; MATING NOT CONFIRMED | | |
| 17677 | 74. | | |
| 17678 | 111. | | |
| 17682 | 186. | | |
| 17683 | 109. | | |
| 17685 | 114. | | |
| 17686 | NOT PREGNANT | | |
| 17689 | 141. | | |
| 17691 | 133. | | |
| 17692 | 106. | | |
| 17696 | SACRIFICED DUE TO NO SURVIVING PUPS ON DAY 2 OF LACTATION | | |
| 17699 | 113. | | |
| 17711 | SACRIFICED DUE TO NO SURVIVING PUPS ON DAY 2 OF LACTATION | | |
| 17712 | 155. | | |
| 17714 | 113. | | |

DAY = DAY OF LACTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C37 (PAGE 1): MATING AND FERTILITY, ESTROUS CYCLING AND DAYS IN COHABITATION - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| RAT # | PRECOHABITATION ESTROUS STAGES/ 14 DAYS | DAYS IN COHABITATION | MATING STATUS | MATING DATE | PREGNANCY STATUS |
|-----------------|---|-------------------------|-----------------------|----------------|---------------------|
| ----- | | | | | |
| DOSAGE GROUP I | | VEHICLE | 0 (VEHICLE) MG/KG/DAY | | |
| ----- | | | | | |
| 17662 | 3 | 3 | M | C | P |
| 17672 | 4 | 4 | M | C | P |
| 17673 | 2 | 1 | M | C | P |
| 17674 | 3 | 1 | M | C | P |
| 17680 | 4 | 3 | M | C | P |
| 17681 | 3 | 3 | M | C | P |
| 17690 | 4 | 3 | M | C | P |
| 17694 | 3 | 1 | M | C | P |
| 17695 | 2 | 2 | M | C | P |
| 17703 | 4 | 3 | M | C | P |
| 17713 | 4 | 3 | M | C | P |
| 17715 | 4 | 4 | M | C | P |
| 17716 | 4 | 4 | M | C | P |
| 17717 | 1a | 1 | M | C | P |
| 17719 | 1 | 9 | M | C | P |
| ----- | | | | | |
| DOSAGE GROUP II | | LOW DOSAGE | 10 MG/KG/DAY | | |
| ----- | | | | | |
| 17663 | 4 | 3 | M | C | NP |
| 17665 | 3 | 3 | M | C | P |
| 17666 | 3 | 1 | M | C | P |
| 17668 | 4 | 3 | M | C | P |
| 17671 | 4 | 3 | M | C | P |
| 17675 | 3 | 2 | M | C | P |
| 17679 | 3 | 3 | M | C | P |
| 17684 | 4 | 4 | M | C | P |
| 17688 | 4 | 3 | M | C | P |
| 17698 | 4 | 3 | M | C | P |
| 17702 | 1 | 1 | M | C | P |
| 17704 | 3 | 2 | M | C | P |
| 17707 | 3 | 4 | M | C | P |
| 17708 | 4 | 1 | M | C | P |
| 17710 | 4 | 4 | M | C | P |
| ----- | | | | | |

M = MATED C = CONFIRMED P = PREGNANT NP = NOT PREGNANT

a. Six or more consecutive days of diestrus were observed.

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TABLE C37 (PAGE 2): MATING AND FERTILITY, ESTROUS CYCLING AND DAYS IN COHABITATION - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| | PRECOHABITATION ESTROUS STAGES/ 14 DAYS | DAYS IN COHABITATION | MATING STATUS | MATING DATE | PREGNANCY STATUS |
|------------------|---|-------------------------|------------------|----------------|---------------------|
| ----- | | | | | |
| DOSAGE GROUP III | | MIDDLE DOSAGE | 50 MG/KG/DAY | | |
| 17661 | 3 | 2 | M | C | P |
| 17667 | 3 | 2 | M | C | P |
| 17669 | 4 | 3 | M | C | P |
| 17670 | 4 | 4 | M | C | P |
| 17676 | 3 | 2 | M | C | P |
| 17687 | 3 | 4 | M | C | P |
| 17693 | 3 | 1 | M | C | P |
| 17697 | 3 | 3 | M | C | P |
| 17700 | 4 | 3 | M | C | P |
| 17701 | 4 | 3 | M | C | P |
| 17705 | 4 | 3 | M | C | P |
| 17706 | 1 | 4 | M | C | P |
| 17709 | 4 | 13 | M | C | P |
| 17718 | 4 | 13 | M | C | P |
| 17720 | 1a | 4 | M | C | P |
| ----- | | | | | |
| DOSAGE GROUP IV | | HIGH DOSAGE | 250 MG/KG/DAY | | |
| 17664 | 4 | 14 | DID NOT MATE | - | - |
| 17677 | 3 | 4 | M | C | P |
| 17678 | 3 | 4 | M | C | P |
| 17682 | 3 | 13 | M | C | P |
| 17683 | 3 | 3 | M | C | P |
| 17685 | 2 | 1 | M | C | P |
| 17686 | 4 | 1 | M | C | NP |
| 17689 | 4 | 1 | M | C | P |
| 17691 | 4 | 4 | M | C | P |
| 17692 | 3 | 1 | M | C | P |
| 17696 | 4 | 1 | M | C | P |
| 17699 | 4 | 3 | M | C | P |
| 17711 | 3 | 1 | M | C | P |
| 17712 | 3 | 1 | M | C | P |
| 17714 | 4 | 3 | M | C | P |

M = MATED C = CONFIRMED P = PREGNANT NP = NOT PREGNANT
a. Six or more consecutive days of diestrus were observed.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C38 (PAGE 1): FUNCTIONAL OBSERVATIONAL BATTERY - INDIVIDUAL DATA - FEMALE RATS

| DOSAGE GROUP I | | | | | |
|----------------------------|-------|-------|-------|-------|-------|
| 0 (VEHICLE) MG/KG/DAY | | | | | |
| RAT # | 17662 | 17672 | 17673 | 17674 | 17680 |
| HOME CAGE BEHAVIOR | 2 | 1 | 1 | 1 | 2 |
| ALTERATIONS (HOME CAGE) | 1 | 1 | 1 | 1 | 1 |
| REACTION TO REMOVAL | 1 | 1 | 1 | 1 | 1 |
| REACTION TO HANDLING | 1 | 1 | 1 | 1 | 1 |
| REARS IN OPEN FIELD | 6 | 9 | 6 | 8 | 10 |
| DEFECATION IN OPEN FIELD | 1 | 1 | 1 | 1 | 1 |
| URINATION IN OPEN FIELD | 1 | 1 | 1 | 1 | 1 |
| LEVEL OF AROUSAL | 3 | 3 | 3 | 3 | 3 |
| ALTERATIONS (OPEN FIELD) | 1 | 1 | 1 | 1 | 4c |
| GAIT PATTERN | 1 | 1 | 1 | 1 | 1 |
| GAIT ABNORMALITY, SEVERITY | 1 | 1 | 1 | 1 | 1 |
| PALPEBRAL CLOSURE | 1 | 1 | 1 | 1 | 1 |
| PROMINENCE OF THE EYE | 1 | 1 | 1 | 1 | 1 |
| LACRIMATION | 1 | 1 | 1 | 1 | 1 |
| SALIVATION | 1 | 1 | 1 | 1 | 1 |
| PILOERECTION | 0 | 0 | 0 | 0 | 0 |
| ABNORMAL RESPIRATION | 0 | 0 | 0 | 0 | 0 |
| APPEARANCE | 1 | 1 | 1 | 1 | 1 |
| VISUAL REACTION | 2 | 2 | 2 | 2 | 2 |
| TACTILE REACTION | 2 | 2 | 2 | 2 | 2 |
| AUDITORY REACTION | 3 | 3 | 3 | 3 | 3 |
| TAIL-PINCH REACTION | 2 | 2 | 2 | 2 | 2 |
| VISUAL PLACING RESPONSE | 1 | 1 | 1 | 1 | 1 |
| AIR RIGHTING RESPONSE | 1 | 1 | 1 | 1 | 1 |
| PUPIL RESPONSE TO LIGHT | 1 | 1 | 1 | 1 | 1 |
| FORELIMB GRIP TEST #1 | 310a | 315 | 355 | 320b | 225 |
| FORELIMB GRIP TEST #2 | 355 | 325 | 255 | 285 | 220 |
| HINDLIMB GRIP TEST #1 | 145 | 305 | 205 | 370 | 375 |
| HINDLIMB GRIP TEST #2 | 190 | 325 | 215 | 220 | 390 |
| LANDING FOOT SPLAY #1 | 6.6 | 6.1 | 7.2 | 6.7 | 6.7 |
| LANDING FOOT SPLAY #2 | 7.7 | 6.8 | 5.5 | 6.8 | 6.8 |
| BODY WEIGHT (G) | 343 | 360 | 295 | 324 | 342 |

VALUES ARE THE QUANTITY, CATEGORY NUMBER, QUANTAL RESPONSE OR SCORE RECORDED FOR EACH ITEM IN THE BATTERY.

- a. Soft or liquid feces were observed during the forelimb grip testing.
- b. Animal fell approximately 3 feet to floor, animal appeared normal.
- c. Value appeared incorrectly recorded and was excluded from group averages and statistical analyses.

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TABLE C38 (PAGE 2): FUNCTIONAL OBSERVATIONAL BATTERY - INDIVIDUAL DATA - FEMALE RATS

| DOSAGE GROUP II | | | | |
|----------------------------|-------|-------|-------|-------|
| 10 MG/KG/DAY | | | | |
| RAT # | 17665 | 17666 | 17668 | 17671 |
| HOME CAGE BEHAVIOR | 1 | 2 | 2 | 1 |
| ALTERATIONS (HOME CAGE) | 1 | 1 | 1 | 1 |
| REACTION TO REMOVAL | 1 | 1 | 1 | 1 |
| REACTION TO HANDLING | 1 | 1 | 1 | 1 |
| REARS IN OPEN FIELD | 12 | 8 | 11 | 10 |
| DEFECATION IN OPEN FIELD | 1 | 1 | 2 | 1 |
| URINATION IN OPEN FIELD | 1 | 1 | 2 | 1 |
| LEVEL OF AROUSAL | 3 | 3 | 3 | 3 |
| ALTERATIONS (OPEN FIELD) | 1 | 1 | 1 | 1 |
| GAIT PATTERN | 1 | 1 | 1 | 1 |
| GAIT ABNORMALITY, SEVERITY | 1 | 1 | 1 | 1 |
| PALPEBRAL CLOSURE | 1 | 1 | 1 | 1 |
| PROMINENCE OF THE EYE | 1 | 1 | 1 | 1 |
| LACRIMATION | 1 | 1 | 1 | 1 |
| SALIVATION | 1 | 1 | 1 | 1 |
| PILOERECTION | 0 | 0 | 0 | 0 |
| ABNORMAL RESPIRATION | 0 | 0 | 0 | 0 |
| APPEARANCE | 1a | 1 | 1 | 1c |
| VISUAL REACTION | 2 | 2 | 2 | 2 |
| TACTILE REACTION | 2 | 2 | 2 | 2 |
| AUDITORY REACTION | 3 | 3 | 3 | 3 |
| TAIL-PINCH REACTION | 2 | 2 | 2 | 2 |
| VISUAL PLACING RESPONSE | 1 | 1 | 1 | 1 |
| AIR RIGHTING RESPONSE | 1 | 1 | 1 | 1 |
| PUPIL RESPONSE TO LIGHT | 1 | 1 | 1 | 1 |
| FORELIMB GRIP TEST #1 | 210 | 385 | 175b | 280 |
| FORELIMB GRIP TEST #2 | 170 | 455 | 270 | 270 |
| HINDLIMB GRIP TEST #1 | 285 | 370 | 335 | 220 |
| HINDLIMB GRIP TEST #2 | 340 | 325 | 350 | 225 |
| LANDING FOOT SPLAY #1 | 6.7 | 6.5 | 7.7 | 4.1 |
| LANDING FOOT SPLAY #2 | 6.8 | 6.4 | 8.1 | 4.1 |
| BODY WEIGHT (G) | 335 | 310 | 353 | 292 |

VALUES ARE THE QUANTITY, CATEGORY NUMBER, QUANTAL RESPONSE OR SCORE RECORDED FOR EACH ITEM IN THE BATTERY.

- a. Localized alopecia: both forepaws (0.5 cm in diameter).
- b. Animal fell approximately 3 to 4 feet and appeared normal.
- c. Localized alopecia: both forepaws and forelimbs (2.0 cm x 0.5 cm).

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C38 (PAGE 3): FUNCTIONAL OBSERVATIONAL BATTERY - INDIVIDUAL DATA - FEMALE RATS

| DOSAGE GROUP III | | | | | |
|----------------------------|-------|-------|-------|-------|-------|
| 50 MG/KG/DAY | | | | | |
| RAT # | 17661 | 17667 | 17669 | 17670 | 17676 |
| HOME CAGE BEHAVIOR | 2 | 2 | 2 | 2 | 2 |
| ALTERATIONS (HOME CAGE) | 1 | 1 | 1 | 1 | 1 |
| REACTION TO REMOVAL | 1 | 1 | 1 | 1 | 1 |
| REACTION TO HANDLING | 1 | 1 | 1 | 1 | 1 |
| REARS IN OPEN FIELD | 9 | 9 | 15 | 8 | 9 |
| DEFECATION IN OPEN FIELD | 1 | 1 | 1 | 1 | 1 |
| URINATION IN OPEN FIELD | 1 | 1 | 1 | 1 | 1 |
| LEVEL OF AROUSAL | 3 | 3 | 3 | 3 | 3 |
| ALTERATIONS (OPEN FIELD) | 1 | 1 | 1 | 1 | 1 |
| GAIT PATTERN | 1 | 1 | 1 | 1 | 1 |
| GAIT ABNORMALITY, SEVERITY | 1 | 1 | 1 | 1 | 1 |
| PALPEBRAL CLOSURE | 1 | 1 | 1 | 1 | 1 |
| PROMINENCE OF THE EYE | 1 | 1 | 1 | 1 | 1 |
| LACRIMATION | 1 | 1 | 1 | 1 | 1 |
| SALIVATION | 2 | 1 | 1 | 1 | 1 |
| PILOERECTION | 0 | 0 | 0 | 0 | 0 |
| ABNORMAL RESPIRATION | 0 | 0 | 0 | 0 | 0 |
| APPEARANCE | 1 | 1 | 1a | 1 | 1 |
| VISUAL REACTION | 2 | 2 | 2 | 2 | 2 |
| TACTILE REACTION | 2 | 2 | 2 | 2 | 2 |
| AUDITORY REACTION | 3 | 3 | 3 | 3 | 3 |
| TAIL-PINCH REACTION | 2 | 2 | 2 | 2 | 2 |
| VISUAL PLACING RESPONSE | 1 | 1 | 1 | 1 | 1 |
| AIR RIGHTING RESPONSE | 1 | 1 | 1 | 1 | 1 |
| PUPIL RESPONSE TO LIGHT | 1 | 1 | 1 | 1 | 1 |
| FORELIMB GRIP TEST #1 | 190 | 200 | 245 | 275 | 230 |
| FORELIMB GRIP TEST #2 | 310 | 200 | 245 | 240 | 270 |
| HINDLIMB GRIP TEST #1 | 270 | 180 | 280 | 310 | 135 |
| HINDLIMB GRIP TEST #2 | 170 | 235 | 215 | 220 | 195 |
| LANDING FOOT SPLAY #1 | 8.7 | 6.1 | 6.0 | 6.7 | 5.7 |
| LANDING FOOT SPLAY #2 | 6.8 | 7.7 | 5.8 | 6.6 | 6.7 |
| BODY WEIGHT (G) | 308 | 346 | 347 | 295 | 310 |

VALUES ARE THE QUANTITY, CATEGORY NUMBER, QUANTAL RESPONSE OR SCORE RECORDED FOR EACH ITEM IN THE BATTERY.

a. Localized alopecia: both forepaws and forelimbs (2.0 cm x 0.5 cm).

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TABLE C38 (PAGE 4): FUNCTIONAL OBSERVATIONAL BATTERY - INDIVIDUAL DATA - FEMALE RATS

| DOSAGE GROUP IV | | | | | |
|----------------------------|-------|-------|-------|-------|-------|
| 250 MG/KG/DAY | | | | | |
| RAT # | 17677 | 17678 | 17682 | 17683 | 17691 |
| HOME CAGE BEHAVIOR | 1 | 2 | 2 | 1 | 2 |
| ALTERATIONS (HOME CAGE) | 1 | 1 | 1 | 1 | 1 |
| REACTION TO REMOVAL | 1 | 1 | 1 | 1 | 1 |
| REACTION TO HANDLING | 1 | 1 | 1 | 1 | 1 |
| REARS IN OPEN FIELD | 9 | 8 | 12 | 6 | 10 |
| DEFECATION IN OPEN FIELD | 1 | 1 | 1 | 1 | 1 |
| URINATION IN OPEN FIELD | 1 | 1 | 1 | 1 | 1 |
| LEVEL OF AROUSAL | 3 | 3 | 3 | 3 | 3 |
| ALTERATIONS (OPEN FIELD) | 1 | 1 | 1 | 1 | 1 |
| GAIT PATTERN | 1 | 1 | 1 | 1 | 1 |
| GAIT ABNORMALITY, SEVERITY | 1 | 1 | 1 | 1 | 1 |
| PALPEBRAL CLOSURE | 1 | 1 | 1 | 1 | 1 |
| PROMINENCE OF THE EYE | 1 | 1 | 1 | 1 | 1 |
| LACRIMATION | 1 | 1 | 1 | 1 | 1 |
| SALIVATION | 1 | 1 | 1 | 1 | 1 |
| PILORECTION | 0 | 0 | 0 | 0 | 0 |
| ABNORMAL RESPIRATION | 0 | 0 | 0 | 0 | 0 |
| APPEARANCE | 1 | 1 | 1 | 1a | 1 |
| VISUAL REACTION | 2 | 2 | 2 | 2 | 2 |
| TACTILE REACTION | 2 | 2 | 2 | 2 | 2 |
| AUDITORY REACTION | 3 | 3 | 3 | 3 | 3 |
| TAIL-PINCH REACTION | 2 | 2 | 2 | 2 | 2 |
| VISUAL PLACING RESPONSE | 1 | 1 | 1 | 1 | 1 |
| AIR RIGHTING RESPONSE | 1 | 1 | 1 | 1 | 1 |
| PUPIL RESPONSE TO LIGHT | 1 | 1 | 1 | 1 | 1 |
| FORELIMB GRIP TEST #1 | 405 | 200 | 455 | 350 | 455 |
| FORELIMB GRIP TEST #2 | 330 | 190 | 410 | 290 | 495 |
| HINDLIMB GRIP TEST #1 | 210 | 365 | 510 | 190 | 225 |
| HINDLIMB GRIP TEST #2 | 345 | 360 | 535 | 270 | 280 |
| LANDING FOOT SPLAY #1 | 5.5 | 6.3 | 6.2 | 7.6 | 6.5 |
| LANDING FOOT SPLAY #2 | 6.8 | 7.4 | 5.2 | 8.6 | 7.6 |
| BODY WEIGHT (G) | 316 | 340 | 337 | 296 | 280 |

VALUES ARE THE QUANTITY, CATEGORY NUMBER, QUANTAL RESPONSE OR SCORE RECORDED FOR EACH ITEM IN THE BATTERY.

a. Localized alopecia: right forelimb (1.5 cm x 1.0 cm), right inguinal area (6.0 cm x 2.0 cm) and right hindlimb (2.0 cm x 2.0 cm).

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TABLE C39 (PAGE 1): MOTOR ACTIVITY - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| DOSAGE GROUP I | 0 (VEHICLE) MG/KG/DAY | | | | |
|---------------------|-----------------------|-------|-------|-------|-------|
| RAT NUMBER | 17662 | 17672 | 17673 | 17674 | 17680 |
| DAY 86 | | | | | |
| NUMBER OF MOVEMENTS | | | | | |
| BLOCK 1 | 70 | 70 | 90 | 71 | 74 |
| BLOCK 2 | 78 | 84 | 92 | 90 | 60 |
| BLOCK 3 | 56 | 84 | 47 | 85 | 77 |
| BLOCK 4 | 40 | 51 | 26 | 103 | 70 |
| BLOCK 5 | 25 | 77 | 92 | 91 | 42 |
| BLOCK 6 | 14 | 50 | 91 | 93 | 77 |
| BLOCK 7 | 42 | 76 | 27 | 98 | 75 |
| BLOCK 8 | 47 | 5 | 8 | 72 | 60 |
| BLOCK 9 | 75 | 29 | 1 | 78 | 51 |
| BLOCK 10 | 76 | 64 | 4 | 79 | 57 |
| BLOCK 11 | 37 | 77 | 3 | 90 | 94 |
| BLOCK 12 | 7 | 74 | 8 | 74 | 75 |
| BLOCK 13 | 40 | 60 | 12 | 78 | 61 |
| BLOCK 14 | 38 | 75 | 80 | 62 | 47 |
| BLOCK 15 | 44 | 58 | 56 | 70 | 48 |
| BLOCK 16 | 46 | 44 | 41 | 75 | 61 |
| BLOCK 17 | 28 | 63 | 71 | 104 | 83 |
| BLOCK 18 | 34 | 61 | 62 | 48 | 67 |
| TOTAL | 797 | 1102 | 811 | 1461 | 1179 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C39 (PAGE 2): MOTOR ACTIVITY - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP I | 0 (VEHICLE) MG/KG/DAY | | | | |
|----------------------------------|-----------------------|-------|-------|-------|-------|
| RAT NUMBER | 17662 | 17672 | 17673 | 17674 | 17680 |
| DAY 86 | | | | | |
| TIME (SECONDS) SPENT IN MOVEMENT | | | | | |
| BLOCK 1 | 179 | 180 | 139 | 231 | 222 |
| BLOCK 2 | 172 | 172 | 113 | 193 | 244 |
| BLOCK 3 | 135 | 157 | 27 | 146 | 187 |
| BLOCK 4 | 58 | 69 | 20 | 164 | 148 |
| BLOCK 5 | 16 | 105 | 105 | 159 | 112 |
| BLOCK 6 | 9 | 97 | 75 | 113 | 138 |
| BLOCK 7 | 55 | 119 | 30 | 118 | 117 |
| BLOCK 8 | 89 | 10 | 7 | 108 | 124 |
| BLOCK 9 | 158 | 50 | 0 | 90 | 75 |
| BLOCK 10 | 146 | 126 | 2 | 83 | 83 |
| BLOCK 11 | 38 | 113 | 1 | 92 | 133 |
| BLOCK 12 | 7 | 129 | 17 | 91 | 115 |
| BLOCK 13 | 42 | 137 | 9 | 116 | 111 |
| BLOCK 14 | 63 | 115 | 95 | 65 | 91 |
| BLOCK 15 | 95 | 112 | 68 | 105 | 82 |
| BLOCK 16 | 114 | 77 | 26 | 78 | 96 |
| BLOCK 17 | 28 | 82 | 67 | 146 | 122 |
| BLOCK 18 | 47 | 96 | 62 | 44 | 102 |
| TOTAL | 1451 | 1946 | 863 | 2142 | 2302 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C39 (PAGE 3): MOTOR ACTIVITY - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| DOSAGE GROUP II | 10 MG/KG/DAY | | | |
|---------------------|--------------|-------|-------|-------|
| RAT NUMBER | 17665 | 17666 | 17668 | 17671 |
| DAY 86 | | | | |
| NUMBER OF MOVEMENTS | | | | |
| BLOCK 1 | 66 | 75 | 75 | 76 |
| BLOCK 2 | 85 | 72 | 83 | 73 |
| BLOCK 3 | 69 | 87 | 84 | 71 |
| BLOCK 4 | 96 | 17 | 74 | 63 |
| BLOCK 5 | 76 | 37 | 20 | 74 |
| BLOCK 6 | 71 | 60 | 1 | 92 |
| BLOCK 7 | 108 | 68 | 1 | 69 |
| BLOCK 8 | 74 | 57 | 2 | 78 |
| BLOCK 9 | 56 | 61 | 77 | 68 |
| BLOCK 10 | 76 | 71 | 80 | 51 |
| BLOCK 11 | 45 | 62 | 42 | 63 |
| BLOCK 12 | 2 | 27 | 65 | 70 |
| BLOCK 13 | 28 | 4 | 54 | 51 |
| BLOCK 14 | 14 | 33 | 3 | 68 |
| BLOCK 15 | 74 | 58 | 2 | 64 |
| BLOCK 16 | 83 | 65 | 2 | 68 |
| BLOCK 17 | 12 | 16 | 0 | 73 |
| BLOCK 18 | 7 | 3 | 57 | 59 |
| TOTAL | 1042 | 873 | 722 | 1231 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C39 (PAGE 4): MOTOR ACTIVITY - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| DOSAGE GROUP II | 10 MG/KG/DAY | | | |
|----------------------------------|--------------|-------|-------|-------|
| RAT NUMBER | 17665 | 17666 | 17668 | 17671 |
| DAY 86 | | | | |
| TIME (SECONDS) SPENT IN MOVEMENT | | | | |
| BLOCK 1 | 194 | 220 | 156 | 163 |
| BLOCK 2 | 176 | 138 | 163 | 126 |
| BLOCK 3 | 194 | 90 | 139 | 126 |
| BLOCK 4 | 151 | 20 | 70 | 174 |
| BLOCK 5 | 91 | 54 | 17 | 164 |
| BLOCK 6 | 104 | 104 | 0 | 96 |
| BLOCK 7 | 125 | 116 | 0 | 99 |
| BLOCK 8 | 101 | 81 | 0 | 155 |
| BLOCK 9 | 99 | 100 | 129 | 148 |
| BLOCK 10 | 128 | 122 | 93 | 88 |
| BLOCK 11 | 63 | 117 | 34 | 202 |
| BLOCK 12 | 0 | 37 | 73 | 187 |
| BLOCK 13 | 21 | 2 | 77 | 82 |
| BLOCK 14 | 5 | 44 | 2 | 142 |
| BLOCK 15 | 89 | 61 | 0 | 126 |
| BLOCK 16 | 77 | 120 | 0 | 111 |
| BLOCK 17 | 7 | 15 | 0 | 155 |
| BLOCK 18 | 6 | 1 | 64 | 151 |
| TOTAL | 1631 | 1442 | 1017 | 2495 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C39 (PAGE 5): MOTOR ACTIVITY - INDIVIDUAL DATA - P₀ GENERATION FEMALE RATS

| DOSAGE GROUP III | | 50 MG/KG/DAY | | | | |
|---------------------|-------|--------------|-------|-------|-------|--|
| RAT NUMBER | 17661 | 17667 | 17669 | 17670 | 17676 | |
| DAY 86 | | | | | | |
| NUMBER OF MOVEMENTS | | | | | | |
| BLOCK 1 | 59 | 57 | 74 | 58 | 86 | |
| BLOCK 2 | 81 | 85 | 43 | 73 | 78 | |
| BLOCK 3 | 78 | 81 | 13 | 13 | 89 | |
| BLOCK 4 | 75 | 73 | 2 | 0 | 82 | |
| BLOCK 5 | 68 | 15 | 9 | 45 | 100 | |
| BLOCK 6 | 60 | 0 | 76 | 66 | 56 | |
| BLOCK 7 | 66 | 74 | 62 | 81 | 79 | |
| BLOCK 8 | 64 | 65 | 43 | 53 | 46 | |
| BLOCK 9 | 84 | 81 | 6 | 54 | 2 | |
| BLOCK 10 | 61 | 60 | 33 | 63 | 45 | |
| BLOCK 11 | 64 | 70 | 15 | 44 | 70 | |
| BLOCK 12 | 59 | 25 | 5 | 19 | 61 | |
| BLOCK 13 | 61 | 9 | 3 | 46 | 56 | |
| BLOCK 14 | 52 | 4 | 31 | 63 | 66 | |
| BLOCK 15 | 68 | 3 | 54 | 67 | 80 | |
| BLOCK 16 | 67 | 3 | 72 | 60 | 31 | |
| BLOCK 17 | 65 | 4 | 73 | 62 | 73 | |
| BLOCK 18 | 60 | 2 | 12 | 58 | 64 | |
| TOTAL | 1192 | 711 | 626 | 925 | 1164 | |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C39 (PAGE 6): MOTOR ACTIVITY - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| DOSAGE GROUP III | | 50 MG/KG/DAY | | | | |
|----------------------------------|-------|--------------|-------|-------|-------|--|
| RAT NUMBER | 17661 | 17667 | 17669 | 17670 | 17676 | |
| DAY 86 | | | | | | |
| TIME (SECONDS) SPENT IN MOVEMENT | | | | | | |
| BLOCK 1 | 242 | 251 | 196 | 231 | 182 | |
| BLOCK 2 | 190 | 177 | 54 | 128 | 159 | |
| BLOCK 3 | 179 | 116 | 12 | 10 | 104 | |
| BLOCK 4 | 140 | 67 | 0 | 0 | 107 | |
| BLOCK 5 | 193 | 17 | 8 | 39 | 129 | |
| BLOCK 6 | 96 | 0 | 104 | 123 | 62 | |
| BLOCK 7 | 122 | 86 | 121 | 126 | 99 | |
| BLOCK 8 | 134 | 144 | 45 | 79 | 36 | |
| BLOCK 9 | 136 | 154 | 3 | 66 | 1 | |
| BLOCK 10 | 82 | 67 | 23 | 114 | 35 | |
| BLOCK 11 | 127 | 118 | 10 | 68 | 90 | |
| BLOCK 12 | 99 | 27 | 2 | 25 | 73 | |
| BLOCK 13 | 107 | 10 | 1 | 70 | 96 | |
| BLOCK 14 | 75 | 1 | 86 | 102 | 81 | |
| BLOCK 15 | 98 | 2 | 117 | 114 | 107 | |
| BLOCK 16 | 129 | 1 | 89 | 97 | 27 | |
| BLOCK 17 | 113 | 3 | 94 | 114 | 109 | |
| BLOCK 18 | 116 | 2 | 5 | 77 | 81 | |
| TOTAL | 2378 | 1243 | 970 | 1583 | 1578 | |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C39 (PAGE 7): MOTOR ACTIVITY - INDIVIDUAL DATA - F₀ GENERATION FEMALE RATS

| DOSAGE GROUP IV | 250 MG/KG/DAY | | | | |
|---------------------|---------------|-------|-------|-------|-------|
| RAT NUMBER | 17677 | 17678 | 17682 | 17683 | 17691 |
| DAY 86 | | | | | |
| NUMBER OF MOVEMENTS | | | | | |
| BLOCK 1 | 71 | 88 | 59 | 76 | 91 |
| BLOCK 2 | 49 | 91 | 57 | 105 | 86 |
| BLOCK 3 | 55 | 88 | 69 | 77 | 87 |
| BLOCK 4 | 64 | 80 | 80 | 96 | 53 |
| BLOCK 5 | 48 | 51 | 80 | 98 | 69 |
| BLOCK 6 | 76 | 50 | 73 | 79 | 42 |
| BLOCK 7 | 88 | 31 | 82 | 69 | 48 |
| BLOCK 8 | 87 | 9 | 77 | 73 | 71 |
| BLOCK 9 | 61 | 3 | 12 | 52 | 71 |
| BLOCK 10 | 68 | 27 | 0 | 68 | 72 |
| BLOCK 11 | 74 | 79 | 21 | 63 | 71 |
| BLOCK 12 | 79 | 78 | 90 | 43 | 76 |
| BLOCK 13 | 4 | 74 | 67 | 55 | 50 |
| BLOCK 14 | 1 | 44 | 11 | 65 | 53 |
| BLOCK 15 | 3 | 60 | 0 | 77 | 72 |
| BLOCK 16 | 5 | 61 | 14 | 53 | 62 |
| BLOCK 17 | 5 | 50 | 2 | 73 | 62 |
| BLOCK 18 | 81 | 62 | 6 | 54 | 48 |
| TOTAL | 919 | 1026 | 800 | 1276 | 1184 |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C39 (PAGE 8): MOTOR ACTIVITY - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS

| DOSAGE GROUP IV | | 250 MG/KG/DAY | | | | |
|----------------------------------|-------|---------------|-------|-------|-------|--|
| RAT NUMBER | 17677 | 17678 | 17682 | 17683 | 17691 | |
| DAY 86 | | | | | | |
| TIME (SECONDS) SPENT IN MOVEMENT | | | | | | |
| BLOCK 1 | 160 | 186 | 225 | 166 | 156 | |
| BLOCK 2 | 133 | 150 | 155 | 204 | 129 | |
| BLOCK 3 | 98 | 118 | 122 | 182 | 103 | |
| BLOCK 4 | 73 | 104 | 142 | 157 | 74 | |
| BLOCK 5 | 53 | 118 | 112 | 163 | 91 | |
| BLOCK 6 | 126 | 71 | 92 | 109 | 48 | |
| BLOCK 7 | 114 | 44 | 128 | 120 | 75 | |
| BLOCK 8 | 100 | 6 | 107 | 112 | 80 | |
| BLOCK 9 | 78 | 0 | 10 | 135 | 89 | |
| BLOCK 10 | 72 | 36 | 0 | 88 | 109 | |
| BLOCK 11 | 102 | 138 | 15 | 114 | 80 | |
| BLOCK 12 | 121 | 105 | 109 | 101 | 138 | |
| BLOCK 13 | 0 | 93 | 117 | 77 | 57 | |
| BLOCK 14 | 0 | 40 | 10 | 86 | 77 | |
| BLOCK 15 | 3 | 131 | 0 | 119 | 72 | |
| BLOCK 16 | 2 | 83 | 13 | 82 | 69 | |
| BLOCK 17 | 4 | 67 | 2 | 104 | 85 | |
| BLOCK 18 | 85 | 97 | 3 | 96 | 51 | |
| TOTAL | 1324 | 1587 | 1362 | 2215 | 1583 | |

TOTAL = SUM OF BLOCKS; EACH BLOCK CONSISTS OF A 5 MINUTE PERIOD.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C40 (PAGE 1): NATURAL DELIVERY, IMPLANTATION SITES, AND PUP VIABILITY AND SEX - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS/F1 GENERATION LITTERS

| RAT/ LITTER NUMBER | DURATION OF GESTATION (DAYS) N | LITTER DELIVERED | | | NUMBER OF LIVE PUPS AT COMPLETION OF DAY POSTPARTUM | | | | TOTAL IMPLAN- TATIONS N |
|--------------------------|---|-------------------|---------------------|--------------------|--|----|----|----|----------------------------------|
| | | LIVE BORN N | STILL- BORN N | TOTAL BORN N | 1 | | 5 | | |
| | | | | | M | F | M | F | |
| DOSAGE GROUP I | | VEHICLE | | | 0 (VEHICLE) MG/KG/DAY | | | | |
| 17662 | 23 | 14 | 0 | 14 | 8 | 6 | 8 | 6 | 15 |
| 17672 | 23 | 16 | 0 | 16 | 10 | 6 | 10 | 6 | 17 |
| 17673 | 23 | 13 | 0 | 13 | 5 | 8 | 5 | 8 | 15 |
| 17674 | 23 | 18 | 0 | 18 | 12 | 6 | 12 | 6 | 18 |
| 17680 | 23 | 17 | 0 | 17 | 8 | 9 | 8 | 9 | 18 |
| 17681 | 23 | 16 | 0 | 16 | 9 | 7 | 9 | 7 | 18 |
| 17690 | 23 | 18 | 0 | 18 | 9 | 9 | 9 | 9 | 20 |
| 17694 | 22 | 16(1) | 0 | 16 | 10 | 5 | 10 | 5 | 18 |
| 17695 | 22 | 15 | 0 | 15 | 9 | 6 | 9 | 6 | 15 |
| 17703 | 22 | 20(1) | 1 | 21 | 8 | 11 | 8 | 11 | 22 |
| 17713 | 23 | 14 | 0 | 14 | 6 | 8 | 6 | 8 | 15 |
| 17715 | 23 | 13 | 0 | 13 | 8 | 5 | 8 | 5 | 15 |
| 17716 | 23 | 14 | 0 | 14 | 8 | 6 | 8 | 6 | 14 |
| 17717 | 22 | 13 | 0 | 13 | 5 | 8 | 5 | 8 | 13 |
| 17719 | 23 | 18 | 0 | 18 | 9 | 9 | 9 | 9 | 18 |
| DOSAGE GROUP II | | LOW DOSAGE | | | 10 MG/KG/DAY | | | | |
| 17663 | NOT PREGNANT | | | | | | | | |
| 17665 | 23 | 15 | 0 | 15 | 8 | 7 | 8 | 7 | 15 |
| 17666 | 22 | 14 | 0 | 14 | 4 | 10 | 4 | 10 | 15 |
| 17668 | 23 | 16 | 0 | 16 | 7 | 9 | 7 | 9 | 16 |
| 17671 | 22 | 13 | 0 | 13 | 5 | 8 | 5 | 8 | 14 |
| 17675 | 23 | 18 | 0 | 18 | 12 | 6 | 12 | 6 | 18 |
| 17679 | 23 | 9 | 0 | 9 | 4 | 5 | 4 | 5 | 10 |
| 17684 | 22 | 16 | 0 | 16 | 9 | 7 | 9 | 7 | 16 |
| 17688 | 22 | 14 | 0 | 14 | 9 | 5 | 9 | 5 | 17 |
| 17698 | 22 | 16 | 0 | 16 | 9 | 7 | 9 | 6 | 17 |
| 17702 | 22 | 15 | 0 | 15 | 8 | 7 | 8 | 7 | 15 |
| 17704 | 23 | 19 | 0 | 19 | 13 | 6 | 13 | 6 | 20 |
| 17707 | 23 | 15 | 0 | 15 | 6 | 9 | 6 | 9 | 16 |
| 17708 | 22 | 16 | 0 | 16 | 9 | 7 | 9 | 7 | 17 |
| 17710 | 23 | 19 | 0 | 19 | 13 | 6 | 12 | 6 | 20 |

M = MALE F = FEMALE

() = NUMBER OF PUPS DYING PRIOR TO WEIGHING ON DAY 1 POSTPARTUM.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C40 (PAGE 2): NATURAL DELIVERY, IMPLANTATION SITES, AND PUP VIABILITY AND SEX - INDIVIDUAL DATA - F0 GENERATION FEMALE RATS/F1 GENERATION LITTERS

| RAT/ LITTER NUMBER | DURATION OF GESTATION (DAYS) N | LITTER DELIVERED | | | NUMBER OF LIVE PUPS AT COMPLETION OF DAY POSTPARTUM | | | | TOTAL IMPLAN- TATIONS N |
|--------------------------|---|-------------------|---------------------|--------------------|--|----|----|----|----------------------------------|
| | | LIVE BORN N | STILL- BORN N | TOTAL BORN N | 1 | | 5 | | |
| | | | | | M | F | M | F | |
| DOSAGE GROUP III | | MIDDLE DOSAGE | | | 50 MG/KG/DAY | | | | |
| 17661 | 23 | 15 | 0 | 15 | 10 | 5 | 10 | 5 | 16 |
| 17667 | 23 | 13 | 0 | 13 | 7 | 6 | 7 | 6 | 15 |
| 17669 | 23 | 16 | 0 | 16 | 2 | 14 | 2 | 14 | 17 |
| 17670 | 23 | 16 | 0 | 16 | 6 | 10 | 6 | 10 | 16 |
| 17676 | 23 | 15 | 0 | 15 | 11 | 4 | 11 | 4 | 15 |
| 17687 | 23 | 15 | 0 | 15 | 8 | 7 | 8 | 7 | 16 |
| 17693 | 23 | 15 | 2 | 17 | 8 | 7 | 8 | 6 | 17 |
| 17697 | 23 | 15 | 0 | 15 | 9 | 6 | 9 | 6 | 16 |
| 17700 | 22 | 14 | 0 | 14 | 10 | 4 | 10 | 4 | 16 |
| 17701 | 23 | 14 | 0 | 14 | 4 | 10 | 4 | 10 | 19 |
| 17705 | 23 | 16 | 2 | 18 | 7 | 9 | 7 | 9 | 18 |
| 17706 | 23 | 15 | 0 | 15 | 10 | 5 | 10 | 4 | 16 |
| 17709 | 23 | 16 | 0 | 16 | 7 | 9 | 7 | 9 | 16 |
| 17718 | 22 | 16 | 0 | 16 | 11 | 5 | 11 | 5 | 18 |
| 17720 | 22 | 16 | 0 | 16 | 8 | 8 | 8 | 8 | 16 |
| DOSAGE GROUP IV | | HIGH DOSAGE | | | 250 MG/KG/DAY | | | | |
| 17664 | NOT PREGNANT; MATING NOT CONFIRMED | | | | | | | | |
| 17677 | 23 | 4 (4) | 0 | 7 [3] | - | - | - | - | 13 |
| 17678 | 23 | 12 | 0 | 12 | 5 | 7 | 5 | 7 | 15 |
| 17682 | 22 | 14 | 0 | 14 | 6 | 8 | 6 | 8 | 15 |
| 17683 | 23 | 16 | 0 | 16 | 10 | 6 | 10 | 6 | 16 |
| 17685 | 23 | 16 | 1 | 17 | 3 | 13 | 2 | 13 | 17 |
| 17686 | NOT PREGNANT | | | | | | | | |
| 17689 | 23 | 17 | 0 | 18 [1] | 12 | 5 | 12 | 5 | 18 |
| 17691 | 23 | 12 | 0 | 12 | 4 | 8 | 4 | 8 | 13 |
| 17692 | 23 | 14 | 2 | 16 | 7 | 7 | 7 | 7 | 16 |
| 17696 | 23 | 13 | 2 | 15 | 4 | 9 | - | - | 17 |
| 17699 | 23 | 14 | 0 | 14 | 8 | 6 | 7 | 6 | 16 |
| 17711 | 23 | 12 | 1 | 13 | 5 | 7 | - | - | 15 |
| 17712 | 23 | 13 | 0 | 13 | 8 | 5 | 8 | 5 | 16 |
| 17714 | 23 | 16 | 0 | 16 | 5 | 11 | 5 | 10 | 17 |

M = MALE F = FEMALE

() = NUMBER OF PUPS DYING PRIOR TO WEIGHING ON DAY 1 POSTPARTUM.

[] = NUMBER OF PUPS IN WHICH CANNIBALIZATION AND/OR AUTOLYSIS PRECLUDED THE DETERMINATION OF VIABILITY.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C41 (PAGE 1): PUP BODY WEIGHT LITTER AVERAGES FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION LITTERS

| RAT/ LITTER NUMBER | DAY 1 | | | DAY 5 | | |
|--------------------------|--------------|-----|------------|-------|------|-----------------------|
| | M | F | T | M | F | T |
| MATERNAL DOSAGE GROUP I | | | VEHICLE | | | 0 (VEHICLE) MG/KG/DAY |
| 17662 | 7.0 | 6.5 | 6.8 | 11.1 | 10.2 | 10.7 |
| 17672 | 6.4 | 6.2 | 6.4 | 10.9 | 9.7 | 10.4 |
| 17673 | 6.5 | 5.9 | 6.1 | 8.7 | 8.5 | 8.6 |
| 17674 | 6.7 | 6.5 | 6.6 | 9.2 | 8.7 | 9.0 |
| 17680 | 7.5 | 6.8 | 7.1 | 11.4 | 10.5 | 10.9 |
| 17681 | 6.1 | 5.8 | 6.0 | 9.8 | 9.5 | 9.6 |
| 17690 | 6.3 | 6.1 | 6.2 | 9.8 | 9.5 | 9.6 |
| 17694 | 6.2 | 5.7 | 6.0 | 10.0 | 9.2 | 9.8 |
| 17695 | 5.9 | 5.7 | 5.8 | 9.3 | 9.1 | 9.2 |
| 17703 | 5.5 | 5.2 | 5.4 | 8.7 | 7.9 | 8.2 |
| 17713 | 6.5 | 6.4 | 6.4 | 10.1 | 10.0 | 10.0 |
| 17715 | 8.1 | 8.5 | 8.3 | 11.8 | 12.4 | 12.0 |
| 17716 | 7.2 | 6.8 | 7.0 | 9.4 | 9.1 | 9.3 |
| 17717 | 6.3 | 6.0 | 6.1 | 8.8 | 8.8 | 8.8 |
| 17719 | 6.2 | 6.0 | 6.1 | 8.3 | 8.4 | 8.4 |
| MATERNAL DOSAGE GROUP II | | | LOW DOSAGE | | | 10 MG/KG/DAY |
| 17663 | NOT PREGNANT | | | | | |
| 17665 | 7.1 | 6.9 | 7.0 | 10.4 | 10.0 | 10.2 |
| 17666 | 6.3 | 5.9 | 6.0 | 10.0 | 9.4 | 9.5 |
| 17668 | 6.2 | 5.9 | 6.0 | 10.4 | 9.4 | 9.8 |
| 17671 | 6.5 | 6.4 | 6.4 | 9.5 | 9.3 | 9.4 |
| 17675 | 6.0 | 5.9 | 6.0 | 9.1 | 8.6 | 8.9 |
| 17679 | 7.3 | 7.1 | 7.2 | 12.1 | 12.0 | 12.0 |
| 17684 | 6.8 | 6.6 | 6.7 | 10.6 | 10.0 | 10.3 |
| 17688 | 6.0 | 5.7 | 5.9 | 10.6 | 10.4 | 10.5 |
| 17698 | 6.3 | 6.4 | 6.3 | 10.6 | 10.1 | 10.4 |
| 17702 | 6.2 | 5.7 | 6.0 | 9.8 | 9.0 | 9.5 |
| 17704 | 6.0 | 6.2 | 6.0 | 9.0 | 9.4 | 9.1 |
| 17707 | 6.0 | 5.9 | 6.0 | 10.2 | 10.2 | 10.2 |
| 17708 | 6.2 | 5.9 | 6.0 | 10.4 | 9.6 | 10.0 |
| 17710 | 6.6 | 6.2 | 6.5 | 10.5 | 9.8 | 10.3 |

M = MALE F = FEMALE T = TOTAL (SUM OF PUP WEIGHTS/NUMBER OF LIVE PUPS) DAY = DAY POSTPARTUM
 ALL WEIGHTS WERE RECORDED IN GRAMS (G). MEAN LITTER WEIGHTS INCLUDE ONLY WEIGHTS OF LIVE PUPS.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C41 (PAGE 2): PUP BODY WEIGHT LITTER AVERAGES FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION LITTERS

| RAT/ LITTER NUMBER | DAY 1 | | | DAY 5 | | |
|---------------------------|---|-----|---------------|---|------|---------------|
| | M | F | T | M | F | T |
| MATERNAL DOSAGE GROUP III | | | MIDDLE DOSAGE | | | 50 MG/KG/DAY |
| 17661 | 6.7 | 6.1 | 6.5 | 9.8 | 8.6 | 9.4 |
| 17667 | 7.1 | 6.9 | 7.0 | 10.8 | 10.2 | 10.5 |
| 17669 | 6.8 | 5.9 | 6.0 | 10.4 | 9.0 | 9.2 |
| 17670 | 7.0 | 6.8 | 6.8 | 9.5 | 9.1 | 9.2 |
| 17676 | 6.3 | 6.2 | 6.3 | 9.3 | 8.9 | 9.2 |
| 17687 | 6.8 | 6.4 | 6.6 | 12.0 | 11.8 | 11.9 |
| 17693 | 6.4 | 6.3 | 6.4 | 10.0 | 9.6 | 9.8 |
| 17697 | 6.5 | 6.2 | 6.4 | 10.0 | 9.3 | 9.7 |
| 17700 | 6.6 | 6.2 | 6.5 | 11.2 | 10.7 | 11.1 |
| 17701 | 7.1 | 6.8 | 6.9 | 11.0 | 9.9 | 10.2 |
| 17705 | 7.1 | 6.4 | 6.7 | 10.8 | 9.0 | 9.8 |
| 17706 | 7.1 | 6.6 | 6.9 | 11.9 | 11.5 | 11.8 |
| 17709 | 6.0 | 5.6 | 5.7 | 9.0 | 8.5 | 8.7 |
| 17718 | 6.5 | 6.2 | 6.4 | 9.6 | 9.8 | 9.7 |
| 17720 | 6.3 | 6.2 | 6.3 | 10.1 | 10.7 | 10.4 |
| MATERNAL DOSAGE GROUP IV | | | HIGH DOSAGE | | | 250 MG/KG/DAY |
| 17664 | NOT PREGNANT; MATING NOT CONFIRMED | | | | | |
| 17677 | NO SURVIVING PUPS ON DAY 1 OF LACTATION | | | | | |
| 17678 | 7.0 | 6.5 | 6.7 | 10.9 | 10.4 | 10.6 |
| 17682 | 6.8 | 6.8 | 6.8 | 11.5 | 11.2 | 11.3 |
| 17683 | 6.2 | 6.1 | 6.2 | 7.7 | 7.2 | 7.5 |
| 17685 | 5.5 | 5.4 | 5.4 | 7.4 | 7.7 | 7.7 |
| 17686 | NOT PREGNANT | | | | | |
| 17689 | 5.8 | 5.8 | 5.8 | 9.2 | 9.2 | 9.2 |
| 17691 | 7.2 | 7.0 | 7.0 | 9.8 | 9.6 | 9.7 |
| 17692 | 5.7 | 5.5 | 5.6 | 8.1 | 8.0 | 8.1 |
| 17696 | 4.8 | 4.5 | 4.6 | NO SURVIVING PUPS ON DAY 2 OF LACTATION | | |
| 17699 | 5.8 | 5.5 | 5.7 | 9.0 | 8.8 | 8.9 |
| 17711 | 4.9 | 4.5 | 4.7 | NO SURVIVING PUPS ON DAY 2 OF LACTATION | | |
| 17712 | 6.5 | 6.0 | 6.3 | 11.0 | 9.9 | 10.5 |
| 17714 | 7.0 | 6.1 | 6.4 | 10.5 | 9.2 | 9.6 |

M = MALE F = FEMALE T = TOTAL (SUM OF PUP WEIGHTS/NUMBER OF LIVE PUPS) DAY = DAY POSTPARTUM
 ALL WEIGHTS WERE RECORDED IN GRAMS (G). MEAN LITTER WEIGHTS INCLUDE ONLY WEIGHTS OF LIVE PUPS.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C42 (PAGE 1): PUP BODY WEIGHTS FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| PUP # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | |
|------------------|-------------------------|-----|-----|-----|-----|---------|-----|-----------------------|------|-----|-----|-----|------------------|-----|-----|------|-----|-----|-----|-----|--|
| | 21 | 22 | 23 | | | | | | | | | | | | | | | | | | |
| RAT/ LITTER # | MATERNAL DOSAGE GROUP I | | | | | VEHICLE | | 0 (VEHICLE) MG/KG/DAY | | | | | POSTPARTUM DAY 1 | | | | | | | | |
| 17662 | 6.8 | 7.3 | 7.3 | 7.5 | 7.1 | 7.0 | 6.5 | 6.9 | 6.6 | 5.3 | 6.5 | 6.7 | 6.5 | 7.2 | | | | | | | |
| 17672 | 6.6 | 6.2 | 6.7 | 6.9 | 6.0 | 6.1 | 6.5 | 6.8 | 6.0 | 6.3 | 6.5 | 7.0 | 6.1 | 6.4 | 5.9 | 5.6 | | | | | |
| 17673 | 6.6 | 6.7 | 6.7 | 6.2 | 6.2 | 6.1 | 6.2 | 6.6 | 6.2 | 5.8 | 5.6 | 6.0 | 4.9 | | | | | | | | |
| 17674 | 6.0 | 5.8 | 6.8 | 7.0 | 6.2 | 7.0 | 6.7 | 7.0 | 7.4 | 7.2 | 7.0 | 6.7 | 7.1 | 6.6 | 6.5 | 6.4 | 5.8 | 6.6 | | | |
| 17680 | 7.0 | 7.3 | 7.4 | 7.9 | 7.4 | 7.6 | 7.6 | 7.6 | 7.0 | 6.0 | 6.6 | 7.0 | 6.5 | 7.6 | 6.9 | 7.5 | 6.6 | | | | |
| 17681 | 5.9 | 5.9 | 6.6 | 6.0 | 5.3 | 6.5 | 5.6 | 6.2 | 6.6 | 5.9 | 5.7 | 6.0 | 5.9 | 6.1 | 5.7 | 5.7 | | | | | |
| 17690 | 6.8 | 5.0 | 6.3 | 7.0 | 6.1 | 6.4 | 5.9 | 6.7 | 6.4 | 5.7 | 6.2 | 5.7 | 5.9 | 5.9 | 7.0 | 5.6 | 6.3 | 6.3 | | | |
| 17694 | 6.5 | 6.4 | 5.7 | 6.1 | 6.0 | 6.2 | 6.4 | 6.5 | 6.0 | 6.5 | 6.2 | 5.5 | 5.6 | 5.2 | 5.8 | FD 1 | | | | | |
| 17695 | 5.9 | 6.0 | 6.2 | 6.0 | 5.6 | 6.1 | 5.6 | 5.7 | 5.7 | 5.9 | 5.8 | 5.2 | 5.7 | 5.8 | 5.7 | | | | | | |
| 17703 | 5.7 | 5.8 | 5.6 | 5.7 | 5.4 | 5.2 | 5.7 | 5.1 | MD 1 | MS | 5.8 | 4.7 | 5.5 | 5.3 | 5.5 | 5.0 | 5.4 | 5.1 | 5.5 | 5.3 | |
| | 4.6 | | | | | | | | | | | | | | | | | | | | |
| 17713 | 6.6 | 6.6 | 6.5 | 6.8 | 6.3 | 6.3 | 6.1 | 6.7 | 6.3 | 6.3 | 6.1 | 6.2 | 6.9 | 6.2 | | | | | | | |
| 17715 | 7.0 | 9.0 | 8.0 | 7.1 | 8.9 | 7.3 | 8.9 | 8.8 | 8.4 | 9.0 | 8.5 | 8.6 | 8.0 | | | | | | | | |
| 17716 | 7.4 | 7.1 | 7.1 | 7.2 | 7.3 | 7.3 | 6.9 | 7.3 | 6.9 | 6.8 | 6.6 | 6.1 | 7.3 | 6.8 | | | | | | | |
| 17717 | 6.0 | 6.2 | 6.5 | 6.5 | 6.1 | 5.3 | 5.9 | 5.9 | 6.4 | 5.8 | 6.4 | 6.4 | 6.0 | | | | | | | | |
| 17719 | 6.3 | 6.3 | 6.6 | 6.0 | 6.8 | 5.2 | 5.7 | 6.6 | 6.2 | 5.5 | 5.9 | 6.2 | 6.6 | 5.6 | 6.2 | 6.1 | 5.9 | 6.1 | | | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). MEAN LITTER WEIGHTS INCLUDE ONLY WEIGHTS OF LIVE PUPS.
 FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
 SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED)
 NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C42 (PAGE 2): PUP BODY WEIGHTS FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| PUP # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|------------------|--------------------------|-----|-----|-----|------------|-----|-----|-----|--------------|-----|-----|-----|------------------|-----|-----|-----|-----|-----|-----|----|
| | 21 | 22 | 23 | | | | | | | | | | | | | | | | | |
| RAT/ LITTER # | MATERNAL DOSAGE GROUP II | | | | LOW DOSAGE | | | | 10 MG/KG/DAY | | | | POSTPARTUM DAY 1 | | | | | | | |
| 17663 | NOT PREGNANT | | | | | | | | | | | | | | | | | | | |
| 17665 | 7.1 | 6.9 | 7.3 | 7.4 | 6.7 | 6.7 | 7.1 | 7.3 | 6.9 | 6.8 | 6.8 | 6.9 | 7.3 | 6.7 | 6.7 | | | | | |
| 17666 | 6.3 | 6.4 | 6.3 | 6.2 | 5.6 | 5.9 | 6.2 | 6.1 | 5.5 | 5.9 | 6.1 | 6.0 | 5.9 | 5.9 | | | | | | |
| 17668 | 6.2 | 6.5 | 6.3 | 6.4 | 5.6 | 6.3 | 6.4 | 5.8 | 5.9 | 5.8 | 6.0 | 5.6 | 5.7 | 6.1 | 6.0 | 6.0 | | | | |
| 17671 | 6.8 | 6.5 | 6.0 | 6.9 | 6.3 | 6.4 | 6.2 | 6.6 | 6.5 | 6.3 | 6.2 | 6.5 | 6.5 | | | | | | | |
| 17675 | 6.1 | 6.3 | 5.4 | 6.2 | 6.1 | 6.6 | 6.5 | 5.8 | 6.0 | 5.5 | 6.1 | 5.7 | 6.2 | 5.9 | 5.5 | 6.1 | 5.9 | 6.0 | | |
| 17679 | 7.4 | 7.3 | 7.2 | 7.4 | 7.4 | 6.8 | 6.9 | 7.6 | 6.9 | | | | | | | | | | | |
| 17684 | 6.7 | 6.5 | 6.6 | 7.1 | 7.2 | 6.9 | 6.8 | 7.0 | 6.7 | 7.0 | 6.7 | 6.4 | 6.2 | 6.5 | 6.3 | 6.9 | | | | |
| 17688 | 6.3 | 6.0 | 6.1 | 6.1 | 6.2 | 6.4 | 6.4 | 5.0 | 5.3 | 5.7 | 5.9 | 5.7 | 5.3 | 5.8 | | | | | | |
| 17698 | 7.0 | 6.2 | 6.0 | 3.8 | 6.6 | 7.5 | 6.6 | 7.0 | 5.8 | 6.2 | 6.2 | 6.6 | 6.4 | 6.6 | 6.9 | 6.0 | | | | |
| 17702 | 6.0 | 6.0 | 6.1 | 6.5 | 6.4 | 6.0 | 6.2 | 6.5 | 5.5 | 6.2 | 5.4 | 5.6 | 5.9 | 6.2 | 5.1 | | | | | |
| 17704 | 6.3 | 5.7 | 5.8 | 4.9 | 6.5 | 6.6 | 6.3 | 5.5 | 6.0 | 6.8 | 5.1 | 6.4 | 5.7 | 6.1 | 6.1 | 6.3 | 6.3 | 6.1 | 6.2 | |
| 17707 | 6.6 | 6.4 | 5.8 | 6.0 | 6.1 | 5.3 | 6.1 | 5.5 | 6.1 | 5.3 | 5.8 | 6.2 | 5.9 | 6.3 | 6.0 | | | | | |
| 17708 | 6.1 | 6.1 | 6.2 | 5.9 | 5.6 | 6.6 | 6.5 | 6.3 | 6.4 | 5.8 | 6.2 | 5.4 | 6.0 | 5.7 | 5.9 | 6.2 | | | | |
| 17710 | 6.7 | 6.7 | 7.2 | 6.6 | 6.9 | 6.6 | 6.3 | 7.1 | 5.7 | 6.3 | 6.3 | 6.9 | 7.0 | 6.7 | 6.1 | 6.3 | 6.1 | 6.3 | 5.6 | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). MEAN LITTER WEIGHTS INCLUDE ONLY WEIGHTS OF LIVE PUPS.
 FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
 SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED)
 NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C42 (PAGE 3): PUP BODY WEIGHTS FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| PUP # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|------------------|---------------------------|-----|-----|-----|-----|---------------|-----|-----|--------------|-----|-----|-----|-----|------------------|-----|-----|-----|----|----|----|
| | 21 | 22 | 23 | | | | | | | | | | | | | | | | | |
| RAT/ LITTER # | MATERNAL DOSAGE GROUP III | | | | | MIDDLE DOSAGE | | | 50 MG/KG/DAY | | | | | POSTPARTUM DAY 1 | | | | | | |
| 17661 | 6.5 | 6.8 | 6.6 | 6.4 | 6.7 | 6.7 | 6.8 | 6.3 | 7.6 | 7.0 | 6.0 | 6.4 | 5.2 | 6.1 | 6.6 | | | | | |
| 17667 | 6.9 | 6.8 | 6.5 | 8.7 | 6.5 | 7.5 | 6.9 | 6.5 | 5.6 | 7.8 | 6.7 | 6.4 | 8.3 | | | | | | | |
| 17669 | 6.6 | 7.1 | 5.7 | 5.6 | 5.4 | 6.1 | 6.1 | 6.0 | 6.1 | 6.1 | 6.2 | 6.1 | 6.1 | 5.5 | 6.2 | 5.9 | | | | |
| 17670 | 6.9 | 6.2 | 7.1 | 7.5 | 6.6 | 7.4 | 6.7 | 7.5 | 6.8 | 7.4 | 6.1 | 6.9 | 5.1 | 6.9 | 7.0 | 7.1 | | | | |
| 17676 | 6.6 | 6.5 | 6.6 | 5.8 | 5.0 | 6.7 | 6.2 | 6.0 | 6.7 | 6.8 | 6.4 | 6.0 | 6.4 | 6.2 | 6.1 | | | | | |
| 17687 | 6.6 | 6.8 | 6.5 | 6.0 | 6.9 | 7.0 | 7.2 | 7.2 | 6.2 | 6.7 | 6.1 | 6.7 | 6.5 | 6.0 | 6.5 | | | | | |
| 17693 | 5.5 | 6.4 | 6.4 | 6.8 | 6.6 | 6.9 | 6.5 | 6.1 | 6.8 | MS | 6.3 | 6.3 | 6.6 | 6.1 | 6.0 | 6.1 | FS | | | |
| 17697 | 6.7 | 6.7 | 6.5 | 6.5 | 6.7 | 6.7 | 6.1 | 6.6 | 6.2 | 5.7 | 6.5 | 6.4 | 5.3 | 6.5 | 6.8 | | | | | |
| 17700 | 6.2 | 6.9 | 7.0 | 6.5 | 6.6 | 6.9 | 5.8 | 7.0 | 6.8 | 6.1 | 6.2 | 6.2 | 6.0 | 6.4 | | | | | | |
| 17701 | 7.2 | 6.7 | 7.5 | 7.0 | 7.3 | 6.5 | 6.7 | 6.7 | 6.7 | 7.0 | 6.7 | 7.3 | 6.6 | 6.3 | | | | | | |
| 17705 | 6.7 | 7.1 | 6.8 | 6.9 | 7.3 | 7.4 | 7.4 | MS | 6.4 | 7.1 | 6.7 | 6.4 | 6.7 | 6.5 | 4.6 | 6.4 | 6.6 | FS | | |
| 17706 | 7.3 | 7.4 | 7.4 | 6.9 | 7.3 | 6.7 | 6.9 | 7.1 | 6.6 | 7.6 | 6.6 | 6.6 | 6.6 | 6.4 | 6.7 | | | | | |
| 17709 | 5.9 | 5.8 | 5.8 | 5.7 | 6.4 | 6.0 | 6.1 | 6.0 | 5.1 | 5.6 | 5.6 | 5.5 | 5.8 | 5.5 | 5.8 | 5.2 | | | | |
| 17718 | 7.1 | 6.6 | 6.1 | 6.1 | 6.0 | 7.0 | 6.7 | 6.6 | 6.1 | 6.5 | 6.5 | 6.1 | 5.9 | 6.1 | 6.6 | 6.5 | | | | |
| 17720 | 6.0 | 6.5 | 4.4 | 6.5 | 6.9 | 6.9 | 6.4 | 6.7 | 6.5 | 6.0 | 6.9 | 6.1 | 6.3 | 5.7 | 6.6 | 5.8 | | | | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). MEAN LITTER WEIGHTS INCLUDE ONLY WEIGHTS OF LIVE PUPS.
 FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
 SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED)
 NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C42 (PAGE 4): PUP BODY WEIGHTS FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| PUP # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|------------------|------------------------------------|-----|-----|------|-------------|------|-----|-----|---------------|-----|-----|-----|------------------|-----|-----|-----|-----|----|----|----|
| | 21 | 22 | 23 | | | | | | | | | | | | | | | | | |
| RAT/ LITTER # | MATERNAL DOSAGE GROUP IV | | | | HIGH DOSAGE | | | | 250 MG/KG/DAY | | | | POSTPARTUM DAY 1 | | | | | | | |
| 17664 | NOT PREGNANT; MATING NOT CONFIRMED | | | | | | | | | | | | | | | | | | | |
| 17677 | MD 1 | UU | UU | FD 1 | FD 1 | FD 1 | UU | | | | | | | | | | | | | |
| 17678 | 6.9 | 7.4 | 7.0 | 7.0 | 6.5 | 6.9 | 6.2 | 6.7 | 5.8 | 6.1 | 7.1 | 6.7 | | | | | | | | |
| 17682 | 6.9 | 6.5 | 7.1 | 6.7 | 6.9 | 6.5 | 6.8 | 7.1 | 6.6 | 7.2 | 6.7 | 6.1 | 6.9 | 6.6 | | | | | | |
| 17683 | 6.8 | 5.7 | 6.8 | 6.0 | 6.3 | 6.0 | 6.2 | 6.1 | 6.1 | 6.3 | 6.3 | 6.6 | 5.6 | 6.0 | 5.9 | 6.2 | | | | |
| 17685 | 5.4 | 5.2 | 6.0 | 4.9 | 5.6 | 5.4 | 5.6 | 5.3 | 5.2 | 5.5 | 5.4 | 5.4 | 5.4 | 5.1 | 5.9 | 5.1 | FS | | | |
| 17686 | NOT PREGNANT | | | | | | | | | | | | | | | | | | | |
| 17689 | 5.6 | 5.8 | 6.0 | 5.6 | 6.2 | 5.7 | 5.7 | 6.0 | 5.2 | 6.0 | 5.5 | 5.7 | 5.5 | 6.0 | 5.7 | 5.7 | 5.9 | UU | | |
| 17691 | 7.1 | 7.8 | 6.6 | 7.3 | 6.9 | 7.4 | 6.4 | 7.1 | 6.5 | 6.9 | 7.4 | 7.3 | | | | | | | | |
| 17692 | 6.0 | 5.4 | 5.4 | 5.6 | 5.3 | 6.7 | 5.7 | MS | MS | 5.7 | 5.5 | 5.7 | 5.5 | 5.2 | 5.2 | 5.9 | | | | |
| 17696 | 4.5 | 5.0 | 5.1 | 4.8 | 4.6 | 4.7 | 4.5 | 4.1 | 4.1 | 4.6 | 5.2 | 4.1 | 4.6 | FS | FS | | | | | |
| 17699 | 5.8 | 5.5 | 6.2 | 5.5 | 5.4 | 6.2 | 5.4 | 6.5 | 5.4 | 5.2 | 5.8 | 5.4 | 5.5 | 5.6 | | | | | | |
| 17711 | 5.0 | 4.9 | 4.8 | 4.9 | 4.8 | MS | 4.5 | 4.7 | 4.3 | 4.5 | 4.5 | 4.4 | 4.8 | | | | | | | |
| 17712 | 6.1 | 6.5 | 6.3 | 6.8 | 6.6 | 6.8 | 6.3 | 6.5 | 5.9 | 6.4 | 5.8 | 6.1 | 5.8 | | | | | | | |
| 17714 | 7.0 | 6.8 | 7.0 | 7.3 | 7.0 | 6.0 | 6.1 | 6.2 | 6.3 | 5.6 | 6.4 | 6.7 | 5.8 | 5.6 | 6.6 | 6.0 | | | | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). MEAN LITTER WEIGHTS INCLUDE ONLY WEIGHTS OF LIVE PUPS.
 FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
 SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED)
 NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C42 (PAGE 5): PUP BODY WEIGHTS FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| PUP # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | |
|------------------|-------------------------|------|------|------|------|---------|------|------|------|------|-----------------------|------|------|------|------|------------------|------|-----|-----|-----|--|
| | 21 | 22 | 23 | | | | | | | | | | | | | | | | | | |
| RAT/ LITTER # | MATERNAL DOSAGE GROUP I | | | | | VEHICLE | | | | | 0 (VEHICLE) MG/KG/DAY | | | | | POSTPARTUM DAY 5 | | | | | |
| 17662 | 11.6 | 11.1 | 10.2 | 10.5 | 11.7 | 11.1 | 11.2 | 11.7 | 11.6 | 8.2 | 10.2 | 10.5 | 10.3 | 10.4 | | | | | | | |
| 17672 | 9.8 | 10.8 | 11.2 | 11.0 | 11.6 | 10.5 | 10.5 | 11.1 | 11.6 | 10.6 | 9.0 | 9.1 | 9.7 | 10.0 | 10.6 | 9.7 | | | | | |
| 17673 | 8.4 | 7.7 | 8.8 | 9.0 | 9.8 | 8.2 | 9.3 | 8.9 | 8.8 | 8.7 | 8.0 | 8.4 | 8.0 | | | | | | | | |
| 17674 | 9.3 | 9.7 | 8.1 | 9.8 | 8.7 | 9.5 | 9.5 | 8.8 | 9.8 | 9.7 | 8.2 | 9.6 | 8.6 | 8.4 | 8.8 | 9.0 | 8.7 | 8.6 | | | |
| 17680 | 11.8 | 11.6 | 10.8 | 11.9 | 11.7 | 10.8 | 11.4 | 11.0 | 10.8 | 10.9 | 10.6 | 11.4 | 9.7 | 10.1 | 11.7 | 9.7 | 10.0 | | | | |
| 17681 | 10.1 | 10.6 | 9.7 | 9.2 | 10.9 | 9.1 | 9.1 | 11.0 | 8.2 | 9.4 | 9.0 | 9.6 | 9.9 | 9.9 | 9.6 | 9.2 | | | | | |
| 17690 | 10.7 | 10.2 | 10.5 | 10.5 | 7.0 | 10.5 | 9.2 | 10.2 | 9.5 | 10.9 | 9.2 | 9.3 | 9.4 | 9.4 | 9.3 | 9.2 | 9.6 | 9.0 | | | |
| 17694 | 10.9 | 10.5 | 9.9 | 10.4 | 10.0 | 9.5 | 8.6 | 10.1 | 11.0 | 9.5 | 10.5 | 9.7 | 8.4 | 9.0 | 8.5 | FD 1 | | | | | |
| 17695 | 9.7 | 8.9 | 9.7 | 9.0 | 9.4 | 9.1 | 9.0 | 9.5 | 9.2 | 9.0 | 8.9 | 9.5 | 8.9 | 8.7 | 9.8 | | | | | | |
| 17703 | 8.7 | 9.3 | 9.3 | 8.3 | 9.1 | 8.4 | 8.5 | 8.2 | MD 1 | MS | 7.9 | 7.0 | 7.5 | 7.8 | 9.2 | 8.3 | 8.1 | 8.8 | 6.7 | 8.2 | |
| | 7.2 | | | | | | | | | | | | | | | | | | | | |
| 17713 | 10.1 | 10.4 | 9.5 | 9.3 | 10.9 | 10.4 | 10.0 | 9.8 | 9.6 | 10.6 | 10.1 | 10.0 | 10.2 | 9.5 | | | | | | | |
| 17715 | 12.2 | 11.1 | 10.8 | 12.4 | 12.5 | 12.7 | 12.2 | 10.4 | 12.6 | 12.3 | 12.6 | 12.3 | 12.3 | | | | | | | | |
| 17716 | 9.6 | 9.9 | 9.7 | 8.5 | 9.7 | 8.9 | 9.6 | 9.4 | 8.2 | 9.5 | 9.4 | 10.0 | 8.4 | 9.2 | | | | | | | |
| 17717 | 8.6 | 7.6 | 9.9 | 9.2 | 8.9 | 8.6 | 8.6 | 8.5 | 9.0 | 9.5 | 8.3 | 8.9 | 9.3 | | | | | | | | |
| 17719 | 9.2 | 8.6 | 6.7 | 7.9 | 6.6 | 9.0 | 9.8 | 7.0 | 9.7 | 7.8 | 8.6 | 7.5 | 8.8 | 8.3 | 8.8 | 8.0 | 9.4 | 8.8 | | | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). MEAN LITTER WEIGHTS INCLUDE ONLY WEIGHTS OF LIVE PUPS.

FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE

SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED)

NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C42 (PAGE 6): PUP BODY WEIGHTS FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| PUP # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|------------------|--------------------------|------|------|------|------------|------|------|------|--------------|------|------|------|------------------|------|------|------|-----|------|-----|----|
| | 21 | 22 | 23 | | | | | | | | | | | | | | | | | |
| RAT/ LITTER # | MATERNAL DOSAGE GROUP II | | | | LOW DOSAGE | | | | 10 MG/KG/DAY | | | | POSTPARTUM DAY 5 | | | | | | | |
| 17663 | NOT PREGNANT | | | | | | | | | | | | | | | | | | | |
| 17665 | 10.7 | 10.9 | 10.4 | 10.4 | 10.1 | 11.0 | 10.2 | 9.9 | 10.8 | 10.3 | 10.4 | 10.0 | 9.7 | 9.6 | 9.2 | | | | | |
| 17666 | 10.2 | 9.4 | 9.7 | 10.5 | 9.1 | 9.6 | 9.1 | 9.4 | 9.1 | 9.3 | 10.7 | 8.9 | 9.8 | 8.8 | | | | | | |
| 17668 | 11.0 | 10.5 | 10.3 | 10.6 | 10.8 | 9.2 | 10.1 | 9.8 | 9.6 | 9.5 | 9.7 | 9.2 | 9.3 | 9.2 | 9.5 | 9.3 | | | | |
| 17671 | 9.4 | 9.5 | 9.1 | 9.7 | 9.9 | 9.4 | 8.7 | 9.5 | 9.5 | 9.0 | 9.6 | 9.5 | 9.2 | | | | | | | |
| 17675 | 9.1 | 9.7 | 8.1 | 9.7 | 8.1 | 9.2 | 9.1 | 10.1 | 8.7 | 9.5 | 9.6 | 8.4 | 7.8 | 9.0 | 8.9 | 8.7 | 8.5 | 8.6 | | |
| 17679 | 12.5 | 11.8 | 12.2 | 11.9 | 12.8 | 12.1 | 11.6 | 11.4 | 12.1 | | | | | | | | | | | |
| 17684 | 10.2 | 11.6 | 10.2 | 9.7 | 10.3 | 11.4 | 10.5 | 10.7 | 10.8 | 9.7 | 11.1 | 9.3 | 10.2 | 9.8 | 9.7 | 10.0 | | | | |
| 17688 | 11.2 | 7.3 | 10.5 | 10.9 | 11.4 | 11.7 | 11.4 | 9.7 | 11.4 | 10.8 | 9.9 | 10.6 | 10.4 | 10.4 | | | | | | |
| 17698 | 10.5 | 10.5 | 10.5 | 11.6 | 10.9 | 10.6 | 11.1 | 11.0 | 8.3 | 10.1 | 9.8 | 10.7 | 10.7 | 9.2 | 10.1 | FD 2 | | | | |
| 17702 | 10.4 | 10.3 | 10.0 | 9.4 | 9.2 | 9.2 | 10.3 | 10.0 | 10.4 | 8.6 | 9.4 | 8.2 | 8.4 | 9.2 | 9.2 | | | | | |
| 17704 | 7.6 | 9.2 | 9.1 | 9.0 | 10.3 | 9.3 | 10.0 | 9.8 | 9.2 | 8.8 | 7.9 | 9.1 | 8.0 | 8.5 | 10.7 | 10.0 | 9.0 | 8.9 | 9.4 | |
| 17707 | 11.1 | 8.3 | 10.4 | 10.1 | 11.1 | 10.1 | 9.3 | 10.5 | 10.8 | 9.3 | 10.5 | 11.1 | 9.1 | 10.7 | 10.3 | | | | | |
| 17708 | 10.4 | 11.5 | 10.6 | 10.1 | 10.9 | 10.5 | 10.2 | 10.1 | 9.0 | 8.5 | 9.9 | 10.6 | 9.9 | 9.3 | 9.2 | 9.7 | | | | |
| 17710 | 10.9 | 10.5 | 9.0 | 10.3 | 10.3 | 11.3 | 9.6 | 10.6 | 10.5 | 10.2 | 11.4 | 11.3 | MM 2 | 10.3 | 10.3 | 10.2 | 8.5 | 10.4 | 9.1 | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). MEAN LITTER WEIGHTS INCLUDE ONLY WEIGHTS OF LIVE PUPS.
 FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
 SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED)
 NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C42 (PAGE 7): PUP BODY WEIGHTS FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| PUP # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | |
|------------------|---------------------------|------|------|------|------|---------------|------|------|--------------|------|------|------|------|------------------|------|------|-----|----|----|----|--|
| | 21 | 22 | 23 | | | | | | | | | | | | | | | | | | |
| RAT/ LITTER # | MATERNAL DOSAGE GROUP III | | | | | MIDDLE DOSAGE | | | 50 MG/KG/DAY | | | | | POSTPARTUM DAY 5 | | | | | | | |
| 17661 | 9.8 | 9.4 | 10.0 | 9.7 | 10.8 | 10.1 | 9.6 | 10.3 | 9.4 | 9.3 | 9.7 | 9.1 | 7.9 | 7.6 | 8.7 | | | | | | |
| 17667 | 9.7 | 10.6 | 11.8 | 10.0 | 9.8 | 13.6 | 10.2 | 9.7 | 12.0 | 7.8 | 10.0 | 12.2 | 9.3 | | | | | | | | |
| 17669 | 10.4 | 10.5 | 8.5 | 7.6 | 9.2 | 9.0 | 8.6 | 9.8 | 9.3 | 9.0 | 9.5 | 8.2 | 9.5 | 9.6 | 9.6 | 8.2 | | | | | |
| 17670 | 9.5 | 9.9 | 9.8 | 10.3 | 9.0 | 8.6 | 8.8 | 9.6 | 9.2 | 9.8 | 9.8 | 9.5 | 8.3 | 7.5 | 9.2 | 9.2 | | | | | |
| 17676 | 9.3 | 9.8 | 10.0 | 9.2 | 9.8 | 9.8 | 8.6 | 7.9 | 9.2 | 9.6 | 9.1 | 9.6 | 9.0 | 9.1 | 7.8 | | | | | | |
| 17687 | 12.7 | 11.2 | 11.7 | 12.5 | 12.4 | 11.7 | 12.0 | 11.6 | 12.1 | 11.7 | 12.5 | 11.7 | 11.5 | 11.3 | 11.7 | | | | | | |
| 17693 | 10.4 | 10.3 | 9.6 | 10.6 | 10.1 | 10.3 | 9.0 | 10.1 | 9.3 | MS | 8.8 | 9.6 | 9.7 | 9.9 | 10.1 | FM 3 | FS | | | | |
| 17697 | 9.9 | 9.8 | 9.9 | 10.2 | 10.1 | 9.7 | 9.8 | 10.3 | 9.9 | 10.0 | 9.2 | 9.2 | 9.5 | 10.5 | 7.5 | | | | | | |
| 17700 | 11.2 | 11.7 | 9.7 | 10.8 | 12.5 | 12.6 | 10.9 | 11.8 | 10.5 | 10.4 | 11.1 | 11.1 | 10.9 | 9.8 | | | | | | | |
| 17701 | 10.6 | 10.5 | 11.3 | 11.8 | 10.4 | 11.0 | 8.7 | 10.2 | 10.6 | 10.8 | 10.3 | 9.5 | 9.5 | 8.4 | | | | | | | |
| 17705 | 11.5 | 9.9 | 12.2 | 11.6 | 9.2 | 10.3 | 11.2 | MS | 9.2 | 8.1 | 9.5 | 10.1 | 9.4 | 7.1 | 9.7 | 10.6 | 7.7 | FS | | | |
| 17706 | 12.3 | 12.3 | 12.1 | 12.4 | 11.2 | 10.9 | 12.7 | 12.8 | 11.3 | 11.4 | 12.0 | 11.0 | 11.3 | 11.6 | FD 5 | | | | | | |
| 17709 | 9.6 | 9.5 | 8.5 | 9.0 | 8.3 | 8.6 | 9.5 | 8.6 | 8.3 | 7.8 | 9.2 | 9.3 | 8.2 | 7.8 | 8.4 | 8.6 | | | | | |
| 17718 | 8.3 | 10.7 | 10.1 | 9.9 | 9.7 | 9.4 | 9.9 | 10.5 | 10.6 | 9.6 | 7.1 | 10.3 | 10.1 | 9.0 | 9.9 | 9.5 | | | | | |
| 17720 | 11.3 | 11.4 | 10.5 | 5.7 | 10.9 | 10.4 | 9.4 | 11.4 | 10.7 | 9.5 | 10.2 | 11.0 | 11.3 | 11.0 | 11.7 | 10.1 | | | | | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). MEAN LITTER WEIGHTS INCLUDE ONLY WEIGHTS OF LIVE PUPS.
 FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
 SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED)
 NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C42 (PAGE 8): PUP BODY WEIGHTS FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| PUP # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|------------------|------------------------------------|------|------|-------------|------|------|------|---------------|------|------|------|------|------------------|------|-----|------|-----|----|----|----|
| | 21 | 22 | 23 | | | | | | | | | | | | | | | | | |
| RAT/ LITTER # | MATERNAL DOSAGE GROUP IV | | | HIGH DOSAGE | | | | 250 MG/KG/DAY | | | | | POSTPARTUM DAY 5 | | | | | | | |
| 17664 | NOT PREGNANT; MATING NOT CONFIRMED | | | | | | | | | | | | | | | | | | | |
| 17677 | MD 1 | UU | UU | FD 1 | FD 1 | FD 1 | UU | | | | | | | | | | | | | |
| 17678 | 11.0 | 10.5 | 11.2 | 10.7 | 11.3 | 10.5 | 9.4 | 10.3 | 10.4 | 11.4 | 9.8 | 11.0 | | | | | | | | |
| 17682 | 11.7 | 11.6 | 11.9 | 11.4 | 11.4 | 10.8 | 11.0 | 11.9 | 11.5 | 10.6 | 11.4 | 11.4 | 10.9 | 10.5 | | | | | | |
| 17683 | 8.4 | 8.5 | 7.7 | 7.3 | 7.7 | 8.2 | 7.0 | 7.3 | 7.0 | 7.5 | 7.6 | 7.2 | 7.3 | 7.1 | 7.3 | 6.9 | | | | |
| 17685 | 7.2 | 7.6 | MM 2 | 7.9 | 6.8 | 7.1 | 8.2 | 8.7 | 7.3 | 7.5 | 6.8 | 8.2 | 7.9 | 8.2 | 8.1 | 7.5 | FS | | | |
| 17686 | NOT PREGNANT | | | | | | | | | | | | | | | | | | | |
| 17689 | 9.1 | 8.9 | 8.9 | 9.2 | 9.5 | 9.4 | 9.9 | 9.3 | 8.6 | 8.5 | 9.8 | 9.3 | 9.0 | 9.1 | 9.3 | 9.2 | 9.5 | UU | | |
| 17691 | 9.9 | 9.3 | 9.4 | 10.8 | 10.3 | 10.2 | 10.0 | 10.2 | 9.5 | 8.6 | 8.2 | 10.1 | | | | | | | | |
| 17692 | 8.1 | 7.9 | 8.1 | 8.8 | 7.8 | 7.8 | 8.5 | MS | MS | 8.1 | 8.0 | 8.6 | 8.2 | 8.0 | 8.1 | 7.2 | | | | |
| 17696 | MD 2 | MD 2 | MD 2 | MD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FM 2 | FM 2 | FM 2 | FM 2 | FS | FS | | | | | |
| 17699 | 8.9 | 9.0 | 8.4 | 8.9 | 9.0 | 8.9 | 10.0 | MM 2 | 8.7 | 9.0 | 9.2 | 8.8 | 8.4 | 8.6 | | | | | | |
| 17711 | MD 2 | MD 2 | MD 2 | MD 2 | MM 2 | MS | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | | | | | | |
| 17712 | 11.4 | 10.9 | 10.6 | 11.5 | 10.8 | 10.1 | 10.8 | 11.6 | 9.4 | 9.8 | 11.0 | 9.7 | 9.4 | | | | | | | |
| 17714 | 10.7 | 9.9 | 10.3 | 10.8 | 11.0 | 8.4 | 8.7 | 9.3 | 9.0 | 9.7 | 9.8 | 9.5 | 8.7 | 9.4 | 9.6 | FM 2 | | | | |

ALL WEIGHTS WERE RECORDED IN GRAMS (G). MEAN LITTER WEIGHTS INCLUDE ONLY WEIGHTS OF LIVE PUPS.
 FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
 SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED)
 NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C43 (PAGE 1): PUP VITAL STATUS AND SEX FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| PUP # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
|------------------|-------------------------|-----|-----|-----|-----|-----|-----|-----|---------|------|-----------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|
| RAT/ LITTER # | MATERNAL DOSAGE GROUP I | | | | | | | | VEHICLE | | 0 (VEHICLE) MG/KG/DAY | | | | | | | | | | | | | |
| 17662 | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | | | | | | | | |
| 17672 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17673 | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | | | | | | | | |
| 17674 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17680 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17681 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17690 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17694 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | FD 1 | | | |
| 17695 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17703 | M A | M A | M A | M A | M A | M A | M A | M A | M A | MD 1 | MS | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17713 | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | | | | | | | | |
| 17715 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | | | | | | | | |
| 17716 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | | | | | | | |
| 17717 | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | | | | | | | | |
| 17719 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |

FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
 SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED)
 NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C43 (PAGE 2): PUP VITAL STATUS AND SEX FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| PUP # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
|------------------|--------------------------|-----|-----|-----|-----|-----|------------|-----|-----|-----|-----|-----|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| RAT/ LITTER # | MATERNAL DOSAGE GROUP II | | | | | | LOW DOSAGE | | | | | | 10 MG/KG/DAY | | | | | | | | | | | |
| 17663 | NOT PREGNANT | | | | | | | | | | | | | | | | | | | | | | | |
| 17665 | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | | | | | | | | |
| 17666 | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | | | | | | | | | |
| 17668 | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | | | | | | | |
| 17671 | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | | | | | | | | | | |
| 17675 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | | | | | |
| 17679 | M A | M A | M A | M A | F A | F A | F A | F A | F A | | | | | | | | | | | | | | | |
| 17684 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | | | | | | |
| 17688 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | | | | | | | | | |
| 17698 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F D | 2 | | | |
| 17702 | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | | | | | | | | |
| 17704 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17707 | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | | | | | | | | |
| 17708 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | | | | |
| 17710 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M M | 2 | F A | F A | F A | F A | F A | F A | F A | F A | F A |

FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
 SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED)
 NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C43 (PAGE 3): PUP VITAL STATUS AND SEX FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| PUP # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
|------------------|---------------------------|---|---|---|---|---|---------------|---|---|----|----|----|--------------|----|----|----|----|----|----|----|----|----|----|---|
| RAT/ LITTER # | MATERNAL DOSAGE GROUP III | | | | | | MIDDLE DOSAGE | | | | | | 50 MG/KG/DAY | | | | | | | | | | | |
| 17661 | M | A | M | A | M | A | M | A | M | A | M | A | F | A | F | A | F | A | F | A | F | A | F | A |
| 17667 | M | A | M | A | M | A | M | A | M | A | M | A | F | A | F | A | F | A | F | A | F | A | F | A |
| 17669 | M | A | M | A | F | A | F | A | F | A | F | A | F | A | F | A | F | A | F | A | F | A | F | A |
| 17670 | M | A | M | A | M | A | M | A | M | A | F | A | F | A | F | A | F | A | F | A | F | A | F | A |
| 17676 | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A |
| 17687 | M | A | M | A | M | A | M | A | M | A | M | A | F | A | F | A | F | A | F | A | F | A | F | A |
| 17693 | M | A | M | A | M | A | M | A | M | A | M | A | F | A | M | S | F | A | F | A | F | A | F | A |
| 17697 | M | A | M | A | M | A | M | A | M | A | M | A | F | A | F | A | F | A | F | A | F | A | F | A |
| 17700 | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A |
| 17701 | M | A | M | A | M | A | F | A | F | A | F | A | F | A | F | A | F | A | F | A | F | A | F | A |
| 17705 | M | A | M | A | M | A | M | A | M | A | M | A | M | S | F | A | F | A | F | A | F | A | F | A |
| 17706 | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | F | A | F | A | F | A | F | A |
| 17709 | M | A | M | A | M | A | M | A | M | A | M | A | F | A | F | A | F | A | F | A | F | A | F | A |
| 17718 | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A | M | A |
| 17720 | M | A | M | A | M | A | M | A | M | A | M | A | F | A | F | A | F | A | F | A | F | A | F | A |

FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
 SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED)
 NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C43 (PAGE 4): PUP VITAL STATUS AND SEX FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| PUP # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
|------------------|------------------------------------|------|------|------|-------------|------|------|------|---------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| RAT/ LITTER # | MATERNAL DOSAGE GROUP IV | | | | HIGH DOSAGE | | | | 250 MG/KG/DAY | | | | | | | | | | | | | | | |
| 17664 | NOT PREGNANT; MATING NOT CONFIRMED | | | | | | | | | | | | | | | | | | | | | | | |
| 17677 | MD 1 | U U | U U | FD 1 | FD 1 | FD 1 | U U | | | | | | | | | | | | | | | | | |
| 17678 | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | | | | | | | | | | |
| 17682 | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17683 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17685 | M A | M A | MM 2 | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F S | F S |
| 17686 | NOT PREGNANT | | | | | | | | | | | | | | | | | | | | | | | |
| 17689 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | U U |
| 17691 | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | | | | | | | | | | |
| 17692 | M A | M A | M A | M A | M A | M A | M A | M A | M S | M S | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17696 | MD 2 | MD 2 | MD 2 | MD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FM 2 | FM 2 | FM 2 | FM 2 | FM 2 | FM 2 | FM 2 | FM 2 | FM 2 | FM 2 | FM 2 | FM 2 | FM 2 | FM 2 |
| 17699 | M A | M A | M A | M A | M A | M A | M A | M A | MM 2 | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17711 | MD 2 | MD 2 | MD 2 | MD 2 | MM 2 | M S | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 | FD 2 |
| 17712 | M A | M A | M A | M A | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A |
| 17714 | M A | M A | M A | M A | M A | M A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | F A | FM 2 |

FIRST LETTER -- M-MALE, F-FEMALE, U-SEX UNDETERMINABLE
 SECOND LETTER -- A-ALIVE, S-STILLBORN, U-UNCERTAIN, D-DIED, M-MISSING (PRESUMED CANNIBALIZED)
 NUMBER FOLLOWING "SECOND LETTER" INDICATES THE DAY POSTPARTUM THE EVENT OCCURRED.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C44 (PAGE 1): CLINICAL OBSERVATIONS FROM BIRTH TO DAY 5 POSTPARTUM - INDIVIDUAL DATA - F1 GENERATION PUPS

| MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) | LITTER NUMBER | DAY (S) POSTPARTUM | OBSERVATIONS a |
|--|------------------|-----------------------|---|
| I 0 (VEHICLE) | 17690 | 1- 2 | 1/18 PUPS: HEAD, BRUISE (DID NOT EXCEED 0.8 CM X 0.3 CM). |
| II 10 | 17688 | 1- 4 1- 2 3- 5 | 1/14 PUPS: BACK, BRUISE (DID NOT EXCEED 0.5 CM X 1.0 CM). 1/14 PUPS: LOWER MIDLINE, BRUISE (DID NOT EXCEED 1.5 CM X 2.0 CM); PALE. 1/14 PUPS: LOWER MIDLINE, BRUISE (DID NOT EXCEED 1.5 CM X 1.0 CM). |
| III 50 | 17720 | 1- 2 | 1/16 PUPS: NECK, BRUISE (DID NOT EXCEED 2.0 CM X 2.5 CM). |
| IV 250 | 17683 | 1- 4 | 1/16 PUPS: BACK, BRUISE (DID NOT EXCEED 2.0 CM X 1.5 CM). |
| | 17685 | 1 2- 3 | 1/16 PUPS: CHEST AND NECK, BRUISE (1.0 CM IN DIAMETER). 1/15 PUPS: CHEST AND NECK, BRUISE (1.0 CM IN DIAMETER). |
| | 17696 | 1 | 2/15 PUPS: MOUTH, BRUISE (0.2 CM X 0.1 CM). |
| | 17699 | 4 | 2/13 PUPS: COLD TO TOUCH; NOT NESTING OR NURSING. |

a. Tabulation restricted to adverse observations; all other pups appeared normal.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C45 (PAGE 1): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS

| MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) | LITTER NUMBER | DAY POSTPARTUM | OBSERVATIONS a |
|--|------------------|-------------------|---|
| I | | | |
| 0 (VEHICLE) | 17662 | 5 | 14 PUPS: APPEARED NORMAL. |
| | 17672 | 5 | 16 PUPS: APPEARED NORMAL. |
| | 17673 | 5 | 13 PUPS: APPEARED NORMAL. |
| | 17674 | 5 | 18 PUPS: APPEARED NORMAL. |
| | 17680 | 5 | 17 PUPS: APPEARED NORMAL. |
| | 17681 | 5 | 16 PUPS: APPEARED NORMAL. |
| | 17690 | 5 | 18 PUPS: APPEARED NORMAL. |
| | 17694 | 1 | 1 PUP: FOUND DEAD. ALL TISSUES APPEARED NORMAL. |
| | | 5 | 15 PUPS: APPEARED NORMAL. |
| | 17695 | 5 | 15 PUPS: APPEARED NORMAL. |
| | 17703 | 1 | 1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL. |
| | | | 1 PUP: FOUND DEAD. NO MILK IN STOMACH. |
| | | 5 | 19 PUPS: APPEARED NORMAL. |
| | 17713 | 5 | 14 PUPS: APPEARED NORMAL. |
| | 17715 | 5 | 13 PUPS: APPEARED NORMAL. |
| | 17716 | 5 | 14 PUPS: APPEARED NORMAL. |
| | 17717 | 5 | 13 PUPS: APPEARED NORMAL. |
| | 17719 | 5 | 18 PUPS: APPEARED NORMAL. |

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C45 (PAGE 2): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS

| MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) | LITTER NUMBER | DAY POSTPARTUM | OBSERVATIONS a |
|--|------------------|-------------------|--|
| II | | | |
| 10 | 17665 | 5 | 15 PUPS: APPEARED NORMAL. |
| | 17666 | 5 | 14 PUPS: APPEARED NORMAL. |
| | 17668 | 5 | 16 PUPS: APPEARED NORMAL. |
| | 17671 | 5 | 13 PUPS: APPEARED NORMAL. |
| | 17675 | 5 | 18 PUPS: APPEARED NORMAL. |
| | 17679 | 5 | 9 PUPS: APPEARED NORMAL. |
| | 17684 | 5 | 16 PUPS: APPEARED NORMAL. |
| | 17688 | 5 | 14 PUPS: APPEARED NORMAL. |
| | 17698 | 2 | 1 PUP: FOUND DEAD. AUTOLYSIS PRECLUDED FURTHER EVALUATION. |
| | | 5 | 15 PUPS: APPEARED NORMAL. |
| | 17702 | 5 | 15 PUPS: APPEARED NORMAL. |
| | 17704 | 5 | 1 PUP: KIDNEYS: BILATERAL, PELVIS, SLIGHT DILATION. ALL OTHER TISSUES APPEARED NORMAL. |
| | | | 18 PUPS: APPEARED NORMAL. |
| | 17707 | 5 | 15 PUPS: APPEARED NORMAL. |
| | 17708 | 5 | 16 PUPS: APPEARED NORMAL. |
| | 17710 | 5 | 18 PUPS: APPEARED NORMAL. |

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)

TABLE C45 (PAGE 3): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS

| MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) | LITTER NUMBER | DAY POSTPARTUM | OBSERVATIONS a |
|--|------------------|-------------------|--|
| III 50 | 17661 | 5 | 15 PUPS: APPEARED NORMAL. |
| | 17667 | 5 | 13 PUPS: APPEARED NORMAL. |
| | 17669 | 5 | 16 PUPS: APPEARED NORMAL. |
| | 17670 | 5 | 16 PUPS: APPEARED NORMAL. |
| | 17676 | 5 | 15 PUPS: APPEARED NORMAL. |
| | 17687 | 5 | 15 PUPS: APPEARED NORMAL. |
| | 17693 | 1 | 2 PUPS: STILLBORN. ALL TISSUES APPEARED NORMAL. |
| | | 5 | 14 PUPS: APPEARED NORMAL. |
| | 17697 | 5 | 15 PUPS: APPEARED NORMAL. |
| | 17700 | 5 | 14 PUPS: APPEARED NORMAL. |
| | 17701 | 5 | 14 PUPS: APPEARED NORMAL. |
| | 17705 | 1 | 2 PUPS: STILLBORN. ALL TISSUES APPEARED NORMAL. |
| | | 5 | 16 PUPS: APPEARED NORMAL. |
| | 17706 | 5 | 1 PUP: FOUND DEAD. AUTOLYSIS PRECLUDED FURTHER EVALUATION. |
| | | | 14 PUPS: APPEARED NORMAL. |
| | 17709 | 5 | 16 PUPS: APPEARED NORMAL. |
| | 17718 | 5 | 16 PUPS: APPEARED NORMAL. |
| | 17720 | 5 | 16 PUPS: APPEARED NORMAL. |

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation. Refer to the individual pup clinical observations table (Table C44) for external clinical observations confirmed at necropsy.

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST (SPONSOR'S STUDY NUMBER: T-7599)


TABLE C45 (PAGE 4): NECROPSY OBSERVATIONS - INDIVIDUAL DATA - F1 GENERATION PUPS

| MATERNAL DOSAGE GROUP MATERNAL DOSAGE (MG/KG/DAY) | LITTER NUMBER | DAY POSTPARTUM | OBSERVATIONS a |
|--|------------------|-------------------|---|
| IV 250 | 17677 | 1 | 1 PUP: FOUND DEAD. NO MILK IN STOMACH. ALL TISSUES APPEARED NORMAL. 1 PUP: FOUND DEAD. ALL TISSUES APPEARED NORMAL. 2 PUPS: FOUND DEAD. NO MILK IN STOMACH. AUTOLYSIS PRECLUDED FURTHER EVALUATION. |
| | 17678 | 5 | 12 PUPS: APPEARED NORMAL. |
| | 17682 | 5 | 14 PUPS: APPEARED NORMAL. |
| | 17683 | 5 | 16 PUPS: APPEARED NORMAL. |
| | 17685 | 1 5 | 1 PUP: STILLBORN. ALL TISSUES APPEARED NORMAL. 15 PUPS: APPEARED NORMAL. |
| | 17689 | 5 | 17 PUPS: APPEARED NORMAL. |
| | 17691 | 5 | 12 PUPS: APPEARED NORMAL. |
| | 17692 | 1 5 | 2 PUPS: STILLBORN. ALL TISSUES APPEARED NORMAL. 14 PUPS: APPEARED NORMAL. |
| | 17696 | 1 2 | 2 PUPS: STILLBORN. AUTOLYSIS PRECLUDED FURTHER EVALUATION. 3 PUPS: FOUND DEAD. AUTOLYSIS PRECLUDED FURTHER EVALUATION. 6 PUPS: FOUND DEAD. CANNIBALIZATION PRECLUDED FURTHER EVALUATION. |
| | 17699 | 5 | 13 PUPS: APPEARED NORMAL. |
| | 17711 | 1 2 | 1 PUP: STILLBORN. AUTOLYSIS PRECLUDED FURTHER EVALUATION. 11 PUPS: FOUND DEAD. AUTOLYSIS PRECLUDED FURTHER EVALUATION. |
| | 17712 | 5 | 13 PUPS: APPEARED NORMAL. |
| | 17714 | 5 | 15 PUPS: APPEARED NORMAL. |

a. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation. Refer to the individual pup clinical observations table (Table C44) for external clinical observations confirmed at necropsy.

APPENDIX D
PROTOCOL AND AMENDMENTS

905 Sheehy Drive, Bldg. A
Horsham, PA 19044
Telephone: (215) 443-8710
Telefax: (215) 443-8587


ARGUS RESEARCH
Charles River Laboratories
Discovery and Development Services

PROTOCOL 418-027

SPONSOR'S STUDY NUMBER: T-7599

STUDY TITLE: Oral (Gavage) Combined Repeated Dose Toxicity Study of T 7599.7 with the Reproduction/Developmental Toxicity Screening Test

PURPOSE: The purpose of this study is to provide information on the possible health hazards that may result from repeated exposure of CrI:CD®(SD)IGS BR VAF/Plus® male and female rats to a test substance beginning before cohabitation, through mating and continuing for at least 28 days (male rats) or through parturition until day 4 or 5 of lactation (female rats). This repeated dose study incorporates a reproduction/developmental toxicity screening test that can be used to provide initial information on possible effects on male and female reproductive performance (e.g., gonadal function, mating behavior, conception, development of the conceptus and parturition). The study also places emphasis on neurological effects as a specific endpoint and should identify the neurotoxic potential of a test substance, which may warrant further in-depth investigation.

Because of the selectivity of the endpoints and the short duration of the study, the screening test will not provide evidence for definitive claims of no reproduction/developmental effects. In particular, it offers only limited means of detecting postnatal manifestations of prenatal exposure or effects that may be induced during postnatal exposure.

TESTING FACILITY:

Argus Research
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044-1297
Telephone: (215) 443-8710
Telefax: (215) 443-8587

STUDY DIRECTOR:

Raymond G. York, Ph.D., DABT
Associate Director of Research
Address as cited above for Testing Facility.
Email: raymond.york@criver.com

SPONSOR: 3M Corporate Toxicology
3M Center, Building 220-2E-02
St. Paul, Minnesota 55144-1000

**STUDY
MONITOR:** Paul H. Lieder, Ph.D., DABT
3M Corporate Toxicology
3M Medical Department
Telephone: (651) 737-2678
Telefax: (651) 733-1773
Email: phlieder1@mmm.com

REGULATORY CITATIONS:

Organisation for Economic Co-operation and Development (1996). *OECD Guideline for Testing of Chemicals*. Section 4, No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, adopted 22 March 1996.

Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97)186/Final].

U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58.

Japanese Ministry of Health and Welfare (1997). *Good Laboratory Practice Standard for Safety Studies on Drugs*, MHW Ordinance Number 21, March 26, 1997.

REGULATORY COMPLIANCE:

This study will be conducted in compliance with the Good Laboratory Practice (GLP) regulations cited above with the exception of analysis of blood and liver samples sent to Southern Research Institute for metabolite analysis.

All changes or revisions of this protocol shall be documented, signed by the Study Director and the Sponsor, dated and maintained with the protocol.

The Testing Facility's Quality Assurance Unit (QAU) will audit the protocol, the raw data and the report, and will inspect critical phases of those portions of the study conducted at the Testing Facility in accordance with the Standard Operating Procedures of the Testing Facility.

The final report will include a compliance statement signed by the Study Director that the report accurately reflects the raw data obtained during the performance of the study and that all applicable GLP regulations were followed in the conduct of the study. Should significant deviations from GLP regulations occur, each will be described in detail, together with how the deviation might affect the quality or integrity of the study.

Should any portion of the study be conducted by a subcontractor or by the Sponsor, the Study Director will ensure that a qualified Principal Investigator is identified by the facility conducting that portion of the study. The QAU for that facility will conduct critical phase inspections and audit respective results and reports for that study portion according to the SOPs of that facility. Such critical phase inspection reports and report audits will be submitted by that facility to the Principal Investigator and the Study Director. The dates of the inspections and report submissions will be incorporated into a QAU Statement generated by that facility and provided to the Testing Facility for inclusion in the final report. In addition, that facility will provide a statement of GLP compliance, as described above, signed by the Principal Investigator for inclusion in the final report.

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE:

See ATTACHMENT 1 to the protocol.

TEST SUBSTANCE AND VEHICLE:

Identification:

Test Substance:

T 7599.7. Lot identification to be documented in the raw data.

The Sponsor will provide to the Testing Facility documentation or certification of the identity, composition, method of synthesis, strength and activity/purity of the test substance. This documentation will be included in the final report.

Vehicle:

Aqueous 0.5% carboxymethylcellulose (CMC) (medium viscosity) prepared using reverse osmosis membrane processed deionized water (R.O. deionized water). Lot identification to be documented in the raw data.

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the vehicle that would interfere with the results of this study. Therefore, no analyses other than those mentioned in this protocol will be conducted.

Safety Precautions:

Gloves, dust-mist/HEPA-filtered mask, appropriate eye protection and uniform/lab coat to be worn during formulation preparation and dosage. The Material Safety Data Sheet (MSDS) will be included in the raw data.

Storage:

| | |
|--|---|
| Bulk Test Substance: | Room temperature, protected from light. |
| Bulk Vehicle Components: | Room temperature. |
| Prepared Test Substance and Vehicle Formulations: | Room temperature, protected from light. |

All test substance shipments to the Testing Facility should be addressed to the attention of Julian Gulbinski, Manager of Formulation Laboratory, at the previously cited address and telephone number.

Shipments should include information concerning storage conditions and shipping cartons should be labeled appropriately. The recipient should be notified in advance of shipment.

FORMULATION:**Frequency of Preparation:**

Formulations (suspensions) will be prepared weekly at the Testing Facility.

Detailed preparation procedures are attached to this protocol (ATTACHMENT 2).

Adjustment for Purity:

The test substance will be considered 100% pure for the purpose of dosage calculations.

Testing Facility Reserve Samples:

The Testing Facility will reserve a sample (approximately 1 g) of each lot of bulk test substance and bulk vehicle components used during the course of the study. Samples will be stored under the previously cited conditions.

ANALYSES:

Results of required analyses will be provided to the Testing Facility for inclusion in the study report.

Samples additional to those described below may be taken if deemed necessary during the course of the study. Additional analyses, if required, will be documented by protocol amendment.

Bulk Test Substance Sampling:

A sample (approximately 1 g) of the test substance will be taken on the last day of treatment and sent (ambient conditions, protected from light) to the Sponsor for analysis. This sample will be sent to:

Principal Investigator: Gregory S. Gorman, Ph.D.
Staff Chemist
Bioanalytical Chemistry Group
Southern Research Institute
2000 Ninth Avenue South
Birmingham, Alabama 35255-5305

Telephone: (205) 581-2725
Telefax: (205) 581-2044
Email: gorman@sri.org

The recipient will be notified in advance of sample shipment.

Analyses of Prepared Formulations:**Concentration and Homogeneity:**

Concentration and homogeneity of the prepared formulations will be verified during the course of this study. Quadruplicate samples (2 mL each) will be taken from the top, middle and bottom of each concentration on the first day of preparation. Two samples from each quadruplicate set will be shipped for analysis; the remaining samples will be retained at the Testing Facility as backup samples. Quadruplicate samples will be taken from each concentration on the last day of preparation. Two samples from each quadruplicate set will be shipped for analysis; the remaining samples will be retained as backup samples. Backup samples will be stored under the previously cited conditions and discarded at the Testing Facility upon the request of the Sponsor.

Stability:

Stability of the prepared formulations will be documented during this study. Two sets of duplicate samples (2 mL each) from each concentration will be taken on the first day of preparation. One sample of each duplicate set will be shipped on the day of preparation. These samples will be analyzed at the following time points: as soon after preparation as possible and ten days after the first analysis. The remaining samples will be retained at the Testing Facility as backup samples. Backup samples will be stored under the previously cited conditions and discarded at the Testing Facility upon the request of the Sponsor.

Shipping Instructions:

Samples to be analyzed will be shipped (ambient conditions) to:

Gregory S. Gorman, Ph.D.
Staff Chemist
Bioanalytical Chemistry Group
Southern Research Institute
2000 Ninth Avenue South
Birmingham, Alabama 35255-5305

Telephone: (205) 581-2725
Telefax: (205) 581-2044
Email: gorman@sri.org

The recipient will be notified in advance of sample shipment.

DISPOSITION:

Prepared formulations will be discarded at the Testing Facility. All remaining bulk test substance will be returned to the Sponsor at the previously cited address.

TEST SYSTEM:**Species/Strain and Reason for Selection:**

The CrI:CD®(SD)IGS BR VAF/Plus® rat was selected as the Test System because: 1) it is one mammalian species accepted for use in toxicity studies and it has been widely used throughout industry; 2) this strain of rat has been demonstrated to be sensitive to reproductive and developmental toxins; and 3) historical data and experience exist at the Testing Facility⁽¹⁻³⁾.

Number:

Initial population acclimated: 70 male and 70 virgin female rats.
Population selected for study: 60 male and 60 virgin female rats (15 per sex per dosage group).

Body Weight and Age:

Male rats will be ordered to weigh from 300 g to 325 g each at receipt, at which time they will be expected to be at least 60 days of age. Female rats will be ordered to weigh from 200 g to 225 g each at receipt, at which time they will be expected to be at least 60 days of age. Actual body weights will be recorded the day after receipt and will be documented in the raw data. The weight ranges will be included in the final report. At study initiation, the weight variation of the rats will not exceed $\pm 20\%$ of the mean weight of each sex.

Sex:

Both male and female rats will be evaluated.

Source:

Charles River Laboratories, Inc.

The rats will be shipped in filtered cartons by air freight and/or truck from Charles River Laboratories, Inc., to the Testing Facility.

Identification:

Rats are permanently identified using Monel® self-piercing ear tags (Gey Band and Tag Co., Inc., No. MSPT 20101). Male and female rats are assigned temporary numbers at receipt and given unique permanent identification numbers when assigned to the study before administration of the first dosage. Pups will not be individually identified during lactation; all parameters will be evaluated in terms of the litter.

ANIMAL HUSBANDRY:

All cage sizes and housing conditions are in compliance with the *Guide for the Care and Use of Laboratory Animals*⁽⁴⁾.

Housing:

Fo generation rats will be individually housed in stainless steel, wire-bottomed cages, except during the cohabitation and postpartum periods. During cohabitation, each pair of rats will be housed in the male rat's cage. Beginning no later than day 20 of presumed gestation, Fo generation female rats will be individually housed in nesting boxes. Each dam and delivered litter will be housed in a common nesting box during the postpartum period.

Nesting Material:

Nesting material (bed-o'cobs®) will be provided.

Bedding will be changed as often as necessary to keep the animals dry and clean. Analyses for possible contamination are conducted semi-annually and documented in the raw data.

Room Air, Temperature and Humidity:

The animal room is independently supplied with at least ten changes per hour of 100% fresh air that has been passed through 99.97% HEPA filters. Room temperature will be maintained at 66°F to 77°F (19°C to 25°C) and monitored constantly. Room humidity will also be monitored constantly and maintained at 30% to 70%.

Light:

An automatically controlled 12-hour light:12-hour dark fluorescent light cycle will be maintained. Each dark period will begin at 1900 hours EST. The light cycle may be adjusted by the Study Director or designee if deemed necessary to accommodate scheduled laboratory activities. Any such adjustment will be documented in the raw data.

Diet:

Rats will be given Certified Rodent Diet® #5002 (PMI Nutrition International), available *ad libitum* from individual feeders except during fasting.

Water:

Water will be available *ad libitum* from individual bottles attached to the cages or from an automatic watering access system. All water will be from a local source and passed through a reverse osmosis membrane before use. Chlorine will be added to the processed water as a bacteriostat; processed water is expected to contain no more than 1.2 ppm chlorine at the time of analysis. Water is analyzed monthly for possible bacterial contamination and twice annually for possible chemical contamination.

Contaminants:

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the certified diet, in the drinking water or in the nesting materials at levels that would interfere with the results of this study. Therefore, no analyses other than those routinely performed by the feed supplier or those mentioned in this protocol will be conducted.

DAY NUMBERING SYSTEM:

Gestation day 0 is defined as the day spermatozoa are observed in a smear of the vaginal contents and/or a copulatory plug observed *in situ*.

The day of birth is designated lactation day 0 (postpartum day 0) in the Health Effects Test Guidelines - Reproduction and Fertility Effects (Office of Prevention, Pesticides and Toxic Substances 870.3800, August, 1998) and in the OECD Guideline for the Testing of Chemicals - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (Section 4, No. 422, 22 March 1966). This same day is designated day 1 postpartum (day 1 of lactation) in the Standard Operating Procedures of the Testing Facility. Throughout this protocol, the day of birth will be designated day 1 postpartum (day 1 of lactation) and all subsequent ages of the F1 generation rats and days of the lactation period will be determined and cited accordingly.

RANDOMIZATION AND COHABITATION:

Upon arrival, rats will be assigned to individual housing on the basis of computer-generated random units. After an acclimation period of at least five days, male and female rats will be selected for study on the basis of physical appearance and body weights recorded during acclimation. The rats will be assigned to dosage groups based on computer-generated (weight-ordered) randomization procedures.

Within each dosage group, consecutive order will be used to assign rats to cohabitation, one male rat per female rat. The cohabitation period will consist of a maximum of 14 days. Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug observed *in situ* will be considered to be at day 0 of presumed gestation and assigned to individual housing. Female rats not mated within the first seven days of cohabitation will be assigned alternate male rats that have mated (same dosage group) and will remain in cohabitation for a maximum of seven additional days.

Day 1 of lactation (postpartum) is defined as the day of birth and is also the first day on which all pups in a litter are individually weighed (pup body weights will be recorded after all pups in a litter are delivered and groomed by the dam).

Within each dosage group, consecutive order will be used to assign the first five male and the first five female rats to a functional observational battery (FOB) and motor activity assessment. The next five rats per sex in each group will be assigned to hematology and clinical biochemistry evaluations. The last five rats per sex in each group will be assigned to metabolite analysis. Histological evaluations will be performed on the last ten rats per sex in each group.

ADMINISTRATION:**Route and Reason for Choice:**

The oral (gavage) route was selected for use because: 1) in comparison with the dietary route, the exact dosage can be accurately administered; and 2) it is one possible route of human exposure.

Method and Frequency:

Dosages will be adjusted daily for body weight changes and given at approximately the same time each day.

Male rats will be given the test substance and/or the vehicle once daily beginning 14 days before cohabitation (maximum 14 days) and continuing until sacrifice, after completion of the cohabitation period, after a minimum of 28 days of dosage.

Female rats will be given the test substance and/or the vehicle once daily beginning 14 days before cohabitation (maximum 14 days) and continuing until the day before scheduled sacrifice on day 6 of lactation.

Pups will not be directly given the test substance or the vehicle but may be possibly exposed to the test substance during maternal gestation (*in utero* exposure) or via maternal milk during the lactation period.

Rationale for Dosage Selection:

Dosages will be selected by the Sponsor based on previous studies conducted with the test substance, taking into account possible differences in sensitivity between pregnant and nonpregnant rats. The highest dosage will be expected to cause toxic effects but not mortality or obvious suffering. The descending sequence of the lower dosage levels will be selected for the purpose of demonstrating any dosage-related response, with no adverse effects expected at the lowest level.

Dosage Levels, Concentrations and Volumes:

| Dosage Group | Number Of Rats Per Sex | Dosage (mg/kg/day) | Concentration (mg/mL) | Dosage Volume (mL/kg) | Argus Batch Number |
|--------------|------------------------|--------------------|-----------------------|-----------------------|-----------------------------|
| I | 15 | 0 (Vehicle) | 0 | 10 | B-418-027-A(Day.Month.Year) |
| II | 15 | 10 | 1 | 10 | B-418-027-B(Day.Month.Year) |
| III | 15 | 50 | 5 | 10 | B-418-027-C(Day.Month.Year) |
| IV | 15 | 250 | 25 | 10 | B-418-027-D(Day.Month.Year) |

The test substance will be considered 100% pure for the purpose of dosage calculations.

TESTS, ANALYSES AND MEASUREMENTS - Fo GENERATION:

Viability - Male and Female Rats:

All Periods: At least twice daily.

Clinical Observations and/or General Appearance - Male and Female Rats:

Acclimation Period: Weekly.

Dosage Period: Daily before dosage. On the first day of dosage, postdosage observations will be recorded at approximately hourly intervals after administration for the first four hours and at the end of the normal working day. Postdosage observations for subsequent days of dosage will be recorded at intervals determined appropriate by the Study Director and/or Study Monitor after determination of the onset of peak pharmacologic/toxicologic effects.

Postdosage Period: Before sacrifice.

Maternal Behavior: Days 1 and 5 postpartum. Observed abnormal behavior recorded daily.

Clinical observations may be recorded more frequently than cited above, if deemed appropriate by the Study Director and/or Study Monitor.

Detailed Clinical Observations - Male and Female Rats:

Once before the first dosage and at least once weekly thereafter, detailed clinical observations will be conducted for all male and female rats. These observations will be made outside the cage in a standard arena at the same time each day of conduct. Effort will be made to ensure that variations in the test conditions are minimal and that observations are conducted by observers unaware of treatment groups. Signs noted should include, but not be limited to: changes in skin, fur, eyes, mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g., lacrimation, piloerection, pupil size, unusual respiratory pattern). Changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypic behavior (e.g., excessive grooming, repetitive circling), difficult or prolonged parturition or bizarre behavior (e.g., self-mutilation, walking backwards) should also be recorded.

Body Weights - Male and Female Rats:

Acclimation Period: Weekly.

Dosage Period: Daily.

Sacrifice: Terminal weight.

Feed Consumption Values - Male Rats (recorded and tabulated):

Dosage Period: Weekly. Feed left recorded on the day before sacrifice. Rats will be fasted overnight before sacrifice.

Feed Consumption Values - Female Rats (recorded and tabulated):

Dosage Period: Weekly to cohabitation.

Days 0, 7, 10, 12, 15, 18, 20 and 25 (if necessary) of presumed gestation and days 1 and 5 postpartum. Feed left will be recorded on the day before sacrifice. Rats will be fasted overnight before sacrifice.

Feed Consumption Values - Male and Female Rats:

Feed consumption values may be recorded more frequently than cited above if it is necessary to replenish the feed. During cohabitation, when two rats occupy the same cage with one feed jar, replenishment of the feed jars will be documented. Individual values will not be recorded or tabulated.

Estrous Cycling and Mating:

Estrous cycling will be evaluated by examination of vaginal cytology beginning with the day after the first administration and then until spermatozoa are observed in a smear of the vaginal contents and/or a copulatory plug is observed *in situ* during the cohabitation period.

Natural Delivery:

Female rats will be evaluated for:

Adverse Clinical Signs Observed During Parturition.

Duration of Gestation (day 0 of presumed gestation to the time the first pup is observed).

Litter Size (defined as all pups delivered).

Pup Viability at Birth.

Functional Observational Battery:

On one occasion during the course of the study, a functional observational battery (FOB)⁽⁵⁻⁸⁾ will be conducted on five male and five female rats per group. For male rats, this assessment will be conducted shortly before scheduled sacrifice. Female rats should be tested during the lactation period, shortly before scheduled sacrifice. To avoid hyperthermia of pups, dams will be separated from their litters for no longer than 30 to 40 minutes.

The FOB, to be conducted by an observer unaware of the group assignment of the rat, will assess the following parameters:

1. Lacrimation, salivation, palpebral closure, prominence of the eye, pupillary reaction to light, piloerection, respiration, and urination and defecation (autonomic functions).
2. Sensorimotor responses to visual, auditory, tactile and painful stimuli (reactivity and sensitivity).
3. Reactions to handling and behavior in the open field (excitability).
4. Gait pattern in the open field, severity of gait abnormalities, air righting reaction, visual placing response and landing foot splay (gait and sensorimotor coordination).
5. Forelimb and hindlimb grip strength.
6. Abnormal clinical signs including but not limited to convulsions, tremors and other unusual behavior, hypotonia or hypertonia, emaciation, dehydration, unkempt appearance and deposits around the eyes, nose or mouth.

Evidence of the ability of this battery to detect the effects of positive control substances will be provided (Testing Facility Positive Control Data). Data will also be provided to document interobserver reliability if more than one observer is involved in the testing.

Motor Activity Test:

Motor activity will be evaluated on five male and five female rats per group once during the course of the study. For male rats, this assessment will be conducted shortly before scheduled sacrifice. Female rats should be tested during the lactation period, shortly before scheduled sacrifice.

The movements of each rat will be monitored by a passive infrared sensor mounted outside a stainless steel, wire-bottomed cage (40.6 x 25.4 x 17.8 cm). Each test session will be 1.5 hours in duration with the number of movements and time spent in movement tabulated at each five-minute interval. The apparatus will monitor a rack of up to 32 cages and sensors during each session, with each rat tested in the same location on the rack across test sessions. Groups will be counterbalanced across testing sessions and cages.

Data will be provided to demonstrate that the test system is capable of detecting increases in activity produced by positive control substances (Testing Facility Positive Control Data).

HEMATOLOGY AND CLINICAL CHEMISTRY:

At scheduled sacrifice, the five male and five female rats per group assigned to hematology and clinical chemistry sample collection will be exsanguinated from the inferior vena cava following sacrifice by carbon dioxide asphyxiation. Rats will be fasted overnight before sacrifice. Approximately 5 mL of blood (fasted) will be collected and processed as described below. Determinations additional to those described below may be conducted if the known properties of the test substance may, or are suspected to, affect related metabolic profiles (e.g., calcium, phosphate, fasting triglycerides and fasting glucose, specific hormones, and cholinesterase). The tubes containing the samples will be labeled with the protocol number, Sponsor study number, animal number, group number, dosage level, day of study, collection interval, date of collection, species, generation and storage conditions.

Hematology:

Approximately 1 mL of blood will be collected into EDTA-coated tubes and maintained on wet ice or refrigerated until shipment for analysis of the following hematologic parameters:

| | |
|---|-------------------------------|
| Erythrocyte Count (RBC) | Mean Corpuscular Volume (MCV) |
| Hematocrit (HCT) | Leukocyte Count, Total (WBC) |
| Hemoglobin (HGB) | Leukocyte Count, Differential |
| Mean Corpuscular Hemoglobin (MCH) | Platelet Count (PLAT) |
| Mean Corpuscular Hemoglobin Concentration (MCHC) | Mean Platelet Volume (MPV) |
| | Cell Morphology |

Two blood smear slides will be prepared at the Testing Facility for each sample for measurements of differential leukocyte count. All samples (on wet ice) and slides (ambient conditions) will be shipped on the day of collection to Redfield Laboratories at the following address.

Approximately 1.8 mL of blood will be added to a tube containing 0.2 mL of sodium citrate (0.129 M). The contents will be mixed and maintained on wet ice until the tubes are centrifuged (within 30 minutes of the collection time). The resulting plasma will be transferred to a transport tube and immediately frozen. Plasma samples will be maintained on dry ice or in a freezer ($\leq -70^{\circ}\text{C}$) until shipped on dry ice to Redfield Laboratories at the following address, for measurement of prothrombin time (PT) and activated partial thromboplastin time (APTT).

Clinical Chemistry:

Approximately 2 mL of blood will be collected into serum separator tubes and centrifuged. The resulting sera samples will be immediately frozen on dry ice and maintained frozen ($\leq -70^{\circ}\text{C}$) until shipment for analysis of the following parameters:

| | |
|------------------------------|----------------------------------|
| Total Protein (TP) | Creatinine (CREAT) |
| Triglycerides (TRI) | Alanine Aminotransferase (ALT) |
| Albumin (A) | Aspartate Aminotransferase (AST) |
| Globulin (G) | Alkaline Phosphatase (ALK) |
| Albumin/Globulin Ratio (A/G) | Calcium (CA) |
| Glucose (GLU) | Phosphorus (PHOS) |
| Cholesterol (CHOL) | Sodium (NA) |
| Total Bilirubin (TBILI) | Potassium (K) |
| Urea Nitrogen (BUN) | Chloride (CL) |

Samples will be shipped (on dry ice) to arrive on Monday through Friday at Redfield Laboratories at the following address.

Shipping Instructions:

Samples will be shipped according to the conditions described above to:

Principal Investigator: Ms. Phyllis Powell
Redfield Laboratories
A Division of CRL-DDS
100 East Boone Street
P.O. Box 308
Redfield, Arkansas 72132
Telephone: (501) 397-2540
Telefax: (501) 397-2002

The recipient will be notified in advance of sample shipment.

URINALYSIS:

Urinalysis will not be conducted unless indicated based on expected or observed toxicity of the test substance.

METHOD OF SACRIFICE:

Fo generation rats will be sacrificed by carbon dioxide asphyxiation.

GROSS NECROPSY AND HISTOPATHOLOGY - F₀ GENERATION RATS:**Scheduled Sacrifice:**

Scheduled sacrifice of male rats will be conducted on the day following the last dosage administration, after a minimum of 28 days of dosage. Scheduled sacrifice of female rats will be conducted on day 6 of lactation.

Gross necropsy of all male and female rats will include an initial physical examination of external surfaces and all orifices, as well as the cranial, thoracic and abdominal cavities and their contents. Special attention will be paid to the organs of the reproductive system. The number of implantation sites and corpora lutea will be recorded.

Male and female rats will be examined for gross lesions. Gross lesions will be retained in neutral buffered 10% formalin and examined histologically. Tissue trimming and histopathology will be performed under the supervision of or by a Board-Certified Veterinary Pathologist.

The testes and epididymides of all male rats will be weighed, and the testes, epididymides, seminal vesicles with coagulating gland and prostate will be retained in neutral buffered 10% formalin. The testes will be fixed in Bouin's solution for 48 to 96 hours before being retained in neutral buffered 10% formalin. The ovaries and the uterus with cervix of each female rat will be weighed, and ovaries, uterus, vagina and a mammary gland will be retained in neutral buffered 10% formalin. Uteri of apparently nonpregnant rats will be examined after being pressed between glass plates to confirm the absence of implantation sites, and retained in neutral buffered 10% formalin.

Blood samples (approximately 3 mL) will be collected from the five rats per sex per group assigned to metabolite analysis. Blood will be collected from the vena cava. Each sample will be divided into two aliquots. One aliquot of 2 mL will be transferred into an EDTA-coated (purple top) tube and refrigerated. The second aliquot (approximately 1 mL) will be transferred into a serum tube, allowed to clot and spun in a centrifuge. The resulting serum will be transferred into polypropylene tubes labeled with the protocol number, Sponsor study number, animal number, group number, dosage level, day of study, collection interval, date of collection, species, generation and storage conditions. All samples will be immediately frozen on dry ice and maintained frozen ($\leq -70^{\circ}\text{C}$) until shipment for analysis.

The liver will be excised and the organ weight recorded. One lobe (right lateral) will be placed in a conical tube and flash frozen in an ice/alcohol bath. Liver samples will be maintained frozen ($\leq -70^{\circ}\text{C}$) until shipment for analysis.

Shipping Instructions:

Liver and serum samples will be shipped on dry ice and whole blood will be shipped on ice packs. Samples to be analyzed will be shipped to:

Principal Investigator: Gregory S. Gorman, Ph.D.
Staff Chemist
Bioanalytical Chemistry Group
Southern Research Institute
200 Ninth Avenue South
Birmingham, Alabama 35255-5305

Telephone: (205) 581-2725
Telefax: (205) 581-2044
Email: gorman@sri.org

The recipient will be notified in advance of sample shipment.

See ATTACHMENT 3 for additional tissues to be weighed and retained from the ten rats per sex per group assigned to histological sample collection and evaluation.

All other tissues will be discarded.

Scheduled Sacrifice of Female Rats that Do Not Deliver Litters:

Rats that do not deliver a litter will be sacrificed on day 25 of presumed gestation. Gross necropsy, examination and tissue retention will be conducted as described above for rats at scheduled sacrifice.

Dams with No Surviving Pups:

Dams with no surviving pups will be sacrificed after the last pup is found dead, missing or presumed cannibalized. Gross necropsy, examination and tissue retention will be conducted as described above for rats at scheduled sacrifice.

Rats Found Dead or Moribund:

Rats that die or are sacrificed because of moribund condition, abortion or premature delivery will be examined for the cause of death or moribund condition on the day the observation is made. The rats will be examined for gross lesions. Testes and epididymides of male rats will be excised and paired organ weights will be recorded. The epididymides will be retained in neutral buffered 10% formalin. The testes will be fixed in Bouin's solution for 48 to 96 hours and then retained in neutral buffered 10% formalin. Pregnancy status and uterine contents of female rats will be recorded. Aborted fetuses and/or delivered pups will be examined to the extent possible. Uteri of apparently nonpregnant rats will be examined after being pressed between glass plates to confirm the absence of implantation sites. Ovaries and uteri will be retained in neutral buffered 10% formalin.

TESTS, ANALYSES AND MEASUREMENTS - F1 GENERATION:**Viability:**

Preweaning Period: Litters will be observed for dead pups at least twice daily. The pups in each litter will be counted once daily.

Clinical Observations and/or General Appearance:

Preweaning Period: Once daily.

Clinical observations may be recorded more frequently than cited above, if deemed appropriate by the Study Director and/or the Study Monitor.

Body Weights:

Preweaning Period: Days 1 (birth) and 5 postpartum.

Sacrifice: Terminal weight.

Feed Consumption Values (recorded and tabulated):

Preweaning Period: Not recorded.

METHOD OF SACRIFICE - F1 GENERATION PUPS:

F1 generation pups will be sacrificed by carbon dioxide asphyxiation.

NECROPSY - F1 GENERATION:

Gross lesions will be retained in neutral buffered 10% formalin for possible future evaluation. Unless specifically cited below, all other tissues will be discarded.

Pups Found Dead on Day 1 Postpartum:

Pups that die before examination of the litter for pup viability will be evaluated for vital status at birth. The lungs will be removed and immersed in water. Pups with lungs that sink will be identified as stillborn; pups with lungs that float will be identified as liveborn, and to have died shortly after birth. Pups with gross lesions will be preserved in Bouin's solution for possible future evaluation.

Pups Found Dead or Moribund on Days 2 to 4 Postpartum:

Pups found dead or sacrificed because of moribundity will be examined for gross lesions and for the cause of death or the moribund condition. Pups with gross lesions will be preserved in Bouin's solution for possible future evaluation.

Scheduled Sacrifice:

On day 5 postpartum, pups will be will be sacrificed and examined for gross lesions; gross lesions will be preserved in neutral buffered 10% formalin. Necropsy will include a single cross-section of the head at the level of the frontal-parietal suture and examination of the cross-sectioned brain for apparent hydrocephaly.

PROPOSED STATISTICAL TESTS:

When possible results will be evaluated by appropriate and acceptable statistical methods. Because of the limited dimensions of the study, statistical analysis in the form of tests for significance are of limited value for many endpoints, particularly reproductive and neurological endpoints. Some of the most widely used methods, especially parametric tests for measures of central tendency, are inappropriate. If statistical analyses are to be conducted, the methods selected will be appropriate for the distribution of the variable examined and added to the protocol prior to finalization or by amendment.

DATA ACQUISITION, VERIFICATION AND STORAGE:

Data generated during the course of this study will be recorded either by hand or using the *Argus Automated Data Collection and Management System*, the *Vivarium Temperature and Relative Humidity Monitoring System*, the *Coulbourn Instruments Passive Infrared Motor Activity System*, the *Coulbourn Instruments Auditory Startle System*, the *Coulbourn Instruments Spatial Delayed Alternation System*, and/or the passive avoidance software. All data will be tabulated, summarized and/or statistically analyzed using the *Argus Automated Data Collection and Management System*, the *Vivarium Temperature and Relative Humidity Monitoring System*, *Microsoft Excel* [part of Microsoft Office 97 (version SR-2)] and/or *The SAS System* (version 6.12).

Records will be reviewed by the Study Director and/or appropriate management personnel within 21 days after generation. All original records will be stored in the archives of the Testing Facility. All original data will be bound and indexed. A copy of all raw data will be supplied to the Sponsor upon request. Preserved tissues will be stored at the Testing Facility at no charge for one year after mailing of the draft final report, after which time the Sponsor will be contacted to determine the disposition of these materials.

KEY PERSONNEL:

Executive Director of Research: Mildred S. Christian, Ph.D., Fellow, ATS
Director of Research: Alan M. Hoberman, Ph.D., DABT
Associate Director of Research and Study Director: Raymond G. York, Ph.D., DABT
Director of Operations and Compliance: Barbara J. Patterson, B.A.
Director of Laboratory Operations: John F. Barnett, B.S.
Director of Study Management: Valerie A. Sharper, M.S.
Manager of Animal Operations: Dena C. Lebo, V.M.D.
Chairperson, Institutional Animal Care and Use Committee: Douglas B. Learn, Ph.D.
Consultant, Veterinary Pathology: W. Ray Brown, D.V.M., Ph.D., ACVP

RECORDS TO BE MAINTAINED:

Protocol and Amendments.
Test Substance, Vehicle and/or Reagent Receipt, Preparation and Use.
Animal Acquisition.
Randomization Schedules.
Mating History.
Treatment (if prescribed by Staff Veterinarian).
General Comments.
Clinical Observations and/or General Appearance.
Body Weights.
Feed Consumption Values.
Natural Delivery Observations.
FOB and Motor Activity Observations.
Blood Sample Collection, Processing and Shipment.
Gross Necropsy Observations.
Organ Weights.
Photographs (if required).
Study Maintenance (room and environmental records).
Feed and Water Analyses.
Packing and/or Shipment Lists.

FINAL REPORT:

The Study Director will provide periodic updates of study progress to the Sponsor. Draft summary tables of unaudited computer-recorded data may accompany these updates. Statistical analyses will not be performed on these interim data.

A comprehensive draft final report will be prepared on completion of the study and will be finalized following consultation with the Sponsor. The report will include the following:

Summary and Conclusion.

Experimental Design and Method.

Evaluation of Test Results.

Appendices: Figures, Summary and Individual Tables Summarizing the Above Data, Protocol and Associated Amendments and Deviations, Study Director's GLP Compliance Statement, Reports of Supporting Data (if appropriate) and QAU Statement.

The Sponsor will receive one copy of the draft report and two copies of the final report. Data will be hand- and/or computer-recorded. Records will be reviewed by the Study Director and/or appropriate management personnel within 21 days after generation. All original records will be stored in the archives of the Testing Facility. All original data will be bound and indexed. A copy of all raw data will be supplied to the Sponsor upon request. Preserved tissues will be stored at the Testing Facility at no charge for one year after mailing of the draft final report, after which time the Sponsor will be contacted to determine the disposition of these materials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE STATEMENT:

The procedures described in this protocol have been reviewed by the Testing Facility's Institutional Animal Care and Use Committee. All procedures described in this protocol that involve study animals will be conducted in a manner to avoid or minimize discomfort, distress or pain to the animals.

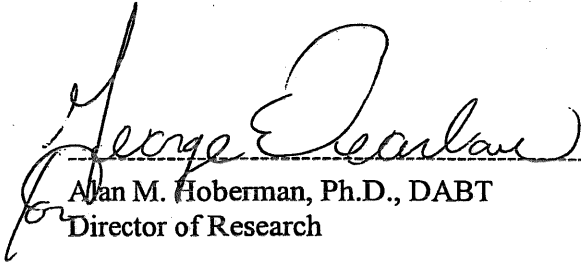
The Sponsor's signature below documents the fact that information concerning the necessity for conducting this study and the fact that this is not an unnecessarily duplicative study may be obtained from the Sponsor. No alternative (*in vitro*) procedures were available for meeting the stated purposes of the study.

REFERENCES:

1. Christian, M.S. and Voytek, P.E. (1982). *In Vivo Reproductive and Mutagenicity Tests*. Environmental Protection Agency, Washington, D.C. National Technical Information Service, U.S. Department of Commerce, Springfield, VA 22161.
2. Christian, M.S. (1984). Reproductive toxicity and teratology evaluations of naltrexone (Proceedings of Naltrexone Symposium, New York Academy of Sciences, November 7, 1983), *J. Clin. Psychiat.* 45(9):7-10.
3. Lang, P.L. (1988). *Embryo and Fetal Developmental Toxicity (Teratology) Control Data in the Charles River Crl:CD@BR Rat*. Charles River Laboratories, Inc., Wilmington, MA 01887-0630. (Data base provided by Argus Research Laboratories, Inc.)
4. Institute of Laboratory Animal Resources (1996). *Guide for the Care and Use of Laboratory Animals*. National Academy Press, Washington, D.C.
5. Haggerty, G.C. (1989). Development of Tier I neurobehavioral testing capabilities for incorporation into pivotal rodent safety assessment studies. *J. Amer. Col. Toxicol.* 8:53-70.
6. Irwin, S. (1968). Comprehensive observational assessment: Ia. A systemic quantitative procedure for assessing the behavioral and physiologic state of the mouse. *Psychopharmacologia (Berlin)* 13:222-257.
7. Moser, V.C. (1989). Screening approaches to neurotoxicity: A functional observational battery. *J. Amer. Col. Toxicol.* 8:85-94.
8. O'Donoghue, J.L. (1989). Screening for neurotoxicity using a neurologically based examination and neuropathology. *J. Amer. Col. Toxicol.* 8:97-116.

PROTOCOL APPROVAL:

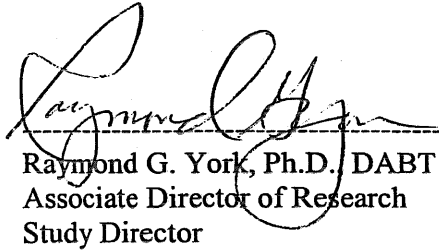
FOR THE TESTING FACILITY



Alan M. Hoberman, Ph.D., DABT
Director of Research

15 Feb 02

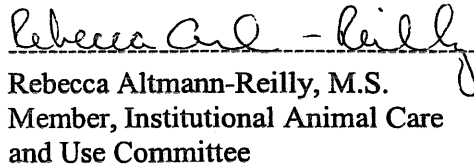
Date



Raymond G. York, Ph.D., DABT
Associate Director of Research
Study Director

15 FEB 2002

Date

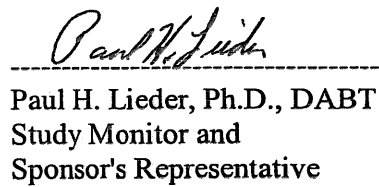


Rebecca Altmann-Reilly, M.S.
Member, Institutional Animal Care
and Use Committee

15 Feb. 2002

Date

FOR THE SPONSOR



Paul H. Lieder, Ph.D., DABT
Study Monitor and
Sponsor's Representative

19 Feb 2002

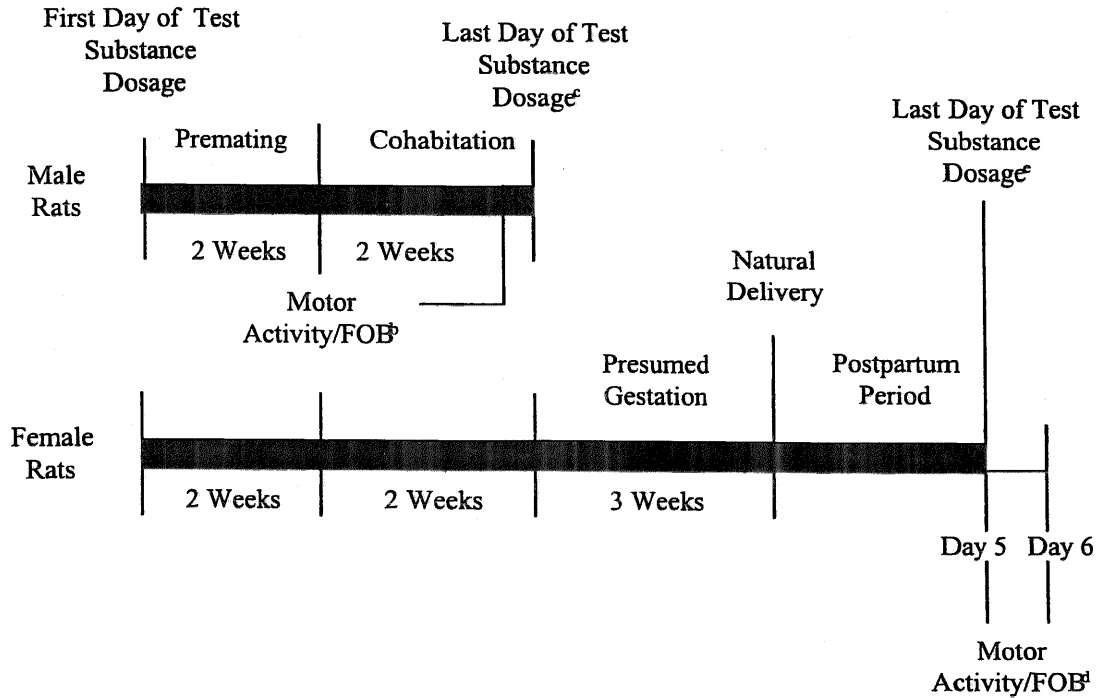
Date

ATTACHMENT 1

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE

STUDY SCHEMATIC

COMBINED REPEAT DOSE AND REPRODUCTIVE/DEVELOPMENTAL TOXICITY SCREEN^a



Dosage Period

- a. For additional details see "Tests, Analyses and Measurements" section of the protocol.
- b. FOB and motor activity evaluations conducted on five males per group.
- c. Male rats sacrificed after completion of at least 28 days of dosage; necropsy and retention of male reproductive organs. Hematology and clinical biochemistry samples (five male and five female rats per group) and histological samples (ten male and ten female rats per group) collected.
- d. Five female rats per group assigned to FOB evaluation on day 5 postpartum and motor activity evaluation on day 6 postpartum.
- e. Last day of dosage for female rats is day 5 postpartum. Pups sacrificed on day 5 postpartum. Female rats sacrificed on day 6 postpartum; necropsy and retention of female reproductive organs. Hematology, clinical biochemistry and histological samples collected.

SCHEDULE^a

| | |
|--|--|
| 12 FEB 02 | Animal Receipt - Acclimation Begins. |
| 18 FEB 02 | Start of Dosage Period - Male Rats (14 days before cohabitation and through a 14-day cohabitation period until the of sacrifice after at least 28 days of dosage). |
| 18 FEB 02 - 16 APR 02 | Dosage Period - Female Rats (14 days before cohabitation through Day 4 or Day 5 of lactation). |
| 19 FEB 02 - 04 MAR 02 | Dosage Period Estrous Cycle Evaluation. |
| 04 MAR 02 PM - 11 MAR 02 AM 11 MAR 02 PM - 18 MAR 02 AM | Cohabitation Period (Maximum of 14 days). Male 1 (7 days) Male 2 (7 days) |
| 05 MAR 02 18 MAR 02 | First Possible Day 0 of Presumed Gestation. Last Possible Day 0 of Presumed Gestation. |
| 19 MAR 02 - 22 MAR 02 | FOB and Motor Activity Evaluation - Five Male Rats per Group |
| 25 MAR 02 | Scheduled Sacrifice - Male Rats (Earliest possible date). Hematology, Clinical Biochemistry and Histological Sample Collection. |

-
- a. The start date of the study is the day the Study Director signs the protocol.
- b. Throughout this schedule, the day of birth is designated day 1 postpartum (day 1 of lactation) and all subsequent ages of the F1 generation rats and days of the lactation period will be determined and cited accordingly, as described above the protocol section, "Day Numbering System."

| | |
|-----------------------|--|
| 26 MAR 02 | First Possible Delivery (Day 21 of presumed gestation). |
| 12 APR 02 | Last Possible Delivery (Day 25 of presumed gestation). |
| 30 MAR 02 | First Possible Day 25 of Presumed Gestation Female Sacrifice. |
| 12 APR 02 | Last Possible Day 25 of Presumed Gestation Female Sacrifice. |
| 30 MAR 02 - 16 APR 02 | FOB Evaluation - Five Female Rats per Group. |
| 30 MAR 02 - 16 APR 02 | Day 5 Postpartum - Pups Sacrificed. |
| 31 MAR 02 - 17 APR 02 | Motor Activity Evaluation - Five Female Rats per Group. |
| 31 MAR 02 - 17 APR 02 | Day 6 Postpartum - Sacrifice of Female Rats. Hematology, Clinical Biochemistry and Histological Sample Collection. |
| 01 AUG 02 | Draft Final Report |

ATTACHMENT 2

TEST SUBSTANCE PREPARATION PROCEDURE

ATTACHMENT 2

Protocol 418-027
Version: 418-027(14 FEB 02)
Page 1 of 2

TEST SUBSTANCE PREPARATION PROCEDURE

Test Substance: T 7559.7
Vehicle: Aqueous 0.5% CMC (medium viscosity)

A. Purpose:

The purpose of this procedure is to provide a method for the preparation of dosage suspensions of T 7559.7 for oral (gavage) administration to rats on Argus Research Study number 418-027.

B. General Information:

1. All suspension containers will be labeled and color-coded. Each label will specify the protocol number, test substance identification, Argus batch number, concentration, dosage level, preparation date, expiration date and storage conditions.
2. Suspensions will be prepared:
 Daily Weekly For days of use
 Approximately every ten days By Sponsor
3. Suspensions will be administered at a final dosage volume of 10 mL/kg.
4. Safety:
 Gloves, uniform/lab coat, goggles or safety glasses with side shields
 Dust-mist/HEPA-filtered Mask
 Half-Face Respirator if not used in a chemical fume hood
 Full-Face Respirator/Positive Pressure Hood
 Tyvek Suit or tyvek apron and sleeves
5. Dosage suspensions adjusted for % Activity/Purity or Correction Factor:
 Yes No (Calculations based on 100%)
 % Activity % Purity Correction Factor
6. Sampling requirements: Cited in protocol
7. Storage: Cited in protocol

ATTACHMENT 2

Protocol 418-027
 Version: 418-027(14 FEB 02)
 Page 2 of 2

TEST SUBSTANCE PREPARATION PROCEDURE

NOTE: Prior to test substance preparation accurately measure the required amount of the appropriate vehicle (R.O. deionized water should be used for calibration purposes) in a graduated cylinder, pour the required amount of vehicle into a beaker. Carefully mark each beaker at the meniscus. This mark will be used during the preparation to bring the test substance slurry up to volume.

C. Dosage Suspension Preparation:

1. Weigh the required amount of test substance on a piece of weigh paper or into an appropriately sized mortar (see PREPARATION CALCULATIONS).
2. If weigh paper is used, transfer the test substance to an appropriately sized mortar. If necessary, grind the test substance into a fine powder. Slowly add a small amount of vehicle and grind. Continue to add vehicle slowly and grind the vehicle and the test substance together to form a fine slurry. Transfer the vehicle/test substance slurry to a marked beaker.
3. Rinse the mortar and pestle with additional vehicle to remove any remaining test substance. Transfer rinse to beaker.
4. Add additional vehicle to the beaker to bring volume up to the mark. Place on magnetic stir plate and agitate prior to and during aliquotting, administration and/or sampling.
5. Repeat steps (1) through (4) for each concentration.

Written By: Patricia A. Kelly

Approved by: [Signature] Date: 15 FEB 2002

Clarification: No Yes [see attached clarification form]

Initial/Date : GC 13.19.03

ATTACHMENT 3

TISSUES TO BE WEIGHED, RETAINED AND EXAMINED HISTOLOGICALLY

**TISSUES TO WEIGHED AND RETAINED FOR POSSIBLE EXAMINATION
FROM TEN RATS PER SEX PER GROUP**

Ten rats per sex per group not assigned to functional observational battery and motor activity tests will be assigned to histological evaluations.

Tissues to be Weighed:

The following organs will be excised, trimmed and individually weighed as soon as possible after excision to avoid drying.

| | |
|--------------|----------------------|
| liver | spleen |
| kidneys | brain |
| adrenals | heart |
| thymus | ovaries |
| testes | uterus (with cervix) |
| epididymides | |

Tissues to be Retained:

The following tissues or representative samples will be retained in neutral buffered 10% formalin.

| | |
|---|---|
| brain (representative regions including cerebrum, cerebellum, pons) | |
| small and large intestines (including Peyer's patches) | |
| lungs (perfused with neutral buffered 10% formalin) | |
| lymph nodes (submandibular and mediastinal) | |
| peripheral nerve (sciatic) | |
| gross lesions | spinal cord (cervical, thoracic and lumbar) |
| stomach | liver |
| kidneys | adrenals |
| spleen | heart |
| thymus | thyroid/parathyroid |
| trachea | uterus |
| urinary bladder | bone marrow |
| testes* | ovaries |
| epididymides | uterus |
| seminal vesicles (with coagulating gland) | vagina |
| prostate | mammary gland (female rats only) |

* Testes will be fixed in Bouin's solution for 48 to 96 hours before being retained in neutral buffered 10% formalin.

Histological Examination:

Histological examination of retained tissues, including reproductive organs, will be conducted for the assigned ten rats per sex from the control and high dosage groups. If lesions attributed to the test substance are observed in the rats exposed to the high test substance dosage, the same tissues will be examined from the assigned five rats per sex exposed to the lower test substance dosages. Should results warrant examination of the lower dosage groups and conduct of quantitative evaluation, scheduled report date and prices will be adjusted accordingly.


Shipping Instructions:

Tissues to be examined histologically will be shipped (ambient conditions) to:

Principal Investigator: W. Ray Brown, D.V.M., Ph.D., ACVP
Veterinary Pathologist
Research Pathology Services, Inc.
438 E. Butler Avenue
New Britain, Pennsylvania 18901
Telephone: (215) 345-7070

The recipient will be notified in advance of sample shipment.

905 Sheehy Drive, Bldg. A
Horsham, PA 19044
Telephone: (215) 443-8710
Telefax: (215) 443-8587


ARGUS RESEARCH
Charles River Laboratories
Discovery and Development Services

PROTOCOL 418-027

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY
OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL
TOXICITY SCREENING TEST

SPONSOR'S STUDY NUMBER: T-7599

Amendment 1 - 15 March 2002

1. Purpose (page 1 of the protocol):

[Effective Date: 1 March 2002] The purpose of this study is to provide information on the possible health hazards that may result from repeated exposure of CrI:CD®(SD)IGS BR VAF/Plus® male and female rats to a test substance beginning before cohabitation, through mating and continuing for at least 28 days (male rats), or through parturition until day 5, rather than day 4 or 5, of lactation (female rats).

Reason for Change:

This change corrects the protocol and is consistent with the method and frequency of administration to female rats on page 10 of the protocol.

2. Vehicle (page 3 of the protocol):

[Effective Date: 22 February 2002] The vehicle will be aqueous 1.0% carboxymethylcellulose (CMC) (medium viscosity), rather than aqueous 0.5% carboxymethylcellulose.

Reason for Change:

This change was made because the test substance is precipitating out of suspension during shipment for analysis and cannot be analyzed.

Any revisions to this finalized amendment must be made by subsequent amendment.

3. Safety Precautions (page 3 of the protocol):

[Effective Date: 18 February 2002] A half-face respirator will be worn when the bulk test substance is not being used in a chemical fume hood.

Reason for Change:

This addition was made so that safety precautions are consistent with the MSDS.

4. Storage (page 4 of the protocol):

[Effective Date: 18 February 2002] The prepared test substance and vehicle formulations will be stored refrigerated, protected from light, rather than at room temperature, protected from light.

Reason for Change:

This change was made at the request of the Sponsor based on the stability of the test substance.

5. Analyses (page 4 of the protocol):

Additional analyses for concentration and homogeneity and stability will be performed on samples taken from the second test substance preparation using 1.0% carboxymethylcellulose. These samples will be taken and analyzed as described in the protocol.

Reason for Change:

This change was made to provide an analysis of samples prepared using 1.0% carboxymethylcellulose as the vehicle.

6. Bulk Test Substance Sampling (page 5 of the protocol)

[Effective Date: 25 February 2002] The 1 g sample of the test substance taken on the last day of treatment will be sent directly to Southern Research Institute at the address in the protocol, rather than to the Sponsor, for analysis.

Reason for Change:

This change corrects the protocol to indicate that the sample will be sent to Southern Research Institute, rather than to the Sponsor.

Any revisions to this finalized amendment must be made by subsequent amendment.

7. Bulk Test Substance Sampling (page 5 of the protocol)

[Effective Date: 25 February 2002] A sample (approximately 5 g) of the test substance will be taken and sent (ambient conditions, protected from light) for use in the preparation of analytical standards and for possible spectrophotometric analysis. The sample will be sent to:

Principal Investigator, Gregory S. Gorman, Ph.D.
Staff Chemist
Bioanalytical Chemistry Group
Southern Research Institute
2000 Ninth Avenue South
Birmingham, Alabama 35255-5305

Telephone: (205) 581-2725
Telefax (205) 581-2044
Email: gorman@sri.org

8. Shipping Instructions (page 6 of the protocol):

[Effective Date: 18 February 2002] The samples to be analyzed will be shipped refrigerated, protected from light, rather than at ambient conditions.

Reason for Change:

This change was made at the request of the Sponsor based on the stability of the test substance.

9. Schedule (Page 2 of Attachment 1 to the protocol):

[Effective Date: 25 February 2002] The dosage period for female rats will be 14 days before cohabitation through Day 5 of lactation, rather than through Day 4 or 5 of lactation.

Reason for Change:

This change corrects the protocol and is consistent with the method and frequency of administration to female rats on page 10 of the protocol.

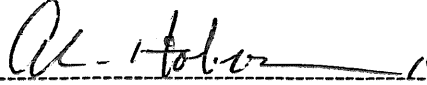
10. Safety (Page 1 of Attachment 2 to the protocol):

[Effective Date: 18 February 2002] There should be an "X" before "Half-Face Respirator if not used in a chemical fume hood" to indicate an additional safety precaution.

Any revisions to this finalized amendment must be made by subsequent amendment.

Reason for Change:

This addition was made so that safety precautions are consistent with the MSDS.

 15-MAR-02


Alan M. Hoberman, Ph.D., DABT Date
Director of Research

 15-MAR-02

Raymond G. York, Ph.D., DABT Date
Associate Director of Research
Study Director

 3/15/02


Rebecca Altmann-Reilly, M.S. Date
Member, Institutional Animal Care
and Use Committee

 19-MAR-02

Paul H. Lieder, Ph.D., DABT Date
Study Monitor
Sponsor's Representative

Any revisions to this finalized amendment must be made by subsequent amendment.

905 Sheehy Drive, Bldg. A
Horsham, PA 19044
Telephone: (215) 443-8710
Telefax: (215) 443-8587



ARGUS RESEARCH
Charles River Laboratories
Discovery and Development Services

PROTOCOL 418-027

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY
OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL
TOXICITY SCREENING TEST

SPONSOR'S STUDY NUMBER: T-7599

Amendment 2 - 5 September 2002

1. Proposed Statistical Tests (page 19 of the protocol):

[Effective Date: 25 June 2002]: Attachment 1 to this amendment describes the proposed statistical methods.

Body weight data, feed consumption values and organ weights will be analyzed as described under the Parametric heading of the schematic. Bartlett's Test of Homogeneity of Variances⁽⁹⁾ will be used to estimate the probability that the groups had different variances. A nonsignificant result ($p > 0.001$) will indicate that an assumption of homogeneity of variance is not inappropriate, and the data will be compared using the Analysis of Variance Test⁽¹⁰⁾. If that test is significant ($p \leq 0.05$), the groups exposed to the test substance will be compared with the control group using Dunnett's Test⁽¹¹⁾. If Bartlett's Test is significant ($p \leq 0.001$), the Analysis of Variance Test is not appropriate, and the data will be analyzed as described under the Nonparametric heading of the schematic. When 75% or fewer of the scores in all the groups are tied, the Kruskal-Wallis Test⁽¹²⁾ will be used to analyze the data, and in the event of a significant result ($p \leq 0.05$), Dunn's Test⁽¹³⁾ will be used to compare the groups exposed to the test substance with the control group. When more than 75% of the scores in any group are tied, Fisher's Exact Test⁽¹⁴⁾ will be used to compare the proportion of ties in the groups.

Data from the motor activity test, with repeated measurements within a session, will be analyzed using an Analysis of Variance with Repeated Measures⁽¹⁵⁾, as described under that heading in the schematic. A significant effect ($p \leq 0.05$) in that test can appear as effect of Concentration (a difference between groups in the total across all measurements in a session) or as an interaction between

Any revisions to this finalized amendment must be made by subsequent amendment.

Concentration and Block (a difference between groups at specific measurement periods). If the Concentration effect is significant, the totals for the control group and the groups given the test substance will be compared using Dunnett's Test. If the Concentration x Block interaction is significant, an Analysis of Variance Test will be used to evaluate the data at each measurement period, and a significant result ($p \leq 0.05$) will be followed by a comparison of the groups using Dunnett's Test.

Test items in the FOB having graded or count scores will be analyzed using the procedures described under the Nonparametric heading of the schematic.

Clinical observation incidence data will be analyzed as contingency tables using the Variance Test for Homogeneity of the Binomial Distribution⁽¹⁶⁾.

Alternate or additional statistical evaluations may be performed if deemed necessary or appropriate.

Reason for Change:

The statistical methods were to be added by amendment.

2. References (page 22 of the protocol):

[Effective Date: 25 June 2002]: The following references are added to the protocol.

9. Sokal, R.R. and Rohlf, F.J. (1969). Bartlett's test of homogeneity of variances. *Biometry*, W.H. Freeman and Co., San Francisco, pp. 370-371.
10. Snedecor, G.W. and Cochran, W.G. (1967). *Analysis of Variance. Statistical Methods*, 6th Edition, Iowa State University Press, Ames, pp. 258-275.11. Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Amer. Stat. Assoc.* 50:1096-1121.
11. Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Amer. Stat. Assoc.* 50:1096-1129.
12. Sokal, R.R. and Rohlf, F.J. (1969). Kruskal-Wallis Test. *Biometry*, W.H. Freeman and Co., San Francisco, pp. 388-389.

Any revisions to this finalized amendment must be made by subsequent amendment.

13. Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* 6(3):241-252.
14. Siegel, S. (1956). *Nonparametric Statistics for the Behavioral Sciences*, McGraw-Hill, New York, pp. 96-105.
15. SAS Institute, Inc. (1988). Repeated measures analysis of variance. *SAS/STAT™ User's Guide*, Release 6.03 Edition, Cary, NC, pp. 602-609.
16. Snedecor, G.W. and Cochran, W.G. (1967). Variance test for homogeneity of the binomial distribution. *Statistical Methods*, 6th Edition, Iowa State University Press, Ames, pp. 240-241.

Reason for Change:

The proposed statistical tests cite these references.

3. Histological Examination (page 2 of Attachment 3 of the protocol):

[Effective Date: 4 June 2002]: If lesions attributed to the test substance are observed in the rats exposed to the high test substance dosage, the same tissues will be examined from the assigned ten rats, rather than five rats, per sex exposed to the lower test substance dosages.

Reason for Change:

This change was made to correct the protocol. The Randomization and cohabitation section of the protocol, page 9, states that histological evaluations will be performed on the last ten rats per sex in each group exposed to the lower test substance dosages.

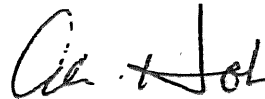

4. Histological Examination (page 2 of Attachment 3 of the protocol):

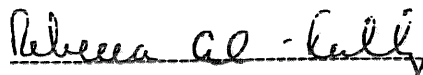

[Effective Date: 4 June 2002]: Histological evaluations will be performed on the livers of ten male and ten female rats, the thymuses of ten female rats and the stomachs of ten male rats exposed to each of the lower test substance dosages.

Any revisions to this finalized amendment must be made by subsequent amendment.

Reason for Change:

This change was made to clarify that additional histological evaluation would be performed because lesions of the livers, thymuses and stomachs were found in male and/or female rats assigned to the 250 mg/kg/day dosage group.

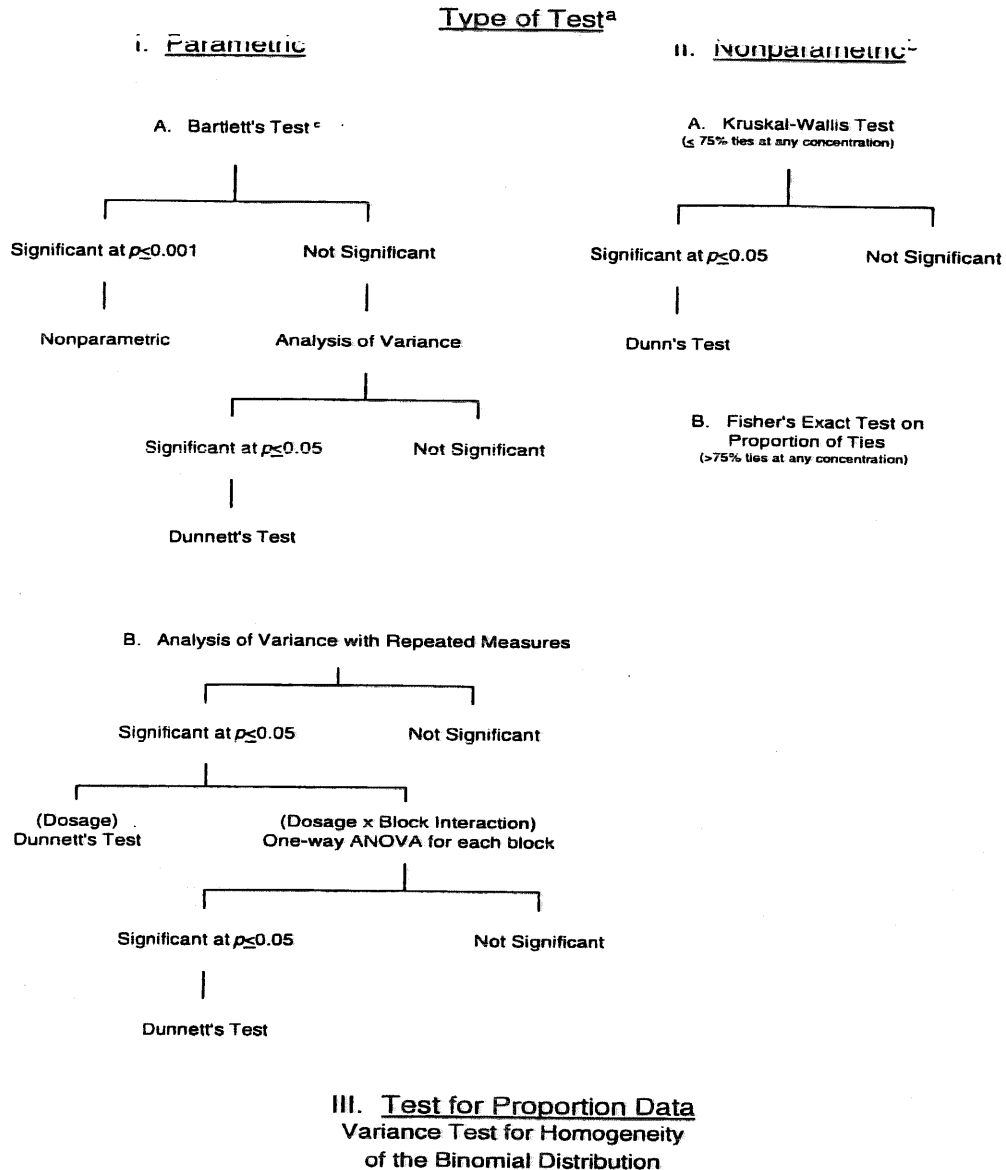
| | |
|---|--|
|  |  |
| Alan M. Hoberman, Ph.D., DABT Director of Research | Raymond G. York, Ph.D., DABT Associate Director of Research Study Director |
| 5-29-02 | 05/29/02 |

| | |
|--|--|
|  |  |
| Rebecca Altmann-Reilly, M.S. Member, Institutional Animal Care and Use Committee | Paul H. Lieder, Ph.D., DABT Study Monitor Sponsor's Representative |
| 9/5/02 | 9/11/2002 |

Any revisions to this finalized amendment must be made by subsequent amendment.

PROPOSED STATISTICAL TESTS⁽⁹⁻¹⁶⁾:

The following schematic represents statistical analyses of the data.



-
- a. Statistically significant probabilities are reported as either $p \leq 0.05$ or $p \leq 0.001$.
 - b. Proportion data are not included in this category.
 - c. Test for homogeneity of variance.

Any revisions to this finalized amendment must be made by subsequent amendment.

APPENDIX E

**DEVIATIONS FROM THE PROTOCOL AND THE
STANDARD OPERATING PROCEDURES OF
THE TESTING FACILITY**

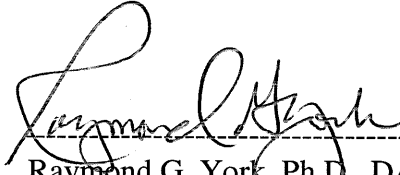
DEVIATIONS FROM THE PROTOCOL AND THE STANDARD OPERATING PROCEDURES OF THE TESTING FACILITY

1. On 25 March 2002, day 36 of study (DS 36), male rat 17632 in the 10 mg/kg/day dosage group refluxed approximately 1 mL of the 4.9 mL test substance that was administered. This deviation did not adversely affect the outcome or interpretation of the study because the rat was administered most of the dosage.
2. On 3 March 2002, DS 14, and on 26 March 2002, day 19 of presumed gestation (DG 19), the postdosage observations for female rats 17716 in the 0 (Vehicle) mg/kg/day dosage group and 17683 in the 250 mg/kg/day dosage group were performed one minute early from the range of 60 ± 10 minutes. These deviations did not adversely affect the outcome or interpretation of the study because the extent of the deviation was minimal.
3. On 3 March 2002, DS 14, the postdosage observation for male rat 17630 in the 0 (Vehicle) mg/kg/day dosage group was not performed. This deviation did not adversely affect the outcome or interpretation of the study because sufficient data were available for evaluation of this parameter and it was a single event.
4. On 30 March 2002, DG 25, ovaries of female rat 17686 in the 250 mg/kg/day dosage group were not retained after necropsy. This deviation did not adversely affect the outcome or interpretation of the study because sufficient tissues were saved from other rats in this dosage group to evaluate ovaries.
5. On 4 April 2002, plasma and serum samples from the following rats were processed and immediately frozen on dry ice. On 5 April 2002, these samples were found in a styrofoam box after they had thawed because of insufficient dry ice to keep the samples frozen. Samples were immediately refrozen and transferred to a -70° C chest freezer for storage.

| Dosage Group | Dosage (mg/kg/day) | Rat Number | Sample Type |
|--------------|--------------------|------------|------------------|
| I | 0 | 17715 | Serum |
| II | 10 | 17684 | Serum and Plasma |
| | | 17707 | Serum |
| | | 17710 | Serum |
| III | 50 | 17687 | Serum and Plasma |
| | | 17706 | Serum |
| | | 17720 | Serum |
| IV | 250 | 17678 | Serum |

This deviation did not adversely affect the outcome or interpretation of the study because sufficient samples were available for evaluation.

All deviations are documented in the raw data.

 25 MAR 2003
Raymond G. York, Ph.D., DABT Date
Associate Director of Research
Study Director

APPENDIX F
CERTIFICATE OF ANALYSIS

Certificate of Analysis

N-MeFBSE [$C_4F_9SO_2N(CH_3)CH_2CH_2OH$]
41-2601-1878-5 Lot 6

30 January 2002

Gibbes Bailie

Sample purity – 95.55%.

This sample was analyzed using GC, GC/MS, LC/MS, 1H -NMR, and ^{19}F -NMR analyses techniques. The results of these tests show the sample to contain the following composition:

| | |
|--|----------|
| $C_4F_9SO_2N(CH_3)_2$ | 0.009 % |
| $C_4F_9SO_2N(CH_3)H$ | 0.63 % |
| $C_4F_9SO_2N(CH_3)C_2H_4OC_4F_8H$ | 0.14 % |
| $C_4F_9SO_2N(CH_3)CH_2CH_2OH$ | 95.55 % |
| $C_4F_9SO_2N(CH_3)C_2H_4N(CH_3)_2$ | 0.002 % |
| $C_4F_9SO_2N(CH_3)C_2H_4N(CH_3)H$ | 0.17 % |
| $C_4F_8HSO_2N(CH_3)CH_2CH_2OH$ | 1.80 % |
| $C_4F_9SO_2N(CH_3)CH_2CH_2OCH_2CH_2OH$ | 1.71 % |
| $C_3F_7C(O)N(CH_3)H$ | 0.0004 % |
| $C_3F_7CO_2^-$ | < 30 ppm |
| $C_4F_9SO_3^-$ | < 7 ppm |
| $C_4F_8HSO_3^-$ | 10 ppm |

Additionally, the isomer distribution of the C4 alcohol ($C_4F_9SO_2N(Me)-CH_2CH_2OH$) was determined using ^{19}F -NMR techniques and found to contain the following relative composition:

| | |
|--|--------|
| $CF_3CF_2CF_2CF_2SO_2N(CH_3)CH_2CH_2OH$ [linear] | 98.8 % |
| $(CF_3)_2CF_2CF_2SO_2N(CH_3)CH_2CH_2OH$ [iso-branch] | 0.97 % |
| $CF_3CF_2CF(CF_3)SO_2N(CH_3)CH_2CH_2OH$ [alpha-branch] | 0.20 % |

Gibbes Bailie

APPENDIX G
ANALYTICAL REPORT

FINAL REPORT

**ANALYSIS OF DOSING SOLUTIONS USED AT ARGUS RESEARCH LABORATORY
FOR SPONSOR'S STUDY NUMBER T-7599.7 (ARGUS RESEARCH LABORATORY
PROTOCOL NUMBER: 418-027), SOUTHERN RESEARCH INSTITUTE STUDY
A536.2**

STUDY ID: A536.2

**SPONSOR STUDY NO. T-7599.7 (ARGUS RESEARCH LABORATORY PROTOCOL
NUMBER: 418-027)**

Southern Research Institute
2000 Ninth Avenue South
P.O. Box 55305
Birmingham, AL 35255-5305

Study Initiation Date: 3/15/02
Study Completion Date: 2/12/2003
Experimental Initiation Date: 3/11/02
Experimental Completion Date: 6/14/02

SUMMARY

All samples were analyzed according to analytical method BACG-3592. A total of 8 formulated dose samples including vehicles ranging in concentration from 0 to 25 mg/mL were analyzed to determine the 10 day stability of 1-Butanesulfonamide, 1,1,2,2,3,3,4,4,4-nonafluoro-n-(2-hydroxyethyl)-N-methyl (T-7599.7) in the formulated mixture. A total of 8 formulated dose samples including vehicles ranging in concentration from 0 to 25 mg/ml were analyzed to determine concentration of T-7599.7 in the formulated mixture. To test for homogeneity of dose formulation a total of 24 formulated dose samples including vehicles ranging in concentration from 0 to 25 mg/ml were analyzed to determine concentration of T-7599.7 in the top, middle and bottom of the formulated mixture. Samples were stored refrigerated as per sponsor's shipping recommendations. For the 10-day stability, study samples were found to be within $\pm 11\%$ of the day 1 values except for the 5 mg/mL samples which were within $\pm 15\%$ of the expected dose concentration but twice (204% and 196% of Day 1 values) that found on day 1. For the dose analysis, 1 mg/ml dose formulation samples were found to be within $\pm 15\%$ of the reported concentrations but the 5 and 25 mg/mL samples were lower than expected, ranging from 55% to 69% of the expected value. For the homogeneity samples the 1 mg/mL and 5 mg/mL samples were lower than their expected concentrations ranging from 55% to 70%, but values between top, middle, and bottom samples differed by less than $\pm 16\%$. The 25 mg/mL dose samples were within $\pm 16\%$ of expected values for both concentration and homogeneity between top, middle, and bottom samples.

KEY PERSONNEL

Raymond G. York, Ph.D., D.A.B.T.
Study Director
Argus Research Laboratories

Gregory S. Gorman, Ph.D.
Manager
Bioanalytical Chemistry Group

Lara Cook, M.S.
Research Associate II
Bioanalytical Chemistry Group

1.0 Objective

The objective of this study was to determine the stability, dose concentration, and homogeneity of dose formulations (top, middle and bottom samples) of 1-Butanesulfonamide, 1,1,2,2,3,3,4,4,4-nonafluoro-n-(2-hydroxyethyl)-N-methyl (T-7599.7) in the supplied dosing solutions received from the sponsor and to confirm the identity of the test solution.

2.0 Safety

All necessary procedures to ensure safety of the analysts were based on information contained in the Material Safety and Data Sheets, provided by the producer of the test article and the study director.

3.0 Compliance

The study described in this final report was conducted in accordance with the FDA Good Laboratory Practice Standards (21 CFR Part 58), OECD Principles of Good Laboratory Practices [C(97)186/Final], and Japanese Ministry of Health and Welfare (MHW Ordinance Number 21, March 26, 1997). The final report accurately reflects the raw data obtained during the performance of the study. There were no adverse circumstances that affected the quality or integrity of the study.

4.0 Experimental

4.1 Analytical Procedures

The sample preparation and analysis procedures as described in the analytical method BACG-3592 were employed for all analyses. For the stability study each sample was allowed to warm to room temperature, was sonicated for about 15 minutes and was then vortexed well before being sampled. An aliquot was taken from each and diluted as described in the method. For samples that were analyzed for the dose analysis and homogeneity studies, samples were allowed to come to room temperature and sonicated for 15 minutes, but would not go into solution. Samples were then run under hot water and sonicated further but would not go into solution and remained instead a suspension. These samples were quantitatively transferred and diluted as described in the chemical analysis sheets. Multiple calibration curves were prepared over a concentration range of 500 to 10,000 ng/mL and analyzed along with the samples as described in the method. The correlation coefficient for each curve was equal to or greater than 0.9991.

4.2 Results

The results of the identity testing confirmed that the found spectra (LC/MS, FT-IR and ¹³C NMR results) were consistent with the submitted substance, T-7599.7. The results of the formulation analyses are presented (Tables I - VII) corresponding to the sponsor's study number at the end of the report.

4.3 Calculations

Calculations were performed using TurboQuan (Version 1.0). The amount of analyte in the diluted dose formulation samples (ng/mL) was back calculated using a calibration curve generated from a set of calibration standards containing the equivalent amount of carboxy methyl cellulose (CMC) as in the diluted samples. The calibration curve was generated by a regression analysis to determine the best fit curve (e.g., linear, quadratic, etc.) and amount of weighting. A quadratic fit with 1/X weighting was determined to be the best fit :

$$y = ax^2 + bx + c$$

where:

y = Peak area response of test article

x = Concentration of the test article in standards.

a, b, c = Constants derived from the regression analysis.

5.0 Storage

A copy of the final report and all raw data will be stored in the Southern Research Institute archives.

6.0 Conclusion

A total of 40 T-7599.7 dose formulation samples ranging in concentration from 0 to 25 mg/mL were analyzed using method BACG-3592. For the 10-day stability study, samples were found to be within $\pm 11\%$ of the Day 1 values except for the 5 mg/mL samples which were within $\pm 15\%$ of the expected dose concentration but twice (204% and 196% of Day 1 values) that found on Day 1. This may have been due to the low values found for the 5 mg/mL samples on Day 1 (52% of expected concentration). For the dose analysis, the 1 mg/ml dose formulation samples were found to be within $\pm 15\%$ of the reported concentrations but the 5 and 25 mg/mL samples were lower than expected, ranging from 55% to 69% of the expected value. For the homogeneity samples the 1 mg/mL and 5 mg/mL samples were lower than their expected concentrations, ranging from 55% to 70% but values between top, middle, and bottom samples differed by less than $\pm 15\%$. The 25 mg/mL dose samples were within $\pm 16\%$ of expected values for both concentration and homogeneity between top, middle, and bottom samples. The variation in expected concentrations may have been due to the fact that samples were in a suspension rather than in solution and instead of assisting in solubility the presence of the 1% CMC made the samples very viscous and quantitative transfer difficult to perform.

Data presented in Tables I through VII are based on non-truncated numbers and may not be reproducible based on rounded numbers displayed. Values for each measured concentration are based on the average of two replicates per sample.

Table I

Day 1 of the 10-Day Stability Study for a Dose Formulation Containing T-7599.7 1% CMC
Sponsor Study Number T-7599.7 (Argus Research Laboratory Protocol Number: 418-027)

Day 1

| Nominal | Target | Measured | Dose | |
|---------------------------------------|------------------|---------------|--------------|------------------|
| Dose concentration (mg/mL) & Sample # | Dilution (ug/mL) | Conc. (ug/mL) | Conc.(mg/mL) | % of Theoretical |
| 0 (1 of 4) | NA | Not detected | ----- | ----- |
| 0 (2 of 4) | NA | Not detected | ----- | ----- |
| 1 (1 of 4) | 3.0 | 2.3 | 0.8 | 78 |
| 1 (2 of 4) | 3.0 | 2.5 | 0.8 | 83 |
| 5 (1 of 4) | 3.0 | 1.7 | 2.8 | 55 |
| 5 (2 of 4) | 3.0 | 1.5 | 2.6 | 51 |
| 25 (1 of 4) | 3.0 | 3.0 | 25.2 | 101 |
| 25 (2 of 4) | 3.0 | 2.8 | 23.1 | 93 |

Table II

Day 10 of the 10-Day Stability Study for a Dose Formulation Containing T-7599.7 1% CMC
Sponsor Study Number T-7599.7 (Argus Research Laboratory Protocol Number: 418-027)

Day 10

| Nominal | Target | Measured | Dose | | |
|---------------------------------------|------------------|---------------|--------------|------------------|------------|
| Dose concentration (mg/mL) & Sample # | Dilution (ug/mL) | Conc. (ug/mL) | Conc.(mg/mL) | % of Theoretical | % of Day 1 |
| 0 (1 of 4) | NA | Not detected | ----- | ----- | ----- |
| 0 (2 of 4) | NA | Not detected | ----- | ----- | ----- |
| 1 (1 of 4) | 3.0 | 2.3 | 0.8 | 76 | 98 |
| 1 (2 of 4) | 3.0 | 2.2 | 0.7 | 75 | 89 |
| 5 (1 of 4) | 3.0 | 3.4 | 5.6 | 113 | 204 |
| 5 (2 of 4) | 3.0 | 3.0 | 5.0 | 101 | 196 |
| 25 (1 of 4) | 3.0 | 2.9 | 24.4 | 98 | 97 |
| 25 (2 of 4) | 3.0 | 3.0 | 24.7 | 99 | 107 |

Table III**Dose Formulation Analysis of T-7599.7 in 1% CMC**

Sponsor Study Number T-7599.7 (Argus Research Laboratory Protocol Number: 418-027)

| Nominal | Target | Measured | Dose | |
|--|------------------|-----------------------|-----------------------|------------------|
| Dose concentration (mg/mL) & Sample I.D. | Dilution (ug/mL) | Concentration (ug/mL) | Concentration (mg/mL) | % of Theoretical |
| 0 (1 of 4) | NA | not detected | ----- | ----- |
| 0 (2 of 4) | NA | not detected | ----- | ----- |
| 1 (1 of 4) | 2.8 | 2.8 | 1.0 | 98 |
| 1 (2 of 4) | 2.9 | 3.3 | 1.1 | 114 |
| 5 (1 of 4) | 3.0 | 2.1 | 3.4 | 69 |
| 5 (2 of 4) | 3.0 | 2.1 | 3.4 | 69 |
| 25 (1 of 4) | 3.0 | 1.8 | 14.9 | 60 |
| 25 (2 of 4) | 3.0 | 1.7 | 13.7 | 55 |

Tables IV, V, VI and VII**Homogeneity Dose Formulation Analysis of T-7599.7 in 1% CMC**

Sponsor Study Number T-7599.7 (Argus Research Laboratory Protocol Number: 418-027)

(In the sample ID, T = top, M = middle, and B = bottom)

Table IV**Controls (0 mg/ml)**

| Nominal | Target | Measured | Dose | |
|--|------------------|-----------------------|-----------------------|------------------|
| Dose concentration (mg/mL) & Sample I.D. | Dilution (ug/mL) | Concentration (ug/mL) | Concentration (mg/mL) | % of Theoretical |
| 0 (1 of 12T) | NA | not detected | ----- | ----- |
| 0 (2 of 12T) | NA | not detected | ----- | ----- |
| 0 (5 of 12M) | NA | not detected | ----- | ----- |
| 0 (6 of 12M) | NA | not detected | ----- | ----- |
| 0 (9 of 12B) | NA | not detected | ----- | ----- |
| 0 (10 of 12B) | NA | not detected | ----- | ----- |

Table V**1 mg/ml**

| Nominal | Target | Measured | Dose | |
|--|------------------|-----------------------|-----------------------|------------------|
| Dose concentration (mg/mL) & Sample I.D. | Dilution (ug/mL) | Concentration (ug/mL) | Concentration (mg/mL) | % of Theoretical |
| 1 (1 of 12T) | 3.0 | 2.0 | 0.7 | 65 |
| 1 (2 of 12T) | 3.0 | 1.8 | 0.6 | 61 |
| 1 (5 of 12M) | 3.0 | 1.7 | 0.6 | 55 |
| 1 (6 of 12M) | 3.0 | 1.8 | 0.6 | 59 |
| 1 (9 of 12B) | 3.0 | 2.1 | 0.7 | 69 |
| 1 (10 of 12B) | 3.0 | 2.1 | 0.7 | 70 |

Table VI
5 mg/ml


| Nominal | Target | Measured | Dose | |
|--|------------------|-----------------------|-----------------------|------------------|
| Dose concentration (mg/mL) & Sample I.D. | Dilution (ug/mL) | Concentration (ug/mL) | Concentration (mg/mL) | % of Theoretical |
| 5 (1 of 12T) | 2.9 | 1.7 | 2.8 | 56 |
| 5 (2 of 12T) | 3.0 | 1.7 | 2.8 | 56 |
| 5 (5 of 12M) | 3.0 | 1.8 | 2.9 | 58 |
| 5 (6 of 12M) | 3.0 | 1.9 | 3.2 | 63 |
| 5 (9 of 12B) | 3.0 | 2.0 | 3.4 | 67 |
| 5 (10 of 12B) | 3.0 | 1.9 | 3.2 | 64 |

Table VII
25 mg/ml

| Nominal | Target | Measured | Dose | |
|--|------------------|-----------------------|-----------------------|------------------|
| Dose concentration (mg/mL) & Sample I.D. | Dilution (ug/mL) | Concentration (ug/mL) | Concentration (mg/mL) | % of Theoretical |
| 25 (1 of 12T) | 3.0 | 3.0 | 24.6 | 98 |
| 25 (2 of 12T) | 3.0 | 3.1 | 25.6 | 103 |
| 25 (5 of 12M) | 2.9 | 3.4 | 28.9 | 116 |
| 25 (6 of 12M) | 3.0 | 2.7 | 22.5 | 90 |
| 25 (9 of 12B) | 3.0 | 2.9 | 23.9 | 96 |
| 25 (10 of 12B) | 3.0 | 3.0 | 25.7 | 103 |

Calculated values are based upon non-truncated numbers and may not be reproducible based on rounded numbers displayed in tables I through VII.

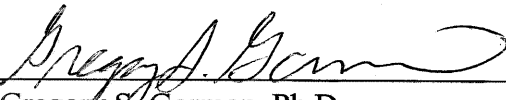
7.0 Approvals



Lara Cook, M.S.
Research Associate II
Bioanalytical Chemistry Group

2-11-03

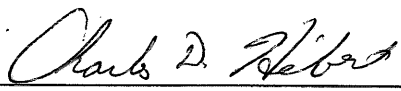
Date



Gregory S. Gorman, Ph.D.
Manager
Bioanalytical Chemistry Group

2/11/03

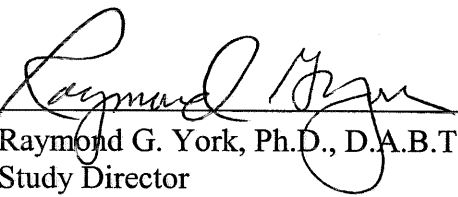
Date



Charles D. Hébert, Ph.D., D.A.B.T.
Director
Safety Assessment Department

2-11-03

Date



Raymond G. York, Ph.D., D.A.B.T.
Study Director
Argus Research Laboratories

12-FEB-2003

Date

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 Initials/Date PAC 2/13/03

QUALITY ASSURANCE STATEMENT

Final Report On:

**Analysis of Dosing Solutions Used at Argus Research Laboratory
 For Sponsor's Study Number T-7599.7 (Argus Research Laboratory
 Protocol Number: 418-027), SRI Study A536.2**

Study No.: A536.2

Listed below are the phases and/or procedures performed by Southern Research Institute that were inspected and audited by the Quality Assurance Unit during the study described in the report. Findings were reported to the study director and management periodically.

| <i>Phases/Procedures</i> | <i>Inspection/ Audit Date</i> | <i>Date Management Notified</i> | <i>Date Study Director Notified</i> |
|--|------------------------------------|-------------------------------------|---|
| Test Substance Characterization: Liquid Chromatography/Mass Spectrometry | 6/18/02 | 1/23/03 | 1/24/03 |
| Final (Draft) Report Review And Data Audit | 1/7/03-1/9/03; 1/13/03; 1/21/03 | 1/23/03 | 1/24/03 |
| Final Report Review | 2/11/03 | 2/11/03 | 2/11/03 |

The results presented in this final report accurately reflect the raw data.


 Kelly K. Crick, Assistant Manager, Quality Assurance

2/11/03
 Date

APPENDIX H

TEMPERATURE AND RELATIVE HUMIDITY REPORT

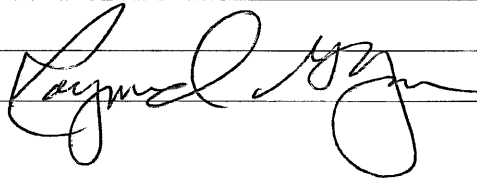
ARGUS

| Temperature and Relative Humidity Report Location: Room 01 | | |
|---|-----------------------------|---------------------------------|
| Protocol Number: 418-027 | | |
| Range of Dates: 12-Feb-2002 13:35 to 13-Apr-2002 09:59 | | |
| Target Range: Species: Rat | Temperature 66°F to 77°F | Relative Humidity 30% to 70% |
| Total Number of Days: | 61 | 61 |
| Total Number of Hours: | 1436.0 | 1436.0 |
| Total Number of Data Points: | 1436 | 1436 |
| Mean (± SD): | 70.6 (± 1.1) | 54.5 (± 4.4) |
| Maximum: | 73.3 | 66.9 |
| Median: | 70.8 | 55.0 |
| Minimum: | 66.6 | 35.3 |
| Number of Points in Range (%): | 1436 (100.0) | 1436 (100.0) |
| Number of Points High (%): | 0 (0.0) | 0 (0.0) |
| Number of Points Low (%): | 0 (0.0) | 0 (0.0) |

Report Generated: 24-Jun-2002 at 14:03

COMMENTS: _____

REVIEWED BY: _____



DATE: _____

6/25/02

APPENDIX I
POSITIVE CONTROL DATA

Historical Control Data

This Functional Observation Battery Standard Operating Procedure and Studies conducted to document the training and competency of the technical staff and Motor Activity Negative Control Data and Positive Control Data are available at the Testing Facility.

Summary Information for Functional Observation Battery

| Study Number – Title | In-Life Start | Test Substance | Dosage Information | | |
|--|---------------|----------------|--------------------|-------|-------------------|
| | | | mg/kg | mL/kg | Number of Dosages |
| 012-006 – Validation of Functional Observational Battery and Motor Activity Measure Using Positive Test Substances | 12/89 | acrylamide | 50 | 1 | 7 |
| | | physostigmine | 0.75 | 1.5 | 1 |
| | | DDT | 75 | 1 | 1 |
| 012-014 – Neurotoxicity Evaluation of Positive Control Substances in CrI:CD®BR VAF/Plus® Rats | 9/91 | acrylamide | 40 | 1 | 9 |
| | | IDPN | 200 | 1 | 3 |
| | | carbaryl | 75 | 5 | 1 |
| | | DDT | 75 | 5 | 1 |
| | | triadimefon | 200 | 5 | 1 |
| 012-015 – Neurotoxicity Evaluation of DDT in CrI:CD®BR VAF/Plus® Rats | 3/92 | DDT | 75 | 1 | 1 |
| 012-017 – Neurotoxicity Evaluation of Positive Control Substances in CrI:CD®BR VAF/Plus® Rats | 5/92 | acrylamide | 40 | 1 | 9 |
| | | IDPN | 200 | 1 | 3 |
| | | carbaryl | 40 | 5 | 1 |
| | | DDT | 75 | 1 | 1 |
| | | d-amphetamine | 4.0 | 1 | 1 |
| 012-022 – Neurotoxicity Evaluation of Carbaryl in CrI:CD®BR VAF/Plus® Rats | 10/92 | carbaryl | 40, 200 | 5 | 1 |
| 012-031 - Neurotoxicity Evaluation of Positive Control Substances in CrI:CD®BR VAF/Plus® Rats | 7/93 | acrylamide | 45 | 1 | 10 |
| | | IDPN | 250 | 1 | 4 |
| | | carbaryl | 40 | 5 | 1 |
| | | DDT | 75 | 1 | 1 |
| | | d-amphetamine | 4 | 1 | 1 |

| | | | | | |
|---|-------|---------------|-----|---|----|
| 012-056 – Neurotoxicity Evaluation of Positive Control Substances in Crl:CD®BR VAF/Plus® Rats | | | | | |
| | 11/95 | acrylamide | 45 | 1 | 10 |
| | | IDPN | 250 | 1 | 5 |
| | | carbaryl | 40 | 1 | 1 |
| | | DDT | 75 | 1 | 1 |
| | | d-amphetamine | 4.0 | 1 | 1 |
| 012-075 – Neurotoxicity Evaluation of Positive Control Substances in Crl:CD®BR VAF/Plus® Rats | | | | | |
| | 3/98 | acrylamide | 30 | 1 | 17 |
| | | trimethyltin | 8 | 1 | 1 |
| | | MK-801 | 0.3 | 1 | 1 |
| | | carbaryl | 100 | 4 | 1 |
| | | DDT | 100 | 2 | 1 |
| 012-081 – Neurotoxicity Evaluation of Positive Control Substances in Crl:CD®BR VAF/Plus® Rats | | | | | |
| | 11/01 | acrylamide | 30 | 1 | 10 |
| | | IDPN | 250 | 1 | 1 |
| | | d-amphetamine | 40 | 1 | 1 |
| | | carbaryl | 100 | 4 | 1 |
| | | DDT | 100 | 2 | 5 |

Summary Information for Motor Activity

| Study – Title | In-Life Start | Test Substance | Dosage Information | | |
|--|---------------|----------------|--------------------|-------|-------------------|
| | | | mg/kg | mL/kg | Number of Dosages |
| 012-011 – The Assessment of Motor Activity in Neonatal and Adult Rodents using Passive Infrared Sensors | 5/91 | d-amphetamine | 0.75, 1.5, 4 | 1 | 1 |
| | | chlorpromazine | 1, 2, 4 | 1 | 1 |
| 012-014 – Neurotoxicity Evaluation of Positive Control Substances in CrI:CD®BR VAF/Plus® Rats | 9/91 | acrylamide | 40 | 1 | 9 |
| | | IDPN | 200 | 1 | 3 |
| | | carbaryl | 75 | 5 | 1 |
| | | DDT | 75 | 5 | 1 |
| | | triadimefon | 200 | 5 | 1 |
| 012-016 – Motor Activity Evaluation in CrI:CD®BR VAF/Plus® Rats Administered Chlorpromazine and d-Amphetamine (Positive Control Study) | | d-amphetamine | 0.5, 1, 4 | 1 | 1 |
| | | chlorpromazine | 1, 2, 4 | 1 | 1 |
| 012-058 – Neurotoxicity Evaluation of Positive Control Substances in CrI:CD®BR VAF/Plus® Rats | 4/96 | acrylamide | 45 | 1 | 10 |
| | | d-amphetamine | 0.75 | 1 | 1 |
| | | trimethyltin | 8 | 1 | 1 |
| | | MK-801 | 10 | 1 | 1 |

APPENDIX J
HISTOPATHOLOGY REPORT

RESEARCH PATHOLOGY SERVICES, INC.

438 East Butler Avenue, New Britain, PA 18901
Phone: 215-345-7070 • Fax: 215-345-4326

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY
OF T 7599.7 WITH THE REPRODUCTION/DEVELOPMENTAL
TOXICITY SCENING TEST
PROTOCOL 418-027
SPONSOR'S STUDY NUMBER T-7599
HISTOPATHOLOGY REPORT

SUBMITTED TO:
Raymond G. York, Ph.D., D.A.B.T.
Argus Research
905 Sheehy Drive
Horsham, PA 19044

SUBMITTED BY:

W. Ray Brown Feb. 25, 2003

W. Ray Brown, D.V.M., Ph.D.
Veterinary Pathologist

February 25, 2003

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HISTOPATHOLOGY REPORT

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METHOD

Microscopic examination was made of the specified tissues from 40 male and 40 female CrI:CD[®](SD)IGS BR VAF/Plus[®] rats in an oral (gavage) combined repeated dose toxicity study of T 7599.7 with the reproduction/developmental toxicity screening test. A brief outline of the study design showing the dose group identification, dosage levels of the test and control substances and number of male and female rats examined group are shown below.

| DOSAGE GROUP | NUMBER OF RATS PER SEX | DOSAGE (mg/kg/day) | CONCENTRATION (mg/mL) | DOSE VOLUME (mL/kg) |
|--------------|------------------------|--------------------|-----------------------|---------------------|
| I | 10 | 0 (Vehicle) | 0 | 10 |
| II | 10 | 10 | 1 | 10 |
| III | 10 | 50 | 5 | 10 |
| IV | 10 | 250 | 25 | 10 |

The test substance was considered to be 100% active for the purpose of dosage calculations.

The rats were given the test substance and/or vehicle beginning before cohabitation, through mating and continued for at least 28 days (male rats), or through parturition until Day 5 of lactation (female rats). Dosages were adjusted daily for body weight changes and given at approximately the same time each day. Scheduled sacrifice of male rats was on the day following the last dosage administration, after a minimum of 28 days of dosage. Scheduled sacrifice of female rats was on Day 6 of lactation.

All rats were necropsied and the specified tissues were collected and placed in 10% neutral buffered formalin for fixation. The testes were fixed in Bouin's solution for 48 to 96 hours and then retained in 10% neutral buffered formalin. The in-life portion of the study, necropsies, and recording of the gross necropsy observations were performed by the staff of Argus Research, Horsham, PA. The tissue processing, microscopic slide preparation and histopathologic evaluation were performed by Research Pathology Services, Inc.

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The tissues specified for microscopic evaluation from the male and female rats of Groups I and IV included: brain, duodenum, jejunum, ileum, cecum, colon, rectum, Peyer's patch, lung, submandibular and mediastinal lymph nodes, sciatic nerve, stomach, kidneys, spleen, thymus, trachea, urinary bladder, testes, epididymides, seminal vesicles, coagulating gland, prostate, spinal cord (cervical, lumbar and thoracic), liver, adrenal glands, heart, thyroid, parathyroid, uterus, bone marrow (sternum), ovaries, vagina, mammary gland (female rats) and all other tissues with gross changes. In addition, the liver of male and female rats, stomach of male rats and thymus of female rats were examined from the intermediate dosage groups. Representative samples of these tissues were routinely processed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic evaluation.

Upon completion of the project, all raw data (remaining wet tissue, paraffin blocks, microscopic slides and histology records) will be returned to Argus Research for archiving.

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RESULTS

The type, incidence and degree of severity of the histomorphologic changes in the specified tissues for the male and female rats are presented in Table 1. The microscopic observations in each rat are summarized in tabular form in Appendix I (Tables I-1 to I-8). A key to the histomorphologic observations precedes Table I-1. The gross necropsy observations, detailed descriptions of the microscopic observations, and a correlation of the microscopic findings with the gross changes in these rats, when applicable, are contained in Appendix II.

No treatment-related microscopic changes were observed in any of the male rats given 10 mg/kg/day or in female rats given 10 or 50 mg/kg/day of the test substance.

Treatment-related microscopic changes were observed in the liver of male rats of the 50 and 250 mg/kg/day dosage groups and female rats of the 250 mg/kg/day dosage group, thymus of female rats of the 250 mg/kg/day dosage group and stomach of the male rats of the 250 mg/kg/day dosage group.

The treatment-related microscopic change in the liver consisted of minimal or mild enlargement (hypertrophy) of centrilobular hepatocytes in most male and female rats of the 250 mg/kg/day dosage group and in 4/10 male rats of the 50 mg/kg/day dosage group. The enlargement was due to an increased amount of finely granular, dense eosinophilic cytoplasm. The incidence and severity of the change occurred in a dose-related manner. Also, in three of the affected high dose male rats, necrosis of individual enlarged hepatocytes was seen in centrilobular areas (Table 1).

The treatment-related effect in the thymus consisted of an increased incidence and severity of atrophy of the thymic lobules in female rats of the 250 mg/kg/day dosage group. Single incidences of thymic atrophy occurred in female rats of the control and lower dosage groups, but the increased incidence and severity of this effect in the high dosage group was considered to be treatment-related.

Microscopic examination of the stomach revealed focal erosions in the pyloric glandular mucosa of two high dose male rats. Although the incidence was low, this

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change may be treatment-related. Other changes observed in the stomach which occurred at a somewhat varied and sporadic incidence in the control and compound-treated male rats included edema with or without inflammation (infiltrations of polymorphonuclear inflammatory cells) in the submucosa of the glandular and nonglandular (forestomach) areas. The very slight increased incidence and severity (Table 1) of these changes in these areas of the stomach of the high dose male rats may also be treatment-related. However, these changes were not clearly associated with the erosions.

All other microscopic changes were considered to have occurred spontaneously and to be incidental and unrelated to compound administration. The type, incidence and severity of these changes were not influenced by compound administration. These changes also are listed in the attached histomorphology tables.

One high dosage group male rat had early lymphosarcoma in the spleen only. There was no evidence of disseminated involvement. Although this is a Group IV rat, it is still considered to have been incidental and a spontaneously-occurring effect.

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SUMMARY

Microscopic examination was made of the specified tissues from four groups of 10 male and 10 female CrI:CD[®](SD)IGS BR VAF/Plus[®] rats used in an oral (gavage) combined repeated dose toxicity study of T 7599.7 with the reproduction/developmental toxicity screening test. The four groups of rats had been given 0 (vehicle), or 10, 50 or 250 mg/kg/day of T 7599.7, orally by gavage, once daily for the protocol-specified number of days.

No treatment-related microscopic changes were observed in the male rats given 10 mg/kg/day or female rats given 10 or 50 mg/kg/day of the test substance.

Treatment-related microscopic changes were observed in the liver of male rats of the 50 and 250 mg/kg/day dosage groups and female rats of the 250 mg/kg/day dosage group, thymus of female rats given 250 mg/kg/day and stomach of male rats given 250 mg/kg/day of the test substance.

The treatment-related effect in the liver consisted of minimal to mild hypertrophy of centrilobular hepatocytes in the mid and high dosage group male rats and in the high dosage group female rats. A low incidence of high dose male rats had individual-cell necrosis of affected centrilobular hepatocytes.

The treatment-related change in the thymus was an increased incidence and severity of atrophy of the thymic lobules in female rats of the high dosage group. There were single incidences of atrophy in each of the control and lower dosage groups, but this increased incidence in the 250 mg/kg/day dosage group was considered to be treatment-related.

The treatment-related change in the stomach in male rats of the high dosage group consisted of a low incidence of focal erosions of the pyloric glandular mucosa. A varied incidence of edema and inflammation of the submucosa of the nonglandular and glandular areas also was observed in a few rats at a slightly higher incidence and severity in Group 4 and this may also be related to compound-related.

All other changes were considered to be spontaneous in origin and not treatment-related. The type, incidence or severity of these changes were not considered to be influenced by administration of T 7599.7.

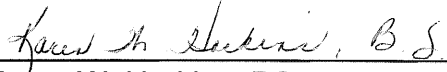
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QUALITY ASSURANCE UNIT STATEMENT

All aspects of the tissue processing, microscopic slide preparation, histopathologic evaluation and report preparation for the study listed above have been performed according to the Standard Operating Procedures of Research Pathology Services, Inc. and were audited in accordance with the procedures established by the Quality Assurance Unit of Research Pathology Services, Inc. in compliance with the regulations as specified in the protocol.

Quality Assurance inspections were performed on 04/08/02, 04/12/02, 04/18/02, 04/19/02, 04/23/02, 04/24/02, 05/22/02, 06/05/02, 06/07/02, 07/10/02, 07/11/02, 07/12/02, and 02/25/03 and findings were reported to management on 04/30/02, 05/31/02, 06/28/02 and 02/25/03. There were no deviations from the protocol, Standard Operating Procedures and/or appropriate Good Laboratory Practice regulations noted during the conduct of the study that had an impact on study integrity. The summary report of QA inspections is included in the final report submitted to the Study Director on February 25, 2003.



Karen W. Harkins, BS
Quality Assurance Unit

02-25-03

Date

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TABLE 1

Incidence and Degree of Severity of Histomorphologic Observations

| Dose Group: | I | II | III | IV | I | II | III | IV |
|--|----------|----------|----------|----------|----------|----------|----------|----------|
| Sex: | M | M | M | M | F | F | F | F |
| Number of Animals/Group: | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| <u>ADRENAL GLANDS:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 8 | 0 | 0 | 6 | 9 | 0 | 0 | 10 |
| -infiltration, mononuclear-cell, multifocal minimal | [0] 0 | [0] 0 | [0] 0 | [0] 0 | [1] 1 | [0] 0 | [0] 0 | [0] 0 |
| -vacuolation, cortex minimal | [2] 1 | [0] 0 | [0] 0 | [3] 3 | [0] 0 | [0] 0 | [0] 0 | [0] 0 |
| mild | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| <u>BONE MARROW (STERNUM):</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| <u>BRAIN:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| <u>CECUM:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 9 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| -inflammation, mucosa, chronic mild | [1] 1 | [0] 0 | [0] 0 | [0] 0 | [0] 0 | [0] 0 | [0] 0 | [0] 0 |
| <u>COAGULATING GLAND:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | | | | |
| NO. NORMAL | 10 | 0 | 0 | 10 | | | | |
| <u>COLON:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| <u>DUODENUM:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| <u>EPIDIDYMIDES:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | | | | |
| NO. NORMAL | 8 | 0 | 0 | 9 | | | | |
| -infiltration, mononuclear-cell, focal minimal | [2] 2 | [0] 0 | [0] 0 | [1] 1 | | | | |
| <u>EXTREMITIES:</u> | | | | | | | | |
| NO. EXAMINED | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| NO. NORMAL | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -dermatitis, ulcerative, focal mild | [0] 0 | [0] 0 | [0] 0 | [1] 1 | [0] 0 | [0] 0 | [0] 0 | [0] 0 |
| <u>HEART:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 9 | 0 | 0 | 9 | 9 | 0 | 0 | 9 |

[] = Total incidence of specified lesion, all grades.

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TABLE 1 (Continued)

Incidence and Degree of Severity of Histomorphologic Observations

| Dose Group: | I | II | III | IV | I | II | III | IV |
|--|-----|-----|-----|-----|-----|-----|-----|-----|
| Sex: | M | M | M | M | F | F | F | F |
| Number of Animals/Group: | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| <u>HEART (Continued):</u> | | | | | | | | |
| -inflammation, subacute, focal/multifocal | [1] | [0] | [0] | [1] | [0] | [0] | [0] | [1] |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| mild | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -pericarditis, chronic, focal | [0] | [0] | [0] | [0] | [1] | [0] | [0] | [0] |
| minimal | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| <u>ILEUM:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| <u>JEJUNUM:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| <u>KIDNEYS:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 7 | 0 | 0 | 6 | 8 | 0 | 0 | 6 |
| -cyst(s), medulla | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| -dilatation, pelvis | [1] | [0] | [0] | [0] | [0] | [0] | [0] | [0] |
| mild | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -edema, papillary | [1] | [0] | [0] | [0] | [0] | [0] | [0] | [0] |
| minimal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -infiltration, mononuclear-cell, focal | [1] | [0] | [0] | [0] | [0] | [0] | [0] | [0] |
| minimal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -mineralization, multifocal | [0] | [0] | [0] | [1] | [2] | [0] | [0] | [2] |
| minimal | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 2 |
| -nephritis, chronic, focal | [0] | [0] | [0] | [1] | [0] | [0] | [0] | [0] |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| -pyelitis, chronic | [0] | [0] | [0] | [0] | [0] | [0] | [0] | [1] |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| -vacuolation, cortical tubular epithelium | [0] | [0] | [0] | [0] | [0] | [0] | [0] | [1] |
| mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| <u>LIVER:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| NO. NORMAL | 3 | 1 | 1 | 0 | 5 | 8 | 3 | 1 |
| -hematopoiesis, extramedullary, multifocal | [0] | [0] | [0] | [0] | [0] | [0] | [1] | [0] |
| minimal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |

[] = Total incidence of specified lesion, all grades.

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TABLE 1 (Continued)

Incidence and Degree of Severity of Histomorphologic Observations

| Dose Group: | I | II | III | IV | I | II | III | IV |
|---|-----|-----|-----|------|-----|-----|-----|-----|
| Sex: | M | M | M | M | F | F | F | F |
| Number of Animals/Group: | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| <u>LIVER (Continued):</u> | | | | | | | | |
| -hypertrophy, hepatocellular, centrilobular | [0] | [0] | [4] | [10] | [0] | [0] | [0] | [8] |
| minimal | 0 | 0 | 4 | 2 | 0 | 0 | 0 | 6 |
| mild | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 2 |
| -inflammation, chronic, focal/multifocal | [7] | [7] | [6] | [4] | [3] | [2] | [6] | [5] |
| minimal | 6 | 5 | 6 | 3 | 3 | 2 | 6 | 5 |
| mild | 1 | 2 | 0 | 1 | 0 | 0 | 0 | 0 |
| -lipidosis, tension, focal | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 |
| -necrosis, focal | [0] | [0] | [0] | [1] | [1] | [1] | [0] | [0] |
| minimal | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 |
| -necrosis, individual hepatocytes | [0] | [0] | [0] | [3] | [0] | [0] | [0] | [0] |
| minimal | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| -vacuolation, hepatocellular, multifocal | [0] | [0] | [0] | [0] | [1] | [0] | [0] | [0] |
| minimal | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| -vacuolation, hepatocellular, periportal | [1] | [2] | [0] | [0] | [0] | [0] | [0] | [1] |
| minimal | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 1 |
| <u>LUNG:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 9 | 0 | 0 | 9 | 8 | 0 | 0 | 10 |
| -inflammation, interstitial, multifocal | [1] | [0] | [0] | [1] | [1] | [0] | [0] | [0] |
| minimal | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| -macrophages, alveoli, focal | [0] | [0] | [0] | [1] | [1] | [0] | [0] | [0] |
| minimal | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| <u>LYMPH NODE, MEDIASTINAL:</u> | | | | | | | | |
| NO. EXAMINED | 9 | 0 | 0 | 10 | 9 | 0 | 0 | 9 |
| NO. NORMAL | 8 | 0 | 0 | 8 | 7 | 0 | 0 | 7 |
| -congestion/erythrophagocytosis | [1] | [0] | [0] | [2] | [1] | [0] | [0] | [2] |
| minimal | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 |
| -hyperplasia, lymphocytic/plasmacytic | [0] | [0] | [0] | [0] | [1] | [0] | [0] | [0] |
| minimal | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| -macrophages, pigmented | [0] | [0] | [0] | [0] | [2] | [0] | [0] | [0] |
| minimal | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| <u>LYMPH NODE, SUBMANDIBULAR:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 5 | 0 | 0 | 4 | 1 | 0 | 0 | 2 |

[] = Total incidence of specified lesion, all grades.

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TABLE 1 (Continued)

Incidence and Degree of Severity of Histomorphologic Observations

| Dose Group: | I | II | III | IV | I | II | III | IV |
|---|-----|-----|-----|-----|-----|-----|-----|-----|
| Sex: | M | M | M | M | F | F | F | F |
| Number of Animals/Group: | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| <u>LYMPH NODE, SUBMANDIBULAR (Continued):</u> | | | | | | | | |
| -hyperplasia, lymphocytic/plasmacytic | [5] | [0] | [0] | [6] | [9] | [0] | [0] | [8] |
| minimal | 3 | 0 | 0 | 4 | 4 | 0 | 0 | 1 |
| mild | 2 | 0 | 0 | 1 | 3 | 0 | 0 | 3 |
| moderate | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 4 |
| <u>MAMMARY GLAND:</u> | | | | | | | | |
| NO. EXAMINED | | | | | 10 | 0 | 0 | 10 |
| NO. NORMAL | | | | | 0 | 0 | 0 | 0 |
| -hyperplasia, physiological | | | | | 10 | 0 | 0 | 10 |
| -inflammation, subacute | | | | | [1] | [0] | [0] | [0] |
| mild | | | | | 1 | 0 | 0 | 0 |
| <u>NERVE, SCIATIC:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| <u>OVARIES:</u> | | | | | | | | |
| NO. EXAMINED | | | | | 10 | 0 | 0 | 9 |
| NO. NORMAL | | | | | 10 | 0 | 0 | 9 |
| <u>PARATHYROID:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 8 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 8 | 10 | 0 | 0 | 10 |
| <u>PEYER'S PATCH:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 9 | 10 | 0 | 0 | 10 |
| -mineralization | | | | | [0] | [0] | [0] | [0] |
| minimal | [0] | [0] | [0] | [1] | 0 | 0 | 0 | 0 |
| <u>PROSTATE:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | | | | |
| NO. NORMAL | 8 | 0 | 0 | 6 | | | | |
| -atrophy, focal | | | | | [1] | [0] | [0] | [1] |
| minimal | [1] | [0] | [0] | [1] | 1 | 0 | 0 | 1 |
| -inflammation, chronic, multifocal | | | | | [1] | [0] | [0] | [2] |
| minimal | [1] | [0] | [0] | [2] | 1 | 0 | 0 | 2 |
| -prostatitis, suppurative | | | | | [0] | [0] | [0] | [1] |
| marked | [0] | [0] | [0] | [1] | 0 | 0 | 0 | 1 |
| <u>RECTUM:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 9 | 0 | 0 | 8 | 10 | 0 | 0 | 10 |

[] = Total incidence of specified lesion, all grades.

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TABLE 1 (Continued)

Incidence and Degree of Severity of Histomorphologic Observations

| Dose Group: | I | II | III | IV | I | II | III | IV |
|--|----------|----------|----------|----------|----------|----------|----------|----------|
| Sex: | M | M | M | M | F | F | F | F |
| Number of Animals/Group: | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| <u>RECTUM (Continued):</u> | | | | | | | | |
| -edema/inflammation, submucosa moderate | [1] 1 | [0] 0 | [0] 0 | [0] 0 | [0] 0 | [0] 0 | [0] 0 | [0] 0 |
| -parasite(s) | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| <u>SEMINAL VESICLES:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | | | | |
| NO. NORMAL | 10 | 0 | 0 | 10 | | | | |
| <u>SPINAL CORD, CERVICAL:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| <u>SPINAL CORD, LUMBAR:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| <u>SPINAL CORD, THORACIC:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| <u>SPLEEN:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 8 | 6 | 0 | 0 | 6 |
| -atrophy mild | [0] 0 | [0] 0 | [0] 0 | [0] 0 | [0] 0 | [0] 0 | [0] 0 | [1] 1 |
| -hematopoiesis, extramedullary, increased minimal | [0] 0 | [0] 0 | [0] 0 | [1] 1 | [4] 1 | [0] 0 | [0] 0 | [3] 3 |
| mild | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| -lymphosarcoma | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| <u>STOMACH:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 10 | 10 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 6 | 7 | 8 | 3 | 9 | 0 | 0 | 10 |
| -dilatation, mucosal glands minimal | [3] 3 | [2] 1 | [2] 2 | [3] 2 | [1] 1 | [0] 0 | [0] 0 | [0] 0 |
| mild | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| -edema/inflammation, submucosa, glandular area minimal | [2] 1 | [0] 0 | [2] 2 | [3] 0 | [0] 0 | [0] 0 | [0] 0 | [0] 0 |
| mild | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| moderate | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |

[] = Total incidence of specified lesion, all grades.

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TABLE 1 (Continued)

Incidence and Degree of Severity of Histomorphologic Observations

| Dose Group: | I | II | III | IV | I | II | III | IV |
|---|-----|-----|-----|-----|-----|-----|-----|-----|
| Sex: | M | M | M | M | F | F | F | F |
| Number of Animals/Group: | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| <u>STOMACH (Continued):</u> | | | | | | | | |
| -edema/inflammation, submucosa, nonglandular area | [1] | [1] | [0] | [4] | [0] | [0] | [0] | [0] |
| minimal | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| moderate | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| -erosion(s), glandular mucosa | [0] | [0] | [0] | [2] | [0] | [0] | [0] | [0] |
| minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| <u>TAIL:</u> | | | | | | | | |
| NO. EXAMINED | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| NO. NORMAL | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| <u>TESTES:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | | | | |
| NO. NORMAL | 10 | 0 | 0 | 10 | | | | |
| <u>THYMUS:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 10 | 10 | 9 |
| NO. NORMAL | 10 | 0 | 0 | 10 | 9 | 9 | 9 | 4 |
| -atrophy | [0] | [0] | [0] | [0] | [1] | [1] | [1] | [5] |
| minimal | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 2 |
| mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| <u>THYROID:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 7 | 0 | 0 | 7 | 7 | 0 | 0 | 5 |
| -hypertrophy, follicular epithelium | [1] | [0] | [0] | [0] | [0] | [0] | [0] | [0] |
| mild | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -ultimobranchial body/cyst | 3 | 0 | 0 | 3 | 3 | 0 | 0 | 5 |
| <u>TRACHEA:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 9 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| -inflammation, chronic, focal | [1] | [0] | [0] | [0] | [0] | [0] | [0] | [0] |
| minimal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| <u>URINARY BLADDER:</u> | | | | | | | | |
| NO. EXAMINED | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| NO. NORMAL | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| <u>UTERUS:</u> | | | | | | | | |
| NO. EXAMINED | | | | | 10 | 0 | 0 | 10 |
| NO. NORMAL | | | | | 2 | 0 | 0 | 1 |

[] = Total incidence of specified lesion, all grades.

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TABLE 1 (Continued)

Incidence and Degree of Severity of Histomorphologic Observations

| Dose Group: | I | II | III | IV | I | II | III | IV |
|-------------------------------------|----|----|-----|----|-----|-----|-----|-----|
| Sex: | M | M | M | M | F | F | F | F |
| Number of Animals/Group: | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| <u>UTERUS (Continued):</u> | | | | | | | | |
| -distention, lumen | | | | | [1] | [0] | [0] | [1] |
| minimal | | | | | 1 | 0 | 0 | 0 |
| moderate | | | | | 0 | 0 | 0 | 1 |
| -hemorrhage, endometrium | | | | | [0] | [0] | [0] | [1] |
| mild | | | | | 0 | 0 | 0 | 1 |
| -inflammation, endometrium, diffuse | | | | | [0] | [0] | [0] | [1] |
| mild | | | | | 0 | 0 | 0 | 1 |
| -macrophages, pigmented | | | | | [8] | [0] | [0] | [9] |
| minimal | | | | | 1 | 0 | 0 | 2 |
| mild | | | | | 0 | 0 | 0 | 2 |
| moderate | | | | | 7 | 0 | 0 | 5 |
| -thrombus | | | | | 2 | 0 | 0 | 1 |
| <u>VAGINA:</u> | | | | | | | | |
| NO. EXAMINED | | | | | 10 | 0 | 0 | 10 |
| NO. NORMAL | | | | | 8 | 0 | 0 | 8 |
| -inflammation, acute | | | | | [0] | [0] | [0] | [1] |
| moderate | | | | | 0 | 0 | 0 | 1 |
| -mucification | | | | | [2] | [0] | [0] | [2] |
| moderate | | | | | 2 | 0 | 0 | 1 |
| marked | | | | | 0 | 0 | 0 | 1 |

[] = Total incidence of specified lesion, all grades.

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HISTOPATHOLOGY REPORT

APPENDIX I

HISTOMORPHOLOGIC OBSERVATIONS

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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HISTOPATHOLOGY REPORT

KEY TO HISTOMORPHOLOGIC OBSERVATIONS

- = No change (not remarkable, within normal histologic limits or indicated change not present).
- * = Tissue not available (specified tissue missing, insufficient tissue in plane of section, artifact precludes evaluation, or specified tissue not present in section).
- < > = Microscopic finding(s) in tissue(s) with gross observation(s).
- <-> = Within normal limits [no microscopic change(s) to correlate with the gross observation(s)].
- XM = Primary malignant neoplasm present.
- P = Indicated change or lesion present
- 1 = Minimal degree or amount of indicated change or lesion.
- 2 = Mild degree or amount of indicated change or lesion.
- 3 = Moderate degree or amount of indicated change or lesion.
- 4 = Marked degree or amount of indicated change or lesion.
- SS = Scheduled Sacrifice

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TABLE I-1

Histomorphologic Observations

| Dose Group: | I | I | I | I | I | I | I | I | I | I |
|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Animal Number: | 17608 | 17618 | 17630 | 17631 | 17639 | 17648 | 17652 | 17656 | 17658 | 17660 |
| Sex: | M | M | M | M | M | M | M | M | M | M |
| Death Type: | SS | SS | SS | SS | SS | SS | SS | SS | SS | SS |
| <u>ADRENAL GLANDS:</u> | | | | | | | | | | |
| -vacuolation, cortex | 2 | - | 1 | - | - | - | - | - | - | - |
| <u>BONE MARROW (STERNUM):</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>BRAIN:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>CECUM:</u> | | | | | | | | | | |
| -inflammation, mucosa, chronic | - | 2 | - | - | - | - | - | - | - | - |
| <u>COAGULATING GLAND:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>COLON:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>DUODENUM:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>EPIDIDYMIDES:</u> | | | | | | | | | | |
| -infiltration, mononuclear-cell, focal | - | - | - | - | 1 | - | - | 1 | - | - |
| <u>HEART:</u> | | | | | | | | | | |
| -inflammation, subacute, focal/multifocal | - | - | - | - | - | 2 | - | - | - | - |
| <u>ILEUM:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>JEJUNUM:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>KIDNEYS:</u> | | | | | | | | | | |
| -dilatation, pelvis | - | - | - | 2 | - | - | - | - | - | - |
| -edema, papillary | - | - | - | - | - | - | - | 1 | - | - |
| -infiltration, mononuclear-cell, focal | - | - | - | - | - | 1 | - | - | - | - |
| <u>LIVER:</u> | | | | | | | | | | |
| -inflammation, chronic, focal/multifocal | 1 | 2 | 1 | 1 | - | 1 | 1 | - | - | 1 |
| -vacuolation, hepatocellular, periportal | - | - | - | 1 | - | - | - | - | - | - |
| <u>LUNG:</u> | | | | | | | | | | |
| -inflammation, interstitial, multifocal | 1 | - | - | - | - | - | - | - | - | - |
| <u>LYMPH NODE, MEDIASTINAL:</u> | | | | | | | | | | |
| -congestion/erythrophagocytosis | - | - | * | - | 1 | - | - | - | - | - |
| <u>LYMPH NODE, SUBMANDIBULAR:</u> | | | | | | | | | | |
| -hyperplasia, lymphocytic/plasmacytic | - | - | - | 2 | 1 | 2 | - | 1 | - | 1 |
| <u>NERVE, SCIATIC:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>PARATHYROID:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>PEYER'S PATCH:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>PROSTATE:</u> | | | | | | | | | | |
| -atrophy, focal | - | - | - | 1 | - | - | - | - | - | - |

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TABLE I-1 (Continued)

Histomorphologic Observations

| Dose Group: | I | I | I | I | I | I | I | I | I | I |
|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Animal Number: | 17608 | 17618 | 17630 | 17631 | 17639 | 17648 | 17652 | 17656 | 17658 | 17660 |
| Sex: | M | M | M | M | M | M | M | M | M | M |
| Death Type: | SS | SS | SS | SS | SS | SS | SS | SS | SS | SS |
| <u>PROSTATE (Continued):</u> | | | | | | | | | | |
| -inflammation, chronic, multifocal | - | - | - | - | - | - | - | 1 | - | - |
| <u>RECTUM:</u> | | | | | | | | | | |
| -edema/inflammation, submucosa | - | - | - | - | - | - | 3 | - | - | - |
| <u>SEMINAL VESICLES:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>SPINAL CORD, CERVICAL:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>SPINAL CORD, LUMBAR:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>SPINAL CORD, THORACIC:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>SPLEEN:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>STOMACH:</u> | | | | | | | | | | |
| -dilatation, mucosal glands | - | 1 | 1 | - | - | 1 | - | - | - | - |
| -edema/inflammation, submucosa, glandular area | - | 1 | - | - | - | - | 2 | - | - | - |
| -edema/inflammation, submucosa, nonglandular area | - | - | 1 | - | - | - | - | - | - | - |
| <u>TESTES:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>THYMUS:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>THYROID:</u> | | | | | | | | | | |
| -hypertrophy, follicular epithelium | - | - | - | 2 | - | - | - | - | - | - |
| -ultimobranchial body/cyst | P | - | - | P | - | - | - | - | P | - |
| <u>TRACHEA:</u> | | | | | | | | | | |
| -inflammation, chronic, focal | 1 | - | - | - | - | - | - | - | - | - |
| <u>URINARY BLADDER:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |

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TABLE I-2

Histomorphologic Observations

| Dose Group: | II | II | II | II | II | II | II | II | II | II |
|--|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Animal Number: | 17634 | 17635 | 17638 | 17642 | 17643 | 17645 | 17649 | 17651 | 17653 | 17655 |
| Sex: | M | M | M | M | M | M | M | M | M | M |
| Death Type: | SS | SS | SS | SS | SS | SS | SS | SS | SS | SS |
| <u>LIVER:</u> | | | | | | | | | | |
| -inflammation, chronic, focal/multifocal | 1 | 1 | - | 2 | 2 | 1 | 1 | - | - | 1 |
| -lipidosis, tension, focal | - | - | P | - | - | - | - | - | - | - |
| -vacuolation, hepatocellular, periportal | - | 1 | - | - | - | - | - | - | 1 | - |
| <u>STOMACH:</u> | | | | | | | | | | |
| -dilatation, mucosal glands | - | 1 | - | - | 2 | - | - | - | - | - |
| -edema/inflammation, submucosa, nonglandular area | - | - | - | - | - | - | 3 | - | - | - |

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TABLE I-3

Histomorphologic Observations

| Dose Group: | III | III | III | III | III | III | III | III | III | III |
|--|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Animal Number: | 17620 | 17623 | 17627 | 17628 | 17633 | 17640 | 17646 | 17650 | 17657 | 17659 |
| Sex: | M | M | M | M | M | M | M | M | M | M |
| Death Type: | SS | SS | SS | SS | SS | SS | SS | SS | SS | SS |
| <u>LIVER:</u> | | | | | | | | | | |
| -hypertrophy, hepatocellular, centrilobular | 1 | - | 1 | - | 1 | - | - | 1 | - | - |
| -inflammation, chronic, focal/multifocal | - | 1 | 1 | 1 | - | - | 1 | - | 1 | 1 |
| <u>STOMACH:</u> | | | | | | | | | | |
| -dilatation, mucosal glands | 1 | - | - | - | - | - | - | 1 | - | - |
| -edema/inflammation, submucosa, glandular area | 1 | - | - | - | - | - | - | 1 | - | - |

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TABLE I-4

Histomorphologic Observations

| Dose Group: | IV | IV | IV | IV | IV | IV | IV | IV | IV | IV |
|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Animal Number: | 17621 | 17622 | 17625 | 17629 | 17636 | 17637 | 17641 | 17644 | 17647 | 17654 |
| Sex: | M | M | M | M | M | M | M | M | M | M |
| Death Type: | SS | SS | SS | SS | SS | SS | SS | SS | SS | SS |
| <u>ADRENAL GLANDS:</u> | | | | | | | | | | |
| -vacuolation, cortex | 1 | - | - | - | 1 | - | - | 1 | - | - |
| <u>BONE MARROW (STERNUM):</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>BRAIN:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>CECUM:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>COAGULATING GLAND:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>COLON:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>DUODENUM:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>EPIDIDYMIDES:</u> | | | | | | | | | | |
| -infiltration, mononuclear-cell, focal | - | - | - | - | - | - | - | - | 1 | - |
| <u>EXTREMITIES:</u> | | | | | | | | | | |
| -dermatitis, ulcerative, focal | | <2> | | | | | | | | |
| <u>HEART:</u> | | | | | | | | | | |
| -inflammation, subacute, focal/multifocal | - | - | - | - | - | - | - | - | - | 1 |
| <u>ILEUM:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>JEJUNUM:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>KIDNEYS:</u> | | | | | | | | | | |
| -cyst(s), medulla | - | - | - | P | P | - | - | - | - | - |
| -mineralization, multifocal | - | - | - | - | - | - | 1 | - | - | - |
| -nephritis, chronic, focal | - | - | - | - | - | - | - | - | - | 1 |
| <u>LIVER:</u> | | | | | | | | | | |
| -hypertrophy, hepatocellular, centrilobular | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 1 |
| -inflammation, chronic, focal/multifocal | 2 | - | - | - | 1 | - | 1 | - | - | 1 |
| -lipidosis, tension, focal | - | - | - | - | - | - | - | - | - | P |
| -necrosis, focal | - | - | 1 | - | - | - | - | - | - | - |
| -necrosis, individual hepatocytes | - | - | - | - | - | 1 | 1 | 2 | - | - |
| <u>LUNG:</u> | | | | | | | | | | |
| -inflammation, interstitial, multifocal | - | - | - | 1 | - | - | - | - | - | - |
| -macrophages, alveoli, focal | - | - | - | 1 | - | - | - | - | - | - |
| <u>LYMPH NODE, MEDIASTINAL:</u> | | | | | | | | | | |
| -congestion/erythrophagocytosis | - | - | - | - | 2 | - | 1 | - | - | - |
| <u>LYMPH NODE, SUBMANDIBULAR:</u> | | | | | | | | | | |
| -hyperplasia, lymphocytic/plasmacytic | 1 | 3 | 1 | 2 | - | - | 1 | 1 | - | - |
| <u>NERVE, SCIATIC:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |

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TABLE I-4 (Continued)

Histomorphologic Observations

| Dose Group: | IV | IV | IV | IV | IV | IV | IV | IV | IV | IV |
|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Animal Number: | 17621 | 17622 | 17625 | 17629 | 17636 | 17637 | 17641 | 17644 | 17647 | 17654 |
| Sex: | M | M | M | M | M | M | M | M | M | M |
| Death Type: | SS | SS | SS | SS | SS | SS | SS | SS | SS | SS |
| <u>PARATHYROID:</u> | - | - | - | - | * | - | - | * | - | - |
| <u>PEYER'S PATCH:</u> | | | | | | | | | | |
| -mineralization | - | - | - | - | - | 1 | - | - | - | - |
| <u>PROSTATE:</u> | | | | | | | | | | |
| -atrophy, focal | - | 1 | - | - | - | - | - | - | - | - |
| -inflammation, chronic, multifocal | - | - | - | 1 | - | - | - | 1 | - | - |
| -prostatitis, suppurative | - | - | - | - | <4> | - | - | - | - | - |
| <u>RECTUM:</u> | | | | | | | | | | |
| -parasite(s) | P | - | - | - | P | - | - | - | - | - |
| <u>SEMINAL VESICLES:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>SPINAL CORD, CERVICAL:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>SPINAL CORD, LUMBAR:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>SPINAL CORD, THORACIC:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>SPLEEN:</u> | | | | | | | | | | |
| -hematopoiesis, extramedullary, increased | - | - | - | - | - | - | - | 1 | - | - |
| -lymphosarcoma | <XM> | - | - | - | - | - | - | - | - | - |
| <u>STOMACH:</u> | | | | | | | | | | |
| -dilatation, mucosal glands | - | - | - | 1 | - | 1 | 2 | - | - | - |
| -edema/inflammation, submucosa, glandular area | - | - | - | - | 3 | 2 | - | - | 3 | - |
| -edema/inflammation, submucosa, nonglandular area | - | - | - | 1 | 2 | 1 | - | - | 3 | - |
| -erosion(s), glandular mucosa | 1 | 2 | - | - | - | - | - | - | - | - |
| <u>TESTES:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>THYMUS:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>THYROID:</u> | | | | | | | | | | |
| -ultimobranchial body/cyst | - | - | - | P | P | P | - | - | - | - |
| <u>TRACHEA:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>URINARY BLADDER:</u> | - | - | - | - | - | - | - | - | - | - |

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TABLE I-5

Histomorphologic Observations

| Dose Group: | I | I | I | I | I | I | I | I | I | |
|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Animal Number: | 17681 | 17690 | 17694 | 17695 | 17703 | 17713 | 17715 | 17716 | 17717 | 17719 |
| Sex: | F | F | F | F | F | F | F | F | F | F |
| Death Type: | SS | SS | SS | SS | SS | SS | SS | SS | SS | SS |
| <u>ADRENAL GLANDS:</u> | | | | | | | | | | |
| -infiltration, mononuclear-cell, multifocal | - | - | - | - | - | - | 1 | - | - | - |
| <u>BONE MARROW (STERNUM):</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>BRAIN:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>CECUM:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>COLON:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>DUODENUM:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>HEART:</u> | | | | | | | | | | |
| -pericarditis, chronic, focal | - | - | - | - | - | 1 | - | - | - | - |
| <u>ILEUM:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>JEJUNUM:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>KIDNEYS:</u> | | | | | | | | | | |
| -mineralization, multifocal | 1 | - | - | - | 1 | - | - | - | - | - |
| <u>LIVER:</u> | | | | | | | | | | |
| -inflammation, chronic, focal/multifocal | - | 1 | - | - | 1 | - | 1 | - | - | - |
| -necrosis, focal | - | - | - | - | - | - | - | 1 | - | - |
| -vacuolation, hepatocellular, multifocal | - | - | - | - | - | 1 | - | - | - | - |
| <u>LUNG:</u> | | | | | | | | | | |
| -inflammation, interstitial, multifocal | - | - | - | - | - | - | - | - | 1 | - |
| -macrophages, alveoli, focal | - | - | 1 | - | - | - | - | - | - | - |
| <u>LYMPH NODE, MEDIASTINAL:</u> | | | | | | | | | | |
| -congestion/erythrophagocytosis | - | - | 1 | - | - | - | - | - | - | * |
| -hyperplasia, lymphocytic/plasmacytic | - | - | - | 1 | - | - | - | - | - | * |
| -macrophages, pigmented | - | - | 1 | 1 | - | - | - | - | - | * |
| <u>LYMPH NODE, SUBMANDIBULAR:</u> | | | | | | | | | | |
| -hyperplasia, lymphocytic/plasmacytic | 3 | 1 | 2 | - | 3 | 1 | 2 | 1 | 2 | 1 |
| <u>MAMMARY GLAND:</u> | | | | | | | | | | |
| -hyperplasia, physiological | P | P | P | P | P | P | P | P | P | P |
| -inflammation, subacute | - | - | - | - | - | - | - | - | - | 2 |
| <u>NERVE, SCIATIC:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>OVARIES:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>PARATHYROID:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| <u>PEYER'S PATCH:</u> | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |

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TABLE I-5 (Continued)

Histomorphologic Observations

| Dose Group: | I | I | I | I | I | I | I | I | I | I |
|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Animal Number: | 17681 | 17690 | 17694 | 17695 | 17703 | 17713 | 17715 | 17716 | 17717 | 17719 |
| Sex: | F | F | F | F | F | F | F | F | F | F |
| Death Type: | SS | SS | SS | SS | SS | SS | SS | SS | SS | SS |
| <u>RECTUM:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>SPINAL CORD, CERVICAL:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>SPINAL CORD, LUMBAR:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>SPINAL CORD, THORACIC:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>SPLEEN:</u> | | | | | | | | | | |
| -hematopoiesis, extramedullary, increased | 2 | - | - | 2 | 2 | - | 1 | - | - | - |
| <u>STOMACH:</u> | | | | | | | | | | |
| -dilatation, mucosal glands | - | 1 | - | - | - | - | - | - | - | - |
| <u>THYMUS:</u> | | | | | | | | | | |
| -atrophy | - | - | - | - | - | - | - | - | - | 1 |
| <u>THYROID:</u> | | | | | | | | | | |
| -ultimobranchial body/cyst | P | - | - | - | P | - | - | - | P | - |
| <u>TRACHEA:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>URINARY BLADDER:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>UTERUS:</u> | | | | | | | | | | |
| -distention, lumen | - | - | - | - | - | 1 | - | - | - | - |
| -macrophages, pigmented | - | - | 1 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| -thrombus | - | - | P | - | - | - | P | - | - | - |
| <u>VAGINA:</u> | | | | | | | | | | |
| -mucification | 3 | 3 | - | - | - | - | - | - | - | - |

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TABLE I-6

Histomorphologic Observations

| Dose Group: | II | II | II | II | II | II | II | II | II | II |
|--|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Animal Number: | 17675 | 17679 | 17684 | 17688 | 17698 | 17702 | 17704 | 17707 | 17708 | 17710 |
| Sex: | F | F | F | F | F | F | F | F | F | F |
| Death Type: | SS | SS | SS | SS | SS | SS | SS | SS | SS | SS |
| <u>LIVER:</u> | | | | | | | | | | |
| -inflammation, chronic, focal/multifocal | - | - | - | - | - | - | 1 | 1 | - | - |
| -necrosis, focal | - | - | - | - | - | - | - | 1 | - | - |
| <u>THYMUS:</u> | | | | | | | | | | |
| -atrophy | - | - | - | - | 1 | - | - | - | - | - |

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TABLE I-7

Histomorphologic Observations

| Dose Group: | III | III | III | III | III | III | III | III | III | III |
|--|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Animal Number: | 17687 | 17693 | 17697 | 17700 | 17701 | 17705 | 17706 | 17709 | 17718 | 17720 |
| Sex: | F | F | F | F | F | F | F | F | F | F |
| Death Type: | SS | SS | SS | SS | SS | SS | SS | SS | SS | SS |
| <u>LIVER:</u> | | | | | | | | | | |
| -inflammation, chronic, focal/multifocal | - | 1 | - | 1 | 1 | 1 | 1 | - | - | 1 |
| <u>THYMUS:</u> | | | | | | | | | | |
| -atrophy | - | - | 1 | - | - | - | - | - | - | - |

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TABLE I-8

Histomorphologic Observations

| Dose Group: | IV | IV | IV | IV | IV | IV | IV | IV | IV | IV |
|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Animal Number: | 17685 | 17686 | 17689 | 17691 | 17692 | 17696 | 17699 | 17711 | 17712 | 17714 |
| Sex: | F | F | F | F | F | F | F | F | F | F |
| Death Type: | SS | SS | SS | SS | SS | SS | SS | SS | SS | SS |
| <u>ADRENAL GLANDS:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>BONE MARROW (STERNUM):</u> | - | - | - | - | - | - | - | - | - | - |
| <u>BRAIN:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>CECUM:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>COLON:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>DUODENUM:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>HEART:</u> | | | | | | | | | | |
| -inflammation, subacute, focal/multifocal | - | - | - | - | - | 1 | - | - | - | - |
| <u>ILEUM:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>JEJUNUM:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>KIDNEYS:</u> | | | | | | | | | | |
| -mineralization, multifocal | - | - | - | - | 1 | - | 1 | - | - | - |
| -pyelitis, chronic | 1 | - | - | - | - | - | - | - | - | - |
| -vacuolation, cortical tubular epithelium | - | - | - | - | - | - | - | 2 | - | - |
| <u>LIVER:</u> | | | | | | | | | | |
| -hypertrophy, hepatocellular, centrilobular | 1 | - | 1 | 1 | 1 | - | 1 | 2 | 1 | 2 |
| -inflammation, chronic, focal/multifocal | - | 1 | 1 | 1 | - | - | 1 | - | 1 | - |
| -lipidosis, tension, focal | P | - | - | - | - | - | - | - | - | - |
| -vacuolation, hepatocellular, periportal | - | - | - | - | - | - | - | 1 | - | - |
| <u>LUNG:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>LYMPH NODE, MEDIASTINAL:</u> | | | | | | | | | | |
| -congestion/erythrophagocytosis | - | - | 2 | - | 2 | - | - | - | - | * |
| <u>LYMPH NODE, SUBMANDIBULAR:</u> | | | | | | | | | | |
| -hyperplasia, lymphocytic/plasmacytic | 3 | 3 | 2 | 1 | 3 | 2 | 3 | - | 2 | - |
| <u>MAMMARY GLAND:</u> | | | | | | | | | | |
| -hyperplasia, physiological | P | P | P | P | P | P | P | P | P | P |
| <u>NERVE, SCIATIC:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>OVARIES:</u> | - | * | - | - | - | - | - | - | - | - |
| <u>PARATHYROID:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>PEYER'S PATCH:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>RECTUM:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>SPINAL CORD, CERVICAL:</u> | - | - | - | - | - | - | - | - | - | - |

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TABLE I-8 (Continued)

Histomorphologic Observations

| Dose Group: | IV | IV | IV | IV | IV | IV | IV | IV | IV | IV |
|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Animal Number: | 17685 | 17686 | 17689 | 17691 | 17692 | 17696 | 17699 | 17711 | 17712 | 17714 |
| Sex: | F | F | F | F | F | F | F | F | F | F |
| Death Type: | SS | SS | SS | SS | SS | SS | SS | SS | SS | SS |
| <u>SPINAL CORD, LUMBAR:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>SPINAL CORD, THORACIC:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>SPLEEN:</u> | | | | | | | | | | |
| -atrophy | - | - | - | - | - | - | - | 2 | - | - |
| -hematopoiesis, extramedullary, increased | - | - | 1 | - | - | - | 1 | - | - | 1 |
| <u>STOMACH:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>TAIL:</u> | | | | | | | | | <-> | |
| <u>THYMUS:</u> | | | | | | | | | | |
| -atrophy | - | - | - | - | 2 | <*> | 1 | 3 | 1 | 2 |
| <u>THYROID:</u> | | | | | | | | | | |
| -ultimobranchial body/cyst | - | P | - | P | - | P | P | - | - | P |
| <u>TRACHEA:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>URINARY BLADDER:</u> | - | - | - | - | - | - | - | - | - | - |
| <u>UTERUS:</u> | | | | | | | | | | |
| -distention, lumen | - | - | - | - | - | 3 | - | - | - | - |
| -hemorrhage, endometrium | - | - | - | - | - | - | - | 2 | - | - |
| -inflammation, endometrium, diffuse | - | - | - | - | - | 2 | - | - | - | - |
| -macrophages, pigmented | 1 | 1 | 2 | 3 | - | 3 | 3 | 3 | 2 | 3 |
| -thrombus | - | - | - | - | - | - | - | - | - | P |
| <u>VAGINA:</u> | | | | | | | | | | |
| -inflammation, acute | - | - | - | - | - | - | - | 3 | - | - |
| -mucification | - | 3 | - | - | - | - | - | 4 | - | - |

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APPENDIX II

INDIVIDUAL ANIMAL GROSS AND HISTOMORPHOLOGY DATA

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Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17608 DOSE GROUP: I
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

ADRENAL GLANDS: vacuolation, cortex (mild)
 LIVER: inflammation, chronic, focal/multifocal (minimal)
 LUNG: inflammation, interstitial, multifocal (minimal)
 THYROID: ultimobranchial body/cyst
 TRACHEA: inflammation, chronic, focal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|---------------------------|-----------------------|------------------|-------------------------|
| BONE MARROW (STERNUM) | BRAIN | CECUM | COAGULATING GLAND |
| COLON | DUODENUM | EPIDIDYMIDES | HEART |
| ILEUM | JEJUNUM | KIDNEYS | LYMPH NODE, MEDIASTINAL |
| LYMPH NODE, SUBMANDIBULAR | NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH |
| PROSTATE | RECTUM | SEMINAL VESICLES | SPINAL CORD, CERVICAL |
| SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN | STOMACH |
| TESTES | THYMUS | URINARY BLADDER | |

End of Record- 17608

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17618 DOSE GROUP: I
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

CECUM: inflammation, mucosa, chronic (mild)
 LIVER: inflammation, chronic, focal/multifocal (mild)
 STOMACH: dilatation, mucosal glands (minimal)
 edema/inflammation, submucosa, glandular area (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-------------------------|---------------------------|-----------------------|-------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | COAGULATING GLAND |
| COLON | DUODENUM | EPIDIDYMIDES | HEART |
| ILEUM | JEJUNUM | KIDNEYS | LUNG |
| LYMPH NODE, MEDIASTINAL | LYMPH NODE, SUBMANDIBULAR | NERVE, SCIATIC | PARATHYROID |
| PEYER'S PATCH | PROSTATE | RECTUM | SEMINAL VESICLES |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN |
| TESTES | THYMUS | THYROID | TRACHEA |
| URINARY BLADDER | | | |

End of Record- 17618

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17630 DOSE GROUP: I
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

ADRENAL GLANDS: vacuolation, cortex (minimal)
 LIVER: inflammation, chronic, focal/multifocal (minimal)
 STOMACH: dilatation, mucosal glands (minimal)
 edema/inflammation, submucosa, nonglandular area (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|---------------------------|-----------------------|------------------|-----------------------|
| BONE MARROW (STERNUM) | BRAIN | CECUM | COAGULATING GLAND |
| COLON | DUODENUM | EPIDIDYMIDES | HEART |
| ILEUM | JEJUNUM | KIDNEYS | LUNG |
| LYMPH NODE, SUBMANDIBULAR | NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH |
| PROSTATE | RECTUM | SEMINAL VESICLES | SPINAL CORD, CERVICAL |
| SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN | TESTES |
| THYMUS | THYROID | TRACHEA | URINARY BLADDER |

TISSUE(S) NOT AVAILABLE FOR EVALUATION:

LYMPH NODE, MEDIASTINAL

End of Record- 17630

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17631 DOSE GROUP: I
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

KIDNEYS: dilatation, pelvis (mild)
 LIVER: vacuolation, hepatocellular, periportal (minimal)
 inflammation, chronic, focal/multifocal (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (mild)
 PROSTATE: atrophy, focal (minimal)
 THYROID: ultimobranchial body/cyst
 hypertrophy, follicular epithelium (mild)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-------------------------|-----------------------|-----------------------|---------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | EPIDIDYMIDES |
| HEART | ILEUM | JEJUNUM | LUNG |
| LYMPH NODE, MEDIASTINAL | NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH |
| RECTUM | SEMINAL VESICLES | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR |
| SPINAL CORD, THORACIC | SPLEEN | STOMACH | TESTES |
| THYMUS | TRACHEA | URINARY BLADDER | |

End of Record- 17631

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17639 DOSE GROUP: I
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

EPIDIDYMIDES: infiltration, mononuclear-cell, focal (minimal)
 LYMPH NODE, MEDIASTINAL: congestion/erythrophagocytosis (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|---------------------|-----------------------|------------------|-----------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | HEART |
| ILEUM | JEJUNUM | KIDNEYS | LIVER |
| LUNG | NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH |
| PROSTATE | RECTUM | SEMINAL VESICLES | SPINAL CORD, CERVICAL |
| SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN | STOMACH |
| TESTES | THYMUS | THYROID | TRACHEA |
| URINARY BLADDER | | | |

End of Record- 17639

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17648 DOSE GROUP: I
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

HEART: inflammation, subacute, focal/multifocal (mild)
 KIDNEYS: infiltration, mononuclear-cell, focal (minimal)
 LIVER: inflammation, chronic, focal/multifocal (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (mild)
 STOMACH: dilatation, mucosal glands (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-----------------------|-----------------------|-------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | EPIDIDYMIDES |
| ILEUM | JEJUNUM | LUNG | LYMPH NODE, MEDIASTINAL |
| NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH | PROSTATE |
| RECTUM | SEMINAL VESICLES | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR |
| SPINAL CORD, THORACIC | SPLEEN | TESTES | THYMUS |
| THYROID | TRACHEA | URINARY BLADDER | |

End of Record- 17648

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17652 DOSE GROUP: I
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)
 RECTUM: edema/inflammation, submucosa (moderate)
 STOMACH: edema/inflammation, submucosa, glandular area (mild)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-------------------------|---------------------------|------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | EPIDIDYMIDES |
| HEART | ILEUM | JEJUNUM | KIDNEYS |
| LUNG | LYMPH NODE, MEDIASTINAL | LYMPH NODE, SUBMANDIBULAR | NERVE, SCIATIC |
| PARATHYROID | PEYER'S PATCH | PROSTATE | SEMINAL VESICLES |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN |
| TESTES | THYMUS | THYROID | TRACHEA |
| URINARY BLADDER | | | |

End of Record- 17652

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
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Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17656 DOSE GROUP: I
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

EPIDIDYMIDES: infiltration, mononuclear-cell, focal (minimal)
 KIDNEYS: edema, papillary (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (minimal)
 PROSTATE: inflammation, chronic, multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-------------------------|-----------------------|-----------------------|---------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | HEART |
| ILEUM | JEJUNUM | LIVER | LUNG |
| LYMPH NODE, MEDIASTINAL | NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH |
| RECTUM | SEMINAL VESICLES | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR |
| SPINAL CORD, THORACIC | SPLEEN | STOMACH | TESTES |
| THYMUS | THYROID | TRACHEA | URINARY BLADDER |

End of Record- 17656

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
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Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17658 DOSE GROUP: I
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

THYROID: ultimobranchial body/cyst

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-----------------------|-------------------------|---------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | EPIDIDYMIDES |
| HEART | ILEUM | JEJUNUM | KIDNEYS |
| LIVER | LUNG | LYMPH NODE, MEDIASTINAL | LYMPH NODE, SUBMANDIBULAR |
| NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH | PROSTATE |
| RECTUM | SEMINAL VESICLES | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR |
| SPINAL CORD, THORACIC | SPLEEN | STOMACH | TESTES |
| THYMUS | TRACHEA | URINARY BLADDER | |

End of Record- 17658

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17660 DOSE GROUP: I
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
 GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-------------------------|-----------------------|------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | EPIDIDYIMIDES |
| HEART | ILEUM | JEJUNUM | KIDNEYS |
| LUNG | LYMPH NODE, MEDIASTINAL | NERVE, SCIATIC | PARATHYROID |
| PEYER'S PATCH | PROSTATE | RECTUM | SEMINAL VESICLES |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN |
| STOMACH | TESTES | THYMUS | THYROID |
| TRACHEA | URINARY BLADDER | | |

End of Record- 17660

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17634 DOSE GROUP: II
SEX: M DEATH TYPE: Sacrifice-Scheduled
=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:
LIVER: inflammation, chronic, focal/multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:
STOMACH

End of Record- 17634

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

| | |
|---------------------------------------|---|
| ANIMAL NUMBER: 17635 | DOSE GROUP: II |
| SEX: M | DEATH TYPE: Sacrifice-Scheduled |
| ===== | |
| <u>GROSS OBSERVATION(S):</u> | <u>HISTOMORPHOLOGIC OBSERVATION(S):</u> |
| <u>GENERAL:</u> No gross changes. | Not applicable |
| ----- | |
| <u>HISTOMORPHOLOGIC OBSERVATIONS:</u> | |
| LIVER: | vacuolation, hepatocellular, periportal (minimal) |
| | inflammation, chronic, focal/multifocal (minimal) |
| STOMACH: | dilatation, mucosal glands (minimal) |
| ----- | |
| End of Record- 17635 | |

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17638 DOSE GROUP: II
SEX: M DEATH TYPE: Sacrifice-Scheduled
=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: lipidosis, tension, focal

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

STOMACH

End of Record- 17638

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17642 DOSE GROUP: II
SEX: M DEATH TYPE: Sacrifice-Scheduled

=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:
LIVER: inflammation, chronic, focal/multifocal (mild)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

STOMACH

End of Record- 17642

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

| | |
|----------------------|---------------------------------|
| ANIMAL NUMBER: 17643 | DOSE GROUP: II |
| SEX: M | DEATH TYPE: Sacrifice-Scheduled |

=====

| | |
|-----------------------------------|---|
| <u>GROSS OBSERVATION(S):</u> | <u>HISTOMORPHOLOGIC OBSERVATION(S):</u> |
| <u>GENERAL:</u> No gross changes. | Not applicable |

HISTOMORPHOLOGIC OBSERVATIONS:

| | |
|----------|--|
| LIVER: | inflammation, chronic, focal/multifocal (mild) |
| STOMACH: | dilatation, mucosal glands (mild) |

End of Record- 17643

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17645
SEX: M

DOSE GROUP: II
DEATH TYPE: Sacrifice-Scheduled

=====

GROSS OBSERVATION(S):

HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes.

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

STOMACH

End of Record- 17645

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

| | |
|----------------------|---------------------------------|
| ANIMAL NUMBER: 17649 | DOSE GROUP: II |
| SEX: M | DEATH TYPE: Sacrifice-Scheduled |
| ===== | |

| | |
|-----------------------------------|---|
| <u>GROSS OBSERVATION(S):</u> | <u>HISTOMORPHOLOGIC OBSERVATION(S):</u> |
| <u>GENERAL:</u> No gross changes. | Not applicable |
| ----- | |

HISTOMORPHOLOGIC OBSERVATIONS:

| | |
|----------|---|
| LIVER: | inflammation, chronic, focal/multifocal (minimal) |
| STOMACH: | edema/inflammation, submucosa, nonglandular area (moderate) |
| ----- | |

End of Record- 17649

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17655 DOSE GROUP: II
SEX: M DEATH TYPE: Sacrifice-Scheduled
=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:
LIVER: inflammation, chronic, focal/multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:
STOMACH

End of Record- 17655

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17620 DOSE GROUP: III
SEX: M DEATH TYPE: Sacrifice-Scheduled

=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: hypertrophy, hepatocellular, centrilobular (minimal)
STOMACH: edema/inflammation, submucosa, glandular area (minimal)
 dilatation, mucosal glands (minimal)

End of Record- 17620

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17623 DOSE GROUP: III
SEX: M DEATH TYPE: Sacrifice-Scheduled

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| | |
|-----------------------------------|---|
| <u>GROSS OBSERVATION(S):</u> | <u>HISTOMORPHOLOGIC OBSERVATION(S):</u> |
| <u>GENERAL:</u> No gross changes. | Not applicable |

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

STOMACH

End of Record- 17623

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17633 DOSE GROUP: III
SEX: M DEATH TYPE: Sacrifice-Scheduled

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| | |
|------------------------------|---|
| <u>GROSS OBSERVATION(S):</u> | <u>HISTOMORPHOLOGIC OBSERVATION(S):</u> |
|------------------------------|---|

| | |
|-----------------------------------|----------------|
| <u>GENERAL:</u> No gross changes. | Not applicable |
|-----------------------------------|----------------|

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: hypertrophy, hepatocellular, centrilobular (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

STOMACH

End of Record- 17633

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17640 DOSE GROUP: III
SEX: M DEATH TYPE: Sacrifice-Scheduled
=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
GENERAL: No gross changes. Not applicable

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

LIVER STOMACH

End of Record- 17640

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17646 DOSE GROUP: III
SEX: M DEATH TYPE: Sacrifice-Scheduled

=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

STOMACH

End of Record- 17646

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
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Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17650 DOSE GROUP: III
SEX: M DEATH TYPE: Sacrifice-Scheduled

=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: hypertrophy, hepatocellular, centrilobular (minimal)
STOMACH: dilatation, mucosal glands (minimal)
edema/inflammation, submucosa, glandular area (minimal)

End of Record- 17650

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
PROTOCOL 418-027
SPONSOR'S STUDY NUMBER T-7599

Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17657 DOSE GROUP: III
SEX: M DEATH TYPE: Sacrifice-Scheduled

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| | |
|-----------------------------------|---|
| <u>GROSS OBSERVATION(S):</u> | <u>HISTOMORPHOLOGIC OBSERVATION(S):</u> |
| <u>GENERAL:</u> No gross changes. | Not applicable |

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

STOMACH

End of Record- 17657

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
PROTOCOL 418-027
SPONSOR'S STUDY NUMBER T-7599

Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17659 DOSE GROUP: III
SEX: M DEATH TYPE: Sacrifice-Scheduled

=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

STOMACH

End of Record- 17659

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17621 DOSE GROUP: IV
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

SPLEEN: Nodule, 0.3cm (trimming observation). lymphosarcoma

HISTOMORPHOLOGIC OBSERVATIONS:

ADRENAL GLANDS: vacuolation, cortex (minimal)
 LIVER: inflammation, chronic, focal/multifocal (mild)
 hypertrophy, hepatocellular, centrilobular (mild)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (minimal)
 RECTUM: parasite(s)
 SPLEEN: lymphosarcoma, malignant
 STOMACH: erosion(s), glandular mucosa (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-------------------------|------------------|-----------------------|---------------------|
| BONE MARROW (STERNUM) | BRAIN | CECUM | COAGULATING GLAND |
| COLON | DUODENUM | EPIDIDYMIDES | HEART |
| ILEUM | JEJUNUM | KIDNEYS | LUNG |
| LYMPH NODE, MEDIASTINAL | NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH |
| PROSTATE | SEMINAL VESICLES | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR |
| SPINAL CORD, THORACIC | TESTES | THYMUS | THYROID |
| TRACHEA | URINARY BLADDER | | |

NEOPLASMS:

SPLEEN lymphosarcoma, malignant

End of Record- 17621

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17622 DOSE GROUP: IV
 SEX: M DEATH TYPE: Sacrifice-Scheduled

=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

EXTREMITIES: Right front leg- scab. dermatitis, ulcerative, focal

HISTOMORPHOLOGIC OBSERVATIONS:

EXTREMITIES: dermatitis, ulcerative, focal (mild)
 LIVER: hypertrophy, hepatocellular, centrilobular (mild)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (moderate)
 PROSTATE: atrophy, focal (minimal)
 STOMACH: erosion(s), glandular mucosa (mild)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|---------------------|-------------------------|------------------|-----------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | EPIDIDYMIDES |
| HEART | ILEUM | JEJUNUM | KIDNEYS |
| LUNG | LYMPH NODE, MEDIASTINAL | NERVE, SCIATIC | PARATHYROID |
| PEYER'S PATCH | RECTUM | SEMINAL VESICLES | SPINAL CORD, CERVICAL |
| SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN | TESTES |
| THYMUS | THYROID | TRACHEA | URINARY BLADDER |

End of Record- 17622

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17625 DOSE GROUP: IV
 SEX: M DEATH TYPE: Sacrifice-Scheduled

=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

ADRENAL GLANDS: hypertrophy/vacuolation, zona glomerulosa (mild)
 LIVER: necrosis, focal (minimal)
 Lymph node, submandibular: hypertrophy, hepatocellular, centrilobular (mild)
 hyperplasia, lymphocytic/plasmacytic (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-------------------------|-----------------------|------------------|-----------------------|
| BONE MARROW (STERNUM) | BRAIN | CECUM | COAGULATING GLAND |
| COLON | DUODENUM | EPIDIDYMIDES | HEART |
| ILEUM | JEJUNUM | KIDNEYS | LUNG |
| LYMPH NODE, MEDIASTINAL | NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH |
| PROSTATE | RECTUM | SEMINAL VESICLES | SPINAL CORD, CERVICAL |
| SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN | STOMACH |
| TESTES | THYMUS | THYROID | TRACHEA |
| URINARY BLADDER | | | |

End of Record- 17625

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17629 DOSE GROUP: IV
 SEX: M DEATH TYPE: Sacrifice-Scheduled

=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

KIDNEYS: cyst(s), medulla
 LIVER: hypertrophy, hepatocellular, centrilobular (mild)
 LUNG: macrophages, alveoli, focal (minimal)
 inflammation, interstitial, multifocal (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (mild)
 PROSTATE: inflammation, chronic, multifocal (minimal)
 STOMACH: edema/inflammation, submucosa, nonglandular area (minimal)
 dilatation, mucosal glands (minimal)
 THYROID: ultimobranchial body/cyst

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-------------------|-----------------------|---------------------|-------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | EPIDIDYMIDES |
| HEART | ILEUM | JEJUNUM | LYMPH NODE, MEDIASTINAL |
| NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH | RECTUM |
| SEMINAL VESICLES | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC |
| SPLEEN | TESTES | THYMUS | TRACHEA |
| URINARY BLADDER | | | |

COMMENTS:

STOMACH The edema/inflammation is most prominent at the limiting ridge.

End of Record- 17629

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17636
 SEX: M

DOSE GROUP: IV
 DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

PROSTATE: Right hemisphere- firm, lobular mass,
 tan in color, measuring 2.8cm x 0.9cm x 0.7cm,
 cut surface reveals tan, smooth surface,
 ventral right side red in color.

HISTOMORPHOLOGIC OBSERVATION(S):

prostatitis, suppurative

HISTOMORPHOLOGIC OBSERVATIONS:

ADRENAL GLANDS:

vacuolation, cortex (minimal)

KIDNEYS:

cyst(s), medulla

LIVER:

inflammation, chronic, focal/multifocal (minimal)

LYMPH NODE, MEDIASTINAL:

hypertrophy, hepatocellular, centrilobular (minimal)

PROSTATE:

congestion/erythrophagocytosis (mild)

RECTUM:

prostatitis, suppurative (marked)

STOMACH:

parasite(s)

THYROID:

edema/inflammation, submucosa, glandular area (moderate)

edema/inflammation, submucosa, nonglandular area (mild)

ultimobranchial body/cyst

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

BONE MARROW (STERNUM)

BRAIN

CECUM

COAGULATING GLAND

COLON

DUODENUM

EPIDIDYMIDES

HEART

ILEUM

JEJUNUM

LUNG

LYMPH NODE, SUBMANDIBULAR

NERVE, SCIATIC

PEYER'S PATCH

SEMINAL VESICLES

SPINAL CORD, CERVICAL

SPINAL CORD, LUMBAR

SPINAL CORD, THORACIC

SPLEEN

TESTES

THYMUS

TRACHEA

URINARY BLADDER

TISSUE(S) NOT AVAILABLE FOR EVALUATION:

PARATHYROID

End of Record- 17636

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17637 DOSE GROUP: IV
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: necrosis, individual hepatocytes (minimal)
 hypertrophy, hepatocellular, centrilobular (mild)
 PEYER'S PATCH: mineralization (minimal)
 STOMACH: edema/inflammation, submucosa, nonglandular area (minimal)
 edema/inflammation, submucosa, glandular area (mild)
 dilatation, mucosal glands (minimal)
 THYROID: ultimobranchial body/cyst

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-------------------------|---------------------------|------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | EPIDIDYMIDES |
| HEART | ILEUM | JEJUNUM | KIDNEYS |
| LUNG | LYMPH NODE, MEDIASTINAL | LYMPH NODE, SUBMANDIBULAR | NERVE, SCIATIC |
| PARATHYROID | PROSTATE | RECTUM | SEMINAL VESICLES |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN |
| TESTES | THYMUS | TRACHEA | URINARY BLADDER |

End of Record- 17637

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17641 DOSE GROUP: IV
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

KIDNEYS: mineralization, multifocal (minimal)
 LIVER: inflammation, chronic, focal/multifocal (minimal)
 hypertrophy, hepatocellular, centrilobular (mild)
 necrosis, individual hepatocytes (minimal)
 LYMPH NODE, MEDIASTINAL: congestion/erythrophagocytosis (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (minimal)
 STOMACH: dilatation, mucosal glands (mild)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-----------------------|-----------------------|---------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | EPIDIDYMIDES |
| HEART | ILEUM | JEJUNUM | LUNG |
| NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH | PROSTATE |
| RECTUM | SEMINAL VESICLES | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR |
| SPINAL CORD, THORACIC | SPLEEN | TESTES | THYMUS |
| THYROID | TRACHEA | URINARY BLADDER | |

End of Record- 17641

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17644 DOSE GROUP: IV
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

| | |
|----------------------------|--|
| ADRENAL GLANDS: | vacuolation, cortex (minimal) |
| LIVER: | hypertrophy, hepatocellular, centrilobular (mild) necrosis, individual hepatocytes (mild) |
| LYMPH NODE, SUBMANDIBULAR: | hyperplasia, lymphocytic/plasmacytic (minimal) |
| PROSTATE: | inflammation, chronic, multifocal (minimal) |
| SPLEEN: | hematopoiesis, extramedullary, increased (minimal) |

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-------------------------|-----------------------|---------------------|-----------------------|
| BONE MARROW (STERNUM) | BRAIN | CECUM | COAGULATING GLAND |
| COLON | DUODENUM | EPIDIDYMIDES | HEART |
| ILEUM | JEJUNUM | KIDNEYS | LUNG |
| LYMPH NODE, MEDIASTINAL | NERVE, SCIATIC | PEYER'S PATCH | RECTUM |
| SEMINAL VESICLES | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC |
| STOMACH | TESTES | THYMUS | THYROID |
| TRACHEA | URINARY BLADDER | | |

TISSUE(S) NOT AVAILABLE FOR EVALUATION:

PARATHYROID

End of Record- 17644

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17647
 SEX: M

DOSE GROUP: IV
 DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

EPIDIDYMIDES: infiltration, mononuclear-cell, focal (minimal)
 LIVER: hypertrophy, hepatocellular, centrilobular (mild)
 STOMACH: edema/inflammation, submucosa, nonglandular area (moderate)
 edema/inflammation, submucosa, glandular area (moderate)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-------------------------|---------------------------|-----------------------|------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | HEART |
| ILEUM | JEJUNUM | KIDNEYS | LUNG |
| LYMPH NODE, MEDIASTINAL | LYMPH NODE, SUBMANDIBULAR | NERVE, SCIATIC | PARATHYROID |
| PEYER'S PATCH | PROSTATE | RECTUM | SEMINAL VESICLES |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN |
| TESTES | THYMUS | THYROID | TRACHEA |
| URINARY BLADDER | | | |

End of Record- 17647

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17654 DOSE GROUP: IV
 SEX: M DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

HEART: inflammation, subacute, focal/multifocal (minimal)
 KIDNEYS: nephritis, chronic, focal (minimal)
 LIVER: lipidosis, tension, focal
 inflammation, chronic, focal/multifocal (minimal)
 hypertrophy, hepatocellular, centrilobular (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|---------------------------|-----------------------|------------------|-------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COAGULATING GLAND | COLON | DUODENUM | EPIDIDYMIDES |
| ILEUM | JEJUNUM | LUNG | LYMPH NODE, MEDIASTINAL |
| LYMPH NODE, SUBMANDIBULAR | NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH |
| PROSTATE | RECTUM | SEMINAL VESICLES | SPINAL CORD, CERVICAL |
| SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN | STOMACH |
| TESTES | THYMUS | THYROID | TRACHEA |
| URINARY BLADDER | | | |

End of Record- 17654

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17681 DOSE GROUP: I
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

| | |
|----------------------------|---|
| KIDNEYS: | mineralization, multifocal (minimal) |
| LYMPH NODE, SUBMANDIBULAR: | hyperplasia, lymphocytic/plasmacytic (moderate) |
| MAMMARY GLAND: | hyperplasia, physiological |
| SPLEEN: | hematopoiesis, extramedullary, increased (mild) |
| THYROID: | ultimobranchial body/cyst |
| VAGINA: | mucification (moderate) |

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|----------------|-----------------------|---------------------|-------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | LIVER | LUNG | LYMPH NODE, MEDIASTINAL |
| NERVE, SCIATIC | OVARIES | PARATHYROID | PEYER'S PATCH |
| RECTUM | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC |
| STOMACH | THYMUS | TRACHEA | URINARY BLADDER |
| UTERUS | | | |

End of Record- 17681

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17690
 SEX: F

DOSE GROUP: I
 DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

| | |
|----------------------------|---|
| LIVER: | inflammation, chronic, focal/multifocal (minimal) |
| LYMPH NODE, SUBMANDIBULAR: | hyperplasia, lymphocytic/plasmacytic (minimal) |
| MAMMARY GLAND: | hyperplasia, physiological |
| STOMACH: | dilatation, mucosal glands (minimal) |
| VAGINA: | mucification (moderate) |

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------|-----------------------|---------------------|-------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | KIDNEYS | LUNG | LYMPH NODE, MEDIASTINAL |
| NERVE, SCIATIC | OVARIES | PARATHYROID | PEYER'S PATCH |
| RECTUM | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC |
| SPLEEN | THYMUS | THYROID | TRACHEA |
| URINARY BLADDER | UTERUS | | |

End of Record- 17690

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17694 DOSE GROUP: I
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LUNG: macrophages, alveoli, focal (minimal)
 LYMPH NODE, MEDIASTINAL: macrophages, pigmented (minimal)
 congestion/erythrophagocytosis (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (mild)
 MAMMARY GLAND: hyperplasia, physiological
 UTERUS: thrombus
 macrophages, pigmented (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-----------------------|-----------------------|----------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | KIDNEYS | LIVER | NERVE, SCIATIC |
| OVARIES | PARATHYROID | PEYER'S PATCH | RECTUM |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN |
| STOMACH | THYMUS | THYROID | TRACHEA |
| URINARY BLADDER | VAGINA | | |

End of Record- 17694

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17695 DOSE GROUP: I
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LYMPH NODE, MEDIASTINAL: hyperplasia, lymphocytic/plasmacytic (minimal)
 macrophages, pigmented (minimal)
 MAMMARY GLAND: hyperplasia, physiological
 SPLEEN: hematopoiesis, extramedullary, increased (mild)
 UTERUS: macrophages, pigmented (moderate)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|---------------------------|-----------------------|-----------------------|---------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | KIDNEYS | LIVER | LUNG |
| LYMPH NODE, SUBMANDIBULAR | NERVE, SCIATIC | OVARIES | PARATHYROID |
| PEYER'S PATCH | RECTUM | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR |
| SPINAL CORD, THORACIC | STOMACH | THYMUS | THYROID |
| TRACHEA | URINARY BLADDER | VAGINA | |

End of Record- 17695

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17703
 SEX: F

DOSE GROUP: I
 DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

| | |
|----------------------------|---|
| KIDNEYS: | mineralization, multifocal (minimal) |
| LIVER: | inflammation, chronic, focal/multifocal (minimal) |
| LYMPH NODE, SUBMANDIBULAR: | hyperplasia, lymphocytic/plasmacytic (moderate) |
| MAMMARY GLAND: | hyperplasia, physiological |
| SPLEEN: | hematopoiesis, extramedullary, increased (mild) |
| THYROID: | ultimobranchial body/cyst |
| UTERUS: | macrophages, pigmented (moderate) |

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-----------------------|-------------------------|----------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | LUNG | LYMPH NODE, MEDIASTINAL | NERVE, SCIATIC |
| OVARIES | PARATHYROID | PEYER'S PATCH | RECTUM |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | STOMACH |
| THYMUS | TRACHEA | URINARY BLADDER | VAGINA |

End of Record- 17703

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17713 DOSE GROUP: I
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

HEART: pericarditis, chronic, focal (minimal)
 LIVER: vacuolation, hepatocellular, multifocal (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (minimal)
 MAMMARY GLAND: hyperplasia, physiological
 UTERUS: macrophages, pigmented (moderate)
 distention, lumen (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-----------------------|-------------------------|----------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | ILEUM | JEJUNUM |
| KIDNEYS | LUNG | LYMPH NODE, MEDIASTINAL | NERVE, SCIATIC |
| OVARIES | PARATHYROID | PEYER'S PATCH | RECTUM |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN |
| STOMACH | THYMUS | THYROID | TRACHEA |
| URINARY BLADDER | VAGINA | | |

End of Record- 17713

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17715 DOSE GROUP: I
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

| | |
|----------------------------|--|
| ADRENAL GLANDS: | infiltration, mononuclear-cell, multifocal (minimal) |
| LIVER: | inflammation, chronic, focal/multifocal (minimal) |
| LYMPH NODE, SUBMANDIBULAR: | hyperplasia, lymphocytic/plasmacytic (mild) |
| MAMMARY GLAND: | hyperplasia, physiological |
| SPLEEN: | hematopoiesis, extramedullary, increased (minimal) |
| UTERUS: | thrombus |
| | macrophages, pigmented (moderate) |

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|---------------------|-------------------------|-----------------|
| BONE MARROW (STERNUM) | BRAIN | CECUM | COLON |
| DUODENUM | HEART | ILEUM | JEJUNUM |
| KIDNEYS | LUNG | LYMPH NODE, MEDIASTINAL | NERVE, SCIATIC |
| OVARIES | PARATHYROID | PEYER'S PATCH | RECTUM |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | STOMACH |
| THYMUS | THYROID | TRACHEA | URINARY BLADDER |
| VAGINA | | | |

End of Record- 17715

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17716 DOSE GROUP: I
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: necrosis, focal (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (minimal)
 MAMMARY GLAND: hyperplasia, physiological
 UTERUS: macrophages, pigmented (moderate)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|----------------|-----------------------|---------------------|-------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | KIDNEYS | LUNG | LYMPH NODE, MEDIASTINAL |
| NERVE, SCIATIC | OVARIES | PARATHYROID | PEYER'S PATCH |
| RECTUM | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC |
| SPLEEN | STOMACH | THYMUS | THYROID |
| TRACHEA | URINARY BLADDER | VAGINA | |

End of Record- 17716

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17717 DOSE GROUP: I
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LUNG: inflammation, interstitial, multifocal (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (mild)
 MAMMARY GLAND: hyperplasia, physiological
 THYROID: ultimobranchial body/cyst
 UTERUS: macrophages, pigmented (moderate)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------|-----------------------|---------------------|-------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | KIDNEYS | LIVER | LYMPH NODE, MEDIASTINAL |
| NERVE, SCIATIC | OVARIES | PARATHYROID | PEYER'S PATCH |
| RECTUM | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC |
| SPLEEN | STOMACH | THYMUS | TRACHEA |
| URINARY BLADDER | VAGINA | | |

End of Record- 17717

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17719 DOSE GROUP: I
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (minimal)
 MAMMARY GLAND: inflammation, subacute (mild)
 THYMUS: hyperplasia, physiological
 UTERUS: atrophy (minimal)
 macrophages, pigmented (moderate)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------|-----------------------|---------------------|-----------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | KIDNEYS | LIVER | LUNG |
| NERVE, SCIATIC | OVARIES | PARATHYROID | PEYER'S PATCH |
| RECTUM | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC |
| SPLEEN | STOMACH | THYROID | TRACHEA |
| URINARY BLADDER | VAGINA | | |

TISSUE(S) NOT AVAILABLE FOR EVALUATION:

LYMPH NODE, MEDIASTINAL

End of Record- 17719

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
PROTOCOL 418-027
SPONSOR'S STUDY NUMBER T-7599

Appendix II
Individual Animal Gross and Histomorphology Data

| | |
|----------------------|---------------------------------|
| ANIMAL NUMBER: 17688 | DOSE GROUP: II |
| SEX: F | DEATH TYPE: Sacrifice-Scheduled |

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| | |
|-----------------------------------|---|
| <u>GROSS OBSERVATION(S):</u> | <u>HISTOMORPHOLOGIC OBSERVATION(S):</u> |
| <u>GENERAL:</u> No gross changes. | Not applicable |

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

LIVER THYMUS

End of Record- 17688

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
PROTOCOL 418-027
SPONSOR'S STUDY NUMBER T-7599

Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17698 DOSE GROUP: II
SEX: F DEATH TYPE: Sacrifice-Scheduled
=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:
THYMUS: atrophy (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:
LIVER

End of Record- 17698

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
PROTOCOL 418-027
SPONSOR'S STUDY NUMBER T-7599

Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17704
SEX: F

DOSE GROUP: II
DEATH TYPE: Sacrifice-Scheduled

=====

GROSS OBSERVATION(S):

HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes.

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

THYMUS

End of Record- 17704

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
PROTOCOL 418-027
SPONSOR'S STUDY NUMBER T-7599

Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17710
SEX: F

DOSE GROUP: II
DEATH TYPE: Sacrifice-Scheduled

=====

GROSS OBSERVATION(S):

HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes.

Not applicable

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

LIVER THYMUS

End of Record- 17710

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
PROTOCOL 418-027
SPONSOR'S STUDY NUMBER T-7599

Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17693 DOSE GROUP: III
SEX: F DEATH TYPE: Sacrifice-Scheduled

=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

THYMUS

End of Record- 17693

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
PROTOCOL 418-027
SPONSOR'S STUDY NUMBER T-7599

Appendix II
Individual Animal Gross and Histomorphology Data

| | |
|---|---|
| ANIMAL NUMBER: 17697 | DOSE GROUP: III |
| SEX: F | DEATH TYPE: Sacrifice-Scheduled |
| ===== | |
| <u>GROSS OBSERVATION(S):</u> | <u>HISTOMORPHOLOGIC OBSERVATION(S):</u> |
| GENERAL: No gross changes. | Not applicable |
| ----- | |
| <u>HISTOMORPHOLOGIC OBSERVATIONS:</u> | |
| THYMUS: | atrophy (minimal) |
| ----- | |
| <u>THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:</u> | |
| LIVER | |
| ----- | |
| End of Record- 17697 | |

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
PROTOCOL 418-027
SPONSOR'S STUDY NUMBER T-7599

Appendix II
Individual Animal Gross and Histomorphology Data

| | |
|----------------------|---------------------------------|
| ANIMAL NUMBER: 17700 | DOSE GROUP: III |
| SEX: F | DEATH TYPE: Sacrifice-Scheduled |

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| | |
|-----------------------------------|---|
| <u>GROSS OBSERVATION(S):</u> | <u>HISTOMORPHOLOGIC OBSERVATION(S):</u> |
| <u>GENERAL:</u> No gross changes. | Not applicable |

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

THYMUS

End of Record- 17700

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
PROTOCOL 418-027
SPONSOR'S STUDY NUMBER T-7599

Appendix II
Individual Animal Gross and Histomorphology Data

| | |
|---|---|
| ANIMAL NUMBER: 17705 | DOSE GROUP: III |
| SEX: F | DEATH TYPE: Sacrifice-Scheduled |
| ===== | |
| <u>GROSS OBSERVATION(S):</u> | <u>HISTOMORPHOLOGIC OBSERVATION(S):</u> |
| GENERAL: No gross changes. | Not applicable |
| ----- | |
| <u>HISTOMORPHOLOGIC OBSERVATIONS:</u> | |
| LIVER: | inflammation, chronic, focal/multifocal (minimal) |
| ----- | |
| <u>THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:</u> | |
| THYMUS | |
| ----- | |
| End of Record- 17705 | |

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
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SPONSOR'S STUDY NUMBER T-7599

Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17718 DOSE GROUP: III
SEX: F DEATH TYPE: Sacrifice-Scheduled
=====

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:
LIVER: hematopoiesis, extramedullary, multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:
THYMUS

End of Record- 17718

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
PROTOCOL 418-027
SPONSOR'S STUDY NUMBER T-7599

Appendix II
Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17720 DOSE GROUP: III
SEX: F DEATH TYPE: Sacrifice-Scheduled

=====

| | |
|------------------------------|---|
| <u>GROSS OBSERVATION(S):</u> | <u>HISTOMORPHOLOGIC OBSERVATION(S):</u> |
| GENERAL: No gross changes. | Not applicable |

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

THYMUS

End of Record- 17720

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
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Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17685 DOSE GROUP: IV
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

KIDNEYS: pyelitis, chronic (minimal)
 LIVER: lipidosis, tension, focal
 hypertrophy, hepatocellular, centrilobular (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (moderate)
 MAMMARY GLAND: hyperplasia, physiological
 UTERUS: macrophages, pigmented (minimal)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-----------------------|-------------------------|----------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | LUNG | LYMPH NODE, MEDIASTINAL | NERVE, SCIATIC |
| OVARIES | PARATHYROID | PEYER'S PATCH | RECTUM |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN |
| STOMACH | THYMUS | THYROID | TRACHEA |
| URINARY BLADDER | VAGINA | | |

End of Record- 17685

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17686 DOSE GROUP: IV
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (moderate)
 MAMMARY GLAND: hyperplasia, physiological
 THYROID: ultimobranchial body/cyst
 UTERUS: macrophages, pigmented (minimal)
 VAGINA: mucification (moderate)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-----------------------|-----------------------|-------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | KIDNEYS | LUNG | LYMPH NODE, MEDIASTINAL |
| NERVE, SCIATIC | PARATHYROID | PEYER'S PATCH | RECTUM |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN |
| STOMACH | THYMUS | TRACHEA | URINARY BLADDER |

TISSUE(S) NOT AVAILABLE FOR EVALUATION:

OVARIES

End of Record- 17686

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
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 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17689 DOSE GROUP: IV
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)
 hypertrophy, hepatocellular, centrilobular (minimal)
 LYMPH NODE, MEDIASTINAL: congestion/erythrophagocytosis (mild)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (mild)
 MAMMARY GLAND: hyperplasia, physiological
 SPLEEN: hematopoiesis, extramedullary, increased (minimal)
 UTERUS: macrophages, pigmented (mild)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-----------------------|-----------------------|-----------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | KIDNEYS | LUNG | NERVE, SCIATIC |
| OVARIES | PARATHYROID | PEYER'S PATCH | RECTUM |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | STOMACH |
| THYMUS | THYROID | TRACHEA | URINARY BLADDER |
| VAGINA | | | |

End of Record- 17689

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
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Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17691 DOSE GROUP: IV
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)
 hypertrophy, hepatocellular, centrilobular (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (minimal)
 MAMMARY GLAND: hyperplasia, physiological
 THYROID: ultimobranchial body/cyst
 UTERUS: macrophages, pigmented (moderate)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------|-----------------------|---------------------|-------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | KIDNEYS | LUNG | LYMPH NODE, MEDIASTINAL |
| NERVE, SCIATIC | OVARIES | PARATHYROID | PEYER'S PATCH |
| RECTUM | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC |
| SPLEEN | STOMACH | THYMUS | TRACHEA |
| URINARY BLADDER | VAGINA | | |

End of Record- 17691

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17692 DOSE GROUP: IV
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

| | |
|----------------------------|--|
| KIDNEYS: | mineralization, multifocal (minimal) |
| LIVER: | hypertrophy, hepatocellular, centrilobular (minimal) |
| LYMPH NODE, MEDIASTINAL: | congestion/erythrophagocytosis (mild) |
| LYMPH NODE, SUBMANDIBULAR: | hyperplasia, lymphocytic/plasmacytic (moderate) |
| MAMMARY GLAND: | hyperplasia, physiological |
| THYMUS: | atrophy (mild) |

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|---------------------|-----------------------|-----------------|-----------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | LUNG | NERVE, SCIATIC | OVARIES |
| PARATHYROID | PEYER'S PATCH | RECTUM | SPINAL CORD, CERVICAL |
| SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | SPLEEN | STOMACH |
| THYROID | TRACHEA | URINARY BLADDER | UTERUS |
| VAGINA | | | |

End of Record- 17692

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17699 DOSE GROUP: IV
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S): HISTOMORPHOLOGIC OBSERVATION(S):
 GENERAL: No gross changes. Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

| | |
|----------------------------|--|
| KIDNEYS: | mineralization, multifocal (minimal) |
| LIVER: | inflammation, chronic, focal/multifocal (minimal) |
| LYMPH NODE, SUBMANDIBULAR: | hypertrophy, hepatocellular, centrilobular (minimal) |
| MAMMARY GLAND: | hyperplasia, lymphocytic/plasmacytic (moderate) |
| SPLEEN: | hyperplasia, physiological |
| THYMUS: | hematopoiesis, extramedullary, increased (minimal) |
| THYROID: | atrophy (minimal) |
| UTERUS: | ultimobranchial body/cyst |
| | macrophages, pigmented (moderate) |

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|-----------------------|-----------------------|-------------------------|----------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | LUNG | LYMPH NODE, MEDIASTINAL | NERVE, SCIATIC |
| OVARIES | PARATHYROID | PEYER'S PATCH | RECTUM |
| SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC | STOMACH |
| TRACHEA | URINARY BLADDER | VAGINA | |

End of Record- 17699

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17711 DOSE GROUP: IV
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

GENERAL: No gross changes.

HISTOMORPHOLOGIC OBSERVATION(S):

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

KIDNEYS: vacuolation, cortical tubular epithelium (mild)
 LIVER: hypertrophy, hepatocellular, centrilobular (mild)
 vacuolation, hepatocellular, periportal (minimal)
 MAMMARY GLAND: hyperplasia, physiological
 SPLEEN: atrophy (mild)
 THYMUS: atrophy (moderate)
 UTERUS: hemorrhage, endometrium (mild)
 macrophages, pigmented (moderate)
 VAGINA: inflammation, acute (moderate)
 mucification (marked)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|----------------|-----------------------|-------------------------|---------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | LUNG | LYMPH NODE, MEDIASTINAL | LYMPH NODE, SUBMANDIBULAR |
| NERVE, SCIATIC | OVARIES | PARATHYROID | PEYER'S PATCH |
| RECTUM | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC |
| STOMACH | THYROID | TRACHEA | URINARY BLADDER |

End of Record- 17711

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17712 DOSE GROUP: IV
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):

TAIL: Bent.

HISTOMORPHOLOGIC OBSERVATION(S):

No microscopic change to correlate

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: inflammation, chronic, focal/multifocal (minimal)
 hypertrophy, hepatocellular, centrilobular (minimal)
 LYMPH NODE, SUBMANDIBULAR: hyperplasia, lymphocytic/plasmacytic (mild)
 MAMMARY GLAND: hyperplasia, physiological
 TAIL: No microscopic change to correlate
 THYMUS: atrophy (minimal)
 UTERUS: macrophages, pigmented (mild)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|----------------|-----------------------|---------------------|-------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | KIDNEYS | LUNG | LYMPH NODE, MEDIASTINAL |
| NERVE, SCIATIC | OVARIES | PARATHYROID | PEYER'S PATCH |
| RECTUM | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC |
| SPLEEN | STOMACH | TAIL | THYROID |
| TRACHEA | URINARY BLADDER | VAGINA | |

End of Record- 17712

ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY STUDY OF T 7599.7
 WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST
 PROTOCOL 418-027
 SPONSOR'S STUDY NUMBER T-7599

Appendix II
 Individual Animal Gross and Histomorphology Data

ANIMAL NUMBER: 17714 DOSE GROUP: IV
 SEX: F DEATH TYPE: Sacrifice-Scheduled

GROSS OBSERVATION(S):HISTOMORPHOLOGIC OBSERVATION(S):

GENERAL: No gross changes.

Not applicable

HISTOMORPHOLOGIC OBSERVATIONS:

LIVER: hypertrophy, hepatocellular, centrilobular (mild)
 MAMMARY GLAND: hyperplasia, physiological
 SPLEEN: hematopoiesis, extramedullary, increased (minimal)
 THYMUS: atrophy (mild)
 THYROID: ultimobranchial body/cyst
 UTERUS: thrombus
 macrophages, pigmented (moderate)

THE FOLLOWING TISSUE(S) WERE WITHIN NORMAL LIMITS:

| | | | |
|----------------|-----------------------|---------------------|---------------------------|
| ADRENAL GLANDS | BONE MARROW (STERNUM) | BRAIN | CECUM |
| COLON | DUODENUM | HEART | ILEUM |
| JEJUNUM | KIDNEYS | LUNG | LYMPH NODE, SUBMANDIBULAR |
| NERVE, SCIATIC | OVARIES | PARATHYROID | PEYER'S PATCH |
| RECTUM | SPINAL CORD, CERVICAL | SPINAL CORD, LUMBAR | SPINAL CORD, THORACIC |
| STOMACH | TRACHEA | URINARY BLADDER | VAGINA |

TISSUE(S) NOT AVAILABLE FOR EVALUATION:

LYMPH NODE, MEDIASTINAL

End of Record- 17714

APPENDIX K

HEMATOLOGY AND CLINICAL CHEMISTRY REPORTS

Study Report for Hematology

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| Animal ID | WBC THSN/CU MM | RBC MILL/CU MM | HGB GRAMS/DL | HCT % | MCV CU MICRONS | MCH PICO GRAMS | MCHC % | PLT THSN/CU MM |
|------------|-------------------|-------------------|-----------------|----------|-------------------|-------------------|-----------|-------------------|
| GROUP: 1-M | | | | | | | | |
| 17608 | 13.5 | 7.61 | 15.7 | 43.5 | 57.1 | 20.6 | 36.1 | 1094 |
| 17618 | 10.9 | 8.24 | 16.3 | 46.8 | 56.8 | 19.8 | 34.8 | 1406 |
| 17630 | 12.6 | 7.67 | 15.7 | 43.3 | 56.5 | 20.5 | 36.3 | 1174 |
| 17631 | 16.6 | 7.34 | 15.8 | 42.4 | 57.7 | 21.5 | 37.3 | 1126 |
| 17639 | 20.0 | 6.89 | 15.7 | 42.4 | 61.6 | 22.8 | 37.0 | 1185 |
| MEAN | 14.7 | 7.55 | 15.8 | 43.7 | 57.9 | 21.0 | 36.3 | 1197 |
| SD | 3.61 | 0.493 | 0.26 | 1.82 | 2.09 | 1.15 | 0.97 | 122.5 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| GROUP: 2-M | | | | | | | | |
| 17634 | 19.1 | 8.05 | 16.3 | 45.0 | 55.9 | 20.2 | 36.2 | 1174 |
| 17635 | 16.9 | 7.98 | 16.3 | 44.0 | 55.2 | 20.4 | 37.0 | 1237 |
| 17638 | 16.5 | 7.45 | 15.5 | 42.1 | 56.5 | 20.8 | 36.8 | 1096 |
| 17642 | 18.3 | 7.29 | 15.5 | 41.9 | 57.5 | 21.3 | 37.0 | 1204 |
| 17643 | 23.9 | 7.01 | 14.6 | 39.5 | 56.3 | 20.8 | 37.0 | 1147 |
| MEAN | 18.9 | 7.56 | 15.6 | 42.5 | 56.3 | 20.7 | 36.8 | 1172 |
| SD | 2.96 | 0.448 | 0.71 | 2.12 | 0.84 | 0.42 | 0.35 | 54.0 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| GROUP: 3-M | | | | | | | | |
| 17620 | 13.6 | 7.17 | 15.6 | 40.5 | 56.5 | 21.8 | 38.5 | 1038 |
| 17623 | 20.7 | 7.74 | 15.6 | 43.3 | 55.9 | 20.2 | 36.0 | 1326 |
| 17627 | 13.1 | 7.21 | 14.9 | 41.6 | 57.7 | 20.7 | 35.8 | 1030 |
| 17628 | 16.5 | 6.95 | 14.9 | 41.6 | 59.8 | 21.4 | 35.8 | 1219 |
| 17633 | 12.7 | 7.30 | 14.8 | 39.9 | 54.7 | 20.3 | 37.1 | 1475 |
| MEAN | 15.3 | 7.27 | 15.2 | 41.4 | 56.9 | 20.9 | 36.6 | 1218 |
| SD | 3.36 | 0.291 | 0.40 | 1.30 | 1.94 | 0.70 | 1.17 | 190.7 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Study Report for Hematology

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| Animal ID | WBC THSN/CU MM | RBC MILL/CU MM | HGB GRAMS/DL | HCT % | MCV CU MICRONS | MCH PICO GRAMS | MCHC % | PLT THSN/CU MM |
|------------|-------------------|-------------------|-----------------|----------|-------------------|-------------------|-----------|-------------------|
| GROUP: 4-M | | | | | | | | |
| 17621 | 17.2 | 7.54 | 16.1 | 43.5 | 57.7 | 21.4 | 37.0 | 1154 |
| 17622 | 11.0 | 6.87 | 14.7 | 38.6 | 56.2 | 21.4 | 38.1 | 1352 |
| 17625 | 14.5 | 7.24 | 14.5 | 41.0 | 56.6 | 20.0 | 35.4 | 1189 |
| 17629 | 22.3 | 7.25 | 14.9 | 39.4 | 54.3 | 20.6 | 37.8 | 1492 |
| 17636 | 31.3 | 6.94 | 15.5 | 40.2 | 57.9 | 22.3 | 38.6 | 1226 |
| MEAN | 19.3 | 7.17 | 15.1 | 40.5 | 56.5 | 21.1 | 37.4 | 1283 |
| SD | 7.90 | 0.270 | 0.65 | 1.88 | 1.44 | 0.88 | 1.25 | 138.9 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Study Report for Hematology

INDIVIDUAL ANIMAL REPORT BY GROUP
PERIOD: TERMINALSTUDY ID: ARGUS #418-027
STUDY NO: 060-063

SEX: FEMALE

| Animal ID | WBC THSN/CU MM | RBC MILL/CU MM | HGB GRAMS/DL | HCT % | MCV CU MICRONS | MCH PICO GRAMS | MCHC % | PLT THSN/CU MM |
|------------|-------------------|-------------------|-----------------|----------|-------------------|-------------------|-----------|-------------------|
| GROUP: 1-F | | | | | | | | |
| 17694 | 16.8 | 5.72 | 14.2 | 37.7 | 65.9 | 24.8 | 37.7 | 1575 |
| 17703 | 23.3 | 5.54 | 13.1 | 35.3 | 63.7 | 23.6 | 37.1 | 1648 |
| 17681 | 19.8 | 6.55 | 14.5 | 38.6 | 59.0 | 22.1 | 37.6 | 1583 |
| 17690 | 20.9 | 5.63 | 13.8 | 35.6 | 63.2 | 24.5 | 38.8 | 1329 |
| 17695 | CL | CL | CL | CL | CL | CL | CL | CL |
| MEAN | 20.2 | 5.86 | 13.9 | 36.8 | 63.0 | 23.8 | 37.8 | 1534 |
| SD | 2.70 | 0.466 | 0.61 | 1.61 | 2.88 | 1.21 | 0.72 | 140.4 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

| | | | | | | | | |
|------------|------|-------|------|------|------|------|------|-------|
| GROUP: 2-F | | | | | | | | |
| 17675 | 16.9 | 6.10 | 14.1 | 37.8 | 61.9 | 23.1 | 37.3 | 1381 |
| 17679 | 13.3 | 6.32 | 14.7 | 39.3 | 62.2 | 23.3 | 37.4 | 1259 |
| 17688 | 14.5 | 5.72 | 14.7 | 39.2 | 68.5 | 25.7 | 37.5 | 128 |
| 17698 | 16.8 | 6.09 | 14.2 | 37.9 | 62.3 | 23.3 | 37.5 | 1273 |
| 17684 | 12.8 | 5.79 | 13.6 | 36.7 | 63.3 | 23.5 | 37.1 | 692 |
| MEAN | 14.9 | 6.00 | 14.3 | 38.2 | 63.6 | 23.8 | 37.4 | 947 |
| SD | 1.92 | 0.246 | 0.46 | 1.08 | 2.77 | 1.08 | 0.17 | 531.0 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

| | | | | | | | | |
|------------|------|-------|------|------|------|------|------|-------|
| GROUP: 3-F | | | | | | | | |
| 17693 | 24.0 | 5.26 | 13.4 | 34.1 | 64.8 | 25.5 | 39.3 | 2292 |
| 17697 | 16.3 | 5.71 | 13.2 | 35.3 | 61.8 | 23.1 | 37.4 | 1874 |
| 17700 | 18.0 | 6.80 | 14.9 | 41.1 | 60.4 | 21.9 | 36.3 | 1375 |
| 17701 | 21.2 | 5.81 | 13.6 | 36.0 | 62.0 | 23.4 | 37.8 | 1554 |
| 17687 | 21.2 | 5.19 | 12.7 | 33.2 | 64.0 | 24.5 | 38.3 | 1101 |
| 17709 | 20.6 | 5.85 | 14.2 | 38.0 | 65.0 | 24.3 | 37.4 | 1393 |
| MEAN | 20.2 | 5.77 | 13.7 | 36.3 | 63.0 | 23.8 | 37.8 | 1598 |
| SD | 2.71 | 0.578 | 0.78 | 2.88 | 1.87 | 1.26 | 1.01 | 423.9 |
| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |

CL - Clotted

LABCAT HE4.43

22-MAY-2002

Study Report for Hematology

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: FEMALE

| Animal ID | WBC THSN/CU MM | RBC MILL/CU MM | HGB GRAMS/DL | HCT % | MCV CU MICRONS | MCH PICO GRAMS | MCHC % | PLT THSN/CU MM |
|------------|-------------------|-------------------|-----------------|----------|-------------------|-------------------|-----------|-------------------|
| GROUP: 4-F | | | | | | | | |
| 17685 | 21.6 | 5.91 | 13.2 | 35.3 | 59.8 | 22.3 | 37.4 | 1570 |
| 17689 | 18.6 | 5.57 | 12.9 | 33.8 | 60.6 | 23.2 | 38.2 | 1803 |
| 17692 | 25.4 | 5.37 | 12.5 | 30.8 | 57.4 | 23.3 | 40.6 | 1230 |
| 17691 | 20.8 | 6.21 | 14.1 | 36.5 | 58.8 | 22.7 | 38.6 | 1584 |
| MEAN | 21.6 | 5.76 | 13.2 | 34.1 | 59.2 | 22.9 | 38.7 | 1547 |
| SD | 2.83 | 0.371 | 0.68 | 2.46 | 1.38 | 0.46 | 1.36 | 236.6 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

Study Report for Hematology

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| Animal ID | PT seconds | APTT seconds | MPV CU MICRONS | NRBC COUNT | Lymphocyte THSN/CU MM | Segmented THSN/CU MM | Bands THSN/CU MM | Monocytes THSN/CU MM |
|------------|---------------|-----------------|-------------------|---------------|--------------------------|-------------------------|---------------------|-------------------------|
| GROUP: 1-M | | | | | | | | |
| 17608 | 14.3 | 25.1 | 9.0 | 0 | 11.2 | 2.0 | 0.0 | 0.1 |
| 17618 | 14.3 | 26.6 | 9.0 | 0 | 8.8 | 1.9 | 0.0 | 0.1 |
| 17630 | 14.0 | 25.3 | 9.6 | 0 | 10.3 | 2.0 | 0.0 | 0.1 |
| 17631 | 15.5 | 27.5 | 9.5 | 0 | 14.9 | 1.5 | 0.0 | 0.2 |
| 17639 | 13.8 | 22.5 | 8.9 | 0 | 17.8 | 2.2 | 0.0 | 0.0 |
| MEAN | 14.4 | 25.4 | 9.2 | 0 | 12.6 | 1.9 | 0.0 | 0.1 |
| SD | 0.66 | 1.89 | 0.32 | 0.0 | 3.67 | 0.26 | 0.00 | 0.07 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

| | | | | | | | | |
|------------|------|------|------|-----|------|------|------|------|
| GROUP: 2-M | | | | | | | | |
| 17634 | 13.4 | 22.4 | 9.6 | 0 | 17.0 | 1.9 | 0.0 | 0.0 |
| 17635 | 14.3 | 27.9 | 9.5 | 0 | 12.7 | 4.1 | 0.0 | 0.2 |
| 17638 | 13.3 | 24.7 | 9.3 | 0 | 13.9 | 2.1 | 0.0 | 0.2 |
| 17642 | 13.7 | 27.0 | 9.1 | 0 | 14.6 | 2.9 | 0.0 | 0.5 |
| 17643 | 13.7 | 27.6 | 11.1 | 0 | 20.8 | 2.9 | 0.0 | 0.0 |
| MEAN | 13.7 | 25.9 | 9.7 | 0 | 15.8 | 2.8 | 0.0 | 0.2 |
| SD | 0.39 | 2.33 | 0.79 | 0.0 | 3.21 | 0.87 | 0.00 | 0.20 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

| | | | | | | | | |
|------------|------|------|------|-----|------|------|------|------|
| GROUP: 3-M | | | | | | | | |
| 17620 | 14.4 | 26.1 | 8.9 | 0 | 11.4 | 2.0 | 0.0 | 0.0 |
| 17623 | 14.1 | 27.9 | 11.0 | 0 | 18.2 | 2.3 | 0.0 | 0.0 |
| 17627 | 14.6 | 24.2 | 8.7 | 0 | 10.9 | 1.8 | 0.0 | 0.0 |
| 17628 | 14.4 | 28.8 | 8.7 | 0 | 15.0 | 1.2 | 0.0 | 0.2 |
| 17633 | 15.9 | 23.9 | 10.1 | 0 | 10.9 | 1.7 | 0.0 | 0.1 |
| MEAN | 14.7 | 26.2 | 9.5 | 0 | 13.3 | 1.8 | 0.0 | 0.1 |
| SD | 0.70 | 2.18 | 1.03 | 0.0 | 3.24 | 0.41 | 0.00 | 0.09 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Study Report for Hematology

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| Animal ID | PT seconds | APTT seconds | MPV CU MICRONS | NRBC COUNT | Lymphocyte THSN/CU MM | Segmented THSN/CU MM | Bands THSN/CU MM | Monocytes THSN/CU MM |
|------------|---------------|-----------------|-------------------|---------------|--------------------------|-------------------------|---------------------|-------------------------|
| GROUP: 4-M | | | | | | | | |
| 17621 | 16.0 | 30.7 | 9.5 | 0 | 15.8 | 1.0 | 0.0 | 0.3 |
| 17622 | 13.5 | 26.1 | 8.4 | 0 | 8.7 | 2.0 | 0.0 | 0.0 |
| 17625 | 14.9 | 27.3 | 9.5 | 0 | 13.1 | 1.5 | 0.0 | 0.0 |
| 17629 | 14.0 | 24.0 | 9.8 | 0 | 19.6 | 2.5 | 0.0 | 0.0 |
| 17636 | 14.4 | 25.6 | 8.4 | 0 | 13.1 | 18.2 | 0.0 | 0.0 |
| MEAN | 14.6 | 26.7 | 9.1 | 0 | 14.1 | 5.0 | 0.0 | 0.1 |
| SD | 0.96 | 2.51 | 0.67 | 0.0 | 4.01 | 7.38 | 0.00 | 0.13 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Study Report for Hematology

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: FEMALE

| Animal ID | PT seconds | APTT seconds | MPV CU MICRONS | NRBC COUNT | Lymphocyte THSN/CU MM | Segmented THSN/CU MM | Bands THSN/CU MM | Monocytes THSN/CU MM |
|------------|---------------|-----------------|-------------------|---------------|--------------------------|-------------------------|---------------------|-------------------------|
| GROUP: 1-F | | | | | | | | |
| 17694 | 12.8 | 18.2 | 7.0 | 0 | 13.6 | 2.7 | 0.0 | 0.3 |
| 17703 | 13.3 | 24.0 | 7.0 | 0 | 17.0 | 5.8 | 0.0 | 0.2 |
| 17681 | 13.9 | 22.2 | 7.9 | 0 | 15.2 | 3.8 | 0.0 | 0.8 |
| 17690 | 13.5 | 21.6 | 8.9 | 0 | 17.6 | 3.1 | 0.0 | 0.0 |
| 17695 | 13.2 | 19.3 | CL | CL | -- | -- | -- | -- |
| MEAN | 13.3 | 21.1 | 7.7 | 0 | 15.9 | 3.9 | 0.0 | 0.3 |
| SD | 0.40 | 2.32 | 0.91 | 0.0 | 1.81 | 1.38 | 0.00 | 0.34 |
| N | 5 | 5 | 4 | 4 | 4 | 4 | 4 | 4 |
| GROUP: 2-F | | | | | | | | |
| 17675 | 12.8 | 19.3 | 9.2 | 0 | 14.4 | 2.2 | 0.0 | 0.3 |
| 17679 | 13.6 | 15.5 | 7.8 | 0 | 10.6 | 2.7 | 0.0 | 0.0 |
| 17688 | 13.4 | 18.2 | 12.3 | 0 | 11.9 | 2.6 | 0.0 | 0.0 |
| 17698 | 13.2 | 19.9 | 7.5 | 0 | 15.6 | 0.8 | 0.0 | 0.3 |
| 17684 | CL | CL | 7.3 | 0 | 10.6 | 1.9 | 0.0 | 0.3 |
| MEAN | 13.3 | 18.2 | 8.8 | 0 | 12.6 | 2.0 | 0.0 | 0.2 |
| SD | 0.34 | 1.95 | 2.08 | 0.0 | 2.28 | 0.76 | 0.00 | 0.16 |
| N | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 5 |
| GROUP: 3-F | | | | | | | | |
| 17693 | 13.3 | 21.5 | 6.8 | 0 | 17.8 | 5.5 | 0.0 | 0.7 |
| 17697 | 13.2 | 19.7 | 7.6 | 0 | 13.7 | 2.6 | 0.0 | 0.0 |
| 17700 | 13.2 | 23.6 | 8.4 | 0 | 12.2 | 5.4 | 0.0 | 0.0 |
| 17701 | 12.9 | 17.7 | 7.3 | 0 | 18.7 | 2.3 | 0.0 | 0.2 |
| 17687 | 13.3 | 27.3 | 8.2 | 0 | 16.1 | 5.1 | 0.0 | 0.0 |
| 17709 | CL | CL | 9.7 | 0 | 14.6 | 5.6 | 0.0 | 0.2 |
| MEAN | 13.2 | 22.0 | 8.0 | 0 | 15.5 | 4.4 | 0.0 | 0.2 |
| SD | 0.16 | 3.70 | 1.02 | 0.0 | 2.48 | 1.54 | 0.00 | 0.27 |
| N | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 |

(--) - Data Unavailable

CL - Clotted

Study Report for Hematology

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: FEMALE

| Animal ID | PT seconds | APTT seconds | MPV CU MICRONS | NRBC COUNT | Lymphocyte THSN/CU MM | Segmented THSN/CU MM | Bands THSN/CU MM | Monocytes THSN/CU MM |
|------------|---------------|-----------------|-------------------|---------------|--------------------------|-------------------------|---------------------|-------------------------|
| GROUP: 4-F | | | | | | | | |
| 17685 | 13.0 | 25.3 | 9.0 | 0 | 13.0 | 6.9 | 0.2 | 1.3 |
| 17689 | 13.1 | 14.9 | 7.7 | 0 | 13.6 | 3.3 | 0.2 | 1.5 |
| 17692 | 13.5 | 20.8 | 7.9 | 0 | 22.1 | 2.5 | 0.0 | 0.5 |
| 17691 | 13.3 | 18.2 | 8.0 | 0 | 16.8 | 3.5 | 0.0 | 0.4 |
| MEAN | 13.2 | 19.8 | 8.2 | 0 | 16.4 | 4.1 | 0.1 | 0.9 |
| SD | 0.22 | 4.39 | 0.58 | 0.0 | 4.17 | 1.95 | 0.12 | 0.56 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

Study Report for Hematology

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| Animal ID | Eosinophil THSN/CU MM | Basophils THSN/CU MM | Abnormal L THSN/CU MM | Other THSN/CU MM |
|------------|--------------------------|-------------------------|--------------------------|---------------------|
| GROUP: 1-M | | | | |
| 17608 | 0.1 | 0.0 | 0.0 | 0.0 |
| 17618 | 0.1 | 0.0 | 0.0 | 0.0 |
| 17630 | 0.1 | 0.0 | 0.0 | 0.0 |
| 17631 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17639 | 0.0 | 0.0 | 0.0 | 0.0 |
| MEAN | 0.1 | 0.0 | 0.0 | 0.0 |
| SD | 0.05 | 0.00 | 0.00 | 0.00 |
| N | 5 | 5 | 5 | 5 |

| | | | | |
|------------|------|------|------|------|
| GROUP: 2-M | | | | |
| 17634 | 0.2 | 0.0 | 0.0 | 0.0 |
| 17635 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17638 | 0.3 | 0.0 | 0.0 | 0.0 |
| 17642 | 0.2 | 0.0 | 0.0 | 0.0 |
| 17643 | 0.2 | 0.0 | 0.0 | 0.0 |
| MEAN | 0.2 | 0.0 | 0.0 | 0.0 |
| SD | 0.11 | 0.00 | 0.00 | 0.00 |
| N | 5 | 5 | 5 | 5 |

| | | | | |
|------------|------|------|------|------|
| GROUP: 3-M | | | | |
| 17620 | 0.1 | 0.0 | 0.0 | 0.0 |
| 17623 | 0.2 | 0.0 | 0.0 | 0.0 |
| 17627 | 0.4 | 0.0 | 0.0 | 0.0 |
| 17628 | 0.2 | 0.0 | 0.0 | 0.0 |
| 17633 | 0.0 | 0.0 | 0.0 | 0.0 |
| MEAN | 0.2 | 0.0 | 0.0 | 0.0 |
| SD | 0.15 | 0.00 | 0.00 | 0.00 |
| N | 5 | 5 | 5 | 5 |

Study Report for Hematology

INDIVIDUAL ANIMAL REPORT BY GROUP
PERIOD: TERMINALSTUDY ID: ARGUS #418-027
STUDY NO: 060-063

SEX: MALE

| Animal ID | Eosinophil THSN/CU MM | Basophils THSN/CU MM | Abnormal L THSN/CU MM | Other THSN/CU MM |
|------------|--------------------------|-------------------------|--------------------------|---------------------|
| GROUP: 4-M | | | | |
| 17621 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17622 | 0.3 | 0.0 | 0.0 | 0.0 |
| 17625 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17629 | 0.2 | 0.0 | 0.0 | 0.0 |
| 17636 | 0.0 | 0.0 | 0.0 | 0.0 |
| MEAN | 0.1 | 0.0 | 0.0 | 0.0 |
| SD | 0.14 | 0.00 | 0.00 | 0.00 |
| N | 5 | 5 | 5 | 5 |

Study Report for Hematology

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: FEMALE

| Animal ID | Eosinophil THSN/CU MM | Basophils THSN/CU MM | Abnormal L THSN/CU MM | Other THSN/CU MM |
|------------|--------------------------|-------------------------|--------------------------|---------------------|
| GROUP: 1-F | | | | |
| 17694 | 0.0 | 0.0 | 0.2 | 0.0 |
| 17703 | 0.2 | 0.0 | 0.0 | 0.0 |
| 17681 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17690 | 0.2 | 0.0 | 0.0 | 0.0 |
| 17695 | -- | -- | -- | -- |
| MEAN | 0.1 | 0.0 | 0.1 | 0.0 |
| SD | 0.12 | 0.00 | 0.10 | 0.00 |
| N | 4 | 4 | 4 | 4 |

| | | | | |
|------------|------|------|------|------|
| GROUP: 2-F | | | | |
| 17675 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17679 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17688 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17698 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17684 | 0.0 | 0.0 | 0.0 | 0.0 |
| MEAN | 0.0 | 0.0 | 0.0 | 0.0 |
| SD | 0.00 | 0.00 | 0.00 | 0.00 |
| N | 5 | 5 | 5 | 5 |

| | | | | |
|------------|------|------|------|------|
| GROUP: 3-F | | | | |
| 17693 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17697 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17700 | 0.4 | 0.0 | 0.0 | 0.0 |
| 17701 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17687 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17709 | 0.2 | 0.0 | 0.0 | 0.0 |
| MEAN | 0.1 | 0.0 | 0.0 | 0.0 |
| SD | 0.17 | 0.00 | 0.00 | 0.00 |
| N | 6 | 6 | 6 | 6 |

(--) - Data Unavailable

Study Report for Hematology

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: FEMALE

| Animal ID | Eosinophil THSN/CU MM | Basophils THSN/CU MM | Abnormal L THSN/CU MM | Other THSN/CU MM |
|------------|--------------------------|-------------------------|--------------------------|---------------------|
| GROUP: 4-F | | | | |
| 17685 | 0.0 | 0.0 | 0.2 | 0.0 |
| 17689 | 0.0 | 0.0 | 0.0 | 0.0 |
| 17692 | 0.0 | 0.0 | 0.3 | 0.0 |
| 17691 | 0.0 | 0.0 | 0.0 | 0.0 |
| MEAN | 0.0 | 0.0 | 0.1 | 0.0 |
| SD | 0.00 | 0.00 | 0.15 | 0.00 |
| N | 4 | 4 | 4 | 4 |

Study Report for Hematology

SUMMARY REPORT
PERIOD: TERMINAL

STUDY ID: ARGUS #418-027
STUDY NO: 060-063

SEX: MALE

| TEST(s): | WBC | RBC | HGB | HCT | MCV | MCH | MCHC | PLT | PT |
|------------|------------|------------|----------|------|---------|------------|--------------|-------|---------|
| UNITS: | THSN/CU MM | MILL/CU MM | GRAMS/DL | % CU | MICRONS | PICO GRAMS | % THSN/CU MM | MM | seconds |
| Group: 1-M | | | | | | | | | |
| MEAN | 14.7 | 7.55 | 15.8 | 43.7 | 57.9 | 21.0 | 36.3 | 1197 | 14.4 |
| SD | 3.61 | 0.493 | 0.26 | 1.82 | 2.09 | 1.15 | 0.97 | 122.5 | 0.66 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group: 2-M | | | | | | | | | |
| MEAN | 18.9 | 7.56 | 15.6 | 42.5 | 56.3 | 20.7 | 36.8 | 1172 | 13.7 |
| SD | 2.96 | 0.448 | 0.71 | 2.12 | 0.84 | 0.42 | 0.35 | 54.0 | 0.39 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group: 3-M | | | | | | | | | |
| MEAN | 15.3 | 7.27 | 15.2 | 41.4 | 56.9 | 20.9 | 36.6 | 1218 | 14.7 |
| SD | 3.36 | 0.291 | 0.40 | 1.30 | 1.94 | 0.70 | 1.17 | 190.7 | 0.70 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group: 4-M | | | | | | | | | |
| MEAN | 19.3 | 7.17 | 15.1 | 40.5 | 56.5 | 21.1 | 37.4 | 1283 | 14.6 |
| SD | 7.90 | 0.270 | 0.65 | 1.88 | 1.44 | 0.88 | 1.25 | 138.9 | 0.96 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Study Report for Hematology

SUMMARY REPORT
PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| TEST(s): | APTT | MPV | NRBC | Lymphocyte | Segmented | Bands | Monocytes | Eosinophil | Basophils |
|----------|---------|------------|-------|------------|------------|------------|------------|------------|------------|
| UNITS: | seconds | CU MICRONS | COUNT | THSN/CU MM | THSN/CU MM | THSN/CU MM | THSN/CU MM | THSN/CU MM | THSN/CU MM |

Group: 1-M

| | | | | | | | | | |
|------|------|------|-----|------|------|------|------|------|------|
| MEAN | 25.4 | 9.2 | 0 | 12.6 | 1.9 | 0.0 | 0.1 | 0.1 | 0.0 |
| SD | 1.89 | 0.32 | 0.0 | 3.67 | 0.26 | 0.00 | 0.07 | 0.05 | 0.00 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Group: 2-M

| | | | | | | | | | |
|------|------|------|-----|------|------|------|------|------|------|
| MEAN | 25.9 | 9.7 | 0 | 15.8 | 2.8 | 0.0 | 0.2 | 0.2 | 0.0 |
| SD | 2.33 | 0.79 | 0.0 | 3.21 | 0.87 | 0.00 | 0.20 | 0.11 | 0.00 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Group: 3-M

| | | | | | | | | | |
|------|------|------|-----|------|------|------|------|------|------|
| MEAN | 26.2 | 9.5 | 0 | 13.3 | 1.8 | 0.0 | 0.1 | 0.2 | 0.0 |
| SD | 2.18 | 1.03 | 0.0 | 3.24 | 0.41 | 0.00 | 0.09 | 0.15 | 0.00 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Group: 4-M

| | | | | | | | | | |
|------|------|------|-----|------|------|------|------|------|------|
| MEAN | 26.7 | 9.1 | 0 | 14.1 | 5.0 | 0.0 | 0.1 | 0.1 | 0.0 |
| SD | 2.51 | 0.67 | 0.0 | 4.01 | 7.38 | 0.00 | 0.13 | 0.14 | 0.00 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Study Report for Hematology

SUMMARY REPORT
PERIOD: TERMINAL

STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| TEST(s): | Abnormal L | Other |
|----------|------------|------------|
| UNITS: | THSN/CU MM | THSN/CU MM |

Group: 1-M

| | | |
|------|------|------|
| MEAN | 0.0 | 0.0 |
| SD | 0.00 | 0.00 |
| N | 5 | 5 |

Group: 2-M

| | | |
|------|------|------|
| MEAN | 0.0 | 0.0 |
| SD | 0.00 | 0.00 |
| N | 5 | 5 |

Group: 3-M

| | | |
|------|------|------|
| MEAN | 0.0 | 0.0 |
| SD | 0.00 | 0.00 |
| N | 5 | 5 |

Group: 4-M

| | | |
|------|------|------|
| MEAN | 0.0 | 0.0 |
| SD | 0.00 | 0.00 |
| N | 5 | 5 |

Study Report for Hematology

SUMMARY REPORT
PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: FEMALE

| TEST(s): | WBC | RBC | HGB | HCT | MCV | MCH | MCHC | PLT | PT |
|------------|------------|------------|----------|------|---------|------------|--------------|--------------|---------|
| UNITS: | THSN/CU MM | MILL/CU MM | GRAMS/DL | % CU | MICRONS | PICO GRAMS | % THSN/CU MM | % THSN/CU MM | seconds |
| Group: 1-F | | | | | | | | | |
| MEAN | 20.2 | 5.86 | 13.9 | 36.8 | 63.0 | 23.8 | 37.8 | 1534 | 13.3 |
| SD | 2.70 | 0.466 | 0.61 | 1.61 | 2.88 | 1.21 | 0.72 | 140.4 | 0.40 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 5 |
| Group: 2-F | | | | | | | | | |
| MEAN | 14.9 | 6.00 | 14.3 | 38.2 | 63.6 | 23.8 | 37.4 | 947 | 13.3 |
| SD | 1.92 | 0.246 | 0.46 | 1.08 | 2.77 | 1.08 | 0.17 | 531.0 | 0.34 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| Group: 3-F | | | | | | | | | |
| MEAN | 20.2 | 5.77 | 13.7 | 36.3 | 63.0 | 23.8 | 37.8 | 1598 | 13.2 |
| SD | 2.71 | 0.578 | 0.78 | 2.88 | 1.87 | 1.26 | 1.01 | 423.9 | 0.16 |
| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 5 |
| Group: 4-F | | | | | | | | | |
| MEAN | 21.6 | 5.76 | 13.2 | 34.1 | 59.2 | 22.9 | 38.7 | 1547 | 13.2 |
| SD | 2.83 | 0.371 | 0.68 | 2.46 | 1.38 | 0.46 | 1.36 | 236.6 | 0.22 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

Study Report for Hematology

SUMMARY REPORT
PERIOD: TERMINAL

STUDY ID: ARGUS #418-027
STUDY NO: 060-063

SEX: FEMALE

| TEST(s): | APTT | MPV | NRBC | Lymphocyte | Segmented | Bands | Monocytes | Eosinophil | Basophils |
|------------|---------|------------|-------|------------|------------|------------|------------|------------|------------|
| UNITS: | seconds | CU MICRONS | COUNT | THSN/CU | MM THSN/CU | MM THSN/CU | MM THSN/CU | MM THSN/CU | MM THSN/CU |
| Group: 1-F | | | | | | | | | |
| MEAN | 21.1 | 7.7 | 0 | 15.9 | 3.9 | 0.0 | 0.3 | 0.1 | 0.0 |
| SD | 2.32 | 0.91 | 0.0 | 1.81 | 1.38 | 0.00 | 0.34 | 0.12 | 0.00 |
| N | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Group: 2-F | | | | | | | | | |
| MEAN | 18.2 | 8.8 | 0 | 12.6 | 2.0 | 0.0 | 0.2 | 0.0 | 0.0 |
| SD | 1.95 | 2.08 | 0.0 | 2.28 | 0.76 | 0.00 | 0.16 | 0.00 | 0.00 |
| N | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group: 3-F | | | | | | | | | |
| MEAN | 22.0 | 8.0 | 0 | 15.5 | 4.4 | 0.0 | 0.2 | 0.1 | 0.0 |
| SD | 3.70 | 1.02 | 0.0 | 2.48 | 1.54 | 0.00 | 0.27 | 0.17 | 0.00 |
| N | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Group: 4-F | | | | | | | | | |
| MEAN | 19.8 | 8.2 | 0 | 16.4 | 4.1 | 0.1 | 0.9 | 0.0 | 0.0 |
| SD | 4.39 | 0.58 | 0.0 | 4.17 | 1.95 | 0.12 | 0.56 | 0.00 | 0.00 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

Study Report for Hematology

SUMMARY REPORT
PERIOD: TERMINAL

STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: FEMALE

| TEST(s): | Abnormal L | Other |
|----------|------------|------------|
| UNITS: | THSN/CU MM | THSN/CU MM |

Group: 1-F

| | | |
|------|------|------|
| MEAN | 0.1 | 0.0 |
| SD | 0.10 | 0.00 |
| N | 4 | 4 |

Group: 2-F

| | | |
|------|------|------|
| MEAN | 0.0 | 0.0 |
| SD | 0.00 | 0.00 |
| N | 5 | 5 |

Group: 3-F

| | | |
|------|------|------|
| MEAN | 0.0 | 0.0 |
| SD | 0.00 | 0.00 |
| N | 6 | 6 |

Group: 4-F

| | | |
|------|------|------|
| MEAN | 0.1 | 0.0 |
| SD | 0.15 | 0.00 |
| N | 4 | 4 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 1-M

SEX: MALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17608 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 83 | 11.2 |
| | Segmented Neutrophils | 15 | 2.0 |
| | Bands | 0 | 0.0 |
| | Monocytes | 1 | 0.1 |
| | Eosinophils | 1 | 0.1 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 13.5 |
| 17618 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 81 | 8.8 |
| | Segmented Neutrophils | 17 | 1.9 |
| | Bands | 0 | 0.0 |
| | Monocytes | 1 | 0.1 |
| | Eosinophils | 1 | 0.1 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 10.9 |
| 17630 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 82 | 10.3 |
| | Segmented Neutrophils | 16 | 2.0 |
| | Bands | 0 | 0.0 |
| | Monocytes | 1 | 0.1 |
| | Eosinophils | 1 | 0.1 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 12.6 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 1-M

SEX: MALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17631 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 90 | 14.9 |
| | Segmented Neutrophils | 9 | 1.5 |
| | Bands | 0 | 0.0 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 16.6 |
| 17639 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 89 | 17.8 |
| | Segmented Neutrophils | 11 | 2.2 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 20.0 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 2-M

SEX: MALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17634 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 89 | 17.0 |
| | Segmented Neutrophils | 10 | 1.9 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 19.1 |
| 17635 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 75 | 12.7 |
| | Segmented Neutrophils | 24 | 4.1 |
| | Bands | 0 | 0.0 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 16.9 |
| 17638 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 84 | 13.9 |
| | Segmented Neutrophils | 13 | 2.1 |
| | Bands | 0 | 0.0 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 2 | 0.3 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 16.5 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 2-M

SEX: MALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17642 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 80 | 14.6 |
| | Segmented Neutrophils | 16 | 2.9 |
| | Bands | 0 | 0.0 |
| | Monocytes | 3 | 0.5 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 18.3 |
| 17643 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 87 | 20.8 |
| | Segmented Neutrophils | 12 | 2.9 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 23.9 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 3-M

SEX: MALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17620 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 84 | 11.4 |
| | Segmented Neutrophils | 15 | 2.0 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 1 | 0.1 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 13.6 |
| 17623 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 88 | 18.2 |
| | Segmented Neutrophils | 11 | 2.3 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 20.7 |
| 17627 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 83 | 10.9 |
| | Segmented Neutrophils | 14 | 1.8 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 3 | 0.4 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 13.1 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 3-M

SEX: MALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17628 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 91 | 15.0 |
| | Segmented Neutrophils | 7 | 1.2 |
| | Bands | 0 | 0.0 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 16.5 |
| 17633 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 86 | 10.9 |
| | Segmented Neutrophils | 13 | 1.7 |
| | Bands | 0 | 0.0 |
| | Monocytes | 1 | 0.1 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 12.7 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 4-M

SEX: MALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17621 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 92 | 15.8 |
| | Segmented Neutrophils | 6 | 1.0 |
| | Bands | 0 | 0.0 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 17.2 |
| 17622 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 79 | 8.7 |
| | Segmented Neutrophils | 18 | 2.0 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 3 | 0.3 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 11.0 |
| 17625 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 90 | 13.1 |
| | Segmented Neutrophils | 10 | 1.5 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 14.5 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 4-M

SEX: MALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17629 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 88 | 19.6 |
| | Segmented Neutrophils | 11 | 2.5 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 22.3 |
| 17636 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 42 | 13.1 |
| | Segmented Neutrophils | 58 | 18.2 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 31.3 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 1-F

SEX: FEMALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17694 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 81 | 13.6 |
| | Segmented Neutrophils | 16 | 2.7 |
| | Bands | 0 | 0.0 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 1 | 0.2 |
| | Other | 0 | 0.0 |
| | WBC | | 16.8 |
| 17703 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 73 | 17.0 |
| | Segmented Neutrophils | 25 | 5.8 |
| | Bands | 0 | 0.0 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 23.3 |
| 17681 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 77 | 15.2 |
| | Segmented Neutrophils | 19 | 3.8 |
| | Bands | 0 | 0.0 |
| | Monocytes | 4 | 0.8 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 19.8 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 1-F

SEX: FEMALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17690 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 84 | 17.6 |
| | Segmented Neutrophils | 15 | 3.1 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 20.9 |
| 17695 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 0 | -- |
| | Segmented Neutrophils | 0 | -- |
| | Bands | 0 | -- |
| | Monocytes | 0 | -- |
| | Eosinophils | 0 | -- |
| | Basophils | 0 | -- |
| | Abnormal Lymphocytes | 0 | -- |
| | Other | 0 | -- |
| | WBC | | -- |

(--) - Data Unavailable

LABCAT HE4.43

22-MAY-2002

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 2-F

SEX: FEMALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17675 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 85 | 14.4 |
| | Segmented Neutrophils | 13 | 2.2 |
| | Bands | 0 | 0.0 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 16.9 |
| 17679 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 80 | 10.6 |
| | Segmented Neutrophils | 20 | 2.7 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 13.3 |
| 17688 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 82 | 11.9 |
| | Segmented Neutrophils | 18 | 2.6 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 14.5 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 2-F

SEX: FEMALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17698 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 93 | 15.6 |
| | Segmented Neutrophils | 5 | 0.8 |
| | Bands | 0 | 0.0 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 16.8 |
| 17684 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 83 | 10.6 |
| | Segmented Neutrophils | 15 | 1.9 |
| | Bands | 0 | 0.0 |
| | Monocytes | 2 | 0.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 12.8 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 3-F

SEX: FEMALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17693 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 74 | 17.8 |
| | Segmented Neutrophils | 23 | 5.5 |
| | Bands | 0 | 0.0 |
| | Monocytes | 3 | 0.7 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 24.0 |
| 17697 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 84 | 13.7 |
| | Segmented Neutrophils | 16 | 2.6 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 16.3 |
| 17700 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 68 | 12.2 |
| | Segmented Neutrophils | 30 | 5.4 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 2 | 0.4 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 18.0 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 3-F

SEX: FEMALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17701 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 88 | 18.7 |
| | Segmented Neutrophils | 11 | 2.3 |
| | Bands | 0 | 0.0 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 21.2 |
| 17687 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 76 | 16.1 |
| | Segmented Neutrophils | 24 | 5.1 |
| | Bands | 0 | 0.0 |
| | Monocytes | 0 | 0.0 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 21.2 |
| 17709 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 71 | 14.6 |
| | Segmented Neutrophils | 27 | 5.6 |
| | Bands | 0 | 0.0 |
| | Monocytes | 1 | 0.2 |
| | Eosinophils | 1 | 0.2 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 20.6 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 4-F

SEX: FEMALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17685 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 60 | 13.0 |
| | Segmented Neutrophils | 32 | 6.9 |
| | Bands | 1 | 0.2 |
| | Monocytes | 6 | 1.3 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 1 | 0.2 |
| | Other | 0 | 0.0 |
| | WBC | | 21.6 |
| 17689 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 73 | 13.6 |
| | Segmented Neutrophils | 18 | 3.3 |
| | Bands | 1 | 0.2 |
| | Monocytes | 8 | 1.5 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 18.6 |
| 17692 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 87 | 22.1 |
| | Segmented Neutrophils | 10 | 2.5 |
| | Bands | 0 | 0.0 |
| | Monocytes | 2 | 0.5 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 1 | 0.3 |
| | Other | 0 | 0.0 |
| | WBC | | 25.4 |

Study Report for Hematology

WHITE DIFFERENTIAL DATA

STUDY ID: ARGUS #418-027

STUDY NO: 060-063

GROUP: 4-F

SEX: FEMALE

| Animal ID | | TERMINAL | |
|-----------|-----------------------|----------|------|
| | | CNT | ABS |
| 17691 | Nucleated Red Cells | 0 | |
| | Lymphocytes | 81 | 16.8 |
| | Segmented Neutrophils | 17 | 3.5 |
| | Bands | 0 | 0.0 |
| | Monocytes | 2 | 0.4 |
| | Eosinophils | 0 | 0.0 |
| | Basophils | 0 | 0.0 |
| | Abnormal Lymphocytes | 0 | 0.0 |
| | Other | 0 | 0.0 |
| | WBC | | 20.8 |

Study Report for Clinical Chemistry

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| Animal ID | TP g/dL | ALB g/dL | GLU mg/dL | CHOL mg/dL | T-BIL mg/dL | BUN mg/dL | CREAT mg/dL | ALT U/L |
|------------|------------|-------------|--------------|---------------|----------------|--------------|----------------|------------|
| GROUP: 1-M | | | | | | | | |
| 17608 | 6.6 | 4.2 | 156 | 71 | 0.1 | 13 | 0.3 | 41 |
| 17618 | 5.9 | 3.9 | 143 | 62 | 0.1 | 10 | 0.3 | 38 |
| 17630 | 6.5 | 4.1 | 163 | 52 | 0.1 | 10 | 0.2 | 35 |
| 17631 | 6.1 | 3.8 | 173 | 39 | 0.1 | 13 | 0.2 | 36 |
| 17639 | 6.2 | 4.1 | 161 | 57 | 0.1 | 13 | 0.3 | 38 |
| MEAN | 6.3 | 4.0 | 159 | 56 | 0.1 | 12 | 0.3 | 38 |
| SD | 0.29 | 0.16 | 11.0 | 11.9 | 0.00 | 1.6 | 0.05 | 2.3 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

| | | | | | | | | |
|------------|------|------|------|-----|------|-----|------|-----|
| GROUP: 2-M | | | | | | | | |
| 17634 | 6.2 | 3.9 | 180 | 51 | 0.1 | 16 | 0.3 | 45 |
| 17635 | 6.7 | 4.1 | 188 | 61 | 0.1 | 11 | 0.3 | 42 |
| 17638 | 6.7 | 4.3 | 185 | 50 | 0.1 | 13 | 0.3 | 42 |
| 17642 | 6.0 | 4.0 | 150 | 51 | 0.1 | 12 | 0.2 | 42 |
| 17643 | 6.1 | 4.1 | 217 | 47 | 0.1 | 16 | 0.3 | 45 |
| MEAN | 6.3 | 4.1 | 184 | 52 | 0.1 | 14 | 0.3 | 43 |
| SD | 0.34 | 0.15 | 23.9 | 5.3 | 0.00 | 2.3 | 0.04 | 1.6 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

| | | | | | | | | |
|------------|------|------|------|-----|------|-----|------|-----|
| GROUP: 3-M | | | | | | | | |
| 17620 | 6.1 | 4.2 | 154 | 43 | 0.1 | 11 | 0.3 | 50 |
| 17623 | 6.4 | 4.1 | 178 | 47 | 0.1 | 12 | 0.4 | 45 |
| 17627 | 5.8 | 3.7 | 153 | 49 | 0.1 | 14 | 0.3 | 50 |
| 17628 | 6.5 | 4.2 | 145 | 48 | 0.1 | 14 | 0.3 | 48 |
| 17633 | 6.0 | 4.1 | 151 | 58 | 0.1 | 12 | 0.3 | 40 |
| MEAN | 6.2 | 4.1 | 156 | 49 | 0.1 | 13 | 0.3 | 47 |
| SD | 0.29 | 0.21 | 12.7 | 5.5 | 0.00 | 1.3 | 0.04 | 4.2 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Study Report for Clinical Chemistry

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| Animal ID | TP g/dL | ALB g/dL | GLU mg/dL | CHOL mg/dL | T-BIL mg/dL | BUN mg/dL | CREAT mg/dL | ALT U/L |
|------------|------------|-------------|--------------|---------------|----------------|--------------|----------------|------------|
| GROUP: 4-M | | | | | | | | |
| 17621 | 6.5 | 4.4 | 117 | 18 | 0.1 | 14 | 0.4 | 38 |
| 17622 | 6.1 | 4.3 | 90 | 32 | 0.1 | 16 | 0.4 | 51 |
| 17625 | 6.2 | 4.4 | 119 | 39 | 0.1 | 9 | 0.2 | 54 |
| 17629 | 6.4 | 4.3 | 106 | 33 | 0.1 | 21 | 0.4 | 45 |
| 17636 | 6.2 | 3.4 | 110 | 24 | 0.1 | 24 | 0.4 | 52 |
| MEAN | 6.3 | 4.2 | 108 | 29 | 0.1 | 17 | 0.4 | 48 |
| SD | 0.16 | 0.43 | 11.5 | 8.2 | 0.00 | 5.9 | 0.09 | 6.5 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Study Report for Clinical Chemistry

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: FEMALE

| Animal ID | TP g/dL | ALB g/dL | GLU mg/dL | CHOL mg/dL | T-BIL mg/dL | BUN mg/dL | CREAT mg/dL | ALT U/L |
|------------|------------|-------------|--------------|---------------|----------------|--------------|----------------|------------|
| GROUP: 1-F | | | | | | | | |
| 17694 | 5.8 | 3.7 | 91 | 43 | 0.1 | 24 | 0.3 | 58 |
| 17695 | 6.5 | 4.3 | 130 | 48 | 0.1 | 16 | 0.4 | 48 |
| 17703 | 6.7 | 4.2 | 111 | 63 | 0.1 | 23 | 0.4 | 62 |
| 17681 | 7.0 | 4.5 | 164 | 66 | 0.2 | 17 | 0.4 | 68 |
| 17690 | 6.3 | 4.1 | 127 | 40 | 0.2 | 21 | 0.4 | 62 |
| MEAN | 6.5 | 4.2 | 125 | 52 | 0.1 | 20 | 0.4 | 60 |
| SD | 0.45 | 0.30 | 26.9 | 11.8 | 0.05 | 3.6 | 0.04 | 7.4 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

| | | | | | | | | |
|------------|------|------|-----|-----|------|-----|------|------|
| GROUP: 2-F | | | | | | | | |
| 17675 | 7.3 | 4.5 | 138 | 71 | 0.2 | 19 | 0.4 | 60 |
| 17679 | 6.3 | 4.2 | 135 | 58 | 0.1 | 17 | 0.2 | 43 |
| 17684 | 5.7 | 3.8 | 144 | 65 | 0.1 | 14 | 0.3 | 77 |
| 17688 | 6.4 | 4.1 | 129 | 51 | 0.1 | 23 | 0.4 | 49 |
| 17698 | 6.9 | 4.2 | 145 | 61 | 0.1 | 17 | 0.4 | 55 |
| MEAN | 6.5 | 4.2 | 138 | 61 | 0.1 | 18 | 0.3 | 57 |
| SD | 0.61 | 0.25 | 6.6 | 7.5 | 0.04 | 3.3 | 0.09 | 13.0 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

| | | | | | | | | |
|------------|------|------|------|------|------|-----|------|------|
| GROUP: 3-F | | | | | | | | |
| 17693 | 6.2 | 4.0 | 98 | 46 | 0.1 | 22 | 0.3 | 47 |
| 17687 | 6.5 | 4.3 | 162 | 72 | 0.1 | 13 | 0.3 | 83 |
| 17697 | 6.0 | 3.8 | 113 | 57 | 0.1 | 19 | 0.4 | 52 |
| 17700 | 6.9 | 4.5 | 145 | 73 | 0.1 | 18 | 0.3 | 70 |
| 17701 | 6.2 | 4.1 | 93 | 61 | 0.1 | 21 | 0.3 | 55 |
| 17709 | 5.6 | 3.6 | 135 | 36 | 0.1 | 21 | 0.3 | 63 |
| MEAN | 6.2 | 4.1 | 124 | 58 | 0.1 | 19 | 0.3 | 62 |
| SD | 0.44 | 0.33 | 27.4 | 14.5 | 0.00 | 3.3 | 0.04 | 13.3 |
| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |

Study Report for Clinical Chemistry

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: FEMALE

| Animal ID | TP g/dL | ALB g/dL | GLU mg/dL | CHOL mg/dL | T-BIL mg/dL | BUN mg/dL | CREAT mg/dL | ALT U/L |
|------------|------------|-------------|--------------|---------------|----------------|--------------|----------------|------------|
| GROUP: 4-F | | | | | | | | |
| 17685 | 6.5 | 4.2 | 100 | 66 | 0.1 | 17 | 0.4 | 89 |
| 17689 | 6.7 | 4.2 | 105 | 69 | 0.2 | 22 | 0.4 | 99 |
| 17692 | 5.4 | 3.9 | 96 | 41 | 0.1 | 22 | 0.3 | 102 |
| 17691 | 6.5 | 4.1 | 156 | 53 | 0.1 | 22 | 0.5 | 87 |
| MEAN | 6.3 | 4.1 | 114 | 57 | 0.1 | 21 | 0.4 | 94 |
| SD | 0.59 | 0.14 | 28.1 | 12.9 | 0.05 | 2.5 | 0.08 | 7.4 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

Study Report for Clinical Chemistry

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| Animal ID | AST U/L | ALP U/L | CA mg/dL | PHOS mg/dL | TRIG mg/dL | NA mmol/L | K mmol/L | CL mmol/L |
|------------|------------|------------|-------------|---------------|---------------|--------------|-------------|--------------|
| GROUP: 1-M | | | | | | | | |
| 17608 | 90 | 106 | 11.6 | 8.3 | 66 | 147 | 5.5 | 94 |
| 17618 | 92 | 63 | 10.6 | 7.7 | 45 | 150 | 6.0 | 98 |
| 17630 | 89 | 131 | 11.2 | 8.6 | 76 | 147 | 4.9 | 94 |
| 17631 | 83 | 129 | 11.2 | 9.9 | 106 | 148 | 5.9 | 96 |
| 17639 | 88 | 106 | 10.9 | 7.9 | 66 | 146 | 6.2 | 97 |
| MEAN | 88 | 107 | 11.1 | 8.5 | 72 | 148 | 5.7 | 96 |
| SD | 3.4 | 27.4 | 0.37 | 0.87 | 22.2 | 1.5 | 0.51 | 1.8 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

| | | | | | | | | |
|------------|------|------|------|------|------|-----|------|-----|
| GROUP: 2-M | | | | | | | | |
| 17634 | 101 | 74 | 11.5 | 9.8 | 39 | 144 | 6.2 | 95 |
| 17635 | 86 | 88 | 11.0 | 8.2 | 69 | 147 | 5.0 | 96 |
| 17638 | 80 | 118 | 11.9 | 8.3 | 69 | 151 | 6.3 | 102 |
| 17642 | 89 | 113 | 11.0 | 8.2 | 66 | 148 | 5.9 | 100 |
| 17643 | 74 | 148 | 11.4 | 13.9 | 53 | 144 | 7.8 | 97 |
| MEAN | 86 | 108 | 11.4 | 9.7 | 59 | 147 | 6.2 | 98 |
| SD | 10.2 | 28.6 | 0.38 | 2.45 | 13.1 | 2.9 | 1.01 | 2.9 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

| | | | | | | | | |
|------------|-----|------|------|------|------|-----|------|-----|
| GROUP: 3-M | | | | | | | | |
| 17620 | 102 | 149 | 11.3 | 9.2 | 48 | 147 | 5.8 | 97 |
| 17623 | 88 | 96 | 11.8 | 8.0 | 68 | 147 | 6.7 | 100 |
| 17627 | 92 | 91 | 11.0 | 9.8 | 52 | 148 | 7.0 | 103 |
| 17628 | 100 | 122 | 11.4 | 10.3 | 56 | 149 | 6.9 | 101 |
| 17633 | 96 | 122 | 11.4 | 9.9 | 105 | 148 | 6.3 | 99 |
| MEAN | 96 | 116 | 11.4 | 9.4 | 66 | 148 | 6.5 | 100 |
| SD | 5.7 | 23.4 | 0.29 | 0.90 | 23.2 | 0.8 | 0.49 | 2.2 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Study Report for Clinical Chemistry

INDIVIDUAL ANIMAL REPORT BY GROUP
PERIOD: TERMINALSTUDY ID: ARGUS #418-027
STUDY NO: 060-063

SEX: MALE

| Animal ID | AST U/L | ALP U/L | CA mg/dL | PHOS mg/dL | TRIG mg/dL | NA mmol/L | K mmol/L | CL mmol/L |
|------------|------------|------------|-------------|---------------|---------------|--------------|-------------|--------------|
| GROUP: 4-M | | | | | | | | |
| 17621 | 89 | 117 | 11.5 | 9.3 | 24 | 151 | 5.9 | 100 |
| 17622 | 105 | 109 | 11.1 | 8.9 | 30 | 147 | 6.3 | 100 |
| 17625 | 109 | 104 | 11.3 | 9.8 | 47 | 150 | 6.3 | 103 |
| 17629 | 108 | 133 | 11.3 | 12.6 | 24 | 144 | 7.9 | 95 |
| 17636 | 98 | 153 | 11.3 | 9.2 | 28 | 147 | 6.1 | 98 |
| MEAN | 102 | 123 | 11.3 | 10.0 | 31 | 148 | 6.5 | 99 |
| SD | 8.3 | 20.0 | 0.14 | 1.51 | 9.5 | 2.8 | 0.80 | 2.9 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Study Report for Clinical Chemistry

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: FEMALE

| Animal ID | AST U/L | ALP U/L | CA mg/dL | PHOS mg/dL | TRIG mg/dL | NA mmol/L | K mmol/L | CL mmol/L |
|------------|------------|------------|-------------|---------------|---------------|--------------|-------------|--------------|
| GROUP: 1-F | | | | | | | | |
| 17694 | 102 | 49 | 11.5 | 9.5 | 44 | 140 | 7.0 | 96 |
| 17695 | 92 | 59 | 11.5 | 9.4 | 51 | 141 | 7.0 | 101 |
| 17703 | 99 | 59 | 11.8 | 9.2 | 46 | 143 | 6.1 | 99 |
| 17681 | 114 | 51 | 12.4 | 9.2 | 66 | 145 | 6.8 | 93 |
| 17690 | 92 | 97 | 11.8 | 9.3 | 72 | 144 | 6.7 | 98 |
| MEAN | 100 | 63 | 11.8 | 9.3 | 56 | 143 | 6.7 | 97 |
| SD | 9.1 | 19.5 | 0.37 | 0.13 | 12.5 | 2.1 | 0.37 | 3.0 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

| | | | | | | | | |
|------------|------|-----|------|------|------|-----|------|-----|
| GROUP: 2-F | | | | | | | | |
| 17675 | 107 | 39 | 12.4 | 8.0 | 84 | 141 | 6.0 | 96 |
| 17679 | 82 | 43 | 11.8 | 9.3 | 27 | 141 | 7.4 | 98 |
| 17684 | 120 | 56 | 10.9 | 7.0 | 47 | 141 | 6.1 | 99 |
| 17688 | 75 | 61 | 11.6 | 8.5 | 72 | 143 | 5.5 | 98 |
| 17698 | 86 | 56 | 11.7 | 7.8 | 53 | 143 | 6.8 | 99 |
| MEAN | 94 | 51 | 11.7 | 8.1 | 57 | 142 | 6.4 | 98 |
| SD | 18.8 | 9.5 | 0.54 | 0.85 | 22.2 | 1.1 | 0.74 | 1.2 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

| | | | | | | | | |
|------------|------|------|------|------|------|-----|------|-----|
| GROUP: 3-F | | | | | | | | |
| 17693 | 95 | 91 | 11.6 | 10.5 | 36 | 141 | 6.9 | 102 |
| 17687 | 107 | 48 | 11.4 | 9.1 | 91 | 143 | 6.2 | 100 |
| 17697 | 104 | 24 | 11.2 | 6.7 | 37 | 143 | 7.1 | 102 |
| 17700 | 114 | 68 | 12.1 | 10.6 | 36 | 143 | 6.7 | 98 |
| 17701 | 129 | 43 | 11.4 | 8.1 | 34 | 142 | 7.3 | 103 |
| 17709 | 150 | 49 | 11.5 | 7.9 | 52 | 144 | 6.0 | 100 |
| MEAN | 117 | 54 | 11.5 | 8.8 | 48 | 143 | 6.7 | 101 |
| SD | 20.0 | 23.0 | 0.31 | 1.54 | 22.2 | 1.0 | 0.51 | 1.8 |
| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |

Study Report for Clinical Chemistry

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: FEMALE

| Animal ID | AST U/L | ALP U/L | CA mg/dL | PHOS mg/dL | TRIG mg/dL | NA mmol/L | K mmol/L | CL mmol/L |
|------------|------------|------------|-------------|---------------|---------------|--------------|-------------|--------------|
| GROUP: 4-F | | | | | | | | |
| 17685 | 93 | 76 | 11.6 | 9.5 | 54 | 140 | 6.7 | 98 |
| 17689 | 147 | 68 | 12.2 | 10.0 | 69 | 140 | 6.8 | 98 |
| 17692 | 109 | 129 | 11.1 | 8.8 | 62 | 138 | 6.4 | 102 |
| 17691 | 131 | 73 | 12.6 | 9.6 | 79 | 143 | 6.9 | 95 |
| MEAN | 120 | 87 | 11.9 | 9.5 | 66 | 140 | 6.7 | 98 |
| SD | 23.8 | 28.5 | 0.66 | 0.50 | 10.6 | 2.1 | 0.22 | 2.9 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

Study Report for Clinical Chemistry

INDIVIDUAL ANIMAL REPORT BY GROUP
PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| Animal ID | GLOB g/dL | A/G none |
|-----------|--------------|-------------|
|-----------|--------------|-------------|

GROUP: 1-M

| | | |
|-------|-----|-----|
| 17608 | 2.4 | 1.8 |
| 17618 | 2.0 | 2.0 |
| 17630 | 2.4 | 1.7 |
| 17631 | 2.3 | 1.7 |
| 17639 | 2.1 | 2.0 |

| | | |
|------|------|------|
| MEAN | 2.2 | 1.8 |
| SD | 0.18 | 0.15 |
| N | 5 | 5 |

GROUP: 2-M

| | | |
|-------|-----|-----|
| 17634 | 2.3 | 1.7 |
| 17635 | 2.6 | 1.6 |
| 17638 | 2.4 | 1.8 |
| 17642 | 2.0 | 2.0 |
| 17643 | 2.0 | 2.1 |

| | | |
|------|------|------|
| MEAN | 2.3 | 1.8 |
| SD | 0.26 | 0.21 |
| N | 5 | 5 |

GROUP: 3-M

| | | |
|-------|-----|-----|
| 17620 | 1.9 | 2.2 |
| 17623 | 2.3 | 1.8 |
| 17627 | 2.1 | 1.8 |
| 17628 | 2.3 | 1.8 |
| 17633 | 1.9 | 2.2 |

| | | |
|------|------|------|
| MEAN | 2.1 | 2.0 |
| SD | 0.20 | 0.22 |
| N | 5 | 5 |

Study Report for Clinical Chemistry

INDIVIDUAL ANIMAL REPORT BY GROUP
PERIOD: TERMINALSTUDY ID: ARGUS #418-027
STUDY NO: 060-063

SEX: MALE

| Animal ID | GLOB g/dL | A/G none |
|------------|--------------|-------------|
| GROUP: 4-M | | |
| 17621 | 2.1 | 2.1 |
| 17622 | 1.8 | 2.4 |
| 17625 | 1.8 | 2.4 |
| 17629 | 2.1 | 2.0 |
| 17636 | 2.8 | 1.2 |
| MEAN | 2.1 | 2.0 |
| SD | 0.41 | 0.49 |
| N | 5 | 5 |

Study Report for Clinical Chemistry

 INDIVIDUAL ANIMAL REPORT BY GROUP
 PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: FEMALE

| Animal ID | GLOB g/dL | A/G none |
|------------|--------------|-------------|
| GROUP: 1-F | | |
| 17694 | 2.1 | 1.8 |
| 17695 | 2.2 | 2.0 |
| 17703 | 2.5 | 1.7 |
| 17681 | 2.5 | 1.8 |
| 17690 | 2.2 | 1.9 |
| MEAN | 2.3 | 1.8 |
| SD | 0.19 | 0.11 |
| N | 5 | 5 |
| GROUP: 2-F | | |
| 17675 | 2.8 | 1.6 |
| 17679 | 2.1 | 2.0 |
| 17684 | 1.9 | 2.0 |
| 17688 | 2.3 | 1.8 |
| 17698 | 2.7 | 1.6 |
| MEAN | 2.4 | 1.8 |
| SD | 0.38 | 0.20 |
| N | 5 | 5 |
| GROUP: 3-F | | |
| 17693 | 2.2 | 1.8 |
| 17687 | 2.2 | 2.0 |
| 17697 | 2.2 | 1.7 |
| 17700 | 2.4 | 1.9 |
| 17701 | 2.1 | 2.0 |
| 17709 | 2.0 | 1.8 |
| MEAN | 2.2 | 1.9 |
| SD | 0.13 | 0.12 |
| N | 6 | 6 |

Study Report for Clinical Chemistry

INDIVIDUAL ANIMAL REPORT BY GROUP
PERIOD: TERMINALSTUDY ID: ARGUS #418-027
STUDY NO: 060-063

SEX: FEMALE

| Animal ID | GLOB g/dL | A/G none |
|------------|--------------|-------------|
| GROUP: 4-F | | |
| 17685 | 2.3 | 1.8 |
| 17689 | 2.5 | 1.7 |
| 17692 | 1.5 | 2.6 |
| 17691 | 2.4 | 1.7 |
| MEAN | 2.2 | 2.0 |
| SD | 0.46 | 0.44 |
| N | 4 | 4 |

Study Report for Clinical Chemistry

SUMMARY REPORT
PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| TEST(s): | TP | ALB | GLU | CHOL | T-BIL | BUN | CREAT | ALT | AST |
|------------|------|------|-------|-------|-------|-------|-------|-----|------|
| UNITS: | g/dL | g/dL | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL | U/L | U/L |
| <hr/> | | | | | | | | | |
| Group: 1-M | | | | | | | | | |
| MEAN | 6.3 | 4.0 | 159 | 56 | 0.1 | 12 | 0.3 | 38 | 88 |
| SD | 0.29 | 0.16 | 11.0 | 11.9 | 0.00 | 1.6 | 0.05 | 2.3 | 3.4 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group: 2-M | | | | | | | | | |
| MEAN | 6.3 | 4.1 | 184 | 52 | 0.1 | 14 | 0.3 | 43 | 86 |
| SD | 0.34 | 0.15 | 23.9 | 5.3 | 0.00 | 2.3 | 0.04 | 1.6 | 10.2 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group: 3-M | | | | | | | | | |
| MEAN | 6.2 | 4.1 | 156 | 49 | 0.1 | 13 | 0.3 | 47 | 96 |
| SD | 0.29 | 0.21 | 12.7 | 5.5 | 0.00 | 1.3 | 0.04 | 4.2 | 5.7 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group: 4-M | | | | | | | | | |
| MEAN | 6.3 | 4.2 | 108 | 29 | 0.1 | 17 | 0.4 | 48 | 102 |
| SD | 0.16 | 0.43 | 11.5 | 8.2 | 0.00 | 5.9 | 0.09 | 6.5 | 8.3 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Study Report for Clinical Chemistry

SUMMARY REPORT
PERIOD: TERMINAL

 STUDY ID: ARGUS #418-027
 STUDY NO: 060-063

SEX: MALE

| TEST(s): | ALP | CA | PHOS | TRIG | NA | K | CL | GLOB | A/G |
|------------|------|-------|-------|-------|--------|--------|--------|------|------|
| UNITS: | U/L | mg/dL | mg/dL | mg/dL | mmol/L | mmol/L | mmol/L | g/dL | none |
| Group: 1-M | | | | | | | | | |
| MEAN | 107 | 11.1 | 8.5 | 72 | 148 | 5.7 | 96 | 2.2 | 1.8 |
| SD | 27.4 | 0.37 | 0.87 | 22.2 | 1.5 | 0.51 | 1.8 | 0.18 | 0.15 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group: 2-M | | | | | | | | | |
| MEAN | 108 | 11.4 | 9.7 | 59 | 147 | 6.2 | 98 | 2.3 | 1.8 |
| SD | 28.6 | 0.38 | 2.45 | 13.1 | 2.9 | 1.01 | 2.9 | 0.26 | 0.21 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group: 3-M | | | | | | | | | |
| MEAN | 116 | 11.4 | 9.4 | 66 | 148 | 6.5 | 100 | 2.1 | 2.0 |
| SD | 23.4 | 0.29 | 0.90 | 23.2 | 0.8 | 0.49 | 2.2 | 0.20 | 0.22 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group: 4-M | | | | | | | | | |
| MEAN | 123 | 11.3 | 10.0 | 31 | 148 | 6.5 | 99 | 2.1 | 2.0 |
| SD | 20.0 | 0.14 | 1.51 | 9.5 | 2.8 | 0.80 | 2.9 | 0.41 | 0.49 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Study Report for Clinical Chemistry

SUMMARY REPORT
PERIOD: TERMINAL

STUDY ID: ARGUS #418-027

SEX: FEMALE

STUDY NO: 060-063

| TEST(s): | TP | ALB | GLU | CHOL | T-BIL | BUN | CREAT | ALT | AST |
|------------|------|------|-------|-------|-------|-------|-------|------|------|
| UNITS: | g/dL | g/dL | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL | U/L | U/L |
| <hr/> | | | | | | | | | |
| Group: 1-F | | | | | | | | | |
| MEAN | 6.5 | 4.2 | 125 | 52 | 0.1 | 20 | 0.4 | 60 | 100 |
| SD | 0.45 | 0.30 | 26.9 | 11.8 | 0.05 | 3.6 | 0.04 | 7.4 | 9.1 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| | | | | | | | | | |
| Group: 2-F | | | | | | | | | |
| MEAN | 6.5 | 4.2 | 138 | 61 | 0.1 | 18 | 0.3 | 57 | 94 |
| SD | 0.61 | 0.25 | 6.6 | 7.5 | 0.04 | 3.3 | 0.09 | 13.0 | 18.8 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| | | | | | | | | | |
| Group: 3-F | | | | | | | | | |
| MEAN | 6.2 | 4.1 | 124 | 58 | 0.1 | 19 | 0.3 | 62 | 117 |
| SD | 0.44 | 0.33 | 27.4 | 14.5 | 0.00 | 3.3 | 0.04 | 13.3 | 20.0 |
| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | | | | | | | | | |
| Group: 4-F | | | | | | | | | |
| MEAN | 6.3 | 4.1 | 114 | 57 | 0.1 | 21 | 0.4 | 94 | 120 |
| SD | 0.59 | 0.14 | 28.1 | 12.9 | 0.05 | 2.5 | 0.08 | 7.4 | 23.8 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

Study Report for Clinical Chemistry

SUMMARY REPORT
PERIOD: TERMINALSTUDY ID: ARGUS #418-027
STUDY NO: 060-063

SEX: FEMALE

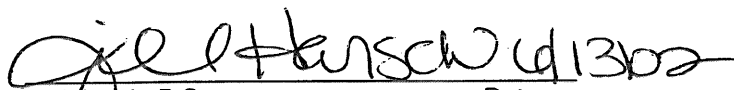
| TEST(s): | ALP | CA | PHOS | TRIG | NA | K | CL | GLOB | A/G |
|------------|------|-------|-------|-------|--------|--------|--------|------|------|
| UNITS: | U/L | mg/dL | mg/dL | mg/dL | mmol/L | mmol/L | mmol/L | g/dL | none |
| Group: 1-F | | | | | | | | | |
| MEAN | 63 | 11.8 | 9.3 | 56 | 143 | 6.7 | 97 | 2.3 | 1.8 |
| SD | 19.5 | 0.37 | 0.13 | 12.5 | 2.1 | 0.37 | 3.0 | 0.19 | 0.11 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group: 2-F | | | | | | | | | |
| MEAN | 51 | 11.7 | 8.1 | 57 | 142 | 6.4 | 98 | 2.4 | 1.8 |
| SD | 9.5 | 0.54 | 0.85 | 22.2 | 1.1 | 0.74 | 1.2 | 0.38 | 0.20 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group: 3-F | | | | | | | | | |
| MEAN | 54 | 11.5 | 8.8 | 48 | 143 | 6.7 | 101 | 2.2 | 1.9 |
| SD | 23.0 | 0.31 | 1.54 | 22.2 | 1.0 | 0.51 | 1.8 | 0.13 | 0.12 |
| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Group: 4-F | | | | | | | | | |
| MEAN | 87 | 11.9 | 9.5 | 66 | 140 | 6.7 | 98 | 2.2 | 2.0 |
| SD | 28.5 | 0.66 | 0.50 | 10.6 | 2.1 | 0.22 | 2.9 | 0.46 | 0.44 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

QUALITY ASSURANCE STATEMENT

Study Number: 418-027
Redfield Study Number: 060-063

This study has been inspected and audited by the Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) regulations promulgated by the U.S. Food and Drug Administration or U.S. Environmental Protection Agency or other international regulations, as required. The following is a record of the dates that audits/inspections were performed and reported by the QAU.

| DATE OF AUDIT/INSPECTION | TYPE OF AUDIT/INSPECTION | DATES REPORTED TO STUDY DIRECTOR AND MANAGEMENT |
|-----------------------------|--------------------------|--|
| 05/17/02, 05/20/02 | Clinical Pathology | 05/20/02 |

APPROVED BY:


Jill Harsch, B.S.
Quality Assurance Auditor
Redfield Laboratories

Date

APPENDIX L

STATEMENT OF THE STUDY DIRECTOR

905 Sheehy Drive, Bldg. A
 Horsham, PA 19044
 Telephone: (215) 443-8710
 Telefax: (215) 443-8587

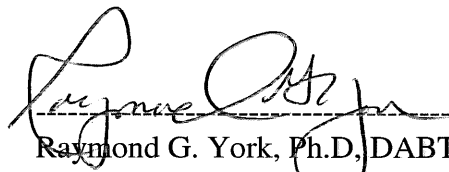

 ARGUS RESEARCH
 Charles River Laboratories
 Discovery and Development Services

PROTOCOL 418-027: ORAL (GAVAGE) COMBINED REPEATED DOSE TOXICITY
 STUDY OF T 7599.7 WITH THE REPRODUCTION/
 DEVELOPMENTAL TOXICITY SCREENING TEST

SPONSOR'S STUDY NUMBER: T-7599

STATEMENT OF THE STUDY DIRECTOR

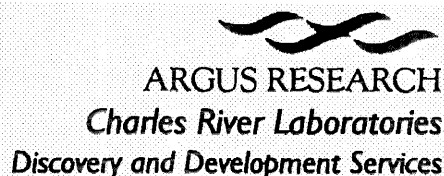
This final report accurately reflects the raw data obtained during the performance of the study. No deviations from the U.S. Food and Drug Administration (FDA) Good Laboratory Practice Regulations; Final Rule^a, the Japanese Ministry of Health and Welfare (MHW) Good Laboratory Practice Standard for Safety Studies on Drugs^b, the Organisation for Economic Co-operation and Development (OECD), the Revised OECD Principles of Good Laboratory Practices^c and the Organisation for Economic Co-operation and Development (OECD), The OECD Guideline for Testing of Chemicals^d occurred that affected the quality or integrity of the study.


 Raymond G. York, Ph.D., DABT 25 MAR 2003
 Associate Director of Research Date
 Study Director
 Argus Research

-
- a. U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58.
- b. Japanese Ministry of Health and Welfare (1997). Good Laboratory Practice Standard for Safety Studies on Drugs, MHW Ordinance No. 21, March 26, 1997.
- c. Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97)186/Final].
- d. Organisation for Economic Co-operation and Development (1996). OECD Guideline for Testing of Chemicals. Section 4, No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, adopted 22 March 1996.

APPENDIX M
QUALITY ASSURANCE STATEMENT

905 Sheehy Drive, Bldg. A
Horsham, PA 19044
Telephone: (215) 443-8710
Telefax: (215) 443-8587



ARGUS RESEARCH
Charles River Laboratories
Discovery and Development Services

QUALITY ASSURANCE STATEMENT

Argus Protocol: 418-027

Sponsor's Study Number: T-7599

Study Director: Raymond G. York, Ph.D., DABT

The protocol, critical phases, raw data and final report were inspected by the Quality Assurance Unit (QAU), to assure conformance with:

Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97)186/Final].

U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58.



Japanese Ministry of Health and Welfare (1997). *Good Laboratory Practice Standard for Safety Studies on Drugs*, MHW Ordinance Number 21, March 26, 1997.

The undersigned indicate that the report is an accurate representation of the raw data. Data provided by the Sponsor or a subcontractor were not audited by the Argus Research Quality Assurance Unit.

The QAU inspection and report audit dates are listed below:

| <u>Inspection Phase</u> | <u>Inspection Date(s)</u> | <u>Date(s) Findings Submitted to Study Director</u> | <u>Date(s) Findings Submitted to Management</u> |
|--|---------------------------|---|---|
| Protocol | 12 FEB 02 | 12 FEB 02 | 12 FEB 02 |
| | 15 FEB 02 | 15 FEB 02 | 15 FEB 02 |
| TS Administration | 22 FEB 02 | 22 FEB 02 | 22 FEB 02 |
| TS Preparation | 28 FEB 02 | 28 FEB 02 | 28 FEB 02 |
| Motor Activity | 20 MAR 02 | 20 MAR 02 | 20 MAR 02 |
| FOB ¹ | 20 MAR 02 | 01 APR 02 | 01 APR 02 |
| Natural Delivery/ Litter Observations | 27 MAR 02 | 27 MAR 02 | 27 MAR 02 |
| Blood Collection | 04 APR 02 | 19 APR 02 | 19 APR 02 |
| Dam/Litter Sacrifice | 04 APR 02 | 19 APR 02 | 19 APR 02 |
| Male Sacrifice- Raw Data Check | 01 AUG 02 | 01 AUG 02 | 01 AUG 02 |
| In-Life Data | 17-19, 22-24 JUL 02 | 24 JUL 02 | 24 JUL 02 |
| | 18, 22 JUL 02 | 23 JUL 02 | 23 JUL 02 |
| Necropsy Data | 03, 31 JUL 02 | 31 JUL 02 | 31 JUL 02 |
| Formulations Data | 26-30 JUL 02 | 30 JUL 02 | 30 JUL 02 |
| Report Tables | 25-26 JUL 02 | 26 JUL 02 | 26 JUL 02 |
| Report Text | 30 JUL 02 | 30 JUL 02 | 30 JUL 02 |
| | 01 AUG 02 | 01 AUG 02 | 01 AUG 02 |

¹Functional Observational Battery

for Matthew J. Vaneman, B.S. Date Maureen O'Brien, B.S. Date
 Manager of Regulatory Compliance Quality Assurance Associate and
 Principal Auditor