

# **RCC Study Number 857092**

Repeated Dose 90-Day Oral Toxicity Study  
with

**2-Amino-4-Hydroxyethylaminoaniso  
Sulfate (A084, WR 23081)**

in Wistar Rats

**Final Report (Part I of III)**



Date of Issue: 20 July 2005  
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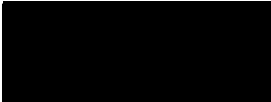





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# 1    PREFACE

## 1.1   GENERAL

|                      |   |
|----------------------|---|
| Title                | Repeated Dose 90-Day Oral Toxicity Study with 2-Amino-4-Hydroxyethylaminoaniso le Sulfate (A084, WR 23081) in Wistar Rats   |
| Sponsor              |   |
| Monitoring Scientist |   |
| Test Facility        | RCC Ltd<br>Toxicology<br>CH – 4452 Itingen / Switzerland (a)<br>CH – 4414 Füllinsdorf / Switzerland (b)   |
| Test Site(s)         | RCC Ltd<br>Environmental Chemistry & Pharmanalytics<br>CH – 4452 Itingen / Switzerland (c)  |
| Lead QA              | RCC Ltd<br>Quality Assurance GLP<br>Toxicology<br>CH–4452 Itingen / Switzerland   |
| Test Site QAs        | RCC Ltd<br>Quality Assurance GLP<br>Environmental Chemistry & Pharmanalytics<br>CH–4452 Itingen / Switzerland<br>Contact person: D. Bürgin<br>(Responsible for test site c) |

## 1.2   RESPONSIBILITIES

### Study Personnel:

|                           |                     |
|---------------------------|---------------------|
| Study Director            | W. H. Braun (a)     |
| Deputy Study Director     | Dr. B. Damme (a)    |
| Laboratory Coordinator    | R. Sacher (a)       |
| Clinical Diagnostic       | Dr. P. Gretener (b) |
| Necropsy/ Histotechnology | Dr. K. Weber (a)    |
| Pathology                 | Dr. D. Nehrbass (a) |

**Principal Investigators:**

Study Phase:  
Analytical Chemistry                      Dr. D. Flade (c)  
Thyroid Hormone                          Dr. R. Burri (c)

**Quality Assurance:**

Head of Lead QA                          I. Wüthrich

**1.3 SCHEDULE**

|                              |   |
|------------------------------|---|
| Experimental Starting Date   | 25 October 2004                         |
| Experimental Completion Date | 19 July 2005                            |
| Delivery of Animals          | 25 October 2004                         |
| Acclimatization              | 25 to 31 October 2004                   |
| Administration/Treatment     | 01 November 2004 to 15-17 February 2005 |
| Termination (Necropsy)       | 16 to 18 February 2005                  |
| Study Completion Date        | 20 July 2005                            |

**1.4 ARCHIVING**

RCC Ltd (CH-4452 Itingen / Switzerland) will retain the study plan, amendments, raw data, sample of test item(s), specimens (as long as the quality permits evaluation) and the final report of the present study for at least ten years. Wet tissue samples will be archived at RCC Ltd for a minimum of five years. Thereafter, in agreement with the Sponsor, these samples may be further archived at RCC Ltd or transferred to another GLP archive facility for the remainder of the prescribed period. No data will be discarded without the Sponsor's written consent.

**1.5 TEST GUIDELINES**

The study procedures described in this report meet or exceed with the following guidelines:

"Repeated Dose 90-Day Oral Toxicity Study in Rodents", OECD Guidelines for the testing of Chemicals, Section 4, Health Effects, Number 408, 21 September 1998.

**1.6 ANIMAL WELFARE**

This study was performed in an AAALAC-approved laboratory in accordance with the Swiss Animal Protection Law under license no. 27.


**1.7 ACCREDITATION**

"RCC Ltd, Toxicology" is accredited as a testing laboratory for analysis in the fields of clinical chemistry, hematology, blood-coagulation and urine diagnostics in accordance with the Standard ISO/IEC 17025 under accreditation number STS 085 by the Swiss Accreditation Service.

## 1.8 SIGNATURES

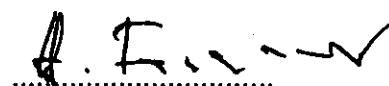
Study Director:

W. H. Braun

  
.....  
date: 20 July 2005

Management:

Dr. H. Fankhauser

  
.....  
date: 20 July 2005

The signatures of Dr. D. Flade (Analytical Chemistry), Dr. R. Burri (Hormone Analysis) and Dr. D. Nehrbass (Study Pathologist) are included in the relevant attached reports.

## GOOD LABORATORY PRACTICE

### 1.9 STATEMENT OF COMPLIANCE / GLP GUIDELINES

RCC STUDY NUMBER:                      857092  
TEST ITEM:                                      HYDROXYETHYLAMINOANISOLE SULFATE (A084,  
WR 23081)  
STUDY DIRECTOR:                              W. H. Braun  
TITLE:    Repeated Dose 90-Day Oral Toxicity Study with  
2-Amino-4-Hydroxyethylaminoanisole Sulfate (A084,  
WR 23081) in Wistar Rats


This study has been performed in compliance with the:

Swiss Ordinance relating to Good Laboratory Practice, adopted February 2<sup>nd</sup>, 2000 [RS 813.016.5] This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26<sup>th</sup>, 1997 by decision of the OECD Council [C (97)186/Final].

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

Study Director:

W. H. Braun

  
date: 20 July 2005



## 1.10 QUALITY ASSURANCE GLP TOXICOLOGY

RCC Ltd, Toxicology, CH-4452 Itingen / Switzerland

### STATEMENT

RCC STUDY NUMBER: 857092  
 TEST ITEM: HYDROXYETHYLAMINOANISOLE SULFATE (A084, WR 23081)  
 STUDY DIRECTOR: W. H. Braun  
 TITLE: Repeated Dose 90-Day Oral Toxicity Study with 2-Amino-4-Hydroxyethylaminoanisol Sulfate (A084, WR 23081) in Wistar Rats

The general facilities and activities are inspected periodically and the results are reported to the responsible person and the management.

Study procedures were periodically inspected. The study plan and this report were audited by the Quality Assurance. The dates are given below.

| Dates and Types of QA Inspections                            |   | Dates of Reports to the Study Director and to Management |
|--|---|--|
| 25 October 2004<br>01 November 2004                          | Study plan<br>Test system, test item, dose preparation, body weight, raw data, treatment, sample collection | 25 October 2004<br>01 November 2004                      |
| 29 November 2004<br>29 December 2004                         | Test system, body weight, treatment<br>Test system, test item, treatment, raw data                          | 29 November 2004<br>29 December 2004                     |
| 20 January 2005<br>17 February 2005                          | Test system, test item, treatment, raw data<br>Urine sampling, blood sampling, test system, raw data        | 20 January 2005<br>17 February 2005                      |
| 17 February 2005<br>18 February 2005<br>14 June–01 July 2005 | Clinical laboratory investigations<br>Process-based (Histotechnology)<br>Report                             | 17 February 2005<br>18 February 2005<br>08 July 2005     |

This statement also confirms that this final report reflects the raw data.

In addition, this final report includes a QA-Statement issued by the Test Site Quality Assurance.

Quality Assurance

M.C. Schlepper

*M.C. Schlepper*  
 Date: 20 July 2005



## **OPHTHALMOSCOPIC EXAMINATIONS**

No ocular changes were seen after 14 weeks of treatment.

## **FOOD CONSUMPTION**

No test item-related changes in the mean daily food consumption were noted at any time point during the study.

## **BODY WEIGHT**

Marginally lower body weights were noted from day 29 of treatment onwards in the test item-treated males, but as the differences were not clearly dose-related, they were not accorded any toxicological relevance. The mean body weights and the mean body weight gain of the test item-treated females compared favorably with those of the controls throughout the treatment period.

## **CLINICAL LABORATORY INVESTIGATIONS**

### **Hematology**

In females treated with 50 mg/kg/day or both sexes treated with 200 mg/kg/day, lower red blood cell counts were recorded. In females treated with 50 mg/kg/day or 200 mg/kg/day, lower hemoglobin and lower hematocrit were noted when compared with controls. The mean absolute and relative reticulocyte counts were elevated in females treated with 50 mg/kg/day and in both sexes treated with 200 mg/kg/day. The elevated values noted in the females treated with 200 mg/kg/day exceeded the ranges of the historical control values. Changes were also seen in the reticulocyte maturity indices of females treated with 50 mg/kg/day and of both sexes treated with 200 mg/kg/day. These changes were primarily shifts towards high fluorescence reticulocytes from low fluorescence reticulocytes. These changes remained within the ranges of the historical control data, yet were considered to be slight effects upon hematopoiesis, correlating with microscopical changes seen in the spleens of rats at the highest dose. The methemoglobin level noted in the blood of females treated with 50 mg/kg/day or 200 mg/kg/day was higher than that of the control females. Although Heinz bodies were not seen, this finding was considered to be a slight test item-related change.

### **Clinical Biochemistry**

In females treated with 200 mg/kg/day, reduced creatinine levels and elevated triglyceride levels exceeded the historical control ranges and were considered to be test item-related changes. Although the mean phospholipid levels were elevated in males and females treated with 200 mg/kg/day, they remained within the ranges of the historical control data. Elevated plasma sodium and chloride levels were seen more distinctly in females than in males. Although changes were seen in males treated with 15 mg/kg/day and 50 mg/kg/day, they were less apparent in males at 200 mg/kg/day. These electrolytes were clearly elevated in females treated with 50 mg/kg/day or 200 mg/kg/day. Elevated potassium levels were seen in test item-treated males, but a clear dose-response relationship was not seen and the control value was slightly low when compared with the historical control data. Potassium levels were unaffected in test item treated females.

### **Urinalysis**

With increasing dose, yellow/brown to brown to black discoloration of the urine was noted in test item-treated males and females. This discoloration was considered likely to be excreted test item, and precluded evaluation of most urinalysis parameters.

### **Urine Sediment**

Evaluation of urine sediment did not reveal test item-related changes.

### **HORMONE ANALYSIS**

No test item-related changes in the thyroid hormones (TSH, free and total T3 and T4) were noted at any dose level after 15 weeks of treatment.

### **ORGAN WEIGHTS**

Marginally elevated thyroid-to-brain weight ratios were noted in both sexes treated with 200 mg/kg/day, whereas females treated with 200 mg/kg/day showed elevated mean absolute and relative weights were noted in liver, kidney and spleen. These differences were considered to be test item related. All other organ weights and ratios were unaffected.

### **MACROSCOPIC / MICROSCOPIC FINDINGS**

At necropsy, dark red or black discoloration of the thyroid was recorded in most animals treated with 50 mg/kg/day or 200 mg/kg/day, which was assessed as a test item-related gross lesion.

Histopathologically, test item-related changes were recorded at thyroid, pituitary, kidneys, and spleen.

At the thyroid, follicular cell enlargement due to minimal to slight cytoplasmic storage of brown, fine-granular pigment, and increased cytoplasmic vacuolation was recorded in animals treated with 50 mg/kg/day and 200 mg/kg/day.

In the pituitary, minimal to slight hypertrophy of chromophobic cells was recorded in males treated with 50 mg/kg/day or 200 mg/kg/day.

In the kidneys, pigment storage in vacuolar basophilic tubulus cells was recorded in most test item-treated groups except females treated with 15 mg/kg/day. However, in males treated with 15 mg/kg/day, this change was considered of non-adverse character, because of minimal severity, low incidence, and lack of clinical relevance. Additionally, minimal to slight vacuolar tubulus cell swelling of non-adverse character at the corticomedullary junction along with cytoplasmic storage of brown fine-granular pigment was recorded in females of all test item-treated groups. Furthermore, brown pigment in "normal" (non-swollen, non-basophilic) tubulus cells, and minimal brown-pigmented tubular casts were recorded in males treated with 200 mg/kg/day.

In the spleen, increased mean grade of extra medullary hemopoiesis in combination with slightly increased mean grade of hemosiderin storage was recorded in animals treated with 200 mg/kg/day.

Under the conditions of this experiment, the test item 2-Amino-4-Hydroxyethylaminoanazole Sulfate (A084, WR 23081) produced morphological changes in thyroid, pituitary, kidneys, and spleen.

According to the results of pathology, a No-Observed-Adverse Effect-Level (NOAEL) may be established at 15 mg/kg/day.

### 3      **ASSESSMENT**

Oral administration of HYDROXYETHYLAMINOANISOLE SULFATE (A084, WR 23081) to Wistar rats at doses of 15, 50 and 200 mg/kg/day, for 108/109 days resulted in no test item-related deaths, no clinical signs of toxicological relevance during daily or weekly observations, no clinical signs of toxicological relevance during the functional observational battery at week 15, no differences in fore- or hindlimb grip strength, no differences in locomotor activity, no ophthalmoscopic findings and no effects on food consumption. The results of thyroid hormone analyses (TSH, and free and total T3 and T4) did not show differences that were test item related.

Minor differences were seen in the mean body weights of test item-treated males from day 29 of treatment onwards but these differences were not clearly dose-related and therefore considered to be of no toxicological relevance.

Test item-related findings included passive clinical signs (discoloration of the urine) in males at 50 or 200 mg/kg/day and in females at all dose levels, changes in hematology parameters, which are generally indicative of slight anemia with compensatory reticulocytosis, changes in clinical biochemistry that are generally indicative of effects upon the liver and kidney.

At necropsy, dark red to black discoloration of the thyroid gland was noted in most animals treated with 50 mg/kg/day or 200 mg/kg/day.

Under the conditions of this study, the test item 2-Amino-4-Hydroxyethylaminoanisole Sulfate (A084, WR 23081) induced histopathological changes in thyroid, pituitary, kidneys, and spleen.

In the thyroid, a follicular cell enlargement due to cytoplasmic storage of brown fine-granular pigment, partly along with increased cytoplasmic vacuolation was recorded in animals treated with 50 mg/kg/day and 200 mg/kg/day. The brown pigment was deemed to be the histological correlate of the test item, and correlated to a dark red or black discoloration of the organ and to a slightly increased mean organ weight (statistically not significant) both recorded at necropsy. Hormone testing did not reveal increased serum levels of thyroid hormones (TSH, total T3, total T4, free T3, free T4). So the enlargement of the follicular cells was not accompanied by increased hormone production, but caused by the storage of the test item. Pathomechanistically, these changes were probably caused by an interaction of the test item, a dyestuff with anisol core, with thyroid hormones or its precursors (= iodinated tyrosines), which share some structural similarities. The thyroid changes were assessed as effects of the test item, which predict an adverse effect on the thyroid.

In the pituitary, minimal to slight hypertrophy/plasia of chromophobic cells (characterized by increased cell size and increased vacuolation) was recorded in males treated with 50 mg/kg/day and 200 mg/kg/day. These chromophobic pituitary cells most likely represent hyperfunctional degranulated basophilic cells, which produced TSH (thyreotropin). As TSH stimulates the subordinated thyroid follicle cells, a pathomechanistic relationship between the pituitary and thyroid changes cannot be excluded.

In the kidneys, pigment storage in vacuolar basophilic tubulus cells was recorded in most test item-treated groups except females treated with 15 mg/kg/day. This renal change was assessed as an adverse effect in rats treated with 50 mg/kg/day and 200 mg/kg/day. However, in males treated with 15 mg/kg/day, this change was considered to be of non-adverse character because of minimal severity, low number of animals affected (three of ten males), and lack of clinical relevance. Additionally, a non-adverse, minimal to slight vacuolar tubulus cell swelling at the corticomedullary junction was recorded in females of all test item-treated groups. In animals treated with 200 mg/kg/day, this change was sometimes accompanied by necrosis of single tubulus cells, and thickened basal membranes. These histopathological changes were accompanied by an increased organ weight recorded at necropsy in females treated with 200 mg/kg/day, and by changes recorded by blood chemistry (increased sodium, increased chloride) and by urinalysis (slight proteinuria, increased urinary bilirubin and nitrite). Furthermore, brown pigment in "normal" (non-swollen, non-basophilic) tubulus cells, and minimal brown pigmented tubular casts were recorded in males treated with 200 mg/kg/day. The origin of the brown pigment could be either endogenous (hemosiderin, lipofuscin, or bilirubin) or exogenous (test item). Pathomechanistically, the basophilic tubulus cells were assessed as regeneration after an preceding tubular damage starting with vacuolar tubulus cell swelling induced by the pigment stored in the cytoplasm.

In the spleen, an increased extramedullary hemopoiesis in combination with slightly increased hemosiderin storage was recorded in animals treated with 200 mg/kg/day. This change, which was more pronounced in female animals and correlated to an increased organ weight recorded at necropsy and was accompanied by alterations recorded by hematology in animals treated with 200 mg/kg/day (decreased RBC, decreased MCHC [females only], increased MCV, increased reticulocytes). Summarized, these changes reflected a slight macrocytic, partly hypochromatic, regenerative anemia in animals treated with 200 mg/kg/day. Pathomechanistically, the reasons for these changes were unclear.

Based on the results of this study, a no-observed-adverse-effect-level (NOAEL) for HYDROXYETHYLAMINOANISOLE SULFATE (A084, WR 23081) may be established. at 15 mg/kg/day.

## 4 OBJECTIVE

### 4.1 PURPOSE AND RATIONALE

The purpose of this oral toxicity study was to assess the cumulative toxicity of HYDROXYETHYLAMINOANISOLE SULFATE (A084, WR 23081) when administered daily to rats by gavage for a period of 108/109 days.

This study should provide a rational basis for risk assessment in man and should indicate potential target organs.

## 5 MATERIALS AND METHODS

### 5.1 TEST SYSTEM

|                                      |  |
|--------------------------------------|--|
| Test system                          | Rat, HanBrl:WIST (SPF)   |
| Rationale                            | Recognized by the international guidelines as the recommended test system.   |
| Source                               | RCC Ltd<br>Laboratory Animal Services<br>CH-4414 Füllinsdorf / Switzerland   |
| Number of animals per group          | 15 males; 15 females (Groups 1-4)  |
| Total number of animals used         | 60 males; 60 females   |
| Total number of animals ordered      | 63 males; 63 females   |
| Age at delivery                      | 6 weeks  |
| Body weight range at acclimatization | Males: 134.8 – 159.0 grams (mean 146.5 grams)<br>Females: 114.0 – 132.8 grams (mean 124.2 grams)                           |
| Identification:                      |  |
| Acclimatization                      | Cage card and tail mark (later ear tattoo)   |
| Treatment                            | Cage card and individual ear tattoo  |
| Randomization                        | Computer-generated random algorithm  |
| Acclimatization                      | Under test conditions after health examination. Only animals without any visible signs of illness were used for the study. |





## 5.4 TEST ITEM

|                        |   |
|------------------------|---|
| Identity               | 2-Amino-4-Hydroxyethylaminoanazole Sulfate (A084, WR 23081)                       |
| Description            | pale grey powder  |
| Batch number           | 57  |
| Purity                 | 99.6 area% HPLC   |
| Stability of test item | Stable under storage conditions   |
| Expiry date            | July 2005   |
| Storage conditions     | at room temperature (15-25°C) in the original container away from direct sunlight |
| Safety precautions     | Routine hygienic procedures (gloves, goggles, face mask)                          |

These data were provided by the sponsor.

## 5.5 ANALYTICAL STANDARD

|          |   |
|----------|---|
| Identity | 2-Amino-4-Hydroxyethylaminoanazole Sulfate (A084, WR 23081) (the test item will serve as its own analytical standard) |
|----------|---|

## 5.6 DOSE FORMULATION

The dose formulations were prepared daily.

HYDROXYETHYLAMINOANISOLE SULFATE (A084, WR 23081) was weighed into a glass beaker on a tared Mettler balance and the vehicle added. The mixtures were prepared using a magnetic stirrer and used at room temperature (15-25°C), protected from light (i.e. in aluminum foil).

Homogeneity of the test item in the vehicle was maintained during the daily administration period using a magnetic stirrer.

### 5.6.1 ANALYSIS OF DOSE FORMULATIONS

Concentration, homogeneity and stability (after 4 hours) of the dose formulations were determined in samples taken after experimental start. Concentration and homogeneity of the dose formulations were determined in samples taken monthly during treatment. The analyses were performed by RCC Ltd (Environmental Chemistry & Pharamalytics Division) according to a HPLC method supplied by the Sponsor. The results are presented in Appendix V.

See pp. 345 - 361

## 5.7 VEHICLE AND CONTROL ITEMS

Identity    bidistilled water

## 5.8 TREATMENT

Method    Oral, by gavage.

Rationale    Accidental oral ingestion is a possible route of human exposure.

Daily dose levels                                      Group 1:     0 mg/kg body weight  
    Group 2:     15 mg/kg body weight  
    Group 3:     50 mg/kg body weight  
    Group 4:     200 mg/kg body weight  
Dose levels are expressed in terms of the test item as supplied.

Rationale for dose level selection              The dose levels were provided by the sponsor.

Frequency of administration                      Daily

Dose volume    10 ml/kg

Duration of acclimatization period              7 days

Duration of treatment                                      108/109 days

## 5.9 OBSERVATIONS

### 5.9.1 MORTALITY / VIABILITY

Observations for mortality/viability were recorded twice daily.

### 5.9.2 GENERAL CAGESIDE OBSERVATIONS (DAILY)

The animals were observed for clinical signs once before commencement of administration; and once daily during the treatment period.

### 5.9.3 DETAILED CLINICAL OBSERVATIONS (WEEKLY)

The animals were observed in their home cages, outside their home cages in a standard arena and in the hand. These observations were performed in random sequence once before commencement of administration and once weekly (weeks 1-14) thereafter.

### 5.9.4 FOOD CONSUMPTION

The food consumption was recorded once during the pretest period and weekly thereafter, using an on-line electronic recording system consisting of a Mettler balance connected to the RCC computer.

### 5.9.5 BODY WEIGHTS

Body weights were recorded weekly during pretest, treatment and before necropsy, using an on-line electronic recording system consisting of a Mettler balance connected to the RCC computer.

## 5.10 OPHTHALMOSCOPIC EXAMINATIONS

The ophthalmoscopic examinations of both eyes of all animals were performed after the application of a mydriatic solution (Ciba Vision AG, CH-3172 Niederwangen) using a Miroflex 2 Ophthalmoscope (Eisenhut Vet. AG, CH-4123 Allschwil). A description of any abnormality was recorded. For unilateral findings unless otherwise indicated in the tables, the contralateral eye was without abnormalities.

### 5.10.1 FUNCTIONAL OBSERVATIONAL BATTERY

During week 15, relevant parameters (presented in Appendix I) from a modified Irwin screen test were evaluated in all animals.

NB. For technical reasons, the results of the Functional Observational Battery are presented in the summary and individual tables of the Detailed Clinical Observations (Weekly) under week 13.

### GRIP STRENGTH

Forelimb and hind limb grip strength measurements were performed using a push-pull strain gauge (Mecmesin, AFG 25N). The animals were placed with the forepaws inside a triangular grasping ring and with the hind paws outside a triangular grasping ring. Using one hand, the animals were held towards the base of the tail and steadily pulled away or towards the ring until the grip was broken. Each measurement was repeated three times, the means were calculated and recorded.

### LOCOMOTOR ACTIVITY

Locomotor (decreased or increased) activity was measured quantitatively with AMS Föhr Medical Instruments GmbH (FMI) and DeMeTec GmbH Activity Monitor System. Animals were monitored during treatment week 14 for a 60-minute period and the total activity of this time period was recorded.

Low beams count was reported in 10-minute intervals as well as the total activity of the measuring period.

## 5.11 CLINICAL LABORATORY INVESTIGATIONS

Blood and urine sampling:  
at 16 weeks (Allocation A)                      17 February 2005

Blood samples for hematology and clinical biochemistry were collected from all animals under light isoflurane anesthesia. The animals were fasted in metabolism cages for approximately 18 hours before blood sampling but allowed access to water *ad libitum*. Blood samples were collected early in the working day to reduce biological variation caused by circadian rhythms. Blood samples were drawn from the retro-orbital plexus using a micro-hematocrit glass capillary tube.

Urine was collected during the 18-hour fasting period into a specimen vial.

The assays were performed at RCC Ltd (Füllinsdorf) under internal laboratory quality control conditions to assure reliable test results.

In the summary and individual tables the names of some parameters have been abbreviated. Any abbreviation has been defined in Appendix IV.

Detailed methodology, abbreviations and general remarks are described in Appendix IV.

Clinical laboratory data are expressed, with a few exceptions, in general accordance with the International System of Units (SI).

### 5.11.1 HEMATOLOGY

The following hematology parameters were determined:

|   |   |
|---|---|
| Erythrocyte count                           | Reticulocyte maturity index   |
| Hemoglobin                                  | Methemoglobin   |
| Hematocrit                                  | Heinz bodies (to be completely assessed only if changes in methemoglobin are noted) |
| Mean corpuscular volume                     | Total leukocyte count   |
| Red cell volume distribution width          | Differential leukocyte count  |
| Mean corpuscular hemoglobin                 | Coagulation:  |
| Mean corpuscular hemoglobin concentration   | Thromboplastin time   |
| Hemoglobin concentration distribution width | Activated partial thromboplastin time   |
| Platelet (thrombocyte) count                |   |
| Reticulocyte count                          |   |

### 5.11.2 CLINICAL BIOCHEMISTRY

The following clinical biochemistry parameters were determined:

|                            |                            |
|----------------------------|----------------------------|
| Glucose                    | Creatine kinase            |
| Urea                       | Alkaline phosphatase       |
| Creatinine                 | Gamma-glutamyl-transferase |
| Bilirubin, total           | Sodium                     |
| Cholesterol, total         | Potassium                  |
| Triglycerides              | Chloride                   |
| Phospholipids              | Calcium                    |
| Aspartate aminotransferase | Phosphorus inorganic       |
| Alanine aminotransferase   | Protein, total             |
| Lactate dehydrogenase      | Protein, electrophoresis   |
| Glutamate dehydrogenase    | Albumin/Globulin ratio     |

### 5.11.3 URINALYSIS

The following urinalysis parameters were determined:

|                                     |              |
|-------------------------------------|--------------|
| Volume (18 hours)                   | Glucose      |
| Specific gravity (relative density) | Ketones      |
| Color                               | Urobilinogen |
| Appearance                          | Bilirubin    |
| pH                                  | Erythrocytes |
| Nitrite                             | Leukocytes   |
| Protein                             | Sediment     |

## 5.12 HORMONE ANALYSIS

Blood samples were drawn from the retro-orbital plexus prior to scheduled necropsy for hormone analysis and placed on ice. After serum samples were taken, they were deep-frozen (ca.  $-80^{\circ}\text{C}$ ). Five (5) aliquots of 300  $\mu\text{l}$  serum each were provided to Dr. R. Burri for the analysis of total  $T_3$ , total  $T_4$ , free  $T_3$ , free  $T_4$  and TSH, and the reported results were provided to the study director for inclusion in the report.

## 5.13 PATHOLOGY

### 5.13.1 NECROPSY

Necropsy:

after 16 weeks (Allocation A)                      17/18 February 2005  
after 16 weeks (Allocation B)                      16 February 2005

All animals were weighed and necropsied. Descriptions of all macroscopic abnormalities were recorded.

All animals were anesthetized by intraperitoneal injection of sodium pentobarbitone and killed by exsanguination.

Samples of the following tissues and organs were collected from all animals at necropsy and fixed in neutral phosphate buffered 4 % formaldehyde solution (unless otherwise indicated):

|   |   |
|---|---|
| <b>Adrenal glands</b>                                       | Nasal cavity (turbinates)                                 |
| <b>Aorta</b>  | <b>Ovaries</b>  |
| Bone (sternum, femur including joint)                       | <b>Pancreas</b>   |
| <b>Bone marrow (femur)</b>                                  | <b>Pituitary gland</b>                                    |
| <b>Brain (4 levels)</b>                                     | <b>Prostate gland (incl. coagulating glands)</b>          |
| <b>Cecum</b>  | <b>Rectum</b>   |
| <b>Colon</b>  | <b>Salivary glands - mandibular, sublingual</b>           |
| <b>Duodenum</b>   | <b>Sciatic nerve</b>                                      |
| <b>Epididymides (fixed in Bouin's solution)</b>             | <b>Seminal vesicles</b>                                   |
| <b>Esophagus</b>  | Skeletal muscle   |
| Exorbital lacrimal glands                                   | <b>Skin</b>   |
| <b>Eyes with optic nerve (fixed in Davidson's solution)</b> | <b>Spinal cord - cervical, midthoracic, lumbar</b>        |
| Harderian gland (fixed in Davidson's solution)              | <b>Spleen</b>   |
| <b>Heart</b>  | <b>Stomach</b>  |
| <b>Ileum, with Peyer's patches</b>                          | <b>Testes (fixed in Bouin's solution)</b>                 |
| <b>Jejunum with Peyer's patches</b>                         | <b>Thymus</b>   |
| <b>Kidneys</b>  | <b>Thyroid (including parathyroid gland, if possible)</b> |
| Larynx  | Tongue  |
| Lacrimal gland, exorbital                                   | <b>Trachea</b>  |
| <b>Liver</b>  | <b>Urinary bladder, infused with formalin at necropsy</b> |
| <b>Lungs, infused with formalin at necropsy</b>             | <b>Uterus</b>   |
| <b>Lymph nodes - mesenteric, mandibular</b>                 | <b>Vagina</b>   |
| <b>Mammary gland area</b>                                   | <b>Gross lesions</b>                                      |

### 5.13.2 ABSOLUTE AND RELATIVE ORGAN WEIGHTS

The following organ weights were recorded on the scheduled dates of necropsy:

|                         |          |              |
|-------------------------|----------|--------------|
| Brain                   | Thymus   | Spleen       |
| Heart                   | Kidneys  | Testes       |
| Liver                   | Adrenals | Epididymides |
| Thyroids w/parathyroids | Uterus   | Ovaries      |

The organ to terminal body weight ratios as well as organ to brain weight ratios were determined.

The determination of the terminal body weight was performed immediately prior to necropsy.

### 5.13.3 HISTOTECHNIQUE

All organ and tissue samples, as defined under Histopathology (following), were processed, embedded and cut at an approximate thickness of 2 to 4 micrometers, and stained with hematoxylin and eosin.

### 5.13.4 HISTOPATHOLOGY

Slides of all organs and tissues listed in boldface type (see Necropsy, above) that were collected at scheduled sacrifice from the animals of control and high-dose groups, as well as thyroid glands of the Allocation B were examined by the study pathologist.

Because test item-related morphologic changes were detected in the organs of high-dose animals, the same organs (thyroid glands) from animals of the mid- and low-dose groups were examined.

## 5.14 DATA COMPILATION

### 5.14.1 GENERAL

The RCC-TOX LIMS computer was used to sort and present suitable data for inclusion in the report. All electronically recorded data are conserved on a magnetic medium.

Individual values were rounded before printing. All derived values that appear in the tables represent the rounded results of calculations that used the exact raw data value.

Locomotor activity was recorded on-line, and the results were printed and transcribed into the computer system for compilation and analysis.

Cageside and detailed clinical signs, data from the functional observational battery and grip strength were recorded on data sheets and transcribed into the computer system for compilation and analysis.

## 5.15 DATA CALCULATION

### 5.15.1 FOOD CONSUMPTION

The food consumption was calculated per rat and per food consumption interval. It expresses the average food consumed per animal and per day over the food consumption interval.

$$FC = \frac{C}{AD}$$

where

FC is Food consumption in grams of food per animal and day;  
C is measured food consumption in grams per cage over the consumption interval and  
AD is total consumption days over all animals in the cage during the consumption interval.

### 5.15.2 RELATIVE FOOD CONSUMPTION

The relative food consumption was calculated according to the following formula:

$$RFC = \left[ \frac{FC}{BW(i)} \right] \times 1000$$

where

BW(i) is the most ideal body weight in grams or the body weight (of the corresponding rats) recorded on the day most close to the middle of the food consumption interval. In cases of equal "closeness" of two body weight records the later one was chosen;  
RFC is relative food consumption in grams of food per kg body weight and day, and  
FC is food consumption in grams of food per animal and day.

## 5.16 STATISTICAL ANALYSIS

The following statistical methods were used to analyze the grip strength, locomotor activity, body weight, organ weights and ratios, as well as:

- The Dunnett-test (many to one t-test) based on a pooled variance estimate were applied if the variables could be assumed to follow a normal distribution for the comparison of the treated groups and the control groups for each sex.
- The Steel-test (many-one rank test) were applied instead of the Dunnett-test when the data can not be assumed to follow a normal distribution.
- Fisher's exact-test were applied to the macroscopic findings.

The following statistical methods were used for statistical analysis of clinical laboratory data:

- Quantitative data were analyzed by a one-way analysis of variance (ANOVA) when the variances are considered homogeneous according to Bartlett. Alternatively, if the variances are considered to be heterogenous ( $p \leq 0.05$ ), a non-parametric Kruskal-Wallis test was used. Treated groups were compared to the control groups using Dunnett's test if the ANOVA was significant at the 5% level and by Dunn's test in the case of a significant Kruskal-Wallis test ( $p \leq 0.05$ ).
- Ordinal data such as urine sediment were analyzed using the Kruskal-Wallis test. If this test was significant ( $p \leq 0.05$ ), comparisons were made between the control group and each of the treatment groups using Dunn's test.

References :

- C.W. Dunnett: A Multiple Comparison Procedure for Comparing Several Treatments with a Control, J. Amer. Stat. Assoc. 50, 1096-1121 (1955).
- S.C. Gad and C.S. Weil: Statistics and Experimental Design for Toxicologists. The Telford Press, Caldwell, New Jersey, 43-45 (1986).
- W.H. Kruskal and W.A. Wallis: Use of ranks in one-criterion variance analysis. Journal of the American Statistical Association, 47, 583-621 (1952).
- O.J. Dunn: Multiple comparisons using rank sums. Technometrics 6, 241-252 (1964).
- R.G. Miller: Simultaneous Statistical Inference, Springer Verlag, New York (1981).
- R.A. Fisher: Statistical Methods for Research Workers, Oliver and Boyd, Edinburgh (1950).



## 6 RESULTS

### 6.1 DOSE FORMULATION ANALYSIS

The results of homogeneity and concentration analyses showed that the formulation procedure resulted in adequate dose formulations.

| <b>Concentration as Percent of Target</b> |              |              |               |
|---|--------------|--------------|---------------|
| Sample Date                               | 15 mg/kg/day | 50 mg/kg/day | 200 mg/kg/day |
| 01 Nov 2004                               | 96.7%        | 96.0%        | 99.2%         |
| 23 Nov 2004                               | 97.2%        | 95.0%        | 96.6%         |
| 07 Dec 2004                               | 88.3%        | 90.4%        | 83.4%         |
| 04 Jan 2005                               | 101.4%       | 96.6%        | 100.0%        |

The dose formulations were prepared daily. The 2-hour and 4-hour stability of the dose formulations were confirmed on one occasion each.

| <b>Stability after 2 hours</b> |              |              |               |
|--------------------------------|--------------|--------------|---------------|
| Sample Date                    | 15 mg/kg/day | 50 mg/kg/day | 200 mg/kg/day |
| 01 Nov 2004                    | 96.8%        | 96.5%        | 97.8%         |
| <b>Stability after 4 hours</b> |              |              |               |
| Sample Date                    | 15 mg/kg/day | 50 mg/kg/day | 200 mg/kg/day |
| 23 Nov 2004                    | 96.3%        | 95.6%        | 98.7%         |

During the initial dose formulation analyses, the stability of the dose formulations was found to insufficient for weekly formulation. A study plan amendment was written to change to daily formulation and the study was extended to include a minimum of 90 days' treatment with dose formulations prepared daily.

| <b>Stability after 7 days</b> |              |              |               |
|-------------------------------|--------------|--------------|---------------|
| Sample Date                   | 15 mg/kg/day | 50 mg/kg/day | 200 mg/kg/day |
| 01 Nov 2004                   | 9.1%         | 33.3%        | 72.0%         |

See pp. 345 - 361

### 6.2 VIABILITY/MORTALITY

All animals survived until scheduled necropsy.

See pp. 106 - 113

## 6.3 OBSERVATIONS

### 6.3.1 GENERAL CAGESIDE OBSERVATIONS (DAILY)

In males and females treated with 50 mg/kg/day, blue discoloration of the urine was noted from days 9-16 of treatment and again from day 24 of treatment onwards. Rats treated with 200 mg/kg/day had blue discoloration of the urine from treatment day 3 onwards. This finding was considered likely to be excreted test item.

In three females treated with 200 mg/kg/day (nos. 116, 119 and 120), slight alopecia was noted from day 50 onwards. This finding was considered to be a background change and, as it was noted in cage mates, probably due to internecine conflict and not accorded any toxicological relevance.

See pp. 44 – 59, 114 - 137

### 6.3.2 DETAILED CLINICAL OBSERVATIONS (WEEKLY)

Detailed weekly clinical observations performed during weeks 1-14<sup>1</sup> of treatment showed blue discoloration of the urine in rats treated with 50 mg/kg/day or 200 mg/kg/day. This finding began during week 2 of treatment and was noted during each subsequent weekly observation. This finding was considered likely to be excreted test item.

Blue discoloration of the urine was also noted in females treated with 15 mg/kg/day from weeks 7-14.

Bilateral miosis was noted during week 14 in one female treated with 15 mg/kg/day. This finding was not seen in other females treated with 15 mg/kg/day nor in any rat at 50 mg/kg/day or 200 mg/kg/day and therefore considered to be incidental.

No other findings were evident in any animal during weekly clinical observations.

See pp. 60 – 67, 138 - 145

### 6.3.3 FUNCTIONAL OBSERVATIONAL BATTERY

No test item-related findings were noted in any male or female during the functional observational battery performed at week 15.<sup>2</sup>

See pp. 60 – 67, 138 - 145

#### Grip Strength

No test item-related differences in the mean fore- and hind-limb grip strength values were noted at any dose level.

The mean hindlimb grip strength of the females treated with 50 mg/kg/day was significantly elevated ( $p < 0.05$ ) when compared with the controls. In the absence of dose-response relationship, this isolated difference was considered to be incidental.

See pp. 68, 146

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<sup>1</sup> Although the animals were observed weekly during weeks 1-14, they appear in the summary and individual tables as weeks 1-13. This is due to technicalities of formatting in which the weeks appear in sequential columns. Week 13 is recorded under the "tens" column, whereas Week 14 is recorded under the "ones" column.

<sup>2</sup> Since the Week 15 Functional Observational Battery yielded no findings, the computer was unable to generate specific summary or individual tables.

### **Locomotor Activity**

No test item-related differences in mean locomotor activity were noted at any dose level. In males treated with 15 mg/kg/day, a reduction in the mean locomotor activity was noted from 20-30 minutes ( $p < 0.05$ ) whereas in females treated with 50 mg/kg/day, a reduction in mean locomotor activity was noted during 30-40 minutes ( $p < 0.05$ ). No toxicological relevance was equated with these transient changes. Rats treated with 200 mg/kg/day were unaffected.

See pp. 69 – 70, 147 - 150

### **6.3.4 OPHTHALMOSCOPIC EXAMINATIONS**

No ocular changes of toxicological relevance were seen after 14 weeks of treatment.

See pp.87 – 90, 199 - 202

## **6.4 FOOD CONSUMPTION**

No test item-related changes in the mean daily food consumption were noted at any time point during the study.

From days 85-92, the mean daily food consumption values of the test item-treated males were markedly lower than those of the control males, but this was considered to be an artifact related to probable spillage of the feed in one cage of control males. Therefore, no toxicological relevance was attributed to the differences observed in the test item-treated groups.

See pp. 35 – 38, 71 – 78, 151 - 166

## **6.5 BODY WEIGHTS**

The mean body weights of the test item-treated males were marginally lower than those of the control males from day 29 of treatment onwards, but the differences were not clearly dose-related.

The lower body weights recorded on days 78, 85 and 92 of treatment in males treated with 200 mg/kg/day attained statistical significance ( $p < 0.05$ ) when compared with the controls. On day 1 of treatment, the mean body weights of the males treated with 15 mg/kg/day were significantly lower ( $p < 0.01$ ) than those of the control males, but compared favorably on days 8, 15, 22 and 29 of treatment. These differences were considered to be incidental.

The mean body weights and the mean body weight gain of the test item-treated females compared favorably with those of the controls throughout the treatment period.

See pp. 39 – 42, 79 – 86, 167 - 198

## 6.6 CLINICAL LABORATORY INVESTIGATIONS

### 6.6.1 HEMATOLOGY

In both sexes treated with 200 mg/kg/day, significantly lower red blood cell counts ( $p < 0.01$ ) were recorded. In females treated with 200 mg/kg/day, significantly lower hemoglobin ( $p < 0.01$ ) and lower hematocrit ( $p < 0.01$ ) were recorded when compared with controls. Although the mean corpuscular volume was significantly elevated in both sexes treated with 200 mg/kg/day ( $p < 0.01$ ), these differences were partly due to low control values. The red cell distribution width was significantly reduced in females treated with 200 mg/kg/day ( $p < 0.05$ ), but marginally elevated without significance in females treated with 15 mg/kg/day or 50 mg/kg/day. The mean absolute and relative reticulocyte counts were significantly elevated in females treated with 50 mg/kg/day ( $p < 0.01$ ) and in both sexes treated with 200 mg/kg/day ( $p < 0.01$ ). The elevated values noted in the females treated with 200 mg/kg/day exceeded the ranges of the historical control values.

These changes remained within the ranges of the historical control data, yet were considered to be slight effects upon hematopoiesis, and correlated with microscopical changes seen in the spleens of rats at the highest dose.

Statistically significant changes were seen in the reticulocyte maturity indices of females treated with 50 mg/kg/day ( $p < 0.01$ ) and of both sexes treated with 200 mg/kg/day ( $p < 0.01$  in males and mostly  $p < 0.05$  in females). These changes were primarily shifts towards high fluorescence reticulocytes from low fluorescence reticulocytes. Although the changes remained within the ranges of the historical control values, they were considered to be a slight test item-related effect.

In females treated with 50 mg/kg/day, significantly lower red blood cell counts ( $p < 0.01$ ), lower hemoglobin ( $p < 0.01$ ) and lower hematocrit ( $p < 0.01$ ) were evident when compared with control females. Insofar as similar findings were also seen at the higher dose of 200 mg/kg/day, these were considered to be slight test item-related effects.

The methemoglobin level noted in the blood of females treated with 50 mg/kg/day or 200 mg/kg/day was significantly higher (both  $p < 0.05$ ) than that of the control females, and was in the upper range of the historical control data. This finding was considered to be a slight test item-related change. Heinz bodies were not seen.

Some incidental differences in the mean hematology data were seen: In males treated with 50 mg/kg/day, the mean relative monocyte count was significantly elevated ( $p < 0.01$ ) when compared with the control males. In the absence of a clear dose-response relationship, the difference was considered to be incidental. Also, the mean relative thromboplastin time was significantly elevated in males treated with 200 mg/kg/day ( $p < 0.05$ ) but remained within the range of the historical control data and therefore considered unrelated to the treatment with the test item.

See pp. 260 - 344

### 6.6.2 CLINICAL BIOCHEMISTRY

In females treated with 200 mg/kg/day, significantly reduced creatinine levels ( $p < 0.05$ ) and significantly elevated triglyceride levels ( $p < 0.01$ ) exceeded the historical control ranges and were considered to be test item-related changes.

Although the mean phospholipid levels were significantly elevated in males and females treated with 200 mg/kg/day ( $p < 0.01$ ), they remained within the ranges of the historical control data.

A number of statistically significant differences were seen in several electrolytes:

- The sodium levels of males treated with 15 mg/kg/day ( $p < 0.05$ ) and 50 mg/kg/day ( $p < 0.01$ ) were elevated whereas no effects were ascertained in males at 200 mg/kg/day. In females, the sodium levels were significantly higher at 50 mg/kg/day ( $p < 0.01$ ) and 200 mg/kg/day ( $p < 0.01$ ) and both exceeded the historical control data.
- The potassium levels of males at all doses were significantly elevated ( $p < 0.01$ ) when compared with controls. However, there was no clear dose response relationship and the control value (when compared with the historical control data) was slightly low.
- The chloride levels seen in males reflected the differences noted for sodium, in that statistically significant changes were seen in males at 15 mg/kg/day ( $p < 0.01$ ) and 50 mg/kg/day ( $p < 0.05$ ), whereas no changes were seen at 200 mg/kg/day. In females treated with 50 mg/kg/day or 200 mg/kg/day, significantly higher chloride levels (both  $p < 0.01$ ) were noted when compared with the control. Both of the latter differences exceeded the historical control data ranges.

During electrophoresis, significant reductions of mean relative alpha-2 globulin were noted in females treated with 15 mg/kg/day ( $p < 0.05$ ), 50 mg/kg/day ( $p < 0.01$ ) or 200 mg/kg/day ( $p < 0.05$ ) when compared with the controls. All were below the range of the historical control data. Only the mean absolute alpha-2 globulin level was significantly reduced ( $p < 0.05$ ) in females at 50 mg/kg/day when compared with the control.

Elevated blood glucose levels were noted in males treated with 15 mg/kg/day ( $p < 0.05$ ) and in females treated with 50 mg/kg/day ( $p < 0.05$ ). Elevated total bilirubin was noted in females treated with 50 mg/kg/day ( $p < 0.05$ ) when compared with the controls. The mean absolute and relative albumin levels of females treated with 15 mg/kg/day were significantly elevated ( $p < 0.01$ ) when compared with control females. The mean absolute albumin level of females treated with 50 mg/kg/day was significantly elevated ( $p < 0.05$ ) when compared with control females. A significantly elevated albumin/globulin ratio was noted in females treated with 15 mg/kg/day ( $p < 0.01$ ). In the absence of dose-response relationships, these differences were considered to be incidental.

See pp. 260 - 344

### 6.6.3 URINALYSIS

With increasing dose, yellow/brown to brown to black discoloration of the urine was noted in test item-treated males and females. This was considered likely to be excreted test item.

Urinary discoloration at 200 mg/kg/day precluded measurement of nearly all parameters.

At 50 mg/kg/day, a number of significant differences were likely to be the result of the urine discoloration and therefore were considered to be artifacts. These differences included elevated pH in males at 50 mg/kg/day ( $p < 0.01$ ), elevated nitrates in males and females at 50 mg/kg/day ( $p < 0.01$  or  $p < 0.05$ ), elevated protein in males and females at 50 mg/kg/day ( $p < 0.01$  or  $p < 0.05$ ), increased urobilinogen in males at 50 mg/kg/day ( $p < 0.01$ ), increased bilirubin in males ( $p < 0.01$ ) and females ( $p < 0.01$ ), increased erythrocytes in females at 50 mg/kg/day ( $p < 0.01$ ) and increased leukocytes in males and females at 50 mg/kg/day ( $p < 0.01$ ).

### 6.6.4 URINE SEDIMENT

Evaluation of urine sediment did not reveal test item-related changes.

Calcium oxalate and uric acid crystals were significantly increased in females treated with 200 mg/kg/day ( $p < 0.05$  and  $p < 0.01$ , respectively), whereas the amount of unidentifiable crystals was increased in males treated with 200 mg/kg/day ( $p < 0.01$ ). These findings were considered to be within the range of typical variation.

See pp. 260 - 344

## 6.7 THYROID HORMONES

No test item-related changes in the thyroid hormones (TSH, free and total T3 and T4) were noted at any dose level after 15 weeks of treatment.

### 6.7.1 TSH

#### Males

No differences between control and test item-treated animals were observed. Average values for all groups ranged from 0.046  $\mu\text{IU/mL}$  (15 mg/kg/day) to 0.115  $\mu\text{IU/mL}$  (200 mg/kg/day).

#### Females

No differences between control and test item-treated animals were observed. Average values for all groups ranged from 0.028  $\mu\text{IU/mL}$  (200 mg/kg/day) to 0.043  $\mu\text{IU/mL}$  (50 mg/kg/day).

### **6.7.2 TOTAL T3**

#### **Males**

No differences between control and test item-treated animals were observed. Average values ranged from 141.2 ng/dL (control) to 160.8 ng/dL (200 mg/kg/day).

#### **Females**

No differences between control and test item-treated animals were observed. Average values ranged from 108.9 ng/dL (50 mg/kg/day) to 126.6 ng/dL (control).

### **6.7.3 TOTAL T4**

#### **Males**

No differences between control and test item-treated animals were observed. Average values ranged from 6.47 µg/dL (control) to 7.22 µg/dL (15 mg/kg/day).

#### **Females**

No differences between control and test item-treated animals were observed. Average values ranged from 4.05 µg/dL (control) to 4.71 µg/dL (50 mg/kg/day).

### **6.7.4 FREE T3**

#### **Males**

No differences between control and test item-treated animals were observed. Average values ranged from 1.7 pg/mL (control and 200 mg/kg/day) to 2.1 pg/mL (50 mg/kg/day).

#### **Females**

No differences between control and test item-treated animals were observed. Average values ranged from 1.8 pg/mL (200 mg/kg/day) to 2.2 pg/mL (15 mg/kg/day and 50 mg/kg/day).

### **6.7.5 FREE T4**

#### **Males**

No differences between control and test item-treated animals were observed. Average values ranged from 3.30 ng/dL (50 mg/kg/day) to 3.70 ng/dL (200 mg/kg/day).

#### **Females**

No differences between control and test item-treated animals were observed. Average values ranged from 2.05 ng/dL (control) to 2.76 ng/dL (200 mg/kg/day).

See pp. 362 - 386

## 6.8 PATHOLOGY

### 6.8.1 ORGAN WEIGHTS

No statistically significant differences were noted in the mean absolute or relative organ weights of test item-treated males. Marginally elevated thyroid-to-brain weight ratios were noted in males and females treated with 200 mg/kg/day, which were considered to coincide with microscopical findings seen in the thyroid, and therefore considered to be test item-related changes.

In females treated with 200 mg/kg/day, significantly elevated mean absolute and relative liver weights were noted in liver ( $p < 0.01$ ), kidney ( $p < 0.01$  or  $p < 0.05$ ) and spleen ( $p < 0.01$ ). These differences were considered to be test item related.

All other organ weights and ratios were considered to be unaffected.

See pp. 93 – 104, 219 - 242

### 6.8.2 MACROSCOPIC FINDINGS

At the end of the treatment period, dark red or black discoloration of the thyroid was recorded in 14 of 15 males and seven of 15 females treated with 50 mg/kg/day, as well as 13 of 15 males and 14 of 15 females treated with 200 mg/kg/day. This change was assessed as a test item-related gross lesion.

All other macroscopic findings recorded were considered to be within the range of normal background lesions, which may be seen in rats of this strain and age in oral toxicity studies and were considered incidental, reflecting the usual individual variability. They consisted of renal pelvic dilation, eschar of the skin (nose region), alopecia (shoulder region), watery cyst(s) on the ovaries, and watery contents in the uterus (often combined with dilation of the organ), as well as discoloration or discolored foci in various organs (lungs, stomach, cecum, pancreas, thymus, mandibular lymph node, extra-orbital lacrimal glands, ovaries, uterus).

See pp. 91 – 92, 203 - 218

### 6.8.3 MICROSCOPIC FINDINGS

There were a number of findings, which distinguished test item-treated animals from controls.

#### thyroid:

- Follicular cell enlargement<sup>3</sup> due to minimal to slight a cytoplasmic storage of brown, finely granular pigment, partly along with minimally to slightly increased cytoplasmic vacuolation in animals treated with 50 mg/kg/day or 200 mg/kg/day. This change was more pronounced in male animals (allocations A and B cumulated: twelve of fifteen males and six of ten females treated with 50 mg/kg/day; fourteen of fifteen males and eleven of fifteen females treated with 200 mg/kg/day).

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<sup>3</sup>.Reported as "follicular cell hypertrophy" in the table part of the pathology report.



**pituitary:**

- Minimal to slight hypertrophy/plasia of chromophobic cells (characterized by increased cell size and increased vacuolation) in males treated with 50 mg/kg/day or 200 mg/kg/day (seven of ten males treated with 50 mg/kg/day; six of ten males treated with 200 mg/kg/day; this change was also recorded in one of ten control males and two of ten males treated with 15 mg/kg/day).

**kidneys:**

- Pigment storage in vacuolar basophilic tubulus cells was recorded in most test item-treated groups except females treated with 15 mg/kg/day (three of ten males treated with 15 mg/kg/day; six of ten males and three of ten females treated with 50 mg/kg/day; eight of ten males and six of ten females treated with 200 mg/kg/day).
- Minimal to slight vacuolar tubulus cell swelling at the corticomedullary junction (five of ten females treated with 15 mg/kg/day; six of ten females treated with 50 mg/kg/day; nine of ten females treated with 200 mg/kg/day), along with minimal to slight cytoplasmic storage of brown finely granular pigment in females of all test item-treated groups. In animals treated with 200 mg/kg/day, this change was sometimes accompanied by necrosis of single tubulus cells, and thickened basal membranes.
- Minimal storage of brown pigment in "normal" (non-swollen, non-basophilic) tubulus cells, and minimal brown pigmented tubular casts in three of ten males at 200 mg/kg/day.

**spleen:**

- Increased mean grade of extra medullary hemopoiesis in combination with slightly increased mean grade of hemosiderin storage in animals treated with 200 mg/kg/day. This change was more pronounced in female animals.

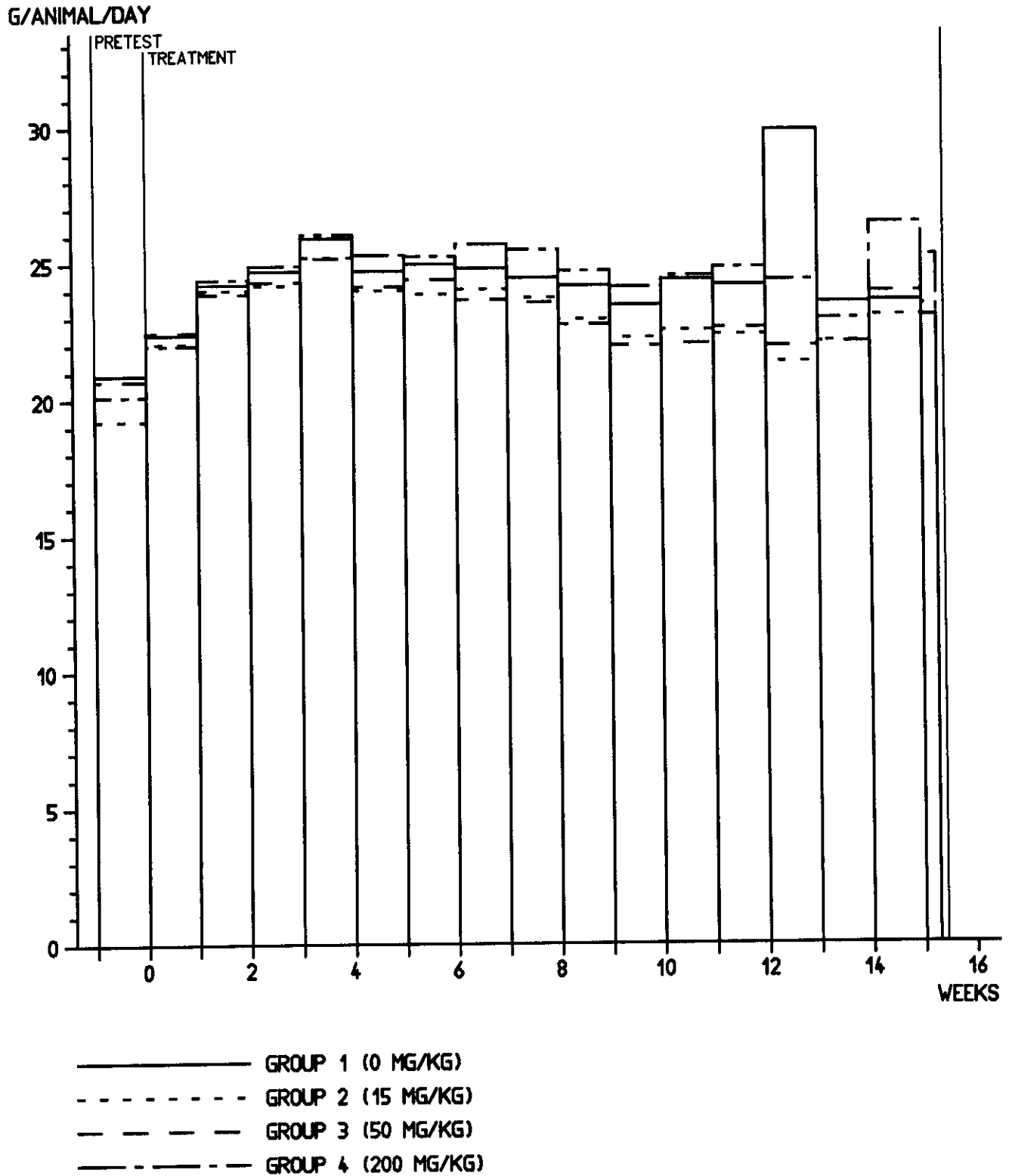
**Incidental microscopic findings**

Additionally, a variety of other changes were found in this study. They commonly occur in laboratory rats of this strain and age under the conditions of oral toxicity studies. Neither their incidences nor their distribution or morphologic appearance gave any indication of a treatment-related association.

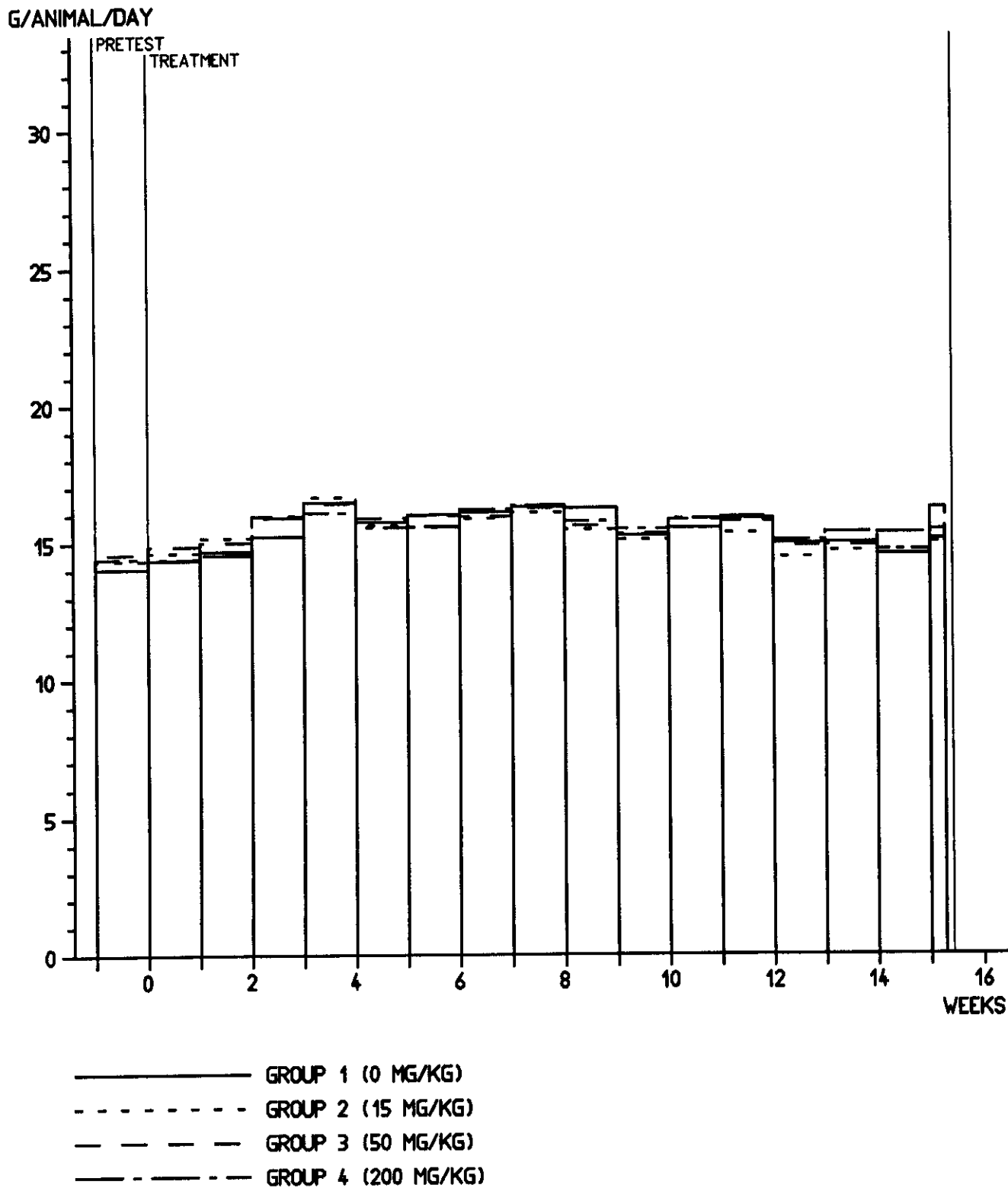
See pp. 387 - 629

## **7      FIGURES**

# FOOD CONSUMPTION MALES

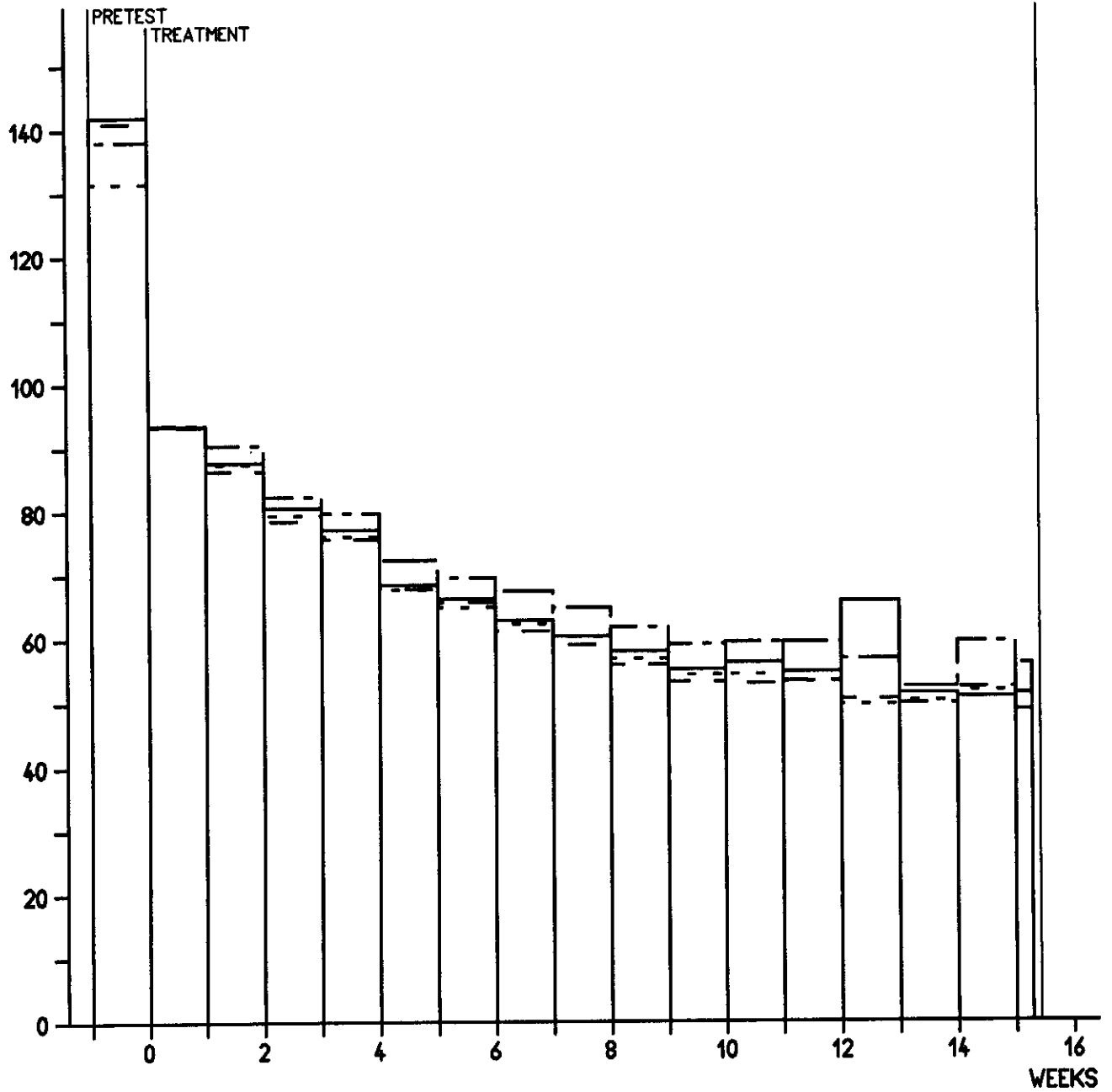


# FOOD CONSUMPTION FEMALES



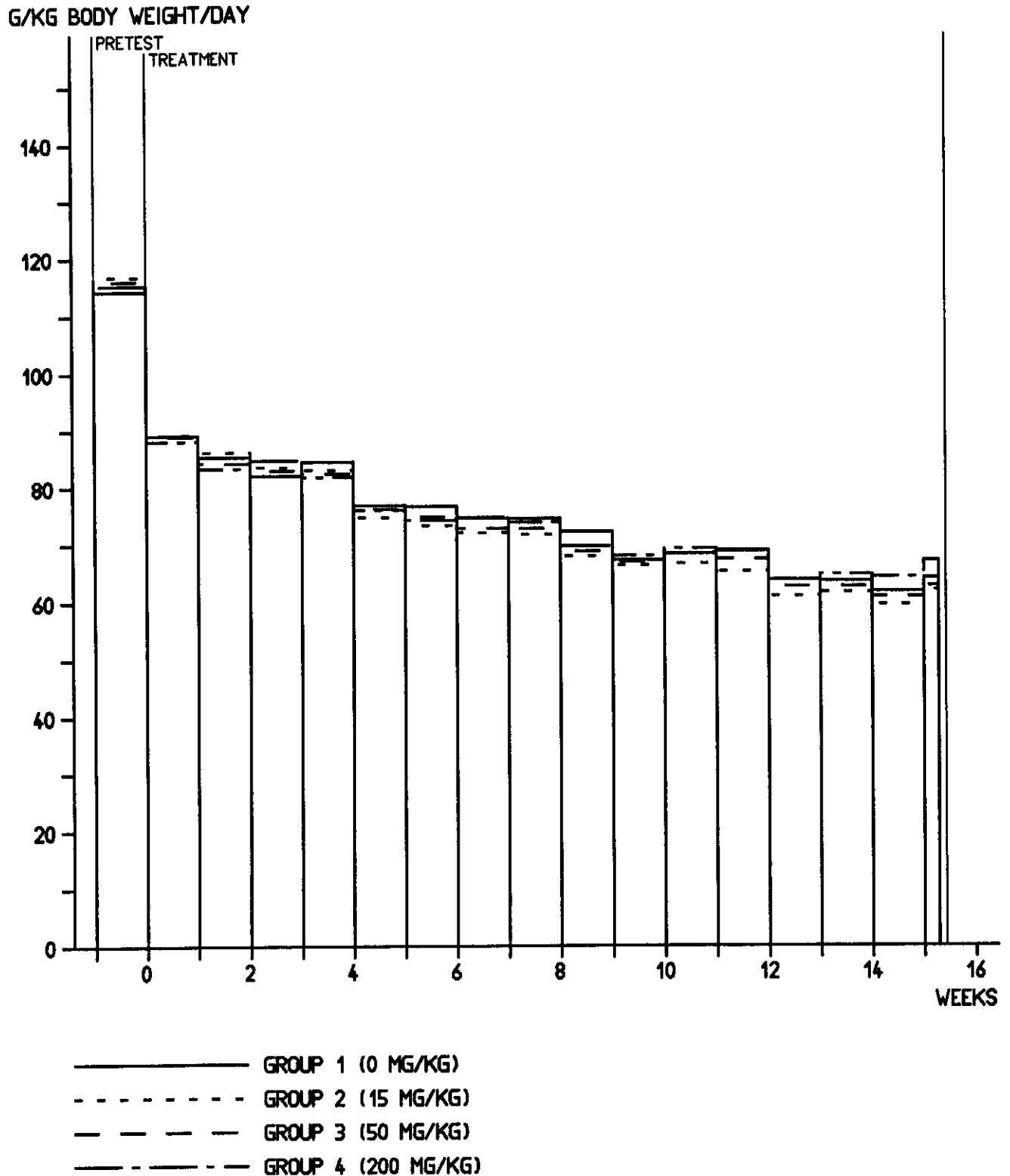
# RELATIVE FOOD CONSUMPTION MALES

G/KG BODY WEIGHT/DAY

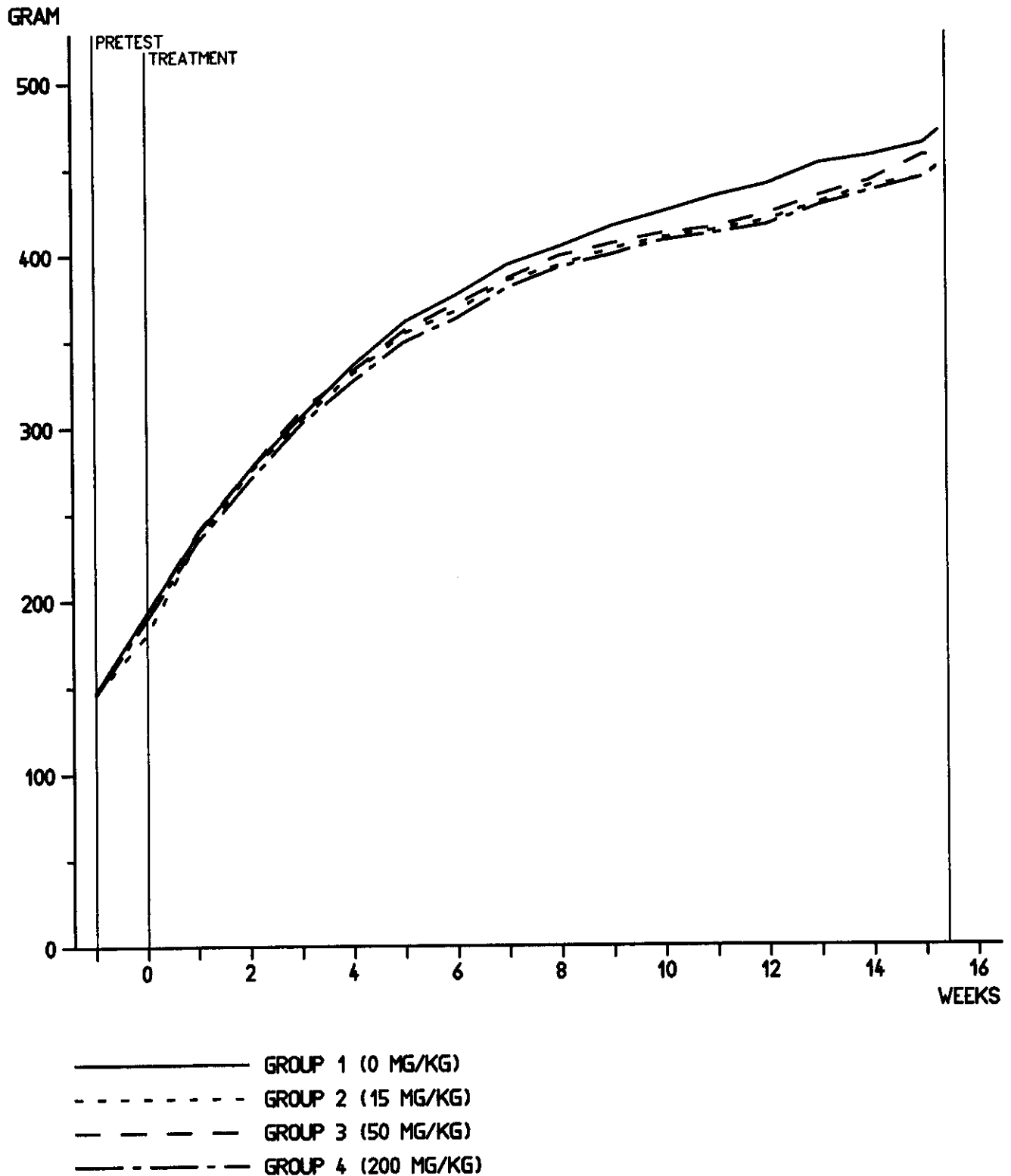


- GROUP 1 (0 MG/KG)
- - - - - GROUP 2 (15 MG/KG)
- - - - - GROUP 3 (50 MG/KG)
- - - - - GROUP 4 (200 MG/KG)

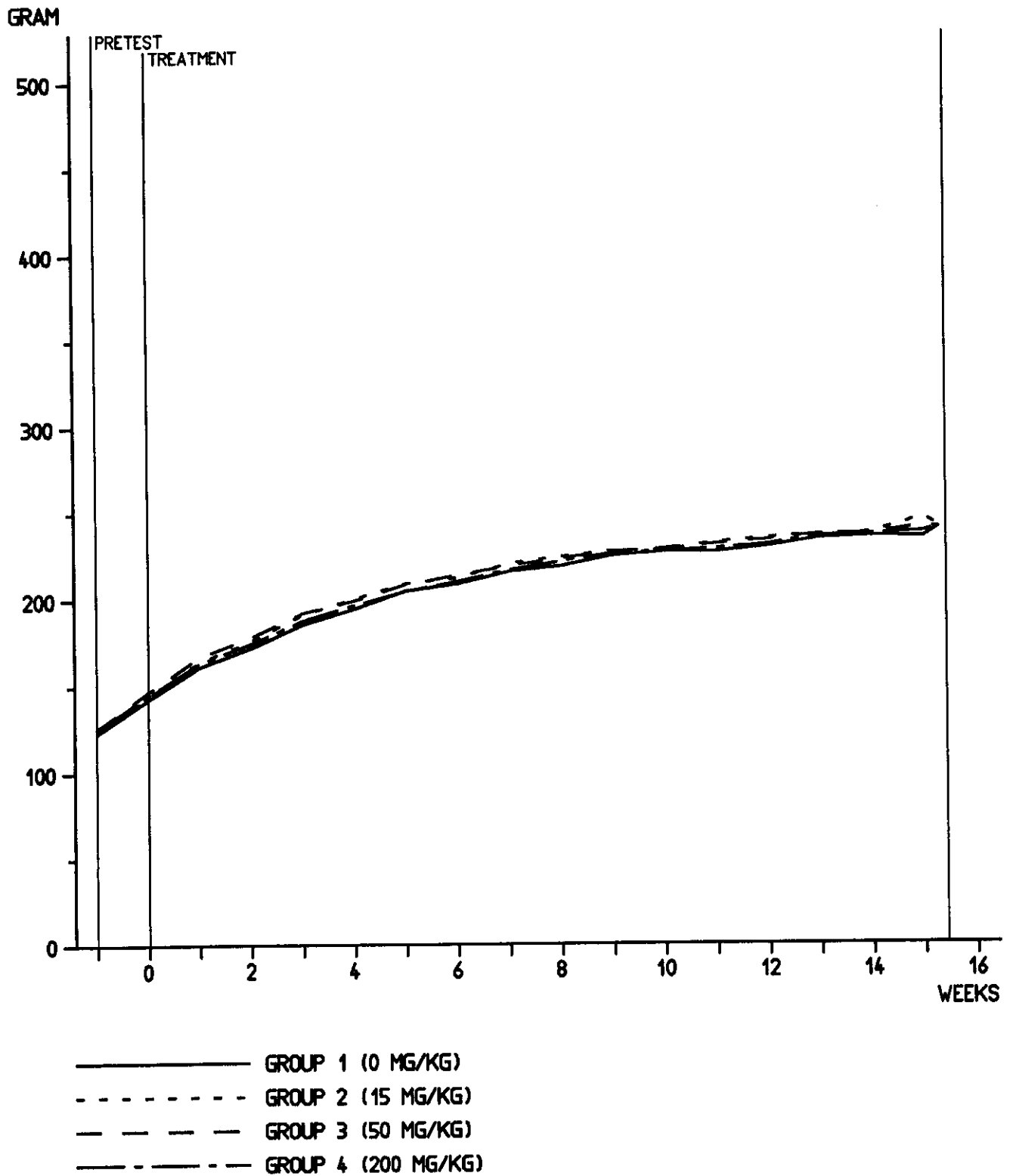
# RELATIVE FOOD CONSUMPTION FEMALES



# BODY WEIGHTS MALES

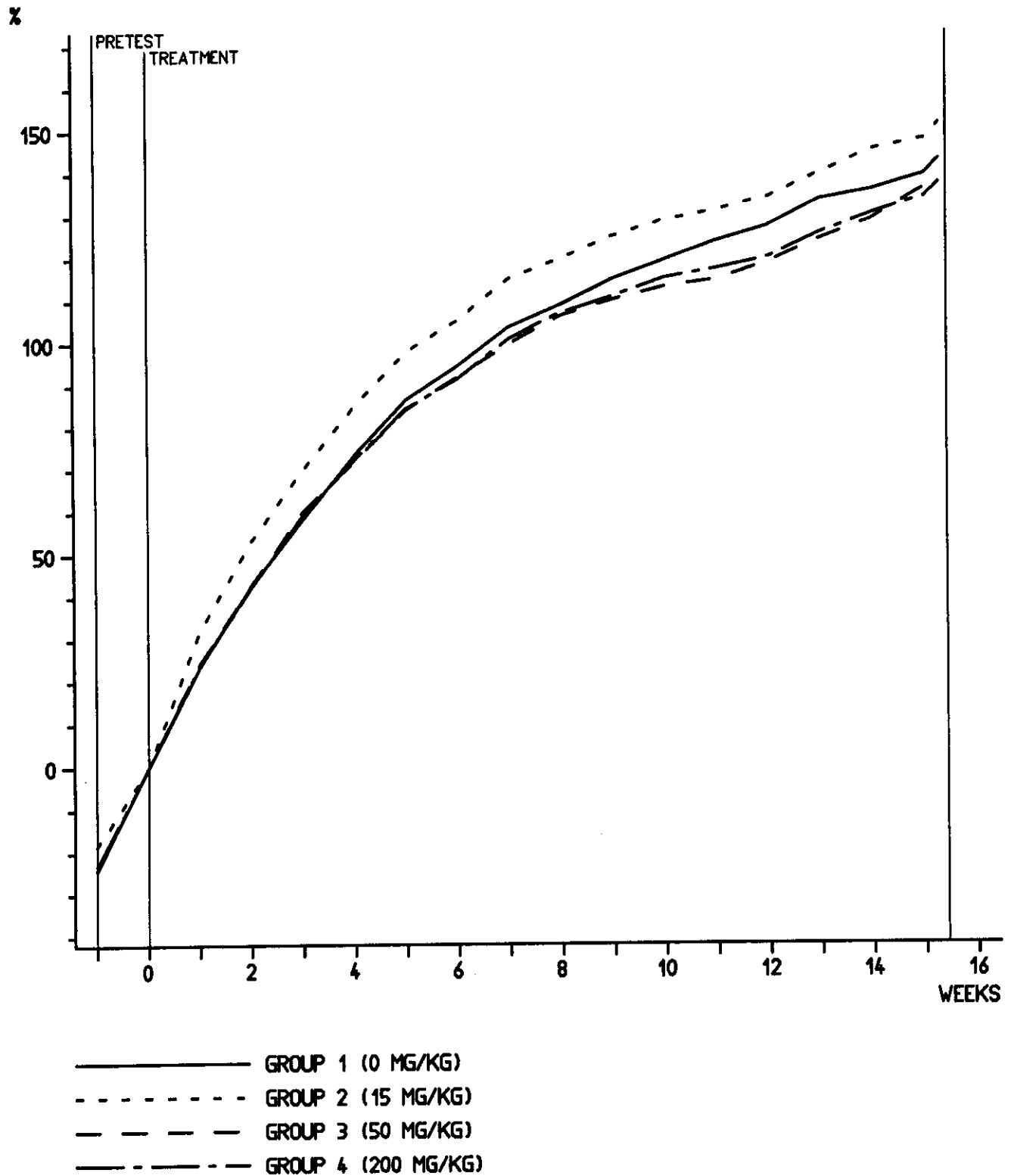


# BODY WEIGHTS FEMALES

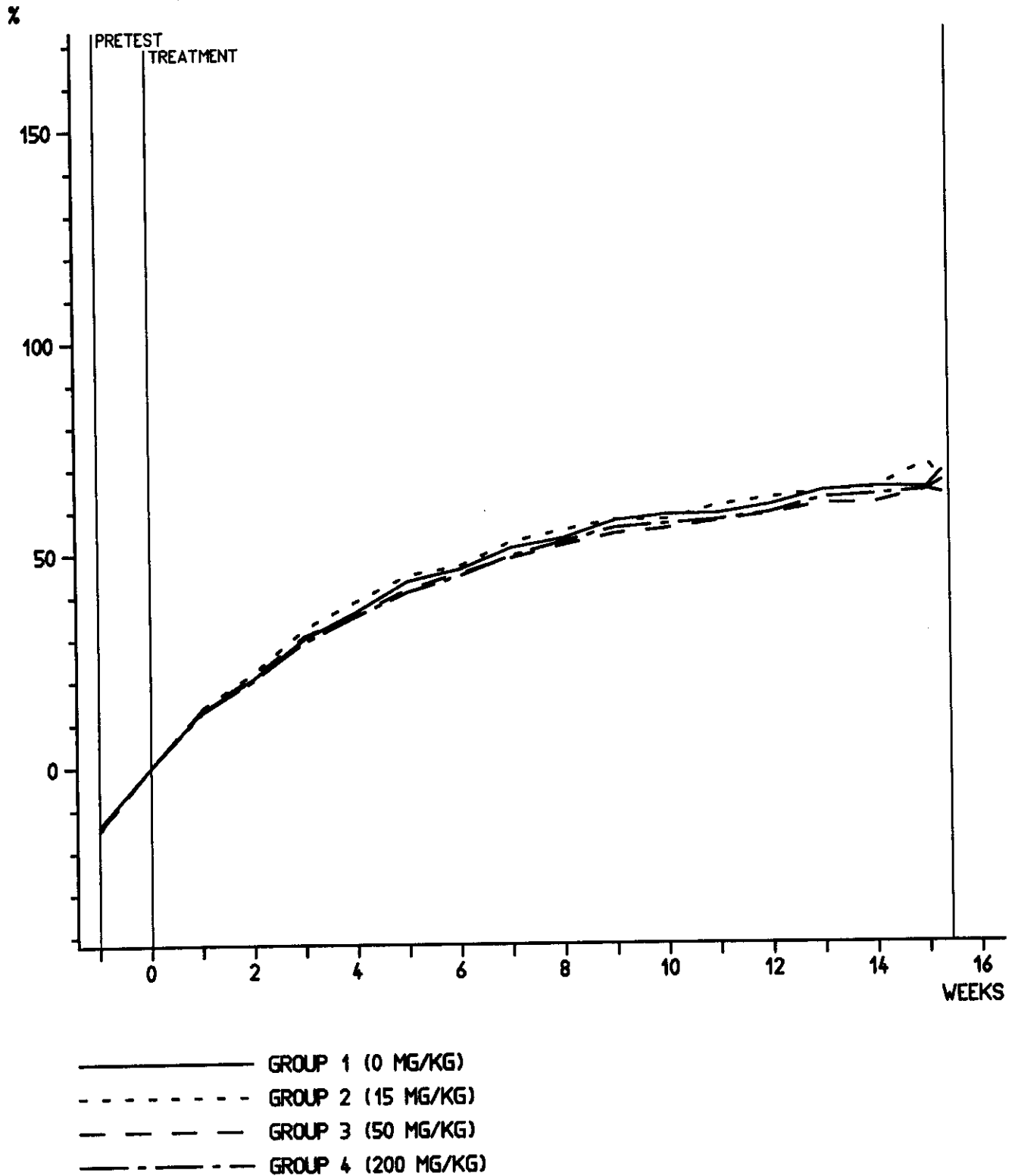




# BODY WEIGHT GAIN MALES



# BODY WEIGHT GAIN FEMALES



## **8    SUMMARY TABLES**

RCC STUDY NUMBER 857092  
A 084, WR 23081

SYM-SUM - 1  
22-APR-05

CLINICAL SIGNS, DAILY (SUMMARY)  
MALES  
GROUP 1 (0 MG/KG)

| SIGN (MAX.GRADE)<br>LOCATION | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|------------------------------|--------------------------|---|
|------------------------------|--------------------------|---|

---

NO CLINICAL SIGNS NOTED

RCC STUDY NUMBER 857092  
A 084, WR 23081

SYM-SUM - 2  
22-APR-05

CLINICAL SIGNS, DAILY (SUMMARY)  
MALES  
GROUP 2 (15 MG/KG)

| SIGN (MAX.GRADE)<br>LOCATION | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|------------------------------|--------------------------|---|
|------------------------------|--------------------------|---|

---

NO CLINICAL SIGNS NOTED

CLINICAL SIGNS, DAILY (SUMMARY)  
 MALES  
 GROUP 3 (50 MG/KG)

| SIGN (MAX.GRADE)<br>LOCATION | PRETEST       | TREATMENT                                  |
|------------------------------|---------------|--|
|                              | WEEKS: 1..... | 1.....2.....3.....4.....5.....6.....7..... |
| <b>SECRETION / EXCRETION</b> |               |  |
| -----                        |               |  |
| URINE BLUE (1)               | G: .....      | .....11111111.....111111111111111111111111 |
|                              | %: .....      | .....99999999.....AAAAAAAAAAAAAAAAAAAAAAAA |

G: Median value of the highest individual daily grades  
 %: Percent of affected animals (0 = less than 5%, 1 = between 5% and 15%, ..., A = more than 95%)



RCC STUDY NUMBER 857092  
A 084, WR 23081

SYM-SUM - 5  
22-APR-05

CLINICAL SIGNS, DAILY (SUMMARY)  
MALES  
GROUP 1 (0 MG/KG)

| SIGN (MAX.GRADE) | TREATMENT  |
|------------------|--|
| LOCATION         | WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16... |

---

NO CLINICAL SIGNS NOTED



RCC STUDY NUMBER 857092  
A 084, WR 23081

SYM-SUM - 6  
22-APR-05

CLINICAL SIGNS, DAILY (SUMMARY)  
MALES  
GROUP 2 (15 MG/KG)

| SIGN (MAX.GRADE) | TREATMENT  |
|------------------|--|
| LOCATION         | WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16... |

---

NO CLINICAL SIGNS NOTED





RCC STUDY NUMBER 857092  
A 084, WR 23081

SYM-SUM - 9  
22-APR-05

CLINICAL SIGNS, DAILY (SUMMARY)  
FEMALES  
GROUP 1 (0 MG/KG)

| SIGN (MAX.GRADE)<br>LOCATION | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|------------------------------|--------------------------|---|
|------------------------------|--------------------------|---|

---

NO CLINICAL SIGNS NOTED

CLINICAL SIGNS, DAILY (SUMMARY)  
FEMALES  
GROUP 2 (15 MG/KG)

| SIGN (MAX.GRADE)<br>LOCATION | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|------------------------------|--------------------------|---|
|------------------------------|--------------------------|---|

---

NO CLINICAL SIGNS NOTED





RCC STUDY NUMBER 857092  
A 084, WR 23081

SYM-SUM - 13  
22-APR-05

CLINICAL SIGNS, DAILY (SUMMARY)  
FEMALES  
GROUP 1 (0 MG/KG)

| SIGN (MAX.GRADE) | TREATMENT  |
|------------------|--|
| LOCATION         | WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16... |

---

NO CLINICAL SIGNS NOTED



RCC STUDY NUMBER 857092  
A 084, WR 23081

SYM-SUM - 14  
22-APR-05

CLINICAL SIGNS, DAILY (SUMMARY)  
FEMALES  
GROUP 2 (15 MG/KG)

| SIGN (MAX.GRADE)<br>LOCATION | TREATMENT<br>WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16... |
|------------------------------|---|
|------------------------------|---|

---

NO CLINICAL SIGNS NOTED





RCC STUDY NUMBER 857092  
A 084, WR 23081

SYM-SUM - 1  
26-APR-05

CLINICAL SIGNS, WEEKLY (SUMMARY)  
MALES  
GROUP 1 (0 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST<br>WEEKS: 1 | TREATMENT<br>1...5...9...13 |
|--------------------------------|---------------------|-----------------------------|
|--------------------------------|---------------------|-----------------------------|

---

NO CLINICAL SIGNS NOTED

RCC STUDY NUMBER 857092  
A 084, WR 23081

SYM-SUM - 2  
26-APR-05

CLINICAL SIGNS, WEEKLY (SUMMARY)  
MALES  
GROUP 2 (15 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST TREATMENT |                |
|--------------------------------|-------------------|----------------|
|                                | WEEKS: 1          | 1...5...9...13 |

---

NO CLINICAL SIGNS NOTED

CLINICAL SIGNS, WEEKLY (SUMMARY)  
MALES  
GROUP 3 (50 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST TREATMENT |                 |
|--------------------------------|-------------------|-----------------|
|                                | WEEKS: 1          | 1...5...9...13  |
| <hr/>                          |                   |                 |
| SECRETION / EXCRETION          |                   |                 |
| -----                          |                   |                 |
| URINE BLUE (1)                 | G: .              | .11111111111111 |
|                                | %: .              | .AAAAAAAAAAAA   |

---

G: Median value of the highest individual weekly grades  
%: Percent of affected animals (0 = less than 5%, 1 = between 5% and 15%, ..., A = more than 95%)

CLINICAL SIGNS, WEEKLY (SUMMARY)  
MALES  
GROUP 4 (200 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST TREATMENT |                |
|--------------------------------|-------------------|----------------|
|                                | WEEKS: 1          | 1...5...9...13 |
| <hr/>                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| -----                          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
|                                | %: .              | .AAAAAAAAAAAAA |

---

G: Median value of the highest individual weekly grades  
%: Percent of affected animals (0 = less than 5%, 1 = between 5% and 15%, ..., A = more than 95%)

RCC STUDY NUMBER 857092  
A 084, WR 23081

SYM-SUM - 5  
26-APR-05

CLINICAL SIGNS, WEEKLY (SUMMARY)  
FEMALES  
GROUP 1 (0 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST<br>WEEKS: 1 | TREATMENT<br>1...5...9...13 |
|--------------------------------|---------------------|-----------------------------|
|--------------------------------|---------------------|-----------------------------|

---

NO CLINICAL SIGNS NOTED



CLINICAL SIGNS, WEEKLY (SUMMARY)  
 FEMALES  
 GROUP 2 (15 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST TREATMENT |                |
|--------------------------------|-------------------|----------------|
|                                | WEEKS: 1          | 1...5...9...13 |
| <b>SECRETION / EXCRETION</b>   |                   |                |
| -----                          |                   |                |
| URINE BLUE (1)                 | G: .              | .....1111111.  |
|                                | %: .              | .....AAAAAAA.  |
| <b>VARIOUS</b>                 |                   |                |
| -----                          |                   |                |
| MIOSIS (1)<br>(EYE LEFT)       | G: .              | .....1         |
|                                | %: .              | .....1         |
| MIOSIS (1)<br>(EYE RIGHT)      | G: .              | .....1         |
|                                | %: .              | .....1         |

G: Median value of the highest individual weekly grades  
 %: Percent of affected animals (0 = less than 5%, 1 = between 5% and 15%, ..., A = more than 95%)

CLINICAL SIGNS, WEEKLY (SUMMARY)  
FEMALES  
GROUP 3 (50 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST TREATMENT |                 |
|--------------------------------|-------------------|-----------------|
|                                | WEEKS: 1          | 1...5...9...13  |
| <hr/>                          |                   |                 |
| SECRETION / EXCRETION          |                   |                 |
| -----                          |                   |                 |
| URINE BLUE (1)                 | G: .              | .11111111111111 |
|                                | %: .              | .AAAAAAAAAAAA   |

---

G: Median value of the highest individual weekly grades  
%: Percent of affected animals (0 = less than 5%, 1 = between 5% and 15%, ..., A = more than 95%)

CLINICAL SIGNS, WEEKLY (SUMMARY)  
FEMALES  
GROUP 4 (200 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST TREATMENT |                 |
|--------------------------------|-------------------|-----------------|
|                                | WEEKS: 1          | 1...5...9...13  |
| <hr/>                          |                   |                 |
| SECRETION / EXCRETION<br>----- |                   |                 |
| URINE BLUE (1)                 | G: .              | .11111111111111 |
|                                | %: .              | .AAAAAAAAAAAA   |

---

G: Median value of the highest individual weekly grades  
%: Percent of affected animals (0 = less than 5%, 1 = between 5% and 15%, ..., A = more than 95%)

**GRIP STRENGTH , SUMMARY**

**WEEK 15**

|                  | <b>MALES</b>    |                 | <b>Mean (g)</b> | <b>FEMALES</b>  |                 | <b>Mean (g)</b> |
|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| <b>GROUP 1</b>   |                 |                 |                 |                 |                 |                 |
| <b>0 mg/kg</b>   | <b>Forelimb</b> | <b>Hindlimb</b> |                 | <b>Forelimb</b> | <b>Hindlimb</b> |                 |
| <b>Mean</b>      | 1739            | 1182            |                 | 1320            | 914             |                 |
| <b>St.dev.</b>   | 161             | 64              |                 | 53              | 52              |                 |
| <b>N</b>         | 10              | 10              |                 | 10              | 10              |                 |
| <b>GROUP 2</b>   |                 |                 |                 |                 |                 |                 |
| <b>15 mg/kg</b>  | <b>Forelimb</b> | <b>Hindlimb</b> |                 | <b>Forelimb</b> | <b>Hindlimb</b> |                 |
| <b>Mean</b>      | 1746            | 1203            |                 | 1339            | 953             |                 |
| <b>St.dev.</b>   | 76              | 30              |                 | 29              | 42              |                 |
| <b>N</b>         | 10              | 10              |                 | 10              | 10              |                 |
| <b>GROUP 3</b>   |                 |                 |                 |                 |                 |                 |
| <b>50 mg/kg</b>  | <b>Forelimb</b> | <b>Hindlimb</b> |                 | <b>Forelimb</b> | <b>Hindlimb</b> |                 |
| <b>Mean</b>      | 1749            | 1203            |                 | 1351            | 959 *           |                 |
| <b>St.dev.</b>   | 72              | 51              |                 | 55              | 35              |                 |
| <b>N</b>         | 10              | 10              |                 | 10              | 10              |                 |
| <b>GROUP 4</b>   |                 |                 |                 |                 |                 |                 |
| <b>200 mg/kg</b> | <b>Forelimb</b> | <b>Hindlimb</b> |                 | <b>Forelimb</b> | <b>Hindlimb</b> |                 |
| <b>Mean</b>      | 1744            | 1212            |                 | 1318            | 928             |                 |
| <b>St.dev.</b>   | 87              | 38              |                 | 62              | 35              |                 |
| <b>N</b>         | 10              | 10              |                 | 10              | 10              |                 |

\*\*\* T-Test sig. at 5% or 1% level

**LOCOMOTOR ACTIVITY, SUMMARY**

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| LOW BEAMS COUNT | MALES          |                |                |                |                |                | AT WEEK 15   |
|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|--------------|
|                 | 15 min.        | 20 Min.        | 30 min.        | 40 min.        | 50 min.        | 60 min.        |              |
| <b>Group 1</b>  |                |                |                |                |                |                | <b>Total</b> |
| Mean            | 364            | 249            | 175            | 114            | 107            | 74             | 1082         |
| St.dev.         | 124            | 36             | 61             | 91             | 95             | 60             | 337          |
| N               | 10             | 10             | 10             | 10             | 10             | 10             | 10           |
| <b>Group 2</b>  | <b>10 min.</b> | <b>20 Min.</b> | <b>30 min.</b> | <b>40 min.</b> | <b>50 min.</b> | <b>60 min.</b> | <b>Total</b> |
| Mean            | 365            | 226            | 120 *          | 112            | 94             | 76             | 993          |
| St.dev.         | 69             | 91             | 48             | 99             | 85             | 85             | 251          |
| N               | 10             | 10             | 10             | 10             | 10             | 10             | 10           |
| <b>Group 3</b>  | <b>10 min.</b> | <b>20 Min.</b> | <b>30 min.</b> | <b>40 min.</b> | <b>50 min.</b> | <b>60 min.</b> | <b>Total</b> |
| Mean            | 340            | 187            | 130            | 139            | 88             | 72             | 955          |
| St.dev.         | 85             | 101            | 106            | 71             | 89             | 74             | 347          |
| N               | 10             | 10             | 10             | 10             | 10             | 10             | 10           |
| <b>Group 4</b>  | <b>10 min.</b> | <b>20 Min.</b> | <b>30 min.</b> | <b>40 min.</b> | <b>50 min.</b> | <b>60 min.</b> | <b>Total</b> |
| Mean            | 408            | 189            | 127            | 102            | 74             | 60             | 958          |
| St.dev.         | 110            | 90             | 61             | 96             | 67             | 66             | 296          |
| N               | 10             | 10             | 10             | 10             | 10             | 10             | 10           |

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\*/\*\* T-Test sig. at 5% or 1% level

**LOCOMOTOR ACTIVITY, SUMMARY**

---

| LOW BEAMS COUNT | FEMALES        |                |                |                |                |                | AT WEEK 15   |
|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|--------------|
|                 | 15 min.        | 20 Min.        | 30 min.        | 40 min.        | 50 min.        | 60 min.        |              |
| <b>Group 1</b>  |                |                |                |                |                |                | <b>Total</b> |
| Mean            | 321            | 189            | 131            | 200            | 121            | 76             | 1037         |
| St.dev.         | 101            | 59             | 84             | 90             | 159            | 117            | 394          |
| N               | 10             | 10             | 10             | 10             | 10             | 10             | 10           |
| <b>Group 2</b>  | <b>10 min.</b> | <b>20 Min.</b> | <b>30 min.</b> | <b>40 min.</b> | <b>50 min.</b> | <b>60 min.</b> | <b>Total</b> |
| Mean            | 293            | 189            | 141            | 135            | 95             | 84             | 937          |
| St.dev.         | 105            | 78             | 77             | 74             | 71             | 74             | 306          |
| N               | 10             | 10             | 10             | 10             | 10             | 10             | 10           |
| <b>Group 3</b>  | <b>10 min.</b> | <b>20 Min.</b> | <b>30 min.</b> | <b>40 min.</b> | <b>50 min.</b> | <b>60 min.</b> | <b>Total</b> |
| Mean            | 323            | 200            | 110            | 116 *          | 96             | 68             | 912          |
| St.dev.         | 107            | 91             | 97             | 96             | 86             | 73             | 324          |
| N               | 10             | 10             | 10             | 10             | 10             | 10             | 10           |
| <b>Group 4</b>  | <b>10 min.</b> | <b>20 Min.</b> | <b>30 min.</b> | <b>40 min.</b> | <b>50 min.</b> | <b>60 min.</b> | <b>Total</b> |
| Mean            | 346            | 194            | 167            | 117            | 64             | 89             | 976          |
| St.dev.         | 115            | 50             | 85             | 101            | 62             | 79             | 329          |
| N               | 10             | 10             | 10             | 10             | 10             | 10             | 10           |

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\*/\*\* T-Test sig. at 5% or 1% level

RCC STUDY NUMBER 857092  
A 084, WR 23081

FC-SUM - 1  
22-APR-05

**FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY  
MALES**

---

| PRETEST   |          | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|-----------|----------|--------------------|---------------------|---------------------|----------------------|
| DAYS 1-8  | MEAN     | 20.9               | 19.2                | 20.7                | 20.1                 |
| WEEKS 1/2 | ST.DEV.  | 0.2                | 1.4                 | 0.4                 | 0.4                  |
|           | N (CAGE) | 3                  | 3                   | 3                   | 3                    |

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**FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY  
 MALES**

| TREATMENT                       |          | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|---------------------------------|----------|--------------------|---------------------|---------------------|----------------------|
| DAYS 1-8                        | MEAN     | 22.4               | 22.1                | 22.5                | 22.0                 |
| WEEKS 1/2                       | ST.DEV.  | 0.7                | 0.4                 | 0.1                 | 0.2                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 8-15                       | MEAN     | 24.2               | 24.0                | 23.9                | 24.4                 |
| WEEKS 2/3                       | ST.DEV.  | 1.2                | 0.3                 | 0.3                 | 0.9                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 15-22                      | MEAN     | 24.7               | 24.2                | 24.3                | 24.9                 |
| WEEKS 3/4                       | ST.DEV.  | 1.0                | 0.6                 | 0.5                 | 0.7                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 22-29                      | MEAN     | 25.9               | 25.2                | 25.2                | 26.0                 |
| WEEKS 4/5                       | ST.DEV.  | 1.2                | 0.8                 | 0.8                 | 0.7                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 29-36                      | MEAN     | 24.7               | 24.0                | 24.1                | 25.3                 |
| WEEKS 5/6                       | ST.DEV.  | 0.8                | 1.0                 | 0.8                 | 1.0                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 36-43                      | MEAN     | 25.0               | 23.8                | 24.4                | 25.2                 |
| WEEKS 6/7                       | ST.DEV.  | 0.8                | 1.1                 | 0.7                 | 1.1                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 43-50                      | MEAN     | 24.8               | 24.0                | 23.6                | 25.7                 |
| WEEKS 7/8                       | ST.DEV.  | 0.5                | 1.4                 | 0.6                 | 1.0                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 50-57                      | MEAN     | 24.4               | 23.7                | 23.5                | 25.5                 |
| WEEKS 8/9                       | ST.DEV.  | 0.6                | 0.7                 | 0.4                 | 0.6                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 57-64                      | MEAN     | 24.2               | 22.9                | 22.7                | 24.7                 |
| WEEKS 9/10                      | ST.DEV.  | 0.8                | 0.9                 | 0.0                 | 0.2                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 64-71                      | MEAN     | 23.4               | 22.2                | 21.9                | 24.1                 |
| WEEKS 10/11                     | ST.DEV.  | 0.6                | 0.8                 | 0.4                 | 0.5                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 71-78                      | MEAN     | 24.4               | 22.5                | 22.0                | 24.5                 |
| WEEKS 11/12                     | ST.DEV.  | 0.7                | 0.7                 | 0.5                 | 0.8                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 78-85                      | MEAN     | 24.2               | 22.4                | 22.6                | 24.8                 |
| WEEKS 12/13                     | ST.DEV.  | 0.7                | 1.0                 | 0.2                 | 0.7                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 85-92                      | MEAN     | 29.8               | 21.3                | 21.9                | 24.3                 |
| WEEKS 13/14                     | ST.DEV.  | 11.5               | 0.9                 | 0.1                 | 0.3                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 92-99                      | MEAN     | 23.5               | 22.1                | 22.1                | 22.9                 |
| WEEKS 14/15                     | ST.DEV.  | 1.2                | 1.0                 | 0.3                 | 0.2                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 99-106                     | MEAN     | 23.6               | 23.0                | 23.9                | 26.5                 |
| WEEKS 15/16                     | ST.DEV.  | 0.8                | 1.0                 | 0.2                 | 0.5                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 106-108                    | MEAN     | 23.0               | 22.4                | 23.4                | 25.3                 |
| WEEK 16                         | ST.DEV.  | 1.1                | 1.0                 | 0.6                 | 1.0                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| MEAN OF MEANS<br>OVER TREATMENT |          | 24.5               | 23.1                | 23.3                | 24.7                 |



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FC-SUM - 3  
22-APR-05

**FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY  
FEMALES**

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| PRETEST   |          | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|-----------|----------|--------------------|---------------------|---------------------|----------------------|
| DAYS 1-8  | MEAN     | 14.1               | 14.4                | 14.6                | 14.4                 |
| WEEKS 1/2 | ST.DEV.  | 0.6                | 0.1                 | 0.3                 | 0.4                  |
|           | N (CAGE) | 3                  | 3                   | 3                   | 3                    |

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**FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY  
FEMALES**

| TREATMENT                       |          | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|---------------------------------|----------|--------------------|---------------------|---------------------|----------------------|
| DAYS 1-8                        | MEAN     | 14.4               | 14.6                | 14.9                | 14.4                 |
| WEEKS 1/2                       | ST.DEV.  | 0.5                | 0.2                 | 0.5                 | 0.2                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 8-15                       | MEAN     | 14.7               | 15.2                | 15.0                | 14.6                 |
| WEEKS 2/3                       | ST.DEV.  | 0.4                | 0.3                 | 0.5                 | 0.5                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 15-22                      | MEAN     | 15.2               | 16.0                | 16.0                | 15.9                 |
| WEEKS 3/4                       | ST.DEV.  | 0.6                | 0.2                 | 0.5                 | 0.7                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 22-29                      | MEAN     | 16.4               | 16.6                | 16.4                | 16.1                 |
| WEEKS 4/5                       | ST.DEV.  | 0.6                | 0.2                 | 0.6                 | 0.7                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 29-36                      | MEAN     | 15.7               | 15.6                | 15.9                | 15.5                 |
| WEEKS 5/6                       | ST.DEV.  | 0.4                | 0.7                 | 0.3                 | 0.3                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 36-43                      | MEAN     | 16.0               | 15.6                | 16.0                | 15.6                 |
| WEEKS 6/7                       | ST.DEV.  | 0.3                | 0.5                 | 0.3                 | 0.4                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 43-50                      | MEAN     | 16.1               | 15.9                | 15.9                | 16.2                 |
| WEEKS 7/8                       | ST.DEV.  | 0.3                | 0.8                 | 0.4                 | 0.4                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 50-57                      | MEAN     | 16.3               | 16.1                | 16.2                | 16.3                 |
| WEEKS 8/9                       | ST.DEV.  | 0.4                | 0.6                 | 0.5                 | 0.3                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 57-64                      | MEAN     | 16.2               | 15.5                | 15.6                | 15.8                 |
| WEEKS 9/10                      | ST.DEV.  | 0.2                | 0.8                 | 0.3                 | 0.5                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 64-71                      | MEAN     | 15.2               | 15.1                | 15.3                | 15.5                 |
| WEEKS 10/11                     | ST.DEV.  | 0.3                | 1.0                 | 0.5                 | 0.5                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 71-78                      | MEAN     | 15.5               | 15.5                | 15.8                | 15.8                 |
| WEEKS 11/12                     | ST.DEV.  | 0.1                | 0.7                 | 0.2                 | 0.8                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 78-85                      | MEAN     | 15.9               | 15.3                | 15.8                | 15.9                 |
| WEEKS 12/13                     | ST.DEV.  | 0.2                | 0.7                 | 0.5                 | 0.7                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 85-92                      | MEAN     | 15.0               | 14.5                | 14.9                | 15.1                 |
| WEEKS 13/14                     | ST.DEV.  | 0.1                | 0.8                 | 0.4                 | 0.6                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 92-99                      | MEAN     | 15.0               | 14.7                | 14.9                | 15.4                 |
| WEEKS 14/15                     | ST.DEV.  | 0.6                | 1.0                 | 0.3                 | 0.4                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 99-106                     | MEAN     | 14.6               | 14.7                | 14.7                | 15.3                 |
| WEEKS 15/16                     | ST.DEV.  | 0.1                | 0.9                 | 0.2                 | 0.4                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 106-108                    | MEAN     | 15.5               | 15.0                | 15.1                | 16.2                 |
| WEEK 16                         | ST.DEV.  | 0.4                | 0.7                 | 0.2                 | 0.6                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| MEAN OF MEANS<br>OVER TREATMENT |          | 15.5               | 15.4                | 15.5                | 15.6                 |

RCC STUDY NUMBER 857092  
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RELATIVE FOOD CONSUMPTION SUMMARY  
(G/KG BODY WEIGHT/DAY)  
MALES

| PRETEST   |          | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|-----------|----------|--------------------|---------------------|---------------------|----------------------|
| DAYS 1-8  | MEAN     | 142                | 132                 | 141                 | 138                  |
| WEEKS 1/2 | ST.DEV.  | 2.8                | 7.3                 | 0.4                 | 2.3                  |
|           | N (CAGE) | 3                  | 3                   | 3                   | 3                    |

**RELATIVE FOOD CONSUMPTION SUMMARY  
 (G/KG BODY WEIGHT/DAY)  
 MALES**

| TREATMENT                       |          | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|---------------------------------|----------|--------------------|---------------------|---------------------|----------------------|
| DAYS 1-8                        | MEAN     | 94                 | 93                  | 93                  | 94                   |
| WEEKS 1/2                       | ST.DEV.  | 1.9                | 4.0                 | 0.5                 | 0.9                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 8-15                       | MEAN     | 88                 | 87                  | 86                  | 90                   |
| WEEKS 2/3                       | ST.DEV.  | 2.5                | 2.9                 | 0.2                 | 2.5                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 15-22                      | MEAN     | 81                 | 79                  | 78                  | 82                   |
| WEEKS 3/4                       | ST.DEV.  | 2.3                | 2.2                 | 0.6                 | 3.1                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 22-29                      | MEAN     | 77                 | 76                  | 76                  | 80                   |
| WEEKS 4/5                       | ST.DEV.  | 1.8                | 0.6                 | 1.1                 | 2.4                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 29-36                      | MEAN     | 68                 | 68                  | 68                  | 72                   |
| WEEKS 5/6                       | ST.DEV.  | 0.9                | 0.8                 | 1.2                 | 2.9                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 36-43                      | MEAN     | 66                 | 65                  | 66                  | 70                   |
| WEEKS 6/7                       | ST.DEV.  | 0.6                | 1.2                 | 1.0                 | 2.6                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 43-50                      | MEAN     | 63                 | 62                  | 61                  | 67                   |
| WEEKS 7/8                       | ST.DEV.  | 0.2                | 1.7                 | 0.5                 | 2.4                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 50-57                      | MEAN     | 60                 | 60                  | 59                  | 65                   |
| WEEKS 8/9                       | ST.DEV.  | 0.4                | 0.7                 | 0.5                 | 2.1                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 57-64                      | MEAN     | 58                 | 57                  | 56                  | 62                   |
| WEEKS 9/10                      | ST.DEV.  | 0.9                | 0.4                 | 1.2                 | 0.4                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 64-71                      | MEAN     | 55                 | 54                  | 53                  | 59                   |
| WEEKS 10/11                     | ST.DEV.  | 0.3                | 0.3                 | 0.9                 | 1.6                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 71-78                      | MEAN     | 56                 | 54                  | 53                  | 59                   |
| WEEKS 11/12                     | ST.DEV.  | 0.4                | 0.7                 | 1.2                 | 2.3                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 78-85                      | MEAN     | 55                 | 53                  | 53                  | 59                   |
| WEEKS 12/13                     | ST.DEV.  | 0.5                | 0.9                 | 1.1                 | 2.0                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 85-92                      | MEAN     | 66                 | 50                  | 51                  | 57                   |
| WEEKS 13/14                     | ST.DEV.  | 25.0               | 0.7                 | 1.4                 | 1.0                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 92-99                      | MEAN     | 51                 | 50                  | 50                  | 52                   |
| WEEKS 14/15                     | ST.DEV.  | 1.4                | 1.4                 | 1.7                 | 0.1                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 99-106                     | MEAN     | 51                 | 52                  | 52                  | 60                   |
| WEEKS 15/16                     | ST.DEV.  | 0.2                | 1.0                 | 1.7                 | 1.2                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 106-108                    | MEAN     | 49                 | 50                  | 51                  | 56                   |
| WEEK 16                         | ST.DEV.  | 1.1                | 0.8                 | 0.9                 | 2.6                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| MEAN OF MEANS<br>OVER TREATMENT |          | 65                 | 63                  | 63                  | 68                   |

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RFC-SUM - 3  
22-APR-05

RELATIVE FOOD CONSUMPTION SUMMARY  
(G/KG BODY WEIGHT/DAY)  
FEMALES

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| PRETEST   |          | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|-----------|----------|--------------------|---------------------|---------------------|----------------------|
| DAYS 1-8  | MEAN     | 114                | 117                 | 116                 | 115                  |
| WEEKS 1/2 | ST.DEV.  | 4.9                | 0.9                 | 1.7                 | 1.9                  |
|           | N (CAGE) | 3                  | 3                   | 3                   | 3                    |

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RELATIVE FOOD CONSUMPTION SUMMARY  
 (G/KG BODY WEIGHT/DAY)  
 FEMALES

| TREATMENT                       |          | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|---------------------------------|----------|--------------------|---------------------|---------------------|----------------------|
| DAYS 1-8                        | MEAN     | 89                 | 89                  | 89                  | 88                   |
| WEEKS 1/2                       | ST.DEV.  | 1.6                | 0.2                 | 2.3                 | 0.8                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 8-15                       | MEAN     | 85                 | 86                  | 84                  | 83                   |
| WEEKS 2/3                       | ST.DEV.  | 0.8                | 1.4                 | 1.5                 | 1.5                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 15-22                      | MEAN     | 82                 | 84                  | 83                  | 85                   |
| WEEKS 3/4                       | ST.DEV.  | 2.0                | 1.4                 | 1.4                 | 1.0                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 22-29                      | MEAN     | 84                 | 83                  | 82                  | 82                   |
| WEEKS 4/5                       | ST.DEV.  | 0.5                | 1.6                 | 1.8                 | 1.2                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 29-36                      | MEAN     | 77                 | 75                  | 76                  | 76                   |
| WEEKS 5/6                       | ST.DEV.  | 3.1                | 3.1                 | 2.2                 | 0.1                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 36-43                      | MEAN     | 77                 | 73                  | 75                  | 74                   |
| WEEKS 6/7                       | ST.DEV.  | 0.2                | 2.4                 | 2.0                 | 0.5                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 43-50                      | MEAN     | 75                 | 72                  | 73                  | 75                   |
| WEEKS 7/8                       | ST.DEV.  | 0.3                | 3.3                 | 1.2                 | 0.8                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 50-57                      | MEAN     | 74                 | 72                  | 73                  | 74                   |
| WEEKS 8/9                       | ST.DEV.  | 0.5                | 2.2                 | 2.2                 | 0.8                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 57-64                      | MEAN     | 72                 | 68                  | 69                  | 70                   |
| WEEKS 9/10                      | ST.DEV.  | 2.6                | 3.4                 | 2.2                 | 0.6                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 64-71                      | MEAN     | 67                 | 66                  | 67                  | 68                   |
| WEEKS 10/11                     | ST.DEV.  | 0.5                | 3.9                 | 1.2                 | 0.8                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 71-78                      | MEAN     | 68                 | 67                  | 68                  | 69                   |
| WEEKS 11/12                     | ST.DEV.  | 1.2                | 2.9                 | 2.1                 | 1.0                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 78-85                      | MEAN     | 69                 | 65                  | 67                  | 69                   |
| WEEKS 12/13                     | ST.DEV.  | 0.9                | 3.2                 | 1.0                 | 0.8                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 85-92                      | MEAN     | 64                 | 61                  | 63                  | 64                   |
| WEEKS 13/14                     | ST.DEV.  | 0.8                | 3.2                 | 2.0                 | 0.6                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 92-99                      | MEAN     | 64                 | 62                  | 63                  | 65                   |
| WEEKS 14/15                     | ST.DEV.  | 1.9                | 4.2                 | 1.4                 | 0.6                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 99-106                     | MEAN     | 62                 | 60                  | 61                  | 64                   |
| WEEKS 15/16                     | ST.DEV.  | 1.3                | 3.0                 | 1.9                 | 3.2                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| DAYS 106-108                    | MEAN     | 64                 | 62                  | 63                  | 67                   |
| WEEK 16                         | ST.DEV.  | 0.8                | 2.8                 | 2.9                 | 0.6                  |
|                                 | N (CAGE) | 3                  | 3                   | 3                   | 3                    |
| MEAN OF MEANS<br>OVER TREATMENT |          | 73                 | 72                  | 72                  | 73                   |

**BODY WEIGHTS (GRAM) SUMMARY  
MALES**

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| PRETEST |   | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|---------|---|--------------------|---------------------|---------------------|----------------------|
| DAY     | 1 | 147                | 146                 | 147                 | 146                  |
| WEEK    | 1 | 6.6                | 5.0                 | 7.2                 | 6.1                  |
|         |   | N                  | 15                  | 15                  | 15                   |

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\* / \*\* : Dunnett-Test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

**BODY WEIGHTS (GRAM) SUMMARY  
 MALES**

| TREATMENT |     |         | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|-----------|-----|---------|--------------------|---------------------|---------------------|----------------------|
| DAY       | 1   | MEAN    | 194                | 181 **              | 194                 | 190                  |
| WEEK      | 1   | ST.DEV. | 6.3                | 19.4                | 7.8                 | 6.6                  |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 8   | MEAN    | 239                | 237                 | 241                 | 235                  |
| WEEK      | 2   | ST.DEV. | 7.5                | 9.0                 | 8.4                 | 6.8                  |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 15  | MEAN    | 276                | 275                 | 276                 | 270                  |
| WEEK      | 3   | ST.DEV. | 9.1                | 8.7                 | 9.0                 | 8.8                  |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 22  | MEAN    | 307                | 305                 | 310                 | 302                  |
| WEEK      | 4   | ST.DEV. | 12.3               | 13.6                | 12.1                | 15.8                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 29  | MEAN    | 336                | 331                 | 333                 | 327                  |
| WEEK      | 5   | ST.DEV. | 12.9               | 13.0                | 14.5                | 12.5                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 36  | MEAN    | 361                | 354                 | 356                 | 350                  |
| WEEK      | 6   | ST.DEV. | 14.7               | 15.2                | 15.6                | 15.5                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 43  | MEAN    | 377                | 367                 | 371                 | 363                  |
| WEEK      | 7   | ST.DEV. | 17.5               | 15.9                | 16.7                | 15.5                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 50  | MEAN    | 394                | 385                 | 386                 | 381                  |
| WEEK      | 8   | ST.DEV. | 20.2               | 18.6                | 17.7                | 18.3                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 57  | MEAN    | 405                | 394                 | 399                 | 393                  |
| WEEK      | 9   | ST.DEV. | 23.5               | 19.6                | 18.0                | 18.1                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 64  | MEAN    | 416                | 403                 | 406                 | 400                  |
| WEEK      | 10  | ST.DEV. | 25.6               | 21.0                | 19.9                | 24.7                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 71  | MEAN    | 425                | 410                 | 412                 | 408                  |
| WEEK      | 11  | ST.DEV. | 28.1               | 20.4                | 20.3                | 24.5                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 78  | MEAN    | 434                | 414                 | 416                 | 412 *                |
| WEEK      | 12  | ST.DEV. | 29.3               | 20.5                | 19.9                | 26.0                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 85  | MEAN    | 441                | 420                 | 423                 | 417 *                |
| WEEK      | 13  | ST.DEV. | 32.4               | 20.2                | 20.4                | 27.1                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 92  | MEAN    | 453                | 430                 | 434                 | 428 *                |
| WEEK      | 14  | ST.DEV. | 35.1               | 21.7                | 22.7                | 26.5                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 99  | MEAN    | 457                | 440                 | 443                 | 437                  |
| WEEK      | 15  | ST.DEV. | 36.3               | 21.6                | 23.5                | 27.5                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 106 | MEAN    | 464                | 444                 | 457                 | 445                  |
| WEEK      | 16  | ST.DEV. | 36.5               | 22.5                | 28.8                | 29.5                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |
| DAY       | 108 | MEAN    | 471                | 451                 | 456                 | 450                  |
| WEEK      | 16  | ST.DEV. | 36.1               | 22.6                | 23.7                | 29.3                 |
|           |     | N       | 15                 | 15                  | 15                  | 15                   |

\* / \*\* : Dunnett-Test based on pooled variance significant at 5% (\*) or 1% (\*\*) level



**BODY WEIGHTS (GRAM) SUMMARY  
FEMALES**

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| PRETEST |   | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|---------|---|--------------------|---------------------|---------------------|----------------------|
| DAY     | 1 | 123                | 123                 | 126                 | 125                  |
| WEEK    | 1 | 3.7                | 4.7                 | 5.3                 | 5.2                  |
|         |   | N                  | 15                  | 15                  | 15                   |

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\* / \*\* : Dunnett-Test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

**BODY WEIGHTS (GRAM) SUMMARY  
 FEMALES**

| TREATMENT |     | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|-----------|-----|--------------------|---------------------|---------------------|----------------------|
| DAY       | 1   | MEAN               | 143                 | 144                 | 147                  |
| WEEK      | 1   | ST.DEV.            | 5.0                 | 5.4                 | 7.1                  |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 8   | MEAN               | 161                 | 164                 | 167                  |
| WEEK      | 2   | ST.DEV.            | 7.3                 | 8.0                 | 8.0                  |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 15  | MEAN               | 172                 | 176                 | 178                  |
| WEEK      | 3   | ST.DEV.            | 7.9                 | 8.0                 | 8.8                  |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 22  | MEAN               | 186                 | 191                 | 192                  |
| WEEK      | 4   | ST.DEV.            | 8.2                 | 10.7                | 9.9                  |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 29  | MEAN               | 195                 | 200                 | 199                  |
| WEEK      | 5   | ST.DEV.            | 10.5                | 10.5                | 11.4                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 36  | MEAN               | 205                 | 209                 | 208                  |
| WEEK      | 6   | ST.DEV.            | 10.5                | 10.2                | 11.0                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 43  | MEAN               | 209                 | 212                 | 214                  |
| WEEK      | 7   | ST.DEV.            | 10.1                | 9.3                 | 11.6                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 50  | MEAN               | 216                 | 220                 | 219                  |
| WEEK      | 8   | ST.DEV.            | 10.1                | 10.0                | 11.5                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 57  | MEAN               | 219                 | 224                 | 223                  |
| WEEK      | 9   | ST.DEV.            | 11.3                | 11.1                | 12.4                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 64  | MEAN               | 225                 | 228                 | 227                  |
| WEEK      | 10  | ST.DEV.            | 11.9                | 10.7                | 12.5                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 71  | MEAN               | 227                 | 228                 | 229                  |
| WEEK      | 11  | ST.DEV.            | 12.8                | 9.5                 | 12.0                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 78  | MEAN               | 227                 | 232                 | 231                  |
| WEEK      | 12  | ST.DEV.            | 12.4                | 11.2                | 10.3                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 85  | MEAN               | 230                 | 235                 | 234                  |
| WEEK      | 13  | ST.DEV.            | 12.6                | 11.8                | 12.3                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 92  | MEAN               | 235                 | 237                 | 237                  |
| WEEK      | 14  | ST.DEV.            | 12.3                | 11.7                | 12.6                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 99  | MEAN               | 236                 | 238                 | 237                  |
| WEEK      | 15  | ST.DEV.            | 13.4                | 10.8                | 11.6                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 106 | MEAN               | 236                 | 247                 | 242                  |
| WEEK      | 16  | ST.DEV.            | 14.3                | 16.9                | 11.3                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 108 | MEAN               | 241                 | 242                 | 241                  |
| WEEK      | 16  | ST.DEV.            | 14.8                | 12.8                | 12.7                 |
|           |     | N                  | 15                  | 15                  | 15                   |

\* / \*\* : Dunnett-Test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

**BODY WEIGHT GAIN (%) SUMMARY  
MALES**

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| PRETEST |   | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |       |
|---------|---|--------------------|---------------------|---------------------|----------------------|-------|
| DAY     | 1 | MEAN               | -23.9               | -18.5 **            | -24.2                | -23.2 |
| WEEK    | 1 | ST.DEV.            | 1.5                 | 7.5                 | 2.5                  | 2.0   |
|         |   | N                  | 15                  | 15                  | 15                   | 15    |

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\* / \*\* : Dunnett-Test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

**BODY WEIGHT GAIN (%) SUMMARY  
MALES**

| TREATMENT |     | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|-----------|-----|--------------------|---------------------|---------------------|----------------------|
| DAY       | 1   | MEAN               | 0.0                 | 0.0                 | 0.0                  |
| WEEK      | 1   | ST.DEV.            | 0.0                 | 0.0                 | 0.0                  |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 8   | MEAN               | 23.5                | 32.0 **             | 24.2                 |
| WEEK      | 2   | ST.DEV.            | 1.5                 | 11.2                | 2.9                  |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 15  | MEAN               | 42.6                | 53.3 **             | 42.8                 |
| WEEK      | 3   | ST.DEV.            | 3.6                 | 14.4                | 5.2                  |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 22  | MEAN               | 58.3                | 70.1 **             | 60.2                 |
| WEEK      | 4   | ST.DEV.            | 6.6                 | 16.6                | 7.8                  |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 29  | MEAN               | 73.5                | 85.0 *              | 72.0                 |
| WEEK      | 5   | ST.DEV.            | 6.1                 | 18.1                | 8.7                  |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 36  | MEAN               | 86.5                | 97.9 *              | 84.0                 |
| WEEK      | 6   | ST.DEV.            | 6.8                 | 18.9                | 9.7                  |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 43  | MEAN               | 94.5                | 105.2               | 91.8                 |
| WEEK      | 7   | ST.DEV.            | 8.4                 | 20.1                | 10.7                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 50  | MEAN               | 103.7               | 115.1               | 99.6                 |
| WEEK      | 8   | ST.DEV.            | 9.9                 | 21.0                | 11.6                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 57  | MEAN               | 108.9               | 119.7               | 106.3                |
| WEEK      | 9   | ST.DEV.            | 11.1                | 21.4                | 11.8                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 64  | MEAN               | 114.9               | 125.0               | 110.0                |
| WEEK      | 10  | ST.DEV.            | 12.1                | 22.1                | 13.4                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 71  | MEAN               | 119.3               | 128.8               | 113.1                |
| WEEK      | 11  | ST.DEV.            | 13.3                | 22.4                | 13.7                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 78  | MEAN               | 123.8               | 131.1               | 114.8                |
| WEEK      | 12  | ST.DEV.            | 13.8                | 21.5                | 13.2                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 85  | MEAN               | 127.5               | 134.2               | 118.8                |
| WEEK      | 13  | ST.DEV.            | 15.4                | 21.3                | 14.1                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 92  | MEAN               | 133.7               | 139.9               | 124.4                |
| WEEK      | 14  | ST.DEV.            | 16.7                | 22.2                | 15.6                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 99  | MEAN               | 136.0               | 145.4               | 129.0                |
| WEEK      | 15  | ST.DEV.            | 17.4                | 22.5                | 16.9                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 106 | MEAN               | 139.7               | 147.9               | 136.4                |
| WEEK      | 16  | ST.DEV.            | 17.9                | 22.8                | 17.6                 |
|           |     | N                  | 15                  | 15                  | 15                   |
| DAY       | 108 | MEAN               | 143.2               | 151.6               | 135.9                |
| WEEK      | 16  | ST.DEV.            | 17.3                | 22.8                | 16.5                 |
|           |     | N                  | 15                  | 15                  | 15                   |

\* / \*\* : Dunnett-Test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

**BODY WEIGHT GAIN (%) SUMMARY  
FEMALES**

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| PRETEST |   | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |       |
|---------|---|--------------------|---------------------|---------------------|----------------------|-------|
| DAY     | 1 | MEAN               | -13.7               | -14.9               | -14.6                | -13.8 |
| WEEK    | 1 | ST.DEV.            | 2.1                 | 2.9                 | 2.7                  | 1.6   |
|         |   | N                  | 15                  | 15                  | 15                   | 15    |

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\* / \*\* : Dunnett-Test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

**BODY WEIGHT GAIN (%) SUMMARY  
FEMALES**

| TREATMENT |         | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|-----------|---------|--------------------|---------------------|---------------------|----------------------|
| DAY 1     | MEAN    | 0.0                | 0.0                 | 0.0                 | 0.0                  |
| WEEK 1    | ST.DEV. | 0.0                | 0.0                 | 0.0                 | 0.0                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 8     | MEAN    | 13.0               | 13.7                | 13.6                | 12.6                 |
| WEEK 2    | ST.DEV. | 2.3                | 3.8                 | 2.0                 | 3.0                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 15    | MEAN    | 20.6               | 21.9                | 21.1                | 20.3                 |
| WEEK 3    | ST.DEV. | 2.8                | 3.8                 | 3.2                 | 4.1                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 22    | MEAN    | 30.0               | 32.4                | 30.7                | 29.2                 |
| WEEK 4    | ST.DEV. | 3.4                | 6.1                 | 4.9                 | 4.6                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 29    | MEAN    | 36.3               | 38.7                | 35.4                | 35.2                 |
| WEEK 5    | ST.DEV. | 3.9                | 5.1                 | 4.5                 | 3.9                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 36    | MEAN    | 43.4               | 44.7                | 41.6                | 40.9                 |
| WEEK 6    | ST.DEV. | 4.2                | 5.5                 | 4.3                 | 4.2                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 43    | MEAN    | 46.2               | 46.9                | 45.2                | 44.6                 |
| WEEK 7    | ST.DEV. | 4.0                | 4.4                 | 4.9                 | 6.2                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 50    | MEAN    | 51.2               | 52.6                | 48.8                | 49.3                 |
| WEEK 8    | ST.DEV. | 4.2                | 5.1                 | 6.1                 | 5.8                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 57    | MEAN    | 53.3               | 55.2                | 51.7                | 52.5                 |
| WEEK 9    | ST.DEV. | 4.7                | 6.1                 | 5.9                 | 4.9                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 64    | MEAN    | 57.4               | 57.6                | 54.3                | 55.7                 |
| WEEK 10   | ST.DEV. | 4.6                | 6.1                 | 5.6                 | 5.5                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 71    | MEAN    | 58.8               | 57.7                | 55.4                | 56.6                 |
| WEEK 11   | ST.DEV. | 5.9                | 5.0                 | 5.8                 | 6.6                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 78    | MEAN    | 59.0               | 61.0                | 57.3                | 57.5                 |
| WEEK 12   | ST.DEV. | 6.0                | 5.8                 | 6.5                 | 6.4                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 85    | MEAN    | 61.1               | 62.7                | 58.9                | 59.2                 |
| WEEK 13   | ST.DEV. | 5.6                | 6.1                 | 7.4                 | 5.5                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 92    | MEAN    | 64.4               | 64.3                | 61.2                | 62.7                 |
| WEEK 14   | ST.DEV. | 5.6                | 6.8                 | 6.2                 | 5.8                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 99    | MEAN    | 65.1               | 64.9                | 61.4                | 63.4                 |
| WEEK 15   | ST.DEV. | 6.7                | 6.3                 | 6.6                 | 7.1                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 106   | MEAN    | 65.1               | 70.9                | 64.5                | 64.3                 |
| WEEK 16   | ST.DEV. | 7.8                | 9.9                 | 9.5                 | 8.2                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |
| DAY 108   | MEAN    | 68.6               | 67.5                | 63.7                | 66.4                 |
| WEEK 16   | ST.DEV. | 7.1                | 7.6                 | 7.0                 | 6.3                  |
|           | N       | 15                 | 15                  | 15                  | 15                   |

\* / \*\* : Dunnett-Test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

**OPHTHALMOSCOPIC EXAMINATIONS SUMMARY  
 MALES  
 PRETEST**

|  | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|--|--------------------|---------------------|---------------------|----------------------|
| NUMBER OF ANIMALS EXAMINED                             | 10                 | 10                  | 10                  | 10                   |
| NO ABNORMALITIES DETECTED<br>%                         | 9<br>90.0          | 9<br>90.0           | 9<br>90.0           | 10<br>100.0          |
| CORNEAL OPACITY<br>ANIMALS AFFECTED<br>%               | 0                  | 1<br>10.0           | 0                   | 0                    |
| PERSISTENT PUPILLARY MEMBRANE<br>ANIMALS AFFECTED<br>% | 1<br>10.0          | 0                   | 1<br>10.0           | 0                    |

\*/\*\* : Fisher's Exact Test significant at level 5% (\*) or 1% (\*\*).

**OPHTHALMOSCOPIC EXAMINATIONS SUMMARY  
MALES  
AFTER 13 WEEKS**

|  | GROUP 1<br>0 MG/KG | GROUP 4<br>200 MG/KG |
|--|--------------------|----------------------|
| NUMBER OF ANIMALS EXAMINED                             | 10                 | 10                   |
| NO ABNORMALITIES DETECTED<br>‡                         | 9<br>90.0          | 10<br>100.0          |
| PERSISTENT PUPILLARY MEMBRANE<br>ANIMALS AFFECTED<br>‡ | 1<br>10.0          | 0                    |

‡/‡‡ : Fisher's Exact Test significant at level 5% (‡) or 1% (‡‡).



**OPHTHALMOSCOPIC EXAMINATIONS SUMMARY  
FEMALES  
PRETEST**

|  | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|--|--------------------|---------------------|---------------------|----------------------|
| NUMBER OF ANIMALS EXAMINED               | 10                 | 10                  | 10                  | 10                   |
| NO ABNORMALITIES DETECTED<br>%           | 10<br>100.0        | 10<br>100.0         | 10<br>100.0         | 9<br>90.0            |
| CORNEAL OPACITY<br>ANIMALS AFFECTED<br>% | 0                  | 0                   | 0                   | 1<br>10.0            |

### : Fisher's Exact Test significant at level 5% (#) or 1% (##).

**OPHTHALMOSCOPIC EXAMINATIONS SUMMARY  
FEMALES  
AFTER 13 WEEKS**

|  | GROUP 1<br>0 MG/KG | GROUP 4<br>200 MG/KG |
|--|--------------------|----------------------|
| NUMBER OF ANIMALS EXAMINED             | 10                 | 10                   |
| NO ABNORMALITIES DETECTED<br>%         | 9<br>90.0          | 10<br>100.0          |
| IRIS COLOBOMA<br>ANIMALS AFFECTED<br>% | 1<br>10.0          | 0                    |

MACROSCOPICAL FINDINGS SUMMARY

MALES

|                          | GROUP 1<br>0 MG/KG |     | GROUP 2<br>15 MG/KG |     | GROUP 3<br>50 MG/KG |     | GROUP 4<br>200 MG/KG |     |
|--------------------------|--------------------|-----|---------------------|-----|---------------------|-----|----------------------|-----|
| ANIMALS EXAMINED         | 15                 |     | 15                  |     | 15                  |     | 15                   |     |
| ANIMALS WITHOUT FINDINGS | 8                  |     | 12                  |     | 1                   |     | 2                    |     |
| ANIMALS AFFECTED:        |                    |     |                     |     |                     |     |                      |     |
| LUNGS.....               | 1                  | 7%  | 0                   | 0%  | 0                   | 0%  | 0                    | 0%  |
| FOCUS/FOCI               |                    |     |                     |     |                     |     |                      |     |
| STOMACH.....             | 1                  | 7%  | 0                   | 0%  | 1                   | 7%  | 2                    | 13% |
| FOCUS/FOCI               |                    |     |                     |     |                     |     |                      |     |
| PANCREAS.....            | 0                  | 0%  | 0                   | 0%  | 1                   | 7%  | 0                    | 0%  |
| DISCOLORATION            |                    |     |                     |     |                     |     |                      |     |
| KIDNEYS.....             | 3                  | 20% | 2                   | 13% | 1                   | 7%  | 1                    | 7%  |
| PELVIC DILATION          |                    |     |                     |     |                     |     |                      |     |
| TESTES.....              | 0                  | 0%  | 1                   | 7%  | 0                   | 0%  | 0                    | 0%  |
| REDUCED IN SIZE          |                    |     |                     |     |                     |     |                      |     |
| SEMINAL VESICLES.....    | 1                  | 7%  | 0                   | 0%  | 2                   | 13% | 0                    | 0%  |
| FOCUS/FOCI               |                    |     |                     |     |                     |     |                      |     |
| THYROID GLAND.....       | 0                  | 0%  | 0                   | 0%  | 14 ##               | 93% | 13 ##                | 87% |
| DISCOLORATION            |                    |     |                     |     |                     |     |                      |     |
| THYMUS.....              | 0                  | 0%  | 0                   | 0%  | 0                   | 0%  | 1                    | 7%  |
| FOCUS/FOCI               |                    |     |                     |     |                     |     |                      |     |
| MANDIBULAR L.NODE.....   | 1                  | 7%  | 0                   | 0%  | 0                   | 0%  | 0                    | 0%  |
| FOCUS/FOCI               |                    |     |                     |     |                     |     |                      |     |
| EX. LACRIMAL GLANDS..... | 1                  | 7%  | 0                   | 0%  | 0                   | 0%  | 0                    | 0%  |
| FOCUS/FOCI               |                    |     |                     |     |                     |     |                      |     |
| SKIN.....                | 0                  | 0%  | 1                   | 7%  | 0                   | 0%  | 0                    | 0%  |
| ESCHAR(S)                |                    |     |                     |     |                     |     |                      |     |

# / ## : Fisher's Exact Test based on counts significant at 5% (#) or 1% (##) level

## MACROSCOPICAL FINDINGS SUMMARY

### FEMALES

|                          | GROUP 1<br>0 MG/KG |     | GROUP 2<br>15 MG/KG |     | GROUP 3<br>50 MG/KG |     | GROUP 4<br>200 MG/KG |     |
|--------------------------|--------------------|-----|---------------------|-----|---------------------|-----|----------------------|-----|
| ANIMALS EXAMINED         | 15                 |     | 15                  |     | 15                  |     | 15                   |     |
| ANIMALS WITHOUT FINDINGS | 10                 |     | 12                  |     | 4                   |     | 1                    |     |
| ANIMALS AFFECTED:        |                    |     |                     |     |                     |     |                      |     |
| LUNGS.....               |                    |     |                     |     |                     |     |                      |     |
| DISCOLORATION            | 1                  | 7%  | 0                   | 0%  | 0                   | 0%  | 0                    | 0%  |
| FOCUS/FOCI               | 2                  | 13% | 1                   | 7%  | 0                   | 0%  | 0                    | 0%  |
| CÆCUM.....               |                    |     |                     |     |                     |     |                      |     |
| FOCUS/FOCI               | 0                  | 0%  | 0                   | 0%  | 0                   | 0%  | 1                    | 7%  |
| OVARIES.....             |                    |     |                     |     |                     |     |                      |     |
| DISCOLORATION            | 1                  | 7%  | 0                   | 0%  | 1                   | 7%  | 0                    | 0%  |
| WATERY CYST              | 0                  | 0%  | 0                   | 0%  | 0                   | 0%  | 2                    | 13% |
| UTERUS.....              |                    |     |                     |     |                     |     |                      |     |
| CONTAINS WATERY FLUID    | 0                  | 0%  | 0                   | 0%  | 1                   | 7%  | 0                    | 0%  |
| DILATION                 | 1                  | 7%  | 2                   | 13% | 3                   | 20% | 2                    | 13% |
| DISCOLORATION            | 1                  | 7%  | 0                   | 0%  | 1                   | 7%  | 0                    | 0%  |
| THYROID GLAND.....       |                    |     |                     |     |                     |     |                      |     |
| DISCOLORATION            | 0                  | 0%  | 0                   | 0%  | 7 ##                | 47% | 14 ##                | 93% |
| SKIN.....                |                    |     |                     |     |                     |     |                      |     |
| ALOPECIA                 | 0                  | 0%  | 0                   | 0%  | 0                   | 0%  | 3                    | 20% |

# / ## : Fisher's Exact Test based on counts significant at 5% (#) or 1% (##) level

**ORGAN WEIGHTS (GRAM) SUMMARY  
 AFTER 14 WEEKS  
 MALES**

|              |         | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|--------------|---------|--------------------|---------------------|---------------------|----------------------|
| BODY W.      | MEAN    | 417.57             | 407.25              | 406.15              | 410.43               |
|              | ST.DEV. | 31.46              | 22.26               | 25.71               | 34.87                |
|              | N       | 10                 | 10                  | 10                  | 10                   |
| BRAIN        | MEAN    | 2.15               | 2.11                | 2.11                | 2.13                 |
|              | ST.DEV. | 0.09               | 0.07                | 0.06                | 0.08                 |
|              | N       | 10                 | 10                  | 10                  | 10                   |
| HEART        | MEAN    | 1.165              | 1.145               | 1.071               | 1.109                |
|              | ST.DEV. | 0.131              | 0.068               | 0.064               | 0.135                |
|              | N       | 10                 | 10                  | 10                  | 10                   |
| THYROIDS     | MEAN    | 0.028              | 0.029               | 0.027               | 0.030                |
|              | ST.DEV. | 0.005              | 0.007               | 0.003               | 0.006                |
|              | N       | 10                 | 10                  | 10                  | 10                   |
| LIVER        | MEAN    | 10.52              | 10.01               | 10.00               | 10.95                |
|              | ST.DEV. | 1.17               | 0.76                | 1.00                | 1.35                 |
|              | N       | 10                 | 10                  | 10                  | 10                   |
| THYMUS       | MEAN    | 0.33               | 0.29                | 0.30                | 0.31                 |
|              | ST.DEV. | 0.07               | 0.06                | 0.08                | 0.06                 |
|              | N       | 10                 | 10                  | 10                  | 10                   |
| KIDNEYS      | MEAN    | 2.45               | 2.31                | 2.25                | 2.38                 |
|              | ST.DEV. | 0.34               | 0.18                | 0.17                | 0.23                 |
|              | N       | 10                 | 10                  | 10                  | 10                   |
| ADRENALS     | MEAN    | 0.062              | 0.060               | 0.060               | 0.060                |
|              | ST.DEV. | 0.007              | 0.008               | 0.006               | 0.007                |
|              | N       | 10                 | 10                  | 10                  | 10                   |
| SPLEEN       | MEAN    | 0.869              | 0.823               | 0.888               | 0.877                |
|              | ST.DEV. | 0.138              | 0.095               | 0.113               | 0.130                |
|              | N       | 10                 | 10                  | 10                  | 10                   |
| TESTES       | MEAN    | 3.83               | 3.63                | 3.88                | 3.81                 |
|              | ST.DEV. | 0.30               | 0.63                | 0.25                | 0.38                 |
|              | N       | 10                 | 10                  | 10                  | 10                   |
| EPIDIDYMIDES | MEAN    | 1.537              | 1.503               | 1.504               | 1.529                |
|              | ST.DEV. | 0.140              | 0.168               | 0.131               | 0.171                |
|              | N       | 10                 | 10                  | 10                  | 10                   |

\*/\*\*: Dunnett-test based on pooled variance sig. at 5% or 1% level.

**ORGAN/BODY WEIGHT RATIOS SUMMARY  
 AFTER 14 WEEKS  
 MALES**

|                     |                      | GROUP 1<br>0 MG/KG    | GROUP 2<br>15 MG/KG   | GROUP 3<br>50 MG/KG   | GROUP 4<br>200 MG/KG  |
|---------------------|----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| BODY W.<br>(GRAM)   | MEAN<br>ST.DEV.<br>N | 417.57<br>31.46<br>10 | 407.25<br>22.26<br>10 | 406.15<br>25.71<br>10 | 410.43<br>34.87<br>10 |
| BRAIN<br>(%)        | MEAN<br>ST.DEV.<br>N | 0.52<br>0.04<br>10    | 0.52<br>0.04<br>10    | 0.52<br>0.03<br>10    | 0.52<br>0.03<br>10    |
| HEART<br>(%)        | MEAN<br>ST.DEV.<br>N | 0.279<br>0.019<br>10  | 0.282<br>0.022<br>10  | 0.264<br>0.016<br>10  | 0.270<br>0.017<br>10  |
| THYROIDS<br>(%)     | MEAN<br>ST.DEV.<br>N | 0.007<br>0.001<br>10  | 0.007<br>0.002<br>10  | 0.007<br>0.001<br>10  | 0.007<br>0.001<br>10  |
| LIVER<br>(%)        | MEAN<br>ST.DEV.<br>N | 2.52<br>0.17<br>10    | 2.46<br>0.15<br>10    | 2.46<br>0.16<br>10    | 2.67<br>0.20<br>10    |
| THYMUS<br>(%)       | MEAN<br>ST.DEV.<br>N | 0.08<br>0.01<br>10    | 0.07<br>0.01<br>10    | 0.07<br>0.02<br>10    | 0.08<br>0.02<br>10    |
| KIDNEYS<br>(%)      | MEAN<br>ST.DEV.<br>N | 0.58<br>0.05<br>10    | 0.57<br>0.05<br>10    | 0.56<br>0.04<br>10    | 0.58<br>0.04<br>10    |
| ADRENALS<br>(%)     | MEAN<br>ST.DEV.<br>N | 0.015<br>0.002<br>10  | 0.015<br>0.002<br>10  | 0.015<br>0.002<br>10  | 0.015<br>0.002<br>10  |
| SPLEEN<br>(%)       | MEAN<br>ST.DEV.<br>N | 0.209<br>0.035<br>10  | 0.202<br>0.024<br>10  | 0.219<br>0.025<br>10  | 0.214<br>0.031<br>10  |
| TESTES<br>(%)       | MEAN<br>ST.DEV.<br>N | 0.92<br>0.09<br>10    | 0.89<br>0.15<br>10    | 0.96<br>0.08<br>10    | 0.93<br>0.09<br>10    |
| EPIDIDYMIDES<br>(%) | MEAN<br>ST.DEV.<br>N | 0.370<br>0.041<br>10  | 0.369<br>0.039<br>10  | 0.370<br>0.024<br>10  | 0.373<br>0.029<br>10  |

\*/\*\*: Dunnett-test based on pooled variance sig. at 5% or 1% level.

**ORGAN/BRAIN WEIGHT RATIOS SUMMARY  
 AFTER 14 WEEKS  
 MALES**

|                     |         | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|---------------------|---------|--------------------|---------------------|---------------------|----------------------|
| BRAIN<br>(GRAM)     | MEAN    | 2.15               | 2.11                | 2.11                | 2.13                 |
|                     | ST.DEV. | 0.09               | 0.07                | 0.06                | 0.08                 |
|                     | N       | 10                 | 10                  | 10                  | 10                   |
| HEART<br>(%)        | MEAN    | 54.179             | 54.417              | 50.739              | 52.088               |
|                     | ST.DEV. | 5.153              | 3.840               | 2.263               | 5.325                |
|                     | N       | 10                 | 10                  | 10                  | 10                   |
| THYROIDS<br>(%)     | MEAN    | 1.313              | 1.354               | 1.274               | 1.418                |
|                     | ST.DEV. | 0.223              | 0.299               | 0.181               | 0.248                |
|                     | N       | 10                 | 10                  | 10                  | 10                   |
| LIVER<br>(%)        | MEAN    | 490.16             | 475.18              | 473.48              | 514.03               |
|                     | ST.DEV. | 54.85              | 34.09               | 40.07               | 49.02                |
|                     | N       | 10                 | 10                  | 10                  | 10                   |
| THYMUS<br>(%)       | MEAN    | 15.28              | 13.75               | 14.06               | 14.44                |
|                     | ST.DEV. | 3.20               | 2.88                | 3.80                | 3.10                 |
|                     | N       | 10                 | 10                  | 10                  | 10                   |
| KIDNEYS<br>(%)      | MEAN    | 113.81             | 109.66              | 106.72              | 112.01               |
|                     | ST.DEV. | 14.53              | 7.44                | 5.86                | 8.36                 |
|                     | N       | 10                 | 10                  | 10                  | 10                   |
| ADRENALS<br>(%)     | MEAN    | 2.895              | 2.855               | 2.830               | 2.824                |
|                     | ST.DEV. | 0.388              | 0.371               | 0.287               | 0.324                |
|                     | N       | 10                 | 10                  | 10                  | 10                   |
| SPLEEN<br>(%)       | MEAN    | 40.399             | 39.028              | 42.028              | 41.226               |
|                     | ST.DEV. | 6.040              | 4.217               | 4.781               | 5.905                |
|                     | N       | 10                 | 10                  | 10                  | 10                   |
| TESTES<br>(%)       | MEAN    | 178.40             | 172.58              | 184.33              | 179.42               |
|                     | ST.DEV. | 11.83              | 30.28               | 13.76               | 17.16                |
|                     | N       | 10                 | 10                  | 10                  | 10                   |
| EPIDIDYMIDES<br>(%) | MEAN    | 71.412             | 71.399              | 71.263              | 71.920               |
|                     | ST.DEV. | 4.148              | 8.182               | 5.819               | 7.656                |
|                     | N       | 10                 | 10                  | 10                  | 10                   |

\*/\*\*: Dunnett-test based on pooled variance sig. at 5% or 1% level.

**ORGAN WEIGHTS (GRAM) SUMMARY  
 AFTER 14 WEEKS  
 FEMALES**

|          |         | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|----------|---------|--------------------|---------------------|---------------------|----------------------|
| BODY W.  | MEAN    | 212.44             | 212.23              | 214.27              | 215.15               |
|          | ST.DEV. | 14.92              | 11.84               | 12.87               | 11.73                |
|          | N       | 10                 | 10                  | 10                  | 10                   |
| BRAIN    | MEAN    | 1.91               | 1.89                | 1.91                | 1.89                 |
|          | ST.DEV. | 0.07               | 0.08                | 0.07                | 0.06                 |
|          | N       | 10                 | 10                  | 10                  | 10                   |
| HEART    | MEAN    | 0.701              | 0.692               | 0.709               | 0.724                |
|          | ST.DEV. | 0.060              | 0.081               | 0.047               | 0.064                |
|          | N       | 10                 | 10                  | 10                  | 10                   |
| THYROIDS | MEAN    | 0.019              | 0.020               | 0.020               | 0.023                |
|          | ST.DEV. | 0.002              | 0.004               | 0.003               | 0.006                |
|          | N       | 10                 | 10                  | 10                  | 10                   |
| LIVER    | MEAN    | 5.36               | 5.31                | 5.35                | 6.25 **              |
|          | ST.DEV. | 0.53               | 0.27                | 0.30                | 0.83                 |
|          | N       | 10                 | 10                  | 10                  | 10                   |
| THYMUS   | MEAN    | 0.25               | 0.22                | 0.24                | 0.23                 |
|          | ST.DEV. | 0.03               | 0.04                | 0.03                | 0.05                 |
|          | N       | 10                 | 10                  | 10                  | 10                   |
| KIDNEYS  | MEAN    | 1.33               | 1.28                | 1.36                | 1.47 *               |
|          | ST.DEV. | 0.07               | 0.07                | 0.08                | 0.16                 |
|          | N       | 10                 | 10                  | 10                  | 10                   |
| ADRENALS | MEAN    | 0.072              | 0.068               | 0.067               | 0.071                |
|          | ST.DEV. | 0.007              | 0.007               | 0.008               | 0.011                |
|          | N       | 10                 | 10                  | 10                  | 10                   |
| SPLEEN   | MEAN    | 0.603              | 0.562               | 0.579               | 0.759 **             |
|          | ST.DEV. | 0.126              | 0.060               | 0.068               | 0.102                |
|          | N       | 10                 | 10                  | 10                  | 10                   |
| OVARIES  | MEAN    | 0.104              | 0.098               | 0.104               | 0.143                |
|          | ST.DEV. | 0.020              | 0.016               | 0.020               | 0.081                |
|          | N       | 10                 | 10                  | 10                  | 10                   |
| UTERUS   | MEAN    | 1.028              | 1.083               | 1.016               | 1.057                |
|          | ST.DEV. | 0.238              | 0.371               | 0.232               | 0.212                |
|          | N       | 10                 | 10                  | 10                  | 10                   |

\*/\*\*: Dunnett-test based on pooled variance sig. at 5% or 1% level.



**ORGAN/BODY WEIGHT RATIOS SUMMARY  
 AFTER 14 WEEKS  
 FEMALES**

|                   |                      | GROUP 1<br>0 MG/KG    | GROUP 2<br>15 MG/KG   | GROUP 3<br>50 MG/KG   | GROUP 4<br>200 MG/KG    |
|-------------------|----------------------|-----------------------|-----------------------|-----------------------|-------------------------|
| BODY W.<br>(GRAM) | MEAN<br>ST.DEV.<br>N | 212.44<br>14.92<br>10 | 212.23<br>11.84<br>10 | 214.27<br>12.87<br>10 | 215.15<br>11.73<br>10   |
| BRAIN<br>(%)      | MEAN<br>ST.DEV.<br>N | 0.90<br>0.04<br>10    | 0.89<br>0.04<br>10    | 0.89<br>0.05<br>10    | 0.88<br>0.05<br>10      |
| HEART<br>(%)      | MEAN<br>ST.DEV.<br>N | 0.330<br>0.025<br>10  | 0.326<br>0.037<br>10  | 0.332<br>0.030<br>10  | 0.337<br>0.022<br>10    |
| THYROIDS<br>(%)   | MEAN<br>ST.DEV.<br>N | 0.009<br>0.001<br>10  | 0.010<br>0.002<br>10  | 0.009<br>0.001<br>10  | 0.010<br>0.002<br>10    |
| LIVER<br>(%)      | MEAN<br>ST.DEV.<br>N | 2.53<br>0.27<br>10    | 2.51<br>0.17<br>10    | 2.51<br>0.21<br>10    | 2.90 **<br>0.27<br>10   |
| THYMUS<br>(%)     | MEAN<br>ST.DEV.<br>N | 0.12<br>0.01<br>10    | 0.10<br>0.02<br>10    | 0.11<br>0.02<br>10    | 0.11<br>0.02<br>10      |
| KIDNEYS<br>(%)    | MEAN<br>ST.DEV.<br>N | 0.63<br>0.04<br>10    | 0.60<br>0.04<br>10    | 0.64<br>0.05<br>10    | 0.68 *<br>0.06<br>10    |
| ADRENALS<br>(%)   | MEAN<br>ST.DEV.<br>N | 0.034<br>0.003<br>10  | 0.032<br>0.004<br>10  | 0.031<br>0.005<br>10  | 0.033<br>0.004<br>10    |
| SPLEEN<br>(%)     | MEAN<br>ST.DEV.<br>N | 0.283<br>0.051<br>10  | 0.266<br>0.032<br>10  | 0.271<br>0.034<br>10  | 0.353 **<br>0.047<br>10 |
| OVARIES<br>(%)    | MEAN<br>ST.DEV.<br>N | 0.049<br>0.009<br>10  | 0.046<br>0.008<br>10  | 0.049<br>0.010<br>10  | 0.067<br>0.039<br>10    |
| UTERUS<br>(%)     | MEAN<br>ST.DEV.<br>N | 0.486<br>0.121<br>10  | 0.509<br>0.167<br>10  | 0.480<br>0.140<br>10  | 0.495<br>0.117<br>10    |

\*/\*\*: Dunnett-test based on pooled variance sig. at 5% or 1% level.

**ORGAN/BRAIN WEIGHT RATIOS SUMMARY  
AFTER 14 WEEKS  
FEMALES**

|                 |                      | GROUP 1<br>0 MG/KG     | GROUP 2<br>15 MG/KG    | GROUP 3<br>50 MG/KG    | GROUP 4<br>200 MG/KG     |
|-----------------|----------------------|------------------------|------------------------|------------------------|--------------------------|
| BRAIN<br>(GRAM) | MEAN<br>ST.DEV.<br>N | 1.91<br>0.07<br>10     | 1.89<br>0.08<br>10     | 1.91<br>0.07<br>10     | 1.89<br>0.06<br>10       |
| HEART<br>(%)    | MEAN<br>ST.DEV.<br>N | 36.734<br>3.044<br>10  | 36.550<br>3.584<br>10  | 37.206<br>2.511<br>10  | 38.312<br>3.225<br>10    |
| THYROIDS<br>(%) | MEAN<br>ST.DEV.<br>N | 0.978<br>0.128<br>10   | 1.077<br>0.224<br>10   | 1.025<br>0.180<br>10   | 1.197<br>0.326<br>10     |
| LIVER<br>(%)    | MEAN<br>ST.DEV.<br>N | 280.73<br>26.10<br>10  | 280.88<br>11.39<br>10  | 281.00<br>17.21<br>10  | 330.33 **<br>39.26<br>10 |
| THYMUS<br>(%)   | MEAN<br>ST.DEV.<br>N | 12.92<br>1.57<br>10    | 11.51<br>2.27<br>10    | 12.52<br>1.78<br>10    | 12.40<br>2.60<br>10      |
| KIDNEYS<br>(%)  | MEAN<br>ST.DEV.<br>N | 69.58<br>3.99<br>10    | 67.70<br>3.49<br>10    | 71.54<br>3.99<br>10    | 77.47 **<br>7.11<br>10   |
| ADRENALS<br>(%) | MEAN<br>ST.DEV.<br>N | 3.767<br>0.362<br>10   | 3.605<br>0.344<br>10   | 3.511<br>0.466<br>10   | 3.756<br>0.562<br>10     |
| SPLEEN<br>(%)   | MEAN<br>ST.DEV.<br>N | 31.517<br>6.024<br>10  | 29.759<br>3.124<br>10  | 30.413<br>3.785<br>10  | 40.201 **<br>5.466<br>10 |
| OVARIES<br>(%)  | MEAN<br>ST.DEV.<br>N | 5.472<br>1.046<br>10   | 5.205<br>0.820<br>10   | 5.448<br>1.025<br>10   | 7.569<br>4.251<br>10     |
| UTERUS<br>(%)   | MEAN<br>ST.DEV.<br>N | 53.981<br>12.754<br>10 | 57.063<br>18.681<br>10 | 53.371<br>12.564<br>10 | 55.899<br>10.990<br>10   |

\*/\*\*: Dunnett-test based on pooled variance sig. at 5% or 1% level.

**ORGAN WEIGHTS (GRAM) SUMMARY  
AFTER 14 WEEKS  
MALES**

|              |         | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|--------------|---------|--------------------|---------------------|---------------------|----------------------|
| BODY W.      | MEAN    | 450.58             | 422.89 *            | 458.82              | 440.27               |
|              | ST.DEV. | 23.88              | 10.05               | 7.87                | 18.37                |
|              | N       | 5                  | 5                   | 5                   | 5                    |
| BRAIN        | MEAN    | 2.13               | 2.03                | 2.06                | 2.11                 |
|              | ST.DEV. | 0.04               | 0.12                | 0.10                | 0.11                 |
|              | N       | 5                  | 5                   | 5                   | 5                    |
| HEART        | MEAN    | 1.124              | 1.019               | 1.059               | 1.058                |
|              | ST.DEV. | 0.050              | 0.063               | 0.080               | 0.092                |
|              | N       | 5                  | 5                   | 5                   | 5                    |
| THYROIDS     | MEAN    | 0.027              | 0.027               | 0.028               | 0.030                |
|              | ST.DEV. | 0.004              | 0.004               | 0.006               | 0.008                |
|              | N       | 5                  | 5                   | 5                   | 5                    |
| LIVER        | MEAN    | 12.68              | 12.28               | 13.80               | 13.75                |
|              | ST.DEV. | 0.56               | 0.99                | 1.06                | 1.25                 |
|              | N       | 5                  | 5                   | 5                   | 5                    |
| THYMUS       | MEAN    | 0.28               | 0.32                | 0.26                | 0.31                 |
|              | ST.DEV. | 0.06               | 0.07                | 0.04                | 0.04                 |
|              | N       | 5                  | 5                   | 5                   | 5                    |
| KIDNEYS      | MEAN    | 2.26               | 2.13                | 2.22                | 2.30                 |
|              | ST.DEV. | 0.14               | 0.18                | 0.15                | 0.17                 |
|              | N       | 5                  | 5                   | 5                   | 5                    |
| ADRENALS     | MEAN    | 0.060              | 0.052               | 0.057               | 0.060                |
|              | ST.DEV. | 0.004              | 0.004               | 0.008               | 0.009                |
|              | N       | 5                  | 5                   | 5                   | 5                    |
| SPLEEN       | MEAN    | 0.749              | 0.827               | 0.764               | 0.898                |
|              | ST.DEV. | 0.094              | 0.157               | 0.111               | 0.134                |
|              | N       | 5                  | 5                   | 5                   | 5                    |
| TESTES       | MEAN    | 4.09               | 3.51                | 3.82                | 3.63                 |
|              | ST.DEV. | 0.30               | 0.57                | 0.40                | 0.19                 |
|              | N       | 5                  | 5                   | 5                   | 5                    |
| EPIDIDYMIDES | MEAN    | 1.573              | 1.342               | 1.559               | 1.499                |
|              | ST.DEV. | 0.099              | 0.175               | 0.290               | 0.198                |
|              | N       | 5                  | 5                   | 5                   | 5                    |

\*/\*\*: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ORGAN/BODY WEIGHT RATIOS SUMMARY  
 AFTER 14 WEEKS  
 MALES

|                     |                      | GROUP 1<br>0 MG/KG   | GROUP 2<br>15 MG/KG    | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|---------------------|----------------------|----------------------|------------------------|---------------------|----------------------|
| BODY W.<br>(GRAM)   | MEAN<br>ST.DEV.<br>N | 450.58<br>23.88<br>5 | 422.89 *<br>10.05<br>5 | 458.82<br>7.87<br>5 | 440.27<br>18.37<br>5 |
| BRAIN<br>(%)        | MEAN<br>ST.DEV.<br>N | 0.47<br>0.03<br>5    | 0.48<br>0.02<br>5      | 0.45<br>0.02<br>5   | 0.48<br>0.03<br>5    |
| HEART<br>(%)        | MEAN<br>ST.DEV.<br>N | 0.250<br>0.014<br>5  | 0.241<br>0.012<br>5    | 0.231<br>0.015<br>5 | 0.240<br>0.013<br>5  |
| THYROIDS<br>(%)     | MEAN<br>ST.DEV.<br>N | 0.006<br>0.001<br>5  | 0.006<br>0.001<br>5    | 0.006<br>0.001<br>5 | 0.007<br>0.001<br>5  |
| LIVER<br>(%)        | MEAN<br>ST.DEV.<br>N | 2.82<br>0.15<br>5    | 2.90<br>0.21<br>5      | 3.01<br>0.24<br>5   | 3.12<br>0.25<br>5    |
| THYMUS<br>(%)       | MEAN<br>ST.DEV.<br>N | 0.06<br>0.01<br>5    | 0.08<br>0.02<br>5      | 0.06<br>0.01<br>5   | 0.07<br>0.01<br>5    |
| KIDNEYS<br>(%)      | MEAN<br>ST.DEV.<br>N | 0.50<br>0.05<br>5    | 0.50<br>0.03<br>5      | 0.48<br>0.03<br>5   | 0.52<br>0.03<br>5    |
| ADRENALS<br>(%)     | MEAN<br>ST.DEV.<br>N | 0.013<br>0.001<br>5  | 0.012<br>0.001<br>5    | 0.012<br>0.002<br>5 | 0.014<br>0.002<br>5  |
| SPLEEN<br>(%)       | MEAN<br>ST.DEV.<br>N | 0.167<br>0.028<br>5  | 0.195<br>0.035<br>5    | 0.166<br>0.025<br>5 | 0.204<br>0.028<br>5  |
| TESTES<br>(%)       | MEAN<br>ST.DEV.<br>N | 0.91<br>0.05<br>5    | 0.83<br>0.12<br>5      | 0.83<br>0.09<br>5   | 0.83<br>0.04<br>5    |
| EPIDIDYMIDES<br>(%) | MEAN<br>ST.DEV.<br>N | 0.350<br>0.036<br>5  | 0.317<br>0.034<br>5    | 0.340<br>0.065<br>5 | 0.340<br>0.037<br>5  |

\*/\*\*: Dunnett-test based on pooled variance sig. at 5% or 1% level.

**ORGAN/BRAIN WEIGHT RATIOS SUMMARY  
 AFTER 14 WEEKS  
 MALES**

|                     |                      | GROUP 1<br>0 MG/KG   | GROUP 2<br>15 MG/KG  | GROUP 3<br>50 MG/KG   | GROUP 4<br>200 MG/KG  |
|---------------------|----------------------|----------------------|----------------------|-----------------------|-----------------------|
| BRAIN<br>(GRAM)     | MEAN<br>ST.DEV.<br>N | 2.13<br>0.04<br>5    | 2.03<br>0.12<br>5    | 2.06<br>0.10<br>5     | 2.11<br>0.11<br>5     |
| HEART<br>(%)        | MEAN<br>ST.DEV.<br>N | 52.884<br>2.195<br>5 | 50.193<br>2.813<br>5 | 51.442<br>4.127<br>5  | 50.139<br>4.319<br>5  |
| THYROIDS<br>(%)     | MEAN<br>ST.DEV.<br>N | 1.254<br>0.191<br>5  | 1.304<br>0.124<br>5  | 1.364<br>0.250<br>5   | 1.421<br>0.404<br>5   |
| LIVER<br>(%)        | MEAN<br>ST.DEV.<br>N | 597.21<br>36.08<br>5 | 604.76<br>46.02<br>5 | 672.78<br>87.17<br>5  | 651.68<br>55.52<br>5  |
| THYMUS<br>(%)       | MEAN<br>ST.DEV.<br>N | 13.30<br>2.79<br>5   | 15.87<br>3.09<br>5   | 12.47<br>1.55<br>5    | 14.66<br>2.16<br>5    |
| KIDNEYS<br>(%)      | MEAN<br>ST.DEV.<br>N | 106.30<br>5.27<br>5  | 104.71<br>7.01<br>5  | 108.11<br>11.09<br>5  | 108.90<br>7.50<br>5   |
| ADRENALS<br>(%)     | MEAN<br>ST.DEV.<br>N | 2.825<br>0.193<br>5  | 2.560<br>0.245<br>5  | 2.758<br>0.483<br>5   | 2.821<br>0.427<br>5   |
| SPLEEN<br>(%)       | MEAN<br>ST.DEV.<br>N | 35.228<br>3.975<br>5 | 40.644<br>7.160<br>5 | 37.093<br>5.493<br>5  | 42.467<br>5.568<br>5  |
| TESTES<br>(%)       | MEAN<br>ST.DEV.<br>N | 192.50<br>12.87<br>5 | 172.36<br>21.76<br>5 | 184.95<br>15.38<br>5  | 172.48<br>12.67<br>5  |
| EPIDIDYMIDES<br>(%) | MEAN<br>ST.DEV.<br>N | 73.982<br>3.433<br>5 | 66.017<br>7.657<br>5 | 75.335<br>11.953<br>5 | 71.211<br>10.689<br>5 |

\*/\*\*: Dunnett-test based on pooled variance sig. at 5% or 1% level.

**ORGAN WEIGHTS (GRAM) SUMMARY  
 AFTER 14 WEEKS  
 FEMALES**

|          |         | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|----------|---------|--------------------|---------------------|---------------------|----------------------|
| BODY W.  | MEAN    | 230.62             | 237.34              | 226.31              | 230.54               |
|          | ST.DEV. | 12.05              | 17.72               | 16.47               | 8.54                 |
|          | N       | 5                  | 5                   | 5                   | 5                    |
| BRAIN    | MEAN    | 1.90               | 1.87                | 1.87                | 1.89                 |
|          | ST.DEV. | 0.08               | 0.04                | 0.02                | 0.03                 |
|          | N       | 5                  | 5                   | 5                   | 5                    |
| HEART    | MEAN    | 0.711              | 0.743               | 0.748               | 0.766                |
|          | ST.DEV. | 0.092              | 0.065               | 0.049               | 0.097                |
|          | N       | 5                  | 5                   | 5                   | 5                    |
| THYROIDS | MEAN    | 0.020              | 0.020               | 0.022               | 0.021                |
|          | ST.DEV. | 0.004              | 0.004               | 0.004               | 0.004                |
|          | N       | 5                  | 5                   | 5                   | 5                    |
| LIVER    | MEAN    | 7.35               | 7.46                | 6.79                | 7.82                 |
|          | ST.DEV. | 0.73               | 0.84                | 0.56                | 0.31                 |
|          | N       | 5                  | 5                   | 5                   | 5                    |
| THYMUS   | MEAN    | 0.26               | 0.28                | 0.28                | 0.25                 |
|          | ST.DEV. | 0.05               | 0.06                | 0.07                | 0.05                 |
|          | N       | 5                  | 5                   | 5                   | 5                    |
| KIDNEYS  | MEAN    | 1.46               | 1.36                | 1.35                | 1.46                 |
|          | ST.DEV. | 0.12               | 0.09                | 0.11                | 0.03                 |
|          | N       | 5                  | 5                   | 5                   | 5                    |
| ADRENALS | MEAN    | 0.070              | 0.071               | 0.064               | 0.065                |
|          | ST.DEV. | 0.009              | 0.012               | 0.005               | 0.006                |
|          | N       | 5                  | 5                   | 5                   | 5                    |
| SPLEEN   | MEAN    | 0.565              | 0.538               | 0.567               | 0.677                |
|          | ST.DEV. | 0.074              | 0.120               | 0.084               | 0.106                |
|          | N       | 5                  | 5                   | 5                   | 5                    |
| OVARIES  | MEAN    | 0.114              | 0.107               | 0.106               | 0.117                |
|          | ST.DEV. | 0.020              | 0.021               | 0.013               | 0.017                |
|          | N       | 5                  | 5                   | 5                   | 5                    |
| UTERUS   | MEAN    | 1.087              | 0.939               | 1.402               | 0.932                |
|          | ST.DEV. | 0.116              | 0.230               | 0.226               | 0.277                |
|          | N       | 5                  | 5                   | 5                   | 5                    |

\*/\*\*: Dunnett-test based on pooled variance sig. at 5% or 1% level.

**ORGAN/BODY WEIGHT RATIOS SUMMARY  
 AFTER 14 WEEKS  
 FEMALES**

|                   |                      | GROUP 1<br>0 MG/KG   | GROUP 2<br>15 MG/KG  | GROUP 3<br>50 MG/KG  | GROUP 4<br>200 MG/KG |
|-------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| BODY W.<br>(GRAM) | MEAN<br>ST.DEV.<br>N | 230.62<br>12.05<br>5 | 237.34<br>17.72<br>5 | 226.31<br>16.47<br>5 | 230.54<br>8.54<br>5  |
| BRAIN<br>(%)      | MEAN<br>ST.DEV.<br>N | 0.83<br>0.07<br>5    | 0.79<br>0.06<br>5    | 0.83<br>0.06<br>5    | 0.82<br>0.03<br>5    |
| HEART<br>(%)      | MEAN<br>ST.DEV.<br>N | 0.308<br>0.035<br>5  | 0.313<br>0.011<br>5  | 0.331<br>0.020<br>5  | 0.332<br>0.040<br>5  |
| THYROIDS<br>(%)   | MEAN<br>ST.DEV.<br>N | 0.009<br>0.002<br>5  | 0.009<br>0.002<br>5  | 0.010<br>0.001<br>5  | 0.009<br>0.001<br>5  |
| LIVER<br>(%)      | MEAN<br>ST.DEV.<br>N | 3.18<br>0.22<br>5    | 3.14<br>0.18<br>5    | 3.00<br>0.13<br>5    | 3.40<br>0.22<br>5    |
| THYMUS<br>(%)     | MEAN<br>ST.DEV.<br>N | 0.11<br>0.02<br>5    | 0.12<br>0.03<br>5    | 0.12<br>0.03<br>5    | 0.11<br>0.02<br>5    |
| KIDNEYS<br>(%)    | MEAN<br>ST.DEV.<br>N | 0.63<br>0.05<br>5    | 0.57<br>0.04<br>5    | 0.60<br>0.07<br>5    | 0.63<br>0.03<br>5    |
| ADRENALS<br>(%)   | MEAN<br>ST.DEV.<br>N | 0.030<br>0.005<br>5  | 0.030<br>0.006<br>5  | 0.028<br>0.003<br>5  | 0.028<br>0.003<br>5  |
| SPLEEN<br>(%)     | MEAN<br>ST.DEV.<br>N | 0.245<br>0.032<br>5  | 0.227<br>0.047<br>5  | 0.250<br>0.029<br>5  | 0.295<br>0.054<br>5  |
| OVARIES<br>(%)    | MEAN<br>ST.DEV.<br>N | 0.050<br>0.010<br>5  | 0.045<br>0.008<br>5  | 0.047<br>0.007<br>5  | 0.051<br>0.008<br>5  |
| UTERUS<br>(%)     | MEAN<br>ST.DEV.<br>N | 0.473<br>0.064<br>5  | 0.401<br>0.123<br>5  | 0.621<br>0.100<br>5  | 0.404<br>0.119<br>5  |

\*/\*\*: Dunnett-test based on pooled variance sig. at 5% or 1% level.

**ORGAN/BRAIN WEIGHT RATIOS SUMMARY  
 AFTER 14 WEEKS  
 FEMALES**

|                 |         | GROUP 1<br>0 MG/KG | GROUP 2<br>15 MG/KG | GROUP 3<br>50 MG/KG | GROUP 4<br>200 MG/KG |
|-----------------|---------|--------------------|---------------------|---------------------|----------------------|
| BRAIN<br>(GRAM) | MEAN    | 1.90               | 1.87                | 1.87                | 1.89                 |
|                 | ST.DEV. | 0.08               | 0.04                | 0.02                | 0.03                 |
|                 | N       | 5                  | 5                   | 5                   | 5                    |
| HEART<br>(%)    | MEAN    | 37.582             | 39.821              | 39.966              | 40.527               |
|                 | ST.DEV. | 6.091              | 3.496               | 2.585               | 4.535                |
|                 | N       | 5                  | 5                   | 5                   | 5                    |
| THYROIDS<br>(%) | MEAN    | 1.059              | 1.085               | 1.174               | 1.106                |
|                 | ST.DEV. | 0.231              | 0.196               | 0.207               | 0.215                |
|                 | N       | 5                  | 5                   | 5                   | 5                    |
| LIVER<br>(%)    | MEAN    | 387.88             | 399.41              | 362.91              | 414.65               |
|                 | ST.DEV. | 47.20              | 46.26               | 32.99               | 22.04                |
|                 | N       | 5                  | 5                   | 5                   | 5                    |
| THYMUS<br>(%)   | MEAN    | 13.87              | 14.82               | 15.02               | 13.53                |
|                 | ST.DEV. | 2.67               | 3.67                | 3.73                | 2.66                 |
|                 | N       | 5                  | 5                   | 5                   | 5                    |
| KIDNEYS<br>(%)  | MEAN    | 77.06              | 72.85               | 72.29               | 77.39                |
|                 | ST.DEV. | 7.90               | 6.02                | 5.46                | 2.05                 |
|                 | N       | 5                  | 5                   | 5                   | 5                    |
| ADRENALS<br>(%) | MEAN    | 3.676              | 3.833               | 3.420               | 3.442                |
|                 | ST.DEV. | 0.438              | 0.676               | 0.254               | 0.333                |
|                 | N       | 5                  | 5                   | 5                   | 5                    |
| SPLEEN<br>(%)   | MEAN    | 29.736             | 28.870              | 30.272              | 35.905               |
|                 | ST.DEV. | 3.458              | 6.885               | 4.486               | 5.872                |
|                 | N       | 5                  | 5                   | 5                   | 5                    |
| OVARIES<br>(%)  | MEAN    | 5.987              | 5.725               | 5.672               | 6.218                |
|                 | ST.DEV. | 0.991              | 1.178               | 0.721               | 0.871                |
|                 | N       | 5                  | 5                   | 5                   | 5                    |
| UTERUS<br>(%)   | MEAN    | 57.381             | 50.482              | 74.820              | 49.284               |
|                 | ST.DEV. | 7.042              | 13.591              | 11.608              | 14.198               |
|                 | N       | 5                  | 5                   | 5                   | 5                    |

\*/\*\*; Dunnett-test based on pooled variance sig. at 5% or 1% level.



## **9    INDIVIDUAL TABLES**

RCC STUDY NUMBER 857092  
A 084, WR 23081

MORT-IND - 1  
22-APR-05

**MORTALITY DATA  
MALES  
GROUP 1 (0 MG/KG)**

| ANIMAL | SCHEDULED<br>NECROPSY | TREATMENT<br>FROM | TO        |
|--------|-----------------------|-------------------|-----------|
| 1      | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 2      | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 3      | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 4      | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 5      | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 6      | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 7      | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 8      | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 9      | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 10     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 11     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 12     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 13     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 14     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 15     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |

RCC STUDY NUMBER 857092  
A 084, WR 23081

MORT-IND - 2  
22-APR-05

**MORTALITY DATA  
MALES  
GROUP 2 (15 MG/KG)**

| ANIMAL | SCHEDULED<br>NECROPSY | TREATMENT<br>FROM | TO        |
|--------|-----------------------|-------------------|-----------|
| 16     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 17     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 18     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 19     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 20     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 21     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 22     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 23     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 24     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 25     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 26     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 27     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 28     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 29     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 30     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |

RCC STUDY NUMBER 857092  
A 084, WR 23081

MORT-IND - 3  
22-APR-05

**MORTALITY DATA  
MALES  
GROUP 3 (50 MG/KG)**

| ANIMAL | SCHEDULED<br>NECROPSY | TREATMENT<br>FROM | TO        |
|--------|-----------------------|-------------------|-----------|
| 31     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 32     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 33     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 34     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 35     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 36     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 37     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 38     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 39     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 40     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 41     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 42     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 43     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 44     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 45     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |

RCC STUDY NUMBER 857092  
A 084, WR 23081

MORT-IND - 4  
22-APR-05

**MORTALITY DATA**  
**MALES**  
**GROUP 4 (200 MG/KG)**

| ANIMAL | SCHEDULED<br>NECROPSY | TREATMENT<br>FROM | TO        |
|--------|-----------------------|-------------------|-----------|
| 46     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 47     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 48     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 49     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 50     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 51     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 52     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 53     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 54     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 55     | 17-FEB-05             | 01-NOV-04         | 16-FEB-05 |
| 56     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 57     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 58     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 59     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 60     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |

RCC STUDY NUMBER 857092  
A 084, WR 23081

MORT-IND - 5  
22-APR-05

**MORTALITY DATA  
FEMALES  
GROUP 1 (0 MG/KG)**

| ANIMAL | SCHEDULED<br>NECROPSY | TREATMENT<br>FROM | TO        |
|--------|-----------------------|-------------------|-----------|
| 61     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 62     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 63     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 64     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 65     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 66     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 67     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 68     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 69     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 70     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 71     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 72     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 73     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 74     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 75     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |

RCC STUDY NUMBER 857092  
A 084, WR 23081

MORT-IND - 6  
22-APR-05

**MORTALITY DATA  
FEMALES  
GROUP 2 (15 MG/KG)**

| ANIMAL | SCHEDULED<br>NECROPSY | TREATMENT<br>FROM | TO        |
|--------|-----------------------|-------------------|-----------|
| 76     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 77     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 78     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 79     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 80     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 81     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 82     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 83     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 84     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 85     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 86     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 87     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 88     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 89     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 90     | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |

RCC STUDY NUMBER 857092  
A 084, WR 23081

MORT-IND - 7  
22-APR-05

**MORTALITY DATA  
FEMALES  
GROUP 3 (50 MG/KG)**

| ANIMAL | SCHEDULED<br>NECROPSY | TREATMENT<br>FROM | TO        |
|--------|-----------------------|-------------------|-----------|
| 91     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 92     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 93     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 94     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 95     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 96     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 97     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 98     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 99     | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 100    | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 101    | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 102    | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 103    | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 104    | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 105    | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |



RCC STUDY NUMBER 857092  
A 084, WR 23081

MORT-IND - 8  
22-APR-05

**MORTALITY DATA  
FEMALES  
GROUP 4 (200 MG/KG)**

| ANIMAL | SCHEDULED<br>NECROPSY | TREATMENT<br>FROM | TO        |
|--------|-----------------------|-------------------|-----------|
| 106    | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 107    | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 108    | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 109    | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 110    | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 111    | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 112    | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 113    | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 114    | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 115    | 18-FEB-05             | 01-NOV-04         | 17-FEB-05 |
| 116    | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 117    | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 118    | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 119    | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |
| 120    | 16-FEB-05             | 01-NOV-04         | 15-FEB-05 |

CLINICAL SIGNS, DAILY  
MALES  
GROUP 1 (0 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|--------------------------------|--------------------------|---|
|--------------------------------|--------------------------|---|

---

ANIMAL 1  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 2  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 3  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 4  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 5  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 6  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 7  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 8  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 9  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 10  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 11  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 12  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 13  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 14  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 15  
-----  
NO CLINICAL SIGNS NOTED

**CLINICAL SIGNS, DAILY  
MALES  
GROUP 2 (15 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION)                | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|---|--------------------------|---|
| ANIMAL 16<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 17<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 18<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 19<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 20<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 21<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 22<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 23<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 24<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 25<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 26<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 27<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 28<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 29<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 30<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |

**CLINICAL SIGNS, DAILY  
MALES  
GROUP 3 (50 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION)          | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|---|--------------------------|---|
| ANIMAL 31                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |
| ANIMAL 32                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |
| ANIMAL 33                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |
| ANIMAL 34                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |
| ANIMAL 35                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |
| ANIMAL 36                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |
| ANIMAL 37                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |
| ANIMAL 38                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |
| ANIMAL 39                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |
| ANIMAL 40                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |
| ANIMAL 41                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |
| ANIMAL 42                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |
| ANIMAL 43                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....1111111111111111111111111111          |

G: Highest daily grades

CLINICAL SIGNS, DAILY  
MALES  
GROUP 3 (50 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|--------------------------------|--------------------------|---|
| ANIMAL 44                      |                          |   |
| -----                          |                          |   |
| SECRETION / EXCRETION          |                          |   |
| URINE BLUE (1)                 | G: .....                 | .....11111111.....1111111111111111111111111111111111    |
| ANIMAL 45                      |                          |   |
| -----                          |                          |   |
| SECRETION / EXCRETION          |                          |   |
| URINE BLUE (1)                 | G: .....                 | .....1111111111111111111111111111111111                 |

G: Highest daily grades



**CLINICAL SIGNS, DAILY  
 MALES  
 GROUP 4 (200 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION)          | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|---|--------------------------|---|
| <b>ANIMAL 59</b><br>-----               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111 |
| <b>ANIMAL 60</b><br>-----               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111 |

G: Highest daily grades

CLINICAL SIGNS, DAILY  
MALES  
GROUP 1 (0 MG/KG)

SIGN (MAX.GRADE) TREATMENT  
(LOCATION) WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16...

ANIMAL 1  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 2  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 3  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 4  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 5  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 6  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 7  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 8  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 9  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 10  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 11  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 12  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 13  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 14  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 15  
-----  
NO CLINICAL SIGNS NOTED



**CLINICAL SIGNS, DAILY  
MALES  
GROUP 2 (15 MG/KG)**

SIGN (MAX.GRADE) TREATMENT  
(LOCATION) WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16...

---

ANIMAL 16  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 17  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 18  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 19  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 20  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 21  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 22  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 23  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 24  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 25  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 26  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 27  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 28  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 29  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 30  
-----  
NO CLINICAL SIGNS NOTED

---

**CLINICAL SIGNS, DAILY  
MALES  
GROUP 3 (50 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION)          | TREATMENT  |   |   |   |   |   |   |   |   |   |   |   |
|---|--|---|---|---|---|---|---|---|---|---|---|---|
|   | WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16... |   |   |   |   |   |   |   |   |   |   |   |
| ANIMAL 31                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 32                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 33                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 34                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 35                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 36                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 37                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 38                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 39                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 40                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 41                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 42                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 43                               | -----  |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

G: Highest daily grades



### CLINICAL SIGNS, DAILY MALES GROUP 4 (200 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION)                                | TREATMENT<br>WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16... |
|---|---|
| ANIMAL 46<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |
| ANIMAL 47<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |
| ANIMAL 48<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |
| ANIMAL 49<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |
| ANIMAL 50<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |
| ANIMAL 51<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |
| ANIMAL 52<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |
| ANIMAL 53<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |
| ANIMAL 54<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |
| ANIMAL 55<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |
| ANIMAL 56<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |
| ANIMAL 57<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |
| ANIMAL 58<br>-----<br>SECRETION / EXCRETION<br>URINE BLUE (1) | G: 11             |

G: Highest daily grades

RCC STUDY NUMBER 857092  
A 084, WR 23081

SYM-IND - 12  
22-APR-05

CLINICAL SIGNS, DAILY  
MALES  
GROUP 4 (200 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | TREATMENT  |
|--------------------------------|--|
|                                | WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16... |

---

ANIMAL 59

-----  
SECRETION / EXCRETION  
URINE BLUE (1)

G: 11

ANIMAL 60

-----  
SECRETION / EXCRETION  
URINE BLUE (1)

G: 11

CLINICAL SIGNS, DAILY  
FEMALES  
GROUP 1 (0 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION)                | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|---|--------------------------|---|
| ANIMAL 61<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 62<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 63<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 64<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 65<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 66<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 67<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 68<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 69<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 70<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 71<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 72<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 73<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 74<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 75<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |

**CLINICAL SIGNS, DAILY  
FEMALES  
GROUP 2 (15 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION)                | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|---|--------------------------|---|
| ANIMAL 76<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 77<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 78<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 79<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 80<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 81<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 82<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 83<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 84<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 85<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 86<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 87<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 88<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 89<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |
| ANIMAL 90<br>-----<br>NO CLINICAL SIGNS NOTED |                          |   |

CLINICAL SIGNS, DAILY  
FEMALES  
GROUP 3 (50 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION)          | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|---|--------------------------|---|
| ANIMAL 91                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |
| ANIMAL 92                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |
| ANIMAL 93                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |
| ANIMAL 94                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |
| ANIMAL 95                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |
| ANIMAL 96                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |
| ANIMAL 97                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |
| ANIMAL 98                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |
| ANIMAL 99                               |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |
| ANIMAL 100                              |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |
| ANIMAL 101                              |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |
| ANIMAL 102                              |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |
| ANIMAL 103                              |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | .....11111111.....111111111111111111111111              |

G: Highest daily grades



RCC STUDY NUMBER 857092  
A 084, WR 23081

SYM-IND - 16  
22-APR-05

CLINICAL SIGNS, DAILY  
FEMALES  
GROUP 3 (50 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|--------------------------------|--------------------------|---|
| <hr/>                          |                          |   |
| ANIMAL 104                     |                          |   |
| -----                          |                          |   |
| SECRETION / EXCRETION          | G: .....                 | .....11111111.....11111111111111111111111111111111      |
| URINE BLUE (1)                 |                          |   |
| ANIMAL 105                     |                          |   |
| -----                          |                          |   |
| SECRETION / EXCRETION          | G: .....                 | .....11111111.....11111111111111111111111111111111      |
| URINE BLUE (1)                 |                          |   |

---

G: Highest daily grades

# CLINICAL SIGNS, DAILY FEMALES GROUP 4 (200 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION)          | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|---|--------------------------|---|
| ANIMAL 106<br>-----                     |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111   |
| ANIMAL 107<br>-----                     |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111   |
| ANIMAL 108<br>-----                     |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111   |
| ANIMAL 109<br>-----                     |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111   |
| ANIMAL 110<br>-----                     |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111   |
| ANIMAL 111<br>-----                     |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111   |
| ANIMAL 112<br>-----                     |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111   |
| ANIMAL 113<br>-----                     |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111   |
| ANIMAL 114<br>-----                     |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111   |
| ANIMAL 115<br>-----                     |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111   |
| ANIMAL 116<br>-----                     |                          |   |
| SKIN / FUR                              |                          |   |
| HAIR LOSS (3)                           | G: .....                 | .....   |
| (SHOULDER LEFT)                         |                          |   |
| HAIR LOSS (3)                           | G: .....                 | .....   |
| (SHOULDER RIGHT)                        |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111   |
| ANIMAL 117<br>-----                     |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .....                 | ..111   |

# CLINICAL SIGNS, DAILY FEMALES GROUP 4 (200 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION)                 | PRETEST<br>WEEKS: 1..... | TREATMENT<br>1.....2.....3.....4.....5.....6.....7..... |
|--|--------------------------|---|
| ANIMAL 118                                     |                          |   |
| -----  |                          |   |
| SECRETION / EXCRETION<br>URINE BLUE (1)        | G: .....                 | ..11              |
| ANIMAL 119                                     |                          |   |
| -----  |                          |   |
| SKIN / FUR<br>HAIR LOSS (3)<br>(SHOULDER LEFT) | G: .....                 | .....   |
| HAIR LOSS (3)<br>(SHOULDER RIGHT)              | G: .....                 | .....   |
| SECRETION / EXCRETION<br>URINE BLUE (1)        | G: .....                 | ..11              |
| ANIMAL 120                                     |                          |   |
| -----  |                          |   |
| SKIN / FUR<br>HAIR LOSS (3)<br>(SHOULDER LEFT) | G: .....                 | .....   |
| HAIR LOSS (3)<br>(SHOULDER RIGHT)              | G: .....                 | .....   |
| SECRETION / EXCRETION<br>URINE BLUE (1)        | G: .....                 | ..11              |

G: Highest daily grades

CLINICAL SIGNS, DAILY  
FEMALES  
GROUP 1 (0 MG/KG)

SIGN (MAX.GRADE) TREATMENT  
(LOCATION) WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16...

ANIMAL 61  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 62  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 63  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 64  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 65  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 66  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 67  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 68  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 69  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 70  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 71  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 72  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 73  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 74  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 75  
-----  
NO CLINICAL SIGNS NOTED

**CLINICAL SIGNS, DAILY  
FEMALES  
GROUP 2 (15 MG/KG)**

SIGN (MAX.GRADE) TREATMENT  
(LOCATION) WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16...

ANIMAL 76  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 77  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 78  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 79  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 80  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 81  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 82  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 83  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 84  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 85  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 86  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 87  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 88  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 89  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 90  
-----  
NO CLINICAL SIGNS NOTED

**CLINICAL SIGNS, DAILY  
FEMALES  
GROUP 3 (50 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION) | TREATMENT |   |    |    |    |    |    |    |    |    |    |    |    |
|--------------------------------|-----------|---|----|----|----|----|----|----|----|----|----|----|----|
|                                | WEEKS: 8  | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| ANIMAL 91                      |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| ANIMAL 92                      |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| ANIMAL 93                      |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| ANIMAL 94                      |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| ANIMAL 95                      |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| ANIMAL 96                      |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| ANIMAL 97                      |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| ANIMAL 98                      |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| ANIMAL 99                      |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| ANIMAL 100                     |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| ANIMAL 101                     |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| ANIMAL 102                     |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| ANIMAL 103                     |           |   |    |    |    |    |    |    |    |    |    |    |    |
| -----                          |           |   |    |    |    |    |    |    |    |    |    |    |    |
| SECRETION / EXCRETION          | G:        |   |    |    |    |    |    |    |    |    |    |    |    |
| URINE BLUE (1)                 | 1         | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |

G: Highest daily grades

CLINICAL SIGNS, DAILY  
FEMALES  
GROUP 3 (50 MG/KG)

| SIGN (MAX.GRADE)<br>(LOCATION) | TREATMENT  |
|--------------------------------|--|
|                                | WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16... |

ANIMAL 104

-----  
SECRETION / EXCRETION  
URINE BLUE (1) G: 111

ANIMAL 105

-----  
SECRETION / EXCRETION  
URINE BLUE (1) G: 111

**CLINICAL SIGNS, DAILY  
FEMALES  
GROUP 4 (200 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION)          | TREATMENT  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|   | WEEKS: 8.....9.....10.....11.....12.....13.....14.....15.....16... |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| ANIMAL 106                              | -----  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 107                              | -----  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 108                              | -----  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 109                              | -----  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 110                              | -----  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 111                              | -----  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 112                              | -----  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 113                              | -----  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 114                              | -----  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 115                              | -----  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 116                              | -----  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SKIN / FUR                              |  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| HAIR LOSS (3)<br>(SHOULDER LEFT)        | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| HAIR LOSS (3)<br>(SHOULDER RIGHT)       | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANIMAL 117                              | -----  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G:   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

G: Highest daily grades





**CLINICAL SIGNS, WEEKLY  
MALES  
GROUP 1 (0 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION) | WEEKS: 1 | PRETEST TREATMENT<br>1...5...9...13 |
|--------------------------------|----------|-------------------------------------|
|--------------------------------|----------|-------------------------------------|

---

ANIMAL 1  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 2  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 3  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 4  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 5  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 6  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 7  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 8  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 9  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 10  
-----  
NO CLINICAL SIGNS NOTED

**CLINICAL SIGNS, WEEKLY  
MALES  
GROUP 2 (15 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST TREATMENT<br>WEEKS: 1 | 1...5...9...13 |
|--------------------------------|-------------------------------|----------------|
|--------------------------------|-------------------------------|----------------|

---

ANIMAL 16  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 17  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 18  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 19  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 20  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 21  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 22  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 23  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 24  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 25  
-----  
NO CLINICAL SIGNS NOTED

**CLINICAL SIGNS, WEEKLY  
 MALES  
 GROUP 3 (50 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST TREATMENT |                |
|--------------------------------|-------------------|----------------|
|                                | WEEKS: 1          | 1...5...9...13 |
| ANIMAL 31                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 32                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 33                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 34                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 35                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 36                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 37                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 38                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 39                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 40                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |

G: Highest weekly grades

**CLINICAL SIGNS, WEEKLY  
 MALES  
 GROUP 4 (200 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION)          | PRETEST TREATMENT |                |
|---|-------------------|----------------|
|   | WEEKS: 1          | 1...5...9...13 |
| ANIMAL 46                               |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .111111111111  |
| ANIMAL 47                               |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .111111111111  |
| ANIMAL 48                               |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .111111111111  |
| ANIMAL 49                               |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .111111111111  |
| ANIMAL 50                               |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .111111111111  |
| ANIMAL 51                               |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .111111111111  |
| ANIMAL 52                               |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .111111111111  |
| ANIMAL 53                               |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .111111111111  |
| ANIMAL 54                               |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .111111111111  |
| ANIMAL 55                               |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .111111111111  |

G: Highest weekly grades

**CLINICAL SIGNS, WEEKLY  
FEMALES  
GROUP 1 (0 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION) | WEEKS: 1 | PRETEST TREATMENT<br>1...5...9...13 |
|--------------------------------|----------|-------------------------------------|
|--------------------------------|----------|-------------------------------------|

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ANIMAL 61  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 62  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 63  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 64  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 65  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 66  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 67  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 68  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 69  
-----  
NO CLINICAL SIGNS NOTED

ANIMAL 70  
-----  
NO CLINICAL SIGNS NOTED

**CLINICAL SIGNS, WEEKLY  
FEMALES  
GROUP 2 (15 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST TREATMENT |                |
|--------------------------------|-------------------|----------------|
|                                | WEEKS: 1          | 1...5...9...13 |
| ANIMAL 76                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .....1111111.  |
| ANIMAL 77                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .....1111111.  |
| VARIOUS                        |                   |                |
| MIOSIS (1)                     | G: .              | .....1         |
| (EYE LEFT)                     |                   |                |
| MIOSIS (1)                     | G: .              | .....1         |
| (EYE RIGHT)                    |                   |                |
| ANIMAL 78                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .....1111111.  |
| ANIMAL 79                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .....1111111.  |
| ANIMAL 80                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .....1111111.  |
| ANIMAL 81                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .....1111111.  |
| ANIMAL 82                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .....1111111.  |
| ANIMAL 83                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .....1111111.  |
| ANIMAL 84                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .....1111111.  |
| ANIMAL 85                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .....1111111.  |

G: Highest weekly grades

**CLINICAL SIGNS, WEEKLY  
 FEMALES  
 GROUP 3 (50 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION) | PRETEST TREATMENT |                |
|--------------------------------|-------------------|----------------|
|                                | WEEKS: 1          | 1...5...9...13 |
| ANIMAL 91                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 92                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 93                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 94                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 95                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 96                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 97                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 98                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 99                      |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |
| ANIMAL 100                     |                   |                |
| -----                          |                   |                |
| SECRETION / EXCRETION          |                   |                |
| URINE BLUE (1)                 | G: .              | .1111111111111 |

G: Highest weekly grades



**CLINICAL SIGNS, WEEKLY  
 FEMALES  
 GROUP 4 (200 MG/KG)**

| SIGN (MAX.GRADE)<br>(LOCATION)          | PRETEST TREATMENT |                |
|---|-------------------|----------------|
|   | WEEKS: 1          | 1...5...9...13 |
| ANIMAL 106                              |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .1111111111111 |
| ANIMAL 107                              |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .1111111111111 |
| ANIMAL 108                              |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .1111111111111 |
| ANIMAL 109                              |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .1111111111111 |
| ANIMAL 110                              |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .1111111111111 |
| ANIMAL 111                              |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .1111111111111 |
| ANIMAL 112                              |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .1111111111111 |
| ANIMAL 113                              |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .1111111111111 |
| ANIMAL 114                              |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .1111111111111 |
| ANIMAL 115                              |                   |                |
| SECRETION / EXCRETION<br>URINE BLUE (1) | G: .              | .1111111111111 |

G: Highest weekly grades

**GRIP STRENGTH , INDIVIDUAL DATA****WEEK 15**

| <b>MALES</b>      |                 |                 | <b>Mean (g)</b>  | <b>FEMALES</b>    |                 |                 | <b>Mean (g)</b> |
|-------------------|-----------------|-----------------|------------------|-------------------|-----------------|-----------------|-----------------|
| <b>GROUP 1</b>    |                 |                 | <b>0 mg/kg</b>   |                   |                 |                 |                 |
| <b>Animal No.</b> | <b>Forelimb</b> | <b>Hindlimb</b> |                  | <b>Animal No.</b> | <b>Forelimb</b> | <b>Hindlimb</b> |                 |
| 1                 | 2017            | 1190            |                  | 61                | 1267            | 903             |                 |
| 2                 | 1400            | 1093            |                  | 62                | 1407            | 913             |                 |
| 3                 | 1867            | 1220            |                  | 63                | 1353            | 873             |                 |
| 4                 | 1780            | 1210            |                  | 64                | 1313            | 990             |                 |
| 5                 | 1723            | 1197            |                  | 65                | 1363            | 933             |                 |
| 6                 | 1810            | 1223            |                  | 66                | 1373            | 1007            |                 |
| 7                 | 1677            | 1183            |                  | 67                | 1270            | 863             |                 |
| 8                 | 1643            | 1077            |                  | 68                | 1280            | 927             |                 |
| 9                 | 1787            | 1290            |                  | 69                | 1250            | 853             |                 |
| 10                | 1690            | 1133            |                  | 70                | 1327            | 880             |                 |
| <b>GROUP 2</b>    |                 |                 | <b>15 mg/kg</b>  |                   |                 |                 |                 |
| <b>Animal No.</b> | <b>Forelimb</b> | <b>Hindlimb</b> |                  | <b>Animal No.</b> | <b>Forelimb</b> | <b>Hindlimb</b> |                 |
| 16                | 1810            | 1210            |                  | 76                | 1323            | 1000            |                 |
| 17                | 1783            | 1183            |                  | 77                | 1367            | 947             |                 |
| 18                | 1647            | 1173            |                  | 78                | 1350            | 900             |                 |
| 19                | 1683            | 1243            |                  | 79                | 1337            | 973             |                 |
| 20                | 1860            | 1217            |                  | 80                | 1287            | 883             |                 |
| 21                | 1730            | 1143            |                  | 81                | 1333            | 970             |                 |
| 22                | 1787            | 1233            |                  | 82                | 1310            | 977             |                 |
| 23                | 1823            | 1207            |                  | 83                | 1367            | 983             |                 |
| 24                | 1663            | 1220            |                  | 84                | 1383            | 990             |                 |
| 25                | 1673            | 1203            |                  | 85                | 1333            | 903             |                 |
| <b>GROUP 3</b>    |                 |                 | <b>50 mg/kg</b>  |                   |                 |                 |                 |
| <b>Animal No.</b> | <b>Forelimb</b> | <b>Hindlimb</b> |                  | <b>Animal No.</b> | <b>Forelimb</b> | <b>Hindlimb</b> |                 |
| 31                | 1733            | 1183            |                  | 91                | 1257            | 967             |                 |
| 32                | 1830            | 1250            |                  | 92                | 1343            | 903             |                 |
| 33                | 1687            | 1143            |                  | 93                | 1390            | 1010            |                 |
| 34                | 1810            | 1283            |                  | 94                | 1337            | 993             |                 |
| 35                | 1860            | 1260            |                  | 95                | 1443            | 967             |                 |
| 36                | 1677            | 1137            |                  | 96                | 1377            | 943             |                 |
| 37                | 1640            | 1203            |                  | 97                | 1403            | 1003            |                 |
| 38                | 1740            | 1227            |                  | 98                | 1333            | 943             |                 |
| 39                | 1720            | 1157            |                  | 99                | 1290            | 940             |                 |
| 40                | 1790            | 1183            |                  | 100               | 1337            | 923             |                 |
| <b>GROUP 4</b>    |                 |                 | <b>200 mg/kg</b> |                   |                 |                 |                 |
| <b>Animal No.</b> | <b>Forelimb</b> | <b>Hindlimb</b> |                  | <b>Animal No.</b> | <b>Forelimb</b> | <b>Hindlimb</b> |                 |
| 46                | 1653            | 1217            |                  | 106               | 1280            | 973             |                 |
| 47                | 1800            | 1240            |                  | 107               | 1277            | 897             |                 |
| 48                | 1883            | 1277            |                  | 108               | 1387            | 917             |                 |
| 49                | 1760            | 1200            |                  | 109               | 1250            | 923             |                 |
| 50                | 1657            | 1157            |                  | 110               | 1377            | 947             |                 |
| 51                | 1667            | 1173            |                  | 111               | 1293            | 910             |                 |
| 52                | 1883            | 1257            |                  | 112               | 1357            | 910             |                 |
| 53                | 1683            | 1200            |                  | 113               | 1217            | 870             |                 |
| 54                | 1733            | 1183            |                  | 114               | 1357            | 973             |                 |
| 55                | 1720            | 1220            |                  | 115               | 1383            | 963             |                 |

**LOCOMOTOR ACTIVITY, INDIVIDUAL DATA**

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**LOW BEAMS COUNT**

**MALES**

**AT WEEK 15**

| Animal No                                | 10 min. | 20 min. | 30 min. | 40 min. | 50 min. | 60 min. | Total |
|--|---------|---------|---------|---------|---------|---------|-------|
| <b>Group 1      0 mg/kg body weight</b>  |         |         |         |         |         |         |       |
| 1  | 376     | 293     | 183     | 252     | 225     | 12      | 1341  |
| 2  | 407     | 284     | 271     | 258     | 186     | 153     | 1559  |
| 3  | 325     | 199     | 159     | 40      | 189     | 34      | 946   |
| 4  | 471     | 249     | 191     | 76      | 96      | 46      | 1129  |
| 5  | 499     | 263     | 259     | 199     | 209     | 135     | 1564  |
| 6  | 434     | 271     | 160     | 56      | 144     | 108     | 1173  |
| 7  | 315     | 283     | 196     | 115     | 6       | 11      | 926   |
| 8  | 439     | 227     | 125     | 93      | 8       | 0       | 892   |
| 9  | 64      | 227     | 61      | 46      | 2       | 140     | 540   |
| 10                                       | 307     | 195     | 144     | 2       | 0       | 102     | 750   |
| <br>                                     |         |         |         |         |         |         |       |
| <b>Group 2      15 mg/kg body weight</b> |         |         |         |         |         |         |       |
| 16                                       | 454     | 343     | 90      | 0       | 203     | 72      | 1162  |
| 17                                       | 402     | 325     | 165     | 19      | 76      | 172     | 1159  |
| 18                                       | 297     | 154     | 72      | 83      | 60      | 0       | 666   |
| 19                                       | 328     | 209     | 156     | 0       | 67      | 22      | 782   |
| 20                                       | 293     | 266     | 184     | 69      | 0       | 0       | 812   |
| 21                                       | 432     | 307     | 78      | 110     | 211     | 42      | 1180  |
| 22                                       | 416     | 81      | 51      | 310     | 0       | 8       | 866   |
| 23                                       | 272     | 227     | 173     | 194     | 195     | 169     | 1230  |
| 24                                       | 435     | 250     | 137     | 181     | 129     | 234     | 1366  |
| 25                                       | 322     | 101     | 92      | 151     | 3       | 39      | 708   |

**LOCOMOTOR ACTIVITY, INDIVIDUAL DATA**

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**LOW BEAMS COUNT**

**MALES**

**AT WEEK 15**

| Animal No                                 | 10 min. | 20 min. | 30 min. | 40 min. | 50 min. | 60 min. | Total |
|---|---------|---------|---------|---------|---------|---------|-------|
| <b>Group 3      50 mg/kg body weight</b>  |         |         |         |         |         |         |       |
| 31  | 308     | 234     | 160     | 225     | 56      | 51      | 1034  |
| 32  | 205     | 28      | 63      | 121     | 6       | 1       | 424   |
| 33  | 401     | 332     | 331     | 152     | 231     | 200     | 1647  |
| 34  | 310     | 219     | 101     | 191     | 194     | 4       | 1019  |
| 35  | 380     | 166     | 49      | 249     | 73      | 25      | 942   |
| 36  | 490     | 324     | 159     | 135     | 116     | 27      | 1251  |
| 37  | 370     | 152     | 10      | 106     | 0       | 49      | 687   |
| 38  | 214     | 38      | 0       | 95      | 188     | 41      | 576   |
| 39  | 370     | 177     | 238     | 106     | 0       | 143     | 1034  |
| 40  | 347     | 199     | 191     | 5       | 15      | 180     | 937   |
| <b>Group 4      200 mg/kg body weight</b> |         |         |         |         |         |         |       |
| 46  | 408     | 166     | 155     | 185     | 131     | 76      | 1121  |
| 47  | 178     | 112     | 16      | 26      | 0       | 6       | 338   |
| 48  | 398     | 186     | 199     | 52      | 17      | 0       | 852   |
| 49  | 399     | 248     | 144     | 99      | 125     | 19      | 1034  |
| 50  | 481     | 230     | 139     | 1       | 0       | 36      | 887   |
| 51  | 515     | 329     | 158     | 106     | 14      | 6       | 1128  |
| 52  | 586     | 143     | 125     | 194     | 26      | 26      | 1100  |
| 53  | 363     | 71      | 19      | 0       | 170     | 85      | 708   |
| 54  | 418     | 314     | 151     | 294     | 117     | 157     | 1451  |
| 55  | 338     | 88      | 159     | 59      | 135     | 185     | 964   |

**LOCOMOTOR ACTIVITY, INDIVIDUAL DATA**

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**LOW BEAMS COUNT                      FEMALES                      AT WEEK 15**

| Animal No  | 10 min. | 20 min. | 30 min. | 40 min. | 50 min. | 60 min. | Total |
|--|---------|---------|---------|---------|---------|---------|-------|
| <b>Group 1                      0 mg/kg body weight</b>  |         |         |         |         |         |         |       |
| 61   | 258     | 87      | 4       | 214     | 5       | 29      | 597   |
| 62   | 461     | 209     | 2       | 335     | 45      | 14      | 1066  |
| 63   | 223     | 177     | 146     | 125     | 0       | 17      | 688   |
| 64   | 415     | 265     | 152     | 183     | 233     | 76      | 1324  |
| 65   | 205     | 111     | 144     | 137     | 0       | 0       | 597   |
| 66   | 350     | 226     | 148     | 183     | 193     | 46      | 1146  |
| 67   | 258     | 158     | 185     | 347     | 509     | 400     | 1857  |
| 68   | 229     | 187     | 181     | 207     | 71      | 86      | 961   |
| 69   | 470     | 261     | 277     | 214     | 35      | 44      | 1301  |
| 70   | 336     | 211     | 72      | 51      | 115     | 43      | 828   |
| <br>   |         |         |         |         |         |         |       |
| <b>Group 2                      15 mg/kg body weight</b> |         |         |         |         |         |         |       |
| 76   | 223     | 113     | 9       | 224     | 20      | 163     | 752   |
| 77   | 276     | 240     | 201     | 110     | 202     | 103     | 1132  |
| 78   | 327     | 121     | 143     | 54      | 103     | 108     | 856   |
| 79   | 341     | 257     | 179     | 137     | 150     | 164     | 1228  |
| 80   | 270     | 126     | 184     | 139     | 111     | 10      | 840   |
| 81   | 545     | 246     | 257     | 266     | 197     | 103     | 1614  |
| 82   | 317     | 168     | 48      | 20      | 44      | 0       | 597   |
| 83   | 171     | 237     | 96      | 137     | 39      | 184     | 864   |
| 84   | 198     | 74      | 195     | 90      | 84      | 9       | 650   |
| 85   | 259     | 305     | 93      | 174     | 2       | 0       | 833   |

**LOCOMOTOR ACTIVITY, INDIVIDUAL DATA**

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**LOW BEAMS COUNT                      FEMALES                      AT WEEK 15**

| Animal No   | 10 min. | 20 min. | 30 min. | 40 min. | 50 min. | 60 min. | Total |
|---|---------|---------|---------|---------|---------|---------|-------|
| <b>Group 3                      50 mg/kg body weight</b>  |         |         |         |         |         |         |       |
| 91  | 248     | 226     | 192     | 51      | 199     | 49      | 965   |
| 92  | 318     | 186     | 245     | 134     | 49      | 239     | 1171  |
| 93  | 196     | 151     | 12      | 0       | 133     | 0       | 492   |
| 94  | 311     | 51      | 0       | 181     | 230     | 94      | 867   |
| 95  | 346     | 238     | 200     | 123     | 172     | 114     | 1193  |
| 96  | 212     | 369     | 129     | 61      | 18      | 30      | 819   |
| 97  | 348     | 156     | 62      | 78      | 4       | 68      | 716   |
| 98  | 515     | 192     | 13      | 243     | 2       | 2       | 967   |
| 99  | 252     | 126     | 28      | 4       | 25      | 0       | 435   |
| 100   | 484     | 304     | 219     | 283     | 126     | 80      | 1496  |
| <br>  |         |         |         |         |         |         |       |
| <b>Group 4                      200 mg/kg body weight</b> |         |         |         |         |         |         |       |
| 106   | 296     | 123     | 52      | 102     | 0       | 58      | 631   |
| 107   | 567     | 228     | 253     | 281     | 53      | 201     | 1583  |
| 108   | 317     | 180     | 158     | 58      | 66      | 67      | 846   |
| 109   | 309     | 223     | 226     | 284     | 84      | 7       | 1133  |
| 110   | 485     | 287     | 289     | 51      | 2       | 240     | 1354  |
| 111   | 338     | 134     | 65      | 1       | 2       | 129     | 669   |
| 112   | 291     | 229     | 182     | 0       | 15      | 12      | 729   |
| 113   | 245     | 175     | 124     | 116     | 91      | 81      | 832   |
| 114   | 182     | 155     | 75      | 153     | 152     | 24      | 741   |
| 115   | 429     | 205     | 243     | 121     | 173     | 72      | 1243  |

**FOOD CONSUMPTION (G/ANIMAL/DAY)  
 MALES**

**GROUP 1 (0 MG/KG)**

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 1                     | 21.1       | 22.4       | 24.6        | 24.4         | 26.3         | 24.8         | 25.5         | 25.2         |  |
| 2                     | 20.8       | 23.0       | 25.2        | 25.8         | 26.8         | 25.4         | 25.3         | 24.9         |  |
| 3                     | 20.8       | 21.7       | 22.8        | 23.8         | 24.5         | 23.8         | 24.1         | 24.2         |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 1                     | 24.7         | 24.9          | 23.6           | 24.5           | 24.2           | 43.1           | 23.8           | 23.6            | 22.7          |
| 2                     | 24.8         | 24.3          | 23.8           | 25.0           | 24.9           | 24.1           | 24.6           | 24.4            | 24.3          |
| 3                     | 23.8         | 23.3          | 22.8           | 23.7           | 23.4           | 22.3           | 22.2           | 22.8            | 22.1          |

FOOD CONSUMPTION (G/ANIMAL/DAY)  
 MALES

GROUP 2 (15 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 4                     | 20.3       | 22.2       | 23.9        | 24.8         | 26.0         | 24.8         | 24.9         | 25.2         |  |
| 5                     | 19.7       | 21.6       | 23.8        | 23.7         | 25.2         | 24.3         | 24.1         | 24.3         |  |
| 6                     | 17.6       | 22.4       | 24.3        | 24.0         | 24.4         | 22.9         | 22.6         | 22.5         |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 4                     | 24.0         | 23.6          | 22.7           | 23.2           | 23.3           | 22.1           | 23.2           | 23.9            | 23.3          |
| 5                     | 24.2         | 23.2          | 22.7           | 22.5           | 22.4           | 21.5           | 21.9           | 23.2            | 22.4          |
| 6                     | 22.9         | 21.9          | 21.3           | 21.7           | 21.4           | 20.4           | 21.2           | 22.0            | 21.4          |



**FOOD CONSUMPTION (G/ANIMAL/DAY)  
 MALES**

**GROUP 3 (50 MG/KG)**

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 7                     | 20.7       | 22.3       | 23.6        | 23.8         | 24.3         | 23.6         | 23.8         | 23.1         |  |
| 8                     | 21.1       | 22.5       | 24.0        | 24.8         | 25.9         | 25.0         | 25.1         | 24.2         |  |
| 9                     | 20.3       | 22.6       | 24.0        | 24.4         | 25.2         | 23.8         | 24.1         | 23.6         |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 7                     | 23.2         | 22.7          | 21.6           | 21.7           | 22.6           | 22.1           | 22.3           | 23.8            | 23.0          |
| 8                     | 24.0         | 22.7          | 22.3           | 21.7           | 22.4           | 21.8           | 21.7           | 23.7            | 23.2          |
| 9                     | 23.5         | 22.7          | 21.8           | 22.6           | 22.8           | 21.9           | 22.1           | 24.2            | 24.1          |

FOOD CONSUMPTION (G/ANIMAL/DAY)  
 MALES

GROUP 4 (200 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 10                    | 20.3       | 22.1       | 23.4        | 24.1         | 25.2         | 24.5         | 24.1         | 24.8         |  |
| 11                    | 20.4       | 22.1       | 25.0        | 25.2         | 26.3         | 25.0         | 25.3         | 25.4         |  |
| 12                    | 19.7       | 21.8       | 24.7        | 25.4         | 26.6         | 26.4         | 26.3         | 26.7         |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 10                    | 24.9         | 24.7          | 23.5           | 23.8           | 24.3           | 23.9           | 22.9           | 25.9            | 24.3          |
| 11                    | 25.4         | 24.8          | 24.5           | 24.3           | 24.5           | 24.6           | 23.1           | 26.6            | 25.0          |
| 12                    | 26.1         | 24.5          | 24.3           | 25.3           | 25.5           | 24.5           | 22.7           | 26.9            | 26.4          |

FOOD CONSUMPTION (G/ANIMAL/DAY)  
 FEMALES

GROUP 1 (0 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    |  | TREATMENT  |             |              |              |              |              |              |
|-----------------------|------------|--|------------|-------------|--------------|--------------|--------------|--------------|--------------|
|                       | 1-8<br>1/2 |  | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |
| 13                    | 13.9       |  | 14.3       | 14.7        | 15.5         | 16.5         | 16.1         | 16.2         | 16.3         |
| 14                    | 13.6       |  | 13.9       | 14.3        | 14.5         | 15.8         | 15.8         | 15.7         | 15.8         |
| 15                    | 14.7       |  | 15.0       | 15.0        | 15.6         | 17.0         | 15.3         | 16.1         | 16.1         |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |  |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|--|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |  |
| 13                    | 16.6         | 16.2          | 15.6           | 15.5           | 15.9           | 15.0           | 15.6           | 14.5            | 15.7          |  |
| 14                    | 15.9         | 16.5          | 15.0           | 15.6           | 15.7           | 14.8           | 14.9           | 14.6            | 15.0          |  |
| 15                    | 16.4         | 16.0          | 15.2           | 15.4           | 16.0           | 15.0           | 14.5           | 14.6            | 15.6          |  |

FOOD CONSUMPTION (G/ANIMAL/DAY)  
 FEMALES

GROUP 2 (15 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 16                    | 14.2       | 14.5       | 14.9        | 15.8         | 16.6         | 15.3         | 15.1         | 15.3         |  |
| 17                    | 14.5       | 14.8       | 15.1        | 15.9         | 16.5         | 15.2         | 15.4         | 15.5         |  |
| 18                    | 14.3       | 14.6       | 15.5        | 16.2         | 16.8         | 16.4         | 16.1         | 16.8         |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 16                    | 15.4         | 15.0          | 14.4           | 14.9           | 14.9           | 13.9           | 13.9           | 14.3            | 14.6          |
| 17                    | 16.1         | 15.0          | 14.6           | 15.2           | 15.0           | 14.1           | 14.3           | 14.1            | 14.6          |
| 18                    | 16.7         | 16.3          | 16.2           | 16.3           | 16.1           | 15.4           | 15.9           | 15.8            | 15.8          |

**FOOD CONSUMPTION (G/ANIMAL/DAY)  
 FEMALES**

**GROUP 3 (50 MG/KG)**

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 19                    | 14.9       | 15.4       | 15.4        | 16.4         | 16.8         | 16.2         | 16.3         | 16.2         |  |
| 20                    | 14.6       | 14.8       | 15.1        | 16.0         | 16.7         | 15.9         | 16.0         | 16.1         |  |
| 21                    | 14.2       | 14.4       | 14.5        | 15.5         | 15.8         | 15.5         | 15.6         | 15.5         |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 19                    | 16.7         | 15.9          | 15.8           | 16.1           | 16.2           | 15.3           | 15.1           | 15.0            | 15.0          |
| 20                    | 16.2         | 15.6          | 15.3           | 15.7           | 15.8           | 14.7           | 14.9           | 14.6            | 15.1          |
| 21                    | 15.8         | 15.3          | 14.8           | 15.7           | 15.2           | 14.7           | 14.6           | 14.6            | 15.3          |

FOOD CONSUMPTION (G/ANIMAL/DAY)  
FEMALES

GROUP 4 (200 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 22                    | 14.8       | 14.6       | 14.9        | 16.7         | 16.9         | 15.9         | 16.1         | 16.6         |  |
| 23                    | 14.2       | 14.4       | 14.7        | 15.7         | 15.7         | 15.4         | 15.3         | 15.8         |  |
| 24                    | 14.3       | 14.2       | 14.0        | 15.4         | 15.7         | 15.3         | 15.4         | 16.2         |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |  |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|--|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |  |
| 22                    | 16.7         | 16.3          | 16.0           | 16.7           | 16.7           | 15.8           | 15.8           | 15.2            | 16.9          |  |
| 23                    | 16.1         | 15.3          | 15.0           | 15.3           | 15.2           | 14.8           | 15.2           | 15.0            | 16.0          |  |
| 24                    | 16.2         | 15.6          | 15.3           | 15.5           | 15.8           | 14.7           | 15.1           | 15.8            | 15.8          |  |

RELATIVE FOOD CONSUMPTION  
 (G/KG BODY WEIGHT/DAY)  
 MALES

GROUP 1 (0 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 1                     | 144        | 92         | 88          | 79           | 77           | 68           | 67           | 63           |  |
| 2                     | 139        | 96         | 90          | 83           | 79           | 69           | 67           | 63           |  |
| 3                     | 142        | 93         | 85          | 80           | 75           | 68           | 66           | 63           |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 1                     | 61           | 59            | 55             | 56             | 55             | 95             | 52             | 51              | 48            |
| 2                     | 61           | 58            | 55             | 57             | 55             | 52             | 52             | 51              | 50            |
| 3                     | 60           | 57            | 55             | 56             | 54             | 51             | 50             | 51              | 48            |

RELATIVE FOOD CONSUMPTION  
(G/KG BODY WEIGHT/DAY)  
MALES

GROUP 2 (15 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 4                     | 139        | 91         | 85          | 80           | 77           | 68           | 66           | 64           |  |
| 5                     | 132        | 91         | 86          | 77           | 76           | 68           | 65           | 63           |  |
| 6                     | 124        | 98         | 91          | 81           | 76           | 67           | 64           | 60           |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 4                     | 60           | 57            | 54             | 55             | 54             | 50             | 52             | 53              | 50            |
| 5                     | 61           | 57            | 55             | 54             | 52             | 49             | 49             | 51              | 49            |
| 6                     | 60           | 56            | 54             | 55             | 53             | 50             | 50             | 52              | 50            |



RELATIVE FOOD CONSUMPTION  
 (G/KG BODY WEIGHT/DAY)  
 MALES

GROUP 3 (50 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 7                     | 141        | 94         | 86          | 78           | 75           | 68           | 66           | 61           |  |
| 8                     | 141        | 94         | 86          | 79           | 77           | 69           | 67           | 62           |  |
| 9                     | 141        | 93         | 86          | 79           | 75           | 67           | 65           | 61           |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 7                     | 58           | 57            | 54             | 54             | 55             | 52             | 52             | 54              | 52            |
| 8                     | 60           | 55            | 53             | 52             | 53             | 50             | 49             | 53              | 50            |
| 9                     | 59           | 55            | 52             | 54             | 53             | 50             | 49             | 50              | 52            |

RELATIVE FOOD CONSUMPTION  
 (G/KG BODY WEIGHT/DAY)  
 MALES

GROUP 4 (200 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 10                    | 140        | 94         | 88          | 79           | 77           | 70           | 67           | 65           |  |
| 11                    | 139        | 94         | 92          | 85           | 81           | 72           | 70           | 67           |  |
| 12                    | 136        | 93         | 92          | 84           | 81           | 75           | 72           | 70           |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 10                    | 63           | 61            | 57             | 58             | 58             | 56             | 52             | 59              | 54            |
| 11                    | 64           | 62            | 60             | 59             | 59             | 57             | 53             | 59              | 55            |
| 12                    | 67           | 62            | 60             | 62             | 62             | 58             | 52             | 61              | 59            |

RELATIVE FOOD CONSUMPTION  
 (G/KG BODY WEIGHT/DAY)  
 FEMALES

GROUP 1 (0 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 13                    | 112        | 88         | 85          | 83           | 85           | 78           | 77           | 75           |  |
| 14                    | 111        | 88         | 85          | 80           | 84           | 79           | 77           | 75           |  |
| 15                    | 120        | 91         | 86          | 84           | 85           | 73           | 76           | 74           |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 13                    | 75           | 71            | 68             | 67             | 68             | 63             | 65             | 60              | 64            |
| 14                    | 74           | 75            | 67             | 70             | 70             | 65             | 64             | 63              | 63            |
| 15                    | 74           | 71            | 67             | 68             | 69             | 64             | 62             | 62              | 65            |

RELATIVE FOOD CONSUMPTION  
 (G/KG BODY WEIGHT/DAY)  
 FEMALES

GROUP 2 (15 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 16                    | 116        | 89         | 86          | 82           | 83           | 74           | 72           | 70           |  |
| 17                    | 117        | 89         | 85          | 84           | 81           | 72           | 72           | 70           |  |
| 18                    | 117        | 89         | 88          | 85           | 84           | 78           | 76           | 76           |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 16                    | 70           | 67            | 65             | 66             | 65             | 60             | 60             | 59              | 62            |
| 17                    | 71           | 65            | 64             | 64             | 62             | 58             | 59             | 57              | 59            |
| 18                    | 74           | 72            | 71             | 70             | 69             | 65             | 67             | 63              | 65            |

RELATIVE FOOD CONSUMPTION  
 (G/KG BODY WEIGHT/DAY)  
 FEMALES

GROUP 3 (50 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 19                    | 118        | 91         | 85          | 83           | 83           | 76           | 75           | 72           |  |
| 20                    | 116        | 86         | 83          | 81           | 80           | 74           | 73           | 72           |  |
| 21                    | 115        | 90         | 85          | 84           | 84           | 78           | 77           | 74           |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 19                    | 74           | 69            | 67             | 68             | 68             | 63             | 63             | 61              | 61            |
| 20                    | 70           | 66            | 66             | 66             | 66             | 61             | 61             | 59              | 62            |
| 21                    | 74           | 71            | 68             | 71             | 68             | 64             | 64             | 63              | 66            |

RELATIVE FOOD CONSUMPTION  
 (G/KG BODY WEIGHT/DAY)  
 FEMALES

GROUP 4 (200 MG/KG)

| DAYS<br>WEEKS<br>CAGE | PRETEST    | TREATMENT  |             |              |              |              |              |              |  |
|-----------------------|------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--|
|                       | 1-8<br>1/2 | 1-8<br>1/2 | 8-15<br>2/3 | 15-22<br>3/4 | 22-29<br>4/5 | 29-36<br>5/6 | 36-43<br>6/7 | 43-50<br>7/8 |  |
| 22                    | 116        | 88         | 84          | 86           | 83           | 76           | 74           | 75           |  |
| 23                    | 117        | 89         | 85          | 84           | 81           | 76           | 74           | 74           |  |
| 24                    | 113        | 87         | 82          | 84           | 81           | 76           | 75           | 76           |  |

| DAYS<br>WEEKS<br>CAGE | TREATMENT    |               |                |                |                |                |                |                 |               |
|-----------------------|--------------|---------------|----------------|----------------|----------------|----------------|----------------|-----------------|---------------|
|                       | 50-57<br>8/9 | 57-64<br>9/10 | 64-71<br>10/11 | 71-78<br>11/12 | 78-85<br>12/13 | 85-92<br>13/14 | 92-99<br>14/15 | 99-106<br>15/16 | 106-108<br>16 |
| 22                    | 73           | 70            | 68             | 70             | 69             | 64             | 64             | 61              | 68            |
| 23                    | 74           | 69            | 67             | 69             | 68             | 64             | 65             | 64              | 67            |
| 24                    | 74           | 70            | 68             | 68             | 69             | 63             | 65             | 68              | 67            |

**BODY WEIGHTS (GRAM)  
MALES**

**GROUP 1 (0 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |     |     |     |     |     |     |  |
|-------------------------|---------|-----------|-----|-----|-----|-----|-----|-----|--|
|                         | 1       | 1         | 8   | 15  | 22  | 29  | 36  | 43  |  |
|                         | 1       | 1         | 2   | 3   | 4   | 5   | 6   | 7   |  |
| 1                       | 147     | 198       | 248 | 287 | 326 | 353 | 382 | 408 |  |
| 2                       | 146     | 197       | 241 | 274 | 291 | 327 | 354 | 369 |  |
| 3                       | 137     | 188       | 236 | 274 | 306 | 335 | 359 | 376 |  |
| 4                       | 148     | 193       | 242 | 281 | 318 | 350 | 374 | 394 |  |
| 5                       | 152     | 199       | 243 | 280 | 309 | 335 | 356 | 367 |  |
| 6                       | 152     | 198       | 246 | 280 | 295 | 340 | 363 | 373 |  |
| 7                       | 149     | 195       | 244 | 293 | 329 | 363 | 393 | 413 |  |
| 8                       | 153     | 196       | 242 | 278 | 311 | 338 | 360 | 375 |  |
| 9                       | 146     | 193       | 235 | 268 | 302 | 324 | 347 | 356 |  |
| 10                      | 151     | 194       | 238 | 282 | 316 | 342 | 367 | 383 |  |
| 11                      | 158     | 202       | 249 | 279 | 297 | 337 | 367 | 382 |  |
| 12                      | 139     | 184       | 227 | 262 | 297 | 320 | 345 | 362 |  |
| 13                      | 137     | 183       | 226 | 261 | 289 | 313 | 335 | 350 |  |
| 14                      | 156     | 203       | 244 | 279 | 313 | 336 | 361 | 375 |  |
| 15                      | 140     | 185       | 228 | 265 | 299 | 327 | 352 | 366 |  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |     |     |     |     |     |     |     |     |
|-------------------------|-----------|-----|-----|-----|-----|-----|-----|-----|-----|
|                         | 50        | 57  | 64  | 71  | 78  | 85  | 92  | 99  | 106 |
|                         | 8         | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  |
| 1                       | 431       | 444 | 459 | 475 | 481 | 497 | 518 | 521 | 531 |
| 2                       | 383       | 381 | 393 | 394 | 399 | 404 | 414 | 422 | 425 |
| 3                       | 394       | 401 | 416 | 421 | 427 | 433 | 447 | 450 | 458 |
| 4                       | 410       | 417 | 433 | 440 | 447 | 455 | 468 | 469 | 478 |
| 5                       | 382       | 394 | 403 | 412 | 421 | 422 | 430 | 428 | 438 |
| 6                       | 387       | 397 | 403 | 413 | 419 | 421 | 433 | 440 | 443 |
| 7                       | 439       | 458 | 473 | 486 | 499 | 512 | 526 | 538 | 545 |
| 8                       | 392       | 403 | 419 | 425 | 440 | 449 | 466 | 469 | 482 |
| 9                       | 367       | 378 | 389 | 392 | 402 | 407 | 420 | 419 | 432 |
| 10                      | 402       | 413 | 424 | 435 | 449 | 454 | 470 | 478 | 487 |
| 11                      | 403       | 421 | 431 | 441 | 448 | 456 | 468 | 470 | 465 |
| 12                      | 373       | 380 | 386 | 390 | 395 | 400 | 407 | 413 | 421 |
| 13                      | 373       | 378 | 386 | 401 | 411 | 416 | 424 | 427 | 433 |
| 14                      | 394       | 407 | 420 | 432 | 444 | 451 | 460 | 465 | 469 |
| 15                      | 386       | 396 | 409 | 416 | 423 | 433 | 442 | 448 | 456 |

**BODY WEIGHTS (GRAM)  
MALES**

**GROUP 1 (0 MG/KG)**

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|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

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|    |     |
|----|-----|
| 1  | 539 |
| 2  | 429 |
| 3  | 464 |
| 4  | 479 |
| 5  | 443 |
| 6  | 451 |
| 7  | 548 |
| 8  | 487 |
| 9  | 442 |
| 10 | 490 |
| 11 | 483 |
| 12 | 427 |
| 13 | 442 |
| 14 | 481 |
| 15 | 460 |



**BODY WEIGHTS (GRAM)  
 MALES**

**GROUP 2 (15 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |     |     |     |     |     |     |  |
|-------------------------|---------|-----------|-----|-----|-----|-----|-----|-----|--|
|                         | 1       | 1         | 8   | 15  | 22  | 29  | 36  | 43  |  |
|                         | 1       | 1         | 2   | 3   | 4   | 5   | 6   | 7   |  |
| 16                      | 148     | 200       | 249 | 286 | 320 | 351 | 376 | 393 |  |
| 17                      | 143     | 185       | 232 | 273 | 299 | 329 | 352 | 370 |  |
| 18                      | 148     | 198       | 242 | 274 | 306 | 320 | 346 | 355 |  |
| 19                      | 147     | 194       | 244 | 278 | 332 | 330 | 354 | 362 |  |
| 20                      | 147     | 197       | 250 | 290 | 294 | 361 | 389 | 403 |  |
| 21                      | 153     | 196       | 236 | 272 | 334 | 328 | 349 | 365 |  |
| 22                      | 143     | 188       | 234 | 274 | 298 | 334 | 362 | 370 |  |
| 23                      | 153     | 197       | 247 | 289 | 302 | 345 | 368 | 382 |  |
| 24                      | 150     | 193       | 242 | 274 | 299 | 327 | 346 | 358 |  |
| 25                      | 148     | 186       | 232 | 270 | 307 | 333 | 360 | 375 |  |
| 26                      | 147     | 158       | 235 | 276 | 296 | 337 | 360 | 371 |  |
| 27                      | 148     | 163       | 236 | 274 | 302 | 318 | 336 | 346 |  |
| 28                      | 139     | 151       | 224 | 261 | 288 | 313 | 332 | 350 |  |
| 29                      | 135     | 149       | 222 | 265 | 299 | 324 | 346 | 361 |  |
| 30                      | 140     | 155       | 224 | 261 | 294 | 319 | 339 | 350 |  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |     |     |     |     |     |     |     |     |  |
|-------------------------|-----------|-----|-----|-----|-----|-----|-----|-----|-----|--|
|                         | 50        | 57  | 64  | 71  | 78  | 85  | 92  | 99  | 106 |  |
|                         | 8         | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  |  |
| 16                      | 417       | 423 | 431 | 438 | 443 | 448 | 455 | 465 | 474 |  |
| 17                      | 391       | 398 | 406 | 410 | 418 | 419 | 433 | 439 | 438 |  |
| 18                      | 368       | 375 | 385 | 394 | 398 | 404 | 413 | 429 | 433 |  |
| 19                      | 380       | 388 | 394 | 401 | 408 | 413 | 417 | 429 | 428 |  |
| 20                      | 424       | 433 | 444 | 450 | 456 | 463 | 475 | 486 | 487 |  |
| 21                      | 382       | 392 | 403 | 412 | 420 | 424 | 433 | 441 | 443 |  |
| 22                      | 391       | 400 | 409 | 415 | 416 | 423 | 438 | 443 | 454 |  |
| 23                      | 402       | 414 | 424 | 426 | 433 | 442 | 455 | 467 | 474 |  |
| 24                      | 371       | 380 | 390 | 396 | 403 | 411 | 419 | 427 | 435 |  |
| 25                      | 393       | 407 | 420 | 432 | 431 | 436 | 452 | 461 | 472 |  |
| 26                      | 385       | 393 | 406 | 413 | 413 | 415 | 425 | 437 | 441 |  |
| 27                      | 359       | 359 | 365 | 372 | 378 | 388 | 396 | 408 | 412 |  |
| 28                      | 364       | 372 | 375 | 388 | 391 | 397 | 403 | 413 | 418 |  |
| 29                      | 380       | 387 | 396 | 401 | 401 | 404 | 418 | 425 | 429 |  |
| 30                      | 372       | 383 | 397 | 399 | 401 | 408 | 417 | 425 | 428 |  |

RCC STUDY NUMBER 857092  
A 084, WR 23081

BW-IND - 4  
22-APR-05

**BODY WEIGHTS (GRAM)  
MALES**

**GROUP 2 (15 MG/KG)**

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|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

---

|    |     |
|----|-----|
| 16 | 480 |
| 17 | 455 |
| 18 | 436 |
| 19 | 442 |
| 20 | 496 |
| 21 | 453 |
| 22 | 454 |
| 23 | 475 |
| 24 | 439 |
| 25 | 477 |
| 26 | 447 |
| 27 | 418 |
| 28 | 421 |
| 29 | 437 |
| 30 | 433 |

**BODY WEIGHTS (GRAM)  
MALES**

**GROUP 3 (50 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST |     | TREATMENT |     |     |     |     |     |  |
|-------------------------|---------|-----|-----------|-----|-----|-----|-----|-----|--|
|                         | 1       | 1   | 8         | 15  | 22  | 29  | 36  | 43  |  |
|                         | 1       | 1   | 2         | 3   | 4   | 5   | 6   | 7   |  |
| 31                      | 142     | 191 | 239       | 271 | 290 | 311 | 328 | 341 |  |
| 32                      | 138     | 182 | 223       | 261 | 305 | 317 | 342 | 359 |  |
| 33                      | 155     | 198 | 242       | 273 | 305 | 324 | 344 | 358 |  |
| 34                      | 152     | 205 | 253       | 293 | 333 | 362 | 387 | 401 |  |
| 35                      | 150     | 195 | 235       | 268 | 299 | 319 | 340 | 350 |  |
| 36                      | 148     | 196 | 248       | 283 | 320 | 350 | 370 | 387 |  |
| 37                      | 153     | 198 | 246       | 286 | 317 | 345 | 372 | 388 |  |
| 38                      | 138     | 181 | 224       | 261 | 292 | 319 | 346 | 361 |  |
| 39                      | 146     | 182 | 239       | 284 | 330 | 346 | 373 | 390 |  |
| 40                      | 159     | 200 | 243       | 275 | 311 | 329 | 351 | 364 |  |
| 41                      | 145     | 197 | 246       | 279 | 309 | 333 | 354 | 373 |  |
| 42                      | 138     | 193 | 244       | 281 | 316 | 329 | 356 | 371 |  |
| 43                      | 136     | 187 | 236       | 276 | 308 | 348 | 367 | 385 |  |
| 44                      | 155     | 204 | 246       | 275 | 308 | 330 | 353 | 365 |  |
| 45                      | 148     | 199 | 245       | 281 | 310 | 333 | 361 | 374 |  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |     |     |     |     |     |     |     |     |  |
|-------------------------|-----------|-----|-----|-----|-----|-----|-----|-----|-----|--|
|                         | 50        | 57  | 64  | 71  | 78  | 85  | 92  | 99  | 106 |  |
|                         | 8         | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  |  |
| 31                      | 353       | 358 | 362 | 367 | 367 | 372 | 379 | 388 | 396 |  |
| 32                      | 379       | 392 | 408 | 414 | 420 | 434 | 453 | 461 | 457 |  |
| 33                      | 374       | 385 | 395 | 398 | 404 | 417 | 426 | 439 | 467 |  |
| 34                      | 416       | 432 | 439 | 443 | 444 | 453 | 462 | 468 | 477 |  |
| 35                      | 361       | 412 | 378 | 380 | 381 | 390 | 394 | 400 | 417 |  |
| 36                      | 408       | 411 | 419 | 422 | 425 | 429 | 446 | 449 | 449 |  |
| 37                      | 402       | 414 | 424 | 432 | 428 | 427 | 438 | 442 | 444 |  |
| 38                      | 377       | 390 | 405 | 413 | 418 | 429 | 436 | 454 | 460 |  |
| 39                      | 406       | 414 | 427 | 430 | 429 | 434 | 452 | 466 | 468 |  |
| 40                      | 374       | 383 | 389 | 400 | 405 | 411 | 420 | 422 | 426 |  |
| 41                      | 392       | 404 | 415 | 427 | 429 | 442 | 448 | 457 | 453 |  |
| 42                      | 384       | 393 | 401 | 408 | 411 | 419 | 426 | 437 | 462 |  |
| 43                      | 401       | 414 | 423 | 431 | 428 | 440 | 453 | 464 | 499 |  |
| 44                      | 382       | 391 | 405 | 407 | 418 | 420 | 436 | 445 | 479 |  |
| 45                      | 386       | 394 | 405 | 413 | 426 | 433 | 441 | 451 | 505 |  |

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**BODY WEIGHTS (GRAM)  
MALES**

**GROUP 3 (50 MG/KG)**

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|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

---

|    |     |
|----|-----|
| 31 | 400 |
| 32 | 476 |
| 33 | 451 |
| 34 | 480 |
| 35 | 410 |
| 36 | 461 |
| 37 | 462 |
| 38 | 460 |
| 39 | 479 |
| 40 | 440 |
| 41 | 473 |
| 42 | 449 |
| 43 | 471 |
| 44 | 464 |
| 45 | 466 |

**BODY WEIGHTS (GRAM)  
 MALES**

**GROUP 4 (200 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST |     | TREATMENT |     |     |     |     |     |  |
|-------------------------|---------|-----|-----------|-----|-----|-----|-----|-----|--|
|                         | 1       | 1   | 8         | 15  | 22  | 29  | 36  | 43  |  |
|                         | 1       | 1   | 2         | 3   | 4   | 5   | 6   | 7   |  |
| 46                      | 142     | 189 | 236       | 263 | 285 | 312 | 329 | 339 |  |
| 47                      | 144     | 187 | 226       | 258 | 290 | 313 | 334 | 346 |  |
| 48                      | 155     | 199 | 243       | 282 | 324 | 360 | 389 | 392 |  |
| 49                      | 142     | 189 | 235       | 271 | 310 | 327 | 349 | 360 |  |
| 50                      | 144     | 185 | 232       | 265 | 322 | 326 | 354 | 364 |  |
| 51                      | 145     | 184 | 223       | 261 | 260 | 311 | 334 | 350 |  |
| 52                      | 159     | 206 | 246       | 280 | 310 | 337 | 358 | 377 |  |
| 53                      | 135     | 184 | 232       | 271 | 305 | 335 | 361 | 385 |  |
| 54                      | 150     | 193 | 238       | 280 | 311 | 326 | 348 | 360 |  |
| 55                      | 144     | 193 | 241       | 273 | 302 | 322 | 337 | 349 |  |
| 56                      | 142     | 182 | 228       | 262 | 301 | 330 | 358 | 377 |  |
| 57                      | 152     | 188 | 238       | 271 | 301 | 329 | 358 | 369 |  |
| 58                      | 142     | 183 | 227       | 260 | 294 | 314 | 332 | 344 |  |
| 59                      | 148     | 195 | 243       | 286 | 314 | 335 | 357 | 371 |  |
| 60                      | 142     | 189 | 236       | 268 | 305 | 324 | 347 | 363 |  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |     |     |     |     |     |     |     |     |
|-------------------------|-----------|-----|-----|-----|-----|-----|-----|-----|-----|
|                         | 50        | 57  | 64  | 71  | 78  | 85  | 92  | 99  | 106 |
|                         | 8         | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  |
| 46                      | 356       | 373 | 365 | 373 | 380 | 391 | 399 | 404 | 386 |
| 47                      | 362       | 377 | 384 | 395 | 399 | 405 | 418 | 422 | 434 |
| 48                      | 419       | 436 | 455 | 458 | 461 | 475 | 474 | 487 | 488 |
| 49                      | 379       | 396 | 401 | 408 | 410 | 416 | 425 | 433 | 446 |
| 50                      | 385       | 397 | 407 | 420 | 417 | 418 | 431 | 441 | 459 |
| 51                      | 365       | 375 | 383 | 389 | 397 | 391 | 411 | 418 | 425 |
| 52                      | 397       | 409 | 419 | 427 | 438 | 442 | 454 | 461 | 506 |
| 53                      | 405       | 412 | 440 | 448 | 461 | 464 | 485 | 494 | 469 |
| 54                      | 377       | 384 | 396 | 399 | 403 | 405 | 412 | 423 | 430 |
| 55                      | 360       | 390 | 376 | 379 | 379 | 381 | 395 | 404 | 413 |
| 56                      | 395       | 408 | 415 | 429 | 434 | 439 | 448 | 457 | 454 |
| 57                      | 388       | 392 | 398 | 406 | 412 | 419 | 433 | 443 | 456 |
| 58                      | 360       | 366 | 370 | 384 | 389 | 394 | 407 | 411 | 425 |
| 59                      | 387       | 386 | 399 | 407 | 407 | 414 | 417 | 429 | 439 |
| 60                      | 380       | 387 | 389 | 399 | 396 | 405 | 414 | 427 | 438 |

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**BODY WEIGHTS (GRAM)  
MALES**

**GROUP 4 (200 MG/KG)**

---

|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

---

|    |     |
|----|-----|
| 46 | 410 |
| 47 | 437 |
| 48 | 496 |
| 49 | 452 |
| 50 | 459 |
| 51 | 427 |
| 52 | 475 |
| 53 | 515 |
| 54 | 434 |
| 55 | 415 |
| 56 | 470 |
| 57 | 459 |
| 58 | 425 |
| 59 | 445 |
| 60 | 438 |

**BODY WEIGHTS (GRAM)  
FEMALES**

**GROUP 1 (0 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST |     | TREATMENT |     |     |     |     |     |  |
|-------------------------|---------|-----|-----------|-----|-----|-----|-----|-----|--|
|                         | 1       | 1   | 8         | 15  | 22  | 29  | 36  | 43  |  |
|                         | 1       | 1   | 2         | 3   | 4   | 5   | 6   | 7   |  |
| 61                      | 123     | 143 | 160       | 169 | 179 | 189 | 206 | 209 |  |
| 62                      | 121     | 142 | 153       | 166 | 186 | 188 | 195 | 204 |  |
| 63                      | 131     | 150 | 175       | 190 | 204 | 208 | 223 | 231 |  |
| 64                      | 124     | 140 | 157       | 166 | 179 | 187 | 198 | 200 |  |
| 65                      | 123     | 144 | 164       | 173 | 191 | 201 | 212 | 211 |  |
| 66                      | 123     | 140 | 156       | 171 | 185 | 194 | 204 | 210 |  |
| 67                      | 123     | 143 | 160       | 168 | 179 | 188 | 197 | 202 |  |
| 68                      | 124     | 143 | 159       | 170 | 179 | 190 | 197 | 202 |  |
| 69                      | 124     | 140 | 163       | 173 | 189 | 194 | 206 | 215 |  |
| 70                      | 118     | 133 | 152       | 163 | 176 | 175 | 192 | 193 |  |
| 71                      | 129     | 153 | 176       | 186 | 196 | 212 | 222 | 224 |  |
| 72                      | 127     | 147 | 167       | 178 | 195 | 206 | 211 | 212 |  |
| 73                      | 117     | 144 | 166       | 177 | 187 | 207 | 216 | 216 |  |
| 74                      | 119     | 142 | 161       | 167 | 181 | 194 | 203 | 204 |  |
| 75                      | 121     | 137 | 152       | 164 | 175 | 184 | 190 | 196 |  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |     |     |     |     |     |     |     |     |
|-------------------------|-----------|-----|-----|-----|-----|-----|-----|-----|-----|
|                         | 50        | 57  | 64  | 71  | 78  | 85  | 92  | 99  | 106 |
|                         | 8         | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  |
| 61                      | 212       | 221 | 227 | 229 | 225 | 229 | 236 | 233 | 222 |
| 62                      | 215       | 212 | 216 | 224 | 225 | 230 | 232 | 236 | 239 |
| 63                      | 236       | 236 | 246 | 251 | 255 | 252 | 257 | 265 | 266 |
| 64                      | 207       | 208 | 217 | 217 | 214 | 220 | 225 | 225 | 226 |
| 65                      | 224       | 230 | 235 | 230 | 233 | 238 | 242 | 239 | 245 |
| 66                      | 224       | 226 | 228 | 237 | 237 | 241 | 244 | 252 | 247 |
| 67                      | 209       | 213 | 221 | 223 | 221 | 223 | 226 | 228 | 227 |
| 68                      | 210       | 213 | 217 | 215 | 218 | 221 | 223 | 226 | 227 |
| 69                      | 220       | 221 | 228 | 238 | 236 | 235 | 242 | 244 | 251 |
| 70                      | 197       | 196 | 202 | 201 | 204 | 202 | 213 | 210 | 211 |
| 71                      | 228       | 233 | 244 | 244 | 239 | 246 | 252 | 249 | 241 |
| 72                      | 222       | 222 | 225 | 229 | 227 | 234 | 234 | 238 | 245 |
| 73                      | 216       | 227 | 232 | 230 | 230 | 234 | 241 | 236 | 234 |
| 74                      | 217       | 221 | 225 | 224 | 227 | 229 | 235 | 233 | 236 |
| 75                      | 202       | 203 | 208 | 211 | 212 | 215 | 218 | 222 | 217 |

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**BODY WEIGHTS (GRAM)  
FEMALES**

**GROUP 1 (0 MG/KG)**

---

|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

---

|    |     |
|----|-----|
| 61 | 239 |
| 62 | 236 |
| 63 | 270 |
| 64 | 233 |
| 65 | 248 |
| 66 | 252 |
| 67 | 233 |
| 68 | 231 |
| 69 | 255 |
| 70 | 211 |
| 71 | 258 |
| 72 | 243 |
| 73 | 244 |
| 74 | 238 |
| 75 | 220 |



**BODY WEIGHTS (GRAM)  
 FEMALES**

**GROUP 2 (15 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |     |     |     |     |     |     |
|-------------------------|---------|-----------|-----|-----|-----|-----|-----|-----|
|                         | 1       | 1         | 8   | 15  | 22  | 29  | 36  | 43  |
|                         | 1       | 1         | 2   | 3   | 4   | 5   | 6   | 7   |
| 76                      | 118     | 143       | 161 | 174 | 190 | 203 | 211 | 212 |
| 77                      | 126     | 147       | 169 | 176 | 213 | 204 | 215 | 215 |
| 78                      | 121     | 138       | 154 | 165 | 180 | 190 | 199 | 197 |
| 79                      | 125     | 149       | 167 | 181 | 196 | 204 | 207 | 215 |
| 80                      | 126     | 141       | 162 | 174 | 186 | 192 | 202 | 210 |
| 81                      | 127     | 147       | 165 | 177 | 180 | 203 | 211 | 216 |
| 82                      | 122     | 144       | 161 | 177 | 185 | 196 | 208 | 215 |
| 83                      | 121     | 147       | 168 | 180 | 199 | 211 | 219 | 218 |
| 84                      | 128     | 156       | 168 | 179 | 195 | 209 | 212 | 219 |
| 85                      | 120     | 146       | 168 | 177 | 187 | 193 | 204 | 208 |
| 86                      | 116     | 142       | 164 | 181 | 197 | 210 | 219 | 219 |
| 87                      | 122     | 142       | 160 | 168 | 179 | 185 | 197 | 201 |
| 88                      | 131     | 142       | 177 | 184 | 199 | 208 | 217 | 218 |
| 89                      | 114     | 133       | 145 | 157 | 176 | 180 | 187 | 193 |
| 90                      | 127     | 151       | 175 | 191 | 206 | 216 | 227 | 229 |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |     |     |     |     |     |     |     |     |
|-------------------------|-----------|-----|-----|-----|-----|-----|-----|-----|-----|
|                         | 50        | 57  | 64  | 71  | 78  | 85  | 92  | 99  | 106 |
|                         | 8         | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  |
| 76                      | 222       | 228 | 233 | 230 | 236 | 241 | 240 | 239 | 239 |
| 77                      | 217       | 227 | 233 | 229 | 232 | 238 | 242 | 246 | 251 |
| 78                      | 209       | 213 | 217 | 212 | 218 | 220 | 224 | 225 | 231 |
| 79                      | 223       | 223 | 221 | 223 | 227 | 229 | 225 | 224 | 231 |
| 80                      | 213       | 215 | 219 | 223 | 223 | 224 | 229 | 230 | 250 |
| 81                      | 222       | 225 | 225 | 229 | 230 | 233 | 237 | 238 | 239 |
| 82                      | 217       | 219 | 232 | 228 | 236 | 235 | 238 | 243 | 242 |
| 83                      | 230       | 236 | 238 | 236 | 243 | 253 | 254 | 252 | 265 |
| 84                      | 232       | 235 | 236 | 237 | 249 | 248 | 247 | 246 | 269 |
| 85                      | 211       | 213 | 221 | 221 | 224 | 229 | 232 | 234 | 227 |
| 86                      | 228       | 234 | 238 | 237 | 243 | 244 | 250 | 246 | 239 |
| 87                      | 208       | 207 | 212 | 219 | 220 | 221 | 222 | 227 | 244 |
| 88                      | 230       | 236 | 235 | 231 | 241 | 243 | 246 | 244 | 274 |
| 89                      | 204       | 208 | 209 | 213 | 216 | 215 | 219 | 220 | 226 |
| 90                      | 238       | 241 | 245 | 247 | 250 | 251 | 254 | 255 | 276 |

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**BODY WEIGHTS (GRAM)  
FEMALES**

**GROUP 2 (15 MG/KG)**

---

|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

---

|    |     |
|----|-----|
| 76 | 243 |
| 77 | 250 |
| 78 | 229 |
| 79 | 227 |
| 80 | 234 |
| 81 | 242 |
| 82 | 239 |
| 83 | 262 |
| 84 | 248 |
| 85 | 234 |
| 86 | 253 |
| 87 | 228 |
| 88 | 250 |
| 89 | 223 |
| 90 | 264 |

**BODY WEIGHTS (GRAM)  
FEMALES**

**GROUP 3 (50 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |     |     |     |     |     |     |  |
|-------------------------|---------|-----------|-----|-----|-----|-----|-----|-----|--|
|                         | 1       | 1         | 8   | 15  | 22  | 29  | 36  | 43  |  |
|                         | 1       | 1         | 2   | 3   | 4   | 5   | 6   | 7   |  |
| 91                      | 122     | 141       | 162 | 173 | 182 | 193 | 203 | 208 |  |
| 92                      | 132     | 160       | 180 | 187 | 200 | 211 | 221 | 227 |  |
| 93                      | 129     | 153       | 177 | 189 | 207 | 208 | 218 | 225 |  |
| 94                      | 122     | 147       | 167 | 180 | 199 | 198 | 206 | 212 |  |
| 95                      | 126     | 145       | 164 | 175 | 195 | 205 | 211 | 214 |  |
| 96                      | 133     | 156       | 177 | 187 | 190 | 210 | 221 | 226 |  |
| 97                      | 123     | 142       | 163 | 173 | 189 | 197 | 204 | 207 |  |
| 98                      | 115     | 146       | 167 | 185 | 202 | 207 | 213 | 224 |  |
| 99                      | 130     | 153       | 173 | 182 | 200 | 202 | 213 | 214 |  |
| 100                     | 132     | 156       | 176 | 191 | 204 | 219 | 225 | 229 |  |
| 101                     | 120     | 143       | 154 | 165 | 179 | 187 | 197 | 197 |  |
| 102                     | 127     | 146       | 163 | 171 | 182 | 185 | 195 | 203 |  |
| 103                     | 126     | 140       | 161 | 176 | 192 | 197 | 211 | 218 |  |
| 104                     | 118     | 133       | 155 | 161 | 173 | 175 | 185 | 190 |  |
| 105                     | 129     | 147       | 168 | 180 | 191 | 195 | 203 | 211 |  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |     |     |     |     |     |     |     |     |
|-------------------------|-----------|-----|-----|-----|-----|-----|-----|-----|-----|
|                         | 50        | 57  | 64  | 71  | 78  | 85  | 92  | 99  | 106 |
|                         | 8         | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  |
| 91                      | 217       | 221 | 222 | 224 | 229 | 234 | 234 | 232 | 238 |
| 92                      | 229       | 239 | 243 | 242 | 239 | 244 | 252 | 248 | 245 |
| 93                      | 230       | 232 | 237 | 243 | 241 | 241 | 249 | 249 | 252 |
| 94                      | 217       | 219 | 223 | 228 | 229 | 229 | 230 | 234 | 235 |
| 95                      | 224       | 226 | 232 | 231 | 238 | 245 | 245 | 246 | 249 |
| 96                      | 230       | 235 | 243 | 244 | 241 | 244 | 252 | 249 | 241 |
| 97                      | 216       | 219 | 221 | 224 | 230 | 231 | 233 | 235 | 261 |
| 98                      | 230       | 234 | 233 | 234 | 239 | 237 | 234 | 239 | 247 |
| 99                      | 217       | 225 | 230 | 229 | 231 | 234 | 241 | 240 | 241 |
| 100                     | 231       | 239 | 242 | 239 | 241 | 247 | 251 | 249 | 248 |
| 101                     | 204       | 212 | 212 | 212 | 219 | 220 | 223 | 226 | 223 |
| 102                     | 206       | 207 | 212 | 216 | 220 | 220 | 227 | 223 | 237 |
| 103                     | 227       | 230 | 236 | 239 | 243 | 249 | 250 | 251 | 257 |
| 104                     | 192       | 196 | 202 | 204 | 207 | 205 | 210 | 212 | 221 |
| 105                     | 215       | 215 | 219 | 222 | 225 | 226 | 228 | 230 | 231 |

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**BODY WEIGHTS (GRAM)  
FEMALES**

**GROUP 3 (50 MG/KG)**

---

|        | TREATMENT |
|--------|-----------|
|        | -----     |
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

---

|     |     |
|-----|-----|
| 91  | 241 |
| 92  | 254 |
| 93  | 250 |
| 94  | 236 |
| 95  | 250 |
| 96  | 255 |
| 97  | 233 |
| 98  | 238 |
| 99  | 246 |
| 100 | 255 |
| 101 | 228 |
| 102 | 224 |
| 103 | 255 |
| 104 | 216 |
| 105 | 231 |

**BODY WEIGHTS (GRAM)  
FEMALES**

**GROUP 4 (200 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |     |     |     |     |     |     |  |
|-------------------------|---------|-----------|-----|-----|-----|-----|-----|-----|--|
|                         | 1       | 1         | 8   | 15  | 22  | 29  | 36  | 43  |  |
|                         | 1       | 1         | 2   | 3   | 4   | 5   | 6   | 7   |  |
| 106                     | 132     | 153       | 166 | 178 | 191 | 200 | 208 | 212 |  |
| 107                     | 119     | 137       | 161 | 172 | 189 | 195 | 203 | 209 |  |
| 108                     | 129     | 150       | 165 | 184 | 200 | 210 | 214 | 228 |  |
| 109                     | 133     | 154       | 169 | 180 | 198 | 210 | 216 | 224 |  |
| 110                     | 130     | 151       | 168 | 175 | 193 | 199 | 209 | 211 |  |
| 111                     | 120     | 143       | 160 | 171 | 180 | 191 | 201 | 203 |  |
| 112                     | 125     | 144       | 170 | 183 | 197 | 202 | 213 | 225 |  |
| 113                     | 121     | 141       | 155 | 164 | 175 | 181 | 187 | 187 |  |
| 114                     | 115     | 134       | 157 | 166 | 176 | 183 | 195 | 199 |  |
| 115                     | 124     | 149       | 169 | 187 | 201 | 208 | 214 | 221 |  |
| 116                     | 127     | 142       | 156 | 167 | 176 | 193 | 200 | 205 |  |
| 117                     | 130     | 152       | 172 | 181 | 194 | 204 | 213 | 215 |  |
| 118                     | 128     | 148       | 168 | 182 | 189 | 202 | 212 | 218 |  |
| 119                     | 127     | 142       | 164 | 172 | 182 | 189 | 196 | 199 |  |
| 120                     | 120     | 137       | 155 | 158 | 173 | 180 | 188 | 193 |  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |     |     |     |     |     |     |     |     |
|-------------------------|-----------|-----|-----|-----|-----|-----|-----|-----|-----|
|                         | 50        | 57  | 64  | 71  | 78  | 85  | 92  | 99  | 106 |
|                         | 8         | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  |
| 106                     | 213       | 223 | 229 | 227 | 231 | 236 | 242 | 240 | 235 |
| 107                     | 216       | 217 | 224 | 227 | 230 | 230 | 233 | 237 | 243 |
| 108                     | 226       | 240 | 242 | 250 | 254 | 256 | 256 | 265 | 266 |
| 109                     | 236       | 235 | 239 | 238 | 240 | 243 | 251 | 249 | 253 |
| 110                     | 222       | 228 | 233 | 229 | 236 | 241 | 242 | 242 | 240 |
| 111                     | 204       | 210 | 218 | 219 | 213 | 220 | 224 | 227 | 222 |
| 112                     | 229       | 233 | 237 | 240 | 237 | 237 | 246 | 246 | 255 |
| 113                     | 199       | 205 | 206 | 204 | 206 | 210 | 215 | 213 | 218 |
| 114                     | 206       | 210 | 219 | 217 | 219 | 220 | 230 | 233 | 231 |
| 115                     | 229       | 230 | 229 | 241 | 233 | 235 | 242 | 247 | 248 |
| 116                     | 217       | 217 | 221 | 224 | 227 | 228 | 228 | 227 | 224 |
| 117                     | 220       | 227 | 232 | 233 | 236 | 235 | 241 | 239 | 244 |
| 118                     | 220       | 227 | 237 | 232 | 233 | 232 | 244 | 244 | 246 |
| 119                     | 212       | 214 | 218 | 220 | 220 | 224 | 224 | 227 | 231 |
| 120                     | 203       | 205 | 207 | 209 | 215 | 221 | 224 | 223 | 224 |

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**BODY WEIGHTS (GRAM)  
FEMALES**

**GROUP 4 (200 MG/KG)**

---

|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

---

|     |     |
|-----|-----|
| 106 | 245 |
| 107 | 241 |
| 108 | 260 |
| 109 | 255 |
| 110 | 244 |
| 111 | 232 |
| 112 | 253 |
| 113 | 221 |
| 114 | 237 |
| 115 | 249 |
| 116 | 231 |
| 117 | 243 |
| 118 | 249 |
| 119 | 233 |
| 120 | 230 |

**BODY WEIGHT GAIN (%)**  
**MALES**

**GROUP 1 (0 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |      |      |      |      |       |       |  |
|-------------------------|---------|-----------|------|------|------|------|-------|-------|--|
|                         | 1       | 1         | 8    | 15   | 22   | 29   | 36    | 43    |  |
|                         | 1       | 1         | 2    | 3    | 4    | 5    | 6     | 7     |  |
| 1                       | -25.5   | 0.0       | 25.4 | 45.4 | 64.7 | 78.4 | 93.2  | 106.5 |  |
| 2                       | -25.6   | 0.0       | 22.7 | 39.0 | 47.8 | 66.2 | 79.7  | 87.5  |  |
| 3                       | -26.9   | 0.0       | 25.8 | 45.6 | 63.0 | 78.4 | 90.9  | 100.0 |  |
| 4                       | -23.1   | 0.0       | 25.5 | 45.8 | 65.4 | 81.6 | 94.5  | 104.4 |  |
| 5                       | -23.6   | 0.0       | 22.2 | 40.8 | 55.5 | 68.7 | 79.1  | 84.8  |  |
| 6                       | -23.3   | 0.0       | 24.4 | 41.7 | 49.4 | 71.9 | 83.8  | 88.5  |  |
| 7                       | -23.7   | 0.0       | 24.9 | 50.4 | 68.5 | 86.1 | 101.6 | 111.5 |  |
| 8                       | -22.1   | 0.0       | 23.5 | 41.8 | 58.9 | 72.5 | 84.0  | 91.7  |  |
| 9                       | -24.1   | 0.0       | 21.7 | 39.3 | 56.5 | 68.4 | 80.3  | 84.9  |  |
| 10                      | -21.9   | 0.0       | 22.9 | 45.8 | 63.4 | 76.9 | 89.9  | 97.8  |  |
| 11                      | -21.8   | 0.0       | 23.1 | 38.0 | 46.9 | 66.6 | 81.5  | 89.2  |  |
| 12                      | -24.6   | 0.0       | 23.2 | 42.1 | 61.3 | 73.6 | 87.2  | 96.1  |  |
| 13                      | -25.1   | 0.0       | 23.6 | 43.1 | 58.2 | 71.4 | 83.4  | 91.4  |  |
| 14                      | -23.3   | 0.0       | 20.2 | 37.1 | 53.8 | 65.4 | 77.8  | 84.7  |  |
| 15                      | -24.2   | 0.0       | 22.9 | 42.8 | 61.3 | 76.5 | 90.2  | 97.7  |  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |       |       |       |       |       |       |       |       |
|-------------------------|-----------|-------|-------|-------|-------|-------|-------|-------|-------|
|                         | 50        | 57    | 64    | 71    | 78    | 85    | 92    | 99    | 106   |
|                         | 8         | 9     | 10    | 11    | 12    | 13    | 14    | 15    | 16    |
| 1                       | 117.9     | 124.8 | 132.4 | 140.3 | 143.5 | 151.2 | 162.0 | 163.8 | 168.5 |
| 2                       | 94.5      | 93.7  | 99.5  | 100.2 | 102.8 | 105.2 | 110.2 | 114.4 | 115.7 |
| 3                       | 109.7     | 113.4 | 121.2 | 124.1 | 127.1 | 130.3 | 137.9 | 139.5 | 144.0 |
| 4                       | 112.8     | 116.8 | 124.9 | 128.5 | 132.3 | 136.3 | 142.9 | 143.9 | 148.5 |
| 5                       | 92.2      | 98.3  | 102.6 | 107.1 | 111.7 | 112.2 | 116.1 | 115.4 | 120.2 |
| 6                       | 95.7      | 100.9 | 103.9 | 108.9 | 112.0 | 112.9 | 118.8 | 122.8 | 124.0 |
| 7                       | 124.8     | 134.8 | 142.5 | 149.0 | 155.6 | 162.6 | 169.5 | 175.8 | 179.2 |
| 8                       | 100.4     | 106.0 | 114.0 | 117.1 | 124.8 | 129.6 | 138.3 | 139.5 | 146.2 |
| 9                       | 90.6      | 96.2  | 101.9 | 103.6 | 108.7 | 111.2 | 117.8 | 117.6 | 124.3 |
| 10                      | 107.8     | 113.3 | 119.1 | 124.7 | 131.8 | 134.7 | 142.9 | 147.1 | 151.6 |
| 11                      | 99.6      | 108.4 | 113.3 | 118.2 | 121.6 | 125.5 | 131.5 | 132.3 | 130.0 |
| 12                      | 102.4     | 106.2 | 109.5 | 111.7 | 114.1 | 116.8 | 120.5 | 123.8 | 128.2 |
| 13                      | 104.3     | 107.2 | 111.5 | 119.4 | 124.9 | 127.6 | 132.4 | 133.9 | 137.2 |
| 14                      | 93.9      | 100.1 | 106.6 | 112.5 | 118.2 | 121.8 | 126.4 | 128.5 | 130.9 |
| 15                      | 108.2     | 113.9 | 121.1 | 124.6 | 128.2 | 133.9 | 138.4 | 141.9 | 146.2 |

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**BODY WEIGHT GAIN (%)**  
**MALES**

**GROUP 1 (0 MG/KG)**

---

|        | TREATMENT |
|--------|-----------|
|        | -----     |
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

---

|    |       |
|----|-------|
| 1  | 172.6 |
| 2  | 117.9 |
| 3  | 147.0 |
| 4  | 148.7 |
| 5  | 123.1 |
| 6  | 128.1 |
| 7  | 181.1 |
| 8  | 149.0 |
| 9  | 129.3 |
| 10 | 153.5 |
| 11 | 138.8 |
| 12 | 131.6 |
| 13 | 142.1 |
| 14 | 136.6 |
| 15 | 148.3 |



**BODY WEIGHT GAIN (%)**  
**MALES**

**GROUP 2 (15 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |      |      |       |       |       |       |  |
|-------------------------|---------|-----------|------|------|-------|-------|-------|-------|--|
|                         | 1       | 1         | 8    | 15   | 22    | 29    | 36    | 43    |  |
|                         | 1       | 1         | 2    | 3    | 4     | 5     | 6     | 7     |  |
| 16                      | -26.0   | 0.0       | 24.4 | 42.8 | 60.0  | 75.2  | 88.0  | 96.2  |  |
| 17                      | -23.1   | 0.0       | 24.9 | 47.4 | 61.3  | 77.6  | 90.2  | 99.7  |  |
| 18                      | -25.1   | 0.0       | 22.4 | 38.5 | 54.3  | 61.7  | 74.8  | 79.0  |  |
| 19                      | -24.0   | 0.0       | 25.6 | 43.5 | 71.5  | 70.3  | 82.4  | 86.8  |  |
| 20                      | -25.4   | 0.0       | 26.6 | 47.3 | 49.0  | 83.5  | 97.2  | 104.5 |  |
| 21                      | -21.6   | 0.0       | 20.7 | 39.2 | 70.5  | 67.6  | 78.5  | 86.7  |  |
| 22                      | -23.8   | 0.0       | 24.6 | 45.7 | 58.4  | 77.7  | 92.2  | 96.5  |  |
| 23                      | -22.6   | 0.0       | 25.3 | 46.3 | 53.0  | 74.6  | 86.5  | 93.4  |  |
| 24                      | -22.6   | 0.0       | 25.0 | 41.8 | 54.6  | 68.9  | 78.9  | 85.0  |  |
| 25                      | -20.4   | 0.0       | 24.6 | 44.9 | 64.7  | 78.8  | 93.4  | 101.5 |  |
| 26                      | -6.9    | 0.0       | 48.5 | 74.4 | 87.2  | 113.4 | 128.1 | 135.1 |  |
| 27                      | -9.4    | 0.0       | 44.9 | 68.3 | 85.1  | 94.8  | 106.2 | 112.2 |  |
| 28                      | -7.8    | 0.0       | 48.3 | 73.1 | 91.1  | 107.6 | 120.2 | 132.0 |  |
| 29                      | -9.1    | 0.0       | 49.2 | 78.0 | 100.8 | 117.3 | 132.7 | 142.6 |  |
| 30                      | -9.3    | 0.0       | 44.6 | 68.6 | 89.9  | 106.5 | 119.3 | 126.6 |  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |       |       |       |       |       |       |       |       |
|-------------------------|-----------|-------|-------|-------|-------|-------|-------|-------|-------|
|                         | 50        | 57    | 64    | 71    | 78    | 85    | 92    | 99    | 106   |
|                         | 8         | 9     | 10    | 11    | 12    | 13    | 14    | 15    | 16    |
| 16                      | 108.6     | 111.2 | 115.6 | 118.7 | 121.5 | 123.7 | 127.2 | 132.4 | 136.8 |
| 17                      | 110.9     | 114.6 | 119.2 | 121.5 | 125.6 | 126.3 | 133.7 | 136.8 | 136.3 |
| 18                      | 85.9      | 89.2  | 94.5  | 98.8  | 100.9 | 104.0 | 108.6 | 116.6 | 118.7 |
| 19                      | 95.9      | 100.3 | 103.2 | 106.7 | 110.3 | 113.1 | 115.3 | 121.5 | 120.7 |
| 20                      | 115.3     | 119.6 | 125.4 | 128.4 | 131.3 | 134.9 | 141.0 | 146.8 | 147.0 |
| 21                      | 95.1      | 100.5 | 106.3 | 110.8 | 114.9 | 116.8 | 121.4 | 125.5 | 126.3 |
| 22                      | 107.9     | 112.8 | 117.6 | 120.8 | 121.0 | 125.0 | 132.7 | 135.7 | 141.1 |
| 23                      | 103.8     | 109.8 | 114.9 | 115.7 | 119.6 | 124.0 | 130.3 | 136.7 | 139.9 |
| 24                      | 91.7      | 96.3  | 101.8 | 104.6 | 108.6 | 112.6 | 116.9 | 120.6 | 125.0 |
| 25                      | 110.7     | 118.3 | 125.3 | 131.9 | 131.6 | 134.1 | 142.6 | 147.6 | 153.3 |
| 26                      | 143.6     | 148.6 | 156.9 | 161.6 | 161.6 | 162.4 | 169.1 | 176.5 | 178.8 |
| 27                      | 120.3     | 120.4 | 123.5 | 128.1 | 131.6 | 138.1 | 142.8 | 150.2 | 152.7 |
| 28                      | 140.9     | 146.7 | 148.7 | 156.9 | 159.4 | 162.8 | 167.0 | 174.0 | 177.2 |
| 29                      | 155.4     | 159.9 | 166.0 | 169.5 | 169.4 | 171.4 | 180.5 | 185.2 | 188.2 |
| 30                      | 140.3     | 147.8 | 156.4 | 157.6 | 159.4 | 163.6 | 169.4 | 174.8 | 176.8 |

**BODY WEIGHT GAIN (%)**  
**MALES**

**GROUP 2 (15 MG/KG)**

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|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

---

|    |       |
|----|-------|
| 16 | 140.0 |
| 17 | 145.5 |
| 18 | 120.3 |
| 19 | 128.0 |
| 20 | 151.9 |
| 21 | 131.8 |
| 22 | 141.2 |
| 23 | 140.7 |
| 24 | 127.1 |
| 25 | 155.9 |
| 26 | 182.9 |
| 27 | 156.5 |
| 28 | 178.8 |
| 29 | 193.7 |
| 30 | 179.7 |

**BODY WEIGHT GAIN (%)  
MALES**

**GROUP 3 (50 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |      |      |      |      |       |       |  |
|-------------------------|---------|-----------|------|------|------|------|-------|-------|--|
|                         | 1       | 1         | 8    | 15   | 22   | 29   | 36    | 43    |  |
|                         | 1       | 1         | 2    | 3    | 4    | 5    | 6     | 7     |  |
| 31                      | -25.9   | 0.0       | 25.4 | 42.0 | 52.0 | 62.8 | 71.6  | 78.5  |  |
| 32                      | -24.1   | 0.0       | 22.6 | 43.3 | 67.4 | 74.0 | 88.1  | 97.1  |  |
| 33                      | -21.9   | 0.0       | 22.0 | 37.7 | 53.7 | 63.4 | 73.6  | 80.7  |  |
| 34                      | -25.9   | 0.0       | 23.7 | 42.9 | 62.5 | 76.6 | 89.0  | 95.9  |  |
| 35                      | -23.1   | 0.0       | 20.7 | 37.6 | 53.6 | 63.8 | 74.6  | 79.8  |  |
| 36                      | -24.1   | 0.0       | 26.6 | 44.8 | 63.7 | 79.1 | 89.4  | 98.2  |  |
| 37                      | -22.6   | 0.0       | 24.3 | 44.5 | 60.3 | 74.4 | 87.8  | 95.9  |  |
| 38                      | -23.5   | 0.0       | 23.9 | 44.4 | 61.4 | 76.7 | 91.7  | 100.1 |  |
| 39                      | -19.7   | 0.0       | 31.8 | 56.6 | 81.7 | 90.4 | 105.7 | 114.7 |  |
| 40                      | -20.5   | 0.0       | 21.4 | 37.5 | 55.5 | 64.4 | 75.6  | 82.3  |  |
| 41                      | -26.5   | 0.0       | 25.0 | 41.7 | 56.6 | 69.1 | 79.7  | 89.3  |  |
| 42                      | -28.9   | 0.0       | 26.2 | 45.2 | 63.3 | 70.0 | 83.8  | 92.0  |  |
| 43                      | -27.3   | 0.0       | 26.1 | 47.4 | 64.1 | 85.6 | 95.7  | 105.6 |  |
| 44                      | -24.1   | 0.0       | 20.4 | 35.0 | 51.2 | 61.6 | 72.9  | 79.1  |  |
| 45                      | -25.6   | 0.0       | 23.5 | 41.4 | 55.9 | 67.6 | 81.5  | 88.2  |  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |       |       |       |       |       |       |       |       |  |
|-------------------------|-----------|-------|-------|-------|-------|-------|-------|-------|-------|--|
|                         | 50        | 57    | 64    | 71    | 78    | 85    | 92    | 99    | 106   |  |
|                         | 8         | 9     | 10    | 11    | 12    | 13    | 14    | 15    | 16    |  |
| 31                      | 85.1      | 87.4  | 89.7  | 92.4  | 92.3  | 95.1  | 98.6  | 103.3 | 107.6 |  |
| 32                      | 108.3     | 115.5 | 124.1 | 127.3 | 130.6 | 138.6 | 148.8 | 153.5 | 151.2 |  |
| 33                      | 88.7      | 94.3  | 99.3  | 101.0 | 104.2 | 110.4 | 115.3 | 121.6 | 135.8 |  |
| 34                      | 102.9     | 111.1 | 114.4 | 116.4 | 116.9 | 121.1 | 125.6 | 128.5 | 132.8 |  |
| 35                      | 85.8      | 112.0 | 94.2  | 95.5  | 95.7  | 100.3 | 102.4 | 105.7 | 114.6 |  |
| 36                      | 108.5     | 110.1 | 114.2 | 115.6 | 117.6 | 119.5 | 128.2 | 129.6 | 129.9 |  |
| 37                      | 103.2     | 109.1 | 114.3 | 118.2 | 116.4 | 115.8 | 121.3 | 123.0 | 124.4 |  |
| 38                      | 108.7     | 115.7 | 124.0 | 128.8 | 131.3 | 137.8 | 141.5 | 151.4 | 154.9 |  |
| 39                      | 123.5     | 128.1 | 135.3 | 136.7 | 136.2 | 138.9 | 148.9 | 157.0 | 157.9 |  |
| 40                      | 86.9      | 91.8  | 94.7  | 100.2 | 102.8 | 105.6 | 110.0 | 111.0 | 113.3 |  |
| 41                      | 98.9      | 104.9 | 110.3 | 116.5 | 117.8 | 124.3 | 127.3 | 131.9 | 130.0 |  |
| 42                      | 98.5      | 103.3 | 107.5 | 110.7 | 112.7 | 116.7 | 120.3 | 126.1 | 138.7 |  |
| 43                      | 113.8     | 121.1 | 125.5 | 130.2 | 128.6 | 134.7 | 141.8 | 147.8 | 166.2 |  |
| 44                      | 87.3      | 91.7  | 98.4  | 99.4  | 104.9 | 105.8 | 113.8 | 117.9 | 134.7 |  |
| 45                      | 94.1      | 98.2  | 103.9 | 107.8 | 114.2 | 117.8 | 122.0 | 127.2 | 154.1 |  |

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**BODY WEIGHT GAIN (%)**  
**MALES**

**GROUP 3 (50 MG/KG)**

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|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

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|    |       |
|----|-------|
| 31 | 109.6 |
| 32 | 161.6 |
| 33 | 127.4 |
| 34 | 134.4 |
| 35 | 110.9 |
| 36 | 135.7 |
| 37 | 133.3 |
| 38 | 154.8 |
| 39 | 164.2 |
| 40 | 120.0 |
| 41 | 140.0 |
| 42 | 132.3 |
| 43 | 151.2 |
| 44 | 127.7 |
| 45 | 134.7 |

**BODY WEIGHT GAIN (%)**  
**MALES**

**GROUP 4 (200 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |      |      |      |      |      |       |
|-------------------------|---------|-----------|------|------|------|------|------|-------|
|                         | 1       | 1         | 8    | 15   | 22   | 29   | 36   | 43    |
|                         | 1       | 1         | 2    | 3    | 4    | 5    | 6    | 7     |
| 46                      | -24.8   | 0.0       | 24.9 | 39.2 | 51.1 | 65.4 | 74.5 | 79.8  |
| 47                      | -22.6   | 0.0       | 21.3 | 38.1 | 55.5 | 67.7 | 79.1 | 85.7  |
| 48                      | -22.4   | 0.0       | 22.0 | 41.3 | 62.7 | 80.4 | 95.1 | 96.5  |
| 49                      | -25.1   | 0.0       | 23.9 | 42.9 | 63.5 | 72.8 | 84.3 | 90.3  |
| 50                      | -22.1   | 0.0       | 25.4 | 43.1 | 73.6 | 76.2 | 91.2 | 96.5  |
| 51                      | -21.4   | 0.0       | 21.3 | 42.2 | 41.4 | 68.9 | 81.4 | 90.4  |
| 52                      | -22.9   | 0.0       | 19.2 | 35.7 | 50.5 | 63.4 | 73.7 | 82.7  |
| 53                      | -26.8   | 0.0       | 26.1 | 46.9 | 65.5 | 82.1 | 96.2 | 108.8 |
| 54                      | -21.9   | 0.0       | 23.4 | 45.6 | 61.8 | 69.5 | 81.0 | 86.8  |
| 55                      | -25.4   | 0.0       | 25.1 | 41.6 | 56.9 | 67.0 | 75.1 | 81.0  |
| 56                      | -21.9   | 0.0       | 25.1 | 43.8 | 65.7 | 81.5 | 96.9 | 107.1 |
| 57                      | -19.0   | 0.0       | 26.6 | 44.2 | 60.0 | 74.9 | 90.3 | 96.0  |
| 58                      | -22.4   | 0.0       | 23.9 | 41.6 | 60.4 | 71.2 | 80.9 | 87.3  |
| 59                      | -24.0   | 0.0       | 24.7 | 46.4 | 61.0 | 71.7 | 82.8 | 90.0  |
| 60                      | -25.0   | 0.0       | 24.6 | 41.8 | 61.2 | 71.6 | 83.3 | 92.0  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |       |       |       |       |       |       |       |       |
|-------------------------|-----------|-------|-------|-------|-------|-------|-------|-------|-------|
|                         | 50        | 57    | 64    | 71    | 78    | 85    | 92    | 99    | 106   |
|                         | 8         | 9     | 10    | 11    | 12    | 13    | 14    | 15    | 16    |
| 46                      | 88.6      | 97.8  | 93.8  | 97.8  | 101.4 | 107.4 | 111.5 | 114.1 | 104.6 |
| 47                      | 93.9      | 102.2 | 105.8 | 111.7 | 113.7 | 116.9 | 123.8 | 125.9 | 132.8 |
| 48                      | 110.0     | 118.8 | 128.2 | 129.6 | 131.4 | 138.4 | 137.9 | 144.3 | 144.7 |
| 49                      | 100.1     | 109.3 | 111.8 | 115.4 | 116.3 | 119.8 | 124.4 | 128.6 | 135.4 |
| 50                      | 107.9     | 114.2 | 120.0 | 126.6 | 125.2 | 125.9 | 132.9 | 138.0 | 147.6 |
| 51                      | 98.2      | 103.9 | 108.3 | 111.6 | 115.6 | 112.5 | 123.3 | 127.4 | 131.3 |
| 52                      | 92.6      | 98.3  | 103.4 | 107.4 | 112.4 | 114.4 | 120.1 | 123.6 | 145.6 |
| 53                      | 119.6     | 123.9 | 138.7 | 143.3 | 150.3 | 151.6 | 163.5 | 168.1 | 154.5 |
| 54                      | 95.9      | 99.5  | 105.7 | 107.5 | 109.1 | 110.5 | 114.1 | 119.8 | 123.2 |
| 55                      | 86.8      | 102.3 | 95.2  | 96.5  | 96.9  | 97.7  | 105.2 | 109.6 | 114.5 |
| 56                      | 117.4     | 124.2 | 128.0 | 135.8 | 138.8 | 141.5 | 146.5 | 151.4 | 149.6 |
| 57                      | 106.0     | 108.4 | 111.5 | 116.0 | 118.7 | 122.5 | 130.1 | 135.3 | 142.5 |
| 58                      | 96.5      | 99.6  | 102.0 | 109.3 | 112.2 | 114.6 | 121.9 | 124.0 | 131.9 |
| 59                      | 98.2      | 98.0  | 104.6 | 108.8 | 108.4 | 112.0 | 113.8 | 119.7 | 125.1 |
| 60                      | 100.8     | 104.4 | 105.8 | 110.8 | 109.2 | 114.4 | 119.0 | 125.9 | 131.8 |

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**BODY WEIGHT GAIN (%)**  
**MALES**

**GROUP 4 (200 MG/KG)**

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|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

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|    |       |
|----|-------|
| 46 | 117.4 |
| 47 | 134.1 |
| 48 | 148.7 |
| 49 | 138.8 |
| 50 | 147.8 |
| 51 | 132.0 |
| 52 | 130.3 |
| 53 | 179.4 |
| 54 | 125.7 |
| 55 | 115.4 |
| 56 | 158.6 |
| 57 | 143.9 |
| 58 | 131.7 |
| 59 | 128.1 |
| 60 | 131.4 |

**BODY WEIGHT GAIN (%)  
FEMALES**

**GROUP 1 (0 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |      |      |      |      |      |      |  |
|-------------------------|---------|-----------|------|------|------|------|------|------|--|
|                         | 1       | 1         | 8    | 15   | 22   | 29   | 36   | 43   |  |
|                         | 1       | 1         | 2    | 3    | 4    | 5    | 6    | 7    |  |
| 61                      | -14.2   | 0.0       | 11.9 | 17.7 | 25.2 | 32.3 | 43.6 | 46.3 |  |
| 62                      | -14.9   | 0.0       | 7.4  | 17.2 | 31.1 | 32.3 | 37.0 | 43.9 |  |
| 63                      | -13.2   | 0.0       | 16.0 | 26.5 | 35.4 | 38.4 | 48.3 | 53.3 |  |
| 64                      | -11.5   | 0.0       | 12.3 | 18.5 | 27.9 | 33.6 | 41.1 | 42.9 |  |
| 65                      | -14.9   | 0.0       | 13.4 | 19.6 | 32.2 | 39.2 | 46.9 | 46.2 |  |
| 66                      | -12.4   | 0.0       | 11.8 | 22.5 | 32.2 | 39.1 | 46.2 | 50.1 |  |
| 67                      | -13.6   | 0.0       | 11.9 | 18.1 | 25.5 | 31.8 | 37.8 | 41.7 |  |
| 68                      | -13.6   | 0.0       | 11.3 | 18.6 | 25.4 | 32.5 | 37.5 | 41.2 |  |
| 69                      | -11.0   | 0.0       | 16.9 | 24.2 | 35.3 | 39.0 | 47.8 | 53.9 |  |
| 70                      | -11.5   | 0.0       | 14.2 | 22.3 | 32.6 | 31.6 | 43.9 | 45.4 |  |
| 71                      | -16.0   | 0.0       | 14.8 | 21.6 | 28.1 | 38.5 | 45.1 | 46.2 |  |
| 72                      | -13.3   | 0.0       | 13.7 | 21.4 | 32.4 | 40.5 | 43.5 | 44.1 |  |
| 73                      | -18.3   | 0.0       | 15.3 | 23.0 | 30.4 | 44.4 | 50.4 | 50.5 |  |
| 74                      | -16.3   | 0.0       | 12.7 | 17.6 | 27.4 | 36.0 | 42.6 | 43.4 |  |
| 75                      | -11.6   | 0.0       | 11.4 | 19.8 | 28.5 | 34.7 | 39.2 | 43.5 |  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |      |      |      |      |      |      |      |      |
|-------------------------|-----------|------|------|------|------|------|------|------|------|
|                         | 50        | 57   | 64   | 71   | 78   | 85   | 92   | 99   | 106  |
|                         | 8         | 9    | 10   | 11   | 12   | 13   | 14   | 15   | 16   |
| 61                      | 47.8      | 54.5 | 58.2 | 59.7 | 56.8 | 60.2 | 64.6 | 62.9 | 55.2 |
| 62                      | 51.4      | 49.5 | 52.0 | 57.6 | 58.5 | 62.2 | 63.1 | 66.5 | 68.0 |
| 63                      | 56.7      | 57.2 | 63.8 | 67.0 | 69.4 | 67.6 | 71.1 | 76.2 | 77.2 |
| 64                      | 47.6      | 48.6 | 55.0 | 54.9 | 52.7 | 56.8 | 60.4 | 60.3 | 61.4 |
| 65                      | 54.9      | 59.0 | 62.6 | 59.0 | 61.8 | 65.0 | 67.8 | 65.9 | 69.9 |
| 66                      | 60.0      | 61.7 | 63.2 | 69.3 | 69.4 | 72.5 | 74.3 | 80.1 | 76.4 |
| 67                      | 46.6      | 49.6 | 55.2 | 56.3 | 55.1 | 56.3 | 58.8 | 60.0 | 59.3 |
| 68                      | 47.0      | 48.7 | 51.4 | 50.0 | 52.5 | 54.5 | 55.5 | 58.1 | 58.6 |
| 69                      | 57.3      | 58.3 | 63.1 | 70.2 | 69.0 | 68.5 | 73.6 | 74.8 | 79.6 |
| 70                      | 47.8      | 47.1 | 52.1 | 51.2 | 53.6 | 51.8 | 60.1 | 57.5 | 58.5 |
| 71                      | 48.6      | 52.2 | 58.9 | 58.8 | 55.7 | 60.5 | 64.5 | 62.2 | 57.2 |
| 72                      | 50.9      | 51.3 | 53.3 | 55.8 | 54.5 | 59.1 | 59.0 | 61.7 | 66.9 |
| 73                      | 50.4      | 57.9 | 61.5 | 60.3 | 60.4 | 63.0 | 67.6 | 64.2 | 63.0 |
| 74                      | 52.2      | 55.0 | 58.3 | 57.4 | 59.4 | 60.7 | 65.1 | 63.3 | 65.5 |
| 75                      | 48.2      | 48.8 | 52.6 | 54.8 | 55.5 | 57.7 | 59.9 | 62.6 | 59.2 |

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**BODY WEIGHT GAIN (%)  
FEMALES**

**GROUP 1 (0 MG/KG)**

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|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

---

|    |      |
|----|------|
| 61 | 67.0 |
| 62 | 66.4 |
| 63 | 79.4 |
| 64 | 66.2 |
| 65 | 72.2 |
| 66 | 79.9 |
| 67 | 63.5 |
| 68 | 61.6 |
| 69 | 82.6 |
| 70 | 58.8 |
| 71 | 68.2 |
| 72 | 65.5 |
| 73 | 70.0 |
| 74 | 67.0 |
| 75 | 61.1 |



**BODY WEIGHT GAIN (%)  
 FEMALES**

**GROUP 2 (15 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |      |      |      |      |      |      |  |
|-------------------------|---------|-----------|------|------|------|------|------|------|--|
|                         | 1       | 1         | 8    | 15   | 22   | 29   | 36   | 43   |  |
|                         | 1       | 1         | 2    | 3    | 4    | 5    | 6    | 7    |  |
| 76                      | -17.5   | 0.0       | 13.0 | 21.9 | 33.3 | 42.7 | 48.2 | 48.7 |  |
| 77                      | -14.1   | 0.0       | 15.4 | 20.2 | 45.1 | 39.3 | 46.6 | 46.7 |  |
| 78                      | -12.5   | 0.0       | 11.2 | 19.6 | 30.5 | 37.9 | 43.8 | 42.5 |  |
| 79                      | -16.3   | 0.0       | 12.0 | 21.4 | 31.5 | 36.9 | 39.1 | 44.2 |  |
| 80                      | -11.1   | 0.0       | 14.8 | 23.3 | 32.1 | 36.3 | 43.3 | 48.5 |  |
| 81                      | -13.2   | 0.0       | 12.1 | 20.7 | 22.5 | 38.6 | 43.6 | 47.0 |  |
| 82                      | -15.3   | 0.0       | 12.3 | 22.9 | 28.6 | 36.3 | 44.7 | 49.4 |  |
| 83                      | -17.4   | 0.0       | 14.7 | 22.6 | 35.7 | 43.6 | 49.6 | 48.5 |  |
| 84                      | -18.3   | 0.0       | 7.9  | 14.8 | 24.9 | 34.2 | 35.6 | 40.1 |  |
| 85                      | -17.7   | 0.0       | 14.9 | 21.4 | 28.2 | 32.4 | 39.4 | 42.2 |  |
| 86                      | -18.3   | 0.0       | 15.0 | 26.9 | 38.2 | 47.4 | 53.6 | 53.8 |  |
| 87                      | -14.2   | 0.0       | 12.7 | 18.4 | 25.7 | 30.1 | 38.5 | 41.1 |  |
| 88                      | -7.8    | 0.0       | 24.6 | 29.4 | 40.4 | 46.7 | 53.1 | 53.5 |  |
| 89                      | -14.3   | 0.0       | 8.9  | 18.2 | 32.3 | 35.0 | 40.8 | 45.5 |  |
| 90                      | -15.7   | 0.0       | 16.5 | 27.1 | 37.0 | 43.5 | 51.0 | 52.2 |  |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |      |      |      |      |      |      |      |      |
|-------------------------|-----------|------|------|------|------|------|------|------|------|
|                         | 50        | 57   | 64   | 71   | 78   | 85   | 92   | 99   | 106  |
|                         | 8         | 9    | 10   | 11   | 12   | 13   | 14   | 15   | 16   |
| 76                      | 55.8      | 59.8 | 63.5 | 61.0 | 65.2 | 69.2 | 68.3 | 67.5 | 67.4 |
| 77                      | 48.1      | 55.1 | 59.1 | 56.1 | 58.6 | 62.7 | 65.0 | 67.7 | 71.6 |
| 78                      | 51.6      | 54.5 | 56.9 | 53.4 | 57.6 | 59.6 | 62.2 | 63.0 | 67.6 |
| 79                      | 49.6      | 49.9 | 48.1 | 49.6 | 52.5 | 53.7 | 50.9 | 50.6 | 54.8 |
| 80                      | 51.3      | 52.5 | 55.4 | 58.3 | 57.8 | 58.8 | 62.2 | 63.0 | 77.5 |
| 81                      | 51.1      | 53.0 | 53.5 | 56.3 | 56.9 | 59.1 | 61.2 | 62.5 | 62.9 |
| 82                      | 50.8      | 52.8 | 61.3 | 58.7 | 64.2 | 63.4 | 65.6 | 69.5 | 68.5 |
| 83                      | 56.8      | 60.9 | 62.0 | 60.7 | 66.0 | 72.7 | 73.1 | 72.0 | 80.4 |
| 84                      | 48.6      | 50.8 | 51.2 | 51.6 | 59.4 | 58.7 | 58.5 | 57.5 | 72.6 |
| 85                      | 44.4      | 46.2 | 51.4 | 51.4 | 53.3 | 56.8 | 59.1 | 60.1 | 55.6 |
| 86                      | 60.1      | 64.5 | 67.3 | 66.7 | 71.0 | 71.1 | 75.6 | 73.2 | 67.9 |
| 87                      | 46.4      | 45.6 | 49.5 | 54.1 | 54.8 | 55.7 | 56.2 | 59.5 | 71.5 |
| 88                      | 61.9      | 65.9 | 65.7 | 62.7 | 69.6 | 70.8 | 72.9 | 72.0 | 93.0 |
| 89                      | 53.7      | 56.4 | 57.0 | 60.0 | 62.2 | 61.7 | 64.8 | 65.7 | 69.7 |
| 90                      | 58.4      | 60.5 | 62.9 | 64.2 | 65.8 | 67.0 | 69.1 | 69.2 | 83.1 |

**BODY WEIGHT GAIN (%)  
FEMALES**

**GROUP 2 (15 MG/KG)**

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|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

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|    |      |
|----|------|
| 76 | 70.2 |
| 77 | 70.9 |
| 78 | 66.1 |
| 79 | 52.3 |
| 80 | 65.9 |
| 81 | 64.9 |
| 82 | 66.7 |
| 83 | 78.4 |
| 84 | 58.8 |
| 85 | 60.3 |
| 86 | 77.9 |
| 87 | 60.3 |
| 88 | 76.3 |
| 89 | 67.4 |
| 90 | 75.6 |

**BODY WEIGHT GAIN (%)  
 FEMALES**

**GROUP 3 (50 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |      |      |      |      |      |      |
|-------------------------|---------|-----------|------|------|------|------|------|------|
|                         | 1       | 1         | 8    | 15   | 22   | 29   | 36   | 43   |
|                         | 1       | 1         | 2    | 3    | 4    | 5    | 6    | 7    |
| 91                      | -13.7   | 0.0       | 14.3 | 22.7 | 29.1 | 36.8 | 43.5 | 46.9 |
| 92                      | -17.4   | 0.0       | 12.5 | 16.7 | 24.8 | 32.2 | 38.4 | 41.9 |
| 93                      | -15.8   | 0.0       | 15.5 | 23.1 | 34.9 | 35.7 | 42.3 | 47.2 |
| 94                      | -16.9   | 0.0       | 13.7 | 22.2 | 34.9 | 34.7 | 39.9 | 44.0 |
| 95                      | -13.3   | 0.0       | 13.2 | 20.7 | 34.7 | 41.2 | 45.9 | 47.9 |
| 96                      | -14.9   | 0.0       | 13.2 | 19.7 | 21.9 | 34.7 | 41.5 | 44.7 |
| 97                      | -13.2   | 0.0       | 14.7 | 21.5 | 32.7 | 38.6 | 43.8 | 45.5 |
| 98                      | -21.0   | 0.0       | 14.5 | 27.4 | 38.7 | 42.0 | 46.1 | 54.3 |
| 99                      | -14.9   | 0.0       | 13.6 | 19.0 | 31.2 | 32.6 | 39.6 | 40.5 |
| 100                     | -15.4   | 0.0       | 13.1 | 22.7 | 30.7 | 40.4 | 44.5 | 46.9 |
| 101                     | -16.0   | 0.0       | 7.7  | 15.5 | 24.9 | 30.8 | 37.2 | 37.5 |
| 102                     | -13.2   | 0.0       | 12.0 | 17.3 | 25.0 | 26.6 | 33.9 | 39.3 |
| 103                     | -10.5   | 0.0       | 14.8 | 25.8 | 37.0 | 40.4 | 50.6 | 55.2 |
| 104                     | -11.3   | 0.0       | 16.3 | 20.5 | 29.5 | 31.4 | 38.4 | 42.2 |
| 105                     | -11.9   | 0.0       | 14.2 | 22.4 | 30.3 | 33.1 | 38.3 | 43.6 |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |      |      |      |      |      |      |      |      |
|-------------------------|-----------|------|------|------|------|------|------|------|------|
|                         | 50        | 57   | 64   | 71   | 78   | 85   | 92   | 99   | 106  |
|                         | 8         | 9    | 10   | 11   | 12   | 13   | 14   | 15   | 16   |
| 91                      | 53.7      | 56.1 | 56.8 | 58.8 | 61.9 | 65.4 | 65.8 | 64.4 | 68.4 |
| 92                      | 43.3      | 49.5 | 51.8 | 51.5 | 49.4 | 52.6 | 57.8 | 55.0 | 53.0 |
| 93                      | 49.9      | 51.5 | 54.7 | 58.6 | 57.2 | 57.1 | 62.4 | 62.6 | 64.2 |
| 94                      | 47.1      | 48.7 | 51.6 | 54.9 | 55.4 | 55.5 | 56.1 | 58.7 | 59.8 |
| 95                      | 54.5      | 56.1 | 59.9 | 59.4 | 64.1 | 69.0 | 69.3 | 69.8 | 71.5 |
| 96                      | 47.1      | 50.5 | 55.8 | 56.5 | 54.5 | 56.0 | 61.3 | 59.5 | 54.5 |
| 97                      | 51.8      | 54.2 | 55.8 | 57.3 | 62.2 | 62.5 | 63.9 | 65.4 | 83.9 |
| 98                      | 58.0      | 60.7 | 60.1 | 61.1 | 64.2 | 63.1 | 60.5 | 64.2 | 69.4 |
| 99                      | 42.6      | 47.8 | 51.0 | 50.2 | 51.5 | 53.8 | 58.0 | 57.4 | 58.3 |
| 100                     | 48.4      | 53.1 | 55.3 | 53.1 | 54.3 | 58.7 | 60.9 | 59.6 | 58.8 |
| 101                     | 42.5      | 47.9 | 48.1 | 47.8 | 52.5 | 53.4 | 55.8 | 57.8 | 55.9 |
| 102                     | 41.2      | 41.9 | 45.0 | 48.1 | 51.1 | 50.9 | 55.6 | 52.6 | 62.5 |
| 103                     | 61.6      | 64.4 | 68.1 | 70.2 | 73.2 | 77.9 | 78.1 | 78.9 | 83.4 |
| 104                     | 43.8      | 46.6 | 51.5 | 52.9 | 55.3 | 53.8 | 57.3 | 58.9 | 65.5 |
| 105                     | 46.5      | 46.7 | 49.4 | 50.9 | 53.2 | 54.1 | 55.6 | 56.4 | 57.7 |

**BODY WEIGHT GAIN (%)  
FEMALES**

**GROUP 3 (50 MG/KG)**

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|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

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|     |      |
|-----|------|
| 91  | 70.5 |
| 92  | 58.8 |
| 93  | 63.1 |
| 94  | 60.3 |
| 95  | 72.9 |
| 96  | 63.6 |
| 97  | 64.3 |
| 98  | 63.6 |
| 99  | 61.4 |
| 100 | 63.4 |
| 101 | 58.8 |
| 102 | 53.3 |
| 103 | 82.0 |
| 104 | 62.1 |
| 105 | 57.2 |

**BODY WEIGHT GAIN (%)  
FEMALES**

**GROUP 4 (200 MG/KG)**

| DAYS<br>WEEKS<br>ANIMAL | PRETEST | TREATMENT |      |      |      |      |      |      |
|-------------------------|---------|-----------|------|------|------|------|------|------|
|                         | 1       | 1         | 8    | 15   | 22   | 29   | 36   | 43   |
|                         | 1       | 1         | 2    | 3    | 4    | 5    | 6    | 7    |
| 106                     | -13.7   | 0.0       | 8.9  | 17.0 | 25.1 | 30.9 | 36.2 | 38.9 |
| 107                     | -13.3   | 0.0       | 17.4 | 25.8 | 38.3 | 42.1 | 47.9 | 52.8 |
| 108                     | -14.2   | 0.0       | 9.7  | 22.5 | 33.0 | 39.7 | 42.2 | 51.9 |
| 109                     | -14.1   | 0.0       | 9.7  | 16.6 | 28.3 | 36.1 | 40.1 | 45.1 |
| 110                     | -14.0   | 0.0       | 11.1 | 15.9 | 27.5 | 32.1 | 38.6 | 39.9 |
| 111                     | -16.5   | 0.0       | 11.7 | 19.0 | 25.8 | 33.0 | 40.1 | 41.4 |
| 112                     | -13.6   | 0.0       | 17.7 | 27.1 | 36.7 | 40.0 | 47.6 | 56.0 |
| 113                     | -14.3   | 0.0       | 9.6  | 16.0 | 24.1 | 28.5 | 32.8 | 32.5 |
| 114                     | -14.1   | 0.0       | 16.7 | 23.9 | 31.2 | 36.2 | 45.4 | 47.9 |
| 115                     | -16.5   | 0.0       | 13.3 | 25.8 | 35.0 | 39.7 | 44.0 | 48.8 |
| 116                     | -11.2   | 0.0       | 9.6  | 17.3 | 23.5 | 35.5 | 40.5 | 43.6 |
| 117                     | -14.1   | 0.0       | 13.5 | 19.5 | 27.9 | 34.5 | 40.2 | 41.8 |
| 118                     | -13.8   | 0.0       | 13.2 | 22.6 | 27.7 | 36.7 | 43.0 | 47.1 |
| 119                     | -10.8   | 0.0       | 15.1 | 20.5 | 27.9 | 32.6 | 37.9 | 40.2 |
| 120                     | -12.4   | 0.0       | 12.4 | 14.7 | 25.7 | 31.3 | 37.1 | 40.7 |

| DAYS<br>WEEKS<br>ANIMAL | TREATMENT |      |      |      |      |      |      |      |      |
|-------------------------|-----------|------|------|------|------|------|------|------|------|
|                         | 50        | 57   | 64   | 71   | 78   | 85   | 92   | 99   | 106  |
|                         | 8         | 9    | 10   | 11   | 12   | 13   | 14   | 15   | 16   |
| 106                     | 39.7      | 46.1 | 49.9 | 48.6 | 51.8 | 54.9 | 58.8 | 57.3 | 53.9 |
| 107                     | 57.7      | 58.6 | 63.7 | 65.5 | 67.7 | 67.5 | 69.9 | 73.2 | 77.5 |
| 108                     | 50.0      | 59.7 | 60.7 | 66.5 | 68.9 | 70.0 | 70.5 | 76.0 | 76.9 |
| 109                     | 53.0      | 52.5 | 55.2 | 54.4 | 55.7 | 57.4 | 62.5 | 61.1 | 63.9 |
| 110                     | 46.7      | 51.0 | 54.6 | 52.0 | 56.0 | 59.7 | 60.4 | 60.4 | 58.7 |
| 111                     | 42.5      | 46.7 | 52.1 | 53.0 | 48.8 | 53.7 | 56.4 | 58.2 | 55.0 |
| 112                     | 59.0      | 61.5 | 64.2 | 66.6 | 64.0 | 64.2 | 70.2 | 70.3 | 76.5 |
| 113                     | 40.9      | 45.7 | 45.9 | 44.6 | 46.1 | 48.6 | 52.2 | 51.3 | 54.6 |
| 114                     | 53.7      | 56.1 | 63.1 | 61.4 | 63.3 | 63.9 | 71.6 | 73.4 | 72.3 |
| 115                     | 54.0      | 54.6 | 54.2 | 61.9 | 56.8 | 57.8 | 62.9 | 66.2 | 66.5 |
| 116                     | 52.3      | 52.7 | 54.9 | 57.4 | 59.3 | 60.3 | 60.5 | 59.3 | 57.1 |
| 117                     | 44.8      | 49.3 | 53.1 | 53.9 | 55.6 | 54.7 | 58.5 | 57.8 | 60.6 |
| 118                     | 48.3      | 53.3 | 59.8 | 56.6 | 57.4 | 56.9 | 64.7 | 64.6 | 65.9 |
| 119                     | 48.6      | 50.4 | 53.5 | 54.6 | 54.9 | 57.7 | 57.5 | 59.4 | 62.6 |
| 120                     | 48.1      | 49.4 | 50.7 | 52.5 | 56.3 | 61.1 | 63.2 | 62.5 | 62.8 |

RCC STUDY NUMBER 857092  
A 084, WR 23081

BWG-IND - 16  
22-APR-05

**BODY WEIGHT GAIN (%)  
FEMALES**

**GROUP 4 (200 MG/KG)**

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|        | TREATMENT |
|--------|-----------|
| DAYS   | 108       |
| WEEKS  | 16        |
| ANIMAL |           |

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|     |      |
|-----|------|
| 106 | 60.6 |
| 107 | 76.2 |
| 108 | 72.9 |
| 109 | 65.0 |
| 110 | 61.9 |
| 111 | 61.6 |
| 112 | 75.4 |
| 113 | 56.7 |
| 114 | 76.5 |
| 115 | 67.2 |
| 116 | 62.2 |
| 117 | 60.3 |
| 118 | 68.0 |
| 119 | 63.7 |
| 120 | 67.1 |

**OPHTHALMOSCOPIC EXAMINATIONS  
MALES  
PRETEST**

**GROUP 1 (0 MG/KG)**

| ANIMAL | OBSERVATION                   | LOCATION |
|--------|-------------------------------|----------|
| 1      | NO ABNORMALITIES DETECTED     | BOTH     |
| 2      | NO ABNORMALITIES DETECTED     | BOTH     |
| 3      | NO ABNORMALITIES DETECTED     | BOTH     |
| 4      | PERSISTENT PUPILLARY MEMBRANE | LEFT     |
| 5      | NO ABNORMALITIES DETECTED     | BOTH     |
| 6      | NO ABNORMALITIES DETECTED     | BOTH     |
| 7      | NO ABNORMALITIES DETECTED     | BOTH     |
| 8      | NO ABNORMALITIES DETECTED     | BOTH     |
| 9      | NO ABNORMALITIES DETECTED     | BOTH     |
| 10     | NO ABNORMALITIES DETECTED     | BOTH     |

**GROUP 2 (15 MG/KG)**

| ANIMAL | OBSERVATION               | LOCATION |
|--------|---------------------------|----------|
| 16     | NO ABNORMALITIES DETECTED | BOTH     |
| 17     | NO ABNORMALITIES DETECTED | BOTH     |
| 18     | NO ABNORMALITIES DETECTED | BOTH     |
| 19     | CORNEAL OPACITY           | LEFT     |
| 20     | NO ABNORMALITIES DETECTED | BOTH     |
| 21     | NO ABNORMALITIES DETECTED | BOTH     |
| 22     | NO ABNORMALITIES DETECTED | BOTH     |
| 23     | NO ABNORMALITIES DETECTED | BOTH     |
| 24     | NO ABNORMALITIES DETECTED | BOTH     |
| 25     | NO ABNORMALITIES DETECTED | BOTH     |

**GROUP 3 (50 MG/KG)**

| ANIMAL | OBSERVATION                   | LOCATION |
|--------|-------------------------------|----------|
| 31     | PERSISTENT PUPILLARY MEMBRANE | LEFT     |
| 32     | NO ABNORMALITIES DETECTED     | BOTH     |
| 33     | NO ABNORMALITIES DETECTED     | BOTH     |
| 34     | NO ABNORMALITIES DETECTED     | BOTH     |
| 35     | NO ABNORMALITIES DETECTED     | BOTH     |
| 36     | NO ABNORMALITIES DETECTED     | BOTH     |
| 37     | NO ABNORMALITIES DETECTED     | BOTH     |
| 38     | NO ABNORMALITIES DETECTED     | BOTH     |
| 39     | NO ABNORMALITIES DETECTED     | BOTH     |
| 40     | NO ABNORMALITIES DETECTED     | BOTH     |

**GROUP 4 (200 MG/KG)**

| ANIMAL | OBSERVATION               | LOCATION |
|--------|---------------------------|----------|
| 46     | NO ABNORMALITIES DETECTED | BOTH     |
| 47     | NO ABNORMALITIES DETECTED | BOTH     |
| 48     | NO ABNORMALITIES DETECTED | BOTH     |
| 49     | NO ABNORMALITIES DETECTED | BOTH     |
| 50     | NO ABNORMALITIES DETECTED | BOTH     |
| 51     | NO ABNORMALITIES DETECTED | BOTH     |
| 52     | NO ABNORMALITIES DETECTED | BOTH     |
| 53     | NO ABNORMALITIES DETECTED | BOTH     |
| 54     | NO ABNORMALITIES DETECTED | BOTH     |
| 55     | NO ABNORMALITIES DETECTED | BOTH     |

**OPHTHALMOSCOPIC EXAMINATIONS  
MALES  
AFTER 13 WEEKS**

**GROUP 1 (0 MG/KG)**

| <b>ANIMAL</b> | <b>OBSERVATION</b>            | <b>LOCATION</b> |
|---------------|-------------------------------|-----------------|
| 1             | NO ABNORMALITIES DETECTED     | BOTH            |
| 2             | NO ABNORMALITIES DETECTED     | BOTH            |
| 3             | NO ABNORMALITIES DETECTED     | BOTH            |
| 4             | PERSISTENT PUPILLARY MEMBRANE | LEFT            |
| 5             | NO ABNORMALITIES DETECTED     | BOTH            |
| 6             | NO ABNORMALITIES DETECTED     | BOTH            |
| 7             | NO ABNORMALITIES DETECTED     | BOTH            |
| 8             | NO ABNORMALITIES DETECTED     | BOTH            |
| 9             | NO ABNORMALITIES DETECTED     | BOTH            |
| 10            | NO ABNORMALITIES DETECTED     | BOTH            |

**GROUP 4 (200 MG/KG)**

| <b>ANIMAL</b> | <b>OBSERVATION</b>        | <b>LOCATION</b> |
|---------------|---------------------------|-----------------|
| 46            | NO ABNORMALITIES DETECTED | BOTH            |
| 47            | NO ABNORMALITIES DETECTED | BOTH            |
| 48            | NO ABNORMALITIES DETECTED | BOTH            |
| 49            | NO ABNORMALITIES DETECTED | BOTH            |
| 50            | NO ABNORMALITIES DETECTED | BOTH            |
| 51            | NO ABNORMALITIES DETECTED | BOTH            |
| 52            | NO ABNORMALITIES DETECTED | BOTH            |
| 53            | NO ABNORMALITIES DETECTED | BOTH            |
| 54            | NO ABNORMALITIES DETECTED | BOTH            |
| 55            | NO ABNORMALITIES DETECTED | BOTH            |



**OPHTHALMOSCOPIC EXAMINATIONS  
FEMALES  
PRETEST**

**GROUP 1 (0 MG/KG)**

| ANIMAL | OBSERVATION               | LOCATION |
|--------|---------------------------|----------|
| 61     | NO ABNORMALITIES DETECTED | BOTH     |
| 62     | NO ABNORMALITIES DETECTED | BOTH     |
| 63     | NO ABNORMALITIES DETECTED | BOTH     |
| 64     | NO ABNORMALITIES DETECTED | BOTH     |
| 65     | NO ABNORMALITIES DETECTED | BOTH     |
| 66     | NO ABNORMALITIES DETECTED | BOTH     |
| 67     | NO ABNORMALITIES DETECTED | BOTH     |
| 68     | NO ABNORMALITIES DETECTED | BOTH     |
| 69     | NO ABNORMALITIES DETECTED | BOTH     |
| 70     | NO ABNORMALITIES DETECTED | BOTH     |

**GROUP 2 (15 MG/KG)**

| ANIMAL | OBSERVATION               | LOCATION |
|--------|---------------------------|----------|
| 76     | NO ABNORMALITIES DETECTED | BOTH     |
| 77     | NO ABNORMALITIES DETECTED | BOTH     |
| 78     | NO ABNORMALITIES DETECTED | BOTH     |
| 79     | NO ABNORMALITIES DETECTED | BOTH     |
| 80     | NO ABNORMALITIES DETECTED | BOTH     |
| 81     | NO ABNORMALITIES DETECTED | BOTH     |
| 82     | NO ABNORMALITIES DETECTED | BOTH     |
| 83     | NO ABNORMALITIES DETECTED | BOTH     |
| 84     | NO ABNORMALITIES DETECTED | BOTH     |
| 85     | NO ABNORMALITIES DETECTED | BOTH     |

**GROUP 3 (50 MG/KG)**

| ANIMAL | OBSERVATION               | LOCATION |
|--------|---------------------------|----------|
| 91     | NO ABNORMALITIES DETECTED | BOTH     |
| 92     | NO ABNORMALITIES DETECTED | BOTH     |
| 93     | NO ABNORMALITIES DETECTED | BOTH     |
| 94     | NO ABNORMALITIES DETECTED | BOTH     |
| 95     | NO ABNORMALITIES DETECTED | BOTH     |
| 96     | NO ABNORMALITIES DETECTED | BOTH     |
| 97     | NO ABNORMALITIES DETECTED | BOTH     |
| 98     | NO ABNORMALITIES DETECTED | BOTH     |
| 99     | NO ABNORMALITIES DETECTED | BOTH     |
| 100    | NO ABNORMALITIES DETECTED | BOTH     |

**GROUP 4 (200 MG/KG)**

| ANIMAL | OBSERVATION               | LOCATION |
|--------|---------------------------|----------|
| 106    | NO ABNORMALITIES DETECTED | BOTH     |
| 107    | NO ABNORMALITIES DETECTED | BOTH     |
| 108    | CORNEAL OPACITY           | LEFT     |
| 109    | NO ABNORMALITIES DETECTED | BOTH     |
| 110    | NO ABNORMALITIES DETECTED | BOTH     |
| 111    | NO ABNORMALITIES DETECTED | BOTH     |
| 112    | NO ABNORMALITIES DETECTED | BOTH     |
| 113    | NO ABNORMALITIES DETECTED | BOTH     |
| 114    | NO ABNORMALITIES DETECTED | BOTH     |
| 115    | NO ABNORMALITIES DETECTED | BOTH     |

**OPHTHALMOSCOPIC EXAMINATIONS  
FEMALES  
AFTER 13 WEEKS**

**GROUP 1 (0 MG/KG)**

| ANIMAL | OBSERVATION               | LOCATION |
|--------|---------------------------|----------|
| 61     | NO ABNORMALITIES DETECTED | BOTH     |
| 62     | NO ABNORMALITIES DETECTED | BOTH     |
| 63     | NO ABNORMALITIES DETECTED | BOTH     |
| 64     | NO ABNORMALITIES DETECTED | BOTH     |
| 65     | NO ABNORMALITIES DETECTED | BOTH     |
| 66     | NO ABNORMALITIES DETECTED | BOTH     |
| 67     | NO ABNORMALITIES DETECTED | BOTH     |
| 68     | NO ABNORMALITIES DETECTED | BOTH     |
| 69     | NO ABNORMALITIES DETECTED | BOTH     |
| 70     | IRIS COLOBOMA             | RIGHT    |

**GROUP 4 (200 MG/KG)**

| ANIMAL | OBSERVATION               | LOCATION |
|--------|---------------------------|----------|
| 106    | NO ABNORMALITIES DETECTED | BOTH     |
| 107    | NO ABNORMALITIES DETECTED | BOTH     |
| 108    | NO ABNORMALITIES DETECTED | BOTH     |
| 109    | NO ABNORMALITIES DETECTED | BOTH     |
| 110    | NO ABNORMALITIES DETECTED | BOTH     |
| 111    | NO ABNORMALITIES DETECTED | BOTH     |
| 112    | NO ABNORMALITIES DETECTED | BOTH     |
| 113    | NO ABNORMALITIES DETECTED | BOTH     |
| 114    | NO ABNORMALITIES DETECTED | BOTH     |
| 115    | NO ABNORMALITIES DETECTED | BOTH     |

**MACROSCOPICAL FINDINGS**

**MALES  
GROUP 1 (0 MG/KG)**

ANIMAL 1 (SCHEDULED NECROPSY, 17-FEB-2005)

---

MANDIBULAR L.NODE... FOCUS/FOCI, D=1 MM, ISOLATED, DARK RED.

ANIMAL 2 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 3 (SCHEDULED NECROPSY, 17-FEB-2005)

---

KIDNEYS..... LEFT SIDE: PELVIC DILATION.

ANIMAL 4 (SCHEDULED NECROPSY, 17-FEB-2005)

---

EX. LACRIMAL GLANDS. BOTH SIDES: FOCUS/FOCI, D=1 MM, SEVERAL, GRAY WHITE.

ANIMAL 5 (SCHEDULED NECROPSY, 17-FEB-2005)

---

LUNGS..... LEFT LOBE: FOCUS/FOCI, D=2 MM, ISOLATED, REDDISH.

ANIMAL 6 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 7 (SCHEDULED NECROPSY, 17-FEB-2005)

---

KIDNEYS..... RIGHT SIDE: PELVIC DILATION.  
SEMINAL VESICLES.... BOTH SIDES: FOCUS/FOCI, D=1 MM, ISOLATED, DARK RED.

ANIMAL 8 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 9 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 10 (SCHEDULED NECROPSY, 17-FEB-2005)

---

STOMACH..... MUCOSA, FUNDUS: FOCUS/FOCI, D=4 MM, REDDISH.

MACROSCOPICAL FINDINGS

MALES  
GROUP 1 (0 MG/KG)

ANIMAL 11 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 12 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 13 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 14 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 15 (SCHEDULED NECROPSY, 16-FEB-2005)

---

KIDNEYS..... LEFT SIDE: PELVIC DILATION.

### MACROSCOPICAL FINDINGS

#### MALES GROUP 2 (15 MG/KG)

ANIMAL 16 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 17 (SCHEDULED NECROPSY, 17-FEB-2005)

---

TESTES..... BOTH SIDES: REDUCED IN SIZE, D-17X10 MM.

ANIMAL 18 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 19 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 20 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 21 (SCHEDULED NECROPSY, 17-FEB-2005)

---

KIDNEYS..... LEFT SIDE: PELVIC DILATION.  
SKIN..... NOSE REGION, RIGHT SIDE: ESCHAR(S), D-3 MM.

ANIMAL 22 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 23 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 24 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 25 (SCHEDULED NECROPSY, 17-FEB-2005)

---

KIDNEYS..... LEFT SIDE: PELVIC DILATION.

**MACROSCOPICAL FINDINGS**

**MALES  
GROUP 2 (15 MG/KG)**

ANIMAL 26 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 27 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 28 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 29 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 30 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS**

**MALES  
GROUP 3 (50 MG/KG)**

ANIMAL 31 (SCHEDULED NECROPSY, 17-FEB-2005)

---

PANCREAS..... DISCOLORATION, DARK RED.  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 32 (SCHEDULED NECROPSY, 17-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 33 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 34 (SCHEDULED NECROPSY, 17-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 35 (SCHEDULED NECROPSY, 17-FEB-2005)

---

KIDNEYS..... LEFT SIDE: PELVIC DILATION.  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 36 (SCHEDULED NECROPSY, 17-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 37 (SCHEDULED NECROPSY, 17-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 38 (SCHEDULED NECROPSY, 17-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 39 (SCHEDULED NECROPSY, 17-FEB-2005)

---

STOMACH..... MUCOSA, FUNDUS: FOCUS/FOCI, D=3 MM, ISOLATED, DARK RED.  
SEMINAL VESICLES.... BOTH SIDES: FOCUS/FOCI, D=1 MM, SEVERAL, DARK RED.  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, ISOLATED, DARK RED.

## MACROSCOPICAL FINDINGS

### MALES GROUP 3 (50 MG/KG)

ANIMAL 40 (SCHEDULED NECROPSY, 17-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 41 (SCHEDULED NECROPSY, 16-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 42 (SCHEDULED NECROPSY, 16-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 43 (SCHEDULED NECROPSY, 16-FEB-2005)

---

SEMINAL VESICLES.... BOTH SIDES: FOCUS/FOCI, ISOLATED, D=1 MM, REDDISH.

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 44 (SCHEDULED NECROPSY, 16-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 45 (SCHEDULED NECROPSY, 16-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.



## MACROSCOPICAL FINDINGS

### MALES GROUP 4 (200 MG/KG)

ANIMAL 46 (SCHEDULED NECROPSY, 17-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 47 (SCHEDULED NECROPSY, 17-FEB-2005)

---

KIDNEYS..... LEFT SIDE: PELVIC DILATION.  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 48 (SCHEDULED NECROPSY, 17-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 49 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 50 (SCHEDULED NECROPSY, 17-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 51 (SCHEDULED NECROPSY, 17-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 52 (SCHEDULED NECROPSY, 17-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 53 (SCHEDULED NECROPSY, 17-FEB-2005)

---

STOMACH..... MUCOSA, FUNDUS: FOCUS/FOCI, D=4 MM, ISOLATED, DARK RED.  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.  
THYMUS..... FOCUS/FOCI, D=2 MM, SEVERAL, DARK RED.

ANIMAL 54 (SCHEDULED NECROPSY, 17-FEB-2005)

---

STOMACH..... MUCOSA, FUNDUS: FOCUS/FOCI, D=2 MM, ISOLATED, REDDISH.  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

**MACROSCOPICAL FINDINGS**

**MALES  
GROUP 4 (200 MG/KG)**

ANIMAL 55 (SCHEDULED NECROPSY, 17-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 56 (SCHEDULED NECROPSY, 16-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 57 (SCHEDULED NECROPSY, 16-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 58 (SCHEDULED NECROPSY, 16-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 59 (SCHEDULED NECROPSY, 16-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 60 (SCHEDULED NECROPSY, 16-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

**MACROSCOPICAL FINDINGS**

**FEMALES  
GROUP 1 (0 MG/KG)**

ANIMAL 61 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 62 (SCHEDULED NECROPSY, 18-FEB-2005)

---

LUNGS..... FOCUS/FOCI, D=2 MM, SEVERAL, GRAY WHITE.

ANIMAL 63 (SCHEDULED NECROPSY, 18-FEB-2005)

---

UTERUS..... RIGHT HORN: DISCOLORATION, DARK RED.

ANIMAL 64 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 65 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 66 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 67 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 68 (SCHEDULED NECROPSY, 18-FEB-2005)

---

LUNGS..... DISCOLORATION, REDDISH.

ANIMAL 69 (SCHEDULED NECROPSY, 18-FEB-2005)

---

LUNGS..... FOCUS/FOCI, D=4 MM, SEVERAL, GRAY WHITE.

ANIMAL 70 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 71 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

## MACROSCOPICAL FINDINGS

### FEMALES GROUP 1 (0 MG/KG)

ANIMAL 72 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 73 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 74 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 75 (SCHEDULED NECROPSY, 16-FEB-2005)

---

OVARIES..... BOTH SIDES: DISCOLORATION, DARK RED.  
UTERUS..... BOTH HORNS: DILATION, D=5 MM, CONTAINS WATERY FLUID.

**MACROSCOPICAL FINDINGS**

**FEMALES  
GROUP 2 (15 MG/KG)**

ANIMAL 76 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 77 (SCHEDULED NECROPSY, 18-FEB-2005)

---

UTERUS..... BOTH HORNS: DILATION, D=5 MM.

ANIMAL 78 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 79 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 80 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 81 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 82 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 83 (SCHEDULED NECROPSY, 18-FEB-2005)

---

UTERUS..... BOTH HORNS: DILATION, D=5 MM.

ANIMAL 84 (SCHEDULED NECROPSY, 18-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 85 (SCHEDULED NECROPSY, 18-FEB-2005)

---

LUNGS..... FOCUS/FOCI, D=4 MM, SEVERAL, GRAY WHITE.

ANIMAL 86 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS**

**FEMALES  
GROUP 2 (15 MG/KG)**

ANIMAL 87 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 88 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 89 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 90 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS**

**FEMALES  
GROUP 3 (50 MG/KG)**

ANIMAL 91 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

ANIMAL 92 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

ANIMAL 93 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

ANIMAL 94 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

ANIMAL 95 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
UTERUS..... BOTH HORNS: CONTAINS WATERY FLUID, D=10X5 MM.

ANIMAL 96 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
NO FINDINGS NOTED

ANIMAL 97 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

ANIMAL 98 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
NO FINDINGS NOTED

ANIMAL 99 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

ANIMAL 100 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
UTERUS..... BOTH HORNS: DISCOLORATION, DARK RED.  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

**MACROSCOPICAL FINDINGS**

**FEMALES  
GROUP 3 (50 MG/KG)**

ANIMAL 101 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 102 (SCHEDULED NECROPSY, 16-FEB-2005)

---

OVARIES..... LEFT SIDE: DISCOLORATION, DARK RED.  
UTERUS..... BOTH HORNS: DILATION, D-5 MM, CONTAINS WATERY FLUID.

ANIMAL 103 (SCHEDULED NECROPSY, 16-FEB-2005)

---

UTERUS..... BOTH HORNS: DILATION, D-8 MM, CONTAINS WATERY FLUID.

ANIMAL 104 (SCHEDULED NECROPSY, 16-FEB-2005)

---

UTERUS..... BOTH HORNS: DILATION, D-5 MM, CONTAINS WATERY FLUID.

ANIMAL 105 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED



## MACROSCOPICAL FINDINGS

### FEMALES GROUP 4 (200 MG/KG)

ANIMAL 106 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

ANIMAL 107 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

ANIMAL 108 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

ANIMAL 109 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
OVARIES..... RIGHT SIDE: WATERY CYST, D=10 MM.  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

ANIMAL 110 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

ANIMAL 111 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
UTERUS..... BOTH HORNS: DILATION, D=5 MM, CONTAINS FLUID.  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 112 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, DARK RED.

ANIMAL 113 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 114 (SCHEDULED NECROPSY, 18-FEB-2005)  
-----  
CAECUM..... MUCOSA: FOCUS/FOCI, D=20 MM, DARK RED.  
OVARIES..... LEFT SIDE: WATERY CYST, D=10 MM.  
THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

## MACROSCOPICAL FINDINGS

### FEMALES GROUP 4 (200 MG/KG)

ANIMAL 115 (SCHEDULED NECROPSY, 18-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 116 (SCHEDULED NECROPSY, 16-FEB-2005)

---

UTERUS..... BOTH HORNS: DILATION, D=5 MM, CONTAINS WATERY FLUID.

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

SKIN..... SHOULDER: ALOPECIA, ISOLATED, D=20 MM, SLIGHT.

ANIMAL 117 (SCHEDULED NECROPSY, 16-FEB-2005)

---

NO FINDINGS NOTED

ANIMAL 118 (SCHEDULED NECROPSY, 16-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

ANIMAL 119 (SCHEDULED NECROPSY, 16-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

SKIN..... SHOULDER: ALOPECIA, D=10 MM, SLIGHT.

ANIMAL 120 (SCHEDULED NECROPSY, 16-FEB-2005)

---

THYROID GLAND..... BOTH SIDES: DISCOLORATION, BLACK.

SKIN..... SHOULDER: ALOPECIA, ISOLATED, D=10 MM, SLIGHT.

**ORGAN WEIGHTS (GRAM)  
 AFTER 14 WEEKS  
 MALES**

**GROUP 1 (0 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 1             | 466.86  | 2.30  | 1.382 | 0.032    | 11.65 | 0.39   | 3.10    | 0.065    |
| 2             | 391.05  | 2.15  | 1.002 | 0.021    | 9.64  | 0.30   | 2.21    | 0.053    |
| 3             | 408.85  | 2.06  | 1.029 | 0.021    | 11.30 | 0.24   | 2.44    | 0.068    |
| 4             | 428.70  | 2.12  | 1.178 | 0.030    | 11.94 | 0.36   | 2.56    | 0.071    |
| 5             | 387.01  | 2.18  | 1.108 | 0.026    | 9.28  | 0.37   | 2.36    | 0.054    |
| 6             | 399.27  | 2.13  | 1.114 | 0.023    | 9.99  | 0.37   | 2.32    | 0.073    |
| 7             | 462.54  | 2.16  | 1.394 | 0.032    | 12.37 | 0.33   | 2.99    | 0.064    |
| 8             | 442.57  | 2.03  | 1.123 | 0.031    | 9.89  | 0.42   | 2.27    | 0.056    |
| 9             | 377.31  | 2.06  | 1.126 | 0.031    | 9.20  | 0.27   | 2.11    | 0.063    |
| 10            | 411.56  | 2.29  | 1.195 | 0.034    | 9.99  | 0.22   | 2.10    | 0.054    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYMIUM |
|---------------|--------|--------|-------------|
| 1             | 0.792  | 4.21   | 1.687       |
| 2             | 0.792  | 3.78   | 1.484       |
| 3             | 0.695  | 3.28   | 1.328       |
| 4             | 1.066  | 3.92   | 1.561       |
| 5             | 1.054  | 3.98   | 1.548       |
| 6             | 0.778  | 3.66   | 1.493       |
| 7             | 0.944  | 4.14   | 1.544       |
| 8             | 0.856  | 3.44   | 1.362       |
| 9             | 0.709  | 4.09   | 1.552       |
| 10            | 1.000  | 3.84   | 1.811       |

**GROUP 2 (15 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 16            | 422.79  | 2.09  | 1.107 | 0.027    | 10.00 | 0.29   | 2.57    | 0.050    |
| 17            | 386.89  | 2.11  | 1.259 | 0.025    | 10.30 | 0.18   | 2.54    | 0.059    |
| 18            | 407.61  | 2.10  | 1.090 | 0.028    | 9.44  | 0.27   | 2.15    | 0.052    |
| 19            | 370.24  | 2.18  | 1.092 | 0.039    | 9.66  | 0.29   | 2.27    | 0.071    |
| 20            | 427.88  | 2.07  | 1.257 | 0.023    | 10.94 | 0.39   | 2.34    | 0.068    |
| 21            | 400.12  | 1.99  | 1.164 | 0.030    | 8.72  | 0.32   | 2.08    | 0.062    |
| 22            | 424.97  | 2.13  | 1.163 | 0.042    | 10.54 | 0.37   | 2.21    | 0.068    |
| 23            | 425.22  | 2.00  | 1.066 | 0.022    | 10.03 | 0.24   | 2.13    | 0.050    |
| 24            | 377.99  | 2.18  | 1.102 | 0.026    | 9.28  | 0.28   | 2.28    | 0.054    |
| 25            | 428.80  | 2.22  | 1.152 | 0.024    | 11.18 | 0.26   | 2.53    | 0.067    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYMIUM |
|---------------|--------|--------|-------------|
| 16            | 0.807  | 3.43   | 1.361       |
| 17            | 0.779  | 2.23   | 1.516       |
| 18            | 0.703  | 4.65   | 1.761       |
| 19            | 0.847  | 3.60   | 1.265       |
| 20            | 0.941  | 3.71   | 1.470       |
| 21            | 0.844  | 3.61   | 1.543       |
| 22            | 0.934  | 3.33   | 1.355       |
| 23            | 0.645  | 3.90   | 1.522       |
| 24            | 0.826  | 3.63   | 1.445       |
| 25            | 0.900  | 4.25   | 1.788       |

**ORGAN WEIGHTS (GRAM)  
 AFTER 14 WEEKS  
 MALES**

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 31            | 356.76  | 2.09  | 1.015 | 0.022    | 8.74  | 0.24   | 2.17    | 0.056    |
| 32            | 419.16  | 2.19  | 1.132 | 0.029    | 10.68 | 0.37   | 2.53    | 0.066    |
| 33            | 386.28  | 2.09  | 1.050 | 0.025    | 10.26 | 0.29   | 2.21    | 0.066    |
| 34            | 421.62  | 2.13  | 1.104 | 0.029    | 11.09 | 0.23   | 2.52    | 0.069    |
| 35            | 378.40  | 2.03  | 1.025 | 0.032    | 8.63  | 0.46   | 2.09    | 0.061    |
| 36            | 416.29  | 2.15  | 1.058 | 0.022    | 9.71  | 0.25   | 2.17    | 0.060    |
| 37            | 436.70  | 2.06  | 0.977 | 0.031    | 10.05 | 0.24   | 2.14    | 0.059    |
| 38            | 417.51  | 2.05  | 1.121 | 0.028    | 10.24 | 0.35   | 2.08    | 0.056    |
| 39            | 432.24  | 2.21  | 1.186 | 0.026    | 11.63 | 0.29   | 2.38    | 0.053    |
| 40            | 396.55  | 2.10  | 1.040 | 0.025    | 8.95  | 0.24   | 2.25    | 0.051    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYMI |
|---------------|--------|--------|-----------|
| 31            | 0.853  | 3.96   | 1.399     |
| 32            | 0.924  | 3.60   | 1.563     |
| 33            | 0.791  | 3.95   | 1.422     |
| 34            | 1.015  | 3.73   | 1.683     |
| 35            | 0.712  | 3.68   | 1.414     |
| 36            | 1.098  | 3.76   | 1.615     |
| 37            | 0.782  | 4.48   | 1.699     |
| 38            | 0.915  | 3.75   | 1.330     |
| 39            | 0.900  | 4.03   | 1.516     |
| 40            | 0.886  | 3.89   | 1.394     |

**GROUP 4 (200 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 46            | 386.07  | 2.06  | 1.065 | 0.034    | 9.31  | 0.23   | 2.27    | 0.060    |
| 47            | 395.13  | 2.12  | 1.155 | 0.026    | 11.23 | 0.28   | 2.48    | 0.051    |
| 48            | 452.99  | 2.25  | 1.329 | 0.036    | 13.05 | 0.28   | 2.78    | 0.065    |
| 49            | 389.82  | 2.13  | 0.968 | 0.033    | 10.86 | 0.26   | 2.15    | 0.067    |
| 50            | 414.09  | 1.99  | 1.139 | 0.023    | 10.96 | 0.33   | 2.32    | 0.061    |
| 51            | 394.84  | 2.09  | 0.975 | 0.027    | 9.43  | 0.41   | 2.04    | 0.066    |
| 52            | 436.38  | 2.21  | 1.249 | 0.033    | 11.85 | 0.28   | 2.64    | 0.068    |
| 53            | 478.14  | 2.21  | 1.248 | 0.042    | 12.80 | 0.28   | 2.61    | 0.048    |
| 54            | 391.08  | 2.05  | 1.000 | 0.024    | 9.37  | 0.40   | 2.27    | 0.055    |
| 55            | 365.79  | 2.14  | 0.960 | 0.026    | 10.68 | 0.31   | 2.30    | 0.059    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYMI |
|---------------|--------|--------|-----------|
| 46            | 0.739  | 3.76   | 1.309     |
| 47            | 0.806  | 3.38   | 1.427     |
| 48            | 0.981  | 3.97   | 1.640     |
| 49            | 1.038  | 3.11   | 1.306     |
| 50            | 1.015  | 4.00   | 1.621     |
| 51            | 0.669  | 3.77   | 1.448     |
| 52            | 0.918  | 4.51   | 1.785     |
| 53            | 0.944  | 3.94   | 1.693     |
| 54            | 0.734  | 3.75   | 1.665     |
| 55            | 0.926  | 3.95   | 1.398     |

**ORGAN/BODY WEIGHT RATIOS (%)  
 AFTER 14 WEEKS  
 MALES**

**GROUP 1 (0 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 1             | 466.86         | 0.49  | 0.296 | 0.007    | 2.50  | 0.08   | 0.66    | 0.014    |
| 2             | 391.05         | 0.55  | 0.256 | 0.005    | 2.46  | 0.08   | 0.57    | 0.014    |
| 3             | 408.85         | 0.50  | 0.252 | 0.005    | 2.76  | 0.06   | 0.60    | 0.017    |
| 4             | 428.70         | 0.49  | 0.275 | 0.007    | 2.78  | 0.08   | 0.60    | 0.016    |
| 5             | 387.01         | 0.56  | 0.286 | 0.007    | 2.40  | 0.09   | 0.61    | 0.014    |
| 6             | 399.27         | 0.53  | 0.279 | 0.006    | 2.50  | 0.09   | 0.58    | 0.018    |
| 7             | 462.54         | 0.47  | 0.301 | 0.007    | 2.67  | 0.07   | 0.65    | 0.014    |
| 8             | 442.57         | 0.46  | 0.254 | 0.007    | 2.24  | 0.09   | 0.51    | 0.013    |
| 9             | 377.31         | 0.55  | 0.298 | 0.008    | 2.44  | 0.07   | 0.56    | 0.017    |
| 10            | 411.56         | 0.56  | 0.290 | 0.008    | 2.43  | 0.05   | 0.51    | 0.013    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYMI |
|---------------|--------|--------|-----------|
| 1             | 0.170  | 0.90   | 0.361     |
| 2             | 0.203  | 0.97   | 0.379     |
| 3             | 0.170  | 0.80   | 0.325     |
| 4             | 0.249  | 0.91   | 0.364     |
| 5             | 0.272  | 1.03   | 0.400     |
| 6             | 0.195  | 0.92   | 0.374     |
| 7             | 0.204  | 0.89   | 0.334     |
| 8             | 0.194  | 0.78   | 0.308     |
| 9             | 0.188  | 1.08   | 0.411     |
| 10            | 0.243  | 0.93   | 0.440     |

**GROUP 2 (15 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 16            | 422.79         | 0.49  | 0.262 | 0.006    | 2.37  | 0.07   | 0.61    | 0.012    |
| 17            | 386.89         | 0.54  | 0.325 | 0.007    | 2.66  | 0.05   | 0.66    | 0.015    |
| 18            | 407.61         | 0.51  | 0.267 | 0.007    | 2.32  | 0.07   | 0.53    | 0.013    |
| 19            | 370.24         | 0.59  | 0.295 | 0.010    | 2.61  | 0.08   | 0.61    | 0.019    |
| 20            | 427.88         | 0.48  | 0.294 | 0.005    | 2.56  | 0.09   | 0.55    | 0.016    |
| 21            | 400.12         | 0.50  | 0.291 | 0.007    | 2.18  | 0.08   | 0.52    | 0.016    |
| 22            | 424.97         | 0.50  | 0.274 | 0.010    | 2.48  | 0.09   | 0.52    | 0.016    |
| 23            | 425.22         | 0.47  | 0.251 | 0.005    | 2.36  | 0.06   | 0.50    | 0.012    |
| 24            | 377.99         | 0.58  | 0.291 | 0.007    | 2.45  | 0.08   | 0.60    | 0.014    |
| 25            | 428.80         | 0.52  | 0.269 | 0.006    | 2.61  | 0.06   | 0.59    | 0.016    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYMI |
|---------------|--------|--------|-----------|
| 16            | 0.191  | 0.81   | 0.322     |
| 17            | 0.201  | 0.58   | 0.392     |
| 18            | 0.173  | 1.14   | 0.432     |
| 19            | 0.229  | 0.97   | 0.342     |
| 20            | 0.220  | 0.87   | 0.343     |
| 21            | 0.211  | 0.90   | 0.386     |
| 22            | 0.220  | 0.78   | 0.319     |
| 23            | 0.152  | 0.92   | 0.358     |
| 24            | 0.219  | 0.96   | 0.382     |
| 25            | 0.210  | 0.99   | 0.417     |

**ORGAN/BODY WEIGHT RATIOS (%)  
 AFTER 14 WEEKS  
 MALES**

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 31            | 356.76         | 0.59  | 0.285 | 0.006    | 2.45  | 0.07   | 0.61    | 0.016    |
| 32            | 419.16         | 0.52  | 0.270 | 0.007    | 2.55  | 0.09   | 0.60    | 0.016    |
| 33            | 386.28         | 0.54  | 0.272 | 0.006    | 2.66  | 0.07   | 0.57    | 0.017    |
| 34            | 421.62         | 0.51  | 0.262 | 0.007    | 2.63  | 0.05   | 0.60    | 0.016    |
| 35            | 378.40         | 0.54  | 0.271 | 0.008    | 2.28  | 0.12   | 0.55    | 0.016    |
| 36            | 416.29         | 0.52  | 0.254 | 0.005    | 2.33  | 0.06   | 0.52    | 0.014    |
| 37            | 436.70         | 0.47  | 0.224 | 0.007    | 2.30  | 0.06   | 0.49    | 0.013    |
| 38            | 417.51         | 0.49  | 0.268 | 0.007    | 2.45  | 0.08   | 0.50    | 0.013    |
| 39            | 432.24         | 0.51  | 0.274 | 0.006    | 2.69  | 0.07   | 0.55    | 0.012    |
| 40            | 396.55         | 0.53  | 0.262 | 0.006    | 2.26  | 0.06   | 0.57    | 0.013    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYMI |
|---------------|--------|--------|-----------|
| 31            | 0.239  | 1.11   | 0.392     |
| 32            | 0.220  | 0.86   | 0.373     |
| 33            | 0.205  | 1.02   | 0.368     |
| 34            | 0.241  | 0.89   | 0.399     |
| 35            | 0.188  | 0.97   | 0.374     |
| 36            | 0.264  | 0.90   | 0.388     |
| 37            | 0.179  | 1.02   | 0.389     |
| 38            | 0.219  | 0.90   | 0.319     |
| 39            | 0.208  | 0.93   | 0.351     |
| 40            | 0.223  | 0.98   | 0.351     |

**GROUP 4 (200 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 46            | 386.07         | 0.53  | 0.276 | 0.009    | 2.41  | 0.06   | 0.59    | 0.015    |
| 47            | 395.13         | 0.54  | 0.292 | 0.007    | 2.84  | 0.07   | 0.63    | 0.013    |
| 48            | 452.99         | 0.50  | 0.293 | 0.008    | 2.88  | 0.06   | 0.61    | 0.014    |
| 49            | 389.82         | 0.55  | 0.248 | 0.009    | 2.78  | 0.07   | 0.55    | 0.017    |
| 50            | 414.09         | 0.48  | 0.275 | 0.006    | 2.65  | 0.08   | 0.56    | 0.015    |
| 51            | 394.84         | 0.53  | 0.247 | 0.007    | 2.39  | 0.10   | 0.52    | 0.017    |
| 52            | 436.38         | 0.51  | 0.286 | 0.008    | 2.71  | 0.06   | 0.61    | 0.015    |
| 53            | 478.14         | 0.46  | 0.261 | 0.009    | 2.68  | 0.06   | 0.54    | 0.010    |
| 54            | 391.08         | 0.52  | 0.256 | 0.006    | 2.39  | 0.10   | 0.58    | 0.014    |
| 55            | 365.79         | 0.59  | 0.263 | 0.007    | 2.92  | 0.09   | 0.63    | 0.016    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYMI |
|---------------|--------|--------|-----------|
| 46            | 0.191  | 0.97   | 0.339     |
| 47            | 0.204  | 0.85   | 0.361     |
| 48            | 0.217  | 0.88   | 0.362     |
| 49            | 0.266  | 0.80   | 0.335     |
| 50            | 0.245  | 0.97   | 0.391     |
| 51            | 0.170  | 0.96   | 0.367     |
| 52            | 0.210  | 1.03   | 0.409     |
| 53            | 0.197  | 0.82   | 0.354     |
| 54            | 0.188  | 0.96   | 0.426     |
| 55            | 0.253  | 1.08   | 0.382     |

**ORGAN/BRAIN WEIGHT RATIOS (%)  
 AFTER 14 WEEKS  
 MALES**

**GROUP 1 (0 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 1             | 2.30         | 60.124 | 1.402    | 506.69 | 16.92  | 134.73  | 2.826    | 34.463 |
| 2             | 2.15         | 46.587 | 0.990    | 448.09 | 13.88  | 102.75  | 2.464    | 36.835 |
| 3             | 2.06         | 49.962 | 0.997    | 548.92 | 11.82  | 118.37  | 3.287    | 33.760 |
| 4             | 2.12         | 55.597 | 1.417    | 563.47 | 17.12  | 121.04  | 3.333    | 50.340 |
| 5             | 2.18         | 50.768 | 1.194    | 424.80 | 16.77  | 107.86  | 2.457    | 48.291 |
| 6             | 2.13         | 52.219 | 1.086    | 468.43 | 17.57  | 108.68  | 3.439    | 36.455 |
| 7             | 2.16         | 64.404 | 1.498    | 571.21 | 15.36  | 138.09  | 2.941    | 43.589 |
| 8             | 2.03         | 55.416 | 1.538    | 487.90 | 20.62  | 112.20  | 2.772    | 42.242 |
| 9             | 2.06         | 54.635 | 1.519    | 446.52 | 13.00  | 102.59  | 3.069    | 34.419 |
| 10            | 2.29         | 52.083 | 1.490    | 435.55 | 9.71   | 91.76   | 2.365    | 43.601 |

| ANIMAL NUMBER | TESTES | EPIDIDYIMID |
|---------------|--------|-------------|
| 1             | 183.20 | 73.368      |
| 2             | 175.56 | 68.992      |
| 3             | 159.37 | 64.486      |
| 4             | 184.99 | 73.666      |
| 5             | 182.40 | 70.903      |
| 6             | 171.82 | 69.986      |
| 7             | 191.19 | 71.297      |
| 8             | 169.48 | 67.172      |
| 9             | 198.46 | 75.317      |
| 10            | 167.56 | 78.936      |

**GROUP 2 (15 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 16            | 2.09         | 52.969 | 1.272    | 478.83 | 13.72  | 122.92  | 2.407    | 38.615 |
| 17            | 2.11         | 59.801 | 1.197    | 489.09 | 8.70   | 120.62  | 2.786    | 37.016 |
| 18            | 2.10         | 51.947 | 1.357    | 449.83 | 12.95  | 102.65  | 2.485    | 33.523 |
| 19            | 2.18         | 50.158 | 1.770    | 443.75 | 13.13  | 104.34  | 3.273    | 38.892 |
| 20            | 2.07         | 60.611 | 1.101    | 527.33 | 18.75  | 112.82  | 3.298    | 45.345 |
| 21            | 1.99         | 58.384 | 1.484    | 437.57 | 15.97  | 104.60  | 3.132    | 42.348 |
| 22            | 2.13         | 54.658 | 1.961    | 495.40 | 17.18  | 104.11  | 3.219    | 43.923 |
| 23            | 2.00         | 53.223 | 1.105    | 500.85 | 12.23  | 106.13  | 2.488    | 32.200 |
| 24            | 2.18         | 50.423 | 1.203    | 424.61 | 12.99  | 104.42  | 2.459    | 37.805 |
| 25            | 2.22         | 51.995 | 1.091    | 504.53 | 11.84  | 113.97  | 3.003    | 40.609 |

| ANIMAL NUMBER | TESTES | EPIDIDYIMID |
|---------------|--------|-------------|
| 16            | 163.93 | 65.142      |
| 17            | 105.96 | 72.011      |
| 18            | 221.68 | 83.904      |
| 19            | 165.23 | 58.116      |
| 20            | 179.04 | 70.840      |
| 21            | 181.02 | 77.399      |
| 22            | 156.53 | 63.721      |
| 23            | 194.98 | 75.996      |
| 24            | 165.93 | 66.162      |
| 25            | 191.56 | 80.695      |

**ORGAN/BRAIN WEIGHT RATIOS (%)  
 AFTER 14 WEEKS  
 MALES**

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 31            | 2.09         | 48.511 | 1.072    | 417.84 | 11.41  | 103.52  | 2.690    | 40.781 |
| 32            | 2.19         | 51.724 | 1.316    | 487.66 | 16.86  | 115.60  | 3.007    | 42.205 |
| 33            | 2.09         | 50.321 | 1.182    | 491.49 | 13.88  | 105.99  | 3.177    | 37.920 |
| 34            | 2.13         | 51.818 | 1.384    | 520.53 | 10.60  | 118.33  | 3.257    | 47.631 |
| 35            | 2.03         | 50.525 | 1.585    | 425.40 | 22.84  | 102.91  | 2.998    | 35.126 |
| 36            | 2.15         | 49.262 | 1.034    | 452.06 | 11.84  | 100.90  | 2.778    | 51.129 |
| 37            | 2.06         | 47.426 | 1.489    | 488.12 | 11.67  | 104.13  | 2.843    | 37.973 |
| 38            | 2.05         | 54.727 | 1.354    | 499.93 | 16.87  | 101.35  | 2.721    | 44.686 |
| 39            | 2.21         | 53.593 | 1.154    | 525.50 | 13.24  | 107.42  | 2.395    | 40.666 |
| 40            | 2.10         | 49.488 | 1.168    | 426.27 | 11.39  | 107.02  | 2.434    | 42.167 |

| ANIMAL NUMBER | TESTES | EPIDIDYDYMID |
|---------------|--------|--------------|
| 31            | 189.26 | 66.840       |
| 32            | 164.66 | 71.392       |
| 33            | 189.28 | 68.149       |
| 34            | 175.25 | 78.996       |
| 35            | 181.54 | 69.727       |
| 36            | 175.32 | 75.232       |
| 37            | 217.34 | 82.492       |
| 38            | 183.26 | 64.962       |
| 39            | 182.17 | 68.479       |
| 40            | 185.19 | 66.359       |

**GROUP 4 (200 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 46            | 2.06         | 51.778 | 1.632    | 452.65 | 11.08  | 110.17  | 2.907    | 35.930 |
| 47            | 2.12         | 54.396 | 1.216    | 528.59 | 13.03  | 116.57  | 2.385    | 37.933 |
| 48            | 2.25         | 59.057 | 1.581    | 579.66 | 12.42  | 123.41  | 2.887    | 43.598 |
| 49            | 2.13         | 45.374 | 1.556    | 508.99 | 12.10  | 100.61  | 3.148    | 48.661 |
| 50            | 1.99         | 57.158 | 1.167    | 549.64 | 16.75  | 116.52  | 3.044    | 50.904 |
| 51            | 2.09         | 46.645 | 1.287    | 451.50 | 19.49  | 97.39   | 3.157    | 32.032 |
| 52            | 2.21         | 56.459 | 1.497    | 535.68 | 12.78  | 119.57  | 3.057    | 41.506 |
| 53            | 2.21         | 56.386 | 1.889    | 578.27 | 12.57  | 117.67  | 2.190    | 42.624 |
| 54            | 2.05         | 48.764 | 1.156    | 456.55 | 19.59  | 110.60  | 2.691    | 35.786 |
| 55            | 2.14         | 44.867 | 1.203    | 498.78 | 14.56  | 107.64  | 2.776    | 43.284 |

| ANIMAL NUMBER | TESTES | EPIDIDYDYMID |
|---------------|--------|--------------|
| 46            | 182.98 | 63.649       |
| 47            | 159.07 | 67.177       |
| 48            | 176.21 | 72.870       |
| 49            | 145.82 | 61.254       |
| 50            | 200.53 | 81.317       |
| 51            | 180.56 | 69.279       |
| 52            | 203.81 | 80.725       |
| 53            | 177.76 | 76.464       |
| 54            | 182.75 | 81.142       |
| 55            | 184.74 | 65.323       |



**ORGAN WEIGHTS (GRAM)  
 AFTER 14 WEEKS  
 FEMALES**

**GROUP 1 (0 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 61            | 214.05  | 1.94  | 0.716 | 0.019    | 4.58  | 0.21   | 1.27    | 0.067    |
| 62            | 209.29  | 1.90  | 0.634 | 0.020    | 5.64  | 0.24   | 1.44    | 0.075    |
| 63            | 244.04  | 2.00  | 0.776 | 0.018    | 5.76  | 0.26   | 1.45    | 0.074    |
| 64            | 203.39  | 1.92  | 0.743 | 0.023    | 5.66  | 0.26   | 1.32    | 0.076    |
| 65            | 212.90  | 1.88  | 0.759 | 0.016    | 5.72  | 0.25   | 1.33    | 0.065    |
| 66            | 222.79  | 1.99  | 0.680 | 0.020    | 5.27  | 0.24   | 1.27    | 0.069    |
| 67            | 201.01  | 1.77  | 0.704 | 0.019    | 4.82  | 0.28   | 1.32    | 0.071    |
| 68            | 203.73  | 1.91  | 0.596 | 0.020    | 6.19  | 0.29   | 1.29    | 0.063    |
| 69            | 222.83  | 1.95  | 0.751 | 0.018    | 5.28  | 0.23   | 1.34    | 0.088    |
| 70            | 190.33  | 1.85  | 0.650 | 0.014    | 4.67  | 0.21   | 1.22    | 0.070    |

| ANIMAL NUMBER | SPLEEN | OVARIES | UTERUS |
|---------------|--------|---------|--------|
| 61            | 0.473  | 0.089   | 1.362  |
| 62            | 0.654  | 0.143   | 0.930  |
| 63            | 0.630  | 0.098   | 1.061  |
| 64            | 0.556  | 0.078   | 1.286  |
| 65            | 0.733  | 0.113   | 1.118  |
| 66            | 0.844  | 0.110   | 0.769  |
| 67            | 0.457  | 0.101   | 1.073  |
| 68            | 0.498  | 0.107   | 0.544  |
| 69            | 0.674  | 0.125   | 1.024  |
| 70            | 0.512  | 0.080   | 1.118  |

**GROUP 2 (15 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 76            | 199.69  | 1.83  | 0.790 | 0.018    | 5.20  | 0.23   | 1.23    | 0.075    |
| 77            | 213.93  | 1.90  | 0.732 | 0.030    | 5.11  | 0.31   | 1.40    | 0.078    |
| 78            | 191.35  | 1.86  | 0.621 | 0.016    | 5.63  | 0.18   | 1.26    | 0.066    |
| 79            | 213.25  | 1.84  | 0.712 | 0.024    | 5.30  | 0.18   | 1.34    | 0.073    |
| 80            | 215.36  | 1.84  | 0.604 | 0.020    | 5.27  | 0.19   | 1.20    | 0.057    |
| 81            | 219.57  | 1.96  | 0.658 | 0.019    | 5.57  | 0.19   | 1.31    | 0.071    |
| 82            | 215.52  | 2.00  | 0.777 | 0.016    | 5.31  | 0.24   | 1.33    | 0.067    |
| 83            | 232.72  | 2.04  | 0.801 | 0.021    | 5.64  | 0.20   | 1.28    | 0.073    |
| 84            | 219.48  | 1.87  | 0.627 | 0.019    | 5.31  | 0.22   | 1.22    | 0.062    |
| 85            | 201.38  | 1.78  | 0.595 | 0.020    | 4.76  | 0.24   | 1.22    | 0.060    |

| ANIMAL NUMBER | SPLEEN | OVARIES | UTERUS |
|---------------|--------|---------|--------|
| 76            | 0.565  | 0.102   | 1.255  |
| 77            | 0.551  | 0.127   | 1.875  |
| 78            | 0.586  | 0.097   | 0.930  |
| 79            | 0.526  | 0.074   | 0.948  |
| 80            | 0.633  | 0.086   | 0.627  |
| 81            | 0.660  | 0.104   | 1.019  |
| 82            | 0.605  | 0.080   | 0.880  |
| 83            | 0.492  | 0.119   | 1.532  |
| 84            | 0.535  | 0.097   | 0.906  |
| 85            | 0.470  | 0.100   | 0.854  |

**ORGAN WEIGHTS (GRAM)  
 AFTER 14 WEEKS  
 FEMALES**

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 91            | 212.18  | 1.97  | 0.707 | 0.018    | 5.55  | 0.23   | 1.47    | 0.058    |
| 92            | 222.77  | 1.96  | 0.672 | 0.017    | 5.25  | 0.25   | 1.39    | 0.063    |
| 93            | 220.64  | 1.93  | 0.716 | 0.026    | 5.44  | 0.20   | 1.34    | 0.066    |
| 94            | 206.71  | 1.81  | 0.730 | 0.020    | 5.28  | 0.26   | 1.37    | 0.066    |
| 95            | 182.06  | 1.81  | 0.690 | 0.017    | 5.41  | 0.22   | 1.31    | 0.076    |
| 96            | 225.27  | 1.94  | 0.715 | 0.020    | 5.60  | 0.22   | 1.33    | 0.060    |
| 97            | 210.94  | 1.86  | 0.774 | 0.016    | 5.24  | 0.30   | 1.40    | 0.067    |
| 98            | 219.90  | 1.81  | 0.613 | 0.023    | 5.18  | 0.23   | 1.27    | 0.070    |
| 99            | 217.88  | 1.98  | 0.700 | 0.017    | 4.72  | 0.27   | 1.25    | 0.059    |
| 100           | 224.34  | 1.99  | 0.771 | 0.020    | 5.86  | 0.20   | 1.51    | 0.083    |

| ANIMAL NUMBER | SPLEEN | OVARIES | UTERUS |
|---------------|--------|---------|--------|
| 91            | 0.524  | 0.102   | 1.210  |
| 92            | 0.660  | 0.084   | 1.157  |
| 93            | 0.704  | 0.100   | 0.772  |
| 94            | 0.514  | 0.104   | 0.914  |
| 95            | 0.588  | 0.109   | 1.494  |
| 96            | 0.554  | 0.114   | 0.840  |
| 97            | 0.579  | 0.102   | 0.800  |
| 98            | 0.617  | 0.100   | 0.871  |
| 99            | 0.477  | 0.072   | 0.941  |
| 100           | 0.572  | 0.149   | 1.164  |

**GROUP 4 (200 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 106           | 223.83  | 1.83  | 0.685 | 0.031    | 6.31  | 0.32   | 1.40    | 0.078    |
| 107           | 210.61  | 1.79  | 0.781 | 0.019    | 6.18  | 0.17   | 1.51    | 0.068    |
| 108           | 233.76  | 1.97  | 0.866 | 0.025    | 8.21  | 0.25   | 1.75    | 0.075    |
| 109           | 215.06  | 1.93  | 0.692 | 0.020    | 6.57  | 0.25   | 1.41    | 0.061    |
| 110           | 218.97  | 1.90  | 0.744 | 0.024    | 6.74  | 0.28   | 1.55    | 0.074    |
| 111           | 203.05  | 1.90  | 0.723 | 0.019    | 5.54  | 0.22   | 1.46    | 0.067    |
| 112           | 221.09  | 1.88  | 0.718 | 0.030    | 5.97  | 0.19   | 1.45    | 0.073    |
| 113           | 196.57  | 1.92  | 0.658 | 0.015    | 5.75  | 0.17   | 1.42    | 0.055    |
| 114           | 203.02  | 1.82  | 0.647 | 0.014    | 5.21  | 0.23   | 1.14    | 0.062    |
| 115           | 225.56  | 1.97  | 0.727 | 0.030    | 6.01  | 0.26   | 1.58    | 0.096    |

| ANIMAL NUMBER | SPLEEN | OVARIES | UTERUS |
|---------------|--------|---------|--------|
| 106           | 0.677  | 0.107   | 1.100  |
| 107           | 0.737  | 0.104   | 0.854  |
| 108           | 0.900  | 0.137   | 0.974  |
| 109           | 0.776  | 0.329   | 0.926  |
| 110           | 0.914  | 0.119   | 1.044  |
| 111           | 0.685  | 0.116   | 1.594  |
| 112           | 0.687  | 0.086   | 0.901  |
| 113           | 0.665  | 0.089   | 1.176  |
| 114           | 0.880  | 0.249   | 0.962  |
| 115           | 0.671  | 0.093   | 1.038  |

**ORGAN/BODY WEIGHT RATIOS (%)  
 AFTER 14 WEEKS  
 FEMALES**

**GROUP 1 (0 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 61            | 214.05         | 0.90  | 0.334 | 0.009    | 2.14  | 0.10   | 0.59    | 0.031    |
| 62            | 209.29         | 0.91  | 0.303 | 0.010    | 2.70  | 0.11   | 0.69    | 0.036    |
| 63            | 244.04         | 0.82  | 0.318 | 0.007    | 2.36  | 0.10   | 0.60    | 0.030    |
| 64            | 203.39         | 0.94  | 0.365 | 0.011    | 2.78  | 0.13   | 0.65    | 0.037    |
| 65            | 212.90         | 0.88  | 0.356 | 0.008    | 2.69  | 0.12   | 0.63    | 0.031    |
| 66            | 222.79         | 0.89  | 0.305 | 0.009    | 2.36  | 0.11   | 0.57    | 0.031    |
| 67            | 201.01         | 0.88  | 0.350 | 0.010    | 2.40  | 0.14   | 0.66    | 0.035    |
| 68            | 203.73         | 0.94  | 0.293 | 0.010    | 3.04  | 0.14   | 0.63    | 0.031    |
| 69            | 222.83         | 0.88  | 0.337 | 0.008    | 2.37  | 0.10   | 0.60    | 0.040    |
| 70            | 190.33         | 0.97  | 0.342 | 0.007    | 2.46  | 0.11   | 0.64    | 0.037    |

| ANIMAL NUMBER | SPLEEN | OVARIES | UTERUS |
|---------------|--------|---------|--------|
| 61            | 0.221  | 0.042   | 0.636  |
| 62            | 0.313  | 0.068   | 0.444  |
| 63            | 0.258  | 0.040   | 0.435  |
| 64            | 0.273  | 0.038   | 0.632  |
| 65            | 0.344  | 0.053   | 0.525  |
| 66            | 0.379  | 0.049   | 0.345  |
| 67            | 0.228  | 0.050   | 0.534  |
| 68            | 0.244  | 0.052   | 0.267  |
| 69            | 0.303  | 0.056   | 0.459  |
| 70            | 0.269  | 0.042   | 0.587  |

**GROUP 2 (15 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 76            | 199.69         | 0.92  | 0.396 | 0.009    | 2.60  | 0.12   | 0.61    | 0.037    |
| 77            | 213.93         | 0.89  | 0.342 | 0.014    | 2.39  | 0.15   | 0.66    | 0.036    |
| 78            | 191.35         | 0.97  | 0.325 | 0.008    | 2.94  | 0.10   | 0.66    | 0.034    |
| 79            | 213.25         | 0.86  | 0.334 | 0.011    | 2.48  | 0.08   | 0.63    | 0.034    |
| 80            | 215.36         | 0.85  | 0.280 | 0.009    | 2.45  | 0.09   | 0.56    | 0.026    |
| 81            | 219.57         | 0.89  | 0.300 | 0.009    | 2.53  | 0.08   | 0.60    | 0.032    |
| 82            | 215.52         | 0.93  | 0.360 | 0.008    | 2.47  | 0.11   | 0.62    | 0.031    |
| 83            | 232.72         | 0.88  | 0.344 | 0.009    | 2.42  | 0.08   | 0.55    | 0.031    |
| 84            | 219.48         | 0.85  | 0.286 | 0.008    | 2.42  | 0.10   | 0.55    | 0.028    |
| 85            | 201.38         | 0.88  | 0.295 | 0.010    | 2.36  | 0.12   | 0.61    | 0.030    |

| ANIMAL NUMBER | SPLEEN | OVARIES | UTERUS |
|---------------|--------|---------|--------|
| 76            | 0.283  | 0.051   | 0.628  |
| 77            | 0.258  | 0.059   | 0.876  |
| 78            | 0.306  | 0.051   | 0.486  |
| 79            | 0.247  | 0.034   | 0.445  |
| 80            | 0.294  | 0.040   | 0.291  |
| 81            | 0.301  | 0.047   | 0.464  |
| 82            | 0.281  | 0.037   | 0.408  |
| 83            | 0.211  | 0.051   | 0.658  |
| 84            | 0.244  | 0.044   | 0.413  |
| 85            | 0.233  | 0.050   | 0.424  |

**ORGAN/BODY WEIGHT RATIOS (%)  
 AFTER 14 WEEKS  
 FEMALES**

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 91            | 212.18         | 0.93  | 0.333 | 0.009    | 2.61  | 0.11   | 0.69    | 0.027    |
| 92            | 222.77         | 0.88  | 0.302 | 0.008    | 2.36  | 0.11   | 0.62    | 0.028    |
| 93            | 220.64         | 0.88  | 0.324 | 0.012    | 2.47  | 0.09   | 0.61    | 0.030    |
| 94            | 206.71         | 0.87  | 0.353 | 0.010    | 2.55  | 0.13   | 0.66    | 0.032    |
| 95            | 182.06         | 1.00  | 0.379 | 0.009    | 2.97  | 0.12   | 0.72    | 0.042    |
| 96            | 225.27         | 0.86  | 0.317 | 0.009    | 2.49  | 0.10   | 0.59    | 0.027    |
| 97            | 210.94         | 0.88  | 0.367 | 0.008    | 2.48  | 0.14   | 0.67    | 0.032    |
| 98            | 219.90         | 0.82  | 0.279 | 0.011    | 2.35  | 0.11   | 0.58    | 0.032    |
| 99            | 217.88         | 0.91  | 0.321 | 0.008    | 2.16  | 0.12   | 0.57    | 0.027    |
| 100           | 224.34         | 0.89  | 0.344 | 0.009    | 2.61  | 0.09   | 0.67    | 0.037    |

| ANIMAL NUMBER | SPLEEN | OVARIES | UTERUS |
|---------------|--------|---------|--------|
| 91            | 0.247  | 0.048   | 0.570  |
| 92            | 0.296  | 0.038   | 0.519  |
| 93            | 0.319  | 0.045   | 0.350  |
| 94            | 0.249  | 0.051   | 0.442  |
| 95            | 0.323  | 0.060   | 0.821  |
| 96            | 0.246  | 0.050   | 0.373  |
| 97            | 0.274  | 0.048   | 0.379  |
| 98            | 0.280  | 0.046   | 0.396  |
| 99            | 0.219  | 0.033   | 0.432  |
| 100           | 0.255  | 0.066   | 0.519  |

**GROUP 4 (200 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 106           | 223.83         | 0.82  | 0.306 | 0.014    | 2.82  | 0.14   | 0.62    | 0.035    |
| 107           | 210.61         | 0.85  | 0.371 | 0.009    | 2.93  | 0.08   | 0.71    | 0.032    |
| 108           | 233.76         | 0.84  | 0.371 | 0.011    | 3.51  | 0.11   | 0.75    | 0.032    |
| 109           | 215.06         | 0.90  | 0.322 | 0.009    | 3.06  | 0.12   | 0.66    | 0.029    |
| 110           | 218.97         | 0.87  | 0.340 | 0.011    | 3.08  | 0.13   | 0.71    | 0.034    |
| 111           | 203.05         | 0.94  | 0.356 | 0.009    | 2.73  | 0.11   | 0.72    | 0.033    |
| 112           | 221.09         | 0.85  | 0.325 | 0.014    | 2.70  | 0.09   | 0.66    | 0.033    |
| 113           | 196.57         | 0.98  | 0.335 | 0.007    | 2.93  | 0.09   | 0.72    | 0.028    |
| 114           | 203.02         | 0.90  | 0.319 | 0.007    | 2.57  | 0.11   | 0.56    | 0.031    |
| 115           | 225.56         | 0.87  | 0.322 | 0.013    | 2.66  | 0.12   | 0.70    | 0.043    |

| ANIMAL NUMBER | SPLEEN | OVARIES | UTERUS |
|---------------|--------|---------|--------|
| 106           | 0.303  | 0.048   | 0.491  |
| 107           | 0.350  | 0.049   | 0.405  |
| 108           | 0.385  | 0.059   | 0.417  |
| 109           | 0.361  | 0.153   | 0.431  |
| 110           | 0.417  | 0.055   | 0.477  |
| 111           | 0.338  | 0.057   | 0.785  |
| 112           | 0.311  | 0.039   | 0.408  |
| 113           | 0.338  | 0.045   | 0.598  |
| 114           | 0.434  | 0.122   | 0.474  |
| 115           | 0.298  | 0.041   | 0.460  |

**ORGAN/BRAIN WEIGHT RATIOS (%)  
 AFTER 14 WEEKS  
 FEMALES**

**GROUP 1 (0 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 61            | 1.94         | 36.978 | 0.972    | 236.87 | 10.91  | 65.75   | 3.449    | 24.459 |
| 62            | 1.90         | 33.418 | 1.051    | 297.41 | 12.63  | 75.99   | 3.974    | 34.473 |
| 63            | 2.00         | 38.820 | 0.889    | 287.76 | 12.79  | 72.70   | 3.695    | 31.511 |
| 64            | 1.92         | 38.683 | 1.197    | 294.66 | 13.36  | 68.72   | 3.957    | 28.925 |
| 65            | 1.88         | 40.421 | 0.858    | 304.72 | 13.20  | 71.11   | 3.483    | 39.046 |
| 66            | 1.99         | 34.228 | 1.017    | 265.16 | 11.99  | 64.01   | 3.460    | 42.473 |
| 67            | 1.77         | 39.783 | 1.086    | 272.28 | 15.85  | 74.91   | 3.997    | 25.866 |
| 68            | 1.91         | 31.284 | 1.039    | 324.69 | 15.17  | 67.75   | 3.324    | 26.112 |
| 69            | 1.95         | 38.487 | 0.914    | 270.49 | 11.85  | 68.55   | 4.521    | 34.556 |
| 70            | 1.85         | 35.239 | 0.754    | 253.23 | 11.46  | 66.33   | 3.811    | 27.748 |

| ANIMAL NUMBER | OVARIES | UTERUS |
|---------------|---------|--------|
| 61            | 4.620   | 70.364 |
| 62            | 7.527   | 49.000 |
| 63            | 4.888   | 53.028 |
| 64            | 4.058   | 66.911 |
| 65            | 6.017   | 59.579 |
| 66            | 5.526   | 38.696 |
| 67            | 5.739   | 60.656 |
| 68            | 5.605   | 28.534 |
| 69            | 6.408   | 52.478 |
| 70            | 4.334   | 60.560 |

**GROUP 2 (15 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 76            | 1.83         | 43.114 | 0.973    | 283.56 | 12.76  | 66.97   | 4.082    | 30.824 |
| 77            | 1.90         | 38.554 | 1.569    | 268.84 | 16.56  | 73.92   | 4.095    | 29.014 |
| 78            | 1.86         | 33.469 | 0.854    | 303.30 | 9.96   | 67.91   | 3.550    | 31.580 |
| 79            | 1.84         | 38.749 | 1.311    | 288.25 | 9.56   | 73.09   | 3.979    | 28.614 |
| 80            | 1.84         | 32.799 | 1.095    | 286.55 | 10.06  | 65.27   | 3.098    | 34.392 |
| 81            | 1.96         | 33.585 | 0.973    | 283.95 | 9.46   | 66.69   | 3.613    | 33.678 |
| 82            | 2.00         | 38.930 | 0.817    | 266.36 | 11.90  | 66.46   | 3.355    | 30.323 |
| 83            | 2.04         | 39.255 | 1.027    | 276.21 | 9.69   | 62.69   | 3.587    | 24.092 |
| 84            | 1.87         | 33.575 | 0.994    | 284.10 | 11.77  | 65.15   | 3.314    | 28.629 |
| 85            | 1.78         | 33.473 | 1.153    | 267.73 | 13.36  | 68.84   | 3.376    | 26.444 |

| ANIMAL NUMBER | OVARIES | UTERUS |
|---------------|---------|--------|
| 76            | 5.570   | 68.432 |
| 77            | 6.663   | 98.679 |
| 78            | 5.238   | 50.124 |
| 79            | 4.001   | 51.605 |
| 80            | 4.657   | 34.064 |
| 81            | 5.303   | 52.006 |
| 82            | 3.986   | 44.087 |
| 83            | 5.816   | 75.077 |
| 84            | 5.201   | 48.521 |
| 85            | 5.612   | 48.039 |

**ORGAN/BRAIN WEIGHT RATIOS (%)  
AFTER 14 WEEKS  
FEMALES**

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 91            | 1.97         | 35.868 | 0.925    | 281.39 | 11.71  | 74.37   | 2.920    | 26.590 |
| 92            | 1.96         | 34.245 | 0.854    | 267.50 | 12.73  | 70.64   | 3.230    | 33.640 |
| 93            | 1.93         | 37.068 | 1.371    | 281.93 | 10.57  | 69.59   | 3.399    | 36.454 |
| 94            | 1.81         | 40.388 | 1.122    | 292.01 | 14.37  | 75.63   | 3.629    | 28.411 |
| 95            | 1.81         | 38.053 | 0.949    | 298.31 | 12.13  | 72.26   | 4.206    | 32.420 |
| 96            | 1.94         | 36.922 | 1.014    | 289.15 | 11.23  | 68.61   | 3.103    | 28.621 |
| 97            | 1.86         | 41.519 | 0.864    | 281.10 | 16.02  | 75.39   | 3.606    | 31.059 |
| 98            | 1.81         | 33.864 | 1.284    | 286.06 | 12.82  | 70.35   | 3.849    | 34.081 |
| 99            | 1.98         | 35.418 | 0.874    | 238.57 | 13.44  | 63.04   | 2.985    | 24.133 |
| 100           | 1.99         | 38.716 | 0.995    | 294.01 | 10.19  | 75.57   | 4.181    | 28.726 |

| ANIMAL NUMBER | OVARIES | UTERUS |
|---------------|---------|--------|
| 91            | 5.174   | 61.366 |
| 92            | 4.305   | 58.998 |
| 93            | 5.189   | 39.964 |
| 94            | 5.777   | 50.514 |
| 95            | 6.023   | 82.401 |
| 96            | 5.866   | 43.396 |
| 97            | 5.472   | 42.946 |
| 98            | 5.542   | 48.129 |
| 99            | 3.649   | 47.590 |
| 100           | 7.484   | 58.411 |

**GROUP 4 (200 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 106           | 1.83         | 37.492 | 1.688    | 345.56 | 17.54  | 76.44   | 4.281    | 37.091 |
| 107           | 1.79         | 43.581 | 1.068    | 344.61 | 9.46   | 83.99   | 3.791    | 41.108 |
| 108           | 1.97         | 44.015 | 1.263    | 417.38 | 12.49  | 88.97   | 3.819    | 45.727 |
| 109           | 1.93         | 35.820 | 1.044    | 340.18 | 13.00  | 73.13   | 3.179    | 40.196 |
| 110           | 1.90         | 39.131 | 1.248    | 354.81 | 14.86  | 81.52   | 3.897    | 48.081 |
| 111           | 1.90         | 38.069 | 0.983    | 291.34 | 11.55  | 76.90   | 3.505    | 36.071 |
| 112           | 1.88         | 38.278 | 1.600    | 318.13 | 10.14  | 77.22   | 3.917    | 36.623 |
| 113           | 1.92         | 34.302 | 0.764    | 300.16 | 8.86   | 73.93   | 2.881    | 34.668 |
| 114           | 1.82         | 35.574 | 0.789    | 286.46 | 12.79  | 62.51   | 3.416    | 48.405 |
| 115           | 1.97         | 36.862 | 1.526    | 304.71 | 13.34  | 80.05   | 4.870    | 34.039 |

| ANIMAL NUMBER | OVARIES | UTERUS |
|---------------|---------|--------|
| 106           | 5.854   | 60.200 |
| 107           | 5.795   | 47.638 |
| 108           | 6.959   | 49.473 |
| 109           | 17.041  | 47.962 |
| 110           | 6.284   | 54.913 |
| 111           | 6.110   | 83.892 |
| 112           | 4.606   | 48.039 |
| 113           | 4.637   | 61.368 |
| 114           | 13.672  | 52.899 |
| 115           | 4.735   | 52.606 |

**ORGAN WEIGHTS (GRAM)  
 AFTER 14 WEEKS  
 MALES**

**GROUP 1 (0 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 11            | 477.19  | 2.09  | 1.172 | 0.026    | 13.07 | 0.25   | 2.05    | 0.056    |
| 12            | 419.01  | 2.13  | 1.083 | 0.029    | 12.06 | 0.32   | 2.25    | 0.057    |
| 13            | 434.77  | 2.16  | 1.171 | 0.032    | 12.81 | 0.22   | 2.43    | 0.064    |
| 14            | 468.39  | 2.16  | 1.131 | 0.021    | 12.13 | 0.26   | 2.31    | 0.059    |
| 15            | 453.54  | 2.07  | 1.062 | 0.025    | 13.33 | 0.36   | 2.25    | 0.064    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYMIUM |
|---------------|--------|--------|-------------|
| 11            | 0.671  | 4.29   | 1.471       |
| 12            | 0.879  | 3.84   | 1.610       |
| 13            | 0.763  | 4.03   | 1.701       |
| 14            | 0.788  | 4.50   | 1.609       |
| 15            | 0.647  | 3.80   | 1.474       |

**GROUP 2 (15 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 26            | 438.22  | 2.10  | 1.043 | 0.030    | 13.66 | 0.42   | 2.42    | 0.057    |
| 27            | 414.12  | 2.00  | 0.930 | 0.024    | 12.72 | 0.36   | 2.07    | 0.056    |
| 28            | 414.02  | 1.96  | 0.994 | 0.025    | 12.19 | 0.25   | 2.09    | 0.048    |
| 29            | 421.72  | 1.90  | 1.030 | 0.022    | 10.99 | 0.28   | 1.94    | 0.051    |
| 30            | 426.35  | 2.20  | 1.100 | 0.032    | 11.84 | 0.30   | 2.12    | 0.048    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYMIUM |
|---------------|--------|--------|-------------|
| 26            | 1.036  | 4.27   | 1.643       |
| 27            | 0.935  | 3.66   | 1.274       |
| 28            | 0.641  | 2.89   | 1.189       |
| 29            | 0.744  | 3.01   | 1.296       |
| 30            | 0.779  | 3.74   | 1.308       |

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 41            | 467.27  | 2.16  | 1.093 | 0.032    | 13.01 | 0.32   | 2.38    | 0.050    |
| 42            | 447.47  | 2.03  | 0.942 | 0.020    | 14.51 | 0.22   | 2.14    | 0.061    |
| 43            | 464.38  | 1.90  | 1.063 | 0.027    | 15.29 | 0.25   | 2.40    | 0.064    |
| 44            | 454.95  | 2.12  | 1.039 | 0.034    | 12.84 | 0.27   | 2.11    | 0.061    |
| 45            | 460.05  | 2.10  | 1.160 | 0.028    | 13.36 | 0.23   | 2.10    | 0.047    |

**ORGAN WEIGHTS (GRAM)  
AFTER 14 WEEKS  
MALES**

**GROUP 3 (50 MG/KG)**

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| ANIMAL<br>NUMBER | SPLEEN | TESTES | EPIDIDYMIUM |
|------------------|--------|--------|-------------|
| 41               | 0.871  | 3.76   | 1.437       |
| 42               | 0.875  | 3.66   | 1.504       |
| 43               | 0.729  | 3.35   | 1.169       |
| 44               | 0.610  | 3.85   | 1.781       |
| 45               | 0.733  | 4.46   | 1.901       |

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**GROUP 4 (200 MG/KG)**

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| ANIMAL<br>NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|------------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 56               | 462.56  | 1.97  | 1.107 | 0.041    | 13.42 | 0.36   | 2.35    | 0.065    |
| 57               | 451.01  | 2.22  | 1.170 | 0.028    | 15.07 | 0.32   | 2.30    | 0.055    |
| 58               | 413.55  | 2.02  | 0.924 | 0.020    | 12.52 | 0.27   | 2.02    | 0.047    |
| 59               | 438.48  | 2.13  | 1.058 | 0.031    | 15.07 | 0.27   | 2.34    | 0.060    |
| 60               | 435.73  | 2.22  | 1.031 | 0.030    | 12.67 | 0.32   | 2.49    | 0.071    |

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| ANIMAL<br>NUMBER | SPLEEN | TESTES | EPIDIDYMIUM |
|------------------|--------|--------|-------------|
| 56               | 0.922  | 3.69   | 1.640       |
| 57               | 0.881  | 3.91   | 1.540       |
| 58               | 0.691  | 3.58   | 1.293       |
| 59               | 0.937  | 3.60   | 1.726       |
| 60               | 1.059  | 3.39   | 1.298       |

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**ORGAN/BODY WEIGHT RATIOS (%)  
 AFTER 14 WEEKS  
 MALES**

**GROUP 1 (0 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 11            | 477.19         | 0.44  | 0.246 | 0.005    | 2.74  | 0.05   | 0.43    | 0.012    |
| 12            | 419.01         | 0.51  | 0.258 | 0.007    | 2.88  | 0.08   | 0.54    | 0.014    |
| 13            | 434.77         | 0.50  | 0.269 | 0.007    | 2.95  | 0.05   | 0.56    | 0.015    |
| 14            | 468.39         | 0.46  | 0.241 | 0.004    | 2.59  | 0.06   | 0.49    | 0.013    |
| 15            | 453.54         | 0.46  | 0.234 | 0.006    | 2.94  | 0.08   | 0.50    | 0.014    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYMIUM |
|---------------|--------|--------|-------------|
| 11            | 0.141  | 0.90   | 0.308       |
| 12            | 0.210  | 0.92   | 0.384       |
| 13            | 0.176  | 0.93   | 0.391       |
| 14            | 0.168  | 0.96   | 0.344       |
| 15            | 0.143  | 0.84   | 0.325       |

**GROUP 2 (15 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 26            | 438.22         | 0.48  | 0.238 | 0.007    | 3.12  | 0.10   | 0.55    | 0.013    |
| 27            | 414.12         | 0.48  | 0.225 | 0.006    | 3.07  | 0.09   | 0.50    | 0.013    |
| 28            | 414.02         | 0.47  | 0.240 | 0.006    | 2.95  | 0.06   | 0.50    | 0.012    |
| 29            | 421.72         | 0.45  | 0.244 | 0.005    | 2.61  | 0.07   | 0.46    | 0.012    |
| 30            | 426.35         | 0.52  | 0.258 | 0.007    | 2.78  | 0.07   | 0.50    | 0.011    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYMIUM |
|---------------|--------|--------|-------------|
| 26            | 0.236  | 0.98   | 0.375       |
| 27            | 0.226  | 0.88   | 0.308       |
| 28            | 0.155  | 0.70   | 0.287       |
| 29            | 0.176  | 0.71   | 0.307       |
| 30            | 0.183  | 0.88   | 0.307       |

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 41            | 467.27         | 0.46  | 0.234 | 0.007    | 2.79  | 0.07   | 0.51    | 0.011    |
| 42            | 447.47         | 0.45  | 0.210 | 0.004    | 3.24  | 0.05   | 0.48    | 0.014    |
| 43            | 464.38         | 0.41  | 0.229 | 0.006    | 3.29  | 0.05   | 0.52    | 0.014    |
| 44            | 454.95         | 0.47  | 0.228 | 0.008    | 2.82  | 0.06   | 0.46    | 0.013    |
| 45            | 460.05         | 0.46  | 0.252 | 0.006    | 2.90  | 0.05   | 0.46    | 0.010    |

ORGAN/BODY WEIGHT RATIOS (%)  
 AFTER 14 WEEKS  
 MALES

GROUP 3 (50 MG/KG)

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYIMID |
|---------------|--------|--------|-------------|
| 41            | 0.186  | 0.80   | 0.308       |
| 42            | 0.196  | 0.82   | 0.336       |
| 43            | 0.157  | 0.72   | 0.252       |
| 44            | 0.134  | 0.85   | 0.391       |
| 45            | 0.159  | 0.97   | 0.413       |

GROUP 4 (200 MG/KG)

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 56            | 462.56         | 0.43  | 0.239 | 0.009    | 2.90  | 0.08   | 0.51    | 0.014    |
| 57            | 451.01         | 0.49  | 0.259 | 0.006    | 3.34  | 0.07   | 0.51    | 0.012    |
| 58            | 413.55         | 0.49  | 0.223 | 0.005    | 3.03  | 0.06   | 0.49    | 0.011    |
| 59            | 438.48         | 0.48  | 0.241 | 0.007    | 3.44  | 0.06   | 0.53    | 0.014    |
| 60            | 435.73         | 0.51  | 0.237 | 0.007    | 2.91  | 0.07   | 0.57    | 0.016    |

| ANIMAL NUMBER | SPLEEN | TESTES | EPIDIDYIMID |
|---------------|--------|--------|-------------|
| 56            | 0.199  | 0.80   | 0.355       |
| 57            | 0.195  | 0.87   | 0.341       |
| 58            | 0.167  | 0.87   | 0.313       |
| 59            | 0.214  | 0.82   | 0.394       |
| 60            | 0.243  | 0.78   | 0.298       |

**ORGAN/BRAIN WEIGHT RATIOS (%)  
AFTER 14 WEEKS  
MALES**

**GROUP 1 (0 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 11            | 2.09         | 56.010 | 1.243    | 624.62 | 11.86  | 98.19   | 2.699    | 32.047 |
| 12            | 2.13         | 50.742 | 1.380    | 565.37 | 14.88  | 105.40  | 2.654    | 41.181 |
| 13            | 2.16         | 54.205 | 1.467    | 593.01 | 10.40  | 112.56  | 2.954    | 35.341 |
| 14            | 2.16         | 52.239 | 0.967    | 560.37 | 12.00  | 106.86  | 2.716    | 36.380 |
| 15            | 2.07         | 51.223 | 1.211    | 642.68 | 17.37  | 108.50  | 3.100    | 31.190 |

| ANIMAL NUMBER | TESTES | EPIDIDYMIUM |
|---------------|--------|-------------|
| 11            | 204.95 | 70.310      |
| 12            | 180.09 | 75.445      |
| 13            | 186.73 | 78.758      |
| 14            | 207.68 | 74.342      |
| 15            | 183.03 | 71.055      |

**GROUP 2 (15 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 26            | 2.10         | 49.676 | 1.415    | 650.47 | 20.24  | 115.40  | 2.718    | 49.314 |
| 27            | 2.00         | 46.413 | 1.189    | 634.65 | 17.84  | 103.26  | 2.787    | 46.666 |
| 28            | 1.96         | 50.675 | 1.291    | 621.84 | 12.74  | 106.44  | 2.436    | 32.681 |
| 29            | 1.90         | 54.290 | 1.179    | 579.64 | 14.73  | 102.12  | 2.669    | 39.226 |
| 30            | 2.20         | 49.909 | 1.445    | 537.19 | 13.82  | 96.30   | 2.192    | 35.334 |

| ANIMAL NUMBER | TESTES | EPIDIDYMIUM |
|---------------|--------|-------------|
| 26            | 203.48 | 78.227      |
| 27            | 182.73 | 63.546      |
| 28            | 147.41 | 60.618      |
| 29            | 158.65 | 68.359      |
| 30            | 169.56 | 59.333      |

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 41            | 2.16         | 50.576 | 1.502    | 601.95 | 14.58  | 109.91  | 2.327    | 40.266 |
| 42            | 2.03         | 46.280 | 0.961    | 713.19 | 10.86  | 105.16  | 2.981    | 43.022 |
| 43            | 1.90         | 56.061 | 1.411    | 806.82 | 13.19  | 126.37  | 3.383    | 38.488 |
| 44            | 2.12         | 49.113 | 1.619    | 606.66 | 12.67  | 99.46   | 2.883    | 28.807 |
| 45            | 2.10         | 55.181 | 1.328    | 635.28 | 11.04  | 99.64   | 2.217    | 34.883 |

**ORGAN/BRAIN WEIGHT RATIOS (%)  
 AFTER 14 WEEKS  
 MALES**

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | TESTES | EPIDIDYMIUM |
|---------------|--------|-------------|
| 41            | 173.96 | 66.486      |
| 42            | 179.87 | 73.941      |
| 43            | 176.91 | 61.689      |
| 44            | 182.08 | 84.143      |
| 45            | 211.92 | 90.418      |

**GROUP 4 (200 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 56            | 1.97         | 56.073 | 2.070    | 679.68 | 18.29  | 118.99  | 3.285    | 46.662 |
| 57            | 2.22         | 52.675 | 1.253    | 678.76 | 14.45  | 103.53  | 2.474    | 39.680 |
| 58            | 2.02         | 45.765 | 0.977    | 620.15 | 13.24  | 99.80   | 2.324    | 34.195 |
| 59            | 2.13         | 49.743 | 1.453    | 708.98 | 12.82  | 110.16  | 2.817    | 44.075 |
| 60            | 2.22         | 46.440 | 1.349    | 570.84 | 14.48  | 112.02  | 3.204    | 47.723 |

| ANIMAL NUMBER | TESTES | EPIDIDYMIUM |
|---------------|--------|-------------|
| 56            | 187.02 | 83.057      |
| 57            | 176.03 | 69.356      |
| 58            | 177.19 | 64.023      |
| 59            | 169.32 | 81.160      |
| 60            | 152.82 | 58.459      |

**ORGAN WEIGHTS (GRAM)  
 AFTER 14 WEEKS  
 FEMALES**

**GROUP 1 (0 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 71            | 245.17  | 1.82  | 0.853 | 0.018    | 8.52  | 0.23   | 1.64    | 0.055    |
| 72            | 227.77  | 1.99  | 0.658 | 0.018    | 7.57  | 0.27   | 1.50    | 0.076    |
| 73            | 236.97  | 1.89  | 0.614 | 0.021    | 7.14  | 0.25   | 1.31    | 0.070    |
| 74            | 230.47  | 1.83  | 0.741 | 0.026    | 6.81  | 0.34   | 1.40    | 0.078    |
| 75            | 212.72  | 1.96  | 0.688 | 0.016    | 6.71  | 0.23   | 1.45    | 0.070    |

| ANIMAL NUMBER | SPLEEN | OVARIES | UTERUS |
|---------------|--------|---------|--------|
| 71            | 0.591  | 0.126   | 1.116  |
| 72            | 0.679  | 0.117   | 0.896  |
| 73            | 0.548  | 0.086   | 1.107  |
| 74            | 0.492  | 0.103   | 1.103  |
| 75            | 0.515  | 0.136   | 1.214  |

**GROUP 2 (15 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 86            | 247.26  | 1.83  | 0.796 | 0.016    | 8.49  | 0.30   | 1.51    | 0.087    |
| 87            | 218.44  | 1.81  | 0.693 | 0.022    | 6.57  | 0.36   | 1.35    | 0.069    |
| 88            | 246.96  | 1.90  | 0.801 | 0.025    | 7.34  | 0.28   | 1.35    | 0.062    |
| 89            | 218.22  | 1.90  | 0.657 | 0.017    | 6.75  | 0.25   | 1.27    | 0.080    |
| 90            | 255.83  | 1.89  | 0.770 | 0.021    | 8.13  | 0.19   | 1.31    | 0.059    |

| ANIMAL NUMBER | SPLEEN | OVARIES | UTERUS |
|---------------|--------|---------|--------|
| 86            | 0.750  | 0.142   | 0.919  |
| 87            | 0.485  | 0.096   | 1.340  |
| 88            | 0.452  | 0.106   | 0.813  |
| 89            | 0.499  | 0.097   | 0.836  |
| 90            | 0.504  | 0.093   | 0.785  |

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 101           | 227.62  | 1.84  | 0.716 | 0.018    | 7.33  | 0.24   | 1.29    | 0.059    |
| 102           | 220.56  | 1.90  | 0.786 | 0.025    | 6.67  | 0.35   | 1.49    | 0.070    |
| 103           | 252.82  | 1.87  | 0.785 | 0.026    | 7.38  | 0.32   | 1.29    | 0.064    |
| 104           | 208.05  | 1.89  | 0.678 | 0.018    | 6.06  | 0.18   | 1.25    | 0.059    |
| 105           | 222.52  | 1.86  | 0.776 | 0.024    | 6.51  | 0.32   | 1.45    | 0.068    |

**ORGAN WEIGHTS (GRAM)  
AFTER 14 WEEKS  
FEMALES**

**GROUP 3 (50 MG/KG)**

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| ANIMAL<br>NUMBER | SPLEEN | OVARIES | UTERUS |
|------------------|--------|---------|--------|
| 101              | 0.562  | 0.124   | 1.088  |
| 102              | 0.522  | 0.111   | 1.388  |
| 103              | 0.693  | 0.098   | 1.669  |
| 104              | 0.589  | 0.107   | 1.560  |
| 105              | 0.467  | 0.090   | 1.303  |

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**GROUP 4 (200 MG/KG)**

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| ANIMAL<br>NUMBER | BODY W. | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|------------------|---------|-------|-------|----------|-------|--------|---------|----------|
| 116              | 230.50  | 1.91  | 0.710 | 0.019    | 7.99  | 0.27   | 1.43    | 0.060    |
| 117              | 240.16  | 1.86  | 0.693 | 0.027    | 7.96  | 0.26   | 1.42    | 0.063    |
| 118              | 237.95  | 1.93  | 0.930 | 0.023    | 7.28  | 0.20   | 1.48    | 0.066    |
| 119              | 221.75  | 1.88  | 0.776 | 0.020    | 7.89  | 0.23   | 1.50    | 0.061    |
| 120              | 222.34  | 1.86  | 0.720 | 0.017    | 7.99  | 0.32   | 1.47    | 0.074    |

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| ANIMAL<br>NUMBER | SPLEEN | OVARIES | UTERUS |
|------------------|--------|---------|--------|
| 116              | 0.753  | 0.107   | 1.420  |
| 117              | 0.598  | 0.102   | 0.819  |
| 118              | 0.555  | 0.139   | 0.879  |
| 119              | 0.668  | 0.107   | 0.808  |
| 120              | 0.810  | 0.133   | 0.734  |

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**ORGAN/BODY WEIGHT RATIOS (%)  
 AFTER 14 WEEKS  
 FEMALES**

**GROUP 1 (0 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 71            | 245.17         | 0.74  | 0.348 | 0.008    | 3.47  | 0.09   | 0.67    | 0.023    |
| 72            | 227.77         | 0.87  | 0.289 | 0.008    | 3.32  | 0.12   | 0.66    | 0.033    |
| 73            | 236.97         | 0.80  | 0.259 | 0.009    | 3.01  | 0.11   | 0.55    | 0.030    |
| 74            | 230.47         | 0.79  | 0.321 | 0.011    | 2.96  | 0.15   | 0.61    | 0.034    |
| 75            | 212.72         | 0.92  | 0.323 | 0.008    | 3.15  | 0.11   | 0.68    | 0.033    |

| ANIMAL NUMBER | SPLEEN | OVARIES | UTERUS |
|---------------|--------|---------|--------|
| 71            | 0.241  | 0.051   | 0.455  |
| 72            | 0.298  | 0.051   | 0.393  |
| 73            | 0.231  | 0.036   | 0.467  |
| 74            | 0.214  | 0.045   | 0.479  |
| 75            | 0.242  | 0.064   | 0.571  |

**GROUP 2 (15 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 86            | 247.26         | 0.74  | 0.322 | 0.007    | 3.44  | 0.12   | 0.61    | 0.035    |
| 87            | 218.44         | 0.83  | 0.317 | 0.010    | 3.01  | 0.17   | 0.62    | 0.032    |
| 88            | 246.96         | 0.77  | 0.324 | 0.010    | 2.97  | 0.11   | 0.55    | 0.025    |
| 89            | 218.22         | 0.87  | 0.301 | 0.008    | 3.09  | 0.12   | 0.58    | 0.037    |
| 90            | 255.83         | 0.74  | 0.301 | 0.008    | 3.18  | 0.07   | 0.51    | 0.023    |

| ANIMAL NUMBER | SPLEEN | OVARIES | UTERUS |
|---------------|--------|---------|--------|
| 86            | 0.303  | 0.058   | 0.372  |
| 87            | 0.222  | 0.044   | 0.613  |
| 88            | 0.183  | 0.043   | 0.329  |
| 89            | 0.229  | 0.044   | 0.383  |
| 90            | 0.197  | 0.036   | 0.307  |

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | BODY W. (GRAM) | BRAIN | HEART | THYROIDS | LIVER | THYMUS | KIDNEYS | ADRENALS |
|---------------|----------------|-------|-------|----------|-------|--------|---------|----------|
| 101           | 227.62         | 0.81  | 0.314 | 0.008    | 3.22  | 0.11   | 0.57    | 0.026    |
| 102           | 220.56         | 0.86  | 0.356 | 0.011    | 3.02  | 0.16   | 0.68    | 0.032    |
| 103           | 252.82         | 0.74  | 0.310 | 0.010    | 2.92  | 0.13   | 0.51    | 0.026    |
| 104           | 208.05         | 0.91  | 0.326 | 0.009    | 2.91  | 0.09   | 0.60    | 0.028    |
| 105           | 222.52         | 0.83  | 0.349 | 0.011    | 2.92  | 0.14   | 0.65    | 0.030    |

**ORGAN/BODY WEIGHT RATIOS (%)  
AFTER 14 WEEKS  
FEMALES**

**GROUP 3 (50 MG/KG)**

---

| <b>ANIMAL<br/>NUMBER</b> | <b>SPLEEN</b> | <b>OVARIES</b> | <b>UTERUS</b> |
|--------------------------|---------------|----------------|---------------|
| 101                      | 0.247         | 0.055          | 0.478         |
| 102                      | 0.237         | 0.050          | 0.629         |
| 103                      | 0.274         | 0.039          | 0.660         |
| 104                      | 0.283         | 0.052          | 0.750         |
| 105                      | 0.210         | 0.040          | 0.586         |

---

**GROUP 4 (200 MG/KG)**

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| <b>ANIMAL<br/>NUMBER</b> | <b>BODY W.<br/>(GRAM)</b> | <b>BRAIN</b> | <b>HEART</b> | <b>THYROIDS</b> | <b>LIVER</b> | <b>THYMUS</b> | <b>KIDNEYS</b> | <b>ADRENALS</b> |
|--------------------------|---------------------------|--------------|--------------|-----------------|--------------|---------------|----------------|-----------------|
| 116                      | 230.50                    | 0.83         | 0.308        | 0.008           | 3.47         | 0.12          | 0.62           | 0.026           |
| 117                      | 240.16                    | 0.77         | 0.289        | 0.011           | 3.31         | 0.11          | 0.59           | 0.026           |
| 118                      | 237.95                    | 0.81         | 0.391        | 0.009           | 3.06         | 0.08          | 0.62           | 0.028           |
| 119                      | 221.75                    | 0.85         | 0.350        | 0.009           | 3.56         | 0.10          | 0.68           | 0.027           |
| 120                      | 222.34                    | 0.84         | 0.324        | 0.007           | 3.59         | 0.14          | 0.66           | 0.033           |

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| <b>ANIMAL<br/>NUMBER</b> | <b>SPLEEN</b> | <b>OVARIES</b> | <b>UTERUS</b> |
|--------------------------|---------------|----------------|---------------|
| 116                      | 0.327         | 0.046          | 0.616         |
| 117                      | 0.249         | 0.042          | 0.341         |
| 118                      | 0.233         | 0.058          | 0.369         |
| 119                      | 0.301         | 0.048          | 0.364         |
| 120                      | 0.364         | 0.060          | 0.330         |

---



**ORGAN/BRAIN WEIGHT RATIOS (%)  
 AFTER 14 WEEKS  
 FEMALES**

**GROUP 1 (0 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 71            | 1.82         | 46.875 | 1.010    | 467.68 | 12.41  | 90.32   | 3.041    | 32.479 |
| 72            | 1.99         | 33.050 | 0.916    | 380.24 | 13.78  | 75.51   | 3.826    | 34.127 |
| 73            | 1.89         | 32.453 | 1.127    | 377.16 | 13.25  | 69.28   | 3.724    | 28.953 |
| 74            | 1.83         | 40.517 | 1.420    | 372.75 | 18.39  | 76.38   | 4.243    | 26.919 |
| 75            | 1.96         | 35.016 | 0.824    | 341.59 | 11.53  | 73.82   | 3.547    | 26.202 |

| ANIMAL NUMBER | OVARIES | UTERUS |
|---------------|---------|--------|
| 71            | 6.906   | 61.297 |
| 72            | 5.883   | 44.989 |
| 73            | 4.553   | 58.483 |
| 74            | 5.653   | 60.332 |
| 75            | 6.941   | 61.804 |

**GROUP 2 (15 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 86            | 1.83         | 43.524 | 0.894    | 464.23 | 16.13  | 82.46   | 4.738    | 40.982 |
| 87            | 1.81         | 38.301 | 1.243    | 363.15 | 20.05  | 74.45   | 3.814    | 26.796 |
| 88            | 1.90         | 42.029 | 1.315    | 385.16 | 14.50  | 70.98   | 3.263    | 23.706 |
| 89            | 1.90         | 34.596 | 0.888    | 355.25 | 13.40  | 66.97   | 4.237    | 26.272 |
| 90            | 1.89         | 40.655 | 1.088    | 429.26 | 10.04  | 69.39   | 3.111    | 26.595 |

| ANIMAL NUMBER | OVARIES | UTERUS |
|---------------|---------|--------|
| 86            | 7.784   | 50.225 |
| 87            | 5.297   | 74.033 |
| 88            | 5.565   | 42.679 |
| 89            | 5.090   | 44.022 |
| 90            | 4.892   | 41.450 |

**GROUP 3 (50 MG/KG)**

| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 101           | 1.84         | 38.900 | 0.952    | 398.53 | 13.05  | 70.04   | 3.193    | 30.538 |
| 102           | 1.90         | 41.293 | 1.301    | 350.46 | 18.43  | 78.32   | 3.686    | 27.453 |
| 103           | 1.87         | 41.935 | 1.377    | 394.39 | 16.91  | 68.98   | 3.447    | 37.023 |
| 104           | 1.89         | 35.896 | 0.948    | 320.69 | 9.42   | 66.30   | 3.129    | 31.179 |
| 105           | 1.86         | 41.805 | 1.293    | 350.46 | 17.29  | 77.83   | 3.646    | 25.165 |

**ORGAN/BRAIN WEIGHT RATIOS (%)  
AFTER 14 WEEKS  
FEMALES**

**GROUP 3 (50 MG/KG)**

---

| ANIMAL NUMBER | OVARIES | UTERUS |
|---------------|---------|--------|
| 101           | 6.758   | 59.118 |
| 102           | 5.840   | 72.976 |
| 103           | 5.234   | 89.191 |
| 104           | 5.682   | 82.632 |
| 105           | 4.847   | 70.182 |

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**GROUP 4 (200 MG/KG)**

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| ANIMAL NUMBER | BRAIN (GRAM) | HEART  | THYROIDS | LIVER  | THYMUS | KIDNEYS | ADRENALS | SPLEEN |
|---------------|--------------|--------|----------|--------|--------|---------|----------|--------|
| 116           | 1.91         | 37.176 | 0.979    | 418.71 | 14.07  | 74.94   | 3.159    | 39.467 |
| 117           | 1.86         | 37.315 | 1.449    | 428.35 | 13.98  | 76.47   | 3.384    | 32.174 |
| 118           | 1.93         | 48.080 | 1.164    | 376.24 | 10.21  | 76.54   | 3.435    | 28.700 |
| 119           | 1.88         | 41.292 | 1.040    | 419.98 | 12.03  | 79.93   | 3.228    | 35.581 |
| 120           | 1.86         | 38.773 | 0.897    | 429.98 | 17.35  | 79.07   | 4.002    | 43.605 |

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| ANIMAL NUMBER | OVARIES | UTERUS |
|---------------|---------|--------|
| 116           | 5.580   | 74.375 |
| 117           | 5.464   | 44.080 |
| 118           | 7.175   | 45.450 |
| 119           | 5.711   | 43.008 |
| 120           | 7.157   | 39.508 |

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# **RCC Study Number 857092**

Repeated Dose 90-Day Oral Toxicity Study  
with

**2-Amino-4-Hydroxyethyl-  
aminoanisoie Sulfate  
(A084, WR 23081)**

in Wistar Rats

**Final Report (Part II of III)**

Date of Issue: 20 July 2005  
Page 243 of 385  
Total Number of Pages: 629



**APPENDIX I:**  
**OBSERVATIONS**

| <b>SUMMARY OF PARAMETERS (MINIMUM REQUIREMENT FOR EACH ANIMAL)</b>            |              |                       |          |          |          |          |          |          |                 |
|---|--------------|-----------------------|----------|----------|----------|----------|----------|----------|-----------------|
| <b>OBSERVATIONS: DAILY CAGE-SIDE (D), PRETEST (P), WEEKLY (W) AND FOB (F)</b> |              |                       |          |          |          |          |          |          |                 |
|   | <b>SCORE</b> | <b>PARAMETER</b>      | <b>D</b> | <b>P</b> | <b>W</b> | <b>W</b> | <b>W</b> | <b>F</b> | <b>Comments</b> |
|   |              |                       |          |          | <b>1</b> | <b>2</b> | <b>3</b> | <b>4</b> |                 |
| <b>APPEARANCE</b>   | 1-3          | Piloerection          | X        | X        | X        | X        | X        | X        | None            |
|   | 1-3          | Salivation            | X        | X        | X        | X        | X        | X        | None            |
|   | 1            | Hunched posture       | X        | X        | X        | X        | X        | X        | None            |
| <b>MOTOR</b>  | 1-3          | Ataxia                | X        | X        | X        | X        | X        | X        | None            |
|   | 1-3          | Tremor/twitching      | X        | X        | X        | X        | X        | X        | None            |
|   | 1            | Prostration           | X        | X        | X        | X        | X        | X        | None            |
|   | 1            | Circling              |          | X        | X        | X        | X        | X        | None            |
|   | 1-3          | Spasm                 |          | X        | X        | X        | X        | X        | None            |
| <b>BEHAVIOR</b>   | 1-3          | Hyperactivity         | X        | X        | X        | X        | X        | X        | None            |
|   | 1-3          | Somnolence            | X        | X        | X        | X        | X        | X        | None            |
|   | 1-3          | Increased exploration |          | X        | X        | X        | X        | X        | None            |
|   | 1-3          | Reduced grooming      |          | X        | X        | X        | X        | X        | None            |
|   | 1-3          | Vocalisation          |          | X        | X        | X        | X        | X        | None            |
| <b>RESPIRATION</b>  | 1            | Dyspnea               | X        | X        | X        | X        | X        | X        | None            |
|   | 1            | Tachypnea             | X        | X        | X        | X        | X        | X        | None            |
|   | 1            | Bradypnea             | X        | X        | X        | X        | X        | X        | None            |
| <b>REFLEXES</b>   | 1            | Blink                 |          | X        | X        | X        | X        | X        | None            |
|   | 1            | Pinna                 |          | X        | X        | X        | X        | X        | None            |
|   | 1            | Iridic light reflex   |          | X        | X        | X        | X        | X        | None            |
|   | 1            | Push-off (hind leg)   |          | X        | X        | X        | X        | X        | None            |
|   | 1            | Pain response         |          | X        | X        | X        | X        | X        | None            |
|   | 1            | Startle/hearing       |          | X        | X        | X        | X        | X        | None            |
|   | 1            | Righting reflex       |          | X        | X        | X        | X        | X        | None            |
| <b>Miscellaneous</b>  | 1-3          | Lacrimation           |          | X        | X        | X        | X        | X        | None            |
|   | 1            | Limbs cyanotic        |          | X        | X        | X        | X        | X        | None            |
|   | 1            | Mydriasis             |          | X        | X        | X        | X        | X        | None            |
|   | 1            | Miosis                |          | X        | X        | X        | X        | X        | None            |
|   | 1            | Exophthalmos          |          | X        | X        | X        | X        | X        | None            |
|   | 1-3          | Reduced muscle tone   |          | X        | X        | X        | X        | X        | None            |

NB. Findings described as 'Study-specific' include abnormal findings that were detected during daily observation of the standard parameters and subsequently tracked throughout the study for onset in other animals and progression/regression in the afflicted animals. Parameters marked with 'X' were specifically observed for presence or absence. 'Study specific' findings marked with 'X' were observed in the week noted, and no longer evident if 'X' did not appear in subsequent weeks. 'Cage-specific' findings (if present) refer to observations that could not be ascribed to a single animal in the cage and were therefore ascribed to all individuals in the cage.

X: observed

**APPENDIX II:**  
**DRINKING WATER ANALYSES**

**BACTERIOLOGICAL ASSAY OF DRINKING WATER, ITINGEN**

|                        |   |
|------------------------|---|
| Official Laboratory    | Liestal, 16.07.2004                                   |
| Basel-Landschaft       | Ref.no. 200033666                                     |
| Sampling point:        | 59.99.N    Net water RCC Ltd, Itingen,<br>Room No. 10 |
| Sampled on:            | 06.07.2004  |
| Sample:                |   |
| Time of sampling       | 8.20-8.50   |
| Water temperature (°C) | 15.3  |

**BACTERIOLOGICAL TEST:**

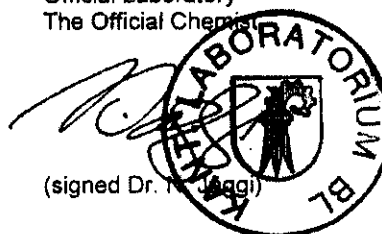
|                                  |     |
|----------------------------------|-----|
| Aerobic mesophilic bacteria / ml | 210 |
| E.coli / 100 ml                  | 0   |
| Enterococci / 100 ml             | 0   |

**ASSESSMENT:**

At the time of sampling, the tested bacteriological parameters met the requirements for drinking water according to article 275 of the "Eidg. Lebensmittelverordnung".

Liestal, September 9, 2004  
Cert. BL040146

Official Laboratory  
The Official Chemist







CONTAMINANT ASSAY OF DRINKING WATER, ITINGEN

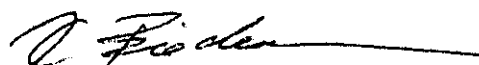
RCC Study No.:                      855528  
 Date of Sampling:                      06.07.2004  
 Sample:                                  H<sub>2</sub>O, RCC Ltd, Itingen, Room No. 10

| PARAMETER                                       | ASSAY LEVEL<br>µg/l | LIMIT *<br>µg/l |
|---|---------------------|-----------------|
| Lindane   | < 0.05              | 0.1             |
| Heptachlor                                      | < 0.05              | 0.1             |
| Malathion                                       | < 0.05              | 0.1             |
| DDT, total                                      | < 0.05              | 0.1             |
| Dieldrin  | < 0.05              | 0.1             |
| Cadmium   | < 0.5               | 5               |
| Arsenic   | < 3                 | 50              |
| Lead  | < 3                 | 50              |
| Mercury   | < 1                 | 1               |
| Selenium  | < 3                 | 10              |
| Copper  | < 4                 | 1500            |
| PCBs<br>(28, 52, 101, 138, 153, 180)            | < 0.05              | 0.1             |
| Nitrosamines, total<br>(DMN, DEN, NPIP, NMORPH) | < 0.002             | ----            |

< 0.05 = less than 0.05 microgram per liter

\* Schweizer Lebensmittelbuch

September 03, 2004



signed K. Biedermann

**BACTERIOLOGICAL ASSAY OF DRINKING WATER, ITINGEN**

|                        |   |
|------------------------|---|
| Official Laboratory    | Liestal, 31.01.2005                                     |
| Basel-Landschaft       | Ref.no. 200037853                                       |
| Sampling point:        | 59.99.N      Net water RCC Ltd, Itingen,<br>Room No. 10 |
| Sampled on:            | 31.01.05  |
| Sample                 |   |
| Time of sampling       | 7.45-8.20   |
| Water temperature (°C) | 13.3  |


**BACTERIOLOGICAL TEST:**


|                                  |   |
|----------------------------------|---|
| Aerobic mesophilic bacteria / ml | 0 |
| E.coli / 100 ml                  | 0 |
| Enterococci / 100 ml             | 0 |

**ASSESSMENT:**

At the time of sampling, the tested bacteriological parameters met the requirements for drinking water according to article 275 of the "Eidg. Lebensmittelverordnung".

Official Laboratory  
The Official Chemist

  
(signed Dr. N. Jäggi)





RCC STUDY NUMBER 857092                      REPORT  
 2-AMINO-4-HYDROXYETHYLAMINOANISOLE SULFATE (A084, WR 23081)

CONTAMINANT ASSAY OF DRINKING WATER, ITINGEN

RCC Study No.:                      859062  
 Date of Sampling:                      31.01.2005  
 Sample:                                  H<sub>2</sub>O, RCC Ltd, Itingen, Room No. 10

| PARAMETER                                       | ASSAY LEVEL<br>µg/l | LIMIT *<br>µg/l |
|---|---------------------|-----------------|
| Lindane   | < 0.05              | 0.1             |
| Heptachlor                                      | < 0.05              | 0.1             |
| Malathion                                       | < 0.05              | 0.1             |
| DDT, total                                      | < 0.05              | 0.1             |
| Dieldrin  | < 0.05              | 0.1             |
| Cadmium   | < 0.5               | 5               |
| Arsenic   | < 3                 | 50              |
| Lead  | < 3                 | 50              |
| Mercury   | < 1                 | 1               |
| Selenium  | < 3                 | 10              |
| Copper  | < 4                 | 1500            |
| PCBs<br>(28, 52, 101, 138, 153, 180)            | < 0.05              | 0.1             |
| Nitrosamines, total<br>(DMN, DEN, NPIP, NMORPH) | < 0.05              | -----           |

< 0.05 = less than 0.05 microgram per liter

\* Schweizer Lebensmittelbuch

February 23, 2005




signed K. Biedermann

**APPENDIX III:**  
**CHEMICAL ANALYSIS OF FEED**

# ANALYTICAL TEST REPORT

RCC Study 847194  
August 24, 2004

|                  |  |
|------------------|--|
| Prepared for     | PROVIMI KLIBA AG<br>4303 Kaiseraugst         |
| Attention of     | Dr. Dietmar Ranz                             |
| Materials tested | KLIBA-NAFAG 3433<br>Batch 53/04 vom 12.08.04 |
| Test performed   | AAS, GC, GC-MS, HPLC                         |
| Test results     | See attached Table 1                         |
| Submitted        | E. Dettwiler                                 |
| Issued by        | K. Biedermann                                |

  
.....  
September 06, 2004/sco

# ATTACHMENT

RCC Study 847194  
 August 24, 2004

Table 1 - Test Results

KLIBA-NAFAG 3433  
 Batch 53/04 vom 12.08.04

| PARAMETER                                     | ASSAY LEVEL<br>mg/kg | LIMIT*<br>mg/kg |
|---|----------------------|-----------------|
| Aflatoxins (B1, B2, G1, G2), total            | < 0.001              | 0.005           |
| Estrogens (DES, Hexestrol, Dienestrol), total | < 0.001              | 0.001           |
| Lindane                                       | < 0.005              | 0.02            |
| Heptachlor                                    | < 0.005              | 0.02            |
| Malathion                                     | < 0.5                | 2.5             |
| DDT, total                                    | < 0.025              | 0.100           |
| Dieldrin                                      | < 0.005              | 0.02            |
| Cadmium                                       | 0.04                 | 0.160           |
| Arsenic                                       | < 0.15               | 1.0             |
| Lead  | < 0.25               | 1.5             |
| Mercury                                       | < 0.05               | 0.1             |
| Selenium                                      | < 0.15               | 0.6             |
| Copper  | 14                   | ---             |
| PCBs  | < 0.025              | 0.05            |
| Nitrosamines (DMN, DEN, NPIP, NMORPH), total  | < 0.002              | 0.010           |

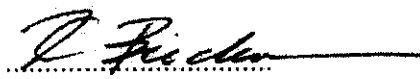
< 0.001 = less than 0.001 milligram per kilogram

\* = USP EPA, Federal Register, Vol. 44, No. 91, May 9, 1979

## ANALYTICAL TEST REPORT

RCC Study 847194  
September 30, 2004

|                  |  |
|------------------|--|
| Prepared for     | PROVIMI KLIBA AG<br>4303 Kaiseraugst         |
| Attention of     | Dr. Dietmar Ranz                             |
| Materials tested | KLIBA-NAFAG 3433<br>Batch 63/04 vom 22.09.04 |
| Test performed   | AAS, GC, GC-MS, HPLC                         |
| Test results     | See attached Table 1                         |
| Submitted        | E. Dettwiler                                 |
| Issued by        | K. Biedermann                                |

  
October 18, 2004/sco



# ATTACHMENT

RCC Study 847194  
 September 30, 2004

Table 1 - Test Results

KLIBA-NAFAG 3433  
 Batch 63/04 vom 22.09.04

| PARAMETER                                     | ASSAY LEVEL<br>mg/kg | LIMIT*<br>mg/kg |
|---|----------------------|-----------------|
| Aflatoxins (B1, B2, G1, G2), total            | < 0.001              | 0.005           |
| Estrogens (DES, Hexestrol, Dienestrol), total | < 0.001              | 0.001           |
| Lindane                                       | < 0.005              | 0.02            |
| Heptachlor                                    | < 0.005              | 0.02            |
| Malathion                                     | < 0.5                | 2.5             |
| DDT, total                                    | < 0.025              | 0.100           |
| Dieldrin                                      | < 0.005              | 0.02            |
| Cadmium                                       | 0.06                 | 0.160           |
| Arsenic                                       | < 0.15               | 1.0             |
| Lead  | < 0.25               | 1.5             |
| Mercury                                       | < 0.05               | 0.1             |
| Selenium                                      | < 0.15               | 0.6             |
| Copper  | 15                   | ---             |
| PCBs  | < 0.025              | 0.05            |
| Nitrosamines (DMN, DEN, NPIP, NMORPH), total  | < 0.002              | 0.010           |

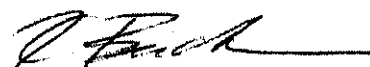
< 0.001 = less than 0.001 milligram per kilogram

\* = USP EPA, Federal Register, Vol. 44, No. 91, May 9, 1979

# ANALYTICAL TEST REPORT

RCC Study 847194  
Oktober 28, 2004

|                  |  |
|------------------|--|
| Prepared for     | PROVIMI KLIBA AG<br>4303 Kaiseraugst         |
| Attention of     | Dr. Dietmar Ranz                             |
| Materials tested | KLIBA-NAFAG 3433<br>Batch 69/04 vom 18.10.04 |
| Test performed   | AAS, GC, GC-MS, HPLC                         |
| Test results     | See attached Table 1                         |
| Submitted        | E. Dettwiler                                 |
| Issued by        | K. Biedermann                                |



November 15, 2004/sco

# ATTACHMENT

RCC Study 847194  
 October 28, 2004

Table 1 - Test Results

KLIBA-NAFAG 3433  
 Batch 69/04 vom 18.10.04

| PARAMETER                                     | ASSAY LEVEL<br>mg/kg | LIMIT*<br>mg/kg |
|---|----------------------|-----------------|
| Aflatoxins (B1, B2, G1, G2), total            | < 0.001              | 0.005           |
| Estrogens (DES, Hexestrol, Dienestrol), total | < 0.001              | 0.001           |
| Lindane                                       | 0.005                | 0.02            |
| Heptachlor                                    | < 0.005              | 0.02            |
| Malathion                                     | < 0.5                | 2.5             |
| DDT, total                                    | < 0.025              | 0.100           |
| Dieldrin                                      | < 0.005              | 0.02            |
| Cadmium                                       | 0.02                 | 0.160           |
| Arsenic                                       | < 0.15               | 1.0             |
| Lead  | < 0.25               | 1.5             |
| Mercury                                       | < 0.05               | 0.1             |
| Selenium                                      | < 0.15               | 0.6             |
| Copper  | 16                   | ----            |
| PCBs  | < 0.025              | 0.05            |
| Nitrosamines (DMN, DEN, NPIP, NMORPH), total  | < 0.002              | 0.010           |

< 0.001 = less than 0.001 milligram per kilogram

\* = USP EPA, Federal Register, Vol. 44, No. 91, May 9, 1979

**APPENDIX IV:**  
**CLINICAL LABORATORY INVESTIGATIONS**

# **RCC Study Number 857092**

Repeated Dose 90-Day Oral Toxicity Study  
with

**2-Amino-4-Hydroxyethylamino-  
anisole Sulfate (A084, WR 23081):**

in Wistar Rats

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## 1.1 CLINICAL LABORATORY INVESTIGATIONS

Blood and urine sampling: after 15 weeks: 17 February 2005 (Allocation A)

Blood samples were drawn from the retro-orbital plexus from all rats per sex and group of Allocation A under light isoflurane anesthesia. The animals were fasted in metabolism cages for approximately 18 hours before blood sampling but allowed access to water ad libitum. The samples were collected early in the working day to reduce biological variation caused by circadian rhythms.

Urine was collected into specimen vials during the 18-hour fasting period while animals were housed in metabolism cages.

In the summary and individual tables the names of some parameters have been abbreviated. Any abbreviation has been defined in this section. Clinical laboratory data are expressed, with a few exceptions, in general accordance with the International System of Units (SI).

Key to abbreviations of units:

|     |        |    |                    |       |                      |
|-----|--------|----|--------------------|-------|----------------------|
| l   | liter  | g  | gram               | m     | milli ( $10^{-3}$ )  |
| mol | mole   | kg | kilogram           | $\mu$ | micro ( $10^{-6}$ )  |
| sec | second | T  | tera ( $10^{12}$ ) | n     | nano ( $10^{-9}$ )   |
| U   | Unit   | G  | giga ( $10^9$ )    | p     | pico ( $10^{-12}$ )  |
|     |        |    |                    | f     | femto ( $10^{-15}$ ) |

General remarks:

n.d. = not determined, no value measured for this parameter

### 1.1.1 HEMATOLOGY

The following anticoagulants were used during blood collection:

|                           |  |
|---------------------------|--|
| Complete blood cell count | Di-potassium-EDTA  |
| Methemoglobin             | Lithium heparin  |
| Coagulation               | Sodium citrate, 3.2% (1 part anticoagulant to 9 parts blood) |

| Complete blood cell count<br>Parameter      | Abbreviation | Unit   | Method<br>code | Instrumentation        |
|---|--------------|--------|----------------|------------------------|
| Erythrocyte count                           | RBC          | T/l    | M01            | Advia 120 <sup>1</sup> |
| Hemoglobin                                  | Hb           | mmol/l | M01            | Advia 120              |
| Hematocrit                                  | Hct          | rel.1  | M01            | Advia 120              |
| Mean corpuscular volume                     | MCV          | fl     | M01            | Advia 120              |
| Red cell volume distribution width          | RDW          | rel.1  | M01            | Advia 120              |
| Mean corpuscular hemoglobin                 | MCH          | fmol   | M01            | Advia 120              |
| Mean corpuscular hemoglobin concentration   | MCHC         | mmol/l | M01            | Advia 120              |
| Hemoglobin concentration distribution width | HDW          | mmol/l | M01            | Advia 120              |

<sup>1</sup> ADVIA 120 hematology system (Bayer)

| <b>Complete blood cell count</b> |              |          |          | Method code | Instrumentation |
|----------------------------------|--------------|----------|----------|-------------|-----------------|
| Parameter                        | Abbreviation | Unit     |          |             |                 |
| Reticulocyte count               | Reti         | relative | absolute | M02         | Advia 120       |
|                                  |              | rel.1    | G/l      |             |                 |
| Reticulocyte maturity index      | L Reti       | rel.1    |          | M01         | Advia 120       |
| (low, medium, high fluorescence) | M Reti       | rel.1    |          | M01         | Advia 120       |
|                                  | H Reti       | rel.1    |          | M01         | Advia 120       |
| Leukocyte count, total           | WBC          | G/l      |          | M01         | Advia 120       |
| Differential leukocyte count     |              | relative | absolute |             | Advia 120       |
| Neutrophils                      | Neut         | rel.1    | G/l      | M01         | Advia 120       |
| Eosinophils                      | Eos          | rel.1    | G/l      | M01         | Advia 120       |
| Basophils                        | Baso         | rel.1    | G/l      | M01         | Advia 120       |
| Lymphocytes                      | Lympho       | rel.1    | G/l      | M01         | Advia 120       |
| Monocytes                        | Mono         | rel.1    | G/l      | M01         | Advia 120       |
| Large unstained cells            | Luc          | rel.1    | G/l      | M01         | Advia 120       |
| Platelet count                   | Plt          | G/l      |          | M01         | Advia 120       |

**Hemoglobin derivatives**

| Parameter     | Abbreviation | Unit   | Method   | Method code | Instrumentation  |
|---------------|--------------|--------|--|-------------|------------------|
| Methemoglobin | MetHb        | rel. 1 | Spectrometry, results given as ratio of total hemoglobin   | M01         | OSM <sup>2</sup> |
| Heinz bodies  | Heinz B      | rel.1  | Microscopic examination of New Methylene Blue stained films, results given as ratio of total RBC | M01         | Microscope       |

**Coagulation**

| Parameter                               | Abbreviation | Unit   | Method   | Method code | Instrumentation  |
|---|--------------|--------|--|-------------|------------------|
| Prothrombin time (=Thromboplastin time) | PT           | rel. 1 | Clotting assay, thromboplastin from rabbit brain tissue, results as ratio of normal activity | M01         | STA <sup>3</sup> |
| Activated partial thromboplastin time   | PTT          | sec    | Clotting assay, cephalin from rabbit cerebral tissue, silica surface activator               | M01         | STA              |

<sup>2</sup> Hemoximeter OSM3

<sup>3</sup> STA-compact analyzer (Roche Diagnostics)



### 1.1.2 CLINICAL CHEMISTRY

Lithium heparin was used as anticoagulant during blood collection.

| Parameter   | Abbreviation | Unit        | Method   | Method code | Instrumentation          |
|---|--------------|-------------|--|-------------|--------------------------|
| Glucose   | Gluc         | mmol/l      | Hexokinase/G6P-DH  | M01         | Hitachi 917 <sup>4</sup> |
| Urea  | Urea         | mmol/l      | Urease/GLDH  | M01         | Hitachi 917              |
| Creatinine  | Creat        | µmol/l      | Enzymatic colorimetric test                                  | M01         | Hitachi 917              |
| Bilirubin, total                                      | Bili-tot     | µmol/l      | Reaction with 2,5-Dichloro-phenyl-diazonium salt             | M01         | Hitachi 917              |
| Cholesterol, total                                    | Chol         | mmol/l      | Enzymatic, CHOD/PAP  | M01         | Hitachi 917              |
| Triglycerides   | Trigly       | mmol/l      | Glycerol-Kinase<br>GPO/PAP method                            | M01         | Hitachi 917              |
| Phospholipids   | Phos-Lip     | mmol/l      | Phospholipase-<br>Cholinoxidase-<br>Peroxidase-reaction      | M01         | Hitachi 917              |
| Aspartate aminotransferase<br>EC 2.6.1.1 <sup>5</sup> | ASAT         | U/l<br>37°C | MDH/NADH coupled reaction                                    | M01         | Hitachi 917              |
| Alanine aminotransferase<br>EC 2.6.1.2                | ALAT         | U/l<br>37°C | LDH/NADH coupled reaction                                    | M01         | Hitachi 917              |
| Lactate dehydrogenase<br>EC 1.1.1.27                  | LDH          | U/l<br>37°C | NADH/LDH coupled reaction<br>using pyruvate as substrate     | M01         | Hitachi 917              |
| Glutamate dehydrogenase<br>EC 1.4.1.3                 | GLDH         | U/l<br>37°C | Standard method, optimized<br>(DGKC)                         | M01         | Hitachi 917              |
| Alkaline phosphatase<br>EC 3.1.3.1                    | AIP          | U/l<br>37°C | p-Nitrophenyl-phosphate as<br>substrate                      | M01         | Hitachi 917              |
| Gamma-glutamyl transferase<br>EC 2.3.2.2              | GGT          | U/l<br>37°C | Substrate: L-gamma-<br>glutamyl-3-carboxy-<br>4-nitroanilide | M01         | Hitachi 917              |
| Creatine kinase<br>EC 2.7.3.2                         | CK           | U/l<br>37°C | HK/ATP and G6P-<br>DH/NADPH<br>coupled reaction method       | M01         | Hitachi 917              |
| Sodium  | Na+          | mmol/l      | Ion selective electrode                                      | M01         | Hitachi 917              |

<sup>4</sup> Hitachi 917 analyzer, Roche Diagnostics

<sup>5</sup> Identification of enzymes with EC-Number (Enzyme Commission) according to Enzyme Nomenclature, Recommendations (1972) of the IUPAC and IUB, Elsevier Scient. Publ. Comp., Amsterdam, 1973

| Parameter            | Abbreviation        | Unit   | Method                              | Method code | Instrumentation |
|----------------------|---------------------|--------|-------------------------------------|-------------|-----------------|
| Potassium            | K <sup>+</sup>      | mmol/l | Ion selective electrode             | M01         | Hitachi 917     |
| Chloride             | Cl <sup>-</sup>     | mmol/l | Ion selective electrode             | M01         | Hitachi 917     |
| Calcium              | Ca <sup>++</sup>    | mmol/l | o-Cresolphthalein complexone method | M01         | Hitachi 917     |
| Phosphorus inorganic | PO <sub>4</sub> -in | mmol/l | Phosphomolybdate reaction           | M01         | Hitachi 917     |
| Protein, total       | Prot                | g/l    | Biuret reaction                     | M01         | Hitachi 917     |

### Electrophoresis

Electrophoretic separation of plasma proteins was performed with a Hydrasys LC system (Sebia) using agarose gels (Method code: M02). The bands were stained with amido black and scanned photometrically to give quantitative results using a Hyrys densitometer (Sebia).

| Parameter              | Abbreviation | Unit (relative values) | Unit (absolute values) |
|------------------------|--------------|------------------------|------------------------|
| Albumin                | Alb-el       | rel.1                  | g/l                    |
| Alpha-1 Globulins      | Glob A1      | rel.1                  | g/l                    |
| Alpha-2 Globulins      | Glob A2      | rel.1                  | g/l                    |
| Beta-1 Globulins       | Glob B       | rel.1                  | g/l                    |
| Gamma Globulins        | Glob G       | rel.1                  | g/l                    |
| Albumin/Globulin Ratio | A/G          | rel.1                  |                        |

### 1.1.3 URINALYSIS

#### Physical examination

| Parameter                                | Abbreviation | Unit         | Method / Instrumentation   | Method code |
|--|--------------|--------------|----------------------------|-------------|
| Urine volume (18-hour)                   | Volume       | ml           | Gravimetric <sup>6</sup>   | M01         |
| Relative Density<br>(= Specific gravity) | Rel dens     | rel.1        | Refractometer <sup>7</sup> | M01         |
| Color                                    | Color        |              | Visual inspection          |             |
|  | NORMAL       |              |                            |             |
|  | COLESS       | colorless    |                            |             |
|  | YE/BR        | yellow-brown |                            |             |
|  | YE/GR        | yellow-green |                            |             |
|  | RED          |              |                            |             |
|  | BROWN        |              |                            |             |
|  | BLACK        |              |                            |             |
|  | RE/BR        | red-brown    |                            |             |
| Appearance                               | Appear       |              | Visual inspection          |             |

The following urine components were investigated using a semi-automated test strip analyzer Miditron (Roche Diagnostics) applying reflectance spectroscopy. Results are given as discrete values representing a concentration range (semi-quantitative results).

One male of group 3 and all males and females of group 4 had black discolored urine preventing test strip reading. In group 3 the results of the test strips might be disturbed by the brown discoloration of the urine.

#### Chemical examination

| Parameter    | Abbreviation | Unit   | Set points                   | Method code | Instru-mentation      |
|--------------|--------------|--------|------------------------------|-------------|-----------------------|
| pH-value     | pH           |        | 5.0, 6.0, 6.5, 7.0, 8.0, 9.0 | M01         | Miditron <sup>8</sup> |
| Nitrite      | NIT          | score  | 0 (negative), 1 (positive)   | M01         | Miditron              |
| Protein      | PRO          | g/l    | 0, 0.25, 0.75, 1.50, 5.00    | M01         | Miditron              |
| Glucose      | GLU          | mmol/l | 0, 3, 6, 17, 56              | M01         | Miditron              |
| Ketones      | KET          | mmol/l | 0, 0.5, 1.5, 5.0, 15.0       | M01         | Miditron              |
| Urobilinogen | UBG          | µmol/l | 0, 17, 68, 135, 203          | M01         | Miditron              |
| Bilirubin    | BIL          | µmol/l | 0, 17, 50, 100               | M01         | Miditron              |
| Blood        |              |        |                              |             |                       |
| Erythrocytes | ERY          | per µl | 0, 10, 25, 50, 150, 250      | M01         | Miditron              |
| Leukocytes   | LEU          | per µl | 0, 25, 100, 500              | M01         | Miditron              |

<sup>6</sup> Mettler balance

<sup>7</sup> Clinical Refractometer SU-202, Kernco

<sup>8</sup> Miditron semi-automated urine chemistry analyzer and reagent test strips, Roche Diagnostics

**Microscopic examination**

After centrifugation of the urine specimen, the sediment was examined microscopically. Results of microscopic estimates for formed elements (cells, casts, crystals) were classified in the following categories:

|          |   |  |
|----------|---|--|
|          | 0   | no abnormalities observed  |
|          | 1   | few  |
|          | 2   | moderate number  |
|          | 3   | many   |
| Cells    | Ery<br>Leu<br>Epi-cells                                 | Erythrocytes<br>Leukocytes<br>Epithelial cells   |
| Casts    | Casts   | Casts  |
| Crystals | Cry-PO4<br>Cry-Caox<br>Cry-UrAc<br>Cry-Uram<br>Cry-Unid | Triple phosphate crystals<br>Calcium oxalate crystals<br>Uric acid crystals<br>Amorphous urate crystals<br>Unidentified crystals |

## 1.2 HEMATOLOGY (MEANS)

### MALES

|         |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg  | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|---------|--------|-----------------------------------|---------------------|---------------------|---------------------|----------------------|
| RBC     | T/l    |                                   |                     |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 9.197 <sup>ad</sup> | 8.964               | 9.030               | 8.558 <sup>**</sup>  |
|         |        | S.D.                              | 0.323               | 0.456               | 0.273               | 0.364                |
|         |        | N                                 | 10                  | 10                  | 10                  | 10                   |
| Hb      | mmol/l |                                   |                     |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 10.15 a             | 9.92                | 10.01               | 9.88                 |
|         |        | S.D.                              | 0.21                | 0.35                | 0.28                | 0.29                 |
|         |        | N                                 | 10                  | 10                  | 10                  | 10                   |
| Hct     | rel. l |                                   |                     |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.444 a             | 0.426               | 0.436               | 0.433                |
|         |        | S.D.                              | 0.013               | 0.018               | 0.012               | 0.013                |
|         |        | N                                 | 10                  | 10                  | 10                  | 10                   |
| MCV     | fl     |                                   |                     |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 48.37 <sup>ad</sup> | 47.64               | 48.27               | 50.75 <sup>**</sup>  |
|         |        | S.D.                              | 1.78                | 1.80                | 1.07                | 1.75                 |
|         |        | N                                 | 10                  | 10                  | 10                  | 10                   |
| RDW     | rel. l |                                   |                     |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.1344 k            | 0.1419              | 0.1318              | 0.1395               |
|         |        | S.D.                              | 0.0169              | 0.0184              | 0.0042              | 0.0153               |
|         |        | N                                 | 10                  | 10                  | 10                  | 10                   |
| MCH     | fmol   |                                   |                     |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 1.107 a             | 1.106               | 1.108               | 1.157                |
|         |        | S.D.                              | 0.053               | 0.056               | 0.034               | 0.044                |
|         |        | N                                 | 10                  | 10                  | 10                  | 10                   |

Statistical key: a=ANOVA ad=ANOVA + Dunnett k=Kruskal-Wallis \*\* = p<0.01

Hematology (means)

| MALES   |        |            |          |          |          |           |
|---------|--------|------------|----------|----------|----------|-----------|
|         |        | Group      | Group 1  | Group 2  | Group 3  | Group 4   |
|         |        | Group Name |          |          |          |           |
|         |        | Dose Level | 0 mg/kg  | 15 mg/kg | 50 mg/kg | 200 mg/kg |
| MCHC    | mmol/l |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 22.851 a | 23.240   | 22.974   | 22.792    |
|         |        | S.D.       | 0.466    | 0.382    | 0.410    | 0.344     |
|         |        | N          | 10       | 10       | 10       | 10        |
| HDW     | mmol/l |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 1.789 a  | 1.847    | 1.818    | 1.901     |
|         |        | S.D.       | 0.103    | 0.103    | 0.077    | 0.127     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Reti    | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.0175ad | 0.0193   | 0.0192   | 0.0252**  |
|         |        | S.D.       | 0.0014   | 0.0026   | 0.0024   | 0.0031    |
|         |        | N          | 10       | 10       | 10       | 10        |
| Reti    | G/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 161.2ad  | 172.4    | 173.7    | 214.4**   |
|         |        | S.D.       | 13.5     | 20.2     | 19.4     | 20.8      |
|         |        | N          | 10       | 10       | 10       | 10        |
| L Reti  | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.7048ad | 0.6902   | 0.6817   | 0.6290**  |
|         |        | S.D.       | 0.0397   | 0.0429   | 0.0369   | 0.0239    |
|         |        | N          | 10       | 10       | 10       | 10        |
| M Reti  | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.2654ad | 0.2779   | 0.2885   | 0.3225**  |
|         |        | S.D.       | 0.0336   | 0.0351   | 0.0279   | 0.0198    |
|         |        | N          | 10       | 10       | 10       | 10        |

Statistical key: a=ANOVA ad=ANOVA + Dunnett \*\* = p<0.01

Hematology (means)

| MALES   |        |            |                      |          |          |                      |
|---------|--------|------------|----------------------|----------|----------|----------------------|
|         |        | Group      | Group 1              | Group 2  | Group 3  | Group 4              |
|         |        | Group Name |                      |          |          |                      |
|         |        | Dose Level | 0 mg/kg              | 15 mg/kg | 50 mg/kg | 200 mg/kg            |
| H Reti  | rel. 1 |            |                      |          |          |                      |
| WEEK 16 |        | MEAN       | 0.0300 <sup>ad</sup> | 0.0322   | 0.0319   | 0.0488 <sup>**</sup> |
|         |        | S.D.       | 0.0084               | 0.0104   | 0.0111   | 0.0082               |
|         |        | N          | 10                   | 10       | 10       | 10                   |
| WBC     | G/l    |            |                      |          |          |                      |
| WEEK 16 |        | MEAN       | 6.365 a              | 6.311    | 6.513    | 6.877                |
|         |        | S.D.       | 0.929                | 0.729    | 1.326    | 1.290                |
|         |        | N          | 10                   | 10       | 10       | 10                   |
| Neut    | rel. 1 |            |                      |          |          |                      |
| WEEK 16 |        | MEAN       | 0.1942 a             | 0.1982   | 0.2196   | 0.2132               |
|         |        | S.D.       | 0.0513               | 0.0309   | 0.0438   | 0.0384               |
|         |        | N          | 10                   | 10       | 10       | 10                   |
| Eos     | rel. 1 |            |                      |          |          |                      |
| WEEK 16 |        | MEAN       | 0.0181 a             | 0.0216   | 0.0180   | 0.0168               |
|         |        | S.D.       | 0.0042               | 0.0074   | 0.0045   | 0.0054               |
|         |        | N          | 10                   | 10       | 10       | 10                   |
| Baso    | rel. 1 |            |                      |          |          |                      |
| WEEK 16 |        | MEAN       | 0.0028 <sup>ad</sup> | 0.0033   | 0.0023   | 0.0025               |
|         |        | S.D.       | 0.0008               | 0.0008   | 0.0007   | 0.0005               |
|         |        | N          | 10                   | 10       | 10       | 10                   |
| Lympho  | rel. 1 |            |                      |          |          |                      |
| WEEK 16 |        | MEAN       | 0.7614 a             | 0.7486   | 0.7302   | 0.7385               |
|         |        | S.D.       | 0.0528               | 0.0314   | 0.0436   | 0.0435               |
|         |        | N          | 10                   | 10       | 10       | 10                   |

Statistical key: a=ANOVA ad=ANOVA + Dunnett \*\* = p<0.01

Hematology (means)

| MALES   |        |            |          |          |          |           |
|---------|--------|------------|----------|----------|----------|-----------|
|         |        | Group      | Group 1  | Group 2  | Group 3  | Group 4   |
|         |        | Group Name |          |          |          |           |
|         |        | Dose Level | 0 mg/kg  | 15 mg/kg | 50 mg/kg | 200 mg/kg |
| Mono    | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.0171ad | 0.0207   | 0.0228** | 0.0205    |
|         |        | S.D.       | 0.0047   | 0.0035   | 0.0033   | 0.0040    |
|         |        | N          | 10       | 10       | 10       | 10        |
| Luc     | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.0065 a | 0.0076   | 0.0070   | 0.0084    |
|         |        | S.D.       | 0.0037   | 0.0038   | 0.0029   | 0.0042    |
|         |        | N          | 10       | 10       | 10       | 10        |
| Neut    | G/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 1.209 k  | 1.241    | 1.461    | 1.493     |
|         |        | S.D.       | 0.222    | 0.189    | 0.542    | 0.477     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Eos     | G/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.116 a  | 0.136    | 0.118    | 0.117     |
|         |        | S.D.       | 0.033    | 0.041    | 0.037    | 0.045     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Baso    | G/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.017 a  | 0.022    | 0.016    | 0.016     |
|         |        | S.D.       | 0.007    | 0.008    | 0.007    | 0.005     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Lympho  | G/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 4.874 a  | 4.734    | 4.727    | 5.048     |
|         |        | S.D.       | 0.911    | 0.676    | 0.818    | 0.834     |
|         |        | N          | 10       | 10       | 10       | 10        |

Statistical key: a=ANOVA ad=ANOVA + Dunnett k=Kruskal-Wallis \*\* = p<0.01



Hematology (means)

MALES

|       |    | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|-------|----|-----------------------------------|--------------------|---------------------|---------------------|----------------------|
| Mono  |    | G/l                               |                    |                     |                     |                      |
| WEEK  | 16 | MEAN                              | 0.106 a            | 0.131               | 0.146               | 0.140                |
|       |    | S.D.                              | 0.029              | 0.026               | 0.037               | 0.039                |
|       |    | N                                 | 10                 | 10                  | 10                  | 10                   |
| Luc   |    | G/l                               |                    |                     |                     |                      |
| WEEK  | 16 | MEAN                              | 0.043 a            | 0.047               | 0.044               | 0.061                |
|       |    | S.D.                              | 0.025              | 0.027               | 0.020               | 0.036                |
|       |    | N                                 | 10                 | 10                  | 10                  | 10                   |
| Plt   |    | G/l                               |                    |                     |                     |                      |
| WEEK  | 16 | MEAN                              | 899.3 a            | 891.0               | 927.0               | 903.0                |
|       |    | S.D.                              | 84.9               | 128.9               | 138.9               | 107.7                |
|       |    | N                                 | 10                 | 10                  | 10                  | 10                   |
| Methb |    | rel. 1                            |                    |                     |                     |                      |
| WEEK  | 16 | MEAN                              | 0.0081 a           | 0.0074              | 0.0079              | 0.0082               |
|       |    | S.D.                              | 0.0011             | 0.0023              | 0.0016              | 0.0014               |
|       |    | N                                 | 9                  | 8                   | 9                   | 10                   |
| PT    |    | rel. 1                            |                    |                     |                     |                      |
| WEEK  | 16 | MEAN                              | 0.772ad            | 0.793               | 0.774               | 0.830*               |
|       |    | S.D.                              | 0.050              | 0.035               | 0.022               | 0.054                |
|       |    | N                                 | 10                 | 10                  | 10                  | 10                   |
| PTT   |    | sec                               |                    |                     |                     |                      |
| WEEK  | 16 | MEAN                              | 17.01 a            | 15.92               | 19.34               | 16.06                |
|       |    | S.D.                              | 4.12               | 3.67                | 2.99                | 3.78                 |
|       |    | N                                 | 10                 | 10                  | 10                  | 10                   |

Statistical key: a=ANOVA ad=ANOVA + Dunnett \* = p<0.05

Hematology (means)

FEMALES

|         |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg   | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|---------|--------|-----------------------------------|----------------------|---------------------|---------------------|----------------------|
| RBC     | T/l    |                                   |                      |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 8.205 <sup>ad</sup>  | 7.894               | 7.518 <sup>**</sup> | 7.215 <sup>**</sup>  |
|         |        | S.D.                              | 0.409                | 0.234               | 0.244               | 0.296                |
|         |        | N                                 | 10                   | 10                  | 10                  | 10                   |
| Hb      | mmol/l |                                   |                      |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 9.81 <sup>ad</sup>   | 9.61                | 9.19 <sup>**</sup>  | 9.06 <sup>**</sup>   |
|         |        | S.D.                              | 0.23                 | 0.20                | 0.28                | 0.34                 |
|         |        | N                                 | 10                   | 10                  | 10                  | 10                   |
| Hct     | rel. l |                                   |                      |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.420 <sup>ad</sup>  | 0.414               | 0.388 <sup>**</sup> | 0.402 <sup>**</sup>  |
|         |        | S.D.                              | 0.014                | 0.010               | 0.010               | 0.011                |
|         |        | N                                 | 10                   | 10                  | 10                  | 10                   |
| MCV     | fl     |                                   |                      |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 51.34 <sup>ad</sup>  | 52.46               | 52.87               | 55.90 <sup>**</sup>  |
|         |        | S.D.                              | 2.08                 | 1.62                | 1.91                | 2.45                 |
|         |        | N                                 | 10                   | 10                  | 10                  | 10                   |
| RDW     | rel. l |                                   |                      |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.1308 <sup>kd</sup> | 0.1425              | 0.1442              | 0.1279 <sup>*</sup>  |
|         |        | S.D.                              | 0.0506               | 0.0505              | 0.0381              | 0.0069               |
|         |        | N                                 | 10                   | 10                  | 10                  | 10                   |
| MCH     | fmo1   |                                   |                      |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 1.199 a              | 1.217               | 1.222               | 1.258                |
|         |        | S.D.                              | 0.056                | 0.038               | 0.058               | 0.054                |
|         |        | N                                 | 10                   | 10                  | 10                  | 10                   |

Statistical key: a=ANOVA ad=ANOVA + Dunnett kd=Kruskal-Wallis + Dunn \* = p<0.05 \*\* = p<0.01

|         |        | Hematology (means) |                      |          |                      |                      |
|---------|--------|--------------------|----------------------|----------|----------------------|----------------------|
| FEMALES |        |                    |                      |          |                      |                      |
|         |        | Group              | Group 1              | Group 2  | Group 3              | Group 4              |
|         |        | Group Name         |                      |          |                      |                      |
|         |        | Dose Level         | 0 mg/kg              | 15 mg/kg | 50 mg/kg             | 200 mg/kg            |
| MCHC    | mmol/l |                    |                      |          |                      |                      |
| WEEK 16 |        | MEAN               | 23.352 <sup>ad</sup> | 23.205   | 23.114               | 22.498 <sup>**</sup> |
|         |        | S.D.               | 0.422                | 0.333    | 0.460                | 0.409                |
|         |        | N                  | 10                   | 10       | 10                   | 10                   |
| HDW     | mmol/l |                    |                      |          |                      |                      |
| WEEK 16 |        | MEAN               | 1.428 <sup>ad</sup>  | 1.517    | 1.515                | 1.459                |
|         |        | S.D.               | 0.063                | 0.083    | 0.105                | 0.053                |
|         |        | N                  | 10                   | 10       | 10                   | 10                   |
| Reti    | rel. 1 |                    |                      |          |                      |                      |
| WEEK 16 |        | MEAN               | 0.0199 <sup>ad</sup> | 0.0222   | 0.0304 <sup>**</sup> | 0.0437 <sup>**</sup> |
|         |        | S.D.               | 0.0037               | 0.0039   | 0.0045               | 0.0068               |
|         |        | N                  | 10                   | 10       | 10                   | 10                   |
| Reti    | G/l    |                    |                      |          |                      |                      |
| WEEK 16 |        | MEAN               | 163.6 <sup>ad</sup>  | 174.4    | 229.1 <sup>**</sup>  | 314.4 <sup>**</sup>  |
|         |        | S.D.               | 27.1                 | 30.3     | 34.2                 | 41.6                 |
|         |        | N                  | 10                   | 10       | 10                   | 10                   |
| L Reti  | rel. 1 |                    |                      |          |                      |                      |
| WEEK 16 |        | MEAN               | 0.6794 <sup>ad</sup> | 0.6403   | 0.5810 <sup>**</sup> | 0.5794 <sup>**</sup> |
|         |        | S.D.               | 0.0671               | 0.0616   | 0.0776               | 0.0605               |
|         |        | N                  | 10                   | 10       | 10                   | 10                   |
| M Reti  | rel. 1 |                    |                      |          |                      |                      |
| WEEK 16 |        | MEAN               | 0.2695 <sup>ad</sup> | 0.3247   | 0.3661 <sup>**</sup> | 0.3593 <sup>*</sup>  |
|         |        | S.D.               | 0.0632               | 0.0509   | 0.0537               | 0.0346               |
|         |        | N                  | 10                   | 10       | 10                   | 10                   |

Statistical key: ad=ANOVA + Dunnett \* = p<0.05 \*\* = p<0.01

Hematology (means)

FEMALES

|         |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|---------|--------|-----------------------------------|--------------------|---------------------|---------------------|----------------------|
| H Reti  | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.0315kd           | 0.0350              | 0.0531              | 0.0611*              |
|         |        | S.D.                              | 0.0102             | 0.0150              | 0.0262              | 0.0290               |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| WBC     | G/l    |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 4.092 a            | 3.394               | 4.207               | 3.851                |
|         |        | S.D.                              | 0.917              | 0.675               | 1.102               | 0.820                |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Neut    | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.1692 a           | 0.1916              | 0.1938              | 0.1912               |
|         |        | S.D.                              | 0.0626             | 0.0400              | 0.0486              | 0.0546               |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Eos     | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.0186kd           | 0.0208              | 0.0179              | 0.0128               |
|         |        | S.D.                              | 0.0100             | 0.0052              | 0.0059              | 0.0036               |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Baso    | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.0020 a           | 0.0020              | 0.0024              | 0.0025               |
|         |        | S.D.                              | 0.0008             | 0.0008              | 0.0008              | 0.0012               |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Lympho  | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.7861 a           | 0.7572              | 0.7622              | 0.7715               |
|         |        | S.D.                              | 0.0666             | 0.0425              | 0.0488              | 0.0581               |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |

Statistical key: a=ANOVA kd=Kruskal-Wallis + Dunn \* = p<0.05

Hematology (means)

FEMALES

|         |        | Group      | Group 1  | Group 2  | Group 3  | Group 4   |
|---------|--------|------------|----------|----------|----------|-----------|
|         |        | Group Name |          |          |          |           |
|         |        | Dose Level | 0 mg/kg  | 15 mg/kg | 50 mg/kg | 200 mg/kg |
| Mono    | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.0179 a | 0.0223   | 0.0173   | 0.0164    |
|         |        | S.D.       | 0.0058   | 0.0081   | 0.0054   | 0.0039    |
|         |        | N          | 10       | 10       | 10       | 10        |
| Luc     | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.0060 a | 0.0059   | 0.0065   | 0.0058    |
|         |        | S.D.       | 0.0027   | 0.0023   | 0.0023   | 0.0021    |
|         |        | N          | 10       | 10       | 10       | 10        |
| Neut    | G/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.676 a  | 0.647    | 0.832    | 0.720     |
|         |        | S.D.       | 0.223    | 0.178    | 0.360    | 0.196     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Eos     | G/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.075kd  | 0.072    | 0.076    | 0.048     |
|         |        | S.D.       | 0.044    | 0.025    | 0.033    | 0.010     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Baso    | G/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.007 k  | 0.007    | 0.009    | 0.011     |
|         |        | S.D.       | 0.005    | 0.005    | 0.003    | 0.009     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Lympho  | G/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 3.234 a  | 2.575    | 3.194    | 2.988     |
|         |        | S.D.       | 0.845    | 0.543    | 0.833    | 0.720     |
|         |        | N          | 10       | 10       | 10       | 10        |

Statistical key: a=ANOVA k=Kruskal-Wallis kd=Kruskal-Wallis + Dunn

Hematology (means)

FEMALES

|         |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|---------|--------|-----------------------------------|--------------------|---------------------|---------------------|----------------------|
| Mono    | G/l    |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.073 a            | 0.076               | 0.069               | 0.062                |
|         |        | S.D.                              | 0.022              | 0.023               | 0.022               | 0.016                |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Luc     | G/l    |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.026 a            | 0.019               | 0.026               | 0.023                |
|         |        | S.D.                              | 0.013              | 0.010               | 0.010               | 0.008                |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Plt     | G/l    |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 953.4 a            | 960.5               | 1016.7              | 1031.6               |
|         |        | S.D.                              | 142.5              | 84.9                | 71.1                | 87.5                 |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Methb   | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.0089ad           | 0.0094              | 0.0105*             | 0.0105*              |
|         |        | S.D.                              | 0.0014             | 0.0010              | 0.0015              | 0.0007               |
|         |        | N                                 | 8                  | 10                  | 10                  | 10                   |
| Heinz B | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.0000 a           |                     | 0.0000              | 0.0000               |
|         |        | S.D.                              | 0.0000             |                     | 0.0000              | 0.0000               |
|         |        | N                                 | 10                 |                     | 10                  | 10                   |
| PT      | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.799 k            | 0.767               | 0.802               | 0.800                |
|         |        | S.D.                              | 0.083              | 0.034               | 0.036               | 0.051                |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| PTT     | sec    |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 16.84 a            | 15.93               | 14.14               | 14.17                |
|         |        | S.D.                              | 2.68               | 2.63                | 2.65                | 2.28                 |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |

Statistical key: a=ANOVA ad=ANOVA + Dunnett k=Kruskal-Wallis \* = p<0.05

### 1.3 BLOOD CHEMISTRY (MEANS)

MALES

|          |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg  | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|----------|--------|-----------------------------------|---------------------|---------------------|---------------------|----------------------|
| Gluc     | mmol/l |                                   |                     |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 4.627 <sup>kd</sup> | 5.252 <sup>*</sup>  | 5.133               | 4.841                |
|          | S.D.   |                                   | 0.286               | 0.444               | 0.375               | 0.817                |
|          | N      |                                   | 10                  | 10                  | 10                  | 10                   |
| Urea     | mmol/l |                                   |                     |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 5.117 <sup>a</sup>  | 5.501               | 5.137               | 5.414                |
|          | S.D.   |                                   | 0.714               | 0.768               | 0.550               | 0.855                |
|          | N      |                                   | 10                  | 10                  | 10                  | 10                   |
| Creat    | μmol/l |                                   |                     |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 25.71 <sup>ad</sup> | 27.39               | 26.69               | 23.54                |
|          | S.D.   |                                   | 2.15                | 1.58                | 1.99                | 3.43                 |
|          | N      |                                   | 10                  | 10                  | 10                  | 10                   |
| Bili-tot | μmol/l |                                   |                     |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 1.810 <sup>a</sup>  | 1.802               | 1.986               | 2.196                |
|          | S.D.   |                                   | 0.242               | 0.391               | 0.469               | 0.418                |
|          | N      |                                   | 10                  | 10                  | 10                  | 10                   |
| Chol     | mmol/l |                                   |                     |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 1.747 <sup>a</sup>  | 1.762               | 1.798               | 2.039                |
|          | S.D.   |                                   | 0.287               | 0.278               | 0.277               | 0.162                |
|          | N      |                                   | 10                  | 10                  | 10                  | 10                   |
| Trigly   | mmol/l |                                   |                     |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 0.635 <sup>a</sup>  | 0.529               | 0.595               | 0.686                |
|          | S.D.   |                                   | 0.213               | 0.322               | 0.226               | 0.386                |
|          | N      |                                   | 10                  | 10                  | 10                  | 10                   |

Statistical key: a=ANOVA ad=ANOVA + Dunnett kd=Kruskal-Wallis + Dunn \* = p<0.05

Blood chemistry (means)

| MALES    |        |                                   |                    |                     |                     |                      |
|----------|--------|-----------------------------------|--------------------|---------------------|---------------------|----------------------|
|          |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
| Phos-Lip | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16  |        | MEAN                              | 1.452ad            | 1.468               | 1.512               | 1.661**              |
|          |        | S.D.                              | 0.155              | 0.155               | 0.140               | 0.149                |
|          |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| ASAT     | U/l    |                                   |                    |                     |                     |                      |
| WEEK 16  |        | MEAN                              | 73.16 a            | 74.51               | 74.35               | 74.41                |
|          |        | S.D.                              | 5.72               | 7.68                | 6.04                | 11.96                |
|          |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| ALAT     | U/l    |                                   |                    |                     |                     |                      |
| WEEK 16  |        | MEAN                              | 34.87 a            | 32.09               | 37.19               | 37.11                |
|          |        | S.D.                              | 5.88               | 6.24                | 5.60                | 8.10                 |
|          |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| LDH      | U/l    |                                   |                    |                     |                     |                      |
| WEEK 16  |        | MEAN                              | 186.27 k           | 217.52              | 153.48              | 217.43               |
|          |        | S.D.                              | 86.32              | 154.44              | 40.22               | 142.54               |
|          |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| GLDH     | U/l    |                                   |                    |                     |                     |                      |
| WEEK 16  |        | MEAN                              | 7.72 k             | 7.55                | 9.80                | 7.60                 |
|          |        | S.D.                              | 1.53               | 2.13                | 5.25                | 2.12                 |
|          |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| ATP      | U/l    |                                   |                    |                     |                     |                      |
| WEEK 16  |        | MEAN                              | 59.83 a            | 62.36               | 60.07               | 60.99                |
|          |        | S.D.                              | 9.85               | 11.11               | 12.34               | 11.10                |
|          |        | N                                 | 10                 | 10                  | 10                  | 10                   |

Statistical key: a=ANOVA ad=ANOVA + Dunnett k=Kruskal-Wallis \*\* = p<0.01



Blood chemistry (means)

| MALES   |        |                                   |                    |                     |                     |                      |
|---------|--------|-----------------------------------|--------------------|---------------------|---------------------|----------------------|
|         |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
| GGT     | U/l    |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 0.00 a             | 0.00                | 0.00                | 0.00                 |
|         | S.D.   |                                   | 0.00               | 0.00                | 0.00                | 0.00                 |
|         | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| CK      | U/l    |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 176.92 k           | 169.52              | 146.68              | 188.75               |
|         | S.D.   |                                   | 98.21              | 54.26               | 34.69               | 87.33                |
|         | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Na+     | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 144.23ad           | 146.47*             | 146.83**            | 145.82               |
|         | S.D.   |                                   | 1.43               | 1.06                | 2.09                | 2.36                 |
|         | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| K+      | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 3.399ad            | 3.710**             | 3.745**             | 3.693**              |
|         | S.D.   |                                   | 0.144              | 0.153               | 0.151               | 0.236                |
|         | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Cl-     | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 104.74kd           | 107.33**            | 106.92*             | 105.53               |
|         | S.D.   |                                   | 1.48               | 0.78                | 0.93                | 2.19                 |
|         | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Ca++    | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 2.646 a            | 2.650               | 2.680               | 2.676                |
|         | S.D.   |                                   | 0.056              | 0.061               | 0.061               | 0.047                |
|         | N      |                                   | 10                 | 10                  | 10                  | 10                   |

Statistical key: a=ANOVA ad=ANOVA + Dunnett k=Kruskal-Wallis kd=Kruskal-Wallis + Dunn \* = p<0.05 \*\* = p<0.01

Blood chemistry (means)

| MALES   |        |            |          |          |          |           |
|---------|--------|------------|----------|----------|----------|-----------|
|         |        | Group      | Group 1  | Group 2  | Group 3  | Group 4   |
|         |        | Group Name | 0 mg/kg  | 15 mg/kg | 50 mg/kg | 200 mg/kg |
|         |        | Dose Level |          |          |          |           |
| PO4-in  | mmol/l |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 1.675 a  | 1.700    | 1.665    | 1.788     |
|         |        | S.D.       | 0.187    | 0.079    | 0.107    | 0.146     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Prot    | g/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 64.298 a | 65.168   | 65.306   | 64.948    |
|         |        | S.D.       | 2.119    | 1.669    | 2.339    | 2.081     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Alb-e1  | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.5273 a | 0.5296   | 0.5227   | 0.5279    |
|         |        | S.D.       | 0.0113   | 0.0078   | 0.0088   | 0.0151    |
|         |        | N          | 10       | 10       | 10       | 10        |
| Glob A1 | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.2047 a | 0.2070   | 0.2055   | 0.1957    |
|         |        | S.D.       | 0.0098   | 0.0071   | 0.0104   | 0.0174    |
|         |        | N          | 10       | 10       | 10       | 10        |
| Glob A2 | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.0684ad | 0.0635   | 0.0701   | 0.0713    |
|         |        | S.D.       | 0.0066   | 0.0056   | 0.0037   | 0.0081    |
|         |        | N          | 10       | 10       | 10       | 10        |
| Glob B  | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.1733 a | 0.1760   | 0.1782   | 0.1812    |
|         |        | S.D.       | 0.0069   | 0.0078   | 0.0104   | 0.0082    |
|         |        | N          | 10       | 10       | 10       | 10        |

Statistical key: a=ANOVA ad=ANOVA + Dunnett

Blood chemistry (means)

MALES

|         |        | Group      | Group 1  | Group 2  | Group 3  | Group 4   |
|---------|--------|------------|----------|----------|----------|-----------|
|         |        | Group Name |          |          |          |           |
|         |        | Dose Level | 0 mg/kg  | 15 mg/kg | 50 mg/kg | 200 mg/kg |
| Glob G  | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.0263 a | 0.0239   | 0.0235   | 0.0239    |
|         |        | S.D.       | 0.0036   | 0.0032   | 0.0048   | 0.0038    |
|         |        | N          | 10       | 10       | 10       | 10        |
| Alb-e1  | g/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 33.914 a | 34.521   | 34.118   | 34.257    |
|         |        | S.D.       | 1.211    | 1.273    | 1.400    | 0.673     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Glob A1 | g/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 13.174 k | 13.486   | 13.429   | 12.715    |
|         |        | S.D.       | 0.972    | 0.455    | 0.960    | 1.293     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Glob A2 | g/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 4.394ad  | 4.134    | 4.575    | 4.636     |
|         |        | S.D.       | 0.407    | 0.342    | 0.263    | 0.587     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Glob B  | g/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 11.139 a | 11.468   | 11.627   | 11.776    |
|         |        | S.D.       | 0.497    | 0.556    | 0.568    | 0.777     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Glob G  | g/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 1.689 a  | 1.559    | 1.539    | 1.555     |
|         |        | S.D.       | 0.232    | 0.212    | 0.340    | 0.274     |
|         |        | N          | 10       | 10       | 10       | 10        |

Statistical key: a=ANOVA ad=ANOVA + Dunnett k=Kruskal-Wallis

Blood chemistry (means)

MALES

|         |  | Group      | Group 1 | Group 2  | Group 3  | Group 4   |
|---------|--|------------|---------|----------|----------|-----------|
|         |  | Group Name |         |          |          |           |
|         |  | Dose Level | 0 mg/kg | 15 mg/kg | 50 mg/kg | 200 mg/kg |
| A/G     |  | rel. 1     |         |          |          |           |
| WEEK 16 |  | MEAN       | 1.111 a | 1.119    | 1.090    | 1.115     |
|         |  | S.D.       | 0.048   | 0.033    | 0.037    | 0.068     |
|         |  | N          | 10      | 10       | 10       | 10        |

Statistical key: a=ANOVA

Blood chemistry (means)

FEMALES

|          |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg  | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|----------|--------|-----------------------------------|---------------------|---------------------|---------------------|----------------------|
| Gluc     | mmol/l |                                   |                     |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 4.729 <sup>kd</sup> | 4.886               | 5.270*              | 5.234                |
|          | S.D.   |                                   | 0.365               | 0.752               | 0.326               | 0.635                |
|          | N      |                                   | 10                  | 10                  | 10                  | 10                   |
| Urea     | mmol/l |                                   |                     |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 6.449 <sup>a</sup>  | 7.083               | 6.709               | 6.641                |
|          | S.D.   |                                   | 0.897               | 0.895               | 0.900               | 0.645                |
|          | N      |                                   | 10                  | 10                  | 10                  | 10                   |
| Creat    | μmol/l |                                   |                     |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 29.96 <sup>ad</sup> | 31.81               | 31.39               | 25.72*               |
|          | S.D.   |                                   | 2.25                | 4.34                | 3.57                | 2.91                 |
|          | N      |                                   | 10                  | 10                  | 10                  | 10                   |
| Bili-tot | μmol/l |                                   |                     |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 2.146 <sup>ad</sup> | 2.418               | 2.814*              | 2.573                |
|          | S.D.   |                                   | 0.436               | 0.434               | 0.512               | 0.551                |
|          | N      |                                   | 10                  | 10                  | 10                  | 10                   |
| Chol     | mmol/l |                                   |                     |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 1.515 <sup>ad</sup> | 1.437               | 1.437               | 1.899                |
|          | S.D.   |                                   | 0.304               | 0.433               | 0.367               | 0.380                |
|          | N      |                                   | 10                  | 10                  | 10                  | 10                   |
| Trigly   | mmol/l |                                   |                     |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 0.264 <sup>ad</sup> | 0.287               | 0.287               | 0.380**              |
|          | S.D.   |                                   | 0.066               | 0.056               | 0.065               | 0.079                |
|          | N      |                                   | 10                  | 10                  | 10                  | 10                   |

Statistical key: a=ANOVA ad=ANOVA + Dunnett kd=Kruskal-Wallis + Dunn \* = p<0.05 \*\* = p<0.01

Blood chemistry (means)

FEMALES

|          |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg   | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|----------|--------|-----------------------------------|----------------------|---------------------|---------------------|----------------------|
| Phos-Lip | mmol/l |                                   |                      |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 1.504 <sup>ad</sup>  | 1.473               | 1.516               | 1.888 <sup>**</sup>  |
|          | S.D.   |                                   | 0.206                | 0.342               | 0.236               | 0.278                |
|          | N      |                                   | 10                   | 10                  | 10                  | 10                   |
| ASAT     | U/l    |                                   |                      |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 72.18 <sup>kd</sup>  | 79.05               | 72.48               | 64.06                |
|          | S.D.   |                                   | 9.23                 | 15.83               | 6.75                | 6.27                 |
|          | N      |                                   | 10                   | 10                  | 10                  | 10                   |
| ALAT     | U/l    |                                   |                      |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 27.29 <sup>k</sup>   | 30.12               | 27.15               | 22.88                |
|          | S.D.   |                                   | 4.98                 | 11.97               | 7.09                | 2.40                 |
|          | N      |                                   | 10                   | 10                  | 10                  | 10                   |
| LDH      | U/l    |                                   |                      |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 200.49 <sup>ad</sup> | 229.71              | 197.25              | 152.72               |
|          | S.D.   |                                   | 41.89                | 36.92               | 52.40               | 60.49                |
|          | N      |                                   | 10                   | 10                  | 10                  | 10                   |
| GLDH     | U/l    |                                   |                      |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 6.27 <sup>k</sup>    | 22.05               | 11.42               | 5.66                 |
|          | S.D.   |                                   | 3.75                 | 23.97               | 13.54               | 3.18                 |
|          | N      |                                   | 10                   | 10                  | 10                  | 10                   |
| ATP      | U/l    |                                   |                      |                     |                     |                      |
| WEEK 16  | MEAN   |                                   | 23.84 <sup>a</sup>   | 19.80               | 23.23               | 24.17                |
|          | S.D.   |                                   | 4.02                 | 3.07                | 5.62                | 4.17                 |
|          | N      |                                   | 10                   | 10                  | 10                  | 10                   |

Statistical key: a=ANOVA ad=ANOVA + Dunnett k=Kruskal-Wallis kd=Kruskal-Wallis + Dunn \*\* = p<0.01

Blood chemistry (means)

FEMALES

|         |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|---------|--------|-----------------------------------|--------------------|---------------------|---------------------|----------------------|
| GGT     | U/l    |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 0.00 a             | 0.00                | 0.00                | 0.00                 |
|         | S.D.   |                                   | 0.00               | 0.00                | 0.00                | 0.00                 |
|         | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| CK      | U/l    |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 166.66 a           | 164.44              | 161.39              | 140.10               |
|         | S.D.   |                                   | 39.66              | 40.46               | 31.57               | 66.24                |
|         | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Na+     | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 144.02kd           | 145.06              | 147.56**            | 149.73**             |
|         | S.D.   |                                   | 1.18               | 0.84                | 2.10                | 0.87                 |
|         | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| K+      | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 3.371 a            | 3.184               | 3.295               | 3.244                |
|         | S.D.   |                                   | 0.158              | 0.210               | 0.320               | 0.324                |
|         | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Cl-     | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 107.25ad           | 108.65              | 111.25**            | 111.67**             |
|         | S.D.   |                                   | 1.34               | 1.03                | 2.04                | 1.64                 |
|         | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Ca++    | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 2.651 a            | 2.665               | 2.728               | 2.719                |
|         | S.D.   |                                   | 0.076              | 0.075               | 0.087               | 0.080                |
|         | N      |                                   | 10                 | 10                  | 10                  | 10                   |

Statistical key: a=ANOVA ad=ANOVA + Dunnett kd=Kruskal-Wallis + Dunn \*\* = p<0.01

Blood chemistry (means)

FEMALES

|         |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|---------|--------|-----------------------------------|--------------------|---------------------|---------------------|----------------------|
| -----   |        |                                   |                    |                     |                     |                      |
| PO4-in  | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 1.343 a            | 1.216               | 1.327               | 1.307                |
|         |        | S.D.                              | 0.165              | 0.218               | 0.179               | 0.162                |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Prot    |        |                                   |                    |                     |                     |                      |
|         | g/l    |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 66.417 a           | 68.595              | 69.527              | 67.844               |
|         |        | S.D.                              | 2.462              | 2.967               | 2.966               | 1.970                |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Alb-e1  |        |                                   |                    |                     |                     |                      |
|         | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.5782ad           | 0.6071**            | 0.5910              | 0.5836               |
|         |        | S.D.                              | 0.0264             | 0.0186              | 0.0180              | 0.0155               |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Glob A1 |        |                                   |                    |                     |                     |                      |
|         | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.1690 a           | 0.1632              | 0.1701              | 0.1720               |
|         |        | S.D.                              | 0.0099             | 0.0074              | 0.0121              | 0.0086               |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Glob A2 |        |                                   |                    |                     |                     |                      |
|         | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.0596ad           | 0.0534*             | 0.0492**            | 0.0532*              |
|         |        | S.D.                              | 0.0053             | 0.0053              | 0.0053              | 0.0046               |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Glob B  |        |                                   |                    |                     |                     |                      |
|         | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.1554ad           | 0.1429              | 0.1531              | 0.1596               |
|         |        | S.D.                              | 0.0158             | 0.0124              | 0.0070              | 0.0091               |
|         |        | N                                 | 10                 | 10                  | 10                  | 10                   |

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 Statistical key: a=ANOVA ad=ANOVA + Dunnett \* = p<0.05 \*\* = p<0.01



Blood chemistry (means)

FEMALES

|         |        | Group      | Group 1  | Group 2  | Group 3  | Group 4   |
|---------|--------|------------|----------|----------|----------|-----------|
|         |        | Group Name |          |          |          |           |
|         |        | Dose Level | 0 mg/kg  | 15 mg/kg | 50 mg/kg | 200 mg/kg |
| Glob G  | rel. 1 |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 0.0378 a | 0.0334   | 0.0366   | 0.0316    |
|         |        | S.D.       | 0.0058   | 0.0044   | 0.0082   | 0.0039    |
|         |        | N          | 10       | 10       | 10       | 10        |
| Alb-e1  | g/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 38.413ad | 41.660** | 41.082*  | 39.595    |
|         |        | S.D.       | 2.488    | 2.428    | 2.283    | 1.686     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Glob A1 | g/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 11.232 a | 11.204   | 11.838   | 11.669    |
|         |        | S.D.       | 0.883    | 0.858    | 1.166    | 0.690     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Glob A2 | g/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 3.954ad  | 3.661    | 3.425*   | 3.612     |
|         |        | S.D.       | 0.324    | 0.384    | 0.453    | 0.362     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Glob B  | g/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 10.304ad | 9.785    | 10.630   | 10.824    |
|         |        | S.D.       | 0.956    | 0.732    | 0.456    | 0.573     |
|         |        | N          | 10       | 10       | 10       | 10        |
| Glob G  | g/l    |            |          |          |          |           |
| WEEK 16 |        | MEAN       | 2.515 a  | 2.286    | 2.527    | 2.139     |
|         |        | S.D.       | 0.413    | 0.277    | 0.504    | 0.247     |
|         |        | N          | 10       | 10       | 10       | 10        |

Statistical key: a=ANOVA ad=ANOVA + Dunnett \* = p<0.05 \*\* = p<0.01

Blood chemistry (means)

| FEMALES    |        |                     |                     |          |           |  |
|------------|--------|---------------------|---------------------|----------|-----------|--|
|            |        | Group 1             | Group 2             | Group 3  | Group 4   |  |
| Group Name |        |                     |                     |          |           |  |
| Dose Level |        | 0 mg/kg             | 15 mg/kg            | 50 mg/kg | 200 mg/kg |  |
| A/G        | rel. 1 |                     |                     |          |           |  |
| WEEK 16    | MEAN   | 1.374 <sup>ad</sup> | 1.549 <sup>**</sup> | 1.442    | 1.401     |  |
|            | S.D.   | 0.146               | 0.127               | 0.108    | 0.092     |  |
|            | N      | 10                  | 10                  | 10       | 10        |  |

Statistical key: ad=ANOVA + Dunnett \*\* = p<0.01

## 1.4 URINE ANALYSIS (MEANS)

### MALES

|          |        | Group      | Group 1  | Group 2  | Group 3  | Group 4   |
|----------|--------|------------|----------|----------|----------|-----------|
|          |        | Group Name | 0 mg/kg  | 15 mg/kg | 50 mg/kg | 200 mg/kg |
|          |        | Dose Level |          |          |          |           |
| Volume   | ml     |            |          |          |          |           |
| WEEK 16  | MEAN   |            | 6.10 a   | 6.56     | 4.42     | 7.00      |
|          | S.D.   |            | 1.85     | 2.58     | 1.69     | 2.51      |
|          | N      |            | 10       | 10       | 10       | 10        |
| Rel dens | rel. 1 |            |          |          |          |           |
| WEEK 16  | MEAN   |            | 1.0445 k | 1.0429   | 1.0599   | 1.0431    |
|          | S.D.   |            | 0.0089   | 0.0089   | 0.0276   | 0.0096    |
|          | N      |            | 10       | 10       | 10       | 10        |
| Color    | Choice |            |          |          |          |           |
| WEEK 16  |        |            |          |          |          |           |
| NORMAL   | N      |            | 10       | 7        | 0        | 0         |
| YELLOW   | N      |            | 0        | 3        | 0        | 0         |
| BROWN    | N      |            | 0        | 0        | 9        | 0         |
| BLACK    | N      |            | 0        | 0        | 1        | 10        |
| Appear   | Choice |            |          |          |          |           |
| WEEK 16  |        |            |          |          |          |           |
| NORMAL   | N      |            | 0        | 2        | 6        |           |
| CLOUDY   | N      |            | 7        | 7        | 2        |           |
| TURBID   | N      |            | 3        | 1        | 0        |           |
| pH       |        |            |          |          |          |           |
| WEEK 16  | MEAN   |            | 6.05kd   | 6.25     | 6.50**   |           |
|          | S.D.   |            | 0.16     | 0.35     | 0.35     |           |
|          | N      |            | 10       | 10       | 9        |           |
| NIT      | Score  |            |          |          |          |           |
| WEEK 16  | MEAN   |            | 0.1kd    | 0.5      | 0.8**    |           |
|          | S.D.   |            | 0.3      | 0.5      | 0.4      |           |
|          | N      |            | 10       | 10       | 9        |           |
| PRO      | g/l    |            |          |          |          |           |
| WEEK 16  | MEAN   |            | 0.350kd  | 0.375    | 0.750**  |           |
|          | S.D.   |            | 0.211    | 0.270    | 0.000    |           |
|          | N      |            | 10       | 10       | 9        |           |

Statistical key: a=ANOVA k=Kruskal-Wallis kd=Kruskal-Wallis + Dunn \*\* = p<0.01

Urine analysis (means)

MALES

|         |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|---------|--------|-----------------------------------|--------------------|---------------------|---------------------|----------------------|
| GLU     | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.0 k              | 0.0                 | 0.0                 |                      |
|         |        | S.D.                              | 0.0                | 0.0                 | 0.0                 |                      |
|         |        | N                                 | 10                 | 10                  | 9                   |                      |
| KET     | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.55 k             | 0.55                | 0.56                |                      |
|         |        | S.D.                              | 0.37               | 0.37                | 0.39                |                      |
|         |        | N                                 | 10                 | 10                  | 9                   |                      |
| UBG     | µmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.0kd              | 0.0                 | 60.3**              |                      |
|         |        | S.D.                              | 0.0                | 0.0                 | 40.6                |                      |
|         |        | N                                 | 10                 | 10                  | 9                   |                      |
| BIL     | µmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 0.0kd              | 3.4                 | 15.1**              |                      |
|         |        | S.D.                              | 0.0                | 7.2                 | 5.7                 |                      |
|         |        | N                                 | 10                 | 10                  | 9                   |                      |
| ERY     | per µl |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 10.0 k             | 12.0                | 16.7                |                      |
|         |        | S.D.                              | 0.0                | 7.5                 | 7.9                 |                      |
|         |        | N                                 | 10                 | 10                  | 9                   |                      |
| LEU     | per µl |                                   |                    |                     |                     |                      |
| WEEK 16 |        | MEAN                              | 12.5kd             | 17.5                | 75.0**              |                      |
|         |        | S.D.                              | 13.2               | 12.1                | 37.5                |                      |
|         |        | N                                 | 10                 | 10                  | 9                   |                      |

Statistical key: k=Kruskal-Wallis kd=Kruskal-Wallis + Dunn \*\* = p<0.01

Urine analysis (means)

FEMALES

|          |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|----------|--------|-----------------------------------|--------------------|---------------------|---------------------|----------------------|
| Volume   | ml     |                                   |                    |                     |                     |                      |
| WEEK 16  |        | MEAN                              | 3.72 k             | 3.63                | 4.57                | 3.97                 |
|          |        | S.D.                              | 2.16               | 3.25                | 4.92                | 1.88                 |
|          |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Rel dens | rel. 1 |                                   |                    |                     |                     |                      |
| WEEK 16  |        | MEAN                              | 1.0430 k           | 1.0521              | 1.0533              | 1.0488               |
|          |        | S.D.                              | 0.0088             | 0.0237              | 0.0270              | 0.0185               |
|          |        | N                                 | 10                 | 10                  | 10                  | 10                   |
| Color    | Choice |                                   |                    |                     |                     |                      |
| WEEK 16  |        | N                                 | 10                 | 6                   | 0                   | 0                    |
| NORMAL   |        | N                                 | 0                  | 4                   | 1                   | 0                    |
| YE1BR    |        | N                                 | 0                  | 0                   | 9                   | 0                    |
| BROWN    |        | N                                 | 0                  | 0                   | 0                   | 10                   |
| BLACK    |        | N                                 | 0                  | 0                   | 0                   | 0                    |
| Appear   | Choice |                                   |                    |                     |                     |                      |
| WEEK 16  |        | N                                 | 7                  | 9                   | 9                   | 0                    |
| NORMAL   |        | N                                 | 3                  | 1                   | 0                   | 0                    |
| CLOUDY   |        | N                                 | 0                  | 0                   | 1                   | 0                    |
| TURBID   |        | N                                 | 0                  | 0                   | 0                   | 0                    |
| pH       |        |                                   |                    |                     |                     |                      |
| WEEK 16  |        | MEAN                              | 6.00 k             | 6.05                | 6.10                |                      |
|          |        | S.D.                              | 0.00               | 0.16                | 0.52                |                      |
|          |        | N                                 | 10                 | 10                  | 10                  |                      |
| NIT      | Score  |                                   |                    |                     |                     |                      |
| WEEK 16  |        | MEAN                              | 0.3kd              | 0.5                 | 0.9*                |                      |
|          |        | S.D.                              | 0.5                | 0.5                 | 0.3                 |                      |
|          |        | N                                 | 10                 | 10                  | 10                  |                      |
| PRO      | g/l    |                                   |                    |                     |                     |                      |
| WEEK 16  |        | MEAN                              | 0.175kd            | 0.200               | 0.475*              |                      |
|          |        | S.D.                              | 0.121              | 0.105               | 0.299               |                      |
|          |        | N                                 | 10                 | 10                  | 10                  |                      |

Statistical key: k=Kruskal-Wallis kd=Kruskal-Wallis + Dunn \* = p<0.05

Urine analysis (means)

FEMALES

|         |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|---------|--------|-----------------------------------|--------------------|---------------------|---------------------|----------------------|
| GLU     | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 0.0 k              | 0.0                 | 0.0                 |                      |
|         | S.D.   |                                   | 0.0                | 0.0                 | 0.0                 |                      |
|         | N      |                                   | 10                 | 10                  | 10                  |                      |
| KET     | mmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 0.10 k             | 0.25                | 0.20                |                      |
|         | S.D.   |                                   | 0.21               | 0.26                | 0.26                |                      |
|         | N      |                                   | 10                 | 10                  | 10                  |                      |
| UBG     | µmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 0.0 k              | 0.0                 | 0.0                 |                      |
|         | S.D.   |                                   | 0.0                | 0.0                 | 0.0                 |                      |
|         | N      |                                   | 10                 | 10                  | 10                  |                      |
| BIL     | µmol/l |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 0.0 kd             | 0.0                 | 11.9**              |                      |
|         | S.D.   |                                   | 0.0                | 0.0                 | 8.2                 |                      |
|         | N      |                                   | 10                 | 10                  | 10                  |                      |
| ERY     | per µl |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 1.0 kd             | 4.0                 | 10.5**              |                      |
|         | S.D.   |                                   | 3.2                | 5.2                 | 6.0                 |                      |
|         | N      |                                   | 10                 | 10                  | 10                  |                      |
| LEU     | per µl |                                   |                    |                     |                     |                      |
| WEEK 16 | MEAN   |                                   | 0.0 kd             | 0.0                 | 17.5**              |                      |
|         | S.D.   |                                   | 0.0                | 0.0                 | 12.1                |                      |
|         | N      |                                   | 10                 | 10                  | 10                  |                      |

Statistical key: k=Kruskal-Wallis kd=Kruskal-Wallis + Dunn \*\* = p<0.01

## 1.5 URINE SEDIMENT (INCIDENCE)

MALES

|           |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
|-----------|--------|-----------------------------------|--------------------|---------------------|---------------------|----------------------|
| Ery       | Choice |                                   |                    |                     |                     |                      |
| WEEK 16   | MEAN   |                                   | 0.0 k              | 0.0                 | 0.0                 | 0.2                  |
|           | S.D.   |                                   | 0.0                | 0.0                 | 0.0                 | 0.4                  |
|           | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Lau       | Choice |                                   |                    |                     |                     |                      |
| WEEK 16   | MEAN   |                                   | 0.0kd              | 0.0                 | 0.3*                | 0.0                  |
|           | S.D.   |                                   | 0.0                | 0.0                 | 0.5                 | 0.0                  |
|           | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Epi-cells | Choice |                                   |                    |                     |                     |                      |
| WEEK 16   | MEAN   |                                   | 0.0 k              | 0.0                 | 0.0                 | 0.0                  |
|           | S.D.   |                                   | 0.0                | 0.0                 | 0.0                 | 0.0                  |
|           | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Casts     | Choice |                                   |                    |                     |                     |                      |
| WEEK 16   | MEAN   |                                   | 0.0 k              | 0.0                 | 0.0                 | 0.0                  |
|           | S.D.   |                                   | 0.0                | 0.0                 | 0.0                 | 0.0                  |
|           | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Cry-PO4   | Choice |                                   |                    |                     |                     |                      |
| WEEK 16   | MEAN   |                                   | 0.7 k              | 0.6                 | 0.7                 | 0.6                  |
|           | S.D.   |                                   | 0.5                | 0.5                 | 0.5                 | 0.5                  |
|           | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Cry-Caox  | Choice |                                   |                    |                     |                     |                      |
| WEEK 16   | MEAN   |                                   | 0.1 k              | 0.0                 | 0.1                 | 0.3                  |
|           | S.D.   |                                   | 0.3                | 0.0                 | 0.3                 | 0.5                  |
|           | N      |                                   | 10                 | 10                  | 10                  | 10                   |

Statistical key: k=Kruskal-Wallis kd=Kruskal-Wallis + Dunn \* = p<0.05

Urine sediment (incidence)

| MALES    |        |            |         |          |          |           |
|----------|--------|------------|---------|----------|----------|-----------|
|          |        | Group      | Group 1 | Group 2  | Group 3  | Group 4   |
|          |        | Group Name | 0 mg/kg | 15 mg/kg | 50 mg/kg | 200 mg/kg |
|          |        | Dose Level |         |          |          |           |
| Cry-UrAc | Choice |            |         |          |          |           |
| WEEK 16  | MEAN   |            | 0.0 k   | 0.0      | 0.0      | 0.0       |
|          | S.D.   |            | 0.0     | 0.0      | 0.0      | 0.0       |
|          | N      |            | 10      | 10       | 10       | 10        |
| Cry-Uran | Choice |            |         |          |          |           |
| WEEK 16  | MEAN   |            | 0.0 k   | 0.0      | 0.0      | 0.0       |
|          | S.D.   |            | 0.0     | 0.0      | 0.0      | 0.0       |
|          | N      |            | 10      | 10       | 10       | 10        |
| Cry-Urid | Choice |            |         |          |          |           |
| WEEK 16  | MEAN   |            | 0.0kd   | 0.0      | 0.2      | 0.7**     |
|          | S.D.   |            | 0.0     | 0.0      | 0.4      | 0.5       |
|          | N      |            | 10      | 10       | 10       | 10        |

Statistical key: k=Kruskal-Wallis kd=Kruskal-Wallis + Dunn \*\* = p<0.01



|           |        | Urine sediment (incidence)        |                    |                     |                     |                      |
|-----------|--------|-----------------------------------|--------------------|---------------------|---------------------|----------------------|
| FEMALES   |        |                                   |                    |                     |                     |                      |
|           |        | Group<br>Group Name<br>Dose Level | Group 1<br>0 mg/kg | Group 2<br>15 mg/kg | Group 3<br>50 mg/kg | Group 4<br>200 mg/kg |
| Ery       | Choice |                                   |                    |                     |                     |                      |
| WEEK 16   | MEAN   |                                   | 0.0 k              | 0.0                 | 0.0                 | 0.0                  |
|           | S.D.   |                                   | 0.0                | 0.0                 | 0.0                 | 0.0                  |
|           | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Leu       | Choice |                                   |                    |                     |                     |                      |
| WEEK 16   | MEAN   |                                   | 0.0 k              | 0.0                 | 0.0                 | 0.0                  |
|           | S.D.   |                                   | 0.0                | 0.0                 | 0.0                 | 0.0                  |
|           | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Epi-cells | Choice |                                   |                    |                     |                     |                      |
| WEEK 16   | MEAN   |                                   | 0.0 k              | 0.0                 | 0.0                 | 0.0                  |
|           | S.D.   |                                   | 0.0                | 0.0                 | 0.0                 | 0.0                  |
|           | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Casts     | Choice |                                   |                    |                     |                     |                      |
| WEEK 16   | MEAN   |                                   | 0.0 k              | 0.0                 | 0.0                 | 0.0                  |
|           | S.D.   |                                   | 0.0                | 0.0                 | 0.0                 | 0.0                  |
|           | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Cry-P04   | Choice |                                   |                    |                     |                     |                      |
| WEEK 16   | MEAN   |                                   | 0.0 k              | 0.0                 | 0.0                 | 0.1                  |
|           | S.D.   |                                   | 0.0                | 0.0                 | 0.0                 | 0.3                  |
|           | N      |                                   | 10                 | 10                  | 10                  | 10                   |
| Cry-Caox  | Choice |                                   |                    |                     |                     |                      |
| WEEK 16   | MEAN   |                                   | 0.0kd              | 0.1                 | 0.2                 | 0.6*                 |
|           | S.D.   |                                   | 0.0                | 0.3                 | 0.6                 | 0.7                  |
|           | N      |                                   | 10                 | 10                  | 10                  | 10                   |

Statistical key: k=Kruskal-Wallis kd=Kruskal-Wallis + Dunn \* = p<0.05

Urine sediment (incidence)

FEMALES

|          |        | Group      | Group 1 | Group 2  | Group 3  | Group 4   |
|----------|--------|------------|---------|----------|----------|-----------|
|          |        | Group Name |         |          |          |           |
|          |        | Dose Level | 0 mg/kg | 15 mg/kg | 50 mg/kg | 200 mg/kg |
| Cry-UrAc | Choice |            |         |          |          |           |
| WEEK 16  | MEAN   |            | 0.1kd   | 0.3      | 0.5      | 1.0**     |
|          | S.D.   |            | 0.3     | 0.5      | 0.7      | 0.7       |
|          | N      |            | 10      | 10       | 10       | 10        |
| Cry-Uram | Choice |            |         |          |          |           |
| WEEK 16  | MEAN   |            | 0.0 k   | 0.0      | 0.0      | 0.0       |
|          | S.D.   |            | 0.0     | 0.0      | 0.0      | 0.0       |
|          | N      |            | 10      | 10       | 10       | 10        |
| Cry-Urid | Choice |            |         |          |          |           |
| WEEK 16  | MEAN   |            | 0.1kd   | 0.0      | 0.0      | 0.4       |
|          | S.D.   |            | 0.3     | 0.0      | 0.0      | 0.5       |
|          | N      |            | 10      | 10       | 10       | 10        |

Statistical key: k=Kruskal-Wallis kd=Kruskal-Wallis + Dunn \*\* = p<0.01

## 1.6 HEMATOLOGY (INDIVIDUALS)

| WEEK 16            |      |        |        |      |        |      |        |        |        |      |        | MALES  |  |
|--------------------|------|--------|--------|------|--------|------|--------|--------|--------|------|--------|--------|--|
| ANLNO              | RBC  | Hb     | Hct    | MCV  | RDW    | MCH  | MCHC   | HDW    | Reti   | Reti | L Reti | M Reti |  |
|                    | T/l  | mmol/l | rel. 1 | fl   | rel. 1 | fml  | mmol/l | mmol/l | rel. 1 | G/l  | rel. 1 | rel. 1 |  |
| Group 1 (0 mg/kg)  |      |        |        |      |        |      |        |        |        |      |        |        |  |
| 1 M                | 9.17 | 10.1   | 0.45   | 48.9 | 0.126  | 1.11 | 22.62  | 1.63   | 0.017  | 152  | 0.696  | 0.277  |  |
| 2 M                | 9.21 | 10.0   | 0.43   | 47.2 | 0.132  | 1.08 | 22.93  | 1.96   | 0.019  | 172  | 0.695  | 0.270  |  |
| 3 M                | 8.54 | 10.4   | 0.44   | 51.8 | 0.143  | 1.22 | 23.48  | 1.84   | 0.018  | 158  | 0.647  | 0.308  |  |
| 4 M                | 9.46 | 10.3   | 0.46   | 48.5 | 0.126  | 1.09 | 22.46  | 1.70   | 0.015  | 144  | 0.713  | 0.263  |  |
| 5 M                | 9.47 | 9.7    | 0.43   | 45.7 | 0.131  | 1.02 | 22.35  | 1.81   | 0.016  | 151  | 0.773  | 0.214  |  |
| 6 M                | 9.07 | 10.3   | 0.44   | 48.8 | 0.130  | 1.14 | 23.33  | 1.87   | 0.018  | 164  | 0.669  | 0.297  |  |
| 7 M                | 9.75 | 10.3   | 0.46   | 47.2 | 0.127  | 1.06 | 22.39  | 1.69   | 0.019  | 185  | 0.702  | 0.263  |  |
| 8 M                | 9.01 | 10.1   | 0.44   | 48.9 | 0.124  | 1.12 | 22.83  | 1.76   | 0.016  | 147  | 0.687  | 0.286  |  |
| 9 M                | 9.15 | 10.3   | 0.46   | 50.1 | 0.125  | 1.13 | 22.53  | 1.74   | 0.019  | 177  | 0.696  | 0.274  |  |
| 10 M               | 9.14 | 10.0   | 0.43   | 46.6 | 0.180  | 1.10 | 23.59  | 1.89   | 0.018  | 162  | 0.770  | 0.202  |  |
| Group 2 (15 mg/kg) |      |        |        |      |        |      |        |        |        |      |        |        |  |
| 16 M               | 8.92 | 9.7    | 0.41   | 46.5 | 0.132  | 1.09 | 23.36  | 1.87   | 0.021  | 186  | 0.617  | 0.333  |  |
| 17 M               | 8.93 | 10.4   | 0.44   | 49.4 | 0.190  | 1.16 | 23.46  | 1.92   | 0.018  | 162  | 0.708  | 0.266  |  |
| 18 M               | 9.18 | 9.7    | 0.42   | 45.5 | 0.135  | 1.05 | 23.14  | 1.93   | 0.019  | 171  | 0.756  | 0.228  |  |
| 19 M               | 8.77 | 10.4   | 0.44   | 49.8 | 0.150  | 1.18 | 23.73  | 1.87   | 0.023  | 203  | 0.641  | 0.312  |  |
| 20 M               | 8.73 | 9.4    | 0.40   | 45.9 | 0.134  | 1.07 | 23.41  | 1.82   | 0.023  | 200  | 0.695  | 0.273  |  |
| 21 M               | 9.04 | 9.8    | 0.42   | 47.0 | 0.142  | 1.08 | 23.04  | 1.92   | 0.019  | 169  | 0.693  | 0.287  |  |
| 22 M               | 8.84 | 9.9    | 0.42   | 47.6 | 0.137  | 1.12 | 23.54  | 1.87   | 0.019  | 172  | 0.695  | 0.271  |  |
| 23 M               | 9.80 | 10.3   | 0.46   | 46.5 | 0.123  | 1.05 | 22.70  | 1.60   | 0.014  | 135  | 0.745  | 0.224  |  |
| 24 M               | 8.05 | 9.6    | 0.41   | 50.9 | 0.142  | 1.20 | 23.48  | 1.92   | 0.019  | 156  | 0.694  | 0.273  |  |
| 25 M               | 9.38 | 10.0   | 0.44   | 47.3 | 0.134  | 1.06 | 22.54  | 1.75   | 0.018  | 170  | 0.658  | 0.312  |  |
| Group 3 (50 mg/kg) |      |        |        |      |        |      |        |        |        |      |        |        |  |
| 31 M               | 9.28 | 10.2   | 0.44   | 47.3 | 0.133  | 1.10 | 23.26  | 1.74   | 0.015  | 144  | 0.748  | 0.230  |  |
| 32 M               | 8.67 | 9.9    | 0.42   | 48.8 | 0.134  | 1.14 | 23.34  | 1.83   | 0.024  | 210  | 0.619  | 0.325  |  |
| 33 M               | 8.88 | 10.0   | 0.43   | 48.7 | 0.130  | 1.13 | 23.12  | 1.85   | 0.017  | 152  | 0.690  | 0.288  |  |
| 34 M               | 9.05 | 10.1   | 0.45   | 49.7 | 0.123  | 1.12 | 22.45  | 1.68   | 0.020  | 180  | 0.656  | 0.304  |  |
| 35 M               | 8.71 | 9.9    | 0.43   | 48.9 | 0.129  | 1.13 | 23.21  | 1.76   | 0.019  | 169  | 0.665  | 0.296  |  |
| 36 M               | 9.30 | 9.5    | 0.43   | 46.4 | 0.139  | 1.02 | 22.10  | 1.92   | 0.018  | 164  | 0.695  | 0.278  |  |
| 37 M               | 9.13 | 10.0   | 0.43   | 46.8 | 0.135  | 1.09 | 23.39  | 1.90   | 0.021  | 196  | 0.653  | 0.309  |  |
| 38 M               | 9.03 | 10.1   | 0.44   | 49.1 | 0.131  | 1.12 | 22.88  | 1.87   | 0.020  | 178  | 0.725  | 0.251  |  |
| 39 M               | 9.48 | 10.6   | 0.46   | 48.5 | 0.131  | 1.11 | 22.96  | 1.77   | 0.018  | 167  | 0.679  | 0.295  |  |
| 40 M               | 8.77 | 9.8    | 0.43   | 48.5 | 0.133  | 1.12 | 23.03  | 1.86   | 0.020  | 177  | 0.687  | 0.289  |  |

| WEEK 16             |      | Hematology (individuals) |        |        |       |        |       |        |        |        |       | MALES  |        |
|---------------------|------|--------------------------|--------|--------|-------|--------|-------|--------|--------|--------|-------|--------|--------|
| ANLND               |      | RBC                      | Hb     | Hct    | MCV   | RDW    | MCH   | MCHC   | HDW    | Reti   | Reti  | L Reti | M Reti |
|                     |      | T/l                      | mmol/l | rel. l | fl    | rel. l | fmol  | mmol/l | mmol/l | rel. l | G/l   | rel. l | rel. l |
| Group 4 (200 mg/kg) |      |                          |        |        |       |        |       |        |        |        |       |        |        |
| 46 M                | 8.16 | 9.5                      | 0.42   | 51.8   | 0.128 | 1.17   | 22.55 | 1.85   | 0.026  | 208    | 0.613 | 0.338  |        |
| 47 M                | 8.91 | 10.0                     | 0.43   | 48.5   | 0.131 | 1.12   | 23.07 | 1.77   | 0.021  | 190    | 0.673 | 0.292  |        |
| 48 M                | 8.44 | 9.4                      | 0.42   | 49.8   | 0.127 | 1.12   | 22.46 | 1.75   | 0.025  | 208    | 0.627 | 0.324  |        |
| 49 M                | 8.84 | 10.4                     | 0.46   | 52.1   | 0.128 | 1.17   | 22.51 | 1.71   | 0.021  | 185    | 0.648 | 0.317  |        |
| 50 M                | 8.39 | 10.0                     | 0.44   | 52.5   | 0.136 | 1.19   | 22.72 | 1.91   | 0.027  | 227    | 0.633 | 0.320  |        |
| 51 M                | 8.86 | 9.8                      | 0.44   | 49.6   | 0.136 | 1.11   | 22.29 | 2.05   | 0.026  | 233    | 0.616 | 0.329  |        |
| 52 M                | 9.09 | 10.1                     | 0.44   | 48.4   | 0.135 | 1.11   | 23.02 | 1.98   | 0.021  | 190    | 0.585 | 0.365  |        |
| 53 M                | 8.19 | 9.8                      | 0.42   | 51.8   | 0.166 | 1.20   | 23.12 | 2.01   | 0.028  | 232    | 0.622 | 0.323  |        |
| 54 M                | 8.66 | 9.8                      | 0.43   | 49.7   | 0.139 | 1.14   | 22.82 | 1.92   | 0.028  | 240    | 0.649 | 0.302  |        |
| 55 M                | 8.04 | 10.0                     | 0.43   | 53.3   | 0.169 | 1.24   | 23.36 | 2.06   | 0.029  | 231    | 0.624 | 0.315  |        |

| WEEK 16            |        | Hematology (individuals) |        |        |        |        |        |        |      |      |      | MALES  |
|--------------------|--------|--------------------------|--------|--------|--------|--------|--------|--------|------|------|------|--------|
| AN_ID              | H Reti | WBC                      | Neut   | Eos    | Baso   | Lympho | Mono   | Luc    | Neut | Eos  | Baso | Lympho |
|                    | rel. 1 | G/l                      | rel. 1 | rel. 1 | rel. 1 | rel. 1 | rel. 1 | rel. 1 | G/l  | G/l  | G/l  | G/l    |
| Group 1 (0 mg/kg)  |        |                          |        |        |        |        |        |        |      |      |      |        |
| 1 M                | 0.028  | 6.45                     | 0.177  | 0.013  | 0.003  | 0.771  | 0.024  | 0.012  | 1.14 | 0.09 | 0.02 | 4.98   |
| 2 M                | 0.035  | 7.85                     | 0.159  | 0.018  | 0.004  | 0.794  | 0.016  | 0.009  | 1.25 | 0.14 | 0.03 | 6.24   |
| 3 M                | 0.045  | 6.92                     | 0.212  | 0.021  | 0.002  | 0.742  | 0.019  | 0.004  | 1.47 | 0.14 | 0.01 | 5.14   |
| 4 M                | 0.024  | 6.99                     | 0.163  | 0.019  | 0.003  | 0.795  | 0.014  | 0.005  | 1.14 | 0.14 | 0.02 | 5.56   |
| 5 M                | 0.013  | 5.27                     | 0.206  | 0.018  | 0.003  | 0.751  | 0.016  | 0.006  | 1.09 | 0.10 | 0.01 | 3.96   |
| 6 M                | 0.035  | 4.73                     | 0.307  | 0.013  | 0.003  | 0.648  | 0.024  | 0.005  | 1.45 | 0.06 | 0.02 | 3.07   |
| 7 M                | 0.035  | 6.47                     | 0.191  | 0.027  | 0.002  | 0.753  | 0.021  | 0.006  | 1.23 | 0.17 | 0.02 | 4.87   |
| 8 M                | 0.027  | 7.11                     | 0.152  | 0.018  | 0.002  | 0.803  | 0.013  | 0.013  | 1.08 | 0.12 | 0.01 | 5.71   |
| 9 M                | 0.030  | 6.08                     | 0.243  | 0.020  | 0.002  | 0.719  | 0.014  | 0.002  | 1.48 | 0.12 | 0.01 | 4.37   |
| 10 M               | 0.028  | 5.78                     | 0.132  | 0.014  | 0.004  | 0.838  | 0.010  | 0.003  | 0.76 | 0.08 | 0.02 | 4.84   |
| Group 2 (15 mg/kg) |        |                          |        |        |        |        |        |        |      |      |      |        |
| 16 M               | 0.050  | 5.51                     | 0.212  | 0.021  | 0.002  | 0.738  | 0.020  | 0.007  | 1.17 | 0.12 | 0.01 | 4.07   |
| 17 M               | 0.026  | 5.48                     | 0.225  | 0.017  | 0.004  | 0.728  | 0.023  | 0.006  | 1.23 | 0.09 | 0.02 | 3.97   |
| 18 M               | 0.016  | 5.75                     | 0.200  | 0.020  | 0.004  | 0.748  | 0.020  | 0.008  | 1.15 | 0.11 | 0.02 | 4.30   |
| 19 M               | 0.046  | 6.85                     | 0.191  | 0.021  | 0.004  | 0.764  | 0.015  | 0.005  | 1.31 | 0.15 | 0.03 | 5.23   |
| 20 M               | 0.033  | 5.44                     | 0.198  | 0.040  | 0.003  | 0.722  | 0.023  | 0.013  | 1.08 | 0.22 | 0.02 | 3.93   |
| 21 M               | 0.020  | 6.34                     | 0.160  | 0.021  | 0.003  | 0.790  | 0.018  | 0.008  | 1.01 | 0.14 | 0.02 | 5.01   |
| 22 M               | 0.035  | 7.37                     | 0.176  | 0.023  | 0.003  | 0.770  | 0.021  | 0.007  | 1.29 | 0.17 | 0.03 | 5.67   |
| 23 M               | 0.032  | 6.70                     | 0.200  | 0.019  | 0.004  | 0.746  | 0.028  | 0.003  | 1.34 | 0.13 | 0.03 | 5.00   |
| 24 M               | 0.034  | 7.20                     | 0.158  | 0.011  | 0.004  | 0.791  | 0.021  | 0.015  | 1.14 | 0.08 | 0.03 | 5.69   |
| 25 M               | 0.030  | 6.47                     | 0.262  | 0.023  | 0.002  | 0.691  | 0.018  | 0.004  | 1.69 | 0.15 | 0.01 | 4.47   |
| Group 3 (50 mg/kg) |        |                          |        |        |        |        |        |        |      |      |      |        |
| 31 M               | 0.023  | 5.52                     | 0.198  | 0.012  | 0.002  | 0.758  | 0.023  | 0.007  | 1.10 | 0.06 | 0.01 | 4.19   |
| 32 M               | 0.056  | 9.06                     | 0.299  | 0.020  | 0.003  | 0.650  | 0.021  | 0.006  | 2.71 | 0.18 | 0.03 | 5.89   |
| 33 M               | 0.021  | 7.41                     | 0.193  | 0.014  | 0.002  | 0.765  | 0.021  | 0.005  | 1.43 | 0.10 | 0.02 | 5.67   |
| 34 M               | 0.040  | 6.38                     | 0.180  | 0.021  | 0.001  | 0.767  | 0.022  | 0.008  | 1.15 | 0.14 | 0.01 | 4.90   |
| 35 M               | 0.039  | 5.77                     | 0.167  | 0.028  | 0.002  | 0.769  | 0.023  | 0.011  | 0.97 | 0.16 | 0.01 | 4.44   |
| 36 M               | 0.028  | 7.31                     | 0.210  | 0.015  | 0.003  | 0.745  | 0.023  | 0.005  | 1.53 | 0.11 | 0.02 | 5.44   |
| 37 M               | 0.038  | 5.96                     | 0.240  | 0.019  | 0.003  | 0.706  | 0.026  | 0.006  | 1.43 | 0.12 | 0.02 | 4.21   |
| 38 M               | 0.024  | 7.48                     | 0.249  | 0.017  | 0.003  | 0.690  | 0.028  | 0.013  | 1.86 | 0.13 | 0.02 | 5.16   |
| 39 M               | 0.026  | 4.34                     | 0.186  | 0.016  | 0.002  | 0.767  | 0.025  | 0.004  | 0.81 | 0.07 | 0.01 | 3.33   |
| 40 M               | 0.024  | 5.90                     | 0.274  | 0.018  | 0.002  | 0.685  | 0.016  | 0.005  | 1.62 | 0.11 | 0.01 | 4.04   |

| WEEK 16             |       | Hematology (individuals) |       |        |        |        |        |        |        |      |      | MALES |        |
|---------------------|-------|--------------------------|-------|--------|--------|--------|--------|--------|--------|------|------|-------|--------|
| AN_ID               |       | H Reti                   | WBC   | Neut   | Eos    | Baso   | Lympho | Mono   | Luc    | Neut | Eos  | Baso  | Lympho |
|                     |       | rel. 1                   | G/l   | rel. 1 | rel. 1 | rel. 1 | rel. 1 | rel. 1 | rel. 1 | G/l  | G/l  | G/l   | G/l    |
| Group 4 (200 mg/kg) |       |                          |       |        |        |        |        |        |        |      |      |       |        |
| 46 M                | 0.050 | 5.68                     | 0.170 | 0.012  | 0.002  | 0.792  | 0.019  | 0.006  | 0.96   | 0.07 | 0.01 | 4.50  |        |
| 47 M                | 0.035 | 8.99                     | 0.225 | 0.014  | 0.003  | 0.730  | 0.019  | 0.010  | 2.02   | 0.13 | 0.02 | 6.56  |        |
| 48 M                | 0.049 | 7.22                     | 0.262 | 0.014  | 0.002  | 0.694  | 0.021  | 0.008  | 1.89   | 0.10 | 0.01 | 5.01  |        |
| 49 M                | 0.036 | 7.72                     | 0.174 | 0.012  | 0.003  | 0.781  | 0.021  | 0.009  | 1.34   | 0.09 | 0.02 | 6.02  |        |
| 50 M                | 0.047 | 7.98                     | 0.272 | 0.025  | 0.002  | 0.657  | 0.027  | 0.017  | 2.17   | 0.20 | 0.02 | 5.24  |        |
| 51 M                | 0.056 | 7.57                     | 0.249 | 0.015  | 0.003  | 0.707  | 0.020  | 0.005  | 1.89   | 0.12 | 0.02 | 5.36  |        |
| 52 M                | 0.050 | 5.77                     | 0.197 | 0.014  | 0.002  | 0.754  | 0.025  | 0.008  | 1.14   | 0.08 | 0.01 | 4.35  |        |
| 53 M                | 0.055 | 6.47                     | 0.189 | 0.017  | 0.002  | 0.756  | 0.022  | 0.013  | 1.23   | 0.11 | 0.02 | 4.89  |        |
| 54 M                | 0.049 | 4.61                     | 0.172 | 0.017  | 0.003  | 0.784  | 0.019  | 0.003  | 0.79   | 0.08 | 0.01 | 3.61  |        |
| 55 M                | 0.061 | 6.76                     | 0.222 | 0.028  | 0.003  | 0.730  | 0.012  | 0.005  | 1.50   | 0.19 | 0.02 | 4.94  |        |

| WEEK 16            | Hematology (individuals) |      |      |        |        |      | MALES |
|--------------------|--------------------------|------|------|--------|--------|------|-------|
|                    | Mono                     | Luc  | Plt  | Mathb  | PT     | PTT  |       |
|                    | ANLND<br>G/l             | G/l  | G/l  | rel. 1 | rel. 1 | sec  |       |
| Group 1 (0 mg/kg)  |                          |      |      |        |        |      |       |
| 1 M                | 0.15                     | 0.07 | 827  | 0.010  | 0.83   | 15.5 |       |
| 2 M                | 0.12                     | 0.07 | 911  | 0.009  | 0.84   | 15.7 |       |
| 3 M                | 0.13                     | 0.03 | 944  | 0.008  | 0.83   | 15.8 |       |
| 4 M                | 0.10                     | 0.04 | 1033 | 0.008  | 0.77   | 22.6 |       |
| 5 M                | 0.08                     | 0.03 | 826  | 0.009  | 0.74   | 19.7 |       |
| 6 M                | 0.11                     | 0.03 | 981  | 0.007  | 0.76   | 17.3 |       |
| 7 M                | 0.14                     | 0.04 | 847  | n.d.   | 0.73   | 12.9 |       |
| 8 M                | 0.09                     | 0.09 | 789  | 0.007  | 0.74   | 14.0 |       |
| 9 M                | 0.08                     | 0.01 | 840  | 0.007  | 0.79   | 12.0 |       |
| 10 M               | 0.06                     | 0.02 | 995  | 0.008  | 0.69   | 24.6 |       |
| Group 2 (15 mg/kg) |                          |      |      |        |        |      |       |
| 16 M               | 0.11                     | 0.04 | 700  | n.d.   | 0.79   | 15.6 |       |
| 17 M               | 0.13                     | 0.03 | 992  | 0.005  | 0.74   | 23.8 |       |
| 18 M               | 0.11                     | 0.05 | 965  | 0.008  | 0.74   | 20.8 |       |
| 19 M               | 0.10                     | 0.03 | 897  | 0.007  | 0.84   | 11.4 |       |
| 20 M               | 0.13                     | 0.07 | 708  | 0.010  | 0.83   | 15.3 |       |
| 21 M               | 0.12                     | 0.05 | 810  | 0.010  | 0.78   | 13.9 |       |
| 22 M               | 0.15                     | 0.05 | 1064 | 0.006  | 0.81   | 14.2 |       |
| 23 M               | 0.19                     | 0.02 | 1035 | n.d.   | 0.77   | 14.1 |       |
| 24 M               | 0.15                     | 0.11 | 923  | 0.009  | 0.82   | 16.1 |       |
| 25 M               | 0.12                     | 0.02 | 816  | 0.004  | 0.81   | 14.0 |       |
| Group 3 (50 mg/kg) |                          |      |      |        |        |      |       |
| 31 M               | 0.12                     | 0.04 | 972  | 0.008  | 0.75   | 25.4 |       |
| 32 M               | 0.19                     | 0.05 | 1071 | 0.008  | 0.81   | 19.7 |       |
| 33 M               | 0.15                     | 0.03 | 873  | 0.009  | 0.75   | 19.0 |       |
| 34 M               | 0.14                     | 0.05 | 1081 | 0.008  | 0.77   | 18.3 |       |
| 35 M               | 0.13                     | 0.06 | 804  | 0.010  | 0.79   | 15.3 |       |
| 36 M               | 0.17                     | 0.04 | 841  | 0.009  | 0.75   | 20.8 |       |
| 37 M               | 0.15                     | 0.03 | 903  | 0.005  | 0.80   | 20.4 |       |
| 38 M               | 0.21                     | 0.09 | 967  | 0.007  | 0.76   | 21.7 |       |
| 39 M               | 0.11                     | 0.02 | 1097 | n.d.   | 0.77   | 16.4 |       |
| 40 M               | 0.09                     | 0.03 | 661  | 0.009  | 0.79   | 16.4 |       |

n.d.=not determined

| WEEK 16 |      | Hematology (individuals) |     |        |        |     | MALES |
|---------|------|--------------------------|-----|--------|--------|-----|-------|
| AN_NO   | Mono | Luc                      | Plt | Methb  | PT     | PTT |       |
|         | G/l  | G/l                      | G/l | rel. 1 | rel. 1 | sec |       |

Group 4 (200 mg/kg)

|      |      |      |      |       |      |      |
|------|------|------|------|-------|------|------|
| 46 M | 0.11 | 0.03 | 812  | 0.008 | 0.80 | 17.3 |
| 47 M | 0.17 | 0.09 | 921  | 0.008 | 0.79 | 14.7 |
| 48 M | 0.15 | 0.06 | 825  | 0.010 | 0.78 | 11.5 |
| 49 M | 0.16 | 0.07 | 1077 | 0.006 | 0.80 | 16.4 |
| 50 M | 0.21 | 0.14 | 882  | 0.008 | 0.94 | 13.4 |
| 51 M | 0.15 | 0.04 | 941  | 0.010 | 0.83 | 16.7 |
| 52 M | 0.14 | 0.05 | 1040 | 0.008 | 0.79 | 18.3 |
| 53 M | 0.14 | 0.06 | 947  | 0.009 | 0.83 | 25.0 |
| 54 M | 0.09 | 0.02 | 871  | 0.006 | 0.83 | 13.7 |
| 55 M | 0.08 | 0.03 | 714  | 0.009 | 0.91 | 13.6 |



| WEEK 16            |      | Hematology (individuals) |        |        |       |        |       |        |        |        | FEMALES |        |        |
|--------------------|------|--------------------------|--------|--------|-------|--------|-------|--------|--------|--------|---------|--------|--------|
| AN_NO              |      | RBC                      | Hb     | Hct    | MCV   | RDW    | MCH   | MCHC   | HDW    | Reti   | Reti    | L Reti | M Reti |
|                    |      | T/l                      | mmol/l | rel. 1 | fl    | rel. 1 | fmoI  | mmol/l | mmol/l | rel. 1 | G/l     | rel. 1 | rel. 1 |
| Group 1 (0 mg/kg)  |      |                          |        |        |       |        |       |        |        |        |         |        |        |
| 61 F               | 8.10 | 9.5                      | 0.41   | 50.9   | 0.115 | 1.17   | 23.06 | 1.43   | 0.022  | 179    | 0.628   | 0.354  |        |
| 62 F               | 8.60 | 9.7                      | 0.42   | 49.3   | 0.114 | 1.13   | 22.98 | 1.40   | 0.018  | 158    | 0.758   | 0.220  |        |
| 63 F               | 7.84 | 9.8                      | 0.41   | 52.7   | 0.115 | 1.25   | 23.68 | 1.42   | 0.027  | 209    | 0.647   | 0.332  |        |
| 64 F               | 7.88 | 9.8                      | 0.41   | 52.0   | 0.125 | 1.25   | 24.00 | 1.46   | 0.019  | 153    | 0.597   | 0.359  |        |
| 65 F               | 8.83 | 10.3                     | 0.45   | 51.3   | 0.109 | 1.17   | 22.85 | 1.32   | 0.019  | 166    | 0.606   | 0.344  |        |
| 66 F               | 8.12 | 9.6                      | 0.42   | 51.2   | 0.115 | 1.18   | 23.00 | 1.42   | 0.018  | 145    | 0.718   | 0.257  |        |
| 67 F               | 8.18 | 9.8                      | 0.41   | 50.4   | 0.112 | 1.20   | 23.72 | 1.39   | 0.019  | 157    | 0.733   | 0.238  |        |
| 68 F               | 8.44 | 10.1                     | 0.44   | 52.0   | 0.114 | 1.19   | 22.96 | 1.40   | 0.023  | 198    | 0.648   | 0.314  |        |
| 69 F               | 7.49 | 9.8                      | 0.42   | 55.7   | 0.274 | 1.31   | 23.52 | 1.56   | 0.021  | 158    | 0.666   | 0.301  |        |
| 70 F               | 8.57 | 9.7                      | 0.41   | 47.9   | 0.113 | 1.14   | 23.75 | 1.48   | 0.013  | 113    | 0.793   | 0.176  |        |
| Group 2 (15 mg/kg) |      |                          |        |        |       |        |       |        |        |        |         |        |        |
| 76 F               | 7.92 | 9.7                      | 0.43   | 54.4   | 0.116 | 1.23   | 22.56 | 1.42   | 0.024  | 191    | 0.535   | 0.399  |        |
| 77 F               | 8.00 | 9.8                      | 0.42   | 52.8   | 0.111 | 1.22   | 23.17 | 1.42   | 0.026  | 206    | 0.598   | 0.360  |        |
| 78 F               | 8.13 | 9.6                      | 0.41   | 50.2   | 0.130 | 1.18   | 23.54 | 1.48   | 0.020  | 161    | 0.652   | 0.333  |        |
| 79 F               | 7.32 | 9.4                      | 0.40   | 54.8   | 0.272 | 1.28   | 23.35 | 1.69   | 0.021  | 154    | 0.682   | 0.290  |        |
| 80 F               | 7.67 | 9.6                      | 0.41   | 53.9   | 0.160 | 1.25   | 23.24 | 1.54   | 0.026  | 203    | 0.587   | 0.380  |        |
| 81 F               | 7.97 | 9.6                      | 0.42   | 52.6   | 0.113 | 1.21   | 22.91 | 1.46   | 0.021  | 164    | 0.691   | 0.282  |        |
| 82 F               | 7.97 | 9.6                      | 0.41   | 51.2   | 0.118 | 1.20   | 23.40 | 1.54   | 0.029  | 227    | 0.612   | 0.353  |        |
| 83 F               | 7.92 | 9.9                      | 0.42   | 52.6   | 0.175 | 1.25   | 23.73 | 1.66   | 0.019  | 152    | 0.621   | 0.329  |        |
| 84 F               | 8.06 | 9.7                      | 0.42   | 51.9   | 0.112 | 1.20   | 23.16 | 1.46   | 0.017  | 133    | 0.678   | 0.286  |        |
| 85 F               | 7.98 | 9.2                      | 0.40   | 50.2   | 0.118 | 1.15   | 22.99 | 1.50   | 0.019  | 153    | 0.747   | 0.235  |        |
| Group 3 (50 mg/kg) |      |                          |        |        |       |        |       |        |        |        |         |        |        |
| 91 F               | 7.32 | 9.0                      | 0.38   | 52.5   | 0.114 | 1.23   | 23.37 | 1.41   | 0.026  | 191    | 0.505   | 0.401  |        |
| 92 F               | 7.03 | 9.5                      | 0.41   | 58.0   | 0.212 | 1.35   | 23.24 | 1.55   | 0.031  | 219    | 0.477   | 0.441  |        |
| 93 F               | 7.66 | 9.8                      | 0.41   | 53.2   | 0.212 | 1.27   | 23.93 | 1.62   | 0.026  | 202    | 0.718   | 0.262  |        |
| 94 F               | 7.67 | 9.2                      | 0.40   | 51.7   | 0.118 | 1.19   | 23.10 | 1.55   | 0.026  | 202    | 0.639   | 0.324  |        |
| 95 F               | 7.86 | 9.1                      | 0.41   | 52.0   | 0.115 | 1.16   | 22.40 | 1.33   | 0.030  | 234    | 0.507   | 0.413  |        |
| 96 F               | 7.68 | 8.9                      | 0.40   | 51.5   | 0.118 | 1.16   | 22.49 | 1.38   | 0.033  | 255    | 0.510   | 0.420  |        |
| 97 F               | 7.27 | 9.1                      | 0.39   | 53.1   | 0.149 | 1.25   | 23.55 | 1.59   | 0.027  | 197    | 0.596   | 0.359  |        |
| 98 F               | 7.59 | 9.3                      | 0.40   | 52.9   | 0.152 | 1.22   | 23.09 | 1.55   | 0.031  | 235    | 0.635   | 0.337  |        |
| 99 F               | 7.51 | 9.1                      | 0.39   | 52.3   | 0.126 | 1.21   | 23.12 | 1.64   | 0.034  | 256    | 0.612   | 0.346  |        |
| 100 F              | 7.59 | 8.9                      | 0.39   | 51.5   | 0.126 | 1.18   | 22.85 | 1.53   | 0.040  | 300    | 0.611   | 0.358  |        |

| WEEK                | Hematology (individuals) |        |        |      |        |      |        |        |        |      |        | FEMALES |        |
|---------------------|--------------------------|--------|--------|------|--------|------|--------|--------|--------|------|--------|---------|--------|
|                     | -----                    |        |        |      |        |      |        |        |        |      |        |         |        |
|                     | RBC                      | Hb     | Hct    | MCV  | RDW    | MCH  | MCHC   | HDW    | Reti   | Reti | L Reti |         | M Reti |
| AN_NO               | T/l                      | mmol/l | rel. 1 | f1   | rel. 1 | fmo1 | mmol/l | mmol/l | rel. 1 | G/l  | rel. 1 | rel. 1  |        |
| -----               |                          |        |        |      |        |      |        |        |        |      |        |         |        |
| Group 4 (200 mg/kg) |                          |        |        |      |        |      |        |        |        |      |        |         |        |
| 106 F               | 7.80                     | 9.5    | 0.41   | 52.4 | 0.126  | 1.21 | 23.16  | 1.46   | 0.039  | 305  | 0.580  | 0.370   |        |
| 107 F               | 6.96                     | 8.4    | 0.38   | 54.7 | 0.129  | 1.20 | 21.94  | 1.49   | 0.047  | 328  | 0.651  | 0.325   |        |
| 108 F               | 7.50                     | 8.8    | 0.40   | 53.5 | 0.116  | 1.18 | 21.98  | 1.40   | 0.037  | 278  | 0.698  | 0.280   |        |
| 109 F               | 7.09                     | 9.3    | 0.41   | 58.5 | 0.138  | 1.32 | 22.54  | 1.52   | 0.048  | 340  | 0.523  | 0.388   |        |
| 110 F               | 6.93                     | 8.8    | 0.39   | 56.8 | 0.123  | 1.27 | 22.35  | 1.39   | 0.045  | 315  | 0.622  | 0.341   |        |
| 111 F               | 6.98                     | 8.8    | 0.40   | 56.7 | 0.134  | 1.27 | 22.34  | 1.44   | 0.049  | 341  | 0.529  | 0.370   |        |
| 112 F               | 7.22                     | 9.3    | 0.41   | 57.5 | 0.136  | 1.29 | 22.41  | 1.55   | 0.053  | 381  | 0.558  | 0.373   |        |
| 113 F               | 7.53                     | 9.1    | 0.40   | 52.7 | 0.121  | 1.21 | 22.92  | 1.48   | 0.032  | 240  | 0.540  | 0.377   |        |
| 114 F               | 7.12                     | 9.3    | 0.40   | 56.7 | 0.130  | 1.30 | 22.98  | 1.40   | 0.038  | 272  | 0.578  | 0.375   |        |
| 115 F               | 7.02                     | 9.3    | 0.42   | 59.5 | 0.126  | 1.33 | 22.36  | 1.46   | 0.049  | 344  | 0.515  | 0.394   |        |

| WEEK 16            |        | Hematology (individuals) |        |        |        |        |        |        |      |      |      | FEMALES |
|--------------------|--------|--------------------------|--------|--------|--------|--------|--------|--------|------|------|------|---------|
| AN_ID              | H Reti | WBC                      | Neut   | Eos    | Baso   | Lympho | Mono   | Luc    | Neut | Eos  | Baso | Lympho  |
|                    | rel. 1 | G/l                      | rel. 1 | rel. 1 | rel. 1 | rel. 1 | rel. 1 | rel. 1 | G/l  | G/l  | G/l  | G/l     |
| Group 1 (0 mg/kg)  |        |                          |        |        |        |        |        |        |      |      |      |         |
| 61 F               | 0.019  | 2.74                     | 0.161  | 0.025  | 0.003  | 0.789  | 0.019  | 0.004  | 0.44 | 0.07 | 0.01 | 2.16    |
| 62 F               | 0.023  | 4.29                     | 0.164  | 0.045  | 0.002  | 0.773  | 0.011  | 0.004  | 0.70 | 0.19 | 0.01 | 3.31    |
| 63 F               | 0.022  | 3.70                     | 0.231  | 0.014  | 0.003  | 0.707  | 0.031  | 0.013  | 0.86 | 0.05 | 0.01 | 2.61    |
| 64 F               | 0.045  | 3.94                     | 0.149  | 0.016  | 0.002  | 0.807  | 0.022  | 0.004  | 0.59 | 0.06 | 0.01 | 3.18    |
| 65 F               | 0.050  | 5.93                     | 0.158  | 0.015  | 0.002  | 0.803  | 0.016  | 0.006  | 0.94 | 0.09 | 0.01 | 4.76    |
| 66 F               | 0.025  | 4.56                     | 0.099  | 0.011  | 0.003  | 0.864  | 0.017  | 0.006  | 0.45 | 0.05 | 0.01 | 3.94    |
| 67 F               | 0.029  | 3.77                     | 0.145  | 0.014  | 0.001  | 0.819  | 0.015  | 0.006  | 0.55 | 0.05 | 0.00 | 3.09    |
| 68 F               | 0.038  | 5.06                     | 0.160  | 0.017  | 0.002  | 0.803  | 0.012  | 0.006  | 0.81 | 0.09 | 0.01 | 4.06    |
| 69 F               | 0.033  | 3.24                     | 0.316  | 0.016  | 0.001  | 0.642  | 0.021  | 0.004  | 1.02 | 0.05 | 0.00 | 2.08    |
| 70 F               | 0.031  | 3.69                     | 0.109  | 0.013  | 0.001  | 0.854  | 0.015  | 0.007  | 0.40 | 0.05 | 0.00 | 3.15    |
| Group 2 (15 mg/kg) |        |                          |        |        |        |        |        |        |      |      |      |         |
| 76 F               | 0.066  | 3.50                     | 0.199  | 0.015  | 0.001  | 0.758  | 0.022  | 0.004  | 0.70 | 0.05 | 0.00 | 2.66    |
| 77 F               | 0.042  | 4.42                     | 0.209  | 0.018  | 0.002  | 0.743  | 0.021  | 0.007  | 0.92 | 0.08 | 0.01 | 3.29    |
| 78 F               | 0.016  | 2.41                     | 0.204  | 0.013  | 0.003  | 0.756  | 0.019  | 0.006  | 0.49 | 0.03 | 0.01 | 1.82    |
| 79 F               | 0.028  | 3.42                     | 0.212  | 0.024  | 0.002  | 0.736  | 0.020  | 0.005  | 0.73 | 0.08 | 0.01 | 2.52    |
| 80 F               | 0.033  | 3.24                     | 0.244  | 0.018  | 0.001  | 0.710  | 0.023  | 0.004  | 0.79 | 0.06 | 0.00 | 2.30    |
| 81 F               | 0.027  | 3.12                     | 0.122  | 0.028  | 0.002  | 0.829  | 0.012  | 0.007  | 0.38 | 0.09 | 0.01 | 2.58    |
| 82 F               | 0.035  | 2.34                     | 0.222  | 0.021  | 0.003  | 0.701  | 0.042  | 0.010  | 0.52 | 0.05 | 0.01 | 1.64    |
| 83 F               | 0.050  | 4.16                     | 0.156  | 0.019  | 0.003  | 0.785  | 0.028  | 0.009  | 0.65 | 0.08 | 0.01 | 3.26    |
| 84 F               | 0.036  | 3.92                     | 0.213  | 0.029  | 0.002  | 0.735  | 0.017  | 0.004  | 0.83 | 0.12 | 0.01 | 2.88    |
| 85 F               | 0.017  | 3.41                     | 0.135  | 0.023  | 0.001  | 0.819  | 0.019  | 0.003  | 0.46 | 0.08 | 0.00 | 2.80    |
| Group 3 (50 mg/kg) |        |                          |        |        |        |        |        |        |      |      |      |         |
| 91 F               | 0.094  | 3.31                     | 0.162  | 0.028  | 0.003  | 0.786  | 0.013  | 0.008  | 0.54 | 0.09 | 0.01 | 2.60    |
| 92 F               | 0.082  | 4.40                     | 0.220  | 0.010  | 0.002  | 0.749  | 0.009  | 0.010  | 0.97 | 0.04 | 0.01 | 3.30    |
| 93 F               | 0.020  | 5.55                     | 0.271  | 0.027  | 0.003  | 0.674  | 0.021  | 0.004  | 1.51 | 0.15 | 0.01 | 3.74    |
| 94 F               | 0.037  | 4.92                     | 0.283  | 0.011  | 0.002  | 0.681  | 0.018  | 0.005  | 1.39 | 0.06 | 0.01 | 3.35    |
| 95 F               | 0.081  | 2.97                     | 0.177  | 0.019  | 0.003  | 0.771  | 0.025  | 0.005  | 0.53 | 0.06 | 0.01 | 2.29    |
| 96 F               | 0.070  | 4.51                     | 0.148  | 0.018  | 0.002  | 0.812  | 0.013  | 0.007  | 0.67 | 0.08 | 0.01 | 3.66    |
| 97 F               | 0.045  | 6.07                     | 0.145  | 0.016  | 0.002  | 0.818  | 0.012  | 0.007  | 0.88 | 0.10 | 0.01 | 4.96    |
| 98 F               | 0.028  | 3.27                     | 0.182  | 0.017  | 0.002  | 0.776  | 0.017  | 0.005  | 0.60 | 0.06 | 0.01 | 2.54    |
| 99 F               | 0.042  | 4.21                     | 0.171  | 0.018  | 0.004  | 0.781  | 0.023  | 0.004  | 0.72 | 0.08 | 0.01 | 3.29    |
| 100 F              | 0.032  | 2.86                     | 0.179  | 0.015  | 0.001  | 0.774  | 0.022  | 0.010  | 0.51 | 0.04 | 0.00 | 2.21    |

| WEEK 16             |        | Hematology (individuals) |        |        |        |        |        |        |      |      |      | FEMALES |  |
|---------------------|--------|--------------------------|--------|--------|--------|--------|--------|--------|------|------|------|---------|--|
| AN_NO               | H Reti | WBC                      | Neut   | Eos    | Baso   | Lympho | Mono   | Luc    | Neut | Eos  | Baso | Lympho  |  |
|                     | rel. 1 | G/l                      | rel. 1 | rel. 1 | rel. 1 | rel. 1 | rel. 1 | rel. 1 | G/l  | G/l  | G/l  | G/l     |  |
| Group 4 (200 mg/kg) |        |                          |        |        |        |        |        |        |      |      |      |         |  |
| 106 F               | 0.049  | 5.05                     | 0.196  | 0.014  | 0.003  | 0.766  | 0.016  | 0.006  | 0.99 | 0.07 | 0.02 | 3.87    |  |
| 107 F               | 0.024  | 4.39                     | 0.208  | 0.009  | 0.002  | 0.759  | 0.014  | 0.007  | 0.91 | 0.04 | 0.01 | 3.33    |  |
| 108 F               | 0.022  | 3.81                     | 0.133  | 0.014  | 0.003  | 0.833  | 0.013  | 0.005  | 0.51 | 0.05 | 0.01 | 3.18    |  |
| 109 F               | 0.089  | 3.61                     | 0.142  | 0.012  | 0.003  | 0.815  | 0.018  | 0.011  | 0.51 | 0.04 | 0.01 | 2.94    |  |
| 110 F               | 0.037  | 3.76                     | 0.226  | 0.012  | 0.001  | 0.736  | 0.020  | 0.004  | 0.85 | 0.05 | 0.00 | 2.77    |  |
| 111 F               | 0.101  | 3.41                     | 0.121  | 0.014  | 0.002  | 0.845  | 0.013  | 0.005  | 0.41 | 0.05 | 0.01 | 2.88    |  |
| 112 F               | 0.069  | 2.53                     | 0.290  | 0.021  | 0.001  | 0.660  | 0.024  | 0.004  | 0.73 | 0.05 | 0.00 | 1.67    |  |
| 113 F               | 0.082  | 5.21                     | 0.158  | 0.010  | 0.005  | 0.806  | 0.018  | 0.004  | 0.82 | 0.05 | 0.03 | 4.20    |  |
| 114 F               | 0.047  | 3.35                     | 0.186  | 0.008  | 0.002  | 0.787  | 0.011  | 0.006  | 0.62 | 0.03 | 0.01 | 2.64    |  |
| 115 F               | 0.091  | 3.39                     | 0.252  | 0.014  | 0.003  | 0.708  | 0.017  | 0.006  | 0.85 | 0.05 | 0.01 | 2.40    |  |

WEEK 16

FEMALES

| AN_ID | Mono<br>G/l | Luc<br>G/l | Plt<br>G/l | MetHb<br>rel. 1 | PT<br>rel. 1 | PTT<br>sec | Heinz_B<br>rel. 1 |
|-------|-------------|------------|------------|-----------------|--------------|------------|-------------------|
|-------|-------------|------------|------------|-----------------|--------------|------------|-------------------|

Group 1 (0 mg/kg)

|      |      |      |      |       |      |      |       |
|------|------|------|------|-------|------|------|-------|
| 61 F | 0.05 | 0.01 | 1092 | 0.008 | 0.76 | 14.4 | 0.000 |
| 62 F | 0.05 | 0.02 | 878  | 0.010 | 1.03 | 23.0 | 0.000 |
| 63 F | 0.12 | 0.05 | 982  | 0.007 | 0.79 | 13.9 | 0.000 |
| 64 F | 0.09 | 0.02 | 717  | n.d.  | 0.77 | 16.8 | 0.000 |
| 65 F | 0.09 | 0.04 | 1122 | 0.010 | 0.80 | 17.9 | 0.000 |
| 66 F | 0.08 | 0.03 | 732  | 0.009 | 0.76 | 15.8 | 0.000 |
| 67 F | 0.06 | 0.02 | 1105 | 0.010 | 0.79 | 14.2 | 0.000 |
| 68 F | 0.06 | 0.03 | 960  | 0.010 | 0.79 | 16.8 | 0.000 |
| 69 F | 0.07 | 0.01 | 974  | 0.007 | 0.75 | 18.6 | 0.000 |
| 70 F | 0.06 | 0.03 | 972  | n.d.  | 0.75 | 17.0 | 0.000 |

Group 2 (15 mg/kg)

|      |      |      |      |       |      |      |  |
|------|------|------|------|-------|------|------|--|
| 76 F | 0.08 | 0.01 | 918  | 0.010 | 0.78 | 16.0 |  |
| 77 F | 0.09 | 0.03 | 905  | 0.007 | 0.73 | 16.6 |  |
| 78 F | 0.05 | 0.01 | 885  | 0.010 | 0.73 | 16.8 |  |
| 79 F | 0.07 | 0.02 | 1089 | 0.009 | 0.83 | 14.4 |  |
| 80 F | 0.07 | 0.01 | 1041 | 0.010 | 0.79 | 11.6 |  |
| 81 F | 0.04 | 0.02 | 1049 | 0.010 | 0.73 | 13.3 |  |
| 82 F | 0.10 | 0.02 | 955  | 0.010 | 0.79 | 18.6 |  |
| 83 F | 0.12 | 0.04 | 812  | 0.009 | 0.79 | 20.8 |  |
| 84 F | 0.07 | 0.02 | 997  | 0.010 | 0.74 | 16.6 |  |
| 85 F | 0.07 | 0.01 | 954  | 0.009 | 0.76 | 14.6 |  |

Group 3 (50 mg/kg)

|       |      |      |      |       |      |      |       |
|-------|------|------|------|-------|------|------|-------|
| 91 F  | 0.04 | 0.03 | 898  | 0.010 | 0.78 | 11.1 | 0.000 |
| 92 F  | 0.04 | 0.04 | 1028 | 0.011 | 0.75 | 12.2 | 0.000 |
| 93 F  | 0.11 | 0.02 | 1024 | 0.009 | 0.84 | 18.7 | 0.000 |
| 94 F  | 0.09 | 0.02 | 1119 | 0.008 | 0.78 | 17.5 | 0.000 |
| 95 F  | 0.07 | 0.01 | 1010 | 0.009 | 0.77 | 13.9 | 0.000 |
| 96 F  | 0.06 | 0.03 | 1062 | 0.012 | 0.83 | 14.5 | 0.000 |
| 97 F  | 0.07 | 0.04 | 1096 | 0.010 | 0.80 | 14.5 | 0.000 |
| 98 F  | 0.06 | 0.02 | 908  | 0.012 | 0.79 | 15.7 | 0.000 |
| 99 F  | 0.09 | 0.02 | 996  | 0.012 | 0.87 | 12.9 | 0.000 |
| 100 F | 0.06 | 0.03 | 1026 | 0.012 | 0.81 | 10.4 | 0.000 |

n.d.=not determined

| WEEK 16             |      | Hematology (individuals) |      |        |        |      |         | FEMALES |
|---------------------|------|--------------------------|------|--------|--------|------|---------|---------|
| AN_NO               | Mono | Luc                      | Plt  | Methb  | PT     | PTT  | Heinz_B |         |
|                     | G/l  | G/l                      | G/l  | rel. 1 | rel. 1 | sec  | rel. 1  |         |
| Group 4 (200 mg/kg) |      |                          |      |        |        |      |         |         |
| 106 F               | 0.08 | 0.03                     | 1040 | 0.010  | 0.82   | 13.5 | 0.000   |         |
| 107 F               | 0.06 | 0.03                     | 988  | 0.011  | 0.82   | 13.1 | 0.000   |         |
| 108 F               | 0.05 | 0.02                     | 1011 | 0.010  | 0.82   | 15.2 | 0.000   |         |
| 109 F               | 0.07 | 0.04                     | 998  | 0.011  | 0.81   | 17.2 | 0.000   |         |
| 110 F               | 0.07 | 0.02                     | 999  | 0.010  | 0.76   | 13.0 | 0.000   |         |
| 111 F               | 0.04 | 0.02                     | 1184 | 0.012  | 0.79   | 12.4 | 0.000   |         |
| 112 F               | 0.06 | 0.01                     | 946  | 0.011  | 0.85   | 11.4 | 0.000   |         |
| 113 F               | 0.09 | 0.02                     | 1136 | 0.010  | 0.74   | 18.2 | 0.000   |         |
| 114 F               | 0.04 | 0.02                     | 903  | 0.010  | 0.88   | 12.1 | 0.000   |         |
| 115 F               | 0.06 | 0.02                     | 1111 | 0.010  | 0.71   | 15.6 | 0.000   |         |

## 1.7 BLOOD CHEMISTRY (INDIVIDUALS)

WEEK 16

MALES

| AN_ID              | Gluc   | Urea   | Creat  | Bili-tot | Chol   | Trigly | Phos-Lip | ASAT | ALAT | LDH   | GLDH | ATP  |
|--------------------|--------|--------|--------|----------|--------|--------|----------|------|------|-------|------|------|
|                    | mmol/l | mmol/l | µmol/l | µmol/l   | mmol/l | mmol/l | mmol/l   | U/l  | U/l  | U/l   | U/l  | U/l  |
| Group 1 (0 mg/kg)  |        |        |        |          |        |        |          |      |      |       |      |      |
| 1 M                | 4.96   | 4.70   | 22.1   | 1.92     | 1.72   | 0.56   | 1.45     | 85.0 | 32.8 | 202.0 | 10.2 | 75.5 |
| 2 M                | 4.50   | 5.61   | 27.5   | 1.42     | 2.05   | 0.80   | 1.70     | 70.1 | 33.0 | 132.1 | 7.4  | 71.4 |
| 3 M                | 4.49   | 5.74   | 24.3   | 1.74     | 2.01   | 0.78   | 1.64     | 70.3 | 36.4 | 155.6 | 7.2  | 60.8 |
| 4 M                | 4.28   | 5.69   | 25.0   | 1.66     | 2.24   | 0.84   | 1.62     | 70.2 | 38.4 | 266.4 | 7.2  | 53.1 |
| 5 M                | 4.86   | 4.12   | 25.4   | 2.37     | 1.72   | 0.31   | 1.43     | 70.0 | 30.2 | 124.0 | 5.0  | 65.7 |
| 6 M                | 4.50   | 4.27   | 25.7   | 1.79     | 1.72   | 0.68   | 1.38     | 76.8 | 30.6 | 397.3 | 7.9  | 46.9 |
| 7 M                | 4.68   | 4.59   | 24.4   | 1.68     | 1.37   | 0.98   | 1.37     | 64.6 | 25.8 | 125.9 | 8.9  | 67.9 |
| 8 M                | 5.08   | 4.67   | 25.1   | 1.86     | 1.68   | 0.45   | 1.37     | 71.1 | 36.2 | 129.4 | 7.4  | 54.7 |
| 9 M                | 4.20   | 6.08   | 29.7   | 1.81     | 1.63   | 0.47   | 1.36     | 77.5 | 47.3 | 152.3 | 6.4  | 52.6 |
| 10 M               | 4.72   | 5.70   | 27.9   | 1.85     | 1.33   | 0.48   | 1.20     | 76.0 | 38.0 | 177.7 | 9.6  | 49.7 |
| Group 2 (15 mg/kg) |        |        |        |          |        |        |          |      |      |       |      |      |
| 16 M               | 5.59   | 5.91   | 28.4   | 1.26     | 2.33   | 0.40   | 1.72     | 85.8 | 43.5 | 131.5 | 11.8 | 85.2 |
| 17 M               | 4.52   | 6.81   | 27.5   | 1.73     | 1.50   | 0.28   | 1.24     | 89.6 | 42.8 | 634.2 | 10.6 | 48.9 |
| 18 M               | 5.98   | 4.84   | 26.4   | 1.59     | 1.81   | 1.06   | 1.61     | 66.6 | 26.3 | 133.3 | 7.5  | 69.4 |
| 19 M               | 5.02   | 5.37   | 26.3   | 2.01     | 1.52   | 0.36   | 1.26     | 77.7 | 33.6 | 176.3 | 5.1  | 51.0 |
| 20 M               | 5.59   | 5.05   | 28.8   | 2.31     | 1.56   | 0.41   | 1.34     | 73.0 | 28.6 | 112.8 | 7.7  | 56.7 |
| 21 M               | 4.93   | 5.92   | 30.7   | 1.47     | 1.52   | 0.72   | 1.42     | 68.2 | 28.8 | 174.2 | 6.4  | 65.7 |
| 22 M               | 5.23   | 5.87   | 27.6   | 2.43     | 2.02   | 0.36   | 1.56     | 69.2 | 26.2 | 152.0 | 6.1  | 52.3 |
| 23 M               | 4.77   | 4.24   | 26.5   | 1.41     | 1.56   | 1.12   | 1.52     | 73.4 | 29.0 | 290.6 | 5.6  | 67.8 |
| 24 M               | 5.52   | 6.16   | 25.3   | 1.75     | 1.89   | 0.26   | 1.46     | 69.3 | 30.4 | 173.1 | 7.4  | 68.5 |
| 25 M               | 5.37   | 4.84   | 26.4   | 2.06     | 1.91   | 0.32   | 1.55     | 72.3 | 31.7 | 197.2 | 7.3  | 58.1 |
| Group 3 (50 mg/kg) |        |        |        |          |        |        |          |      |      |       |      |      |
| 31 M               | 4.63   | 4.54   | 24.4   | 1.45     | 1.72   | 0.57   | 1.40     | 72.7 | 34.7 | 236.4 | 6.2  | 76.3 |
| 32 M               | 4.72   | 4.89   | 26.1   | 1.46     | 2.09   | 0.57   | 1.65     | 66.5 | 35.0 | 126.3 | 6.7  | 45.9 |
| 33 M               | 5.42   | 5.71   | 24.3   | 1.98     | 1.85   | 0.86   | 1.55     | 74.7 | 39.6 | 138.2 | 8.7  | 51.0 |
| 34 M               | 5.25   | 6.09   | 27.3   | 1.86     | 2.01   | 0.38   | 1.58     | 83.1 | 45.8 | 211.0 | 20.3 | 56.5 |
| 35 M               | 5.14   | 5.72   | 30.7   | 2.73     | 1.79   | 0.51   | 1.53     | 76.3 | 29.9 | 118.0 | 4.2  | 58.8 |
| 36 M               | 4.98   | 5.01   | 27.0   | 2.83     | 1.69   | 0.43   | 1.53     | 72.4 | 39.5 | 146.1 | 11.1 | 78.9 |
| 37 M               | 5.73   | 5.23   | 26.9   | 1.63     | 1.70   | 1.08   | 1.55     | 67.4 | 33.4 | 125.0 | 8.6  | 71.2 |
| 38 M               | 5.39   | 4.44   | 26.5   | 1.92     | 1.14   | 0.50   | 1.16     | 68.1 | 36.1 | 125.7 | 8.2  | 41.9 |
| 39 M               | 5.41   | 5.06   | 24.9   | 1.97     | 2.10   | 0.69   | 1.62     | 80.9 | 46.4 | 170.0 | 17.8 | 60.6 |
| 40 M               | 4.66   | 4.68   | 28.8   | 2.03     | 1.89   | 0.36   | 1.55     | 81.4 | 31.5 | 138.1 | 6.2  | 59.6 |

| WEEK 16             |        | Blood chemistry (individuals) |        |          |        |        |          |       |      |       |      | MALES |
|---------------------|--------|-------------------------------|--------|----------|--------|--------|----------|-------|------|-------|------|-------|
| AN_ID               | Gluc   | Urea                          | Creat  | Bili-tot | Chol   | Trigly | Phos-Lip | ASAT  | ALAT | LDH   | GLDH | AIP   |
|                     | mmol/l | mmol/l                        | µmol/l | µmol/l   | mmol/l | mmol/l | mmol/l   | U/l   | U/l  | U/l   | U/l  | U/l   |
| Group 4 (200 mg/kg) |        |                               |        |          |        |        |          |       |      |       |      |       |
| 46 M                | 6.67   | 5.79                          | 22.2   | 2.57     | 1.78   | 0.47   | 1.45     | 55.4  | 26.8 | 81.3  | 6.1  | 50.6  |
| 47 M                | 5.09   | 6.41                          | 28.7   | 2.65     | 2.02   | 0.29   | 1.49     | 101.6 | 46.3 | 282.2 | 7.4  | 71.2  |
| 48 M                | 4.71   | 7.32                          | 29.8   | 2.73     | 2.07   | 0.41   | 1.69     | 82.2  | 37.3 | 219.1 | 5.1  | 67.5  |
| 49 M                | 4.13   | 5.26                          | 21.7   | 2.03     | 2.29   | 1.31   | 1.89     | 72.4  | 36.9 | 260.9 | 8.7  | 52.1  |
| 50 M                | 4.06   | 5.00                          | 21.5   | 2.14     | 1.95   | 1.10   | 1.72     | 71.5  | 43.1 | 156.1 | 11.4 | 70.1  |
| 51 M                | 5.29   | 5.04                          | 25.8   | 1.41     | 2.25   | 0.40   | 1.69     | 75.0  | 36.2 | 146.6 | 6.9  | 37.2  |
| 52 M                | 4.09   | 4.74                          | 23.6   | 2.31     | 1.90   | 0.71   | 1.55     | 66.5  | 35.0 | 133.7 | 6.5  | 63.4  |
| 53 M                | 5.47   | 4.87                          | 21.5   | 1.67     | 2.08   | 1.25   | 1.81     | 71.0  | 49.6 | 161.5 | 9.2  | 70.8  |
| 54 M                | 4.48   | 5.08                          | 20.9   | 2.20     | 1.90   | 0.44   | 1.53     | 69.8  | 22.9 | 148.6 | 4.9  | 61.1  |
| 55 M                | 4.42   | 4.63                          | 19.7   | 2.25     | 2.15   | 0.48   | 1.79     | 78.7  | 37.0 | 584.3 | 9.8  | 65.9  |



| WEEK 16            |     | Blood chemistry (individuals) |        |        |        |        |        |       |        |         |         |        | MALES |
|--------------------|-----|-------------------------------|--------|--------|--------|--------|--------|-------|--------|---------|---------|--------|-------|
| AN_ID              | GGT | CK                            | Na+    | K+     | Cl-    | Ca++   | P04-in | Prot  | Alb-el | Glob_A1 | Glob_A2 | Glob_B |       |
|                    | U/l | U/l                           | mmol/l | mmol/l | mmol/l | mmol/l | mmol/l | g/l   | rel. 1 | rel. 1  | rel. 1  | rel. 1 |       |
| Group 1 (0 mg/kg)  |     |                               |        |        |        |        |        |       |        |         |         |        |       |
| 1 M                | 0.0 | 419.6                         | 141.7  | 3.48   | 104.1  | 2.59   | 1.79   | 60.13 | 0.526  | 0.197   | 0.077   | 0.172  |       |
| 2 M                | 0.0 | 127.0                         | 143.2  | 3.51   | 104.4  | 2.63   | 1.39   | 64.57 | 0.539  | 0.202   | 0.071   | 0.162  |       |
| 3 M                | 0.0 | 140.6                         | 143.4  | 3.37   | 102.8  | 2.71   | 1.89   | 66.17 | 0.512  | 0.216   | 0.070   | 0.171  |       |
| 4 M                | 0.0 | 217.8                         | 142.6  | 3.35   | 102.3  | 2.70   | 1.72   | 66.27 | 0.506  | 0.219   | 0.075   | 0.179  |       |
| 5 M                | 0.0 | 126.4                         | 144.6  | 3.40   | 106.0  | 2.61   | 1.49   | 64.11 | 0.525  | 0.200   | 0.075   | 0.169  |       |
| 6 M                | 0.0 | 246.0                         | 145.2  | 3.14   | 103.8  | 2.68   | 1.43   | 67.38 | 0.537  | 0.211   | 0.060   | 0.167  |       |
| 7 M                | 0.0 | 104.2                         | 146.1  | 3.39   | 106.5  | 2.68   | 1.93   | 63.45 | 0.525  | 0.215   | 0.057   | 0.182  |       |
| 8 M                | 0.0 | 116.1                         | 145.1  | 3.43   | 105.5  | 2.58   | 1.66   | 62.10 | 0.532  | 0.190   | 0.067   | 0.183  |       |
| 9 M                | 0.0 | 98.8                          | 144.8  | 3.67   | 106.1  | 2.71   | 1.67   | 64.88 | 0.530  | 0.200   | 0.064   | 0.178  |       |
| 10 M               | 0.0 | 172.7                         | 145.6  | 3.25   | 105.9  | 2.57   | 1.78   | 63.92 | 0.541  | 0.197   | 0.068   | 0.170  |       |
| Group 2 (15 mg/kg) |     |                               |        |        |        |        |        |       |        |         |         |        |       |
| 16 M               | 0.0 | 185.5                         | 146.1  | 3.51   | 106.1  | 2.55   | 1.70   | 64.61 | 0.532  | 0.211   | 0.060   | 0.172  |       |
| 17 M               | 0.0 | 303.1                         | 145.7  | 3.90   | 107.1  | 2.65   | 1.84   | 67.20 | 0.534  | 0.199   | 0.067   | 0.178  |       |
| 18 M               | 0.0 | 128.0                         | 146.2  | 3.71   | 107.4  | 2.60   | 1.64   | 63.07 | 0.527  | 0.199   | 0.072   | 0.179  |       |
| 19 M               | 0.0 | 164.1                         | 145.6  | 3.69   | 107.0  | 2.63   | 1.74   | 64.63 | 0.516  | 0.211   | 0.059   | 0.183  |       |
| 20 M               | 0.0 | 122.3                         | 145.4  | 3.77   | 107.4  | 2.59   | 1.64   | 63.28 | 0.521  | 0.205   | 0.065   | 0.189  |       |
| 21 M               | 0.0 | 148.2                         | 146.7  | 3.39   | 106.9  | 2.69   | 1.67   | 64.88 | 0.539  | 0.219   | 0.058   | 0.164  |       |
| 22 M               | 0.0 | 115.7                         | 145.9  | 3.83   | 107.3  | 2.71   | 1.89   | 66.38 | 0.532  | 0.207   | 0.055   | 0.182  |       |
| 23 M               | 0.0 | 200.9                         | 147.7  | 3.72   | 107.6  | 2.71   | 1.77   | 66.75 | 0.532  | 0.201   | 0.066   | 0.175  |       |
| 24 M               | 0.0 | 160.9                         | 146.6  | 3.77   | 107.3  | 2.63   | 1.56   | 63.42 | 0.523  | 0.216   | 0.071   | 0.166  |       |
| 25 M               | 0.0 | 166.5                         | 148.8  | 3.81   | 108.2  | 2.74   | 1.75   | 67.46 | 0.540  | 0.202   | 0.062   | 0.172  |       |
| Group 3 (50 mg/kg) |     |                               |        |        |        |        |        |       |        |         |         |        |       |
| 31 M               | 0.0 | 173.4                         | 147.0  | 3.65   | 106.9  | 2.59   | 1.49   | 63.31 | 0.520  | 0.206   | 0.070   | 0.184  |       |
| 32 M               | 0.0 | 136.7                         | 149.0  | 3.65   | 108.3  | 2.73   | 1.71   | 63.65 | 0.518  | 0.201   | 0.071   | 0.188  |       |
| 33 M               | 0.0 | 150.8                         | 147.3  | 4.01   | 107.3  | 2.72   | 1.73   | 66.58 | 0.521  | 0.201   | 0.066   | 0.179  |       |
| 34 M               | 0.0 | 139.9                         | 151.7  | 3.89   | 108.4  | 2.76   | 1.60   | 66.65 | 0.506  | 0.210   | 0.071   | 0.190  |       |
| 35 M               | 0.0 | 135.2                         | 145.9  | 3.84   | 107.3  | 2.64   | 1.87   | 62.96 | 0.525  | 0.191   | 0.070   | 0.185  |       |
| 36 M               | 0.0 | 111.1                         | 145.5  | 3.85   | 105.6  | 2.69   | 1.72   | 64.09 | 0.513  | 0.213   | 0.074   | 0.183  |       |
| 37 M               | 0.0 | 192.8                         | 144.9  | 3.77   | 106.1  | 2.64   | 1.55   | 66.67 | 0.532  | 0.229   | 0.062   | 0.157  |       |
| 38 M               | 0.0 | 101.9                         | 145.9  | 3.52   | 106.2  | 2.70   | 1.69   | 66.72 | 0.532  | 0.202   | 0.070   | 0.171  |       |
| 39 M               | 0.0 | 206.8                         | 145.6  | 3.65   | 106.3  | 2.74   | 1.61   | 69.86 | 0.529  | 0.205   | 0.073   | 0.167  |       |
| 40 M               | 0.0 | 118.2                         | 145.5  | 3.62   | 106.8  | 2.59   | 1.68   | 62.57 | 0.531  | 0.197   | 0.074   | 0.178  |       |

| WEEK 16             |     | Blood chemistry (individuals) |        |        |        |        |        |       |        |         |         |        | MALES |
|---------------------|-----|-------------------------------|--------|--------|--------|--------|--------|-------|--------|---------|---------|--------|-------|
| AN_NO               | GGT | CK                            | Na+    | K+     | Cl-    | Ca++   | P04-in | Prot  | Alb-el | Glob_A1 | Glob_A2 | Glob_B |       |
|                     | U/l | U/l                           | mmol/l | mmol/l | mmol/l | mmol/l | mmol/l | g/l   | rel. 1 | rel. 1  | rel. 1  | rel. 1 |       |
| Group 4 (200 mg/kg) |     |                               |        |        |        |        |        |       |        |         |         |        |       |
| 46 M                | 0.0 | 78.3                          | 145.5  | 3.67   | 107.1  | 2.64   | 1.80   | 60.22 | 0.553  | 0.198   | 0.061   | 0.167  |       |
| 47 M                | 0.0 | 227.2                         | 146.2  | 3.39   | 104.1  | 2.65   | 1.95   | 64.72 | 0.537  | 0.199   | 0.063   | 0.174  |       |
| 48 M                | 0.0 | 178.6                         | 152.0  | 4.05   | 110.8  | 2.75   | 1.87   | 65.92 | 0.530  | 0.178   | 0.077   | 0.187  |       |
| 49 M                | 0.0 | 232.4                         | 145.6  | 3.75   | 104.0  | 2.72   | 1.90   | 66.73 | 0.520  | 0.215   | 0.069   | 0.176  |       |
| 50 M                | 0.0 | 153.3                         | 146.3  | 3.39   | 105.2  | 2.65   | 1.83   | 64.40 | 0.531  | 0.166   | 0.084   | 0.194  |       |
| 51 M                | 0.0 | 137.3                         | 143.5  | 3.87   | 104.4  | 2.69   | 1.55   | 65.40 | 0.509  | 0.206   | 0.075   | 0.183  |       |
| 52 M                | 0.0 | 167.4                         | 144.5  | 3.65   | 104.3  | 2.73   | 1.72   | 67.77 | 0.500  | 0.218   | 0.069   | 0.187  |       |
| 53 M                | 0.0 | 157.4                         | 145.6  | 3.51   | 106.8  | 2.63   | 1.82   | 65.77 | 0.528  | 0.174   | 0.083   | 0.188  |       |
| 54 M                | 0.0 | 151.8                         | 143.9  | 3.62   | 103.6  | 2.69   | 1.91   | 63.18 | 0.534  | 0.201   | 0.067   | 0.181  |       |
| 55 M                | 0.0 | 403.8                         | 145.1  | 4.03   | 105.0  | 2.61   | 1.53   | 65.37 | 0.537  | 0.202   | 0.065   | 0.175  |       |

| WEEK 16            |  | Blood chemistry (individuals) |        |         |         |        |        | MALES  |
|--------------------|--|-------------------------------|--------|---------|---------|--------|--------|--------|
|                    |  | Glob_G                        | Alb-e1 | Glob_A1 | Glob_A2 | Glob_B | Glob_G | A/G    |
| AN_NO              |  | rel. 1                        | g/l    | g/l     | g/l     | g/l    | g/l    | rel. 1 |
| Group 1 (0 mg/kg)  |  |                               |        |         |         |        |        |        |
| 1 M                |  | 0.028                         | 31.63  | 11.85   | 4.63    | 10.34  | 1.68   | 1.10   |
| 2 M                |  | 0.026                         | 34.80  | 13.04   | 4.58    | 10.46  | 1.68   | 1.16   |
| 3 M                |  | 0.031                         | 33.88  | 14.29   | 4.63    | 11.32  | 2.05   | 1.05   |
| 4 M                |  | 0.021                         | 33.59  | 14.51   | 4.97    | 11.86  | 1.39   | 1.02   |
| 5 M                |  | 0.031                         | 33.66  | 12.82   | 4.81    | 10.83  | 1.99   | 1.10   |
| 6 M                |  | 0.025                         | 36.18  | 14.22   | 4.04    | 11.25  | 1.68   | 1.15   |
| 7 M                |  | 0.021                         | 33.31  | 13.64   | 3.62    | 11.55  | 1.33   | 1.10   |
| 8 M                |  | 0.028                         | 33.04  | 11.80   | 4.16    | 11.36  | 1.74   | 1.13   |
| 9 M                |  | 0.028                         | 34.47  | 12.98   | 4.15    | 11.55  | 1.82   | 1.13   |
| 10 M               |  | 0.024                         | 34.58  | 12.59   | 4.35    | 10.87  | 1.53   | 1.17   |
| Group 2 (15 mg/kg) |  |                               |        |         |         |        |        |        |
| 16 M               |  | 0.025                         | 34.37  | 13.63   | 3.88    | 11.11  | 1.62   | 1.13   |
| 17 M               |  | 0.022                         | 35.89  | 13.37   | 4.50    | 11.96  | 1.48   | 1.14   |
| 18 M               |  | 0.023                         | 33.24  | 12.55   | 4.54    | 11.29  | 1.45   | 1.11   |
| 19 M               |  | 0.031                         | 33.35  | 13.64   | 3.81    | 11.83  | 2.00   | 1.06   |
| 20 M               |  | 0.020                         | 32.97  | 12.97   | 4.11    | 11.96  | 1.27   | 1.08   |
| 21 M               |  | 0.020                         | 34.97  | 14.21   | 3.76    | 10.64  | 1.30   | 1.16   |
| 22 M               |  | 0.024                         | 35.31  | 13.74   | 3.65    | 12.08  | 1.59   | 1.13   |
| 23 M               |  | 0.026                         | 35.51  | 13.42   | 4.41    | 11.68  | 1.74   | 1.13   |
| 24 M               |  | 0.024                         | 33.17  | 13.70   | 4.50    | 10.53  | 1.52   | 1.09   |
| 25 M               |  | 0.024                         | 36.43  | 13.63   | 4.18    | 11.60  | 1.62   | 1.16   |
| Group 3 (50 mg/kg) |  |                               |        |         |         |        |        |        |
| 31 M               |  | 0.020                         | 32.92  | 13.04   | 4.43    | 11.65  | 1.27   | 1.08   |
| 32 M               |  | 0.022                         | 32.97  | 12.79   | 4.52    | 11.97  | 1.40   | 1.07   |
| 33 M               |  | 0.033                         | 34.69  | 13.38   | 4.39    | 11.92  | 2.20   | 1.08   |
| 34 M               |  | 0.023                         | 33.74  | 14.00   | 4.73    | 12.66  | 1.53   | 1.02   |
| 35 M               |  | 0.029                         | 33.05  | 12.03   | 4.41    | 11.65  | 1.83   | 1.10   |
| 36 M               |  | 0.017                         | 32.88  | 13.65   | 4.74    | 11.73  | 1.09   | 1.05   |
| 37 M               |  | 0.020                         | 35.47  | 15.27   | 4.13    | 10.47  | 1.33   | 1.14   |
| 38 M               |  | 0.025                         | 35.38  | 13.48   | 4.67    | 11.41  | 1.67   | 1.12   |
| 39 M               |  | 0.026                         | 36.86  | 14.32   | 5.10    | 11.67  | 1.82   | 1.11   |
| 40 M               |  | 0.020                         | 33.22  | 12.33   | 4.63    | 11.14  | 1.25   | 1.13   |

| WEEK 16             |        | Blood chemistry (individuals) |         |         |        |        |        | MALES |
|---------------------|--------|-------------------------------|---------|---------|--------|--------|--------|-------|
| AN_ID               | Glob_G | Alb-el                        | Glob_A1 | Glob_A2 | Glob_B | Glob_G | A/G    |       |
|                     | rel. 1 | g/l                           | g/l     | g/l     | g/l    | g/l    | rel. 1 |       |
| Group 4 (200 mg/kg) |        |                               |         |         |        |        |        |       |
| 46 M                | 0.021  | 33.31                         | 11.82   | 3.67    | 10.06  | 1.26   | 1.23   |       |
| 47 M                | 0.027  | 34.75                         | 12.88   | 4.08    | 11.26  | 1.75   | 1.16   |       |
| 48 M                | 0.028  | 34.94                         | 11.73   | 5.08    | 12.33  | 1.85   | 1.13   |       |
| 49 M                | 0.020  | 34.66                         | 14.35   | 4.80    | 11.74  | 1.33   | 1.08   |       |
| 50 M                | 0.025  | 34.20                         | 10.69   | 5.41    | 12.49  | 1.61   | 1.13   |       |
| 51 M                | 0.027  | 33.29                         | 13.47   | 4.90    | 11.97  | 1.77   | 1.03   |       |
| 52 M                | 0.026  | 33.85                         | 14.77   | 4.68    | 12.67  | 1.76   | 0.99   |       |
| 53 M                | 0.027  | 34.73                         | 11.44   | 5.46    | 12.36  | 1.78   | 1.11   |       |
| 54 M                | 0.017  | 33.74                         | 12.70   | 4.23    | 11.44  | 1.07   | 1.14   |       |
| 55 M                | 0.021  | 35.10                         | 13.20   | 4.25    | 11.44  | 1.37   | 1.15   |       |

| WEEK 16            |        | Blood chemistry (individuals) |        |          |        |        |          |       |      |       |      | FEMALES |
|--------------------|--------|-------------------------------|--------|----------|--------|--------|----------|-------|------|-------|------|---------|
| AN_NO              | Gluc   | Urea                          | Creat  | Bili-tot | Chol   | Trigly | Phos-Lip | ASAT  | ALAT | LDH   | GLDH | AIP     |
|                    | mmol/l | mmol/l                        | µmol/l | µmol/l   | mmol/l | mmol/l | mmol/l   | U/l   | U/l  | U/l   | U/l  | U/l     |
| Group 1 (0 mg/kg)  |        |                               |        |          |        |        |          |       |      |       |      |         |
| 61 F               | 4.02   | 7.02                          | 29.1   | 2.11     | 1.13   | 0.25   | 1.30     | 66.8  | 28.7 | 215.2 | 5.3  | 21.3    |
| 62 F               | 4.91   | 5.36                          | 32.4   | 1.71     | 1.23   | 0.33   | 1.34     | 74.9  | 23.7 | 246.6 | 3.6  | 26.2    |
| 63 F               | 4.98   | 5.37                          | 27.5   | 2.29     | 1.29   | 0.22   | 1.35     | 59.7  | 27.0 | 158.3 | 15.2 | 23.5    |
| 64 F               | 4.42   | 6.18                          | 30.4   | 2.92     | 1.30   | 0.16   | 1.29     | 76.3  | 30.7 | 178.4 | 5.8  | 27.1    |
| 65 F               | 4.88   | 7.14                          | 29.3   | 2.16     | 1.88   | 0.33   | 1.76     | 73.3  | 33.7 | 177.5 | 5.8  | 21.0    |
| 66 F               | 4.46   | 6.80                          | 32.4   | 2.81     | 1.69   | 0.20   | 1.55     | 88.8  | 22.7 | 157.3 | 4.7  | 26.7    |
| 67 F               | 4.76   | 5.93                          | 26.6   | 2.10     | 1.97   | 0.31   | 1.88     | 61.7  | 19.3 | 178.5 | 3.7  | 19.5    |
| 68 F               | 4.60   | 7.33                          | 33.6   | 1.57     | 1.84   | 0.34   | 1.67     | 82.0  | 35.4 | 279.8 | 3.9  | 24.3    |
| 69 F               | 4.94   | 5.51                          | 29.6   | 1.92     | 1.36   | 0.30   | 1.44     | 63.9  | 26.3 | 175.5 | 4.1  | 31.0    |
| 70 F               | 5.32   | 7.85                          | 28.7   | 1.87     | 1.46   | 0.20   | 1.46     | 74.4  | 25.4 | 237.8 | 10.6 | 17.8    |
| Group 2 (15 mg/kg) |        |                               |        |          |        |        |          |       |      |       |      |         |
| 76 F               | 4.42   | 6.61                          | 35.2   | 2.46     | 1.00   | 0.31   | 1.11     | 75.9  | 29.1 | 226.2 | 5.7  | 21.5    |
| 77 F               | 4.37   | 7.00                          | 36.0   | 2.67     | 0.83   | 0.18   | 0.87     | 74.9  | 27.5 | 221.6 | 6.1  | 20.8    |
| 78 F               | 3.94   | 6.16                          | 35.0   | 2.05     | 1.24   | 0.38   | 1.45     | 88.5  | 33.9 | 189.7 | 42.7 | 16.3    |
| 79 F               | 4.82   | 6.40                          | 26.6   | 3.00     | 1.61   | 0.27   | 1.71     | 100.8 | 37.7 | 223.5 | 52.1 | 17.7    |
| 80 F               | 5.50   | 6.01                          | 25.1   | 3.11     | 1.45   | 0.33   | 1.61     | 69.3  | 22.1 | 293.2 | 3.5  | 17.3    |
| 81 F               | 4.39   | 7.01                          | 30.9   | 1.92     | 1.30   | 0.25   | 1.35     | 64.9  | 16.7 | 268.4 | 3.4  | 24.4    |
| 82 F               | 4.69   | 7.86                          | 29.7   | 1.86     | 2.30   | 0.34   | 2.05     | 70.7  | 30.1 | 177.0 | 26.3 | 22.5    |
| 83 F               | 5.30   | 6.92                          | 27.6   | 2.43     | 1.96   | 0.28   | 1.81     | 109.7 | 58.0 | 240.9 | 68.0 | 23.5    |
| 84 F               | 6.58   | 8.78                          | 36.0   | 2.11     | 1.39   | 0.28   | 1.43     | 75.4  | 29.7 | 195.8 | 8.1  | 16.7    |
| 85 F               | 4.85   | 8.08                          | 36.0   | 2.57     | 1.29   | 0.25   | 1.34     | 60.4  | 16.4 | 260.8 | 4.6  | 17.3    |
| Group 3 (50 mg/kg) |        |                               |        |          |        |        |          |       |      |       |      |         |
| 91 F               | 5.32   | 7.03                          | 28.1   | 2.60     | 1.29   | 0.33   | 1.42     | 83.3  | 26.1 | 211.4 | 5.9  | 34.1    |
| 92 F               | 4.77   | 6.38                          | 33.9   | 2.47     | 1.30   | 0.38   | 1.47     | 79.1  | 26.7 | 204.6 | 5.9  | 31.0    |
| 93 F               | 5.34   | 5.25                          | 29.8   | 3.04     | 1.33   | 0.30   | 1.44     | 64.0  | 21.1 | 181.5 | 4.0  | 17.9    |
| 94 F               | 5.98   | 6.48                          | 29.1   | 3.55     | 1.43   | 0.33   | 1.56     | 78.8  | 43.2 | 291.8 | 47.7 | 21.3    |
| 95 F               | 5.51   | 6.04                          | 29.7   | 2.87     | 1.02   | 0.28   | 1.24     | 71.4  | 34.2 | 278.9 | 19.0 | 26.9    |
| 96 F               | 5.06   | 6.72                          | 26.9   | 2.24     | 1.47   | 0.18   | 1.55     | 70.1  | 29.4 | 142.7 | 9.9  | 19.4    |
| 97 F               | 4.99   | 7.20                          | 31.2   | 3.03     | 2.10   | 0.27   | 1.94     | 77.4  | 26.2 | 189.4 | 8.7  | 20.8    |
| 98 F               | 5.23   | 7.80                          | 38.2   | 2.02     | 1.91   | 0.28   | 1.79     | 64.7  | 22.4 | 156.4 | 3.8  | 18.6    |
| 99 F               | 5.18   | 5.93                          | 31.1   | 2.74     | 1.62   | 0.34   | 1.61     | 66.3  | 19.5 | 137.9 | 4.2  | 23.3    |
| 100 F              | 5.32   | 8.26                          | 35.9   | 3.58     | 0.90   | 0.18   | 1.14     | 69.7  | 22.7 | 177.9 | 5.1  | 19.0    |

| WEEK 16             |  | Blood chemistry (individuals) |        |        |          |        |        |          |      |      |       | SEX  |      |         |
|---------------------|--|-------------------------------|--------|--------|----------|--------|--------|----------|------|------|-------|------|------|---------|
|                     |  | Gluc                          | Urea   | Creat  | Bili-tot | Chol   | Trigly | Phos-Lip | ASAT | ALAT | LDH   | GLDH | AIP  | FEMALES |
| AN_NO               |  | mmol/l                        | mmol/l | µmol/l | µmol/l   | mmol/l | mmol/l | mmol/l   | U/l  | U/l  | U/l   | U/l  | U/l  |         |
| Group 4 (200 ng/kg) |  |                               |        |        |          |        |        |          |      |      |       |      |      |         |
| 106 F               |  | 4.95                          | 6.12   | 26.3   | 2.50     | 1.90   | 0.42   | 1.82     | 62.0 | 19.2 | 130.3 | 2.9  | 24.8 |         |
| 107 F               |  | 5.31                          | 6.24   | 24.5   | 3.24     | 2.03   | 0.27   | 1.97     | 60.5 | 22.1 | 101.2 | 6.2  | 30.8 |         |
| 108 F               |  | 4.34                          | 7.02   | 25.1   | 2.38     | 2.42   | 0.42   | 2.13     | 58.6 | 25.1 | 103.5 | 4.6  | 22.3 |         |
| 109 F               |  | 5.05                          | 7.43   | 23.7   | 2.42     | 2.37   | 0.48   | 2.41     | 58.0 | 23.1 | 123.4 | 5.9  | 28.7 |         |
| 110 F               |  | 5.81                          | 6.42   | 29.2   | 2.72     | 2.34   | 0.33   | 2.12     | 66.3 | 19.0 | 131.3 | 4.1  | 20.6 |         |
| 111 F               |  | 5.46                          | 6.96   | 27.4   | 1.91     | 1.50   | 0.39   | 1.67     | 56.7 | 25.4 | 97.1  | 3.5  | 19.9 |         |
| 112 F               |  | 6.41                          | 6.09   | 21.5   | 2.47     | 1.79   | 0.40   | 1.89     | 68.0 | 21.7 | 266.2 | 4.5  | 24.3 |         |
| 113 F               |  | 4.82                          | 5.75   | 23.4   | 1.85     | 1.70   | 0.38   | 1.79     | 62.9 | 25.7 | 144.8 | 5.7  | 18.5 |         |
| 114 F               |  | 4.49                          | 7.78   | 31.3   | 3.68     | 1.55   | 0.24   | 1.54     | 75.3 | 24.3 | 180.7 | 14.2 | 22.8 |         |
| 115 F               |  | 5.70                          | 6.60   | 24.8   | 2.56     | 1.39   | 0.27   | 1.54     | 72.3 | 23.2 | 248.7 | 5.0  | 29.0 |         |

| WEEK 16            |     | Blood chemistry (individuals) |        |        |        |        |        |       |        |         |         | FEMALES |
|--------------------|-----|-------------------------------|--------|--------|--------|--------|--------|-------|--------|---------|---------|---------|
| AN_ID              | GGT | CK                            | Na+    | K+     | Cl-    | Ca++   | PO4-in | Prot  | Alb-eI | Glob_A1 | Glob_A2 | Glob_B  |
|                    | U/l | U/l                           | mmol/l | mmol/l | mmol/l | mmol/l | mmol/l | g/l   | rel. 1 | rel. 1  | rel. 1  | rel. 1  |
| Group 1 (0 mg/kg)  |     |                               |        |        |        |        |        |       |        |         |         |         |
| 61 F               | 0.0 | 132.8                         | 143.7  | 3.47   | 107.1  | 2.62   | 1.20   | 66.20 | 0.610  | 0.167   | 0.055   | 0.141   |
| 62 F               | 0.0 | 208.8                         | 142.7  | 3.43   | 106.1  | 2.60   | 1.29   | 66.67 | 0.567  | 0.165   | 0.064   | 0.158   |
| 63 F               | 0.0 | 119.2                         | 141.6  | 3.46   | 104.9  | 2.54   | 1.26   | 65.62 | 0.575  | 0.160   | 0.066   | 0.155   |
| 64 F               | 0.0 | 134.0                         | 144.0  | 3.23   | 106.8  | 2.66   | 1.36   | 66.30 | 0.576  | 0.169   | 0.061   | 0.153   |
| 65 F               | 0.0 | 128.2                         | 143.6  | 3.70   | 106.2  | 2.81   | 1.74   | 67.94 | 0.531  | 0.194   | 0.059   | 0.177   |
| 66 F               | 0.0 | 164.0                         | 145.0  | 3.30   | 108.1  | 2.68   | 1.44   | 64.59 | 0.582  | 0.169   | 0.058   | 0.159   |
| 67 F               | 0.0 | 177.4                         | 145.2  | 3.21   | 109.2  | 2.70   | 1.26   | 66.72 | 0.617  | 0.160   | 0.051   | 0.130   |
| 68 F               | 0.0 | 237.7                         | 145.3  | 3.44   | 109.0  | 2.59   | 1.24   | 61.72 | 0.564  | 0.163   | 0.063   | 0.175   |
| 69 F               | 0.0 | 162.5                         | 144.5  | 3.26   | 107.9  | 2.61   | 1.20   | 66.92 | 0.556  | 0.175   | 0.066   | 0.169   |
| 70 F               | 0.0 | 202.0                         | 144.6  | 3.21   | 107.2  | 2.70   | 1.44   | 71.49 | 0.604  | 0.168   | 0.053   | 0.137   |
| Group 2 (15 mg/kg) |     |                               |        |        |        |        |        |       |        |         |         |         |
| 76 F               | 0.0 | 167.7                         | 145.6  | 3.02   | 109.2  | 2.62   | 1.11   | 68.83 | 0.593  | 0.176   | 0.047   | 0.150   |
| 77 F               | 0.0 | 142.9                         | 144.5  | 3.04   | 109.6  | 2.61   | 1.18   | 62.90 | 0.584  | 0.153   | 0.060   | 0.166   |
| 78 F               | 0.0 | 104.8                         | 144.6  | 3.32   | 110.3  | 2.62   | 0.81   | 67.97 | 0.614  | 0.164   | 0.049   | 0.139   |
| 79 F               | 0.0 | 153.6                         | 144.9  | 2.92   | 107.4  | 2.69   | 1.05   | 71.47 | 0.635  | 0.158   | 0.048   | 0.124   |
| 80 F               | 0.0 | 215.8                         | 146.3  | 3.37   | 108.9  | 2.65   | 1.26   | 68.11 | 0.638  | 0.160   | 0.051   | 0.127   |
| 81 F               | 0.0 | 245.5                         | 144.6  | 3.59   | 108.8  | 2.64   | 1.44   | 67.10 | 0.604  | 0.167   | 0.049   | 0.143   |
| 82 F               | 0.0 | 148.0                         | 143.9  | 3.22   | 108.3  | 2.62   | 1.08   | 66.61 | 0.594  | 0.161   | 0.060   | 0.152   |
| 83 F               | 0.0 | 131.5                         | 145.2  | 3.28   | 107.1  | 2.86   | 1.52   | 73.58 | 0.595  | 0.171   | 0.059   | 0.146   |
| 84 F               | 0.0 | 166.2                         | 146.5  | 2.97   | 109.3  | 2.70   | 1.25   | 71.18 | 0.595  | 0.168   | 0.058   | 0.147   |
| 85 F               | 0.0 | 168.4                         | 144.5  | 3.11   | 107.6  | 2.64   | 1.46   | 68.20 | 0.619  | 0.154   | 0.053   | 0.135   |
| Group 3 (50 mg/kg) |     |                               |        |        |        |        |        |       |        |         |         |         |
| 91 F               | 0.0 | 179.6                         | 147.3  | 3.62   | 114.2  | 2.63   | 1.25   | 66.74 | 0.612  | 0.146   | 0.047   | 0.153   |
| 92 F               | 0.0 | 178.9                         | 147.7  | 3.19   | 111.0  | 2.66   | 1.20   | 67.74 | 0.596  | 0.167   | 0.044   | 0.155   |
| 93 F               | 0.0 | 124.2                         | 146.4  | 2.94   | 108.6  | 2.86   | 1.32   | 73.64 | 0.575  | 0.176   | 0.060   | 0.156   |
| 94 F               | 0.0 | 199.7                         | 143.8  | 2.81   | 108.6  | 2.63   | 1.02   | 67.74 | 0.603  | 0.169   | 0.045   | 0.151   |
| 95 F               | 0.0 | 183.0                         | 145.1  | 3.41   | 109.0  | 2.82   | 1.59   | 74.58 | 0.616  | 0.174   | 0.051   | 0.137   |
| 96 F               | 0.0 | 173.1                         | 147.6  | 3.73   | 110.6  | 2.84   | 1.57   | 72.29 | 0.580  | 0.188   | 0.041   | 0.155   |
| 97 F               | 0.0 | 145.0                         | 150.9  | 2.90   | 112.7  | 2.71   | 1.50   | 67.56 | 0.567  | 0.170   | 0.050   | 0.162   |
| 98 F               | 0.0 | 134.0                         | 148.2  | 3.38   | 113.6  | 2.67   | 1.27   | 68.66 | 0.600  | 0.155   | 0.053   | 0.157   |
| 99 F               | 0.0 | 106.3                         | 149.8  | 3.44   | 112.0  | 2.76   | 1.23   | 66.35 | 0.566  | 0.180   | 0.050   | 0.158   |
| 100 F              | 0.0 | 190.1                         | 148.8  | 3.53   | 112.2  | 2.70   | 1.32   | 69.97 | 0.595  | 0.176   | 0.051   | 0.147   |

|                     |    | Blood chemistry (individuals) |       |        |        |        |        |        |       |        |         | FEMALES |        |
|---------------------|----|-------------------------------|-------|--------|--------|--------|--------|--------|-------|--------|---------|---------|--------|
| WEEK                | 16 | GGT                           | CK    | Na+    | K+     | Cl-    | Ca++   | PO4-in | Prot  | Alb-e1 | Glob_A1 | Glob_A2 | Glob_B |
| AN_ID               |    | U/l                           | U/l   | mmol/l | mmol/l | mmol/l | mmol/l | mmol/l | g/l   | rel. 1 | rel. 1  | rel. 1  | rel. 1 |
| Group 4 (200 mg/kg) |    |                               |       |        |        |        |        |        |       |        |         |         |        |
| 106                 | F  | 0.0                           | 101.6 | 149.9  | 3.25   | 111.3  | 2.81   | 1.31   | 65.66 | 0.563  | 0.179   | 0.055   | 0.167  |
| 107                 | F  | 0.0                           | 75.2  | 149.5  | 2.97   | 111.8  | 2.80   | 1.23   | 71.83 | 0.578  | 0.177   | 0.053   | 0.164  |
| 108                 | F  | 0.0                           | 99.1  | 148.6  | 3.53   | 109.6  | 2.73   | 1.35   | 66.47 | 0.568  | 0.175   | 0.053   | 0.173  |
| 109                 | F  | 0.0                           | 148.9 | 148.9  | 3.58   | 109.1  | 2.82   | 1.53   | 67.79 | 0.586  | 0.175   | 0.051   | 0.160  |
| 110                 | F  | 0.0                           | 137.1 | 148.7  | 2.76   | 110.2  | 2.62   | 1.11   | 70.13 | 0.590  | 0.168   | 0.061   | 0.152  |
| 111                 | F  | 0.0                           | 90.6  | 151.4  | 3.08   | 113.2  | 2.70   | 1.33   | 68.74 | 0.584  | 0.177   | 0.060   | 0.150  |
| 112                 | F  | 0.0                           | 310.3 | 150.2  | 3.01   | 112.0  | 2.62   | 1.01   | 66.55 | 0.614  | 0.151   | 0.049   | 0.155  |
| 113                 | F  | 0.0                           | 141.4 | 149.7  | 3.33   | 113.5  | 2.67   | 1.53   | 65.68 | 0.567  | 0.178   | 0.053   | 0.172  |
| 114                 | F  | 0.0                           | 163.7 | 150.6  | 3.82   | 113.9  | 2.78   | 1.31   | 67.79 | 0.598  | 0.175   | 0.046   | 0.147  |
| 115                 | F  | 0.0                           | 133.1 | 149.8  | 3.11   | 112.1  | 2.64   | 1.36   | 67.80 | 0.588  | 0.165   | 0.051   | 0.156  |



|                    |    | Blood chemistry (individuals) |        |         |         |        |        | FEMALES |
|--------------------|----|-------------------------------|--------|---------|---------|--------|--------|---------|
| WEEK               | 16 |                               |        |         |         |        |        |         |
|                    |    | Glob_G                        | Alb-e1 | Glob_A1 | Glob_A2 | Glob_B | Glob_G | A/G     |
| AN_NO              |    | rel. 1                        | g/l    | g/l     | g/l     | g/l    | g/l    | rel. 1  |
| Group 1 (0 mg/kg)  |    |                               |        |         |         |        |        |         |
| 61                 | F  | 0.027                         | 40.38  | 11.06   | 3.64    | 9.33   | 1.79   | 1.56    |
| 62                 | F  | 0.046                         | 37.80  | 11.00   | 4.27    | 10.53  | 3.07   | 1.31    |
| 63                 | F  | 0.044                         | 37.73  | 10.50   | 4.33    | 10.17  | 2.89   | 1.35    |
| 64                 | F  | 0.041                         | 38.22  | 11.20   | 4.04    | 10.14  | 2.72   | 1.36    |
| 65                 | F  | 0.039                         | 36.08  | 13.18   | 4.01    | 12.03  | 2.65   | 1.13    |
| 66                 | F  | 0.032                         | 37.59  | 10.92   | 3.75    | 10.27  | 2.07   | 1.38    |
| 67                 | F  | 0.042                         | 41.17  | 10.68   | 3.40    | 8.67   | 2.80   | 1.60    |
| 68                 | F  | 0.035                         | 34.81  | 10.06   | 3.89    | 10.80  | 2.16   | 1.29    |
| 69                 | F  | 0.034                         | 37.17  | 11.71   | 4.42    | 11.31  | 2.28   | 1.25    |
| 70                 | F  | 0.038                         | 43.18  | 12.01   | 3.79    | 9.79   | 2.72   | 1.51    |
| Group 2 (15 mg/kg) |    |                               |        |         |         |        |        |         |
| 76                 | F  | 0.034                         | 40.82  | 12.11   | 3.24    | 10.32  | 2.34   | 1.45    |
| 77                 | F  | 0.037                         | 36.71  | 9.62    | 3.77    | 10.44  | 2.33   | 1.40    |
| 78                 | F  | 0.034                         | 41.73  | 11.15   | 3.33    | 9.45   | 2.31   | 1.59    |
| 79                 | F  | 0.035                         | 45.38  | 11.29   | 3.43    | 8.86   | 2.50   | 1.75    |
| 80                 | F  | 0.024                         | 43.45  | 10.90   | 3.47    | 8.65   | 1.63   | 1.76    |
| 81                 | F  | 0.037                         | 40.59  | 11.21   | 3.29    | 9.60   | 2.48   | 1.53    |
| 82                 | F  | 0.033                         | 39.57  | 10.72   | 4.00    | 10.12  | 2.20   | 1.46    |
| 83                 | F  | 0.029                         | 43.78  | 12.58   | 4.34    | 10.74  | 2.13   | 1.46    |
| 84                 | F  | 0.032                         | 42.35  | 11.96   | 4.13    | 10.46  | 2.28   | 1.47    |
| 85                 | F  | 0.039                         | 42.22  | 10.50   | 3.61    | 9.21   | 2.66   | 1.62    |
| Group 3 (50 mg/kg) |    |                               |        |         |         |        |        |         |
| 91                 | F  | 0.042                         | 40.84  | 9.74    | 3.14    | 10.21  | 2.80   | 1.57    |
| 92                 | F  | 0.038                         | 40.37  | 11.31   | 2.98    | 10.50  | 2.57   | 1.47    |
| 93                 | F  | 0.033                         | 42.34  | 12.96   | 4.42    | 11.49  | 2.43   | 1.34    |
| 94                 | F  | 0.032                         | 40.82  | 11.45   | 3.05    | 10.23  | 2.17   | 1.51    |
| 95                 | F  | 0.022                         | 45.94  | 12.98   | 3.80    | 10.22  | 1.64   | 1.60    |
| 96                 | F  | 0.036                         | 41.94  | 13.59   | 2.96    | 11.20  | 2.60   | 1.38    |
| 97                 | F  | 0.051                         | 38.31  | 11.49   | 3.38    | 10.94  | 3.45   | 1.31    |
| 98                 | F  | 0.035                         | 41.20  | 10.64   | 3.64    | 10.78  | 2.40   | 1.49    |
| 99                 | F  | 0.046                         | 37.55  | 11.94   | 3.32    | 10.48  | 3.05   | 1.29    |
| 100                | F  | 0.031                         | 41.51  | 12.28   | 3.56    | 10.25  | 2.16   | 1.46    |

| WEEK 16             |  | Blood chemistry (individuals) |        |         |         |        |        | FEMALES |
|---------------------|--|-------------------------------|--------|---------|---------|--------|--------|---------|
|                     |  | Glob_G                        | Alb-e1 | Glob_A1 | Glob_A2 | Glob_B | Glob_G | A/G     |
| AN_NO               |  | rel. 1                        | g/l    | g/l     | g/l     | g/l    | g/l    | rel. 1  |
| Group 4 (200 mg/kg) |  |                               |        |         |         |        |        |         |
| 106 F               |  | 0.036                         | 36.97  | 11.75   | 3.61    | 10.97  | 2.36   | 1.28    |
| 107 F               |  | 0.028                         | 41.52  | 12.71   | 3.81    | 11.78  | 2.01   | 1.37    |
| 108 F               |  | 0.031                         | 37.75  | 11.63   | 3.52    | 11.50  | 2.06   | 1.31    |
| 109 F               |  | 0.028                         | 39.72  | 11.86   | 3.46    | 10.85  | 1.90   | 1.41    |
| 110 F               |  | 0.029                         | 41.38  | 11.78   | 4.28    | 10.66  | 2.03   | 1.44    |
| 111 F               |  | 0.029                         | 40.14  | 12.17   | 4.12    | 10.31  | 1.99   | 1.40    |
| 112 F               |  | 0.031                         | 40.86  | 10.05   | 3.26    | 10.32  | 2.06   | 1.59    |
| 113 F               |  | 0.030                         | 37.24  | 11.69   | 3.48    | 11.30  | 1.97   | 1.31    |
| 114 F               |  | 0.034                         | 40.54  | 11.86   | 3.12    | 9.97   | 2.30   | 1.48    |
| 115 F               |  | 0.040                         | 39.83  | 11.19   | 3.46    | 10.58  | 2.71   | 1.42    |

## 1.8 URINE ANALYSIS (INDIVIDUALS)

WEEK 16 MALES

| AN_ID              | Volume | Rel dens | Color  | Appear | pH    | NIT  | PRO    | GLU    | KET    | UBG    | BIL    | ERY  |
|--------------------|--------|----------|--------|--------|-------|------|--------|--------|--------|--------|--------|------|
|                    | ml     | rel. 1   | Choice | Choice | Score | g/l  | mmol/l | mmol/l | µmol/l | µmol/l | per µl |      |
| Group 1 (0 mg/kg)  |        |          |        |        |       |      |        |        |        |        |        |      |
| 1 M                | 7.1    | 1.047    | NORMAL | CLOUDY | 6.0   | 0    | 0.25   | 0      | 0.5    | 0      | 0      | 10   |
| 2 M                | 5.0    | 1.044    | NORMAL | CLOUDY | 6.0   | 0    | 0.25   | 0      | 0.5    | 0      | 0      | 10   |
| 3 M                | 8.7    | 1.034    | NORMAL | TURBID | 6.0   | 0    | 0.25   | 0      | 0.5    | 0      | 0      | 10   |
| 4 M                | 6.5    | 1.036    | NORMAL | TURBID | 6.5   | 0    | 0.25   | 0      | 0.0    | 0      | 0      | 10   |
| 5 M                | 4.1    | 1.061    | NORMAL | CLOUDY | 6.0   | 0    | 0.75   | 0      | 0.5    | 0      | 0      | 10   |
| 6 M                | 2.5    | 1.056    | NORMAL | CLOUDY | 6.0   | 0    | 0.75   | 0      | 1.5    | 0      | 0      | 10   |
| 7 M                | 8.1    | 1.034    | NORMAL | TURBID | 6.0   | 0    | 0.25   | 0      | 0.5    | 0      | 0      | 10   |
| 8 M                | 6.6    | 1.043    | NORMAL | CLOUDY | 6.0   | 0    | 0.25   | 0      | 0.5    | 0      | 0      | 10   |
| 9 M                | 5.8    | 1.046    | NORMAL | CLOUDY | 6.0   | 0    | 0.25   | 0      | 0.5    | 0      | 0      | 10   |
| 10 M               | 6.6    | 1.044    | NORMAL | CLOUDY | 6.0   | 1    | 0.25   | 0      | 0.5    | 0      | 0      | 10   |
| Group 2 (15 mg/kg) |        |          |        |        |       |      |        |        |        |        |        |      |
| 16 M               | 6.5    | 1.047    | NORMAL | CLOUDY | 6.0   | 0    | 0.25   | 0      | 1.5    | 0      | 0      | 10   |
| 17 M               | 9.4    | 1.034    | NORMAL | CLOUDY | 7.0   | 1    | 0.25   | 0      | 0.5    | 0      | 0      | 10   |
| 18 M               | 3.9    | 1.055    | YE\BR  | NORMAL | 6.0   | 1    | 0.75   | 0      | 0.5    | 0      | 17     | 10   |
| 19 M               | 6.8    | 1.046    | NORMAL | CLOUDY | 6.0   | 0    | 0.25   | 0      | 0.5    | 0      | 0      | 10   |
| 20 M               | 4.3    | 1.053    | YE\BR  | NORMAL | 6.5   | 0    | 0.75   | 0      | 0.5    | 0      | 17     | 25   |
| 21 M               | 5.3    | 1.040    | YE\BR  | CLOUDY | 6.0   | 1    | 0.25   | 0      | 0.5    | 0      | 0      | 0    |
| 22 M               | 5.8    | 1.044    | NORMAL | CLOUDY | 6.0   | 0    | 0.25   | 0      | 0.5    | 0      | 0      | 25   |
| 23 M               | 12.5   | 1.025    | NORMAL | TURBID | 6.5   | 0    | 0.00   | 0      | 0.0    | 0      | 0      | 10   |
| 24 M               | 5.7    | 1.046    | NORMAL | CLOUDY | 6.5   | 1    | 0.75   | 0      | 0.5    | 0      | 0      | 10   |
| 25 M               | 5.4    | 1.039    | NORMAL | CLOUDY | 6.0   | 1    | 0.25   | 0      | 0.5    | 0      | 0      | 10   |
| Group 3 (50 mg/kg) |        |          |        |        |       |      |        |        |        |        |        |      |
| 31 M               | 5.1    | 1.048    | BROWN  | CLOUDY | 6.5   | 1    | 0.75   | 0      | 0.5    | 68     | 17     | 10   |
| 32 M               | 5.9    | 1.047    | BROWN  | NORMAL | 6.0   | 1    | 0.75   | 0      | 0.5    | 68     | 17     | 10   |
| 33 M               | 6.0    | 1.037    | BROWN  | NORMAL | 6.5   | 0    | 0.75   | 0      | 0.5    | 135    | 17     | 10   |
| 34 M               | 5.7    | 1.048    | BROWN  | CLOUDY | 6.5   | 1    | 0.75   | 0      | 0.5    | 68     | 17     | 10   |
| 35 M               | 4.5    | 1.056    | BROWN  | NORMAL | 6.5   | 1    | 0.75   | 0      | 1.5    | 0      | 17     | 25   |
| 36 M               | 1.2    | 1.128    | BLACK  | n.d.   | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.   | n.d. |
| 37 M               | 4.8    | 1.048    | BROWN  | n.d.   | 6.5   | 1    | 0.75   | 0      | 0.5    | 68     | 17     | 25   |
| 38 M               | 3.4    | 1.055    | BROWN  | NORMAL | 7.0   | 1    | 0.75   | 0      | 0.0    | 68     | 17     | 25   |
| 39 M               | 5.6    | 1.044    | BROWN  | NORMAL | 6.0   | 1    | 0.75   | 0      | 0.5    | 68     | 17     | 10   |
| 40 M               | 2.0    | 1.088    | BROWN  | NORMAL | 7.0   | 0    | 0.75   | 0      | 0.5    | 0      | 0      | 25   |

n.d.=not determined

| Urine analysis (individuals) |        |          |        |        |      |       |      |        |        |        |        |        |
|------------------------------|--------|----------|--------|--------|------|-------|------|--------|--------|--------|--------|--------|
| WEEK 16                      |        |          |        |        |      |       |      |        |        |        |        | MALES  |
| AN_ID                        | Volume | Rel dens | Color  | Appear | pH   | NIT   | PRO  | GLU    | KET    | UBG    | BIL    | ERY    |
|                              | ml     | rel. 1   | Choice | Choice |      | Score | g/l  | mmol/l | mmol/l | µmol/l | µmol/l | per µl |
| Group 4 (200 mg/kg)          |        |          |        |        |      |       |      |        |        |        |        |        |
| 46 M                         | 2.7    | 1.065    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.   |
| 47 M                         | 6.2    | 1.047    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.   |
| 48 M                         | 6.7    | 1.043    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.   |
| 49 M                         | 8.6    | 1.042    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.   |
| 50 M                         | 8.0    | 1.043    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.   |
| 51 M                         | 7.7    | 1.038    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.   |
| 52 M                         | 12.4   | 1.027    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.   |
| 53 M                         | 6.3    | 1.041    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.   |
| 54 M                         | 6.1    | 1.038    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.   |
| 55 M                         | 5.3    | 1.047    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.   |

n.d.=not determined

Urine analysis (individuals)

WEEK 16 MALES

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LEU

ANLND per  $\mu$ l

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Group 1 (0 mg/kg)

|      |    |
|------|----|
| 1 M  | 0  |
| 2 M  | 0  |
| 3 M  | 25 |
| 4 M  | 25 |
| 5 M  | 0  |
| 6 M  | 25 |
| 7 M  | 0  |
| 8 M  | 0  |
| 9 M  | 25 |
| 10 M | 25 |

Group 2 (15 mg/kg)

|      |    |
|------|----|
| 16 M | 25 |
| 17 M | 25 |
| 18 M | 25 |
| 19 M | 25 |
| 20 M | 25 |
| 21 M | 0  |
| 22 M | 0  |
| 23 M | 0  |
| 24 M | 25 |
| 25 M | 25 |

Group 3 (50 mg/kg)

|      |      |
|------|------|
| 31 M | 100  |
| 32 M | 25   |
| 33 M | 100  |
| 34 M | 100  |
| 35 M | 25   |
| 36 M | n.d. |
| 37 M | 100  |
| 38 M | 100  |
| 39 M | 100  |
| 40 M | 25   |

n.d.=not determined

| WEEK                | Urine analysis (individuals) |  | MALES |
|---------------------|------------------------------|--|-------|
| 16                  | LBU                          |  |       |
| AN_NO               | per $\mu$ l                  |  |       |
| Group 4 (200 mg/kg) |                              |  |       |
| 46 M                | n.d.                         |  |       |
| 47 M                | n.d.                         |  |       |
| 48 M                | n.d.                         |  |       |
| 49 M                | n.d.                         |  |       |
| 50 M                | n.d.                         |  |       |
| 51 M                | n.d.                         |  |       |
| 52 M                | n.d.                         |  |       |
| 53 M                | n.d.                         |  |       |
| 54 M                | n.d.                         |  |       |
| 55 M                | n.d.                         |  |       |

n.d.=not determined

| WEEK 16            |        | Urine analysis (individuals) |        |        |     |       |      |        |        |        |        | FEMALES |  |
|--------------------|--------|------------------------------|--------|--------|-----|-------|------|--------|--------|--------|--------|---------|--|
| AN_NO              | Volume | Rel dens                     | Color  | Appear | pH  | NIT   | PRD  | GLU    | KET    | UBG    | BIL    | ERY     |  |
|                    | ml     | rel. 1                       | Choice | Choice |     | Score | g/l  | mmol/l | mmol/l | μmol/l | μmol/l | per μl  |  |
| Group 1 (0 mg/kg)  |        |                              |        |        |     |       |      |        |        |        |        |         |  |
| 61 F               | 4.4    | 1.041                        | NORMAL | NORMAL | 6.0 | 0     | 0.25 | 0      | 0.0    | 0      | 0      | 0       |  |
| 62 F               | 2.8    | 1.047                        | NORMAL | NORMAL | 6.0 | 0     | 0.25 | 0      | 0.0    | 0      | 0      | 0       |  |
| 63 F               | 6.2    | 1.035                        | NORMAL | CLOUDY | 6.0 | 0     | 0.00 | 0      | 0.5    | 0      | 0      | 0       |  |
| 64 F               | 0.9    | 1.035                        | NORMAL | CLOUDY | 6.0 | 1     | 0.00 | 0      | 0.0    | 0      | 0      | 0       |  |
| 65 F               | 4.0    | 1.046                        | NORMAL | NORMAL | 6.0 | 0     | 0.25 | 0      | 0.0    | 0      | 0      | 0       |  |
| 66 F               | 3.6    | 1.055                        | NORMAL | NORMAL | 6.0 | 0     | 0.00 | 0      | 0.0    | 0      | 0      | 0       |  |
| 67 F               | 2.4    | 1.049                        | NORMAL | NORMAL | 6.0 | 0     | 0.25 | 0      | 0.5    | 0      | 0      | 10      |  |
| 68 F               | 3.7    | 1.042                        | NORMAL | NORMAL | 6.0 | 0     | 0.25 | 0      | 0.0    | 0      | 0      | 0       |  |
| 69 F               | 8.0    | 1.027                        | NORMAL | CLOUDY | 6.0 | 1     | 0.25 | 0      | 0.0    | 0      | 0      | 0       |  |
| 70 F               | 1.2    | 1.053                        | NORMAL | NORMAL | 6.0 | 1     | 0.25 | 0      | 0.0    | 0      | 0      | 0       |  |
| Group 2 (15 mg/kg) |        |                              |        |        |     |       |      |        |        |        |        |         |  |
| 76 F               | 0.5    | 1.110                        | NORMAL | NORMAL | 6.5 | 0     | 0.00 | 0      | 0.5    | 0      | 0      | 10      |  |
| 77 F               | 2.5    | 1.060                        | NORMAL | NORMAL | 6.0 | 0     | 0.25 | 0      | 0.0    | 0      | 0      | 10      |  |
| 78 F               | 3.3    | 1.049                        | NORMAL | NORMAL | 6.0 | 1     | 0.25 | 0      | 0.0    | 0      | 0      | 0       |  |
| 79 F               | 3.1    | 1.052                        | NORMAL | NORMAL | 6.0 | 0     | 0.25 | 0      | 0.5    | 0      | 0      | 0       |  |
| 80 F               | 3.1    | 1.035                        | YE\BR  | NORMAL | 6.0 | 1     | 0.25 | 0      | 0.0    | 0      | 0      | 0       |  |
| 81 F               | 12.5   | 1.016                        | NORMAL | NORMAL | 6.0 | 1     | 0.00 | 0      | 0.0    | 0      | 0      | 0       |  |
| 82 F               | 2.6    | 1.052                        | YE\BR  | NORMAL | 6.0 | 1     | 0.25 | 0      | 0.5    | 0      | 0      | 0       |  |
| 83 F               | 4.0    | 1.048                        | YE\BR  | CLOUDY | 6.0 | 0     | 0.25 | 0      | 0.5    | 0      | 0      | 0       |  |
| 84 F               | 2.8    | 1.052                        | YE\BR  | NORMAL | 6.0 | 0     | 0.25 | 0      | 0.5    | 0      | 0      | 10      |  |
| 85 F               | 1.9    | 1.047                        | NORMAL | NORMAL | 6.0 | 1     | 0.25 | 0      | 0.0    | 0      | 0      | 10      |  |
| Group 3 (50 mg/kg) |        |                              |        |        |     |       |      |        |        |        |        |         |  |
| 91 F               | 6.3    | 1.034                        | BROWN  | NORMAL | 6.0 | 1     | 0.25 | 0      | 0.0    | 0      | 17     | 10      |  |
| 92 F               | 2.0    | 1.045                        | BROWN  | NORMAL | 6.5 | 1     | 0.25 | 0      | 0.0    | 0      | 17     | 10      |  |
| 93 F               | 4.5    | 1.040                        | BROWN  | NORMAL | 6.0 | 1     | 0.75 | 0      | 0.0    | 0      | 17     | 10      |  |
| 94 F               | 3.7    | 1.050                        | BROWN  | NORMAL | 6.0 | 1     | 0.75 | 0      | 0.0    | 0      | 17     | 10      |  |
| 95 F               | 3.1    | 1.037                        | BROWN  | NORMAL | 6.0 | 1     | 0.75 | 0      | 0.5    | 0      | 17     | 10      |  |
| 96 F               | 1.6    | 1.076                        | BROWN  | NORMAL | 6.5 | 1     | 0.75 | 0      | 0.5    | 0      | 0      | 10      |  |
| 97 F               | 2.0    | 1.090                        | BROWN  | NORMAL | 5.0 | 1     | 0.75 | 0      | 0.5    | 0      | 17     | 10      |  |
| 98 F               | 17.9   | 1.011                        | YE\BR  | TURBID | 6.0 | 1     | 0.00 | 0      | 0.0    | 0      | 0      | 0       |  |
| 99 F               | 3.2    | 1.052                        | BROWN  | NORMAL | 6.0 | 1     | 0.25 | 0      | 0.5    | 0      | 17     | 10      |  |
| 100 F              | 1.4    | 1.098                        | BROWN  | NORMAL | 7.0 | 0     | 0.25 | 0      | 0.0    | 0      | 0      | 25      |  |

| Urine analysis (individuals) |        |          |        |        |      |       |      |        |        |        |        |         |
|------------------------------|--------|----------|--------|--------|------|-------|------|--------|--------|--------|--------|---------|
| WEEK                         |        |          |        |        |      |       |      |        |        |        |        | SEX     |
| 16                           |        |          |        |        |      |       |      |        |        |        |        | FEMALES |
| AN_NO                        | Volume | Rel dens | Color  | Appear | pH   | NIT   | PRO  | GLU    | KET    | UBG    | BIL    | ERY     |
|                              | ml     | rel. 1   | Choice | Choice |      | Score | g/l  | mmol/l | mmol/l | µmol/l | µmol/l | per µl  |
| Group 4 (200 mg/kg)          |        |          |        |        |      |       |      |        |        |        |        |         |
| 106 F                        | 6.5    | 1.027    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.    |
| 107 F                        | 4.1    | 1.047    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.    |
| 108 F                        | 3.0    | 1.071    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.    |
| 109 F                        | 3.1    | 1.040    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.    |
| 110 F                        | 7.3    | 1.031    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.    |
| 111 F                        | 3.2    | 1.053    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.    |
| 112 F                        | 5.6    | 1.031    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.    |
| 113 F                        | 2.4    | 1.052    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.    |
| 114 F                        | 1.6    | 1.086    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.    |
| 115 F                        | 2.9    | 1.050    | BLACK  | n.d.   | n.d. | n.d.  | n.d. | n.d.   | n.d.   | n.d.   | n.d.   | n.d.    |

n.d.=not determined



| WEEK 16            | Urine analysis (individuals) |  | FEMALES |
|--------------------|------------------------------|--|---------|
| -----              |                              |  |         |
|                    | LEU                          |  |         |
| AN_NO              | per $\mu$ l                  |  |         |
| -----              |                              |  |         |
| Group 1 (0 mg/kg)  |                              |  |         |
| 61 F               | 0                            |  |         |
| 62 F               | 0                            |  |         |
| 63 F               | 0                            |  |         |
| 64 F               | 0                            |  |         |
| 65 F               | 0                            |  |         |
| 66 F               | 0                            |  |         |
| 67 F               | 0                            |  |         |
| 68 F               | 0                            |  |         |
| 69 F               | 0                            |  |         |
| 70 F               | 0                            |  |         |
| Group 2 (15 mg/kg) |                              |  |         |
| 76 F               | 0                            |  |         |
| 77 F               | 0                            |  |         |
| 78 F               | 0                            |  |         |
| 79 F               | 0                            |  |         |
| 80 F               | 0                            |  |         |
| 81 F               | 0                            |  |         |
| 82 F               | 0                            |  |         |
| 83 F               | 0                            |  |         |
| 84 F               | 0                            |  |         |
| 85 F               | 0                            |  |         |
| Group 3 (50 mg/kg) |                              |  |         |
| 91 F               | 25                           |  |         |
| 92 F               | 0                            |  |         |
| 93 F               | 25                           |  |         |
| 94 F               | 25                           |  |         |
| 95 F               | 25                           |  |         |
| 96 F               | 25                           |  |         |
| 97 F               | 25                           |  |         |
| 98 F               | 0                            |  |         |
| 99 F               | 25                           |  |         |
| 100 F              | 0                            |  |         |

Urine analysis (individuals)

WEEK 16 FEMALES

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LEU

AN\_NO per  $\mu$ l

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Group 4 (200 mg/kg)

|       |      |
|-------|------|
| 106 F | n.d. |
| 107 F | n.d. |
| 108 F | n.d. |
| 109 F | n.d. |
| 110 F | n.d. |
| 111 F | n.d. |
| 112 F | n.d. |
| 113 F | n.d. |
| 114 F | n.d. |
| 115 F | n.d. |

n.d.=not determined

## 1.9 URINE SEDIMENT (INDIVIDUALS)

WEEK 16

MALES

|                    | Ery    | Leu    | Epi-cell | Casts  | Cry-PO4 | Cry-Caox | Cry-UrAc | Cry-Uram | Cry-Unid |
|--------------------|--------|--------|----------|--------|---------|----------|----------|----------|----------|
| AN_NO              | Choice | Choice | Choice   | Choice | Choice  | Choice   | Choice   | Choice   | Choice   |
| Group 1 (0 mg/kg)  |        |        |          |        |         |          |          |          |          |
| 1 M                | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 2 M                | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 3 M                | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 4 M                | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 5 M                | 0      | 0      | 0        | 0      | 1       | 1        | 0        | 0        | 0        |
| 6 M                | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 7 M                | 0      | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| 8 M                | 0      | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| 9 M                | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 10 M               | 0      | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| Group 2 (15 mg/kg) |        |        |          |        |         |          |          |          |          |
| 16 M               | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 17 M               | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 18 M               | 0      | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| 19 M               | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 20 M               | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 21 M               | 0      | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| 22 M               | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 23 M               | 0      | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| 24 M               | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 25 M               | 0      | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| Group 3 (50 mg/kg) |        |        |          |        |         |          |          |          |          |
| 31 M               | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 32 M               | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 33 M               | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 34 M               | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 0        |
| 35 M               | 0      | 0      | 0        | 0      | 1       | 1        | 0        | 0        | 0        |
| 36 M               | 0      | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| 37 M               | 0      | 1      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| 38 M               | 0      | 1      | 0        | 0      | 1       | 0        | 0        | 0        | 1        |
| 39 M               | 0      | 1      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| 40 M               | 0      | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 1        |

|                     |  | Urine sediment (Individuals) |        |          |        |         |          |          |          |          |
|---------------------|--|------------------------------|--------|----------|--------|---------|----------|----------|----------|----------|
| WEEK 16             |  |                              |        |          |        |         |          |          |          | MALES    |
|                     |  | Ery                          | Leu    | Epi-cell | Casts  | Cry-PO4 | Cry-Caox | Cry-UrAc | Cry-Uram | Cry-Unid |
| AN_ID               |  | Choice                       | Choice | Choice   | Choice | Choice  | Choice   | Choice   | Choice   | Choice   |
| Group 4 (200 mg/kg) |  |                              |        |          |        |         |          |          |          |          |
| 46 M                |  | 0                            | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 1        |
| 47 M                |  | 0                            | 0      | 0        | 0      | 1       | 1        | 0        | 0        | 1        |
| 48 M                |  | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| 49 M                |  | 0                            | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 1        |
| 50 M                |  | 0                            | 0      | 0        | 0      | 0       | 1        | 0        | 0        | 0        |
| 51 M                |  | 0                            | 0      | 0        | 0      | 1       | 1        | 0        | 0        | 1        |
| 52 M                |  | 1                            | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 1        |
| 53 M                |  | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| 54 M                |  | 1                            | 0      | 0        | 0      | 1       | 0        | 0        | 0        | 1        |
| 55 M                |  | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 1        |

| WEEK 16            | Urine sediment (individuals) |        |          |        |         |          |          |          |          | FEMALES |
|--------------------|------------------------------|--------|----------|--------|---------|----------|----------|----------|----------|---------|
|                    | Ery                          | Leu    | Epi-cell | Casts  | Cry-P04 | Cry-Caox | Cry-UrAc | Cry-Uram | Cry-Unid |         |
| AN_ID              | Choice                       | Choice | Choice   | Choice | Choice  | Choice   | Choice   | Choice   | Choice   |         |
| Group 1 (0 mg/kg)  |                              |        |          |        |         |          |          |          |          |         |
| 61 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 1        | 0        | 0        |         |
| 62 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 63 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 64 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 1        |         |
| 65 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 66 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 67 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 68 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 69 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 70 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| Group 2 (15 mg/kg) |                              |        |          |        |         |          |          |          |          |         |
| 76 F               | 0                            | 0      | 0        | 0      | 0       | 1        | 1        | 0        | 0        |         |
| 77 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 78 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 1        | 0        | 0        |         |
| 79 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 80 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 81 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 82 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 83 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 84 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 85 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 1        | 0        | 0        |         |
| Group 3 (50 mg/kg) |                              |        |          |        |         |          |          |          |          |         |
| 91 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 1        | 0        | 0        |         |
| 92 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 93 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 94 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 95 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 96 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 1        | 0        | 0        |         |
| 97 F               | 0                            | 0      | 0        | 0      | 0       | 2        | 0        | 0        | 0        |         |
| 98 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |         |
| 99 F               | 0                            | 0      | 0        | 0      | 0       | 0        | 2        | 0        | 0        |         |
| 100 F              | 0                            | 0      | 0        | 0      | 0       | 0        | 1        | 0        | 0        |         |

|                     |    | Urine sediment (individuals) |        |          |        |         |          |          |          | FEMALES  |
|---------------------|----|------------------------------|--------|----------|--------|---------|----------|----------|----------|----------|
| WEEK                | 16 | Ery                          | Leu    | Epi-cell | Casts  | Cry-PO4 | Cry-Caox | Cry-UrAc | Cry-Uram | Cry-Urid |
| AN_NO               |    | Choice                       | Choice | Choice   | Choice | Choice  | Choice   | Choice   | Choice   | Choice   |
| Group 4 (200 mg/kg) |    |                              |        |          |        |         |          |          |          |          |
| 106                 | F  | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 1        |
| 107                 | F  | 0                            | 0      | 0        | 0      | 0       | 1        | 1        | 0        | 1        |
| 108                 | F  | 0                            | 0      | 0        | 0      | 0       | 0        | 0        | 0        | 0        |
| 109                 | F  | 0                            | 0      | 0        | 0      | 0       | 0        | 1        | 0        | 0        |
| 110                 | F  | 0                            | 0      | 0        | 0      | 0       | 0        | 2        | 0        | 1        |
| 111                 | F  | 0                            | 0      | 0        | 0      | 0       | 1        | 1        | 0        | 0        |
| 112                 | F  | 0                            | 0      | 0        | 0      | 1       | 0        | 1        | 0        | 0        |
| 113                 | F  | 0                            | 0      | 0        | 0      | 0       | 1        | 1        | 0        | 0        |
| 114                 | F  | 0                            | 0      | 0        | 0      | 0       | 2        | 2        | 0        | 0        |
| 115                 | F  | 0                            | 0      | 0        | 0      | 0       | 1        | 1        | 0        | 1        |

## 1.10 REFERENCE VALUES - HEMATOLOGY

| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
|------------|------------------|--------|------------------------|-------------------|------------------------------|-------|--------|-------|----------------------|-------|-------|
| SPECIES    | RAT              |        |                        |                   |                              |       |        |       |                      | MALE  |       |
| STRAIN     | HarBr1:WIST(SPF) |        |                        |                   |                              |       |        |       |                      |       |       |
| SUPPLIER   | RCC Ltd          |        |                        |                   |                              |       |        |       |                      |       |       |
| STUDY TYPE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| DOSE ROUTE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| DATES:     | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
| PARAMETER  | UNIT             | METHOD | ANIMAL AGE<br>IN WEEKS | NO. OF<br>ANIMALS | PERCENTILES OF INDIV. VALUES |       |        |       | RANGE OF STUDY MEANS |       |       |
|            |                  |        |                        |                   | N                            | 5%    | MEDIAN | 95%   | N                    | MIN   | MAX   |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
| RBC        | T/l              | MO1    | 17 TO 24               | 632               | 746                          | 8.03  | 8.82   | 9.63  | 44                   | 8.20  | 9.40  |
| Hb         | mmol/l           | MO1    | 17 TO 24               | 632               | 746                          | 9.1   | 9.8    | 10.5  | 44                   | 9.1   | 10.3  |
| Hct        | rel. l           | MO1    | 17 TO 24               | 632               | 746                          | 0.43  | 0.47   | 0.51  | 44                   | 0.44  | 0.49  |
| MCV        | fl               | MO1    | 17 TO 24               | 632               | 746                          | 49.3  | 52.9   | 56.8  | 44                   | 49.4  | 55.5  |
| RDW        | rel. l           | MO1    | 17 TO 24               | 620               | 734                          | 0.118 | 0.128  | 0.191 | 43                   | 0.123 | 0.181 |
| MCH        | fmo1             | MO1    | 17 TO 24               | 632               | 746                          | 1.03  | 1.11   | 1.21  | 44                   | 1.07  | 1.19  |
| MCHC       | mmol/l           | MO1    | 17 TO 24               | 632               | 746                          | 19.52 | 20.97  | 22.75 | 44                   | 19.54 | 22.70 |
| HDW        | mmol/l           | MO1    | 17 TO 24               | 620               | 734                          | 1.35  | 1.56   | 1.94  | 43                   | 1.38  | 1.94  |
| Reti       | rel. l           | MO2    | 17 TO 24               | 414               | 479                          | 0.016 | 0.021  | 0.029 | 31                   | 0.017 | 0.028 |
| Reti       | G/l              | MO2    | 17 TO 24               | 414               | 479                          | 139.  | 188.   | 253.  | 31                   | 152.  | 240.  |
| L Reti     | rel. l           | MO1    | 17 TO 24               | 382               | 447                          | 0.351 | 0.474  | 0.600 | 29                   | 0.333 | 0.573 |
| M Reti     | rel. l           | MO1    | 17 TO 24               | 382               | 447                          | 0.266 | 0.354  | 0.392 | 29                   | 0.243 | 0.382 |
| H Reti     | rel. l           | MO1    | 17 TO 24               | 382               | 447                          | 0.049 | 0.167  | 0.367 | 29                   | 0.077 | 0.425 |
| WBC        | G/l              | MO1    | 17 TO 24               | 632               | 746                          | 4.22  | 6.22   | 9.15  | 44                   | 4.66  | 8.91  |
| Neut       | rel. l           | MO1    | 17 TO 24               | 632               | 746                          | 0.117 | 0.181  | 0.272 | 44                   | 0.148 | 0.233 |
| Eos        | rel. l           | MO1    | 17 TO 24               | 632               | 746                          | 0.010 | 0.017  | 0.030 | 44                   | 0.013 | 0.023 |
| Baso       | rel. l           | MO1    | 17 TO 24               | 632               | 746                          | 0.001 | 0.002  | 0.009 | 44                   | 0.001 | 0.013 |
| Lympho     | rel. l           | MO1    | 17 TO 24               | 632               | 746                          | 0.666 | 0.763  | 0.832 | 44                   | 0.712 | 0.802 |
| Mono       | rel. l           | MO1    | 17 TO 24               | 632               | 746                          | 0.013 | 0.025  | 0.046 | 44                   | 0.017 | 0.040 |
| Luc        | rel. l           | MO1    | 17 TO 24               | 632               | 746                          | 0.002 | 0.007  | 0.027 | 44                   | 0.002 | 0.027 |

Reference values - Hematology

| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
|------------|------------------|--------|------------------------|-------------------|------------------------------|-------|--------|-------|----------------------|-------|-------|
| SPECIES    | RAT              |        |                        |                   |                              |       |        |       |                      |       |       |
| STRAIN     | HanBr1:WIST(SPF) |        |                        |                   |                              |       |        |       |                      |       |       |
| SUPPLIER   | RCC Ltd          |        |                        |                   |                              |       |        |       |                      |       |       |
| STUDY TYPE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| DOSE ROUTE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| DATES:     | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
| PARAMETER  | UNIT             | METHOD | ANIMAL AGE<br>IN WEEKS | NO. OF<br>ANIMALS | PERCENTILES OF INDIV. VALUES |       |        |       | RANGE OF STUDY MEANS |       |       |
|            |                  |        |                        |                   | N                            | 5%    | MEDIAN | 95%   | N                    | MIN   | MAX   |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
| Neut       | G/l              | M01    | 17 TO 24               | 632               | 746                          | 0.68  | 1.11   | 1.88  | 44                   | 0.88  | 1.58  |
| Eos        | G/l              | M01    | 17 TO 24               | 632               | 746                          | 0.06  | 0.11   | 0.21  | 44                   | 0.08  | 0.17  |
| Baso       | G/l              | M01    | 17 TO 24               | 632               | 746                          | 0.00  | 0.02   | 0.07  | 44                   | 0.00  | 0.09  |
| Lympho     | G/l              | M01    | 17 TO 24               | 632               | 746                          | 3.05  | 4.68   | 7.11  | 44                   | 3.54  | 6.63  |
| Mono       | G/l              | M01    | 17 TO 24               | 632               | 746                          | 0.07  | 0.15   | 0.34  | 44                   | 0.09  | 0.32  |
| Luc        | G/l              | M01    | 17 TO 24               | 632               | 746                          | 0.01  | 0.04   | 0.23  | 44                   | 0.01  | 0.23  |
| Plt        | G/l              | M01    | 17 TO 24               | 632               | 746                          | 708.  | 866.   | 1026. | 44                   | 779.  | 965.  |
| PT         | rel. 1           | M01    | 17 TO 24               | 550               | 613                          | 0.69  | 0.82   | 0.95  | 39                   | 0.72  | 1.02  |
| PTT        | sec              | M01    | 17 TO 24               | 402               | 464                          | 15.9  | 18.9   | 30.3  | 30                   | 15.5  | 31.1  |
| Methb      | rel. 1           | M01    | 17 TO 24               | 245               | 320                          | 0.004 | 0.007  | 0.010 | 17                   | 0.004 | 0.011 |



Reference values - Hematology

| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
|------------|------------------|--------|------------------------|-------------------|------------------------------|-------|--------|-------|----------------------|-------|-------|
| SPECIES    | RAT              |        |                        |                   |                              |       |        |       |                      |       |       |
| STRAIN     | HanBrl:WIST(SPF) |        |                        |                   |                              |       |        |       |                      |       |       |
| SUPPLIER   | RCC Ltd          |        |                        |                   |                              |       |        |       |                      |       |       |
| STUDY TYPE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| DOSE ROUTE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| DATES:     | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
| PARAMETER  | UNIT             | METHOD | ANIMAL AGE<br>IN WEEKS | NO. OF<br>ANIMALS | PERCENTILES OF INDIV. VALUES |       |        |       | RANGE OF STUDY MEANS |       |       |
|            |                  |        |                        |                   | N                            | 5%    | MEDIAN | 95%   | N                    | MIN   | MAX   |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
| RBC        | T/l              | M01    | 17 TO 24               | 632               | 742                          | 7.20  | 7.91   | 8.64  | 44                   | 7.51  | 8.40  |
| Hb         | mmol/l           | M01    | 17 TO 24               | 632               | 742                          | 8.6   | 9.4    | 10.1  | 44                   | 8.8   | 10.0  |
| Hct        | rel. l           | M01    | 17 TO 24               | 632               | 742                          | 0.41  | 0.44   | 0.48  | 44                   | 0.42  | 0.47  |
| MCV        | fl               | M01    | 17 TO 24               | 632               | 742                          | 51.9  | 56.0   | 59.8  | 44                   | 52.3  | 59.7  |
| RDW        | rel. l           | M01    | 17 TO 24               | 620               | 730                          | 0.106 | 0.115  | 0.166 | 43                   | 0.108 | 0.142 |
| MCH        | fmo1             | M01    | 17 TO 24               | 632               | 742                          | 1.10  | 1.18   | 1.27  | 44                   | 1.14  | 1.23  |
| MCHC       | mmol/l           | M01    | 17 TO 24               | 632               | 742                          | 19.64 | 21.09  | 22.71 | 44                   | 19.61 | 22.86 |
| HDW        | mmol/l           | M01    | 17 TO 24               | 620               | 730                          | 1.11  | 1.27   | 1.56  | 43                   | 1.15  | 1.55  |
| Reti       | rel. l           | M02    | 17 TO 24               | 414               | 474                          | 0.016 | 0.025  | 0.035 | 31                   | 0.019 | 0.032 |
| Reti       | G/l              | M02    | 17 TO 24               | 414               | 474                          | 128.  | 195.   | 274.  | 31                   | 155.  | 247.  |
| L Reti     | rel. l           | M01    | 17 TO 24               | 382               | 442                          | 0.311 | 0.449  | 0.624 | 29                   | 0.308 | 0.552 |
| M Reti     | rel. l           | M01    | 17 TO 24               | 382               | 442                          | 0.242 | 0.336  | 0.397 | 29                   | 0.235 | 0.382 |
| H Reti     | rel. l           | M01    | 17 TO 24               | 382               | 442                          | 0.045 | 0.206  | 0.436 | 29                   | 0.100 | 0.456 |
| WBC        | G/l              | M01    | 17 TO 24               | 632               | 742                          | 2.31  | 3.76   | 5.88  | 44                   | 2.52  | 5.44  |
| Neut       | rel. l           | M01    | 17 TO 24               | 632               | 742                          | 0.107 | 0.182  | 0.324 | 44                   | 0.121 | 0.285 |
| Eos        | rel. l           | M01    | 17 TO 24               | 632               | 742                          | 0.010 | 0.019  | 0.035 | 44                   | 0.014 | 0.036 |
| Baso       | rel. l           | M01    | 17 TO 24               | 632               | 742                          | 0.001 | 0.002  | 0.008 | 44                   | 0.001 | 0.010 |
| Lympho     | rel. l           | M01    | 17 TO 24               | 632               | 742                          | 0.610 | 0.755  | 0.848 | 44                   | 0.656 | 0.839 |
| Mono       | rel. l           | M01    | 17 TO 24               | 632               | 742                          | 0.013 | 0.023  | 0.046 | 44                   | 0.014 | 0.042 |
| Luc        | rel. l           | M01    | 17 TO 24               | 632               | 742                          | 0.002 | 0.007  | 0.024 | 44                   | 0.002 | 0.028 |

Reference values - Hematology

| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
|------------|------------------|--------|------------------------|-------------------|------------------------------|-------|--------|-------|----------------------|-------|-------|
| SPECIES    | RAT              |        |                        |                   |                              |       |        |       |                      |       |       |
| STRAIN     | HanBr1:wIST(SPF) |        |                        |                   |                              |       |        |       |                      |       |       |
| SUPPLIER   | RCC Ltd          |        |                        |                   |                              |       |        |       |                      |       |       |
| STUDY TYPE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| DOSE ROUTE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| DATES:     | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
| PARAMETER  | UNIT             | METHOD | ANIMAL AGE<br>IN WEEKS | NO. OF<br>ANIMALS | PERCENTILES OF INDIV. VALUES |       |        |       | RANGE OF STUDY MEANS |       |       |
|            |                  |        |                        |                   | N                            | 5%    | MEDIAN | 95%   | N                    | MIN   | MAX   |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
| Neut       | G/l              | MD1    | 17 TO 24               | 632               | 742                          | 0.36  | 0.68   | 1.30  | 44                   | 0.44  | 1.30  |
| Eos        | G/l              | MD1    | 17 TO 24               | 632               | 742                          | 0.04  | 0.07   | 0.13  | 44                   | 0.05  | 0.13  |
| Baso       | G/l              | MD1    | 17 TO 24               | 632               | 742                          | 0.00  | 0.01   | 0.03  | 44                   | 0.00  | 0.04  |
| Lympho     | G/l              | MD1    | 17 TO 24               | 632               | 742                          | 1.58  | 2.82   | 4.47  | 44                   | 1.87  | 3.88  |
| Mono       | G/l              | MD1    | 17 TO 24               | 632               | 742                          | 0.04  | 0.09   | 0.22  | 44                   | 0.05  | 0.24  |
| Luc        | G/l              | MD1    | 17 TO 24               | 632               | 742                          | 0.01  | 0.02   | 0.13  | 44                   | 0.00  | 0.16  |
| Pit        | G/l              | MD1    | 17 TO 24               | 632               | 742                          | 749.  | 940.   | 1150. | 44                   | 760.  | 1111. |
| PT         | rel. 1           | MD1    | 17 TO 24               | 543               | 607                          | 0.75  | 0.89   | 1.09  | 39                   | 0.81  | 1.07  |
| PIT        | sec              | MD1    | 17 TO 24               | 389               | 452                          | 15.9  | 19.3   | 26.6  | 29                   | 16.2  | 24.4  |
| Rethb      | rel. 1           | MD1    | 17 TO 24               | 245               | 320                          | 0.004 | 0.007  | 0.011 | 17                   | 0.004 | 0.010 |

## 1.11 REFERENCE VALUES - BLOOD CHEMISTRY

|            |                  |        |                        |                   |                              |       |        |       |                      | MALE  |       |  |
|------------|------------------|--------|------------------------|-------------------|------------------------------|-------|--------|-------|----------------------|-------|-------|--|
| SPECIES    | RAT              |        |                        |                   |                              |       |        |       |                      |       |       |  |
| STRAIN     | HanBr1:WIST(SPF) |        |                        |                   |                              |       |        |       |                      |       |       |  |
| SUPPLIER   | RCC Ltd          |        |                        |                   |                              |       |        |       |                      |       |       |  |
| STUDY TYPE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |  |
| DOSE ROUTE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |  |
| DATES:     | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |  |
| PARAMETER  | UNIT             | METHOD | ANIMAL AGE<br>IN WEEKS | NO. OF<br>ANIMALS | PERCENTILES OF INDIV. VALUES |       |        |       | RANGE OF STUDY MEANS |       |       |  |
|            |                  |        |                        |                   | N                            | 5%    | MEDIAN | 95%   | N                    | MIN   | MAX   |  |
| Gluc       | mmol/l           | M01    | 17 TO 24               | 630               | 745                          | 4.30  | 6.37   | 10.09 | 44                   | 4.55  | 10.43 |  |
| Urea       | mmol/l           | M01    | 17 TO 24               | 630               | 745                          | 4.53  | 5.91   | 7.82  | 44                   | 4.41  | 7.36  |  |
| Creat      | µmol/l           | M01    | 17 TO 24               | 630               | 745                          | 21.8  | 26.5   | 32.2  | 44                   | 22.5  | 32.0  |  |
| Bil1-tot   | µmol/l           | M01    | 17 TO 24               | 630               | 745                          | 0.97  | 1.51   | 2.16  | 44                   | 0.73  | 2.20  |  |
| Prot       | g/l              | M01    | 17 TO 24               | 630               | 745                          | 61.99 | 67.02  | 72.38 | 44                   | 62.32 | 72.24 |  |
| A/G        | rel. 1           | M03    | 17 TO 24               | 135               | 155                          | 0.90  | 1.07   | 1.26  | 10                   | 0.93  | 1.21  |  |
| Alb-el     | rel. 1           | M02    | 17 TO 24               | 135               | 155                          | 0.475 | 0.517  | 0.557 | 10                   | 0.484 | 0.547 |  |
| Glob A1    | rel. 1           | M02    | 17 TO 24               | 135               | 155                          | 0.176 | 0.195  | 0.220 | 10                   | 0.185 | 0.205 |  |
| Glob A2    | rel. 1           | M02    | 17 TO 24               | 135               | 155                          | 0.068 | 0.080  | 0.092 | 10                   | 0.070 | 0.086 |  |
| Glob B     | rel. 1           | M02    | 17 TO 24               | 135               | 155                          | 0.161 | 0.183  | 0.205 | 10                   | 0.166 | 0.195 |  |
| Glob G     | rel. 1           | M02    | 17 TO 24               | 135               | 155                          | 0.016 | 0.022  | 0.033 | 10                   | 0.017 | 0.031 |  |
| Alb-el     | g/l              | M02    | 17 TO 24               | 135               | 155                          | 30.61 | 34.65  | 38.01 | 10                   | 31.38 | 36.45 |  |
| Glob A1    | g/l              | M02    | 17 TO 24               | 135               | 155                          | 11.29 | 13.11  | 14.80 | 10                   | 12.41 | 13.64 |  |
| Glob A2    | g/l              | M02    | 17 TO 24               | 135               | 155                          | 4.44  | 5.38   | 6.12  | 10                   | 4.52  | 5.71  |  |
| Glob B     | g/l              | M02    | 17 TO 24               | 135               | 155                          | 10.58 | 12.27  | 13.75 | 10                   | 10.67 | 13.23 |  |
| Glob G     | g/l              | M02    | 17 TO 24               | 135               | 155                          | 1.00  | 1.49   | 2.25  | 10                   | 1.12  | 1.98  |  |
| Chol       | mmol/l           | M01    | 17 TO 24               | 630               | 745                          | 1.10  | 1.65   | 2.40  | 44                   | 1.24  | 2.22  |  |
| Trigly     | mmol/l           | M01    | 17 TO 24               | 630               | 745                          | 0.24  | 0.58   | 1.30  | 44                   | 0.25  | 1.20  |  |
| Phos-Lip   | mmol/l           | M01    | 17 TO 24               | 560               | 665                          | 1.16  | 1.50   | 1.97  | 38                   | 1.33  | 1.95  |  |

Reference values - Blood chemistry

| SPECIES    | RAT              |        |                        |                   |                              |       |        |       |                      |       | MALE  |
|------------|------------------|--------|------------------------|-------------------|------------------------------|-------|--------|-------|----------------------|-------|-------|
| STRAIN     | HanBr1:WIST(SPF) |        |                        |                   |                              |       |        |       |                      |       |       |
| SUPPLIER   | ROC Ltd          |        |                        |                   |                              |       |        |       |                      |       |       |
| STUDY TYPE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| DOSE ROUTE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| DATES:     | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| PARAMETER  | UNIT             | METHOD | ANIMAL AGE<br>IN WEEKS | NO. OF<br>ANIMALS | PERCENTILES OF INDIV. VALUES |       |        |       | RANGE OF STUDY MEANS |       |       |
|            |                  |        |                        |                   | N                            | 5%    | MEDIAN | 95%   | N                    | MIN   | MAX   |
| Na+        | mmol/l           | MD1    | 17 TO 24               | 630               | 745                          | 139.9 | 143.2  | 146.9 | 44                   | 137.9 | 148.1 |
| K+         | mmol/l           | MD1    | 17 TO 24               | 630               | 745                          | 3.09  | 3.74   | 4.36  | 44                   | 3.16  | 4.35  |
| Ca++       | mmol/l           | MD1    | 17 TO 24               | 630               | 745                          | 2.48  | 2.70   | 2.89  | 44                   | 2.45  | 2.86  |
| Cl-        | mmol/l           | MD1    | 17 TO 24               | 630               | 745                          | 97.8  | 103.1  | 107.5 | 44                   | 90.2  | 107.0 |
| PO4-in     | mmol/l           | MD1    | 17 TO 24               | 630               | 745                          | 1.36  | 1.71   | 2.07  | 44                   | 1.19  | 1.97  |
| ASAT       | U/l              | MD1    | 17 TO 24               | 630               | 745                          | 57.9  | 71.3   | 90.1  | 44                   | 61.6  | 84.6  |
| ALAT       | U/l              | MD1    | 17 TO 24               | 630               | 745                          | 22.2  | 30.8   | 45.3  | 44                   | 25.6  | 43.5  |
| ATP        | U/l              | MD1    | 17 TO 24               | 630               | 745                          | 44.4  | 61.3   | 91.7  | 44                   | 51.9  | 81.5  |
| GGT        | U/l              | MD1    | 17 TO 24               | 630               | 745                          | 0.0   | 0.0    | 0.0   | 44                   | 0.0   | 0.3   |
| GLDH       | U/l              | MD1    | 17 TO 24               | 194               | 224                          | 4.2   | 7.5    | 18.1  | 14                   | 5.6   | 13.4  |
| CK         | U/l              | MD1    | 17 TO 24               | 356               | 416                          | 84.7  | 122.5  | 297.9 | 27                   | 114.4 | 240.7 |
| LDH        | U/l              | MD1    | 17 TO 24               | 346               | 406                          | 83.2  | 126.5  | 272.1 | 26                   | 100.8 | 223.3 |

Reference values - Blood chemistry

| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
|------------|------------------|--------|------------------------|-------------------|------------------------------|-------|--------|-------|----------------------|-------|-------|
| SPECIES    | RAT              |        |                        |                   |                              |       |        |       |                      |       |       |
| STRAIN     | HanBr1:WIST(SPF) |        |                        |                   |                              |       |        |       |                      |       |       |
| SUPPLIER   | RCC Ltd          |        |                        |                   |                              |       |        |       |                      |       |       |
| STUDY TYPE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| DOSE ROUTE | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| DATES:     | [ALL]            |        |                        |                   |                              |       |        |       |                      |       |       |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
| PARAMETER  | UNIT             | METHOD | ANIMAL AGE<br>IN WEEKS | NO. OF<br>ANIMALS | PERCENTILES OF INDIV. VALUES |       |        |       | RANGE OF STUDY MEANS |       |       |
|            |                  |        |                        |                   | N                            | 5%    | MEDIAN | 95%   | N                    | MIN   | MAX   |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |       |       |
| Gluc       | mmol/l           | M01    | 17 TO 24               | 632               | 746                          | 3.97  | 6.06   | 9.44  | 44                   | 4.38  | 9.49  |
| Urea       | mmol/l           | M01    | 17 TO 24               | 632               | 746                          | 5.70  | 7.32   | 9.37  | 44                   | 6.03  | 8.93  |
| Creat      | µmol/l           | M01    | 17 TO 24               | 632               | 746                          | 24.9  | 31.1   | 38.0  | 44                   | 26.9  | 35.6  |
| Bill-tot   | µmol/l           | M01    | 17 TO 24               | 632               | 746                          | 1.15  | 1.82   | 2.78  | 44                   | 1.33  | 2.80  |
| Prot       | g/l              | M01    | 17 TO 24               | 632               | 746                          | 63.80 | 70.48  | 77.33 | 44                   | 65.36 | 75.93 |
| A/G        | rel. 1           | M03    | 17 TO 24               | 135               | 155                          | 1.19  | 1.45   | 1.65  | 10                   | 1.25  | 1.56  |
| Alb-e1     | rel. 1           | M02    | 17 TO 24               | 135               | 155                          | 0.545 | 0.593  | 0.624 | 10                   | 0.554 | 0.610 |
| Glob A1    | rel. 1           | M02    | 17 TO 24               | 135               | 155                          | 0.141 | 0.161  | 0.182 | 10                   | 0.151 | 0.173 |
| Glob A2    | rel. 1           | M02    | 17 TO 24               | 135               | 155                          | 0.056 | 0.069  | 0.082 | 10                   | 0.058 | 0.076 |
| Glob B     | rel. 1           | M02    | 17 TO 24               | 135               | 155                          | 0.126 | 0.148  | 0.169 | 10                   | 0.126 | 0.165 |
| Glob G     | rel. 1           | M02    | 17 TO 24               | 135               | 155                          | 0.022 | 0.031  | 0.045 | 10                   | 0.026 | 0.037 |
| Alb-e1     | g/l              | M02    | 17 TO 24               | 135               | 155                          | 36.01 | 41.35  | 47.00 | 10                   | 38.49 | 45.09 |
| Glob A1    | g/l              | M02    | 17 TO 24               | 135               | 155                          | 9.73  | 11.29  | 13.17 | 10                   | 10.25 | 12.42 |
| Glob A2    | g/l              | M02    | 17 TO 24               | 135               | 155                          | 3.99  | 4.88   | 5.75  | 10                   | 4.13  | 5.33  |
| Glob B     | g/l              | M02    | 17 TO 24               | 135               | 155                          | 8.90  | 10.45  | 11.83 | 10                   | 9.02  | 11.48 |
| Glob G     | g/l              | M02    | 17 TO 24               | 135               | 155                          | 1.50  | 2.22   | 3.16  | 10                   | 1.86  | 2.61  |
| Chol       | mmol/l           | M01    | 17 TO 24               | 632               | 746                          | 0.91  | 1.50   | 2.28  | 44                   | 1.10  | 2.10  |
| Trigly     | mmol/l           | M01    | 17 TO 24               | 632               | 746                          | 0.22  | 0.38   | 0.67  | 44                   | 0.26  | 0.61  |
| Phos-Lip   | mmol/l           | M01    | 17 TO 24               | 562               | 666                          | 1.14  | 1.66   | 2.26  | 38                   | 1.37  | 2.01  |

Reference values - Blood chemistry

| -----      |                  |        |                        |                   |                              |       |        |       |                      |        |       |
|------------|------------------|--------|------------------------|-------------------|------------------------------|-------|--------|-------|----------------------|--------|-------|
| SPECIES    | RAT              |        |                        |                   |                              |       |        |       |                      | FEMALE |       |
| STRAIN     | HanBr1:WIST(SPF) |        |                        |                   |                              |       |        |       |                      |        |       |
| SUPPLIER   | RCC Ltd          |        |                        |                   |                              |       |        |       |                      |        |       |
| STUDY TYPE | [ALL]            |        |                        |                   |                              |       |        |       |                      |        |       |
| DOSE ROUTE | [ALL]            |        |                        |                   |                              |       |        |       |                      |        |       |
| DATES:     | [ALL]            |        |                        |                   |                              |       |        |       |                      |        |       |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |        |       |
| PARAMETER  | UNIT             | METHOD | ANIMAL AGE<br>IN WEEKS | NO. OF<br>ANIMALS | PERCENTILES OF INDIV. VALUES |       |        |       | RANGE OF STUDY MEANS |        |       |
|            |                  |        |                        |                   | N                            | 5%    | MEDIAN | 95%   | N                    | MIN    | MAX   |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |        |       |
| Na+        | mmol/l           | MO1    | 17 TO 24               | 632               | 746                          | 138.7 | 142.1  | 146.0 | 44                   | 139.2  | 146.0 |
| K+         | mmol/l           | MO1    | 17 TO 24               | 632               | 746                          | 2.55  | 3.23   | 3.88  | 44                   | 2.67   | 4.99  |
| Ca++       | mmol/l           | MO1    | 17 TO 24               | 632               | 745                          | 2.49  | 2.70   | 2.88  | 44                   | 2.47   | 2.86  |
| Cl-        | mmol/l           | MO1    | 17 TO 24               | 632               | 746                          | 98.8  | 103.8  | 108.5 | 44                   | 96.9   | 110.0 |
| PO4-in     | mmol/l           | MO1    | 17 TO 24               | 632               | 746                          | 0.89  | 1.32   | 1.73  | 44                   | 1.01   | 1.57  |
| ASAT       | U/l              | MO1    | 17 TO 24               | 632               | 746                          | 55.7  | 70.3   | 114.8 | 44                   | 65.2   | 105.7 |
| ALAT       | U/l              | MO1    | 17 TO 24               | 632               | 746                          | 16.3  | 24.0   | 48.7  | 44                   | 20.4   | 42.0  |
| AIP        | U/l              | MO1    | 17 TO 24               | 632               | 746                          | 15.2  | 22.3   | 37.1  | 44                   | 16.0   | 35.7  |
| GGT        | U/l              | MO1    | 17 TO 24               | 632               | 746                          | 0.0   | 0.0    | 0.0   | 44                   | 0.0    | 0.4   |
| GLDH       | U/l              | MO1    | 17 TO 24               | 194               | 224                          | 3.8   | 7.4    | 56.6  | 14                   | 7.4    | 33.1  |
| CK         | U/l              | MO1    | 17 TO 24               | 356               | 415                          | 75.1  | 109.5  | 294.8 | 27                   | 93.0   | 277.1 |
| LDH        | U/l              | MO1    | 17 TO 24               | 346               | 405                          | 82.1  | 126.9  | 276.5 | 26                   | 102.3  | 202.9 |

## 1.12 REFERENCE VALUES - URINE ANALYSIS

|            |                  |      |
|------------|------------------|------|
| SPECIES    | RAT              | MALE |
| STRAIN     | HarBr1:WIST(SPF) |      |
| SUPPLIER   | RCC Ltd          |      |
| STUDY TYPE | [ALL]            |      |
| DOSE ROUTE | [ALL]            |      |
| DATES:     | [ALL]            |      |

| PARAMETER | UNIT   | METHOD | ANIMAL AGE<br>IN WEEKS | NO. OF<br>ANIMALS | PERCENTILES OF INDIV. VALUES |       |        |       | RANGE OF STUDY MEANS |       |       |
|-----------|--------|--------|------------------------|-------------------|------------------------------|-------|--------|-------|----------------------|-------|-------|
|           |        |        |                        |                   | N                            | 5%    | MEDIAN | 95%   | N                    | MIN   | MAX   |
| Volume    | ml     | M01    | 17 TO 24               | 622               | 736                          | 1.8   | 5.8    | 10.2  | 43                   | 2.1   | 9.3   |
| Rel dens  | rel. 1 | M01    | 17 TO 24               | 622               | 737                          | 1.029 | 1.043  | 1.092 | 43                   | 1.035 | 1.091 |
| pH        |        | M01    | 17 TO 24               | 622               | 738                          | 6.0   | 6.5    | 8.0   | 43                   | 5.8   | 7.8   |
| NIT       | Score  | M01    | 17 TO 24               | 311               | 356                          | 0.    | 0.     | 1.    | 23                   | 0.    | 0.    |
| PRO       | g/l    | M01    | 17 TO 24               | 622               | 736                          | 0.00  | 0.25   | 0.75  | 43                   | 0.16  | 0.93  |
| GLU       | mmol/l | M01    | 17 TO 24               | 622               | 736                          | 0.    | 0.     | 0.    | 43                   | 0.    | 0.    |
| KET       | mmol/l | M01    | 17 TO 24               | 622               | 736                          | 0.0   | 0.5    | 1.5   | 43                   | 0.0   | 2.7   |
| UBG       | µmol/l | M01    | 17 TO 24               | 622               | 736                          | 0.    | 0.     | 17.   | 43                   | 0.    | 29.   |
| BIL       | µmol/l | M01    | 17 TO 24               | 622               | 736                          | 0.    | 0.     | 17.   | 43                   | 0.    | 13.   |
| ERY       | per µl | M01    | 17 TO 24               | 622               | 736                          | 0.    | 10.    | 25.   | 43                   | 1.    | 31.   |
| LEU       | per µl | M01    | 17 TO 24               | 622               | 736                          | 0.    | 25.    | 100.  | 43                   | 3.    | 96.   |

Reference values - Urine analysis

| -----      |                  |        |                        |                   |                              |       |        |       |                      |        |       |
|------------|------------------|--------|------------------------|-------------------|------------------------------|-------|--------|-------|----------------------|--------|-------|
| SPECIES    | RAT              |        |                        |                   |                              |       |        |       |                      | FEMALE |       |
| STRAIN     | HanBr1:WIST(SPF) |        |                        |                   |                              |       |        |       |                      |        |       |
| SUPPLIER   | RCC Ltd          |        |                        |                   |                              |       |        |       |                      |        |       |
| STUDY TYPE | [ALL]            |        |                        |                   |                              |       |        |       |                      |        |       |
| DOSE ROUTE | [ALL]            |        |                        |                   |                              |       |        |       |                      |        |       |
| DATES:     | [ALL]            |        |                        |                   |                              |       |        |       |                      |        |       |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |        |       |
| PARAMETER  | UNIT             | METHOD | ANIMAL AGE<br>IN WEEKS | NO. OF<br>ANIMALS | PERCENTILES OF INDIV. VALUES |       |        |       | RANGE OF STUDY MEANS |        |       |
|            |                  |        |                        |                   | N                            | 5%    | MEDIAN | 95%   | N                    | MIN    | MAX   |
| -----      |                  |        |                        |                   |                              |       |        |       |                      |        |       |
| Volume     | ml               | M01    | 17 TO 24               | 621               | 736                          | 1.4   | 4.4    | 8.3   | 43                   | 1.7    | 8.2   |
| Rel dens   | rel. 1           | M01    | 17 TO 24               | 621               | 736                          | 1.028 | 1.044  | 1.086 | 43                   | 1.035  | 1.080 |
| pH         |                  | M01    | 17 TO 24               | 622               | 737                          | 5.0   | 6.0    | 8.0   | 43                   | 5.2    | 8.4   |
| NIT        | Score            | M01    | 17 TO 24               | 311               | 356                          | 0.    | 0.     | 1.    | 23                   | 0.     | 1.    |
| PRO        | g/l              | M01    | 17 TO 24               | 622               | 737                          | 0.00  | 0.25   | 0.75  | 43                   | 0.08   | 0.73  |
| GLU        | mmol/l           | M01    | 17 TO 24               | 622               | 737                          | 0.    | 0.     | 0.    | 43                   | 0.     | 0.    |
| KET        | mmol/l           | M01    | 17 TO 24               | 622               | 737                          | 0.0   | 0.5    | 1.5   | 43                   | 0.0    | 1.3   |
| UBG        | µmol/l           | M01    | 17 TO 24               | 622               | 737                          | 0.    | 0.     | 17.   | 43                   | 0.     | 16.   |
| BIL        | µmol/l           | M01    | 17 TO 24               | 622               | 737                          | 0.    | 0.     | 17.   | 43                   | 0.     | 15.   |
| ERY        | per µl           | M01    | 17 TO 24               | 622               | 737                          | 0.    | 0.     | 10.   | 43                   | 0.     | 16.   |
| LEU        | per µl           | M01    | 17 TO 24               | 622               | 737                          | 0.    | 0.     | 25.   | 43                   | 0.     | 46.   |



**APPENDIX V:**

**PHASE REPORT: DOSE FORMULATION ANALYSIS**

# **ANALYTICAL PHASE REPORT**

**Analytical Phase to:**

**REPEATED DOSE 90-DAY ORAL TOXICITY STUDY WITH  
2-AMINO-4-HYDROXYETHYLAMINOANISOLE SULFATE  
(A084, WR 23081) IN WISTAR RATS**

**Subtitle:**

Determination of Concentration, Homogeneity, and Stability  
of 2-Amino-4-Hydroxyethylaminoanisol Sulfate (A084, WR 23081)  
in Bidistilled Water

**Study Director:**

W. H. Braun (RCC Ltd, Toxicology, Itingen)

**Principal Investigator Analytical Phase:**

Dr. D. Flade

**Completion Date of Analytical Phase Report:**

July 15, 2005

**Test Site:**

**RCC Ltd**  
Environmental Chemistry &  
Pharmanalytics  
CH-4452 Itingen / Switzerland

**RCC Study No.:**

857092

Page 1 of 16

## GOOD LABORATORY PRACTICE

# STATEMENT OF COMPLIANCE

RCC Study Number : 857092

Study Director : W. H. Braun, RCC Ltd, Toxicology,  
Itingen / Switzerland

Test Item : 2-Amino-4-Hydroxyethylaminoanisole  
Sulfate (A084, WR 23081)

Principal Investigator  
Analytical Phase : Dr. D. Flade

Analytical Phase to : Repeated Dose 90-Day Oral Toxicity Study  
with 2-Amino-4-Hydroxyethylaminoanisole  
Sulfate (A084, WR 23081) in Wistar Rats

The analytical phase has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted February 2<sup>nd</sup>, 2000 [RS 813.016.5]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26<sup>th</sup>, 1997 by decision of the OECD Council [C(97)186/Final].


Principal Investigator  
Analytical Phase: Dr. D. Flade

.....  
Date: *D. Flade*  
*July 15, 2005*

## SIGNATURES

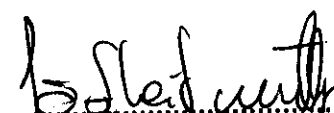
Principal Investigator  
Analytical Phase:

Dr. D. Flade

  
.....  
Date: July 15, 2005

Management:

Dr. J. Schreitmüller

  
.....  
Date: July 15, 2005

## QUALITY ASSURANCE

RCC Ltd, Environmental Chemistry & Pharamalytics, CH-4452 Itingen / Switzerland

### STATEMENT

RCC Study Number : 857092  
Study Director : W. H. Braun, RCC Ltd, Toxicology,  
Itingen / Switzerland  
Test Item : 2-Amino-4-Hydroxyethylaminoanisole  
Sulfate (A084, WR 23081)  
Principal Investigator  
Analytical Phase : Dr. D. Flade  
Analytical Phase to : Repeated Dose 90-Day Oral Toxicity Study  
with 2-Amino-4-Hydroxyethylaminoanisole  
Sulfate (A084, WR 23081) in Wistar Rats

The general facilities and activities are inspected periodically and the results are reported to the responsible person and the management.

Study procedures were periodically inspected. The phase report was audited by the quality assurance. The dates are given below.

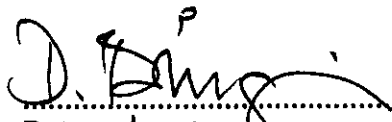
| Dates and Types of QA Inspections |                 | Dates of Reports to the Principal Investigator and to the Management |
|-----------------------------------|-----------------|--|
| November 10, 2004                 | Analytical work | November 10, 2004  |
| May 30, 2005                      | Phase report    | May 30, 2005   |

This statement also confirms that this final phase report reflects the raw data.

Sections of the draft study plan relating to the phase were reviewed and reported to the study director, lead QA and test facility management on: October 26, 2004.

Summary report(s) of study related inspection(s) (if applicable) was/were issued to the study director, lead QA and test facility management.

Quality Assurance:

for A. Güdel  
  
Date: July 15, 2005

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## PREFACE

### GENERAL

Analytical Phase to: Repeated Dose 90-Day Oral Toxicity Study with  
2-Amino-4-Hydroxyethylaminoaniso le Sulfate  
(A084, WR 23081) in Wistar Rats

Sponsor: Wella AG  
Berliner Allee 65  
D-64274 Darmstadt

Study Director:  
(Test Facility) W. H. Braun  
RCC Ltd  
Toxicology  
CH-4452 Itingen / Switzerland  
CH-4414 Füllinsdorf / Switzerland

Test Site: RCC Ltd  
Environmental Chemistry & Pharmanalytics  
Zelgliweg 1  
CH-4452 Itingen / Switzerland

### RESPONSIBILITIES

Principal Investigator  
Analytical Phase: Dr. D. Flade  
Reporting: C. Stutz  
Head of RCC Quality Assurance: I. Wüthrich

### SCHEDULE OF ANALYTICAL PHASE

Experimental Starting Date: November 10, 2004  
Experimental Completion Date: January 06, 2005  
Completion Date of Analytical  
Phase Report: July 15, 2005

### ARCHIVING

RCC Ltd, CH-4452 Itingen/Switzerland will retain a copy of the study plan, the raw data, and the analytical phase report of the present study for at least ten years. No data will be discarded without the sponsor's consent.

# 1 PURPOSE

This phase report describes the analytical method employed and the results obtained for concentration, homogeneity, and stability of 2-Amino-4-Hydroxyethylaminoaniso le Sulfate (A084, WR 23081) in bidistilled water. The analyses were performed by HPLC analysis based on a method provided by the sponsor.

Analysis of homogeneity was performed by analysing samples of each dose group from three different segments (top, middle, bottom) of the respective mixing container.

Evaluation of stability was performed by analysing samples of each dose group stored for two hours, four hours and seven days under storage conditions.

# 2 MATERIALS AND METHODS

## 2.1 TEST ITEM

Detailed information on the test item 2-Amino-4-Hydroxyethylaminoaniso le Sulfate (A084, WR 23081) as used for analytical purposes is given in the toxicology report.

## 2.2 SAMPLE PREPARATION AND STORAGE

Test item/vehicle mixtures were prepared by RCC Ltd, Toxicology, Itingen and about 2 g (weighed to the third decimal place) of each mixture was delivered to the analytical laboratory of RCC Ltd, Environmental Chemistry & Pharamalytics. These samples for analysis of concentration and homogeneity were stored deep-frozen (about -20 °C) until analysis. Storage stability samples were collected after storage (2 hours, 4 hours and 7 days under storage conditions) and then delivered to the analytical laboratory where they were stored deep-frozen until analysis.

## 2.3 ANALYTICAL PROCEDURE

### 2.3.1 Reagents

|   |   |
|---|---|
| Purified water:   | In-house prepared by a Milli-Q water purification system (Millipore)  |
| Acetonitrile (ACN):   | Baker no. 9017  |
| Phosphoric acid (H <sub>3</sub> PO <sub>4</sub> ):                  | Baker no. 6024  |
| Methane sulfonic acid:  | Fluka no. 64280   |
| Di-potassium hydrogen-phosphate (KH <sub>2</sub> PO <sub>4</sub> ): | Merck no. 1.05101.1000  |
| Buffer solution:  | 0.192 ml of methane sulfonic acid and 0.87 g KH <sub>2</sub> PO <sub>4</sub> filled to 1 litre with H <sub>2</sub> O and adjusted to pH 3.6 with H <sub>3</sub> PO <sub>4</sub> |
| Solvent mixture:  | Buffer solution/ACN (88+12 v/v)   |



### 2.3.2 Standard Solutions

Stock solutions of the test item in solvent mixture (see Section 2.3.1) with concentrations in the range from 298  $\mu\text{g/mL}$  to 569.9  $\mu\text{g/mL}$  were prepared by weighing appropriate amounts of the test item accurately into 100-mL volumetric flasks. Then, an appropriate volume (about 3/4 of target volume) of solvent mixture was added to each volumetric flask and dissolution was achieved using an ultrasonic bath (5 min). The flasks were filled to the mark with solvent mixture. Finally, various standard solutions were prepared by respective dilution of these stock solutions with solvent mixture to yield concentrations in the range from 5.970  $\mu\text{g/mL}$  to 136.8  $\mu\text{g/mL}$ . These standard solutions were used for calibration of the HPLC.

### 2.3.3 Analysis of Samples

The delivered samples were dissolved in an appropriate volume (about 3/4 of target volume) of solvent mixture using an ultrasonic bath. Then, the 100-mL volumetric flasks were filled to the mark with solvent mixture. Depending on the dose group, the latter sample solutions were further diluted with solvent mixture to yield concentrations within the calibration range. Finally, a defined aliquot was quantified by HPLC.

### 2.3.4 High Performance Liquid Chromatographic Determination

Typical Apparatus: pump: Merck-Hitachi L-6200 A  
detector: Merck-Hitachi L-4200  
sampling unit: Varian Pro Star  
Interface module: EZ Chrom Software

Column: Lichrospher 60 RP Select B; 5  $\mu\text{m}$ ; 250 x 4 mm  
Eluent: Solvent mixture (s. Section 2.3.1)  
Flow: 1.0 mL/min  
Column temp.: room temperature  
Wave length: 280 nm  
Injection volume: 20  $\mu\text{L}$

### 2.3.5 Evaluation of Results

Injected samples were quantified by the peak areas (counts) of the test item with reference to the calibration curve. The latter was obtained by correlation of the peak areas of the standard solutions with their corresponding concentrations ( $\mu\text{g/mL}$ ), using the following equation 1:

$$Y = a + b \cdot X \quad (1)$$

where

Y = Peak areas of test item in injected sample [counts]  
a = Y-axis intercept  
b = Slope  
X = Concentration of test item in injected sample [ $\mu\text{g/mL}$ ]

The concentrations of test item in vehicle were calculated according to equation 2:

$$C = \frac{X \cdot V \cdot D \cdot Q}{W \cdot 1000} \quad (2)$$

where

- C = Concentration of test item in vehicle [mg/mL]
- X = Concentration of test item in injected sample calculated by equation 1 [ $\mu$ g/mL]
- V = Final volume [mL]
- D = Dilution factor
- Q = Density of test item/vehicle mixtures [set to 1.0 g/mL]
- W = Weight of sample [about 2 g, weighed to the third decimal place]

### 3 RESULTS

This chemical analysis determined concentration, homogeneity, and stability of 2-Amino-4-Hydroxyethylaminoanisoole Sulfate (A084, WR 23081) in bidistilled water.

**Date of Preparation: 01-NOV-2004 to 04-JAN-2005:**

The mean concentrations of the homogeneity samples ranged from 88.3% to 101.4% of the nominal concentration of dose group 2 (1.5 mg/mL), from 90.4% to 96.6% for dose group 3 (5.0 mg/mL), and from 83.4% to 100.0% for dose group 4 (20 mg/mL), respectively. The individual concentrations varied in the range from -4% to +4% of the mean concentrations. Therefore, the test item was found to be homogeneously distributed in the vehicle.

2-Amino-4-Hydroxyethylaminoanisoole Sulfate (A084, WR 23081) was stable in the vehicle under storage conditions for four hours, but not stable for seven days.

In conclusion, the results obtained were within the accepted limits defined in the RCC-SOP.

- Content ( $\pm 20\%$  of nominal)
- homogeneity ( $\pm 15\%$  of the mean value of the homogeneity samples)
- stability ( $\pm 10\%$  of the mean value of the respective homogeneity sample) \*

The results obtained for concentration, homogeneity, and stability of the test item in vehicle are presented in Table 2. An example of a calibration curve is shown in Table 1 and typical chromatograms of standard solutions and test samples are presented in Figures 1 and 2.

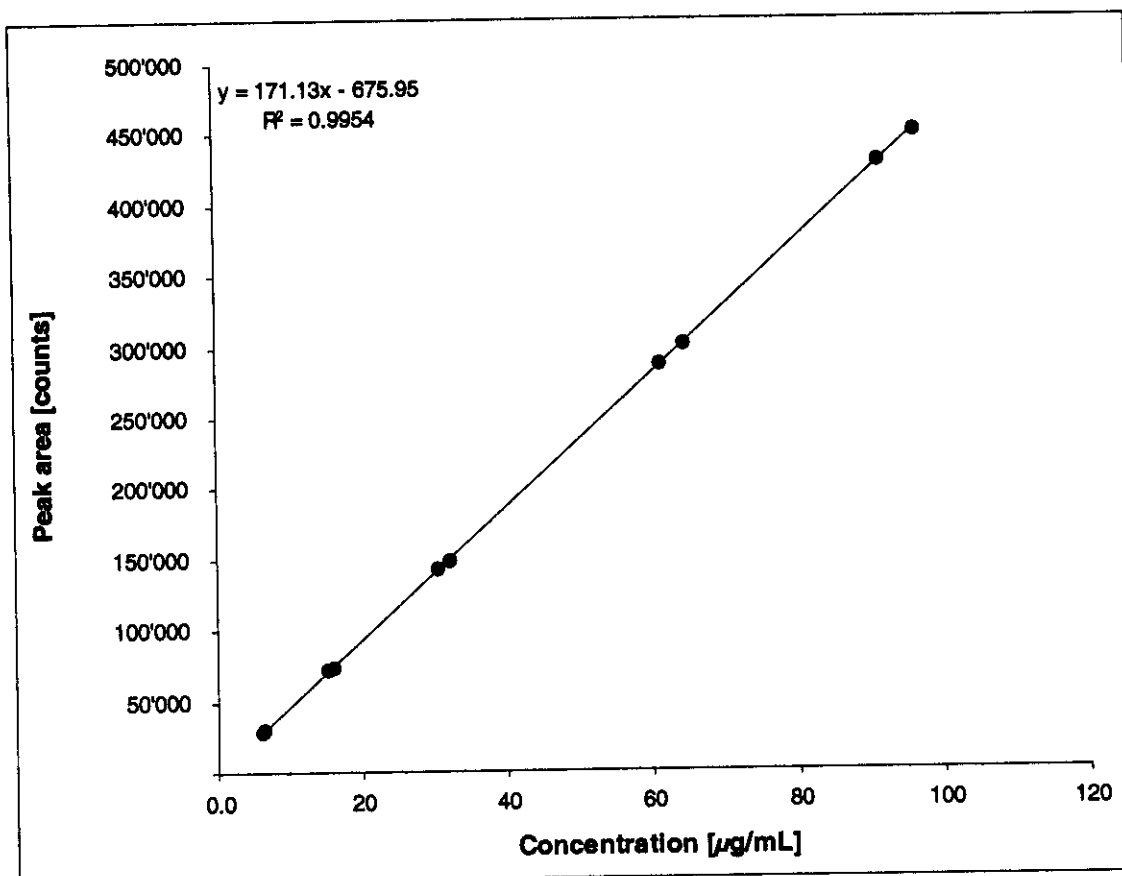
The tabulated values represent rounded-off results by calculations based on the exact raw data.

---

\* except for the 7-Day stability samples

**Table 1: Example of Calibration Curve**

| Concentrations<br>( $\mu\text{g/mL}$ ) | Peak area<br>(counts) | Concentration<br>corrected<br>( $\mu\text{g/mL}$ ) | Peak area<br>corrected<br>(counts) | Bias<br>(%) |
|--|-----------------------|--|------------------------------------|-------------|
| 6.124                                  | 27'869                | 6.139  | 27'799                             | 0.3         |
| 15.31                                  | 71'526                | 15.47  | 70'781                             | 1.0         |
| 30.62                                  | 142'621               | 30.66  | 142'417                            | 0.1         |
| 61.24                                  | 286'316               | 61.37  | 285'691                            | 0.2         |
| 91.86                                  | 429'820               | 92.04  | 428'964                            | 0.2         |
| 6.444                                  | 29'338                | 6.453  | 29'296                             | 0.1         |
| 16.11                                  | 73'919                | 15.98  | 74'524                             | -0.8        |
| 32.22                                  | 148'854               | 32.00  | 149'904                            | -0.7        |
| 64.44                                  | 300'847               | 64.48  | 300'664                            | 0.1         |
| 96.66                                  | 450'354               | 96.43  | 451'424                            | -0.2        |



**Table 2: Concentration, Homogeneity, and Stability of Test Item in Vehicle**

| Dose Group                            | Nominal Conc. (mg/mL) | T<br>M<br>B | Time of Storage <sup>1</sup> | Date of Analysis | Concentration Found |           |                |                     |
|---------------------------------------|-----------------------|-------------|------------------------------|------------------|---------------------|-----------|----------------|---------------------|
|                                       |                       |             |                              |                  | (mg/mL)             | % of Nom. | Mean % of Nom. | ± Dev. in % of Mean |
| <b>Date of Preparation: 01-NOV-04</b> |                       |             |                              |                  |                     |           |                |                     |
| 1                                     | ---                   | --          | 0 h                          | 10-NOV-04        | 0.000               | ---       | ---            | ---                 |
| 2                                     | 1.5                   | T<br>M<br>B | 0 h                          | 10-NOV-04        | 1.451               | 96.7      | 96.7           | -1/+1               |
|                                       |                       |             | 0 h                          | 10-NOV-04        | 1.441               | 96.1      |                |                     |
|                                       |                       |             | 0 h                          | 10-NOV-04        | 1.458               | 97.2      |                |                     |
|                                       |                       | --          | 2 h                          | 10-NOV-04        | 1.452               | 96.8      | ---            | ---                 |
|                                       |                       |             | 7 d                          | 10-NOV-04        | 0.136               | 9.1       |                |                     |
| 3                                     | 5.0                   | T<br>M<br>B | 0 h                          | 10-NOV-04        | 4.826               | 96.5      | 96.0           | -2/+1               |
|                                       |                       |             | 0 h                          | 10-NOV-04        | 4.846               | 96.9      |                |                     |
|                                       |                       |             | 0 h                          | 10-NOV-04        | 4.725               | 94.5      |                |                     |
|                                       |                       | --          | 2 h                          | 10-NOV-04        | 4.827               | 96.5      | ---            | ---                 |
|                                       |                       |             | 7 d                          | 10-NOV-04        | 1.665               | 33.3      |                |                     |
| 4                                     | 20.0                  | T<br>M<br>B | 0 h                          | 10-NOV-04        | 19.71               | 98.5      | 99.2           | -1/+1               |
|                                       |                       |             | 0 h                          | 10-NOV-04        | 19.95               | 99.8      |                |                     |
|                                       |                       |             | 0 h                          | 10-NOV-04        | 19.87               | 99.4      |                |                     |
|                                       |                       | --          | 2 h                          | 10-NOV-04        | 19.55               | 97.8      | ---            | ---                 |
|                                       |                       |             | 7 d                          | 10-NOV-04        | 14.39               | 72.0      |                |                     |
| <b>Date of Preparation: 23-NOV-04</b> |                       |             |                              |                  |                     |           |                |                     |
| 1                                     | ---                   | --          | 0 h                          | 30-NOV-04        | 0.000               | ---       | ---            | ---                 |
| 2                                     | 1.5                   | T<br>M<br>B | 0 h                          | 30-NOV-04        | 1.459               | 97.3      | 97.2           | ±0                  |
|                                       |                       |             | 0 h                          | 30-NOV-04        | 1.465               | 97.6      |                |                     |
|                                       |                       |             | 0 h                          | 30-NOV-04        | 1.451               | 96.8      |                |                     |
|                                       |                       | --          | 4 h                          | 30-NOV-04        | 1.444               | 96.3      | ---            | ---                 |
| 3                                     | 5.0                   | T<br>M<br>B | 0 h                          | 30-NOV-04        | 4.792               | 95.8      | 95.0           | -1/+1               |
|                                       |                       |             | 0 h                          | 30-NOV-04        | 4.699               | 94.0      |                |                     |
|                                       |                       |             | 0 h                          | 30-NOV-04        | 4.757               | 95.1      |                |                     |
|                                       |                       | --          | 4 h                          | 30-NOV-04        | 4.781               | 95.6      | ---            | ---                 |
| 4                                     | 20                    | T<br>M<br>B | 0 h                          | 30-NOV-04        | 19.50               | 97.5      | 96.6           | -1/+1               |
|                                       |                       |             | 0 h                          | 30-NOV-04        | 19.24               | 96.2      |                |                     |
|                                       |                       |             | 0 h                          | 30-NOV-04        | 19.22               | 96.1      |                |                     |
|                                       |                       | --          | 4 h                          | 30-NOV-04        | 19.73               | 98.7      | ---            | ---                 |

T/M/B: Top/Middle/Bottom (segment of mixing container)  
 h/d: hours/days  
 1 Under storage conditions

Table 2: Cont'd

| Dose Group                            | Nominal Conc. (mg/mL) | T<br>M<br>B | Time of Storage <sup>1</sup> | Date of Analysis | Concentration Found |           |                |                     |
|---------------------------------------|-----------------------|-------------|------------------------------|------------------|---------------------|-----------|----------------|---------------------|
|                                       |                       |             |                              |                  | (mg/mL)             | % of Nom. | Mean % of Nom. | ± Dev. in % of Mean |
| <b>Date of Preparation: 07-DEC-04</b> |                       |             |                              |                  |                     |           |                |                     |
| 1                                     | ---                   | --          | 0 h                          | 17-DEC-04        | 0.000               | ---       | ---            | ---                 |
| 2                                     | 1.5                   | T<br>M<br>B | 0 h                          | 17-DEC-04        | 1.267               | 84.4      | 88.3           | -4/+3               |
|                                       |                       |             | 0 h                          | 17-DEC-04        | 1.347               | 89.8      |                |                     |
|                                       |                       |             | 0 h                          | 17-DEC-04        | 1.359               | 90.6      |                |                     |
| 3                                     | 5.0                   | T<br>M<br>B | 0 h                          | 17-DEC-04        | 4.503               | 90.1      | 90.4           | -3/+4               |
|                                       |                       |             | 0 h                          | 17-DEC-04        | 4.373               | 87.5      |                |                     |
|                                       |                       |             | 0 h                          | 17-DEC-04        | 4.689               | 93.8      |                |                     |
| 4                                     | 20.0                  | T<br>M<br>B | 0 h                          | 17-DEC-04        | 17.06               | 85.3      | 83.4           | -2/+2               |
|                                       |                       |             | 0 h                          | 17-DEC-04        | 16.38               | 81.9      |                |                     |
|                                       |                       |             | 0 h                          | 17-DEC-04        | 16.58               | 82.9      |                |                     |
| <b>Date of Preparation: 04-JAN-05</b> |                       |             |                              |                  |                     |           |                |                     |
| 1                                     | ---                   | --          | 0 h                          | 06-JAN-05        | 0.000               | ---       | ---            | ---                 |
| 2                                     | 1.5                   | T<br>M<br>B | 0 h                          | 06-JAN-05        | 1.527               | 101.8     | 101.4          | -1/+1               |
|                                       |                       |             | 0 h                          | 06-JAN-05        | 1.533               | 102.2     |                |                     |
|                                       |                       |             | 0 h                          | 06-JAN-05        | 1.505               | 100.3     |                |                     |
| 3                                     | 5.0                   | T<br>M<br>B | 0 h                          | 06-JAN-05        | 4.731               | 94.6      | 96.6           | -2/+1               |
|                                       |                       |             | 0 h                          | 06-JAN-05        | 4.859               | 97.2      |                |                     |
|                                       |                       |             | 0 h                          | 06-JAN-05        | 4.892               | 97.8      |                |                     |
| 4                                     | 20.0                  | T<br>M<br>B | 0 h                          | 06-JAN-05        | 19.87               | 99.4      | 100.0          | -2/+1               |
|                                       |                       |             | 0 h                          | 06-JAN-05        | 19.79               | 99.0      |                |                     |
|                                       |                       |             | 0 h                          | 06-JAN-05        | 20.36               | 101.8     |                |                     |

T/M/B: Top/Middle/Bottom (segment of mixing container)

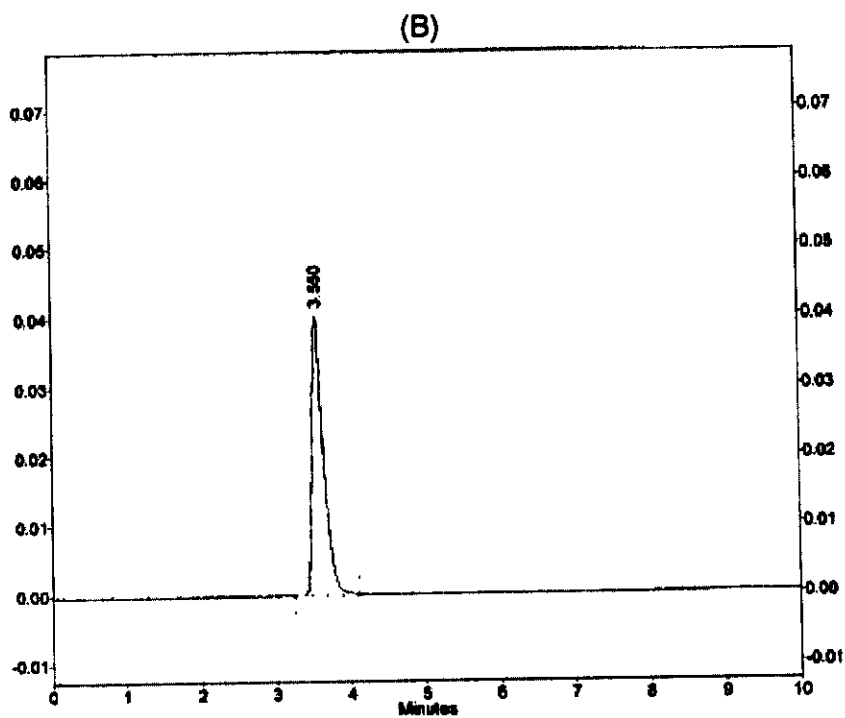
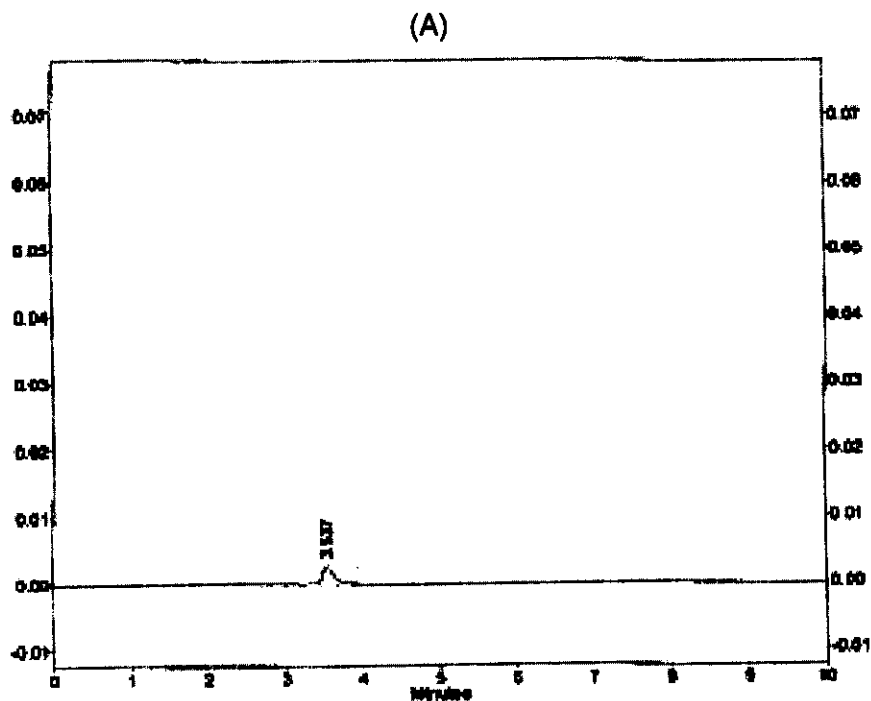
h/d: hours/days

1 Under storage conditions

**Figure 1: Typical Chromatograms of Standard Solutions**

- (A) Standard solution: 6.124  $\mu\text{g/mL}$
- (B) Standard solution: 91.86  $\mu\text{g/mL}$

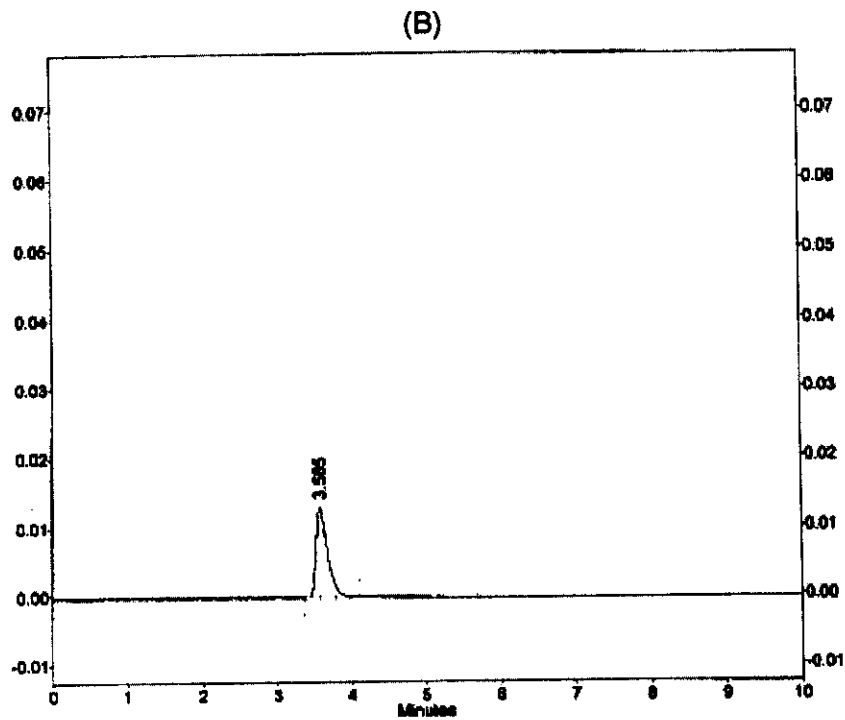
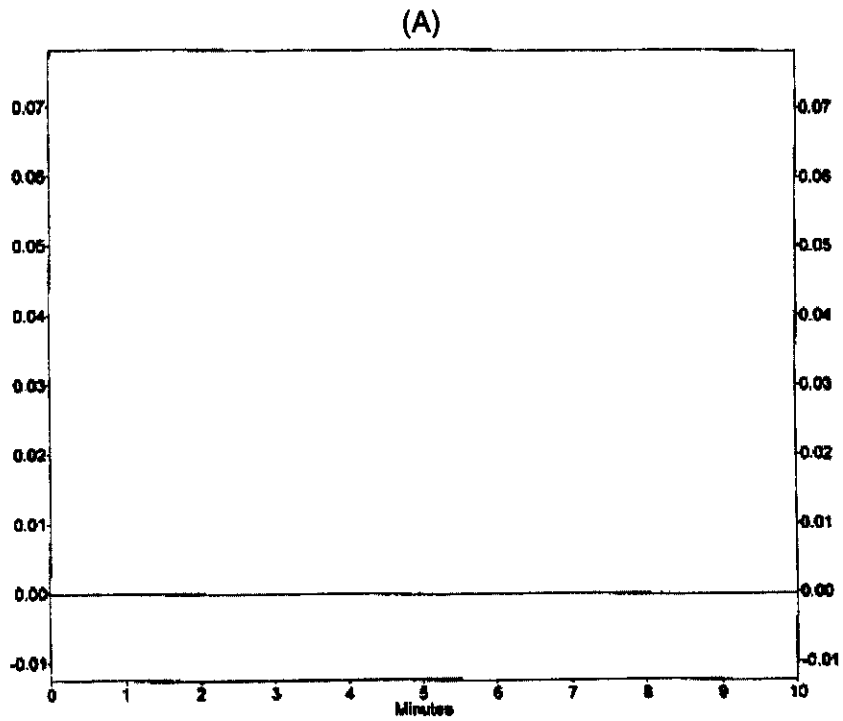
Date of analysis: 30-NOV-04



**Figure 2: Typical Chromatograms of Test Samples**

- (A) Dose group 1, control sample, undiluted
- (B) Dose group 2 (top), nominal concentration: 1.5 mg/mL undiluted

Date of analysis: 30-NOV-04

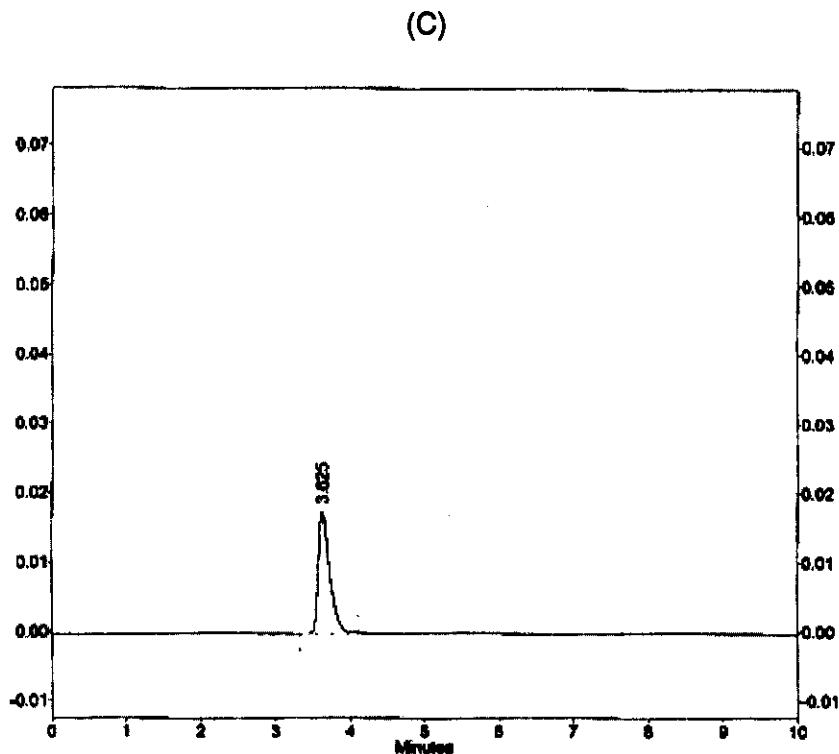




**Figure 2: Cont'd**

(C) Dose group 4 (top), nominal concentration: 20 mg/mL, diluted

Date of analysis: 30-NOV-04



**APPENDIX VI:**

**PHASE REPORT: THYROID HORMONE ANALYSIS**

# **ANALYTICAL PHASE REPORT**

**Analytical Phase to:**

**Repeated Dose 90-Day Oral Toxicity Study with  
2-Amino-4-Hydroxyethylaminoanisoie Sulfate (A 80, WR 23081)**

**Subtitle:**

**DETERMINATION OF TSH, TOTAL T3, TOTAL T4, FREE T3 AND FREE  
T4 IN RAT PLASMA**

**Study Director:**

W. H. Braun  
RCC Ltd, Toxicology

**Principal Investigator Analytical Phase:**

Dr. R. Burri

**Completion Date of the Analytical Phase Report:**

July 15, 2005

**Test Site:**

**RCC Ltd**  
Environmental Chemistry &  
Pharmanalytics  
CH-4452 Itingen  
Switzerland

**RCC Study Number:**

857092

Page 1 of 23

## GOOD LABORATORY PRACTICE

# STATEMENT OF COMPLIANCE

RCC Study Number: 857092

Study Director: W. H. Braun, RCC Ltd, Toxicology

Test Item: 2-Amino-4-Hydroxyethylaminoanisol Sulfate (A 80, WR 23081)

Principal Investigator  
Analytical Phase: Dr. R. Burri

Analytical Phase to: Repeated Dose 90-Day Oral Toxicity Study with 2-Amino-4-Hydroxyethylaminoanisol Sulfate (A 80, WR 23081)

This analytical phase was conducted in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted February 2<sup>nd</sup>, 2000 [RS 813.016.5]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26<sup>th</sup>, 1997 by decision of the OECD Council [C(97)186/Final].

Principal Investigator  
Analytical Phase:

Dr. R. Burri



.....

Date:

July 15, 2005

## SIGNATURES

Principal Investigator  
Hormone Determinations:

Dr. R. Burri

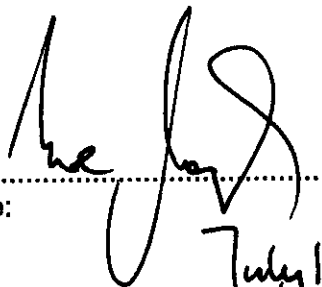


Date:

July 15, 2005

Management:

Dr. U. Morgenroth



Date:

July 15, 2005

## QUALITY ASSURANCE

RCC Ltd, Environmental Chemistry & Pharmanalytics, CH-4452 Itingen / Switzerland

### STATEMENT

RCC Study Number: 857092

Study Director: W. H. Braun, RCC Ltd, Toxicology

Test Item: 2-Amino-4-Hydroxyethylaminoanisoie Sulfate (A 80, WR 23081)

Principal Investigator  
Analytical Phase: Dr. R. Burri

Analytical Phase to: Repeated Dose 90-Day Oral Toxicity Study with 2-Amino-4-Hydroxyethylaminoanisoie Sulfate (A 80, WR 23081)

The general facilities and activities are inspected periodically and the results are reported to the responsible person and the management.

Study procedures were periodically inspected. The phase report was audited by the Quality Assurance. The dates are given below.

| Dates and Types of QA Inspections |                    | Dates of Reports to the Principal Investigator and to the Management |
|-----------------------------------|--------------------|--|
| February 22, 2005                 | Analytical work    | February 22, 2005  |
| April 13, 2005                    | Draft phase report | April 13, 2005   |
| July 15, 2005                     | Phase report       | July 15, 2005  |

This statement also confirms that this final analytical phase report reflects the raw data.

Sections of the draft study plan relating to the phase were reviewed and reported to the study director, Lead QA and test facility management on: October 26, 2004

Summary reports of study related inspections were issued to the study director, lead QA and test facility management.

Quality Assurance: *for* Henry Schneylin

*S. Zeyin*

.....  
Date: *July 15, 2005*

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## PREFACE

### GENERAL

Analytical Phase to: Repeated Dose 90-Day Oral Toxicity Study with 2-Amino-4-Hydroxyethylaminoanisoole Sulfate (A 80, WR 23081)

Subtitle: Determination of TSH, Total T3, Total T4, Free T3 and Free T4 in Rat Plasma

Study Director: W. H. Braun

Sponsor: Wella AG  
Berliner Allee 65  
D-64274 Darmstadt/Germany

Study Monitor: Dr. G. von Bölcshazy

Test Site: RCC Ltd.  
Environmental Chemistry & Pharmanalytics  
Zelgliweg 1  
CH-4452 Itingen/Switzerland

### RESPONSIBILITIES

Principal Investigator  
Analytical Phase: Dr. R. Burri

Technical Coordinator: Ms. A. Scholz

Head of RCC Quality Assurance: Ms. I. Wüthrich

### SCHEDULE OF ANALYTICAL PHASE

Experimental Starting Date: February 21, 2005

Experimental Completion Date: February 23, 2005

Completion Date of Analytical  
Phase Report: July 15, 2005

### ARCHIVING

RCC Ltd, CH-4452 Itingen/Switzerland will retain the study plan, raw data and the analytical phase report of the present study for at least ten years. No data will be discarded without the sponsor's consent.

# 1 PURPOSE

In this phase report the results TSH, total T3, total T4, free T3 and free T4 determinations are described. The measurements of the hormones were performed by immunoassay.

## 2 MATERIALS AND METHODS

### 2.1 TEST ITEM

The test item as described in the toxicological part was not used for this analytical phase.

### 2.2 REAGENTS AND MATERIALS

|                         |  |
|-------------------------|--|
| Test kits for TSH:      | Immulite Third Generation TSH (TSH, LKTS1 Diagnostic Products Corporation)<br>Supplier: Bühlmann Laboratories, Schönenbuch, Switzerland. |
| Test kits for total T3: | Immulite Total T3 (T3, LKT31, Diagnostic Products Corporation)<br>Supplier: Bühlmann Laboratories, Schönenbuch, Switzerland.             |
| Test kits for total T4: | Immulite Total T4 (T4, LKT41, Diagnostic Products Corporation)<br>Supplier: Bühlmann Laboratories, Schönenbuch, Switzerland.             |
| Test kits for free T3:  | Immulite Free T3 (T3F, LKF31, Diagnostic Products Corporation)<br>Supplier: Bühlmann Laboratories, Schönenbuch, Switzerland.             |
| Test kits for free T4:  | Immulite Free T4 (T4F, LKF41, Diagnostic Products Corporation)<br>Supplier: Bühlmann Laboratories, Schönenbuch, Switzerland.             |
| Equipment:              | Immulite Analyzer DPC/Cirrus, S/N F1235  |
| Software:               | Immulite Operating Software, Version 4.12  |
| Water:                  | Purified water, Milli-Q  |

## 2.3 ANALYTICAL PROCEDURE

### 2.3.1 TSH

#### Principle of the procedure:

Immulite Canine TSH is a solid phase, two-site chemiluminescent enzyme immunoassay (automated system).

#### Assay:

The test unit contains one bead coated with monoclonal murine anti-TSH antibody. The sample (75  $\mu$ l plasma) was added to the bead together with the test reagent (alkaline phosphatase conjugated to polyclonal goat anti-TSH antibody in buffer). After a 60 min incubation cycle, the chemiluminescent substrate was added and the signal was measured. The calibration curve covers a range up to 75  $\mu$ U/mL (analytical sensitivity: 0.004  $\mu$ U/mL).

### 2.3.2 Total T3

#### Principle of the procedure:

Immulite Total T3 is a solid phase, competitive chemiluminescent enzyme immunoassay (automated system).

#### Assay:

The test unit contains one bead coated with monoclonal murine anti-T3 antibody. The sample (25  $\mu$ l plasma) was added to the bead together with the test reagent (alkaline phosphatase conjugated to T3 in buffer). After a 30 min incubation cycle, the chemiluminescent substrate was added and the signal was measured. The calibration curve covers a range from 40 to 600 ng/dL.

### 2.3.3 Total T4

#### Principle of the procedure:

Immulite Total T4 is a solid phase, competitive chemiluminescent enzyme immunoassay (automated system).

#### Assay:

The test unit contains one bead coated with monoclonal murine anti-T4 antibody. The sample (15  $\mu$ l plasma) was added to the bead together with the test reagent (alkaline phosphatase conjugated to T4 in buffer). After a 30 min incubation cycle, the chemiluminescent substrate was added and the signal was measured. The calibration curve covers a range from 1.0 to 24  $\mu$ g/dL.

### **2.3.4 Free T3**

#### **Principle of the procedure:**

Immulite Free T3 is a solid phase, competitive chemiluminescent enzyme immunoassay (automated system).

#### **Assay:**

The test unit contains one bead coated with monoclonal murine anti-T3 antibody. The sample (100 µl plasma) was added to the bead together with two test reagents (a: ligand labelled T3 analog in buffer, b: alkaline phosphatase conjugated to anti-ligand in buffer). After a 60 min incubation cycle, the chemiluminescent substrate was added and the signal was measured. The calibration curve covers a range from 1 to 50 pg/mL.

### **2.3.5 Free T4**

#### **Principle of the procedure:**

Immulite Free T4 is a solid phase, competitive chemiluminescent enzyme immunoassay (automated system).

#### **Assay:**

The test unit contains one bead coated with monoclonal murine anti-T4 antibody. The sample (10 µl plasma) was added to the bead together with two test reagents (a: ligand labelled T4 analog in buffer, b: alkaline phosphatase conjugated to anti-ligand in buffer). After a 60 min incubation cycle, the chemiluminescent substrate was added and the signal was measured. The calibration curve covers a range from 0.3 - 6 ng/dL.

## 2.4 CALCULATION OF RESULTS

The standard curves were based on the 4PL algorithm (four parameter logistic) of the Immulite software. Based on these standard curves, the hormone contents in the unknown samples were determined.

## 2.5 DATA ANALYSIS

The Dunnett-test (many to one t-test) based on a pooled variance estimate was applied for the comparison of the results of the treated groups and the control group (significance level:  $p = 0.05$ ).

## 2.6 SAMPLE STORAGE

After arrival at the Environmental Chemistry & Pharamalytics of RCC, the samples were stored frozen at approximately  $-80\text{ }^{\circ}\text{C}$  and protected from light until analyses were performed.

## 3 RESULTS AND DISCUSSION

The results of the hormone determinations are presented in Tables 1-10. Except for free T3, all measurements were performed in duplicate. Individual mean values and group means were presented. There was not enough plasma volume available to perform the free T3 measurements in duplicate.

### 3.1 TSH

#### Males (Table 1)

No differences between groups 1 to 4 were observed. Average values for all groups ranged from 0.046  $\mu$ IU/mL (group 2) to 0.115  $\mu$ IU/mL (group 3).

#### Females (Table 2)

No differences between groups 1 to 4 were observed. Average values for all groups ranged from 0.028  $\mu$ IU/mL (group 4) to 0.043  $\mu$ IU/mL (group 3).

### 3.2 TOTAL T3

#### Males (Table 3)

No differences between groups 1 to 4 were observed. Average values ranged from 141.2 ng/dL (group 1) to 160.8 ng/dL (group 4).

#### Females (Table 4)

No differences between groups 1 to 4 were observed. Average values ranged from 108.9 ng/dL (group 3) to 126.6 ng/dL (group 1).

### 3.3 TOTAL T4

#### Males (Table 5)

No differences between groups 1 to 4 were observed. Average values ranged from 6.47  $\mu$ g/dL (group 1) to 7.22  $\mu$ g/dL (group 2).

#### Females (Table 6)

No differences between groups 1 to 4 were observed. Average values ranged from 4.05  $\mu$ g/dL (group 1) to 4.71  $\mu$ g/dL (group 3).

### **3.4 FREE T3**

#### **Males (Table 7)**

No differences between groups 1 to 4 were observed. Average values ranged from 1.7 pg/mL (groups 1 and 4) to 2.1 pg/mL (group 3).

#### **Females (Table 8)**

No differences between groups 1 to 4 were observed. Average values ranged from 1.8 pg/mL (group 4) to 2.2 pg/mL (groups 2 and 3).

### **3.5 FREE T4**

#### **Males (Table 9)**

No differences between groups 1 to 4 were observed. Average values ranged from 3.30 ng/dL (group 3) to 3.70 ng/dL (group 4).

#### **Females (Table 10)**

No differences between groups 1 to 4 were observed. Average values ranged from 2.05 ng/dL (group 1) to 2.76 ng/dL (group 4).

## 4 TABLES

Table 1: TSH levels in plasma of male rats

Immulin TSH

| Group | Animal No. | Values (µIU/ml) | Mean ± SD           |
|-------|------------|-----------------|---------------------|
| Gr 1  | 11         | 0.059           | 0.083<br>±<br>0.036 |
|       | 12         | 0.058           |                     |
|       | 13         | 0.076           |                     |
|       | 14         | 0.147           |                     |
|       | 15         | 0.078           |                     |
| Gr 2  | 26         | 0.038           | 0.046<br>±<br>0.019 |
|       | 27         | 0.059           |                     |
|       | 28         | 0.059           |                     |
|       | 29         | 0.061           |                     |
|       | 30         | 0.017           |                     |
| Gr 3  | 41         | 0.044           | 0.115<br>±<br>0.133 |
|       | 42         | 0.078           |                     |
|       | 43         | 0.065           |                     |
|       | 44         | 0.037           |                     |
|       | 45         | 0.352           |                     |
| Gr 4  | 56         | 0.144           | 0.106<br>±<br>0.027 |
|       | 57         | 0.120           |                     |
|       | 58         | 0.075           |                     |
|       | 59         | 0.088           |                     |
|       | 60         | 0.102           |                     |



Table 2: TSH levels in plasma of female rats

## Immulite TSH

| Group | Animal No. | Values (µIU/ml) | Mean ± SD           |
|-------|------------|-----------------|---------------------|
| Gr 1  | 71         | 0.035           | 0.039<br>±<br>0.008 |
|       | 72         | 0.043           |                     |
|       | 73         | 0.043           |                     |
|       | 74         | 0.046           |                     |
|       | 75         | 0.027           |                     |
| Gr 2  | 86         | 0.024           | 0.041<br>±<br>0.027 |
|       | 87         | 0.043           |                     |
|       | 88         | 0.018           |                     |
|       | 89         | 0.085           |                     |
|       | 90         | 0.034           |                     |
| Gr 3  | 101        | 0.027           | 0.043<br>±<br>0.016 |
|       | 102        | 0.033           |                     |
|       | 103        | 0.069           |                     |
|       | 104        | 0.045           |                     |
|       | 105        | 0.043           |                     |
| Gr 4  | 116        | 0.053           | 0.028<br>±<br>0.014 |
|       | 117        | 0.023           |                     |
|       | 118        | 0.028           |                     |
|       | 119        | 0.021           |                     |
|       | 120        | 0.018           |                     |

Table 3: Total T3 levels in plasma of male rats

Immulin total T3

| Group | Animal No. | Values (ng/dL) | Mean ± SD          |
|-------|------------|----------------|--------------------|
| Gr 1  | 11         | 128.5          | 141.2<br>±<br>9.1  |
|       | 12         | 147.5          |                    |
|       | 13         | 140.0          |                    |
|       | 14         | 138.0          |                    |
|       | 15         | 152.0          |                    |
| Gr 2  | 26         | 152.0          | 149.6<br>±<br>14.9 |
|       | 27         | 154.5          |                    |
|       | 28         | 170.0          |                    |
|       | 29         | 130.5          |                    |
|       | 30         | 141.0          |                    |
| Gr 3  | 41         | 141.5          | 160.8<br>±<br>12.3 |
|       | 42         | 159.0          |                    |
|       | 43         | 174.5          |                    |
|       | 44         | 162.0          |                    |
|       | 45         | 167.0          |                    |
| Gr 4  | 56         | 162.0          | 142.8<br>±<br>27.4 |
|       | 57         | 124.5          |                    |
|       | 58         | 131.5          |                    |
|       | 59         | 180.5          |                    |
|       | 60         | 115.5          |                    |

Table 4: Total T3 levels in plasma of female rats

Immulite total T3

| Group | Animal No. | Values (ng/dL) | Mean ± SD          |
|-------|------------|----------------|--------------------|
| Gr 1  | 71         | 114.5          | 113.1<br>±<br>8.4  |
|       | 72         | 107.5          |                    |
|       | 73         | 127.0          |                    |
|       | 74         | 106.0          |                    |
|       | 75         | 110.5          |                    |
| Gr 2  | 86         | 140.5          | 121.6<br>±<br>17.5 |
|       | 87         | 105.5          |                    |
|       | 88         | 101.2          |                    |
|       | 89         | 126.0          |                    |
|       | 90         | 135.0          |                    |
| Gr 3  | 101        | 127.0          | 108.9<br>±<br>12.5 |
|       | 102        | 114.0          |                    |
|       | 103        | 106.5          |                    |
|       | 104        | 103.0          |                    |
|       | 105        | 93.9           |                    |
| Gr 4  | 116        | 120.5          | 126.6<br>±<br>24.9 |
|       | 117        | 132.0          |                    |
|       | 118        | 95.1           |                    |
|       | 119        | 164.0          |                    |
|       | 120        | 121.5          |                    |

Table 5: Total T4 levels in plasma of male rats

Immulite total T4

| Group | Animal No. | Values (µg/dL) | Mean ± SD         |
|-------|------------|----------------|-------------------|
| Gr 1  | 11         | 6.50           | 6.47<br>±<br>0.33 |
|       | 12         | 6.45           |                   |
|       | 13         | 7.00           |                   |
|       | 14         | 6.15           |                   |
|       | 15         | 6.25           |                   |
| Gr 2  | 26         | 8.00           | 7.22<br>±<br>1.08 |
|       | 27         | 7.25           |                   |
|       | 28         | 7.40           |                   |
|       | 29         | 5.40           |                   |
|       | 30         | 8.05           |                   |
| Gr 3  | 41         | 7.20           | 6.94<br>±<br>1.49 |
|       | 42         | 5.80           |                   |
|       | 43         | 9.35           |                   |
|       | 44         | 5.65           |                   |
|       | 45         | 6.70           |                   |
| Gr 4  | 56         | 6.80           | 6.60<br>±<br>0.91 |
|       | 57         | 7.35           |                   |
|       | 58         | 5.70           |                   |
|       | 59         | 7.55           |                   |
|       | 60         | 5.60           |                   |

Table 6: Total T4 levels in plasma of female rats

Immulin total T4

| Group | Animal No. | Values (µg/dL) | Mean ± SD         |
|-------|------------|----------------|-------------------|
| Gr 1  | 71         | 2.85           | 4.05<br>±<br>0.93 |
|       | 72         | 4.45           |                   |
|       | 73         | 4.25           |                   |
|       | 74         | 3.45           |                   |
|       | 75         | 5.25           |                   |
| Gr 2  | 86         | 4.80           | 4.06<br>±<br>0.52 |
|       | 87         | 3.70           |                   |
|       | 88         | 3.45           |                   |
|       | 89         | 4.25           |                   |
|       | 90         | 4.10           |                   |
| Gr 3  | 101        | 5.30           | 4.71<br>±<br>0.50 |
|       | 102        | 4.35           |                   |
|       | 103        | 5.10           |                   |
|       | 104        | 4.70           |                   |
|       | 105        | 4.10           |                   |
| Gr 4  | 116        | 5.15           | 4.53<br>±<br>0.93 |
|       | 117        | 4.60           |                   |
|       | 118        | 3.55           |                   |
|       | 119        | 5.70           |                   |
|       | 120        | 3.65           |                   |

Table 7: Free T3 levels in plasma of male rats

Immulate free T3

| Group | Animal No. | Values (pg/mL) | Mean ± SD       |
|-------|------------|----------------|-----------------|
| Gr 1  | 11         | 1.7            | 1.7<br>±<br>0.6 |
|       | 12         | 2.7            |                 |
|       | 13         | 1.1            |                 |
|       | 14         | 1.4            |                 |
|       | 15         | 1.4            |                 |
| Gr 2  | 26         | 2.2            | 1.8<br>±<br>0.5 |
|       | 27         | 2.2            |                 |
|       | 28         | 1.7            |                 |
|       | 29         | 2.0            |                 |
|       | 30         | 1.0            |                 |
| Gr 3  | 41         | 1.1            | 2.1<br>±<br>0.6 |
|       | 42         | 2.3            |                 |
|       | 43         | 2.4            |                 |
|       | 44         | 2.3            |                 |
|       | 45         | 2.4            |                 |
| Gr 4  | 56         | 1.5            | 1.7<br>±<br>0.4 |
|       | 57         | 1.1            |                 |
|       | 58         | 1.5            |                 |
|       | 59         | 2.2            |                 |
|       | 60         | 2.0            |                 |

Table 8: Free T3 levels in plasma of female rats

Immulin free T3

| Group | Animal No. | Values (pg/mL) | Mean ± SD       |
|-------|------------|----------------|-----------------|
| Gr 1  | 71         | 2.4            | 2.1<br>±<br>0.3 |
|       | 72         | 2.2            |                 |
|       | 73         | 1.7            |                 |
|       | 74         | 1.9            |                 |
|       | 75         | 2.1            |                 |
| Gr 2  | 86         | 2.4            | 2.2<br>±<br>0.4 |
|       | 87         | 2.4            |                 |
|       | 88         | 1.7            |                 |
|       | 89         | 2.6            |                 |
|       | 90         | 1.8            |                 |
| Gr 3  | 101        | 2.0            | 2.2<br>±<br>0.3 |
|       | 102        | 2.7            |                 |
|       | 103        | 2.3            |                 |
|       | 104        | 1.8            |                 |
|       | 105        | 2.3            |                 |
| Gr 4  | 116        | 2.1            | 1.8<br>±<br>0.4 |
|       | 117        | 1.7            |                 |
|       | 118        | 1.1            |                 |
|       | 119        | 2.1            |                 |
|       | 120        | 1.8            |                 |

Table 9: Free T4 levels in plasma of male rats

Immulite free T4

| Group | Animal No. | Values (ng/dL) | Mean ± SD         |
|-------|------------|----------------|-------------------|
| Gr 1  | 11         | 3.65           | 3.43<br>±<br>0.29 |
|       | 12         | 3.45           |                   |
|       | 13         | 3.45           |                   |
|       | 14         | 2.95           |                   |
|       | 15         | 3.65           |                   |
| Gr 2  | 26         | 3.90           | 3.59<br>±<br>0.77 |
|       | 27         | 3.65           |                   |
|       | 28         | 3.40           |                   |
|       | 29         | 2.45           |                   |
|       | 30         | 4.55           |                   |
| Gr 3  | 41         | 2.85           | 3.30<br>±<br>0.68 |
|       | 42         | 2.80           |                   |
|       | 43         | 4.45           |                   |
|       | 44         | 3.00           |                   |
|       | 45         | 3.40           |                   |
| Gr 4  | 56         | 3.85           | 3.70<br>±<br>0.31 |
|       | 57         | 3.80           |                   |
|       | 58         | 3.65           |                   |
|       | 59         | 4.00           |                   |
|       | 60         | 3.20           |                   |



Table 10: Free T4 levels in plasma of female rats

Immulite free T4

| Group | Animal No. | Values (ng/dL) | Mean ± SD         |
|-------|------------|----------------|-------------------|
| Gr 1  | 71         | 1.70           | 2.05<br>±<br>0.36 |
|       | 72         | 2.60           |                   |
|       | 73         | 1.80           |                   |
|       | 74         | 1.95           |                   |
|       | 75         | 2.20           |                   |
| Gr 2  | 86         | 2.30           | 2.15<br>±<br>0.36 |
|       | 87         | 1.85           |                   |
|       | 88         | 1.85           |                   |
|       | 89         | 2.70           |                   |
|       | 90         | 2.05           |                   |
| Gr 3  | 101        | 3.00           | 2.76<br>±<br>0.51 |
|       | 102        | 2.50           |                   |
|       | 103        | 3.55           |                   |
|       | 104        | 2.45           |                   |
|       | 105        | 2.30           |                   |
| Gr 4  | 116        | 2.80           | 2.32<br>±<br>0.43 |
|       | 117        | 2.65           |                   |
|       | 118        | 1.90           |                   |
|       | 119        | 2.40           |                   |
|       | 120        | 1.85           |                   |

# **RCC Study Number 857092**

Repeated Dose 90-Day Oral Toxicity Study  
with

**2-Amino-4-Hydroxyethyl-  
aminoanisoie Sulfate  
(A084, WR 23081)**

in Wistar Rats

**Final Report (Part III of III)**

Date of Issue: 20 July 2005  
Page 386 of 629  
Total Number of Pages: 629



**APPENDIX VII:**

**PHASE REPORT: PATHOLOGY**

| <b>PATHOLOGY REPORT</b> |  | <b>RCC STUDY NUMBER 857092</b> |             |
|-------------------------|--|--------------------------------|-------------|
| <b>TEST ITEM</b>        | : 2-AMINO-4-HYDROXYETHYL-AMINOANISOLE SULFATE (A084, WR 23081) | <b>PATH. NO</b>                | : 80076NED  |
| <b>TEST SYSTEM</b>      | : WISTAR RAT   | <b>DATE</b>                    | : 19-JUL-05 |
| <b>STUDY TYPE</b>       | : REPEATED DOSE 90-DAY ORAL TOXICITY STUDY                     | <b>SPONSOR</b>                 | : WELLA AG  |

Prepared by:

Dr. D. Nehrbass  
Veterinary Pathologist

|             |                             |           |             |
|-------------|-----------------------------|-----------|-------------|
| TEST ITEM   | : A084, WR 23081            | PATH. NO. | : 80076 NED |
| TEST SYSTEM | : RAT, 90-DAY ORAL (GAVAGE) | DATE      | : 19-JUL-05 |
| SPONSOR     | : WELLA AG                  |           |             |

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<sup>1</sup> Animal organ finding table

TEST ITEM : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY ORAL (GAVAGE)  
SPONSOR : WELLA AG


PATH. NO. : 80076 NED  
DATE : 19-JUL-05

**AUTHENTICATION**

I, the undersigned hereby declare that the histopathology data (Principal Section and Tables) in this report were compiled by me, and that they accurately reflect the primary data records.


Prepared by:

Dr. D. Nehrbass  
Veterinary Pathologist

  
.....  
date: 19-Jul-05

Cross-checked by:

 K. Weber, PhD  
Toxicologic Pathologist

  
.....  
date: 19-Jul-2005

## PRINCIPAL SECTION

RCC STUDY NUMBER 857092

TEST ITEM : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATH. NO. : 80076 NED  
DATE : 19-JUL-05

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**SUMMARY**

The purpose of this oral toxicity study was to assess the cumulative toxicity of 2-Amino-4-Hydroxyethylaminoanisole Sulfate (A084, WR 23081) when administered to rats via gavage for a period of at least 13 weeks. This study should provide a rational basis for risk assessment in man and should indicate potential target organs.

Eighty rats, HanBrl:WIST(SPF), were assigned to four dose groups each containing 10 animals per sex (allocation A). Additional five animals per sex were available in all groups for hormone testing (allocation B). The test item was administered daily at doses of 15, 50, and 200 mg/kg (groups 2, 3, and 4, respectively). The control group received the vehicle, bidistilled water, alone.

At the end of the treatment period, all animals were weighed, sacrificed, necropsied and examined *post mortem*. Histological examinations were performed on all study plan organs and tissues from all allocation A animals, the thyroid of all allocation B animals, and all gross lesions from all animals were examined by the study pathologist.

---

There were no premature deaths, all animals survived the scheduled study period.

At necropsy, performed at the end of treatment period, a dark red or black discoloration of the thyroid was recorded in most animals of groups 3 and 4, which was assessed as a test item-related gross lesion.

Histopathologically, test item-related changes were recorded at thyroid, pituitary, kidneys, and spleen.

At the thyroid, follicular cell enlargement due to minimal to slight cytoplasmic storage of brown, fine-granular pigment, and increased cytoplasmic vacuolation was recorded in animals of groups 3 and 4.

At the pituitary, minimal to slight hypertrophy of chromophobic cells was recorded in males of groups 3 and 4.

At the kidneys, pigment storage in vacuolar basophilic tubulus cells was recorded in most test item-treated groups except females of group 2. However, in males of group 2, this change was considered of non-adverse character, because of minimal severity, low incidence, and lack of clinical relevance. Additionally, minimal to slight vacuolar tubulus cell swelling of non-adverse character at the corticomedullary junction along with cytoplasmic storage of brown fine-granular pigment was recorded in females of all test item-treated groups. Furthermore, brown pigment in "normal" (non-swollen, non-basophilic) tubulus cells, and minimal brown pigmented tubular casts were recorded in males of group 4.

At the spleen, increased mean grade of extra medullary hemopoiesis in combination with slightly increased mean grade of hemosiderin storage was recorded in animals of group 4.

Under the conditions of this experiment, the test item 2-Amino-4-Hydroxyethylaminoanisole Sulfate (A084, WR 23081) produced morphological changes in thyroid, pituitary, kidneys, and spleen.

According to the results of pathology a No-Observed-Adverse Effect-Level (NOAEL) may be established at 15 mg/kg/day.

## PRINCIPAL SECTION

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## MATERIALS AND METHODS

## Group Allocation

| Allocation  | Group 1    | Group 2   | Group 3   | Group 4   |
|-------------|------------|-----------|-----------|-----------|
| And         | 0          | 15        | 50        | 200       |
| Dose Levels | mg/kg/day* | mg/kg/day | mg/kg/day | mg/kg/day |
| Males A     | 1 – 10     | 16 – 25   | 31 – 40   | 46 – 55   |
| Males B     | 11 – 15    | 26 – 30   | 41 – 45   | 56 – 60   |
| Females A   | 61 – 70    | 76 – 85   | 91 – 100  | 106 – 115 |
| Females B   | 71 – 75    | 86 – 90   | 101 – 105 | 116 – 120 |

A – Toxicity testing (termination after 13 treatment weeks)

B – Hormone testing (termination after 13 treatment weeks, histopathologically only thyroid investigated)

\* – Control animals were treated with the vehicle, bidistilled water, only

## Necropsy

Necropsies were performed at RCC Ltd, Itingen / Switzerland. At the end of the treatment period all animals were weighed, anesthetized by intraperitoneal injection of pentobarbitone, sacrificed by exsanguination, and necropsied. Descriptions of all macroscopic abnormalities were recorded. Samples of the following tissues and organs were collected from all animals at necropsy and, unless otherwise indicated, fixed in neutral phosphate buffered 4% formaldehyde solution.

## Adrenal glands

## Aorta

Bone (sternum, femur including joint)

Bone marrow (femur)

Brain (generally 4 levels)

Cecum

Colon

Duodenum

Epididymides (fixed in Bouin's solution)

Esophagus

Exorbital lacrimal glands

Eyes with optic nerve (fixed in Davidson's solution)

Harderian gland (fixed in Davidson's solution)

Heart

Ileum, with Peyer's patches

Jejunum, with Peyer's patches

Kidneys

Larynx

Lacrimal gland, exorbital

Liver

Lungs, Infused with formalin at necropsy

Lymph nodes - mesenteric, mandibular

Mammary gland area

Nasal cavity (turbinates)

Ovaries

Pancreas

Pituitary gland

Prostate gland (incl. coagulating glands)

Rectum

Salivary glands - mandibular, sublingual

Sciatic nerve

Seminal vesicles

Skeletal muscle

Skin

Spinal cord - cervical, midthoracic, lumbar

Spleen

Stomach

Testes (fixed in Bouin's solution)

Thymus

Thyroid (Including parathyroid gland, if possible)

Tongue

Trachea

Urinary bladder, Infused with formalin at necropsy

Uterus

Vagina

Gross lesions



## PRINCIPAL SECTION

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**Histopathology**

Histological preparation of the tissues were performed at RCC Ltd, Itingen / Switzerland. Slides of all organs and tissues collected at necropsy (see list above) from all allocation A animals, as well as thyroid glands of the allocation B animals, and all gross lesions from all animals of all groups were processed, embedded in paraffin, cut at a nominal thickness of 2-4 micrometers, stained with hematoxylin & eosin (H&E) and examined by light microscope by the study pathologist.

**Data Compilation**

The animal data and necropsy findings were recorded on RCC-TOX Release 7.0, RCC Ltd, and were transferred electronically via transfer file into the PathData System V6.2.

The microscopic findings were recorded during histopathologic examination by the pathologist and entered directly into the PathData System. The slides were evaluated during April 2005.

Histological changes were described, wherever possible, according to distribution, severity and morphologic character. Severity scores were assigned as given under "Explanation of Codes and Symbols". In paired organs, findings occurred sometimes bilaterally and were of different degrees of severity. When this occurred, the higher degree was recorded and comment was made which indicated the severity of the lesion in the contra lateral organ.

All microscopic findings are listed in the "TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS" (= AOFT, animal organ finding table), along with an explanation of the codes and symbols used. Computer-generated incidence tables derived from these data are also presented as well as the complete narrative of the both macroscopic and microscopic findings.

**Data Cross Checking and Peer Review**

Selected sections of the kidneys, thyroid, and pituitary were reviewed by Dr. K. Weber (Head of Pathology Unit, RCC Ltd, Itingen / Switzerland). The assessment of the study pathologist and reviewing pathologist compared favorably.

A Peer Review was performed on June 21<sup>st</sup> – 22<sup>nd</sup>, 2005. Designated peer reviewing pathologist was Dr. Albert Mihaly Ph.D. (Egis Pharmaceuticals Ltd, Budapest / Hungary). All sections of the kidneys, thyroid gland, spleen, and bone marrow were reviewed. Following the Peer Review of the microscopic findings, the results were discussed and appropriate terminology and diagnoses agreed on. The documentation of this Peer Review is archived with the raw data of this study.

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|             |                             |           |             |
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## RESULTS

### Mortality

There were no premature deaths. All animals on study survived the scheduled study period.

### Organ Weights

Increased in organ/brain weight ratios which correlated to microscopic findings and indicating an effect of the test item were recorded in:

- thyroid (in animals of group 4, statistically not significant)
- kidneys (statistically significant in females of group 4,  $p < 0.01$ )
- spleen (statistically significant in females of group 4,  $p < 0.01$ )

A few other statistically significant deviations in average organ weights at the end of treatment period were considered to be incidental, reflecting the usual individual variability.

### Macroscopic Findings

At the end of the treatment period a dark red or black discoloration of the thyroid was recorded in most animals of groups 3 and 4 (14/15 males and 7/15 females of group 3; 13/15 males and 14/15 females of group 4). This change was assessed as a test item-related gross lesion.

All other macroscopic findings recorded were considered to be within the range of normal background lesions, which may be seen in rats of this strain and age in oral toxicity studies and were considered incidental, reflecting the usual individual variability. They consisted of renal pelvic dilation, eschars at the skin (nose region), alopecia (shoulder region), watery cyst(s) at the ovaries, and watery contents in the uterus (often combined with dilation of the organ), as well as discoloration or discolored foci in various organs (lungs, stomach, cecum, pancreas, thymus, mandibular lymph node, extraorbital lacrimal glands, ovaries, uterus).

### Microscopic Findings

There were a number of findings, which distinguished test item-treated animals from controls.

#### thyroid:

- Follicular cell enlargement<sup>2</sup> due to minimal to slight cytoplasmic storage of brown, fine-granular pigment, partly along with minimally to slightly increased cytoplasmic vacuolation in animals of groups 3 and 4. This change was more pronounced in male animals (allocation A and B cumulated: 12/15 males and 6/15 females of group 3; 14/15 males and 11/15 females of group 4).

#### pituitary:

- Minimal to slight hypertrophy/plasia of chromophobic cells (characterized by increased cell size and increased vacuolation) in males of groups 3 and 4 (7/10 males of group 3; 6/10 males of group 4; this change was also recorded in 1/10 males of group 1 [control] and 2/10 males of group 2).

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<sup>2</sup>: in the table part reported as "follicular cell hypertrophy"

## PRINCIPAL SECTION

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**kidneys:**

- Pigment storage in vacuolar basophilic tubulus cells was recorded in most test item-treated groups except females of group 2 (3/10 males of group 2; 6/10 males and 3/10 females of group 3; 8/10 males and 6/10 females of group 4).
- Minimal to slight vacuolar tubulus cell swelling at the corticomedullary junction (5/10 females of group 2; 6/10 females of group 3; 9/10 females of group 4), along with minimal to slight cytoplasmic storage of brown fine-granular pigment in females of all test item-treated groups. In animals of group 4, this change was sometimes accompanied by necrosis of single tubulus cells, and thickened basal membranes.
- Minimal storage of brown pigment in "normal" (non-swollen, non-basophilic) tubulus cells, and minimal brown pigmented tubular casts in 3/10 males of group 4.

**spleen:**

- Increased mean grade of extra medullary hemopoiesis in combination with slightly increased mean grade of hemosiderin storage in animals of group 4. This change was more pronounced in female animals.

**Incidental microscopic findings**

Additionally, a variety of other changes were found in this study. They commonly occur in laboratory rats of this strain and age under the conditions of oral toxicity studies. Neither their incidences nor their distribution or morphologic appearance gave any indication of a treatment-related association. The detailed incidence data for all organs as well as tables of selected changes including their severity appear in "SUMMARY INCIDENCE OF GRADINGS" and "NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS".

**CONCLUSIONS**

Under the conditions of this study, the test item 2-Amino-4-Hydroxyethylaminoanisoole Sulfate (A084, WR 23081) induced histopathological changes in thyroid, pituitary, kidneys, and spleen.

At the thyroid, a follicular cell enlargement due to cytoplasmic storage of brown fine-granular pigment, partly along with increased cytoplasmic vacuolation was recorded in animals of groups 3 and 4. The brown pigment was deemed to be the histological correlate of the test item, and correlated to a dark red or black discoloration of the organ and to a slightly increased mean organ weight (statistically not significant) both recorded at necropsy. Hormone testing did not reveal increased serum levels of thyroid hormones (TSH, total T3, total T4, free T3, free T4). So the enlargement of the follicular cells was not accompanied by increased hormone production, but caused by the storage of the test item. Pathomechanistically, these changes were probably caused by an interaction of the test item, a dye stuff with anisol core, with thyroid hormones or its precursors (= iodinated tyrosines), which share some structural similarities. The thyroid changes were assessed as effects of the test item which predict an adverse effect on the thyroid.

At the pituitary, minimal to slight hypertrophy/plasia of chromophobic cells (characterized by increased cell size and increased vacuolation) was recorded in males of groups 3 and 4. These chromophobic pituitary cells most likely represent hyperfunctional degranulated basophilic cells which produced TSH (thyreotropin). As TSH stimulates the subordinated thyroid follicle cells, a pathomechanistic relationship between the pituitary and thyroid changes can not be excluded.

## PRINCIPAL SECTION

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At the kidneys, pigment storage in vacuolar basophilic tubulus cells was recorded in most test item-treated groups except females of group 2. This renal change was assessed as an adverse effect in group 3 and 4. However, in males of group 2, this change was considered to be of non-adverse character because of minimal severity, low number of animals affected (3/10 males), and lack of clinical relevance. Additionally, a non-adverse, minimal to slight vacuolar tubulus cell swelling at the corticomedullary junction was recorded in females of all test item-treated groups. In animals of group 4, this change was sometimes accompanied by necrosis of single tubulus cells, and thickened basal membranes. These histopathological changes were accompanied by an increased organ weight recorded at necropsy in females of group 4, and by changes recorded by blood chemistry (increased sodium, increased chloride partly potassium) and by urinalysis (yellow/brown to black discoloration). Furthermore, brown pigment in "normal" (non-swollen, non-basophilic) tubulus cells, and minimal brown pigmented tubular casts were recorded in males of group 4. The origin of the brown pigment could be either endogenous (hemosiderin, lipofuscin, or bilirubin) or exogenous (test item). Pathomechanistically, the basophilic tubulus cells were assessed as regeneration after an preceding tubular damage starting with vacuolar tubulus cell swelling induced by the pigment stored in the cytoplasm.

At the spleen, an increased extramedullary hemopoiesis in combination with slightly increased hemosiderin storage was recorded in animals of group 4. This change, which was more pronounced in female animals and correlated to an increased organ weight recorded at necropsy and was accompanied by alterations recorded by hematology in animals of group 4 (decreased RBC, decreased MCHC [females only], increased MCV, increased reticulocytes). Summarized, these changes reflected a slight macrocytic, partly hypochromatic, regenerative anemia in animals of group 4. Pathomechanistically, the reason for these changes were unclear.

According to the results of pathology a No-Observed-Adverse Effect-Level (NOAEL) may be established. at 15 mg/kg/day.

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SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K0  
SELECTED FINDINGS (ALL GRADINGS)

| SEX :                   | MALE |     |     |     |
|-------------------------|------|-----|-----|-----|
| DOSE GROUP:             | 01   | 02  | 03  | 04  |
| NO. ANIMALS:            | 10   | 10  | 10  | 10  |
| <hr/>                   |      |     |     |     |
| KIDNEYS :               | 10   | 10  | 10  | 10  |
| - Pigment tubul. cells  |      |     |     |     |
| GRADE 1 :               | -    | -   | -   | 3   |
| TOTAL AFFECTED :        | -    | -   | -   | 3   |
| MEAN SEVERITY :         | -    | -   | -   | 1.0 |
| .....                   |      |     |     |     |
| - Tubular basophilia    |      |     |     |     |
| GRADE 1 :               | 5    | 8   | 8   | 4   |
| GRADE 2 :               | -    | -   | -   | 4   |
| TOTAL AFFECTED :        | 5    | 8   | 8   | 8   |
| MEAN SEVERITY :         | 1.0  | 1.0 | 1.0 | 1.5 |
| .....                   |      |     |     |     |
| - Pigment basoph. cells |      |     |     |     |
| GRADE 1 :               | -    | 3   | 6   | 8   |
| TOTAL AFFECTED :        | -    | 3   | 6   | 8   |
| MEAN SEVERITY :         | -    | 1.0 | 1.0 | 1.0 |
| .....                   |      |     |     |     |
| - Pigment. tubul. casts |      |     |     |     |
| GRADE 1 :               | -    | -   | -   | 3   |
| TOTAL AFFECTED :        | -    | -   | -   | 3   |
| MEAN SEVERITY :         | -    | -   | -   | 1.0 |
| <hr/>                   |      |     |     |     |
| PITUITARY GLAND :       | 10   | 10  | 10  | 10  |
| - Hypertr/pl. chromoph. |      |     |     |     |
| GRADE 1 :               | 1    | 2   | 2   | 6   |
| GRADE 2 :               | -    | -   | 5   | -   |
| TOTAL AFFECTED :        | 1    | 2   | 7   | 6   |
| MEAN SEVERITY :         | 1.0  | 1.0 | 1.7 | 1.0 |

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SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K0  
SELECTED FINDINGS (ALL GRADINGS)

| SEX :                 | MALE |     |     |     |
|-----------------------|------|-----|-----|-----|
| DOSE GROUP:           | 01   | 02  | 03  | 04  |
| NO. ANIMALS:          | 10   | 10  | 10  | 10  |
| <hr/>                 |      |     |     |     |
| THYROID GLAND :       | 10   | 10  | 10  | 10  |
| - Pigment storage     |      |     |     |     |
| GRADE 1 :             | -    | -   | 5   | -   |
| GRADE 2 :             | -    | -   | 5   | 1   |
| GRADE 3 :             | -    | -   | -   | 7   |
| GRADE 4 :             | -    | -   | -   | 2   |
| TOTAL AFFECTED :      | -    | -   | 10  | 10  |
| MEAN SEVERITY :       | -    | -   | 1.5 | 3.1 |
| .....                 |      |     |     |     |
| - Incr. vacuolation   |      |     |     |     |
| GRADE 1 :             | -    | -   | 1   | 6   |
| GRADE 2 :             | -    | -   | -   | 3   |
| TOTAL AFFECTED :      | -    | -   | 1   | 9   |
| MEAN SEVERITY :       | -    | -   | 1.0 | 1.3 |
| .....                 |      |     |     |     |
| - Follic. hypertrophy |      |     |     |     |
| GRADE 1 :             | -    | 1   | 8   | 5   |
| GRADE 2 :             | -    | -   | -   | 4   |
| TOTAL AFFECTED :      | -    | 1   | 8   | 9   |
| MEAN SEVERITY :       | -    | 1.0 | 1.0 | 1.4 |
| <hr/>                 |      |     |     |     |
| SPLEEN :              | 10   | 10  | 10  | 10  |
| - Extram. hemopoiesis |      |     |     |     |
| GRADE 1 :             | 4    | 5   | 5   | 3   |
| GRADE 2 :             | -    | 1   | 2   | 6   |
| GRADE 3 :             | -    | -   | -   | 1   |
| TOTAL AFFECTED :      | 4    | 6   | 7   | 10  |
| MEAN SEVERITY :       | 1.0  | 1.2 | 1.3 | 1.8 |
| .....                 |      |     |     |     |

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**SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K0  
SELECTED FINDINGS (ALL GRADINGS)**

|               |                  |     |     |     |     | MALE |
|---------------|------------------|-----|-----|-----|-----|------|
| SEX :         |                  |     |     |     |     |      |
| DOSE GROUP:   |                  | 01  | 02  | 03  | 04  |      |
| NO. ANIMALS:  |                  | 10  | 10  | 10  | 10  |      |
| SPLEEN        | CONT'D.          | 10  | 10  | 10  | 10  |      |
| - Hemosiderin |                  |     |     |     |     |      |
|               | GRADE 1 :        | 5   | 6   | 9   | 5   |      |
|               | GRADE 2 :        | 4   | -   | 1   | 4   |      |
|               | GRADE 3 :        | -   | -   | -   | 1   |      |
|               | TOTAL AFFECTED : | 9   | 6   | 10  | 10  |      |
|               | MEAN SEVERITY :  | 1.4 | 1.0 | 1.1 | 1.6 |      |

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**SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX**  
**STATUS AT NECROPSY: K0**  
**SELECTED FINDINGS (ALL GRADINGS)**

| SEX :                   | FEMALE |     |     |     |
|-------------------------|--------|-----|-----|-----|
| DOSE GROUP:             | 01     | 02  | 03  | 04  |
| NO. ANIMALS:            | 10     | 10  | 10  | 10  |
| <hr/>                   |        |     |     |     |
| KIDNEYS :               | 10     | 10  | 10  | 10  |
| - Tubulus cell swell.   |        |     |     |     |
| GRADE 1 :               | -      | 5   | 6   | 1   |
| GRADE 2 :               | -      | -   | -   | 7   |
| GRADE 3 :               | -      | -   | -   | 1   |
| TOTAL AFFECTED :        | -      | 5   | 6   | 9   |
| MEAN SEVERITY :         | -      | 1.0 | 1.0 | 2.0 |
| .....                   |        |     |     |     |
| - Pigment tubul. cells  |        |     |     |     |
| GRADE 1 :               | -      | 4   | 5   | 8   |
| GRADE 2 :               | -      | -   | -   | 1   |
| TOTAL AFFECTED :        | -      | 4   | 5   | 9   |
| MEAN SEVERITY :         | -      | 1.0 | 1.0 | 1.1 |
| .....                   |        |     |     |     |
| - Tubular basophilia    |        |     |     |     |
| GRADE 1 :               | 3      | 1   | 5   | 5   |
| GRADE 2 :               | -      | -   | -   | 1   |
| TOTAL AFFECTED :        | 3      | 1   | 5   | 6   |
| MEAN SEVERITY :         | 1.0    | 1.0 | 1.0 | 1.2 |
| .....                   |        |     |     |     |
| - Pigment basoph. cells |        |     |     |     |
| GRADE 1 :               | -      | -   | 3   | 5   |
| GRADE 2 :               | -      | -   | -   | 1   |
| TOTAL AFFECTED :        | -      | -   | 3   | 6   |
| MEAN SEVERITY :         | -      | -   | 1.0 | 1.2 |
| .....                   |        |     |     |     |
| - Pigment tubul. casts  |        |     |     |     |
| GRADE 1 :               | -      | -   | -   | 1   |
| TOTAL AFFECTED :        | -      | -   | -   | 1   |
| MEAN SEVERITY :         | -      | -   | -   | 1.0 |



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**SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K0  
SELECTED FINDINGS (ALL GRADINGS)**

| SEX :                 | FEMALE |     |     |     |
|-----------------------|--------|-----|-----|-----|
| DOSE GROUP:           | 01     | 02  | 03  | 04  |
| NO. ANIMALS:          | 10     | 10  | 10  | 10  |
| <hr/>                 |        |     |     |     |
| THYROID GLAND :       | 10     | 10  | 10  | 10  |
| - Pigment storage     |        |     |     |     |
| GRADE 1 :             | -      | -   | 4   | -   |
| GRADE 2 :             | -      | -   | 6   | 8   |
| GRADE 3 :             | -      | -   | -   | 2   |
| TOTAL AFFECTED :      | -      | -   | 10  | 10  |
| MEAN SEVERITY :       | -      | -   | 1.6 | 2.2 |
| .....                 |        |     |     |     |
| - Incr. vacuolation   |        |     |     |     |
| GRADE 1 :             | -      | -   | -   | 2   |
| GRADE 2 :             | -      | -   | -   | 1   |
| TOTAL AFFECTED :      | -      | -   | -   | 3   |
| MEAN SEVERITY :       | -      | -   | -   | 1.3 |
| .....                 |        |     |     |     |
| - Follic. hypertrophy |        |     |     |     |
| GRADE 1 :             | -      | 1   | 2   | 6   |
| TOTAL AFFECTED :      | -      | 1   | 2   | 6   |
| MEAN SEVERITY :       | -      | 1.0 | 1.0 | 1.0 |
| <hr/>                 |        |     |     |     |
| SPLEEN :              | 10     | 10  | 10  | 10  |
| - Extram. hemopoiesis |        |     |     |     |
| GRADE 1 :             | -      | 3   | 5   | 3   |
| GRADE 2 :             | -      | -   | 3   | 3   |
| GRADE 3 :             | -      | 1   | 2   | 3   |
| TOTAL AFFECTED :      | -      | 4   | 10  | 9   |
| MEAN SEVERITY :       | -      | 1.5 | 1.7 | 2.0 |
| .....                 |        |     |     |     |

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SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K0  
SELECTED FINDINGS (ALL GRADINGS)

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|             |    |    |    |    |        |
|-------------|----|----|----|----|--------|
| SEX :       |    |    |    |    | FEMALE |
| DOSE GROUP: | 01 | 02 | 03 | 04 |        |
| NO.ANIMALS: | 10 | 10 | 10 | 10 |        |

---

|                  |         |     |     |     |    |
|------------------|---------|-----|-----|-----|----|
| SPLEEN           | CONT'D. | 10  | 10  | 10  | 10 |
| - Hemosiderin    |         |     |     |     |    |
| GRADE 1 :        | 6       | 2   | 3   | 2   |    |
| GRADE 2 :        | 4       | 8   | 6   | 5   |    |
| GRADE 3 :        | -       | -   | 1   | 3   |    |
| TOTAL AFFECTED : | 10      | 10  | 10  | 10  |    |
| MEAN SEVERITY :  | 1.4     | 1.8 | 1.8 | 2.1 |    |

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**SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K1  
SELECTED FINDINGS (ALL GRADINGS)**

| SEX :                 |     |    |     |     | MALE |
|-----------------------|-----|----|-----|-----|------|
| DOSE GROUP:           | 01  | 02 | 03  | 04  |      |
| NO. ANIMALS:          | 5   | 5  | 5   | 5   |      |
| <hr/>                 |     |    |     |     |      |
| THYROID GLAND :       | 5   | 5  | 5   | 5   |      |
| - Pigment storage     |     |    |     |     |      |
| GRADE 1 :             | -   | -  | 2   | -   |      |
| GRADE 2 :             | -   | -  | 3   | 2   |      |
| GRADE 3 :             | -   | -  | -   | 3   |      |
| TOTAL AFFECTED :      | -   | -  | 5   | 5   |      |
| MEAN SEVERITY :       | -   | -  | 1.6 | 2.6 |      |
| .....                 |     |    |     |     |      |
| - Incr. vacuolation   |     |    |     |     |      |
| GRADE 1 :             | -   | -  | 3   | 2   |      |
| GRADE 2 :             | -   | -  | -   | 3   |      |
| TOTAL AFFECTED :      | -   | -  | 3   | 5   |      |
| MEAN SEVERITY :       | -   | -  | 1.0 | 1.6 |      |
| .....                 |     |    |     |     |      |
| - Follic. hypertrophy |     |    |     |     |      |
| GRADE 1 :             | 2   | -  | 4   | 4   |      |
| GRADE 2 :             | -   | -  | -   | 1   |      |
| TOTAL AFFECTED :      | 2   | -  | 4   | 5   |      |
| MEAN SEVERITY :       | 1.0 | -  | 1.0 | 1.2 |      |

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**SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K1  
SELECTED FINDINGS (ALL GRADINGS)**

| SEX :                 | FEMALE |     |     |     |
|-----------------------|--------|-----|-----|-----|
| DOSE GROUP:           | 01     | 02  | 03  | 04  |
| NO. ANIMALS:          | 5      | 5   | 5   | 5   |
| <hr/>                 |        |     |     |     |
| THYROID GLAND :       | 5      | 5   | 5   | 5   |
| - Pigment storage     |        |     |     |     |
| GRADE 1 :             | -      | -   | 1   | -   |
| GRADE 2 :             | -      | -   | 4   | 2   |
| GRADE 3 :             | -      | -   | -   | 3   |
| TOTAL AFFECTED :      | -      | -   | 5   | 5   |
| MEAN SEVERITY :       | -      | -   | 1.8 | 2.6 |
| .....                 |        |     |     |     |
| - Incr. vacuolation   |        |     |     |     |
| GRADE 1 :             | -      | -   | -   | 3   |
| TOTAL AFFECTED :      | -      | -   | -   | 3   |
| MEAN SEVERITY :       | -      | -   | -   | 1.0 |
| .....                 |        |     |     |     |
| - Follic. hypertrophy |        |     |     |     |
| GRADE 1 :             | -      | 1   | 4   | 5   |
| TOTAL AFFECTED :      | -      | 1   | 4   | 5   |
| MEAN SEVERITY :       | -      | 1.0 | 1.0 | 1.0 |

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**NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K0**

| SEX :                   |    |    |    |    | MALE |
|-------------------------|----|----|----|----|------|
| DOSE GROUP:             | 01 | 02 | 03 | 04 |      |
| NO. ANIMALS:            | 10 | 10 | 10 | 10 |      |
| SCIATIC NERVES :        | 10 | 10 | 10 | 10 |      |
| - Axonal degeneration : | 2  | 2  | 3  | -  |      |
| HEART :                 | 10 | 10 | 10 | 10 |      |
| - Inflammatory foci :   | 5  | 2  | 2  | 2  |      |
| - Myocardial inflamm. : | -  | -  | -  | 1  |      |
| - Myocardial fibrosis : | -  | 1  | 2  | 1  |      |
| - Valv. endocardiosis : | -  | -  | -  | 1  |      |
| TRACHEA :               | 10 | 10 | 10 | 10 |      |
| - Glandular dilation :  | 2  | 2  | 3  | 3  |      |
| - Mononuclear foci :    | 1  | 1  | -  | 2  |      |
| LUNGS :                 | 10 | 10 | 10 | 10 |      |
| - Vasc. mineralization: | 6  | 7  | 8  | 9  |      |
| - Osseous metaplasia :  | -  | -  | 1  | -  |      |
| - Alveolar hemorrhage : | 1  | 1  | -  | 2  |      |
| - Alveolar macrophages: | 3  | 3  | 1  | 5  |      |
| ESOPHAGUS :             | 10 | 10 | 10 | 10 |      |
| - Mononuclear foci :    | -  | -  | 1  | -  |      |
| STOMACH :               | 10 | 10 | 10 | 10 |      |
| - Hyperemia :           | -  | -  | -  | 2  |      |
| - Hyperkeratosis :      | 2  | 1  | 1  | 1  |      |
| - Epithel. vacuolation: | 1  | 1  | 2  | 1  |      |
| - Squamous hyperplasia: | -  | -  | 1  | -  |      |
| - Hyaline inclusions :  | 9  | 4  | 8  | 8  |      |
| - Epithelial cyst(s) :  | -  | 2  | 2  | 2  |      |
| - Cryptabscess(es) :    | -  | -  | 1  | -  |      |
| - Mucosal hyperplasia : | 1  | -  | -  | 1  |      |
| PEYERS PATCHES JEJ. :   | 9  | 10 | 10 | 9  |      |
| - Mineralization :      | 3  | -  | 1  | 1  |      |
| COLON :                 | 10 | 10 | 10 | 10 |      |
| - Luminal nematodes :   | -  | -  | -  | 1  |      |

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**NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K0**

|                          | SEX :        |    |    |    |    | MALE |
|--------------------------|--------------|----|----|----|----|------|
|                          | DOSE GROUP:  | 01 | 02 | 03 | 04 |      |
|                          | NO. ANIMALS: | 10 | 10 | 10 | 10 |      |
| RECTUM                   | :            | 10 | 10 | 10 | 10 |      |
| - Luminal dilation       | :            | 1  | 2  | 2  | -  |      |
| - Luminal nematodes      | :            | 1  | 1  | -  | 1  |      |
| LIVER                    | :            | 10 | 10 | 10 | 10 |      |
| - Fatty change           | :            | 6  | 3  | 2  | 3  |      |
| - Hemopoietic foci       | :            | 1  | 1  | -  | -  |      |
| - Inflammatory foci      | :            | 8  | 6  | 8  | 9  |      |
| - Peribiliary inflamm.:  | :            | 1  | 2  | 2  | -  |      |
| - Bile duct prolifer.:   | :            | -  | -  | 1  | -  |      |
| - Hepatoc. hypertrophy:  | :            | 1  | -  | 1  | -  |      |
| PANCREAS                 | :            | 10 | 10 | 10 | 10 |      |
| - Congestion             | :            | -  | -  | 1  | -  |      |
| - Acinar atrophy         | :            | -  | -  | 2  | 2  |      |
| - Basophilic foci        | :            | -  | -  | 1  | 1  |      |
| KIDNEYS                  | :            | 10 | 10 | 10 | 10 |      |
| - Pelvic dilation        | :            | 2  | 2  | 1  | -  |      |
| - Tubular mineraliz.:    | :            | 1  | -  | -  | -  |      |
| - Hyaline droplets       | :            | 9  | 6  | 8  | 7  |      |
| - Inflammatory foci      | :            | 4  | -  | 1  | 3  |      |
| - Pigment tubul. cells:  | :            | -  | -  | -  | 3  |      |
| - Tubular basophilia     | :            | 5  | 8  | 8  | 8  |      |
| - Pigment basoph. cells: | :            | -  | 3  | 6  | 8  |      |
| - Pigment. tubul. casts: | :            | -  | -  | -  | 3  |      |
| URINARY BLADDER          | :            | 10 | 10 | 10 | 10 |      |
| - Mononuclear foci       | :            | -  | -  | -  | 1  |      |

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**NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX**  
**STATUS AT NECROPSY: K0**

| SEX :                   |    |    |    |    | MALE |
|-------------------------|----|----|----|----|------|
| DOSE GROUP:             | 01 | 02 | 03 | 04 |      |
| NO. ANIMALS:            | 10 | 10 | 10 | 10 |      |
| TESTES :                | 10 | 10 | 10 | 10 |      |
| - Rete dilation :       | -  | 1  | -  | -  |      |
| - Tubular hypoplasia :  | -  | 1  | -  | 1  |      |
| - Tubular vacuolation : | 4  | 2  | 3  | 1  |      |
| - Tubular degeneration: | 2  | 2  | 1  | -  |      |
| - Inflammation :        | -  | 1  | -  | -  |      |
| - Inflammatory focus :  | -  | -  | 1  | -  |      |
| - Spermatid retention : | 2  | -  | 1  | -  |      |
| - Multinucl. giant c. : | -  | -  | 2  | 1  |      |
| EPIDIDYMIDES :          | 10 | 10 | 10 | 10 |      |
| - Hypozoospermia :      | -  | 1  | -  | -  |      |
| - Cellular debris :     | -  | 1  | -  | -  |      |
| - Inflammatory foci :   | -  | 1  | -  | -  |      |
| PROSTATE GLAND :        | 10 | 10 | 10 | 10 |      |
| - Inflammatory foci :   | -  | -  | 2  | 2  |      |
| - Glandular atrophy :   | -  | 1  | -  | 3  |      |
| - Glandular hyperplas.: | -  | 2  | 5  | 1  |      |
| COAGULATING GLANDS :    | 10 | 10 | 10 | 10 |      |
| - Glandular atrophy :   | -  | -  | 1  | -  |      |
| SEMINAL VESICLES :      | 10 | 10 | 10 | 10 |      |
| - Glandular atrophy :   | -  | -  | 1  | 2  |      |
| - Fibrosis :            | 1  | -  | -  | -  |      |
| PITUITARY GLAND :       | 10 | 10 | 10 | 10 |      |
| - Cyst, pars nervosa :  | -  | -  | -  | 1  |      |
| - Cyst, pars intermed.: | -  | -  | -  | 1  |      |
| - Cyst, pars distalis : | -  | -  | 1  | 2  |      |
| - Hypertr/pl.chromoph.: | 1  | 2  | 7  | 6  |      |
| - Fatty change :        | -  | -  | -  | 1  |      |

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PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K0**

| SEX :                   |    |    |    |    | MALE |
|-------------------------|----|----|----|----|------|
| DOSE GROUP:             | 01 | 02 | 03 | 04 |      |
| NO. ANIMALS:            | 10 | 10 | 10 | 10 |      |
| THYROID GLAND :         | 10 | 10 | 10 | 10 |      |
| - Thymic remnant :      | -  | -  | 1  | -  |      |
| - Pigment storage :     | -  | -  | 10 | 10 |      |
| - Incr. vacuolation :   | -  | -  | 1  | 9  |      |
| - Follic. hypertrophy : | -  | 1  | 8  | 9  |      |
| ADRENAL CORTICES :      | 10 | 10 | 10 | 10 |      |
| - Access. cort. tiss. : | -  | 2  | -  | 1  |      |
| - Capsular fibrosis :   | 1  | -  | -  | 1  |      |
| - Vacuolation, Z.fasc.: | 3  | 5  | 3  | 7  |      |
| SPLEEN :                | 10 | 10 | 10 | 10 |      |
| - Extram. hemopoiesis : | 4  | 6  | 7  | 10 |      |
| - Hemosiderin :         | 9  | 6  | 10 | 10 |      |
| BONE MARROW, FEMUR :    | 10 | 10 | 10 | 10 |      |
| - Fatty replacement :   | 7  | 6  | 6  | 3  |      |
| - Incr. erythropoiesis: | 1  | -  | 2  | 3  |      |
| - Decr. myelopoiesis :  | -  | -  | 1  | -  |      |
| THYMUS :                | 10 | 10 | 10 | 10 |      |
| - Cyst(s) :             | 5  | 4  | 2  | 3  |      |
| - Hemorrhage :          | 3  | 3  | 3  | 1  |      |
| - Stary sky :           | 1  | -  | -  | -  |      |
| - Lymphoid atrophy :    | -  | -  | 1  | -  |      |
| MESENT. LYMPH NODE :    | 10 | 10 | 10 | 10 |      |
| - Sinus dilation :      | -  | 1  | -  | -  |      |
| - Hemorrhage :          | -  | -  | 1  | 3  |      |
| MANDIB. LYMPH NODES :   | 10 | 10 | 10 | 10 |      |
| - Hemorrhage :          | -  | 1  | -  | -  |      |
| SUBLINGUAL GLANDS :     | 10 | 10 | 10 | 10 |      |
| - Periductular fibros.: | -  | -  | 1  | -  |      |



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**NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K0**

| SEX :                     |    |    |    |    | MALE |
|---------------------------|----|----|----|----|------|
| DOSE GROUP:               | 01 | 02 | 03 | 04 |      |
| NO. ANIMALS:              | 10 | 10 | 10 | 10 |      |
| MANDIBULAR GLANDS :       | 10 | 10 | 10 | 10 |      |
| - Inflammatory foci :     | -  | -  | -  | 1  |      |
| EXORBITAL LACR. GLDS. :   | 1  | -  | -  | -  |      |
| - Harderian gland change: | 1  | -  | -  | -  |      |
| SKIN/SUBCUTIS :           | 10 | 10 | 10 | 10 |      |
| - Inflammation :          | -  | 1  | -  | -  |      |
| - Hemorrhage :            | -  | 1  | -  | -  |      |
| RETROORBITAL TISSUE :     | 10 | 10 | 10 | 10 |      |
| - Hemorrhage :            | 5  | 10 | 10 | 9  |      |
| - Inflammation :          | 2  | 3  | 4  | 2  |      |

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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K0

| SEX :                     |    |    |    |    | FEMALE |
|---------------------------|----|----|----|----|--------|
| DOSE GROUP:               | 01 | 02 | 03 | 04 |        |
| NO. ANIMALS:              | 10 | 10 | 10 | 10 |        |
| SCIATIC NERVES :          | 10 | 10 | 10 | 10 |        |
| - Axonal degeneration :   | 4  | -  | 3  | 3  |        |
| HEART :                   | 10 | 10 | 10 | 10 |        |
| - Inflammatory foci :     | -  | 2  | -  | -  |        |
| - Myocardial fibrosis :   | 1  | -  | -  | 1  |        |
| TRACHEA :                 | 10 | 10 | 10 | 10 |        |
| - Glandular dilation :    | 4  | 2  | -  | 2  |        |
| - Mononuclear foci :      | 1  | 2  | 1  | 1  |        |
| LUNGS :                   | 10 | 10 | 10 | 10 |        |
| - Congestion :            | 1  | -  | -  | -  |        |
| - Vasc. mineralization:   | 6  | 6  | 3  | 1  |        |
| - Osseous metaplasia :    | 1  | -  | -  | -  |        |
| - Alveolar macrophages:   | 3  | 1  | 3  | 3  |        |
| ESOPHAGUS :               | 10 | 10 | 10 | 10 |        |
| - Mononuclear foci :      | 1  | -  | -  | -  |        |
| STOMACH :                 | 10 | 10 | 10 | 10 |        |
| - Hyperkeratosis :        | -  | 1  | -  | -  |        |
| - Epithel. vacuolation:   | 1  | 1  | 2  | -  |        |
| - Squamous hyperplasia:   | 1  | 1  | -  | -  |        |
| - Hyaline inclusions :    | 6  | 4  | 3  | 7  |        |
| - Epithelial cyst(s) :    | 1  | -  | -  | 1  |        |
| - Incr. inflamm. infilt.: | 1  | -  | -  | -  |        |
| - Erosion :               | 1  | -  | -  | -  |        |
| - Ulceration :            | -  | 1  | -  | -  |        |
| PEYERS PATCHES JEJ. :     | 10 | 7  | 10 | 10 |        |
| - Mineralization :        | 1  | 1  | -  | 1  |        |
| CECUM :                   | 10 | 10 | 10 | 10 |        |
| - Hemorrhage :            | -  | -  | -  | 1  |        |

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STATUS AT NECROPSY: K0

| SEX :                    |    |    |    |    | FEMALE |
|--------------------------|----|----|----|----|--------|
| DOSE GROUP:              | 01 | 02 | 03 | 04 |        |
| NO. ANIMALS:             | 10 | 10 | 10 | 10 |        |
| RECTUM :                 | 10 | 10 | 10 | 10 |        |
| - Luminal dilation :     | -  | 1  | -  | -  |        |
| - Luminal nematodes :    | -  | -  | 1  | -  |        |
| LIVER :                  | 10 | 10 | 10 | 10 |        |
| - Fatty change :         | 2  | 1  | -  | 2  |        |
| - Hemopoietic foci :     | -  | -  | 1  | -  |        |
| - Inflammatory foci :    | 5  | 7  | 5  | 5  |        |
| - Peribiliary inflamm.:  | -  | -  | 1  | -  |        |
| - Hepatoc. hypertrophy:  | -  | -  | -  | 1  |        |
| PANCREAS :               | 10 | 10 | 10 | 10 |        |
| - Acinar atrophy :       | -  | -  | -  | 1  |        |
| - Basophilic foci :      | -  | 1  | -  | -  |        |
| KIDNEYS :                | 10 | 10 | 10 | 10 |        |
| - Pelvic dilation :      | -  | 1  | 2  | -  |        |
| - Cortical cyst :        | -  | 1  | -  | -  |        |
| - Tubular mineraliz. :   | 3  | 2  | -  | 5  |        |
| - Inflammatory foci :    | -  | -  | -  | 4  |        |
| - Tubular casts :        | -  | -  | 1  | -  |        |
| - Tubulus cell swell. :  | -  | 5  | 6  | 9  |        |
| - Pigment tubul. cells:  | -  | 4  | 5  | 9  |        |
| - Tubular basophilia :   | 3  | 1  | 5  | 6  |        |
| - Pigment basoph. cells: | -  | -  | 3  | 6  |        |
| - Pigment. tubul. casts: | -  | -  | -  | 1  |        |
| - Pyelonephritis :       | 2  | 2  | -  | -  |        |
| OVARIES :                | 10 | 10 | 10 | 10 |        |
| - Congestion :           | -  | 1  | -  | -  |        |
| - Rete ovarii :          | 1  | -  | 1  | 1  |        |
| - Bursa cyst :           | -  | -  | -  | 2  |        |
| - Corpus luteum cyst :   | 1  | -  | -  | -  |        |
| - Interst. c. hyperpl.:  | 1  | 4  | 2  | 2  |        |
| - Atrophy :              | -  | 1  | 1  | -  |        |

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**NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K0**

| SEX :                   |    |    |    |    | FEMALE |
|-------------------------|----|----|----|----|--------|
| DOSE GROUP:             | 01 | 02 | 03 | 04 |        |
| NO. ANIMALS:            | 10 | 10 | 10 | 10 |        |
| <hr/>                   |    |    |    |    |        |
| UTERUS :                | 10 | 10 | 10 | 10 |        |
| - Congestion :          | 1  | -  | 1  | -  |        |
| - Luminal dilation :    | 4  | 4  | 3  | 2  |        |
| - Epithelial cyst(s) :  | 1  | -  | 1  | -  |        |
| <hr/>                   |    |    |    |    |        |
| VAGINA :                | 10 | 10 | 10 | 10 |        |
| - Proestrus :           | 3  | 4  | 2  | 1  |        |
| - Estrus :              | 2  | 3  | 4  | 4  |        |
| - Metestrus :           | 2  | -  | 1  | 3  |        |
| - Diestrus :            | 3  | 3  | 3  | 2  |        |
| - Hypermucification :   | -  | 1  | -  | -  |        |
| - Luminal plugs :       | -  | 1  | 2  | 2  |        |
| <hr/>                   |    |    |    |    |        |
| PITUITARY GLAND :       | 10 | 10 | 10 | 10 |        |
| - Cyst, pars intermed.: | -  | -  | 1  | -  |        |
| - Cyst, pars distalis : | -  | -  | 2  | -  |        |
| <hr/>                   |    |    |    |    |        |
| THYROID GLAND :         | 10 | 10 | 10 | 10 |        |
| - Thyroglossal d. cyst: | -  | -  | 1  | -  |        |
| - Ultimobranchial cyst: | -  | 1  | -  | 2  |        |
| - Thymic remnant :      | 1  | -  | -  | -  |        |
| - Pigment storage :     | -  | -  | 10 | 10 |        |
| - Incr. vacuolation :   | -  | -  | -  | 3  |        |
| - Follic. hypertrophy : | -  | 1  | 2  | 6  |        |
| <hr/>                   |    |    |    |    |        |
| ADRENAL CORTICES :      | 10 | 10 | 10 | 10 |        |
| - Hemosiderin :         | -  | 1  | -  | -  |        |
| - Hemopoietic foci :    | -  | 1  | -  | -  |        |
| - Vacuolation, Z.glom.: | -  | -  | 1  | -  |        |
| - Hypertrophy, nodular: | -  | 1  | -  | -  |        |
| <hr/>                   |    |    |    |    |        |
| SPLEEN :                | 10 | 10 | 10 | 10 |        |
| - Extram. hemopoiesis : | -  | 4  | 10 | 9  |        |
| - Hemosiderin :         | 10 | 10 | 10 | 10 |        |

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**NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K0**

| SEX :                   | FEMALE |    |    |    |
|-------------------------|--------|----|----|----|
| DOSE GROUP:             | 01     | 02 | 03 | 04 |
| NO. ANIMALS:            | 10     | 10 | 10 | 10 |
| BONE MARROW, FEMUR :    | 10     | 10 | 10 | 10 |
| - Fatty replacement :   | 9      | 7  | 10 | 7  |
| - Incr. erythropoiesis: | 1      | 4  | 3  | 3  |
| THYMUS :                | 10     | 10 | 10 | 10 |
| - Cyst(s) :             | 7      | 7  | 7  | 6  |
| MANDIB. LYMPH NODES :   | 10     | 10 | 10 | 10 |
| - Hemorrhage :          | -      | -  | -  | 1  |
| SUBLINGUAL GLANDS :     | 10     | 10 | 10 | 10 |
| - Serous metaplasia :   | 1      | -  | -  | -  |
| - Glandular atrophy :   | -      | -  | 1  | -  |
| MAMMARY GLAND AREA :    | 10     | 10 | 10 | 10 |
| - Lobular alveoli :     | 1      | -  | 1  | 2  |
| RETROORBITAL TISSUE :   | 10     | 10 | 10 | 10 |
| - Hemorrhage :          | 8      | 7  | 7  | 9  |
| - Inflammation :        | 1      | 2  | 1  | 5  |

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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K1

|                       | SEX :        |    |    |    |    | MALE |
|-----------------------|--------------|----|----|----|----|------|
|                       | DOSE GROUP:  | 01 | 02 | 03 | 04 |      |
|                       | NO. ANIMALS: | 5  | 5  | 5  | 5  |      |
| KIDNEYS               | :            | 1  | -  | -  | -  |      |
| - Pelvic dilation     | :            | 1  | -  | -  | -  |      |
| - Hyaline droplets    | :            | 1  | -  | -  | -  |      |
| SEMINAL VESICLES      | :            | -  | -  | 1  | -  |      |
| - Hemorrhage          | :            | -  | -  | 1  | -  |      |
| THYROID GLAND         | :            | 5  | 5  | 5  | 5  |      |
| - Thymic remnant      | :            | 1  | -  | 1  | -  |      |
| - Pigment storage     | :            | -  | -  | 5  | 5  |      |
| - Incr. vacuolation   | :            | -  | -  | 3  | 5  |      |
| - Follic. hypertrophy | :            | 2  | -  | 4  | 5  |      |

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**NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX  
STATUS AT NECROPSY: K1**

| SEX :                   |    |    |    |    | FEMALE |
|-------------------------|----|----|----|----|--------|
| DOSE GROUP:             | 01 | 02 | 03 | 04 |        |
| NO. ANIMALS:            | 5  | 5  | 5  | 5  |        |
| OVARIES :               | 1  | -  | 1  | -  |        |
| - Congestion :          | 1  | -  | 1  | -  |        |
| UTERUS :                | 1  | -  | 3  | 1  |        |
| - Luminal dilation :    | 1  | -  | 3  | 1  |        |
| THYROID GLAND :         | 5  | 5  | 5  | 5  |        |
| - Thymic remnant :      | -  | -  | 2  | -  |        |
| - Pigment storage :     | -  | -  | 5  | 5  |        |
| - Incr. vacuolation :   | -  | -  | -  | 3  |        |
| - Follic. hypertrophy : | -  | 1  | 4  | 5  |        |
| SKIN/SUBCUTIS :         | -  | -  | -  | 3  |        |
| - Hair follic. atrophy: | -  | -  | -  | 2  |        |

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 01, MALE

NECROPSY OBSERVATION

CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 1

MANDIBULAR LYMPH NODES

- 01: FOCUS/FOCI, D=1 MM, ISOLATED, DARK RED. - No corresponding finding.

ANIMAL NO: 3

KIDNEYS

- 01: LEFT SIDE: PELVIC DILATION. - Pelvic dilation, unilateral.

ANIMAL NO: 4

EXORBITAL LACRIMAL GLANDS

- 01: BOTH SIDES: FOCUS/FOCI, D=1 MM, SEVERAL, GRAY WHITE. - Harderian gland change, multifocal, bilateral, grade 2.

ANIMAL NO: 5

LUNGS

- 01: LEFT LOBE: FOCUS/FOCI, D=2 MM, ISOLATED, REDDISH. - No corresponding finding.

ANIMAL NO: 7

KIDNEYS

- 01: RIGHT SIDE: PELVIC DILATION. - Pelvic dilation, unilateral.

SEMINAL VESICLES

- 01: BOTH SIDES: FOCUS/FOCI, D=1 MM, ISOLATED, DARK RED. - No corresponding finding.



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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 01, MALE

**NECROPSY OBSERVATION**

**CORRESPONDING MICROSCOPIC FINDING**

ANIMAL NO: 10

**STOMACH**

- 01: MUCOSA, FUNDUS: FOCUS/FOCI, D= - No corresponding finding.  
4 MM, REDDISH.

ANIMAL NO: 15

**KIDNEYS**

- 01: LEFT SIDE: PELVIC DILATION. - Pelvic dilation, unilateral.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 01, FEMALE

NECROPSY OBSERVATION

CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 62

LUNGS

- 01: FOCUS/FOCI, D=2 MM, SEVERAL, GRAY WHITE. - No corresponding finding.

ANIMAL NO: 63

UTERUS

- 01: RIGHT HORN: DISCOLORATION, DARK RED. - Congestion, at uterus horn, unilaterally.

ANIMAL NO: 68

LUNGS

- 01: DISCOLORATION, REDDISH. - Congestion.

ANIMAL NO: 69

LUNGS

- 01: FOCUS/FOCI, D=4 MM, SEVERAL, GRAY WHITE. - No corresponding finding.

ANIMAL NO: 75

OVARIES

- 01: BOTH SIDES: DISCOLORATION, DARK RED. - Congestion, bilateral.

UTERUS

- 01: BOTH HORNS: DILATION, D=5 MM, CONTAINS WATERY FLUID. - Luminal dilation, (cyclic change).

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 01, FEMALE

**NECROPSY OBSERVATION**

**CORRESPONDING MICROSCOPIC FINDING**

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 02, MALE

NECROPSY OBSERVATION

CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 17

TESTES

- 01: BOTH SIDES: REDUCED IN SIZE,  
D=17X10 MM.

- Tubular degeneration, diffuse,  
end stage, bilateral, grade 5.

ANIMAL NO: 21

KIDNEYS

- 01: LEFT SIDE: PELVIC DILATION.  
SKIN/SUBCUTIS

- No corresponding finding.

- 01: NOSE REGION, RIGHT SIDE:  
ESCHAR(S), D=3 MM.

- Inflammation, subcutis, mixed-  
cellular, nose-region, grade 2.  
Hemorrhage, subcutis and  
perifollicular sinus, nose  
region, grade 2.

ANIMAL NO: 25

KIDNEYS

- 01: LEFT SIDE: PELVIC DILATION.

- Pelvic dilation, unilateral.

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TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 02, FEMALE

**NECROPSY OBSERVATION**

**CORRESPONDING MICROSCOPIC FINDING.**

ANIMAL NO: 77

**UTERUS**

- 01: BOTH HORNS: DILATION, D=5 MM. - Luminal dilation, (cyclic change).

ANIMAL NO: 83

**UTERUS**

- 01: BOTH HORNS: DILATION, D=5 MM. - Luminal dilation, (cyclic change).

ANIMAL NO: 85

**LUNGS**

- 01: FOCUS/FOCI, D=4 MM, SEVERAL, - No corresponding finding.  
GRAY WHITE.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 03, MALE

NECROPSY OBSERVATION

CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 31

PANCREAS

- 01: DISCOLORATION, DARK RED.

- Congestion.

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 32

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 1.

ANIMAL NO: 34

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 1.

ANIMAL NO: 35

KIDNEYS

- 01: LEFT SIDE: PELVIC DILATION.

- Pelvic dilation, unilateral.

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 03, MALE

**NECROPSY OBSERVATION**

**CORRESPONDING MICROSCOPIC FINDING**

ANIMAL NO: 36

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 37

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 1.

ANIMAL NO: 38

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 39

STOMACH

- 01: MUCOSA, FUNDUS: FOCUS/FOCI, D= 3 MM, ISOLATED, DARK RED.

- No corresponding finding.

SEMINAL VESICLES

- 01: BOTH SIDES: FOCUS/FOCI, D=1 MM, SEVERAL, DARK RED.

- No corresponding finding.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 03, MALE

**NECROPSY OBSERVATION**

**CORRESPONDING MICROSCOPIC FINDING**

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
ISOLATED, DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 1.

ANIMAL NO: 40

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 41

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 1.

ANIMAL NO: 42

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 43

SEMINAL VESICLES

- 01: BOTH SIDES: FOCUS/FOCI,  
ISOLATED, D=1 MM, REDDISH.

- Hemorrhage, multifocal,  
sumbucosa, unilateral, grade 1.



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CORRELATION TABLE: NECROPSY -- MICROSCOPY

DOSE GROUP 03, MALE

NECROPSY OBSERVATION

CORRESPONDING MICROSCOPIC FINDING

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 44

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 45

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 1.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 03, FEMALE

**NECROPSY OBSERVATION**

**CORRESPONDING MICROSCOPIC FINDING**

ANIMAL NO: 91

.....  
THYROID GLAND (BOTH LOBES)  
- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

.....  
ANIMAL NO: 92

THYROID GLAND (BOTH LOBES)  
- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 1.

.....  
ANIMAL NO: 93

THYROID GLAND (BOTH LOBES)  
- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

.....  
ANIMAL NO: 94

THYROID GLAND (BOTH LOBES)  
- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 03, FEMALE

**NECROPSY OBSERVATION**

**CORRESPONDING MICROSCOPIC FINDING**

ANIMAL NO: 95

**UTERUS**

- 01: BOTH HORNS: CONTAINS WATERY  
FLUID, D=10X5 MM.

- Luminal dilation, (cyclic  
change).

ANIMAL NO: 97

**THYROID GLAND (BOTH LOBES)**

- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 99

**THYROID GLAND (BOTH LOBES)**

- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 100

**UTERUS**

- 01: BOTH HORNS: DISCOLORATION,  
DARK RED.

- Congestion, at uterus horn,  
unilaterally.

**THYROID GLAND (BOTH LOBES)**

- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 1.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 03, FEMALE

**NECROPSY OBSERVATION**

**CORRESPONDING MICROSCOPIC FINDING**

ANIMAL NO: 102

**OVARIES**

- 01: LEFT SIDE: DISCOLORATION,  
DARK RED.

- Congestion, unilateral.

**UTERUS**

- 01: BOTH HORNS: DILATION, D=5 MM,  
CONTAINS WATERY FLUID.

- Luminal dilation, (cyclic  
change).

ANIMAL NO: 103

**UTERUS**

- 01: BOTH HORNS: DILATION, D=8 MM,  
CONTAINS WATERY FLUID.

- Luminal dilation, (cyclic  
change).

ANIMAL NO: 104

**UTERUS**

- 01: BOTH HORNS: DILATION, D=5 MM,  
CONTAINS WATERY FLUID.

- Luminal dilation, (cyclic  
change).

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 04, MALE

NECROPSY OBSERVATION

CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 46

THYROID GLAND (BOTH LOBES)  
- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

ANIMAL NO: 47

KIDNEYS

- 01: LEFT SIDE: PELVIC DILATION.

- No corresponding finding.

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 4.

ANIMAL NO: 48

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 4.

ANIMAL NO: 51

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 04, MALE

**NECROPSY OBSERVATION**

**CORRESPONDING MICROSCOPIC FINDING**

ANIMAL NO: 52

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

ANIMAL NO: 53

STOMACH

- 01: MUCOSA, FUNDUS: FOCUS/FOCI, D= 4 MM, ISOLATED, DARK RED.

- Hyperemia, pars glandularis,  
multifocal, superficial, grade 2.

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

THYMUS

- 01: FOCUS/FOCI, D=2 MM, SEVERAL,  
DARK RED.

- No corresponding finding.

ANIMAL NO: 54

STOMACH

- 01: MUCOSA, FUNDUS: FOCUS/FOCI, D= 2 MM, ISOLATED, REDDISH.

- Hyperemia, pars glandularis,  
multifocal, superficial, grade 2.

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 04, MALE

NECROPSY OBSERVATION

CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 55

.....  
THYROID GLAND (BOTH LOBES)  
- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

.....  
ANIMAL NO: 56

.....  
THYROID GLAND (BOTH LOBES)  
- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

.....  
ANIMAL NO: 57

.....  
THYROID GLAND (BOTH LOBES)  
- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

.....  
ANIMAL NO: 58

.....  
THYROID GLAND (BOTH LOBES)  
- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 04, MALE

NECROPSY OBSERVATION

CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 59

.....  
THYROID GLAND (BOTH LOBES)  
- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

.....  
ANIMAL NO: 60

.....  
THYROID GLAND (BOTH LOBES)  
- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.



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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 04, FEMALE

NECROPSY OBSERVATION

CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 106

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 107

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 108

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 109

OVARIES

- 01: RIGHT SIDE: WATERY CYST, D=10  
MM.

- Bursa cyst, unilateral.

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 04, FEMALE

**NECROPSY OBSERVATION**

**CORRESPONDING MICROSCOPIC FINDING**

ANIMAL NO: 110

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 111

UTERUS

- 01: BOTH HORNS: DILATION, D=5 MM,  
CONTAINS FLUID.

- Luminal dilation, (cyclic  
change).

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

ANIMAL NO: 112

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
DARK RED.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 113

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 04, FEMALE

**NECROPSY OBSERVATION**

**CORRESPONDING MICROSCOPIC FINDING**

ANIMAL NO: 114

CECUM

- 01: MUCOSA: FOCUS/FOCI, D=20 MM,  
DARK RED.

- Hemorrhage, submucosa, grade 3.

OVARIES

- 01: LEFT SIDE: WATERY CYST, D=10  
MM.

- Bursa cyst, unilateral.

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 115

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

ANIMAL NO: 116

UTERUS

- 01: BOTH HORNS: DILATION, D=5 MM,  
CONTAINS WATERY FLUID.

- Luminal dilation, (cyclic  
change).

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

SKIN/SUBCUTIS

- 01: SHOULDER: ALOPECIA, ISOLATED,  
D=20 MM, SLIGHT.

- Hair follicle atrophy, focal,  
shoulder region, grade 2.

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CORRELATION TABLE: NECROPSY - MICROSCOPY

DOSE GROUP 04, FEMALE

NECROPSY OBSERVATION

CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 118

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

ANIMAL NO: 119

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 2.

SKIN/SUBCUTIS

- 01: SHOULDER: ALOPECIA, D=10 MM,  
SLIGHT.

- Hair follicle atrophy, focal,  
shoulder region, grade 1.

ANIMAL NO: 120

THYROID GLAND (BOTH LOBES)

- 01: BOTH SIDES: DISCOLORATION,  
BLACK.

- Pigment storage, cytoplasmic,  
brown, fine-granular, bilateral,  
grade 3.

SKIN/SUBCUTIS

- 01: SHOULDER: ALOPECIA, ISOLATED,  
D=10 MM, SLIGHT.

- No corresponding finding.

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EXPLANATION OF CODES AND SYMBOLS

CODES AND SYMBOLS USED AT ANIMAL LEVEL:

M = Male animal  
F = Female animal  
K0 = Terminal sacrifice group  
K1...K9 = Interim sacrifice groups 1...9

CODES AND SYMBOLS USED AT ORGAN LEVEL:

G = Gross observation checked off histologically  
\* = Comment in text of individual animal data  
0 = Tissue not present for histologic examination  
' = Histologic examination not required  
+ = Organ examined, findings present  
- = Organ examined, no pathologic findings noted (AOFT only)  
( = Only one of paired organs examined/present

CODES AND SYMBOLS USED AT FINDING LEVEL:

GRADE 1 = Minimal / very few / very small  
GRADE 2 = Slight / few / small  
GRADE 3 = Moderate / moderate number / moderate size  
GRADE 4 = Marked / many / large  
GRADE 5 = Massive / extensive number / extensive size  
P = Finding present, severity not scored  
( = Finding unilateral in paired organs  
\* = Comment in text of individual animal data

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**INDIVIDUAL ANIMAL DATA**

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**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)**  
DOSE GROUP : 01, 0 MG/KG

ANIMAL NUMBER :

|                        | 1    | 2   | 3    | 4   | 5   | 6   | 7   | 8   | 9   | 10  |
|------------------------|------|-----|------|-----|-----|-----|-----|-----|-----|-----|
|                        | MKO  | MKO | MKO  | MKO | MKO | MKO | MKO | MKO | MKO | MKO |
| CEREBRUM               | -    | -   | -    | -   | -   | -   | -   | -   | -   | -   |
| CEREBELLUM             | -    | -   | -    | -   | -   | -   | -   | -   | -   | -   |
| MEDULLA OBLONGATA      | -    | -   | -    | -   | -   | -   | -   | -   | -   | -   |
| PONS                   | -    | -   | -    | -   | -   | -   | -   | -   | -   | -   |
| SPINAL CORD, CERVIC.   | -    | -   | -    | -   | -   | -   | -   | -   | -   | -   |
| SPINAL CORD, THORAC.   | -    | -   | -    | -   | -   | -   | -   | -   | -   | -   |
| SPINAL CORD, LUMBAR    | -    | -   | -    | -   | -   | -   | -   | -   | -   | -   |
| SCIATIC NERVES         | ( +  | ( - | ( +  | ( - | ( - | ( - | ( - | ( - | ( - | ( - |
| - Axonal degeneration  | ( 1. | .   | ( 1. | .   | .   | .   | .   | .   | .   | .   |
| HEART                  | +    | +   | +    | -   | -   | -   | +   | +   | -   | -   |
| - Inflammatory foci    | 2.   | 1.  | 1.   | .   | .   | .   | 2.  | 1.  | .   | .   |
| AORTA                  | -    | -   | -    | -   | -   | -   | -   | -   | -   | -   |
| TRACHEA                | -    | +   | -    | -   | +   | -   | -   | +   | -   | -   |
| - Glandular dilation   | .    | 1.  | .    | .   | .   | .   | .   | 1.  | .   | .   |
| - Mononuclear foci     | .    | .   | .    | .   | 1.  | .   | .   | .   | .   | .   |
| LUNGS                  | +    | -   | +    | +   | +G  | +   | +   | +   | +   | +   |
| - Vasc. mineralization | .    | .   | .    | 1.  | 1.  | .   | 1.  | 1.  | 1.  | 1.  |
| - Alveolar hemorrhage  | .    | .   | .    | .   | .   | 1.  | .   | .   | .   | .   |
| - Alveolar macrophages | 1.   | .   | 1.   | .   | .   | .   | .   | .   | 1.  | .   |
| ESOPHAGUS              | -    | -   | -    | -   | -   | -   | -   | -   | -   | -   |
| STOMACH                | +    | +   | +    | +   | +   | -   | +   | +   | +   | +G  |
| - Hyperkeratosis       | .    | 1.  | .    | .   | .   | .   | .   | 1.  | .   | .   |
| - Epithel. vacuolation | .    | .   | .    | 1.  | .   | .   | .   | .   | .   | .   |
| - Hyaline inclusions   | 1.   | 1.  | 1.   | 1.  | 1.  | .   | 1.  | 2.  | 2.  | 1.  |
| - Mucosal hyperplasia  | .    | .   | 1.   | .   | .   | .   | .   | .   | .   | .   |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 01, 0 MG/KG**

ANIMAL NUMBER :

|                        | 1   | 2    | 3    | 4    | 5    | 6   | 7    | 8    | 9   | 10  |
|------------------------|-----|------|------|------|------|-----|------|------|-----|-----|
|                        | MKO | MKO  | MKO  | MKO  | MKO  | MKO | MKO  | MKO  | MKO | MKO |
| DUODENUM               | -   | -    | -    | -    | -    | -   | -    | -    | -   | -   |
| .....                  |     |      |      |      |      |     |      |      |     |     |
| JEJUNUM                | -   | -    | -    | -    | -    | -   | -    | -    | -   | -   |
| .....                  |     |      |      |      |      |     |      |      |     |     |
| PEYERS PATCHES JEJ.    | -   | +    | +    | -    | -    | -   | -    | 0    | +   | -   |
| - Mineralization       | .   | 1.   | 1.   | .    | .    | .   | .    | .    | 1.  | .   |
| .....                  |     |      |      |      |      |     |      |      |     |     |
| ILEUM                  | -   | -    | -    | -    | -    | -   | -    | -    | -   | -   |
| .....                  |     |      |      |      |      |     |      |      |     |     |
| PEYERS PATCHES ILEUM   | -   | -    | -    | -    | -    | -   | -    | -    | -   | -   |
| .....                  |     |      |      |      |      |     |      |      |     |     |
| CECUM                  | -   | -    | -    | -    | -    | -   | -    | -    | -   | -   |
| .....                  |     |      |      |      |      |     |      |      |     |     |
| COLON                  | -   | -    | -    | -    | -    | -   | -    | -    | -   | -   |
| .....                  |     |      |      |      |      |     |      |      |     |     |
| RECTUM                 | -   | -    | +    | -    | -    | -   | +    | -    | -   | -   |
| - Luminal dilation     | .   | .    | P.   | .    | .    | .   | .    | .    | .   | .   |
| - Luminal nematodes    | .   | .    | .    | .    | .    | .   | 2.   | .    | .   | .   |
| .....                  |     |      |      |      |      |     |      |      |     |     |
| LIVER                  | +   | +    | +    | +    | +    | +   | +    | +    | +   | +   |
| - Fatty change         | 1.  | .    | .    | .    | 1.   | 1.  | 1.   | 1.   | .   | 1.  |
| - Hemopoietic foci     | .   | .    | 1.   | .    | .    | .   | .    | .    | .   | .   |
| - Inflammatory foci    | 1.  | 1.   | .    | 1.   | .    | 1.  | 1.   | 1.   | 2.  | 1.  |
| - Peribiliary inflamm. | .   | .    | .    | .    | .    | 1.  | .    | .    | .   | .   |
| - Hepatoc. hypertrophy | .   | .    | .    | .    | .    | .   | 1.   | .    | .   | .   |
| .....                  |     |      |      |      |      |     |      |      |     |     |
| PANCREAS               | -   | -    | -    | -    | -    | -   | -    | -    | -   | -   |
| .....                  |     |      |      |      |      |     |      |      |     |     |
| KIDNEYS                | +   | +    | +G   | +    | +    | -   | +G   | +    | +   | +   |
| - Pelvic dilation      | .   | .    | ( P. | .    | .    | .   | ( P. | .    | .   | .   |
| - Tubular mineraliz.   | .   | .    | .    | .    | .    | .   | .    | .    | 1.  | .   |
| - Hyaline droplets     | 1.  | 2*   | 1.   | 1.   | 1.   | .   | 1.   | 1.   | 1.  | 1.  |
| - Inflammatory foci    | .   | ( 1. | ( 1. | .    | ( 1. | .   | .    | 1.   | .   | .   |
| - Tubular basophilia   | 1.  | .    | .    | ( 1. | 1.   | .   | 1.   | ( 1. | .   | .   |
| .....                  |     |      |      |      |      |     |      |      |     |     |
| URINARY BLADDER        | -   | -    | -    | -    | -    | -   | -    | -    | -   | -   |
| .....                  |     |      |      |      |      |     |      |      |     |     |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 01, 0 MG/KG**

ANIMAL NUMBER :

|                        | 1    | 2   | 3    | 4   | 5   | 6   | 7   | 8    | 9   | 10   |
|------------------------|------|-----|------|-----|-----|-----|-----|------|-----|------|
|                        | MKO  | MKO | MKO  | MKO | MKO | MKO | MKO | MKO  | MKO | MKO  |
| TESTES                 | +    | -   | +    | -*  | -*  | +   | -   | -    | -*  | +    |
| - Tubular vacuolation  | ( 1. | .   | 1.   | .   | .   | 2*  | .   | .    | .   | 1.   |
| - Tubular degeneration | .    | .   | 1.   | .   | .   | 1.  | .   | .    | .   | .    |
| - Spermatid retention  | .    | .   | ( 1. | .   | .   | .   | .   | .    | .   | ( 1. |
| .....                  |      |     |      |     |     |     |     |      |     |      |
| EPIDIDYMIDES           | -    | -   | -    | -   | -   | -   | -   | -    | -   | -    |
| .....                  |      |     |      |     |     |     |     |      |     |      |
| PROSTATE GLAND         | -    | -   | -    | -   | -   | -   | -   | -    | -   | -    |
| .....                  |      |     |      |     |     |     |     |      |     |      |
| COAGULATING GLANDS     | -    | -   | -    | -   | -   | -   | -   | -    | -   | -    |
| .....                  |      |     |      |     |     |     |     |      |     |      |
| SEMINAL VESICLES       | -    | -   | -    | -   | -   | -   | -G  | +    | -   | -    |
| - Fibrosis             | .    | .   | .    | .   | .   | .   | .   | ( 1. | .   | .    |
| .....                  |      |     |      |     |     |     |     |      |     |      |
| PITUITARY GLAND        | -    | -   | -    | -   | -   | -   | -   | +    | -   | -    |
| - Hypertr/pl.chromoph. | .    | .   | .    | .   | .   | .   | .   | 1.   | .   | .    |
| .....                  |      |     |      |     |     |     |     |      |     |      |
| THYROID GLAND          | -    | -   | -    | -   | -   | -   | -   | -    | -   | -    |
| .....                  |      |     |      |     |     |     |     |      |     |      |
| PARATHYROID GLANDS     | 0    | 0   | ( -  | ( - | ( - | ( - | -   | ( -  | -   | ( -  |
| .....                  |      |     |      |     |     |     |     |      |     |      |
| ADRENAL CORTICES       | -    | -   | -    | +   | -   | -   | -   | -    | +   | +    |
| - Capsular fibrosis    | .    | .   | .    | .   | .   | .   | .   | .    | .   | ( 1. |
| - Vacuolation, Z.fasc. | .    | .   | .    | 2.  | .   | .   | .   | .    | 1.  | 1.   |
| .....                  |      |     |      |     |     |     |     |      |     |      |
| ADRENAL MEDULLAS       | -    | -   | -    | -   | -   | -   | -   | -    | -   | -    |
| .....                  |      |     |      |     |     |     |     |      |     |      |
| SPLEEN                 | +    | +   | +    | +   | +   | +   | +   | +    | +   | -    |
| - Extram. hemopoiesis  | .    | .   | 1.   | .   | 1.  | 1.  | .   | .    | 1.  | .    |
| - Hemosiderin          | 1.   | 1.  | 1.   | 2.  | 1.  | 2.  | 1.  | 2.   | 2.  | .    |
| .....                  |      |     |      |     |     |     |     |      |     |      |
| BONE MARROW, FEMUR     | -    | +   | -    | -   | +   | +   | +   | +    | +   | +    |
| - Fatty replacement    | .    | 2.  | .    | .   | 1.  | 1.  | 1.  | 1.   | 1.  | 2.   |
| - Incr. erythropoiesis | .    | .   | .    | .   | .   | .   | .   | .    | 1.  | .    |
| .....                  |      |     |      |     |     |     |     |      |     |      |
| THYMUS                 | +    | +   | -    | +   | +   | +   | -   | +    | +   | -    |
| - Cyst(s)              | P.   | P.  | .    | P.  | P.  | .   | .   | P.   | .   | .    |
| - Hemorrhage           | 1.   | .   | .    | 1.  | .   | .   | .   | .    | 1.  | .    |
| - Stary sky            | .    | .   | .    | .   | .   | 2*  | .   | .    | .   | .    |
| .....                  |      |     |      |     |     |     |     |      |     |      |



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SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 01, 0 MG/KG**

ANIMAL NUMBER :

|                          | 1    | 2    | 3    | 4    | 5   | 6   | 7   | 8    | 9    | 10  |
|--------------------------|------|------|------|------|-----|-----|-----|------|------|-----|
|                          | MKO  | MKO  | MKO  | MKO  | MKO | MKO | MKO | MKO  | MKO  | MKO |
| MESENT. LYMPH NODE       | -    | -    | -    | -    | -   | -   | -   | -    | -    | -   |
| MANDIB. LYMPH NODES      | ( -G | ( -  | ( -  | ( -  | ( - | ( - | ( - | ( -  | ( -  | ( - |
| SUBLINGUAL GLANDS        | -    | -    | -    | -    | -   | -   | -   | -    | -    | -   |
| MANDIBULAR GLANDS        | -    | -    | -    | -    | -   | -   | -   | -    | -    | -   |
| EXORBITAL LACR. GLDS.    |      |      |      | +G   |     |     |     |      |      |     |
| - Harderian gland change |      |      |      | 2*   |     |     |     |      |      |     |
| MAMMARY GLAND AREA       | -    | -    | -    | -    | -   | -   | -   | -    | -    | -   |
| SKIN/SUBCUTIS            | -    | -    | -    | -    | -   | -   | -   | -    | -    | -   |
| EYES                     | -    | -    | -    | -    | -   | -   | -   | -    | -    | -   |
| RETROORBITAL TISSUE      | -    | +    | +    | +    | -   | -   | -   | +    | +    | -   |
| - Hemorrhage             | .    | ( 2. | ( 1. | ( 1. | .   | .   | .   | ( 1. | ( 2. | .   |
| - Inflammation           | .    | ( 2. | .    | .    | .   | .   | .   | .    | ( 1. | .   |
| OPTIC NERVES             | -    | -    | -    | -    | -   | -   | -   | -    | -    | ( - |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)**  
DOSE GROUP : 01, 0 MG/KG

**ANIMAL NUMBER :**

11 12 13 14 15  
MK1 MK1 MK1 MK1 MK1

KIDNEYS | | | | (+G  
- Pelvic dilation | | | | ( P.  
- Hyaline droplets | | | | ( 1.

.....  
THYROID GLAND + - + + -  
- Thymic remnant . . ( P. . .  
- Follic. hypertrophy 1. . . 1. .

.....  
PARATHYROID GLANDS ( - ( - - ( - -  
.....

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INDIVIDUAL ANIMAL DATA**

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
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**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 01, 0 MG/KG**

**ANIMAL NUMBER :**

|                        | 61   | 62   | 63  | 64  | 65  | 66   | 67   | 68  | 69  | 70  |
|------------------------|------|------|-----|-----|-----|------|------|-----|-----|-----|
|                        | FKO  | FKO  | FKO | FKO | FKO | FKO  | FKO  | FKO | FKO | FKO |
| CEREBRUM               | -    | -    | -   | -   | -   | -    | -    | -   | -   | -   |
| CEREBELLUM             | -    | -    | -   | -   | -   | -    | -    | -   | -   | -   |
| MEDULLA OBLONGATA      | -    | -    | -   | -   | -   | -    | -    | -   | -   | -   |
| PONS                   | -    | -    | -   | -   | -   | -    | -    | -   | -   | -   |
| SPINAL CORD, CERVIC.   | -    | -    | -   | -   | -   | -    | -    | -   | -   | -   |
| SPINAL CORD, THORAC.   | -    | -    | -   | -   | -   | -    | -    | -   | -   | -   |
| SPINAL CORD, LUMBAR    | -    | -    | -   | -   | -   | -    | -    | -   | -   | -   |
| SCIATIC NERVES         | ( +  | ( +  | ( - | ( - | ( - | ( +  | ( +  | ( - | ( - | ( - |
| - Axonal degeneration  | ( 1. | ( 1. | .   | .   | .   | ( 1. | ( 1. | .   | .   | .   |
| HEART                  | -    | -    | -   | -   | -   | +    | -    | -   | -   | -   |
| - Myocardial fibrosis  | .    | .    | .   | .   | .   | 1.   | .    | .   | .   | .   |
| AORTA                  | -    | -    | -   | -   | -   | -    | -    | -   | -   | -   |
| TRACHEA                | +    | -    | -   | -   | +   | -    | +    | +   | -   | -   |
| - Glandular dilation   | 1.   | .    | .   | .   | 2.  | .    | 1.   | 1.  | .   | .   |
| - Mononuclear foci     | .    | .    | .   | .   | .   | .    | .    | 1.  | .   | .   |
| LUNGS                  | -    | +G   | +   | -   | +   | +    | -    | +G  | +G  | +   |
| - Congestion           | .    | .    | .   | .   | .   | .    | .    | P.  | .   | .   |
| - Vasc. mineralization | .    | 1.   | 1.  | .   | 1.  | .    | .    | 1.  | 1.  | 1.  |
| - Osseous metaplasia   | .    | .    | 1.  | .   | .   | .    | .    | .   | .   | .   |
| - Alveolar macrophages | .    | .    | 1*  | .   | .   | 1.   | .    | 2*  | .   | .   |
| ESOPHAGUS              | +    | -    | -   | -   | -   | -    | -    | -   | -   | -   |
| - Mononuclear foci     | 1.   | .    | .   | .   | .   | .    | .    | .   | .   | .   |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 01, 0 MG/KG**

**ANIMAL NUMBER :**

|                        | 61   | 62  | 63   | 64   | 65  | 66  | 67   | 68   | 69  | 70   |
|------------------------|------|-----|------|------|-----|-----|------|------|-----|------|
|                        | FKO  | FKO | FKO  | FKO  | FKO | FKO | FKO  | FKO  | FKO | FKO  |
| STOMACH                | +    | +   | +    | -    | +   | -   | -    | +    | +   | +    |
| - Epithel. vacuolation | 2.   | .   | .    | .    | .   | .   | .    | .    | .   | .    |
| - Squamous hyperplasia | .    | .   | .    | .    | .   | .   | .    | .    | .   | 1.   |
| - Hyaline inclusions   | 2.   | 1.  | 1.   | .    | .   | .   | .    | 1.   | 1.  | 1.   |
| - Epithelial cyst(s)   | 1.   | .   | .    | .    | .   | .   | .    | .    | .   | .    |
| - Incr.inflamm.infilt. | .    | .   | .    | .    | .   | .   | .    | .    | 1.  | .    |
| - Erosion              | .    | .   | .    | .    | 1.  | .   | .    | .    | .   | .    |
| .....                  |      |     |      |      |     |     |      |      |     |      |
| DUODENUM               | -    | -   | -    | -    | -   | -   | -    | -    | -   | -    |
| .....                  |      |     |      |      |     |     |      |      |     |      |
| JEJUNUM                | -    | -   | -    | -    | -   | -   | -    | -    | -   | -    |
| .....                  |      |     |      |      |     |     |      |      |     |      |
| PEYERS PATCHES JEJ.    | +    | -   | -    | -    | -   | -   | -    | -    | -   | -    |
| - Mineralization       | 1.   | .   | .    | .    | .   | .   | .    | .    | .   | .    |
| .....                  |      |     |      |      |     |     |      |      |     |      |
| ILEUM                  | -    | -   | -    | -    | -   | -   | -    | -    | -   | -    |
| .....                  |      |     |      |      |     |     |      |      |     |      |
| PEYERS PATCHES ILEUM   | -    | -   | -    | -    | -   | -   | -    | -    | -   | -    |
| .....                  |      |     |      |      |     |     |      |      |     |      |
| CECUM                  | -    | -   | -    | -    | -   | -   | -    | -    | -   | -    |
| .....                  |      |     |      |      |     |     |      |      |     |      |
| COLON                  | -    | -   | -    | -    | -   | -   | -    | -    | -   | -    |
| .....                  |      |     |      |      |     |     |      |      |     |      |
| RECTUM                 | -    | -   | -    | -    | -   | -   | -    | -    | -   | -    |
| .....                  |      |     |      |      |     |     |      |      |     |      |
| LIVER                  | +    | -   | +    | +    | -   | +   | -    | +    | -   | -    |
| - Fatty change         | .    | .   | 1.   | 1.   | .   | .   | .    | .    | .   | .    |
| - Inflammatory foci    | 1.   | .   | 1.   | 1.   | .   | 1.  | .    | 1.   | .   | .    |
| .....                  |      |     |      |      |     |     |      |      |     |      |
| PANCREAS               | -    | -   | -    | -    | -*  | -   | -    | -    | -   | -    |
| .....                  |      |     |      |      |     |     |      |      |     |      |
| KIDNEYS                | +    | +   | +    | +    | -   | -   | +    | +    | -   | +    |
| - Tubular mineraliz.   | ( 1. | 1.  | ( 1. | .    | .   | .   | .    | .    | .   | .    |
| - Tubular basophilia   | ( 1. | .   | .    | .    | .   | .   | .    | ( 1. | .   | ( 1. |
| - Pyelonephritis       | .    | .   | .    | ( 1. | .   | .   | ( 1. | .    | .   | .    |
| .....                  |      |     |      |      |     |     |      |      |     |      |
| URINARY BLADDER        | -    | -   | -    | -    | -   | -   | -    | -    | -   | -    |
| .....                  |      |     |      |      |     |     |      |      |     |      |

**PATHOLOGY REPORT  
INDIVIDUAL ANIMAL DATA**

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RCC : 857092

TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 01, 0 MG/KG**

**ANIMAL NUMBER :**

|                           | 61  | 62  | 63   | 64   | 65  | 66  | 67  | 68  | 69  | 70  |
|---------------------------|-----|-----|------|------|-----|-----|-----|-----|-----|-----|
|                           | FKO | FKO | FKO  | FKO  | FKO | FKO | FKO | FKO | FKO | FKO |
| <b>OVARIES</b>            | -   | -   | +    | +    | -   | -   | -   | -   | -   | +   |
| - Rete ovarii             | .   | .   | .    | ( P. | .   | .   | .   | .   | .   | .   |
| - Corpus luteum cyst      | .   | .   | ( 1. | .    | .   | .   | .   | .   | .   | .   |
| - Interst. c. hyperpl.    | .   | .   | .    | .    | .   | .   | .   | .   | .   | 1.  |
| <b>UTERUS</b>             | +   | -   | +G   | +    | +   | -   | -   | -   | -   | +   |
| - Congestion              | .   | .   | P.   | .    | .   | .   | .   | .   | .   | .   |
| - Luminal dilation        | P.  | .   | .    | P.   | P.  | .   | .   | .   | .   | P.  |
| - Epithelial cyst(s)      | .   | .   | .    | .    | .   | .   | .   | .   | .   | P.  |
| <b>VAGINA</b>             | +   | +   | +    | +    | +   | +   | +   | +   | +   | +   |
| - Proestrus               | .   | .   | .    | P.   | P.  | .   | .   | .   | .   | P.  |
| - Estrus                  | P.  | .   | .    | .    | .   | .   | P.  | .   | .   | .   |
| - Metestrus               | .   | .   | P.   | .    | .   | .   | .   | P.  | .   | .   |
| - Diestrus                | .   | P.  | .    | .    | .   | P.  | .   | .   | P.  | .   |
| <b>PITUITARY GLAND</b>    | -   | -   | -    | -    | -   | -   | -   | -   | -   | -   |
| <b>THYROID GLAND</b>      | -   | -   | +    | -    | -   | -   | -   | -   | -   | -   |
| - Thymic remnant          | .   | .   | ( P. | .    | .   | .   | .   | .   | .   | .   |
| <b>PARATHYROID GLANDS</b> | -   | -   | -    | ( -  | -   | ( - | ( - | -   | -   | ( - |
| <b>ADRENAL CORTICES</b>   | -   | -   | -    | -    | -   | -   | -   | -   | -   | -   |
| <b>ADRENAL MEDULLAS</b>   | -   | -   | -    | -    | -   | -   | -   | -   | -   | -   |
| <b>SPLEEN</b>             | +   | +   | +    | +    | +   | +   | +   | +   | +   | +   |
| - Hemosiderin             | 2.  | 1.  | 1.   | 1.   | 2.  | 1.  | 1.  | 1.  | 2.  | 2.  |
| <b>BONE MARROW, FEMUR</b> | +   | +   | +    | +    | +   | +   | +   | +   | +   | +   |
| - Fatty replacement       | 1.  | 1.  | 1.   | 2.   | 1.  | .   | 1.  | 1.  | 2.  | 2.  |
| - Incr. erythropoiesis    | .   | .   | .    | .    | .   | 1.  | .   | .   | .   | .   |
| <b>THYMUS</b>             | +   | +   | +    | +    | +   | -   | -   | +   | +   | -   |
| - Cyst(s)                 | P.  | P.  | P.   | P.   | P.  | .   | .   | P.  | P.  | .   |
| <b>MESENT. LYMPH NODE</b> | -   | -   | -    | -    | -   | -   | -   | -   | -   | -   |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 01, 0 MG/KG**

ANIMAL NUMBER :

|                     | 61   | 62   | 63  | 64   | 65   | 66   | 67   | 68  | 69   | 70   |
|---------------------|------|------|-----|------|------|------|------|-----|------|------|
|                     | FKO  | FKO  | FKO | FKO  | FKO  | FKO  | FKO  | FKO | FKO  | FKO  |
| MANDIB. LYMPH NODES | ( -  | ( -  | ( - | ( -  | ( -  | ( -  | ( -  | ( - | ( -  | ( -  |
| SUBLINGUAL GLANDS   | +    | -    | -   | -    | -    | -    | -    | -   | -    | -    |
| - Serous metaplasia | ( 1. | .    | .   | .    | .    | .    | .    | .   | .    | .    |
| MANDIBULAR GLANDS   | -    | -    | -   | -    | -    | -    | -    | -   | -    | -    |
| MAMMARY GLAND AREA  | -    | -    | -   | -    | -    | -    | -    | -   | -    | +    |
| - Lobular alveoli   | .    | .    | .   | .    | .    | .    | .    | .   | .    | P.   |
| SKIN/SUBCUTIS       | -    | -    | -   | -    | -    | -    | -    | -   | -    | -    |
| EYES                | -    | -    | -   | -    | -    | -    | -*   | -   | -    | -*   |
| RETROORBITAL TISSUE | +    | +    | -   | +    | +    | +    | +    | -   | +    | +    |
| - Hemorrhage        | ( 1. | ( 1. | .   | ( 1. | ( 2. | ( 2. | ( 1. | .   | ( 1. | ( 1. |
| - Inflammation      | ( 1. | .    | .   | .    | .    | .    | .    | .   | .    | .    |
| OPTIC NERVES        | -    | -    | -   | -    | -    | -    | -    | -   | -    | -    |

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TEST ARTICLE : A084, WR 23081  
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PATHOL. NO.: 80076 NED  
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PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 01, 0 MG/KG**

ANIMAL NUMBER :

71 72 73 74 75  
FK1 FK1 FK1 FK1 FK1

|                    | 71  | 72  | 73  | 74    | 75  |
|--------------------|-----|-----|-----|-------|-----|
|                    | FK1 | FK1 | FK1 | FK1   | FK1 |
| OVARIES            | '   | '   | '   | '     | +G  |
| - Congestion       |     |     |     |       | P.  |
| UTERUS             | '   | '   | '   | '     | +G  |
| - Luminal dilation |     |     |     |       | P.  |
| THYROID GLAND      | -   | -   | -   | -     | -   |
| PARATHYROID GLANDS | 0   | 0   | ( - | 0 ( - |     |

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TEST ARTICLE : A084, WR 23081  
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SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 02, 15 MG/KG**

**ANIMAL NUMBER :**

|                        | 16  | 17  | 18  | 19  | 20  | 21  | 22  | 23   | 24   | 25  |
|------------------------|-----|-----|-----|-----|-----|-----|-----|------|------|-----|
|                        | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO  | MKO  | MKO |
| CEREBRUM               | -   | -   | -   | -   | -   | -   | -   | -    | -    | -   |
| CEREBELLUM             | -   | -   | -   | -   | -   | -   | -   | -    | -    | -   |
| MEDULLA OBLONGATA      | -   | -   | -   | -   | -   | -   | -   | -    | -    | -   |
| PONS                   | -   | -   | -   | -   | -   | -   | -   | -    | -    | -   |
| SPINAL CORD, CERVIC.   | -   | -   | -   | -   | -   | -   | -   | -    | -    | -   |
| SPINAL CORD, THORAC.   | -   | -   | -   | -   | -   | -   | -   | -    | -    | -   |
| SPINAL CORD, LUMBAR    | -   | -   | -   | -   | -   | -   | -   | -    | -    | -   |
| SCIATIC NERVES         | ( - | ( - | ( - | ( - | ( - | ( - | ( - | ( +  | ( +  | ( - |
| - Axonal degeneration  | .   | .   | .   | .   | .   | .   | .   | ( 1. | ( 1. | .   |
| HEART                  | -   | -   | -   | +   | -   | -   | -   | +    | -    | -   |
| - Inflammatory foci    | .   | .   | .   | 1.  | .   | .   | .   | 2.   | .    | .   |
| - Myocardial fibrosis  | .   | .   | .   | .   | .   | .   | .   | 1.   | .    | .   |
| AORTA                  | -   | -   | -   | -   | -   | -   | -   | -    | -    | -   |
| TRACHEA                | +   | -   | -   | +   | -   | -   | -   | -    | -    | +   |
| - Glandular dilation   | .   | .   | .   | 1.  | .   | .   | .   | .    | .    | 1.  |
| - Mononuclear foci     | 1.  | .   | .   | .   | .   | .   | .   | .    | .    | .   |
| LUNGS                  | -   | +   | -   | +   | -   | +   | +   | +    | +    | +   |
| - Vasc. mineralization | .   | 1.  | .   | 1.  | .   | 1.  | 1.  | 1.   | 1.   | 1.  |
| - Alveolar hemorrhage  | .   | .   | .   | .   | .   | .   | .   | .    | .    | 1.  |
| - Alveolar macrophages | .   | .   | .   | 1*  | .   | .   | 1.  | 1.   | .    | .   |
| ESOPHAGUS              | -   | -   | -   | -   | -   | -   | -   | -    | -    | -   |
| STOMACH                | -   | -   | -   | +   | +   | +   | +   | +    | -    | +   |
| - Hyperkeratosis       | .   | .   | .   | .   | .   | .   | 1.  | .    | .    | .   |
| - Epithel. vacuolation | .   | .   | .   | .   | 1.  | .   | .   | .    | .    | .   |
| - Hyaline inclusions   | .   | .   | .   | 1.  | 1.  | 1.  | .   | 1.   | .    | .   |
| - Epithelial cyst(s)   | .   | .   | .   | .   | .   | .   | .   | 1.   | .    | 1.  |



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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 02, 15 MG/KG**

**ANIMAL NUMBER :**

|                        | 16  | 17  | 18   | 19   | 20   | 21   | 22   | 23  | 24   | 25   |
|------------------------|-----|-----|------|------|------|------|------|-----|------|------|
|                        | MKO | MKO | MKO  | MKO  | MKO  | MKO  | MKO  | MKO | MKO  | MKO  |
| DUODENUM               | -   | -   | -    | -    | -    | -    | -    | -   | -    | -    |
| .....                  |     |     |      |      |      |      |      |     |      |      |
| JEJUNUM                | -   | -   | -    | -    | -    | -    | -    | -   | -    | -    |
| .....                  |     |     |      |      |      |      |      |     |      |      |
| PEYERS PATCHES JEJ.    | -   | -   | -    | -    | -    | -    | -    | -   | -    | -    |
| .....                  |     |     |      |      |      |      |      |     |      |      |
| ILEUM                  | -   | -   | -    | -    | -    | -    | -    | -   | -    | -    |
| .....                  |     |     |      |      |      |      |      |     |      |      |
| PEYERS PATCHES ILEUM   | -   | -   | -    | -    | -    | -    | -    | -   | -    | -    |
| .....                  |     |     |      |      |      |      |      |     |      |      |
| CECUM                  | -   | -   | -    | -    | -    | -    | -    | -   | -    | -    |
| .....                  |     |     |      |      |      |      |      |     |      |      |
| COLON                  | -   | -   | -    | -    | -    | -    | -    | -   | -    | -    |
| .....                  |     |     |      |      |      |      |      |     |      |      |
| RECTUM                 | -   | +   | -    | +    | -    | -    | -    | -   | +    | -    |
| - Luminal dilation     | .   | .   | .    | P.   | .    | .    | .    | .   | P.   | .    |
| - Luminal nematodes    | .   | 1.  | .    | .    | .    | .    | .    | .   | .    | .    |
| .....                  |     |     |      |      |      |      |      |     |      |      |
| LIVER                  | +   | +   | -    | +    | +    | +    | -    | +   | +    | +    |
| - Fatty change         | 1.  | .   | .    | .    | .    | 2.   | .    | 1.  | .    | .    |
| - Hemopoietic foci     | .   | .   | .    | 1.   | .    | .    | .    | .   | .    | .    |
| - Inflammatory foci    | 1.  | 1.  | .    | .    | 2.   | 2.   | .    | .   | 2.   | 2.   |
| - Peribiliary inflamm. | .   | .   | .    | .    | .    | 1.   | .    | .   | .    | 1.   |
| .....                  |     |     |      |      |      |      |      |     |      |      |
| PANCREAS               | -   | -   | -    | -    | -    | -    | -    | -   | -    | -    |
| .....                  |     |     |      |      |      |      |      |     |      |      |
| KIDNEYS                | +   | -   | +    | +    | +    | +G   | +    | +   | +    | +G   |
| - Pelvic dilation      | .   | .   | ( P. | .    | .    | .    | .    | .   | ( P. | .    |
| - Hyaline droplets     | 1.  | .   | .    | .    | ( 1. | .    | 2.   | 1.  | 3*   | 1.   |
| - Tubular basophilia   | 1.  | .   | ( 1. | ( 1. | ( 1. | ( 1. | ( 1. | .   | ( 1. | ( 1. |
| - Pigment basoph.cells | .   | .   | .    | .    | .    | .    | ( 1. | .   | ( 1. | ( 1. |
| .....                  |     |     |      |      |      |      |      |     |      |      |
| URINARY BLADDER        | -   | -   | -    | -    | -    | -    | -    | -   | -    | -    |
| .....                  |     |     |      |      |      |      |      |     |      |      |

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INDIVIDUAL ANIMAL DATA**

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TEST ARTICLE : A084, WR 23081  
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SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 02, 15 MG/KG**

**ANIMAL NUMBER :**

|                           | 16  | 17   | 18   | 19   | 20   | 21  | 22   | 23  | 24  | 25  |
|---------------------------|-----|------|------|------|------|-----|------|-----|-----|-----|
|                           | MKO | MKO  | MKO  | MKO  | MKO  | MKO | MKO  | MKO | MKO | MKO |
| <b>TESTES</b>             | -   | +G   | +    | +    | +    | -   | -*   | -   | -   | -*  |
| - Rete dilation           | .   | ( P. | .    | .    | .    | .   | .    | .   | .   | .   |
| - Tubular hypoplasia      | .   | .    | .    | .    | ( 1. | .   | .    | .   | .   | .   |
| - Tubular vacuolation     | .   | .    | ( 1. | 1.   | .    | .   | .    | .   | .   | .   |
| - Tubular degeneration    | .   | 5*   | .    | ( 1. | .    | .   | .    | .   | .   | .   |
| - Inflammation            | .   | ( 2. | .    | .    | .    | .   | .    | .   | .   | .   |
| .....                     |     |      |      |      |      |     |      |     |     |     |
| <b>EPIDIDYMIDES</b>       | -   | +    | -    | +    | -    | -   | -    | -   | -   | -   |
| - Hypozoospermia          | .   | 5.   | .    | .    | .    | .   | .    | .   | .   | .   |
| - Cellular debris         | .   | 3.   | .    | .    | .    | .   | .    | .   | .   | .   |
| - Inflammatory foci       | .   | .    | .    | ( 1. | .    | .   | .    | .   | .   | .   |
| .....                     |     |      |      |      |      |     |      |     |     |     |
| <b>PROSTATE GLAND</b>     | -   | +    | -    | -    | -    | +   | -    | +   | -   | -   |
| - Glandular atrophy       | .   | 2.   | .    | .    | .    | .   | .    | .   | .   | .   |
| - Glandular hyperplas.    | .   | .    | .    | .    | .    | 1.  | .    | 1.  | .   | .   |
| .....                     |     |      |      |      |      |     |      |     |     |     |
| <b>COAGULATING GLANDS</b> | -   | -    | -    | -    | -    | -   | -    | -   | -   | -   |
| .....                     |     |      |      |      |      |     |      |     |     |     |
| <b>SEMINAL VESICLES</b>   | -   | -    | -    | -    | -    | -   | -    | -   | -   | -   |
| .....                     |     |      |      |      |      |     |      |     |     |     |
| <b>PITUITARY GLAND</b>    | -   | -    | -    | -    | +    | -   | -    | -   | +   | -   |
| - Hypertr/pl.chromoph.    | .   | .    | .    | .    | 1.   | .   | .    | .   | 1.  | .   |
| .....                     |     |      |      |      |      |     |      |     |     |     |
| <b>THYROID GLAND</b>      | -   | -    | -    | -    | +    | -   | -    | -   | -   | -   |
| - Follic. hypertrophy     | .   | .    | .    | .    | 1.   | .   | .    | .   | .   | .   |
| .....                     |     |      |      |      |      |     |      |     |     |     |
| <b>PARATHYROID GLANDS</b> | -   | ( -  | ( -  | ( -  | ( -  | ( - | -    | ( - | ( - | -   |
| .....                     |     |      |      |      |      |     |      |     |     |     |
| <b>ADRENAL CORTICES</b>   | +   | -    | +    | +    | -    | +   | +    | +   | -   | -   |
| - Access. cort. tiss.     | .   | .    | .    | ( P. | .    | .   | ( P. | .   | .   | .   |
| - Vacuolation, Z.fasc.    | 2*  | .    | 2.   | .    | .    | 1.  | 2.   | 2.  | .   | .   |
| .....                     |     |      |      |      |      |     |      |     |     |     |
| <b>ADRENAL MEDULLAS</b>   | -   | -    | -    | -    | -    | -   | -    | -   | -   | -   |
| .....                     |     |      |      |      |      |     |      |     |     |     |
| <b>SPLEEN</b>             | +   | +    | -    | +    | +    | +   | +    | -   | +   | +   |
| - Extram. hemopoiesis     | 1.  | .    | .    | 1.   | 2.   | 1.  | 1.   | .   | 1.  | .   |
| - Hemosiderin             | 1.  | 1.   | .    | 1.   | 1.   | 1.  | .    | .   | .   | 1.  |
| .....                     |     |      |      |      |      |     |      |     |     |     |

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TEST ARTICLE : A084, WR 23081  
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**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 02, 15 MG/KG**

**ANIMAL NUMBER :**

|                            | 16   | 17   | 18   | 19   | 20   | 21   | 22   | 23   | 24   | 25   |
|----------------------------|------|------|------|------|------|------|------|------|------|------|
|                            | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  |
| <b>BONE MARROW, FEMUR</b>  | -    | +    | +    | -    | -    | +    | +    | +    | +    | -    |
| - Fatty replacement        | .    | 1.   | 1.   | .    | .    | 2.   | 1.   | 1.   | 1.   | .    |
| <b>THYMUS</b>              | -    | +    | -    | +    | +    | +    | +    | +    | -    | -    |
| - Cyst(s)                  | .    | .    | .    | P.   | P.   | P.   | P.   | .    | .    | .    |
| - Hemorrhage               | .    | 1.   | .    | 1.   | .    | .    | .    | 1.   | .    | .    |
| <b>MESENT. LYMPH NODE</b>  | -    | -    | -    | -    | -    | -    | -    | +    | -    | -    |
| - Sinus dilation           | .    | .    | .    | .    | .    | .    | .    | 1.   | .    | .    |
| <b>MANDIB. LYMPH NODES</b> | ( -  | ( -  | ( -  | ( -  | ( -  | ( +  | ( -  | ( -  | ( -  | ( -  |
| - Hemorrhage               | .    | .    | .    | .    | .    | ( 1. | .    | .    | .    | .    |
| <b>SUBLINGUAL GLANDS</b>   | -    | -    | ( -  | ( -  | -    | -    | -    | -    | -    | -    |
| <b>MANDIBULAR GLANDS</b>   | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| <b>MAMMARY GLAND AREA</b>  | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| <b>SKIN/SUBCUTIS</b>       | -    | -    | -    | -    | -    | +G   | -    | -    | -    | -    |
| - Inflammation             | .    | .    | .    | .    | .    | 2.   | .    | .    | .    | .    |
| - Hemorrhage               | .    | .    | .    | .    | .    | 2.   | .    | .    | .    | .    |
| <b>EYES</b>                | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| <b>RETROORBITAL TISSUE</b> | +    | +    | +    | +    | +    | +    | +    | +    | +    | +    |
| - Hemorrhage               | ( 1. | ( 1. | ( 2. | ( 2. | ( 2. | ( 2. | ( 1. | ( 2. | ( 2. | ( 2. |
| - Inflammation             | .    | ( 1. | .    | .    | .    | .    | ( 1. | .    | ( 1. | .    |
| <b>OPTIC NERVES</b>        | -    | -    | -    | -    | -    | ( -  | -    | -    | -    | -    |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 02, 15 MG/KG

ANIMAL NUMBER :

26 27 28 29 30  
MK1 MK1 MK1 MK1 MK1

THYROID GLAND - - - - -  
.....  
PARATHYROID GLANDS - ( - ( - - -  
.....

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INDIVIDUAL ANIMAL DATA**

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)**  
DOSE GROUP : 02, 15 MG/KG

ANIMAL NUMBER :

|                        | 76  | 77  | 78  | 79  | 80  | 81  | 82  | 83  | 84  | 85  |
|------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                        | FKO | FKO | FKO | FKO | FKO | FKO | FKO | FKO | FKO | FKO |
| CEREBRUM               | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| CEREBELLUM             | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| MEDULLA OBLONGATA      | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| PONS                   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| SPINAL CORD, CERVIC.   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| SPINAL CORD, THORAC.   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| SPINAL CORD, LUMBAR    | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| SCIATIC NERVES         | ( - | ( - | ( - | ( - | ( - | ( - | ( - | ( - | ( - | ( - |
| HEART                  | +   | -   | -   | -   | -   | -   | +   | -   | -   | -   |
| - Inflammatory foci    | 1.  | .   | .   | .   | .   | .   | 1.  | .   | .   | .   |
| AORTA                  | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| TRACHEA                | -   | +   | -   | -   | -   | +   | -   | -   | +   | +   |
| - Glandular dilation   | .   | .   | .   | .   | .   | 1.  | .   | .   | .   | 1.  |
| - Mononuclear foci     | .   | 2.  | .   | .   | .   | .   | .   | .   | 1.  | .   |
| LUNGS                  | -*  | -   | +   | -   | +   | +   | +   | +   | +   | -G  |
| - Vasc. mineralization | .   | .   | 1.  | .   | 1.  | 1.  | 1.  | 1.  | 1.  | .   |
| - Alveolar macrophages | .   | .   | .   | .   | .   | .   | .   | .   | 1*  | .   |
| ESOPHAGUS              | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| STOMACH                | -   | +   | +   | -   | +   | -   | +   | -   | -   | +   |
| - Hyperkeratosis       | .   | 1.  | .   | .   | .   | .   | .   | .   | .   | .   |
| - Epithel. vacuolation | .   | .   | .   | .   | .   | .   | .   | .   | .   | 1.  |
| - Squamous hyperplasia | .   | .   | .   | .   | .   | .   | .   | .   | .   | 1.  |
| - Hyaline inclusions   | .   | 1.  | 1.  | .   | 1.  | .   | 1.  | .   | .   | .   |
| - Ulceration           | .   | 2.  | .   | .   | .   | .   | .   | .   | .   | .   |
| DUODENUM               | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 02, 15 MG/KG**

ANIMAL NUMBER :

|                        | 76   | 77  | 78  | 79   | 80   | 81  | 82   | 83   | 84   | 85   |
|------------------------|------|-----|-----|------|------|-----|------|------|------|------|
|                        | FKO  | FKO | FKO | FKO  | FKO  | FKO | FKO  | FKO  | FKO  | FKO  |
| JEJUNUM                | -    | -   | -   | -    | -    | -   | -    | -    | -    | -    |
| .....                  |      |     |     |      |      |     |      |      |      |      |
| PEYERS PATCHES JEJ.    | +    | -   | 0   | -    | -    | -   | 0    | -    | 0    | -    |
| - Mineralization       | 1.   | .   | .   | .    | .    | .   | .    | .    | .    | .    |
| .....                  |      |     |     |      |      |     |      |      |      |      |
| ILEUM                  | -    | -   | -   | -    | -    | -   | -    | -    | -    | -    |
| .....                  |      |     |     |      |      |     |      |      |      |      |
| PEYERS PATCHES ILEUM   | -    | -   | -   | -    | -    | -   | -    | -    | -    | -    |
| .....                  |      |     |     |      |      |     |      |      |      |      |
| CECUM                  | -    | -   | -   | -    | -    | -   | -    | -    | -    | -    |
| .....                  |      |     |     |      |      |     |      |      |      |      |
| COLON                  | -    | -   | -   | -    | -    | -   | -    | -    | -    | -    |
| .....                  |      |     |     |      |      |     |      |      |      |      |
| RECTUM                 | -    | -   | -   | +    | -    | -   | -    | -    | -    | -    |
| - Luminal dilation     | .    | .   | .   | P.   | .    | .   | .    | .    | .    | .    |
| .....                  |      |     |     |      |      |     |      |      |      |      |
| LIVER                  | +    | +   | +   | -    | +    | +   | +    | -    | +    | +    |
| - Fatty change         | .    | .   | 1.  | .    | .    | .   | .    | .    | .    | .    |
| - Inflammatory foci    | 1.   | 1.  | .   | .    | 1.   | 1.  | 1.   | .    | 1.   | 1.   |
| .....                  |      |     |     |      |      |     |      |      |      |      |
| PANCREAS               | -    | -*  | -   | -*   | -    | -   | -    | -    | -    | +    |
| - Basophilic foci      | .    | .   | .   | .    | .    | .   | .    | .    | .    | 1.   |
| .....                  |      |     |     |      |      |     |      |      |      |      |
| KIDNEYS                | +    | +   | -   | +    | +    | -   | +    | +    | +    | +    |
| - Pelvic dilation      | .    | .   | .   | .    | ( P. | .   | .    | .    | .    | .    |
| - Cortical cyst        | .    | .   | .   | ( P. | .    | .   | .    | .    | .    | .    |
| - Tubular mineraliz.   | ( 1. | .   | .   | .    | .    | .   | .    | .    | ( 1. | .    |
| - Tubulus cell swell.  | .    | 1.  | .   | .    | .    | .   | 1.   | 1.   | 1.   | 1.   |
| - Pigment tubul. cells | .    | .   | .   | .    | .    | .   | 1.   | ( 1. | ( 1. | ( 1. |
| - Tubular basophilia   | .    | .   | .   | .    | .    | .   | .    | .    | ( 1. | .    |
| - Pyelonephritis       | .    | .   | .   | 1.   | .    | .   | .    | ( 1. | .    | .    |
| .....                  |      |     |     |      |      |     |      |      |      |      |
| URINARY BLADDER        | -    | -   | -   | -    | -    | -   | -    | -    | -    | -    |
| .....                  |      |     |     |      |      |     |      |      |      |      |
| OVARIES                | +    | -   | -   | +    | -    | -   | +    | -    | +    | -    |
| - Congestion           | .    | .   | .   | .    | .    | .   | ( P. | .    | .    | .    |
| - Interst. c. hyperpl. | ( 1. | .   | .   | 2.   | .    | .   | 1.   | .    | 2.   | .    |
| - Atrophy              | .    | .   | .   | 3.   | .    | .   | .    | .    | .    | .    |
| .....                  |      |     |     |      |      |     |      |      |      |      |

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TEST ARTICLE : A084, WR 23081  
 TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
 SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
 DATE : 19-JUL-05  
 PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)**  
 DOSE GROUP : 02, 15 MG/KG

ANIMAL NUMBER :

|                        | 76   | 77  | 78   | 79   | 80  | 81  | 82  | 83   | 84  | 85  |
|------------------------|------|-----|------|------|-----|-----|-----|------|-----|-----|
|                        | FKO  | FKO | FKO  | FKO  | FKO | FKO | FKO | FKO  | FKO | FKO |
| UTERUS                 | +    | +G  | -    | -    | -   | +   | -   | +G   | -   | -   |
| - Luminal dilation     | P.   | P.  | .    | .    | .   | P.  | .   | P.   | .   | .   |
| VAGINA                 | +    | +   | +    | +    | +   | +   | +   | +    | +   | +   |
| - Proestrus            | P.   | .   | P.   | .    | .   | P.  | .   | P.   | .   | .   |
| - Estrus               | .    | P.  | .    | .    | .   | .   | P.  | .    | .   | P.  |
| - Diestrus             | .    | .   | .    | P.   | P.  | .   | .   | .    | P.  | .   |
| - Hypermucification    | .    | .   | .    | 2.   | .   | .   | .   | .    | .   | .   |
| - Luminal plugs        | .    | .   | .    | .    | 1.  | .   | .   | .    | .   | .   |
| PITUITARY GLAND        | -    | -   | -    | -    | -   | -   | -   | -    | -   | -   |
| THYROID GLAND          | -    | -   | +    | +    | -   | -   | -   | -    | -   | -   |
| - Ultimobranchial cyst | .    | .   | .    | ( P. | .   | .   | .   | .    | .   | .   |
| - Follic. hypertrophy  | .    | .   | ( 1. | .    | .   | .   | .   | .    | .   | .   |
| PARATHYROID GLANDS     | 0    | ( - | ( -  | ( -  | -   | ( - | 0   | ( -  | 0   | -   |
| ADRENAL CORTICES       | +    | -   | -    | -    | -   | -   | -   | +    | -   | -   |
| - Hemosiderin          | ( 1. | .   | .    | .    | .   | .   | .   | .    | .   | .   |
| - Hemopoietic foci     | ( 1. | .   | .    | .    | .   | .   | .   | .    | .   | .   |
| - Hypertrophy, nodular | .    | .   | .    | .    | .   | .   | .   | ( 2. | .   | .   |
| ADRENAL MEDULLAS       | -    | -   | -    | -    | -   | -   | -   | -    | -   | -   |
| SPLEEN                 | +    | +   | +    | +    | +   | +   | +   | +    | +   | +   |
| - Extram. hemopoiesis  | 3.   | .   | .    | .    | .   | 1.  | 1.  | 1.   | .   | .   |
| - Hemosiderin          | 2.   | 2.  | 2.   | 2.   | 1.  | 1.  | 2.  | 2.   | 2.  | 2.  |
| BONE MARROW, FEMUR     | +    | -   | +    | +    | +   | +   | -   | +    | -   | +   |
| - Fatty replacement    | 1.   | .   | 1.   | 1.   | 2.  | 1.  | .   | 1.   | .   | 2.  |
| - Incr. erythropoiesis | 1.   | .   | 1.   | .    | .   | 1.  | .   | 1.   | .   | .   |
| THYMUS                 | +    | +   | +    | -    | +   | -   | -   | +    | +   | +   |
| - Cyst(s)              | P.   | P.  | P.   | .    | P.  | .   | .   | P.   | P.  | P.  |
| MESENT. LYMPH NODE     | -    | -   | -    | -    | -   | -   | -   | -    | -   | -   |
| MANDIB. LYMPH NODES    | ( -  | ( - | ( -  | ( -  | ( - | ( - | ( - | ( -  | ( - | ( - |

**PATHOLOGY REPORT  
INDIVIDUAL ANIMAL DATA**

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 02, 15 MG/KG**

ANIMAL NUMBER :

|                     | 76  | 77   | 78  | 79   | 80   | 81   | 82  | 83   | 84   | 85   |
|---------------------|-----|------|-----|------|------|------|-----|------|------|------|
|                     | FKO | FKO  | FKO | FKO  | FKO  | FKO  | FKO | FKO  | FKO  | FKO  |
| SUBLINGUAL GLANDS   | -   | -    | -   | -    | -    | -    | -   | -    | -    | -    |
| .....               |     |      |     |      |      |      |     |      |      |      |
| MANDIBULAR GLANDS   | -   | -    | -   | -    | -    | -    | -   | -    | -    | -    |
| .....               |     |      |     |      |      |      |     |      |      |      |
| MAMMARY GLAND AREA  | -   | -    | -   | -    | -    | -    | -   | -    | -    | -    |
| .....               |     |      |     |      |      |      |     |      |      |      |
| SKIN/SUBCUTIS       | -   | -    | -   | -    | -    | -    | -   | -    | -    | -    |
| .....               |     |      |     |      |      |      |     |      |      |      |
| EYES                | -   | -    | -   | -    | -    | -    | -   | -    | -    | -    |
| .....               |     |      |     |      |      |      |     |      |      |      |
| RETROORBITAL TISSUE | -   | +    | -   | +    | +    | +    | -   | +    | +    | +    |
| - Hemorrhage        | .   | ( 2. | .   | ( 1. | ( 1. | ( 1. | .   | ( 1. | ( 1. | ( 2. |
| - Inflammation      | .   | .    | .   | .    | ( 1. | .    | .   | .    | .    | ( 1. |
| .....               |     |      |     |      |      |      |     |      |      |      |
| OPTIC NERVES        | -   | -    | -   | -    | -    | -    | -   | -    | -    | -    |
| .....               |     |      |     |      |      |      |     |      |      |      |



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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 02, 15 MG/KG**

ANIMAL NUMBER :

86 87 88 89 90  
FK1 FK1 FK1 FK1 FK1

THYROID GLAND - - - - -  
- Follic. hypertrophy . 1. . . .  
.....  
PARATHYROID GLANDS ( - - ( - - 0  
.....

**PATHOLOGY REPORT  
INDIVIDUAL ANIMAL DATA**

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 03, 50 MG/KG**

**ANIMAL NUMBER :**

|                        | 31     | 32    | 33     | 34     | 35     | 36     | 37     | 38     | 39     | 40     |
|------------------------|--------|-------|--------|--------|--------|--------|--------|--------|--------|--------|
|                        | MKO    | MKO   | MKO    | MKO    | MKO    | MKO    | MKO    | MKO    | MKO    | MKO    |
| CEREBRUM               | -      | -     | -      | -      | -      | -      | -      | -      | -      | -      |
| CEREBELLUM             | -      | -     | -      | -      | -      | -      | -      | -      | -      | -      |
| MEDULLA OBLONGATA      | -      | -     | -      | -      | -      | -      | -      | -      | -      | -      |
| PONS                   | -      | -     | -      | -      | -      | -      | -      | -      | -      | -      |
| SPINAL CORD, CERVIC.   | -      | -     | -      | -      | -      | -      | -      | -      | -      | -      |
| SPINAL CORD, THORAC.   | -      | -     | -      | -      | -      | -      | -      | -      | -      | -      |
| SPINAL CORD, LUMBAR    | -      | -     | -      | -      | -      | -      | -      | -      | -      | -      |
| SCIATIC NERVES         | ( -    | ( +   | ( +    | ( -    | ( -    | ( +    | ( -    | ( -    | ( -    | ( -    |
| - Axonal degeneration  | . ( 1. | ( 1.  | . ( 1. | . ( 1. | . ( 1. | . ( 1. | . ( 1. | . ( 1. | . ( 1. | . ( 1. |
| HEART                  | -      | +     | +      | -      | -      | -      | +      | +      | -      | -      |
| - Inflammatory foci    | . .    | . 1.  | . .    | . .    | . .    | . .    | . 1.   | . 1.   | . .    | . .    |
| - Myocardial fibrosis  | . .    | . 1.  | . .    | . .    | . .    | . .    | . 1.   | . .    | . .    | . .    |
| AORTA                  | -      | -     | -      | -      | -      | -      | -      | -      | -      | -      |
| TRACHEA                | -      | -     | -      | +      | -      | -      | -      | +      | +      | -      |
| - Glandular dilation   | . .    | . .   | . .    | . 1.   | . .    | . .    | . .    | . 2.   | . 1.   | . .    |
| LUNGS                  | +      | +     | +      | +      | +      | +      | -      | +      | +      | -      |
| - Vasc. mineralization | 1. 1.  | 1. 1. | 1. 1.  | 1. 1.  | 1. 1.  | 1. 1.  | . .    | 1. 1.  | 1. 1.  | . .    |
| - Osseous metaplasia   | . .    | . .   | . 1.   | . .    | . .    | . .    | . .    | . .    | . .    | . .    |
| - Alveolar macrophages | . .    | . .   | . .    | . .    | . .    | . .    | . .    | . 1.   | . .    | . .    |
| ESOPHAGUS              | -      | -     | -      | -      | -      | +      | -      | -      | -      | -      |
| - Mononuclear foci     | . .    | . .   | . .    | . .    | . .    | . 2.   | . .    | . .    | . .    | . .    |

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INDIVIDUAL ANIMAL DATA**

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)**  
DOSE GROUP : 03, 50 MG/KG

ANIMAL NUMBER :

|                        | 31  | 32  | 33  | 34  | 35  | 36  | 37  | 38  | 39  | 40  |
|------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                        | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO |
| STOMACH                | +   | -   | +   | +   | +   | +   | +   | +   | +G  | +   |
| - Hyperkeratosis       | .   | .   | .   | .   | 2.  | .   | .   | .   | .   | .   |
| - Epithel. vacuolation | .   | .   | .   | .   | 1.  | .   | .   | .   | .   | 1.  |
| - Squamous hyperplasia | .   | .   | .   | .   | 1.  | .   | .   | .   | .   | .   |
| - Hyaline inclusions   | 1.  | .   | 1.  | 1.  | .   | 1.  | 1.  | 1.  | 1.  | 1.  |
| - Epithelial cyst(s)   | .   | .   | 1.  | .   | .   | .   | .   | .   | 1.  | .   |
| - Cryptabscess(es)     | .   | .   | 1.  | .   | .   | .   | .   | .   | .   | .   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| DUODENUM               | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| JEJUNUM                | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| PEYERS PATCHES JEJ.    | -   | -   | -   | -   | +   | -   | -   | -   | -   | -   |
| - Mineralization       | .   | .   | .   | .   | 1.  | .   | .   | .   | .   | .   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| ILEUM                  | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| PEYERS PATCHES ILEUM   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| CECUM                  | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| COLON                  | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| RECTUM                 | -   | -   | +   | -   | -   | -   | +   | -   | -   | -   |
| - Luminal dilation     | .   | .   | P.  | .   | .   | .   | P.  | .   | .   | .   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| LIVER                  | +   | +   | +   | +   | -   | +   | +   | +   | +   | +   |
| - Fatty change         | .   | .   | .   | .   | .   | 1.  | .   | 1.  | .   | .   |
| - Inflammatory foci    | 1.  | 1.  | 1.  | 1.  | .   | .   | 1.  | 2.  | 1.  | 2.  |
| - Peribiliary inflamm. | 1.  | .   | .   | .   | .   | .   | 1.  | .   | .   | .   |
| - Bile duct prolifer.  | .   | .   | .   | .   | .   | 1.  | .   | .   | .   | .   |
| - Hepatoc. hypertrophy | .   | .   | .   | .   | .   | .   | .   | .   | .   | 1.  |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| PANCREAS               | +G  | -   | -   | -   | -   | +   | -   | +   | +   | -   |
| - Congestion           | P.  | .   | .   | .   | .   | .   | .   | .   | .   | .   |
| - Acinar atrophy       | .   | .   | .   | .   | .   | 1.  | .   | 2.  | .   | .   |
| - Basophilic foci      | .   | .   | .   | .   | .   | .   | .   | .   | 1.  | .   |
| .....                  |     |     |     |     |     |     |     |     |     |     |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 03, 50 MG/KG**

**ANIMAL NUMBER :**

|                           | 31   | 32   | 33   | 34  | 35   | 36   | 37   | 38   | 39   | 40   |
|---------------------------|------|------|------|-----|------|------|------|------|------|------|
|                           | MKO  | MKO  | MKO  | MKO | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  |
| <b>KIDNEYS</b>            | +    | +    | +    | +   | +G   | +    | +    | +    | +    | +    |
| - Pelvic dilation         | .    | .    | .    | .   | ( P. | .    | .    | .    | .    | .    |
| - Hyaline droplets        | 2.   | 1.   | .    | 1.  | 2*   | 2.   | 2.   | 1.   | 1.   | .    |
| - Inflammatory foci       | .    | ( 1. | .    | .   | .    | .    | .    | .    | .    | .    |
| - Tubular basophilia      | ( 1. | 1.   | ( 1. | 1.  | 1.   | ( 1. | .    | .    | 1.   | 1.   |
| - Pigment basoph. cells   | ( 1. | ( 1. | ( 1. | .   | ( 1. | ( 1. | .    | .    | 1.   | .    |
| .....                     |      |      |      |     |      |      |      |      |      |      |
| <b>URINARY BLADDER</b>    | -    | -    | -    | -   | -    | -    | -    | -    | -    | -    |
| .....                     |      |      |      |     |      |      |      |      |      |      |
| <b>TESTES</b>             | +    | -    | +*   | -   | +    | -*   | +*   | +*   | +*   | +*   |
| - Tubular vacuolation     | .    | .    | 1.   | .   | .    | .    | ( 1. | ( 1. | .    | .    |
| - Tubular degeneration    | ( 1. | .    | .    | .   | .    | .    | .    | .    | .    | .    |
| - Inflammatory focus      | .    | .    | .    | .   | .    | .    | .    | .    | ( 1. | .    |
| - Spermatid retention     | .    | .    | .    | .   | .    | .    | .    | .    | .    | ( 1. |
| - Multinucl. giant c.     | .    | .    | .    | .   | ( 1. | .    | .    | .    | .    | ( 1. |
| .....                     |      |      |      |     |      |      |      |      |      |      |
| <b>EPIDIDYMIDES</b>       | -    | -    | -    | -   | -    | -    | -    | -    | -    | -    |
| .....                     |      |      |      |     |      |      |      |      |      |      |
| <b>PROSTATE GLAND</b>     | +    | +    | -    | -   | +    | -    | +    | -    | +    | -    |
| - Inflammatory foci       | .    | 1.   | .    | .   | 1.   | .    | .    | .    | .    | .    |
| - Glandular hyperplas.    | 1.   | 1.   | .    | .   | 1.   | .    | 1.   | .    | 2.   | .    |
| .....                     |      |      |      |     |      |      |      |      |      |      |
| <b>COAGULATING GLANDS</b> | -    | -    | -    | -   | +    | -    | -    | -    | -    | -    |
| - Glandular atrophy       | .    | .    | .    | .   | 1.   | .    | .    | .    | .    | .    |
| .....                     |      |      |      |     |      |      |      |      |      |      |
| <b>SEMINAL VESICLES</b>   | -    | -    | -    | -   | +    | -    | -    | -    | -G   | -    |
| - Glandular atrophy       | .    | .    | .    | .   | 1.   | .    | .    | .    | .    | .    |
| .....                     |      |      |      |     |      |      |      |      |      |      |
| <b>PITUITARY GLAND</b>    | +    | +    | +    | +   | +    | -    | -    | -    | +    | +    |
| - Cyst, pars distalis     | .    | P.   | .    | .   | .    | .    | .    | .    | .    | .    |
| - Hypertr/pl.chromoph.    | 1.   | 2.   | 2.   | 2.  | 2.   | .    | .    | .    | 2.   | 1.   |
| .....                     |      |      |      |     |      |      |      |      |      |      |
| <b>THYROID GLAND</b>      | +G   | +G   | +    | +G  | +G   | +G   | +G   | +G   | +G   | +G   |
| - Thymic remnant          | .    | .    | .    | .   | .    | .    | .    | .    | ( P. | .    |
| - Pigment storage         | 2.   | 1.   | 1.   | 1.  | 2.   | 2.   | 1.   | 2.   | 1.   | 2.   |
| - Incr. vacuolation       | .    | .    | .    | .   | .    | .    | .    | .    | 1.   | .    |
| - Follic. hypertrophy     | 1.   | 1.   | ( 1. | 1.  | .    | 1.   | .    | 1.   | 1.   | 1.   |
| .....                     |      |      |      |     |      |      |      |      |      |      |
| <b>PARATHYROID GLANDS</b> | ( -  | -    | ( -  | -   | ( -  | -    | ( -  | ( -  | -    | -    |
| .....                     |      |      |      |     |      |      |      |      |      |      |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 03, 50 MG/KG**

**ANIMAL NUMBER :**

|                            | 31   | 32   | 33   | 34   | 35   | 36   | 37   | 38   | 39   | 40   |
|----------------------------|------|------|------|------|------|------|------|------|------|------|
|                            | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  |
| <b>ADRENAL CORTICES</b>    | -    | +    | -    | +    | -    | -    | +    | -    | -    | -    |
| - Vacuolation, Z.fasc.     | .    | 2.   | .    | 1.   | .    | .    | 2*   | .    | .    | .    |
| .....                      |      |      |      |      |      |      |      |      |      |      |
| <b>ADRENAL MEDULLAS</b>    | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| .....                      |      |      |      |      |      |      |      |      |      |      |
| <b>SPLEEN</b>              | +    | +    | +    | +    | +    | +    | +    | +    | +    | +    |
| - Extram. hemopoiesis      | 1.   | 2.   | 1.   | .    | 1.   | 1.   | 2.   | .    | .    | 1.   |
| - Hemosiderin              | 1.   | 1.   | 1.   | 1.   | 1.   | 1.   | 2.   | 1.   | 1.   | 1.   |
| .....                      |      |      |      |      |      |      |      |      |      |      |
| <b>BONE MARROW, FEMUR</b>  | +    | -    | +    | +    | +    | +    | -    | +    | +    | -    |
| - Fatty replacement        | 1.   | .    | 2.   | 1.   | .    | 2.   | .    | 1.   | 1.   | .    |
| - Incr. erythropoiesis     | .    | .    | .    | .    | .    | 1.   | .    | 1.   | .    | .    |
| - Decr. myelopoiesis       | .    | .    | .    | .    | 1.   | .    | .    | .    | .    | .    |
| .....                      |      |      |      |      |      |      |      |      |      |      |
| <b>THYMUS</b>              | -    | +    | +    | +    | -    | -    | -    | -    | +    | -    |
| - Cyst(s)                  | .    | P.   | P.   | .    | .    | .    | .    | .    | .    | .    |
| - Hemorrhage               | .    | .    | 1.   | 1.   | .    | .    | .    | .    | 1.   | .    |
| - Lymphoid atrophy         | .    | .    | .    | 1.   | .    | .    | .    | .    | .    | .    |
| .....                      |      |      |      |      |      |      |      |      |      |      |
| <b>MESENT. LYMPH NODE</b>  | -    | -    | -    | -    | -    | -    | -    | -    | -    | +    |
| - Hemorrhage               | .    | .    | .    | .    | .    | .    | .    | .    | .    | 1.   |
| .....                      |      |      |      |      |      |      |      |      |      |      |
| <b>MANDIB. LYMPH NODES</b> | ( -  | ( -  | ( -  | ( -  | ( -  | ( -  | ( -  | ( -  | ( -  | ( -  |
| .....                      |      |      |      |      |      |      |      |      |      |      |
| <b>SUBLINGUAL GLANDS</b>   | -    | -    | -    | -    | -    | -    | -    | -    | ( +  | -    |
| - Periductular fibros.     | .    | .    | .    | .    | .    | .    | .    | .    | ( 1. | .    |
| .....                      |      |      |      |      |      |      |      |      |      |      |
| <b>MANDIBULAR GLANDS</b>   | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| .....                      |      |      |      |      |      |      |      |      |      |      |
| <b>MAMMARY GLAND AREA</b>  | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| .....                      |      |      |      |      |      |      |      |      |      |      |
| <b>SKIN/SUBCUTIS</b>       | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| .....                      |      |      |      |      |      |      |      |      |      |      |
| <b>EYES</b>                | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| .....                      |      |      |      |      |      |      |      |      |      |      |
| <b>RETROORBITAL TISSUE</b> | +    | +    | +    | +    | +    | +    | +    | +    | +    | +    |
| - Hemorrhage               | ( 1. | ( 1. | ( 1. | ( 3. | ( 2. | ( 1. | ( 2. | ( 1. | ( 1. | ( 2. |
| - Inflammation             | .    | .    | ( 1. | ( 2. | .    | .    | ( 1. | .    | .    | ( 1. |
| .....                      |      |      |      |      |      |      |      |      |      |      |

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TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 03, 50 MG/KG**

ANIMAL NUMBER :

|  | 31  | 32  | 33  | 34  | 35  | 36  | 37  | 38  | 39  | 40  |
|--|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|  | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO |

OPTIC NERVES

- ( - - - - - - - - - -

.....

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 03, 50 MG/KG**

ANIMAL NUMBER :

41 42 43 44 45  
MK1 MK1 MK1 MK1 MK1

|                       | 41  | 42  | 43   | 44  | 45  |
|-----------------------|-----|-----|------|-----|-----|
|                       | MK1 | MK1 | MK1  | MK1 | MK1 |
| COAGULATING GLANDS    | '   | '   | -    | '   | '   |
| SEMINAL VESICLES      | '   | '   | +G   | '   | '   |
| - Hemorrhage          |     |     | ( 1. |     |     |
| THYROID GLAND         | +G  | +G  | +G   | +G  | +G  |
| - Thymic remnant      | P.  | .   | .    | .   | .   |
| - Pigment storage     | 1.  | 2.  | 2.   | 2.  | 1.  |
| - Incr. vacuolation   | .   | 1.  | 1.   | .   | 1.  |
| - Follic. hypertrophy | 1.  | 1.  | 1.   | .   | 1.  |
| PARATHYROID GLANDS    | -   | ( - | -    | -   | ( - |

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INDIVIDUAL ANIMAL DATA**

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 03, 50 MG/KG**

**ANIMAL NUMBER :**

|                        | 91  | 92  | 93  | 94  | 95   | 96  | 97   | 98  | 99   | 100 |
|------------------------|-----|-----|-----|-----|------|-----|------|-----|------|-----|
|                        | FKO | FKO | FKO | FKO | FKO  | FKO | FKO  | FKO | FKO  | FKO |
| CEREBRUM               | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| CEREBELLUM             | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| MEDULLA OBLONGATA      | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| PONS                   | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| SPINAL CORD, CERVIC.   | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| SPINAL CORD, THORAC.   | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| SPINAL CORD, LUMBAR    | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| SCIATIC NERVES         | ( - | ( - | ( - | ( - | ( +  | ( - | ( +  | ( - | ( +  | ( - |
| - Axonal degeneration  | .   | .   | .   | .   | ( 1. | .   | ( 1. | .   | ( 1. | .   |
| HEART                  | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| AORTA                  | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| TRACHEA                | +   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| - Mononuclear foci     | 1.  | .   | .   | .   | .    | .   | .    | .   | .    | .   |
| LUNGS                  | +   | +   | -   | -   | -*   | +   | -    | -   | -    | +   |
| - Vasc. mineralization | 1.  | 1.  | .   | .   | .    | 1.  | .    | .   | .    | .   |
| - Alveolar macrophages | 1.  | .   | .   | .   | .    | 1.  | .    | .   | .    | 1*  |
| ESOPHAGUS              | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| STOMACH                | +   | -   | -   | +   | +    | -   | -    | -   | -    | -   |
| - Epithel. vacuolation | .   | .   | .   | 1.  | 1.   | .   | .    | .   | .    | .   |
| - Hyaline inclusions   | 1.  | .   | .   | 1.  | 1.   | .   | .    | .   | .    | .   |
| DUODENUM               | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| JEJUNUM                | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |
| PEYERS PATCHES JEJ.    | -   | -   | -   | -   | -    | -   | -    | -   | -    | -   |



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TEST ARTICLE : A084, WR 23081  
 TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
 SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
 DATE : 19-JUL-05  
 PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)**  
**DOSE GROUP : 03, 50 MG/KG**

ANIMAL NUMBER :

|                         | 91   | 92   | 93   | 94   | 95   | 96   | 97  | 98  | 99   | 100  |
|-------------------------|------|------|------|------|------|------|-----|-----|------|------|
|                         | FKO  | FKO  | FKO  | FKO  | FKO  | FKO  | FKO | FKO | FKO  | FKO  |
| ILEUM                   | -    | -    | -    | -    | -    | -    | -   | -   | -    | -    |
| PEYERS PATCHES ILEUM    | -    | -    | -    | -    | -    | -    | -   | -   | -    | -    |
| CECUM                   | -    | -    | -    | -    | -    | -    | -   | -   | -    | -    |
| COLON                   | -    | -    | -    | -    | -    | -    | -   | -   | -    | -    |
| RECTUM                  | -    | -    | -    | +    | -    | -    | -   | -   | -    | -    |
| - Luminal nematodes     | .    | .    | .    | 2.   | .    | .    | .   | .   | .    | .    |
| LIVER                   | -    | +    | +    | +    | -    | +    | +   | +   | -    | -    |
| - Hemopoietic foci      | .    | .    | .    | .    | .    | .    | .   | 1.  | .    | .    |
| - Inflammatory foci     | .    | 2.   | 1.   | 1.   | .    | 1.   | 1.  | .   | .    | .    |
| - Peribiliary inflamm.  | .    | .    | .    | .    | .    | 1.   | .   | .   | .    | .    |
| PANCREAS                | -    | -    | -    | -    | -    | -    | -   | -   | -    | -    |
| KIDNEYS                 | +    | +    | +    | +    | +    | +    | +   | -   | -    | +    |
| - Pelvic dilation       | ( P. | ( P. | .    | .    | .    | .    | .   | .   | .    | .    |
| - Tubular casts         | .    | .    | .    | .    | ( 2. | .    | .   | .   | .    | .    |
| - Tubulus cell swell.   | 1.   | .    | ( 1. | 1.   | .    | 1.   | 1.  | .   | .    | 1.   |
| - Pigment tubul. cells  | .    | .    | ( 1. | 1.   | .    | 1.   | 1.  | .   | .    | 1.   |
| - Tubular basophilia    | ( 1. | .    | .    | ( 1. | ( 1. | ( 1. | .   | .   | .    | ( 1. |
| - Pigment basoph. cells | ( 1. | .    | .    | ( 1. | .    | ( 1. | .   | .   | .    | .    |
| URINARY BLADDER         | -    | -    | -    | -    | -    | -    | -   | -   | -    | -    |
| OVARIES                 | +    | -    | -    | +    | -    | -    | -   | +   | +    | -    |
| - Rete ovarii           | .    | .    | .    | .    | .    | .    | .   | .   | ( P. | .    |
| - Interst. c. hyperpl.  | 1.   | .    | .    | ( 1. | .    | .    | .   | .   | .    | .    |
| - Atrophy               | .    | .    | .    | .    | .    | .    | .   | 2.  | .    | .    |
| UTERUS                  | +    | +    | -    | +    | +G   | -    | -   | -   | -    | +G   |
| - Congestion            | .    | .    | .    | .    | .    | .    | .   | .   | .    | P.   |
| - Luminal dilation      | P.   | P.   | .    | .    | P.   | .    | .   | .   | .    | .    |
| - Epithelial cyst(s)    | .    | .    | .    | P*   | .    | .    | .   | .   | .    | .    |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
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PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 03, 50 MG/KG**

**ANIMAL NUMBER :**

|                        | 91  | 92   | 93  | 94  | 95  | 96  | 97  | 98  | 99  | 100  |
|------------------------|-----|------|-----|-----|-----|-----|-----|-----|-----|------|
|                        | FKO | FKO  | FKO | FKO | FKO | FKO | FKO | FKO | FKO | FKO  |
| VAGINA                 | +   | +    | +   | +   | +   | +   | +   | +   | +   | +    |
| - Proestrus            | P.  | .    | .   | .   | P.  | .   | .   | .   | .   | .    |
| - Estrus               | .   | P.   | .   | .   | .   | P.  | .   | .   | P.  | P.   |
| - Metestrus            | .   | .    | .   | .   | .   | .   | P.  | .   | .   | .    |
| - Diestrus             | .   | .    | P.  | P.  | .   | .   | .   | P.  | .   | .    |
| - Luminal plugs        | .   | .    | 1.  | 1.  | .   | .   | .   | .   | .   | .    |
| .....                  |     |      |     |     |     |     |     |     |     |      |
| PITUITARY GLAND        | -   | -    | -   | -   | -   | -   | +   | -   | +   | -    |
| - Cyst, pars intermed. | .   | .    | .   | .   | .   | .   | P.  | .   | .   | .    |
| - Cyst, pars distalis  | .   | .    | .   | .   | .   | .   | P.  | .   | P.  | .    |
| .....                  |     |      |     |     |     |     |     |     |     |      |
| THYROID GLAND          | +G  | +G   | +G  | +G  | +   | +   | +G  | +   | +G  | +G   |
| - Thyroglossal d. cyst | .   | .    | .   | .   | .   | .   | .   | .   | .   | ( P. |
| - Pigment storage      | 2.  | 1.   | 2.  | 2.  | 1.  | 1.  | 2.  | 2*  | 2.  | 1.   |
| - Follic. hypertrophy  | .   | .    | .   | .   | .   | .   | .   | .   | 1.  | 1.   |
| .....                  |     |      |     |     |     |     |     |     |     |      |
| PARATHYROID GLANDS     | ( - | -    | -   | ( - | -   | -   | -   | -   | -   | -    |
| .....                  |     |      |     |     |     |     |     |     |     |      |
| ADRENAL CORTICES       | -   | +    | -   | -   | -   | -   | -   | -   | -   | -    |
| - Vacuolation, Z.glom. | .   | ( 2. | .   | .   | .   | .   | .   | .   | .   | .    |
| .....                  |     |      |     |     |     |     |     |     |     |      |
| ADRENAL MEDULLAS       | -   | -    | -   | -   | -   | -   | -   | -   | -   | -    |
| .....                  |     |      |     |     |     |     |     |     |     |      |
| SPLEEN                 | +   | +    | +   | +   | +   | +   | +   | +   | +   | +    |
| - Extram. hemopoiesis  | 1.  | 1.   | 1.  | 1.  | 3.  | 2.  | 3.  | 2.  | 1.  | 2.   |
| - Hemosiderin          | 2.  | 1.   | 1.  | 1.  | 2.  | 2.  | 2.  | 2.  | 3.  | 2.   |
| .....                  |     |      |     |     |     |     |     |     |     |      |
| BONE MARROW, FEMUR     | +   | +    | +   | +   | +   | +   | +   | +   | +   | +    |
| - Fatty replacement    | 1.  | 2.   | 1.  | 1.  | 1.  | 1.  | 1.  | 1.  | 2.  | 1.   |
| - Incr. erythropoiesis | .   | .    | .   | .   | 1.  | .   | 1.  | 1.  | .   | .    |
| .....                  |     |      |     |     |     |     |     |     |     |      |
| THYMUS                 | -   | +    | +   | +   | +   | +   | -   | -   | +   | +    |
| - Cyst(s)              | .   | P.   | P.  | P.  | P.  | P.  | .   | .   | P.  | P.   |
| .....                  |     |      |     |     |     |     |     |     |     |      |
| MESENT. LYMPH NODE     | -   | -    | -   | -   | -   | -   | -   | -   | -   | -    |
| .....                  |     |      |     |     |     |     |     |     |     |      |
| MANDIB. LYMPH NODES    | ( - | ( -  | ( - | ( - | ( - | ( - | ( - | ( - | ( - | ( -  |
| .....                  |     |      |     |     |     |     |     |     |     |      |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 03, 50 MG/KG**

**ANIMAL NUMBER :**

|                     | 91   | 92     | 93     | 94     | 95     | 96   | 97   | 98   | 99   | 100  |
|---------------------|------|--------|--------|--------|--------|------|------|------|------|------|
|                     | FKO  | FKO    | FKO    | FKO    | FKO    | FKO  | FKO  | FKO  | FKO  | FKO  |
| SUBLINGUAL GLANDS   | -    | +      | -      | -      | -      | -    | -    | -    | -    | -    |
| - Glandular atrophy | .    | 1.     | .      | .      | .      | .    | .    | .    | .    | .    |
| .....               |      |        |        |        |        |      |      |      |      |      |
| MANDIBULAR GLANDS   | -    | -      | -      | -      | -      | -    | -    | -    | -    | -    |
| .....               |      |        |        |        |        |      |      |      |      |      |
| MAMMARY GLAND AREA  | -    | -      | -      | -      | -      | +    | -    | -    | -    | -    |
| - Lobular alveoli   | .    | .      | .      | .      | .      | P.   | .    | .    | .    | .    |
| .....               |      |        |        |        |        |      |      |      |      |      |
| SKIN/SUBCUTIS       | -    | -      | -      | -      | -      | -    | -    | -    | -    | -    |
| .....               |      |        |        |        |        |      |      |      |      |      |
| EYES                | -    | -      | -      | -      | -      | -    | -    | -    | -    | -    |
| .....               |      |        |        |        |        |      |      |      |      |      |
| RETROORBITAL TISSUE | +    | +      | +      | -      | -      | +    | +    | +    | +    | +    |
| - Hemorrhage        | ( 1. | . ( 1. | . ( 1. | . ( 1. | . ( 1. | ( 1. | ( 1. | ( 1. | ( 1. | ( 1. |
| - Inflammation      | .    | ( 1.   | .      | .      | .      | .    | .    | .    | .    | .    |
| .....               |      |        |        |        |        |      |      |      |      |      |
| OPTIC NERVES        | -    | -      | -      | -      | -      | -    | -    | -    | -    | -    |
| .....               |      |        |        |        |        |      |      |      |      |      |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 03, 50 MG/KG**

ANIMAL NUMBER :

101 102 103 104 105  
FK1 FK1 FK1 FK1 FK1

|                       | 101  | 102  | 103 | 104 | 105  |
|-----------------------|------|------|-----|-----|------|
|                       | FK1  | FK1  | FK1 | FK1 | FK1  |
| OVARIES               |      | ( +G |     |     |      |
| - Congestion          |      | ( P. |     |     |      |
| UTERUS                |      | +G   | +G  | +G  |      |
| - Luminal dilation    |      | P.   | P.  | P.  |      |
| THYROID GLAND         | +    | +    | +   | +   | +    |
| - Thymic remnant      | .    | ( P. | .   | .   | ( P. |
| - Pigment storage     | 2*   | 2.   | 1.  | 2.  | 2.   |
| - Follic. hypertrophy | ( 1. | 1.   | 1.  | 1.  | .    |
| PARATHYROID GLANDS    | ( -  | -    | ( - | ( - | ( -  |

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TEST ARTICLE : A084, WR 23081  
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SPONSOR : WELLA AG

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**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 04, 200 MG/KG**

**ANIMAL NUMBER :**

|                        | 46  | 47  | 48  | 49  | 50  | 51  | 52  | 53  | 54  | 55  |
|------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                        | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO |
| CEREBRUM               | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| CEREBELLUM             | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| MEDULLA OBLONGATA      | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| PONS                   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| SPINAL CORD, CERVIC.   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| SPINAL CORD, THORAC.   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| SPINAL CORD, LUMBAR    | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| SCIATIC NERVES         | ( - | ( - | ( - | ( - | ( - | ( - | ( - | ( - | ( - | ( - |
| HEART                  | -   | +   | -   | -   | +   | +   | -   | -   | -   | -   |
| - Inflammatory foci    | .   | .   | .   | .   | 1.  | 1.  | .   | .   | .   | .   |
| - Myocardial inflamm.  | .   | 2.  | .   | .   | .   | .   | .   | .   | .   | .   |
| - Myocardial fibrosis  | .   | 2.  | .   | .   | .   | .   | .   | .   | .   | .   |
| - Valv. endocardiosis  | .   | 1.  | .   | .   | .   | .   | .   | .   | .   | .   |
| AORTA                  | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| TRACHEA                | -   | +   | +   | -   | +   | -   | -   | -   | -   | -   |
| - Glandular dilation   | .   | 1.  | 1*  | .   | 1.  | .   | .   | .   | .   | .   |
| - Mononuclear foci     | .   | 1.  | .   | .   | 2.  | .   | .   | .   | .   | .   |
| LUNGS                  | +   | +   | +   | -   | +   | +   | +   | +   | +   | +   |
| - Vasc. mineralization | 1.  | 1.  | 1.  | .   | 1.  | 1.  | 1.  | 1.  | 1.  | 1.  |
| - Alveolar hemorrhage  | .   | .   | .   | .   | .   | .   | .   | .   | 1.  | 1.  |
| - Alveolar macrophages | .   | 1*  | 1.  | .   | .   | .   | .   | 1.  | 1*  | 1.  |
| ESOPHAGUS              | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |

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SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 04, 200 MG/KG**

ANIMAL NUMBER :

|                        | 46  | 47  | 48  | 49  | 50  | 51  | 52  | 53  | 54  | 55  |
|------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                        | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO | MKO |
| STOMACH                | +   | +   | +   | +   | +   | +   | +   | +G  | +G  | +   |
| - Hyperemia            | .   | .   | .   | .   | .   | .   | .   | 2.  | 2.  | .   |
| - Hyperkeratosis       | .   | .   | 1.  | .   | .   | .   | .   | .   | .   | .   |
| - Epithel. vacuolation | .   | .   | .   | .   | .   | 2.  | .   | .   | .   | .   |
| - Hyaline inclusions   | 1.  | 1.  | .   | 1.  | 1.  | 2.  | 1.  | 1.  | .   | 1.  |
| - Epithelial cyst(s)   | .   | .   | .   | .   | .   | .   | 1.  | .   | 1.  | .   |
| - Mucosal hyperplasia  | .   | .   | .   | .   | .   | 2*  | .   | .   | .   | .   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| DUODENUM               | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| JEJUNUM                | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| PEYERS PATCHES JEJ.    | -   | -   | 0   | -   | -   | -   | -   | -   | +   | -   |
| - Mineralization       | .   | .   | .   | .   | .   | .   | .   | .   | 1.  | .   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| ILEUM                  | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| PEYERS PATCHES ILEUM   | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| CECUM                  | -   | -   | -   | -   | -   | -   | -   | -   | -   | -   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| COLON                  | -   | -   | -   | -   | -   | -   | -   | +   | -   | -   |
| - Luminal nematodes    | .   | .   | .   | .   | .   | .   | .   | 1.  | .   | .   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| RECTUM                 | -   | -   | -   | -   | +   | -   | -   | -   | -*  | -   |
| - Luminal nematodes    | .   | .   | .   | .   | 2.  | .   | .   | .   | .   | .   |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| LIVER                  | +   | +   | +   | +   | +   | +   | -   | +   | +   | +   |
| - Fatty change         | .   | 1.  | 2.  | .   | .   | 1.  | .   | .   | .   | .   |
| - Inflammatory foci    | 1.  | 1.  | 1.  | 1.  | 1.  | 2.  | .   | 1.  | 1.  | 2.  |
| .....                  |     |     |     |     |     |     |     |     |     |     |
| PANCREAS               | -   | -   | -   | -   | -   | +   | -   | -   | +   | -   |
| - Acinar atrophy       | .   | .   | .   | .   | .   | 1.  | .   | .   | 1.  | .   |
| - Basophilic foci      | .   | .   | .   | .   | .   | 1.  | .   | .   | .   | .   |
| .....                  |     |     |     |     |     |     |     |     |     |     |

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TEST ARTICLE : A084, WR 23081  
 TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
 SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
 DATE : 19-JUL-05  
 PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)**  
**DOSE GROUP : 04, 200 MG/KG**

ANIMAL NUMBER :

|                           | 46  | 47   | 48  | 49   | 50   | 51   | 52   | 53  | 54  | 55  |
|---------------------------|-----|------|-----|------|------|------|------|-----|-----|-----|
|                           | MKO | MKO  | MKO | MKO  | MKO  | MKO  | MKO  | MKO | MKO | MKO |
| <b>KIDNEYS</b>            | -   | +G   | -   | +    | +    | +    | +    | +   | +   | +   |
| - Hyaline droplets        | .   | 2.   | .   | 1.   | 2.   | 1.   | 2.   | .   | 2.  | 1.  |
| - Inflammatory foci       | .   | ( 1. | .   | .    | .    | ( 1. | ( 1. | .   | .   | .   |
| - Pigment tubul. cells    | .   | .    | .   | .    | 1.   | .    | .    | 1.  | .   | 1.  |
| - Tubular basophilia      | .   | 2*   | .   | ( 1. | 1.   | ( 1. | 2*   | 2*  | 1.  | 2*  |
| - Pigment basoph. cells   | .   | 1.   | .   | ( 1. | 1.   | ( 1. | 1.   | 1.  | 1.  | 1.  |
| - Pigment. tubul. casts   | .   | .    | .   | .    | 1.   | .    | .    | 1.  | .   | 1.  |
| .....                     |     |      |     |      |      |      |      |     |     |     |
| <b>URINARY BLADDER</b>    | -   | -    | -   | -    | -    | -    | +    | -   | -   | -   |
| - Mononuclear foci        | .   | .    | .   | .    | .    | .    | 1.   | .   | .   | .   |
| .....                     |     |      |     |      |      |      |      |     |     |     |
| <b>TESTES</b>             | -   | +*   | -   | -    | +*   | -    | -*   | -   | -*  | -   |
| - Tubular hypoplasia      | .   | ( 1. | .   | .    | .    | .    | .    | .   | .   | .   |
| - Tubular vacuolation     | .   | .    | .   | .    | 1.   | .    | .    | .   | .   | .   |
| - Multinucl. giant c.     | .   | .    | .   | .    | ( 1. | .    | .    | .   | .   | .   |
| .....                     |     |      |     |      |      |      |      |     |     |     |
| <b>EPIDIDYIMIDES</b>      | -   | -    | -   | -    | -    | -    | -    | -   | -   | -   |
| .....                     |     |      |     |      |      |      |      |     |     |     |
| <b>PROSTATE GLAND</b>     | -   | -    | -   | -    | -    | +    | +    | +   | +   | -   |
| - Inflammatory foci       | .   | .    | .   | .    | .    | .    | 1.   | 1.  | .   | .   |
| - Glandular atrophy       | .   | .    | .   | .    | .    | 2.   | .    | 1.  | 1.  | .   |
| - Glandular hyperplas.    | .   | .    | .   | .    | .    | .    | 2.   | .   | .   | .   |
| .....                     |     |      |     |      |      |      |      |     |     |     |
| <b>COAGULATING GLANDS</b> | -   | -    | -   | -    | -    | -    | -    | -   | -   | -   |
| .....                     |     |      |     |      |      |      |      |     |     |     |
| <b>SEMINAL VESICLES</b>   | -   | -    | -   | -    | -    | +    | -    | -   | +   | -   |
| - Glandular atrophy       | .   | .    | .   | .    | .    | 1.   | .    | .   | 1.  | .   |
| .....                     |     |      |     |      |      |      |      |     |     |     |
| <b>PITUITARY GLAND</b>    | +   | +    | -   | +    | -    | -    | +    | +   | +   | +   |
| - Cyst, pars nervosa      | P.  | .    | .   | .    | .    | .    | .    | .   | .   | .   |
| - Cyst, pars intermed.    | .   | .    | .   | .    | .    | .    | P.   | .   | .   | .   |
| - Cyst, pars distalis     | .   | P.   | .   | .    | .    | .    | .    | P.  | .   | .   |
| - Hypertr/pl. chromoph.   | .   | 1.   | .   | 1.   | .    | .    | 1.   | 1.  | 1.  | 1.  |
| - Fatty change            | .   | .    | .   | .    | .    | .    | 1.   | .   | .   | .   |
| .....                     |     |      |     |      |      |      |      |     |     |     |
| <b>THYROID GLAND</b>      | +G  | +G   | +G  | +    | +    | +G   | +G   | +G  | +G  | +G  |
| - Pigment storage         | 3.  | 4.   | 4.  | 3.   | 3.   | 3.   | 3.   | 3.  | 3.  | 2.  |
| - Incr. vacuolation       | 1.  | 2.   | .   | 2.   | 1.   | 1.   | 1.   | 2.  | 1.  | 1.  |
| - Follic. hypertrophy     | 2.  | 2.   | 2.  | 2.   | 1.   | .    | 1.   | 1.  | 1.  | 1.  |
| .....                     |     |      |     |      |      |      |      |     |     |     |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 04, 200 MG/KG**

**ANIMAL NUMBER :**

|                        | 46  | 47   | 48  | 49  | 50  | 51   | 52   | 53  | 54   | 55  |
|------------------------|-----|------|-----|-----|-----|------|------|-----|------|-----|
|                        | MKO | MKO  | MKO | MKO | MKO | MKO  | MKO  | MKO | MKO  | MKO |
| PARATHYROID GLANDS     | ( - | ( -  | -   | -   | ( - | -    | ( -  | -   | ( -  | ( - |
| ADRENAL CORTICES       | -   | -    | +   | +   | -   | +    | +    | +   | +    | +   |
| - Access. cort. tiss.  | .   | .    | .   | .   | .   | .    | ( P. | .   | .    | .   |
| - Capsular fibrosis    | .   | .    | .   | .   | .   | ( 1. | .    | .   | .    | .   |
| - Vacuolation, Z.fasc. | .   | .    | 2*  | 1.  | .   | 1.   | 1.   | 1.  | ( 1. | 2.  |
| ADRENAL MEDULLAS       | -   | -    | -   | -   | -   | -    | -    | -   | -    | -   |
| SPLEEN                 | +   | +    | +   | +   | +   | +    | +    | +   | +    | +   |
| - Extram. hemopoiesis  | 1.  | 2.   | 1.  | 2.  | 1.  | 2.   | 2.   | 3.  | 2.   | 2.  |
| - Hemosiderin          | 3.  | 1.   | 2.  | 1.  | 1.  | 2.   | 1.   | 1.  | 2.   | 2.  |
| BONE MARROW, FEMUR     | +   | +    | +   | +   | -   | +    | -    | -   | -    | -   |
| - Fatty replacement    | 2.  | 1.   | 1.  | .   | .   | .    | .    | .   | .    | .   |
| - Incr. erythropoiesis | 2.  | .    | .   | 1.  | .   | 1.   | .    | .   | .    | .   |
| THYMUS                 | -   | -    | -   | -   | +   | +    | -    | -G  | +    | +   |
| - Cyst (s)             | .   | .    | .   | .   | .   | P.   | .    | .   | P.   | P.  |
| - Hemorrhage           | .   | .    | .   | .   | 1.  | .    | .    | .   | .    | .   |
| MESENT. LYMPH NODE     | -   | -    | +   | -   | -   | -    | -    | +   | +    | -   |
| - Hemorrhage           | .   | .    | 1.  | .   | .   | .    | .    | 1.  | 1.   | .   |
| MANDIB. LYMPH NODES    | ( - | ( -  | ( - | ( - | ( - | ( -  | ( -  | ( - | ( -  | ( - |
| SUBLINGUAL GLANDS      | -   | -    | -   | -   | -   | -    | -    | -   | -    | -   |
| MANDIBULAR GLANDS      | -   | +    | -   | -   | -   | -    | -    | -   | -    | -   |
| - Inflammatory foci    | .   | ( 1. | .   | .   | .   | .    | .    | .   | .    | .   |
| MAMMARY GLAND AREA     | -   | -    | -   | -   | -   | -    | -    | -   | -    | -   |
| SKIN/SUBCUTIS          | -   | -    | -   | -   | -   | -    | -    | -   | -    | -   |
| EYES                   | -   | -    | -   | -   | -   | -    | -    | -   | -    | -   |



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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
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PathData®System V6.2b5

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 04, 200 MG/KG

ANIMAL NUMBER :

|                     | 46   | 47  | 48   | 49   | 50   | 51   | 52   | 53   | 54   | 55   |
|---------------------|------|-----|------|------|------|------|------|------|------|------|
|                     | MKO  | MKO | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  | MKO  |
| RETROORBITAL TISSUE | +    | -   | +    | +    | +    | +    | +    | +    | +    | +    |
| - Hemorrhage        | ( 2. | .   | ( 2. | ( 1. | ( 2. | ( 2. | ( 1. | ( 2. | ( 1. | ( 1. |
| - Inflammation      | .    | .   | .    | .    | .    | ( 1. | .    | ( 1. | .    | .    |
| .....               |      |     |      |      |      |      |      |      |      |      |
| OPTIC NERVES        | -    | -   | -    | -    | -    | -    | -    | -    | -    | -    |
| .....               |      |     |      |      |      |      |      |      |      |      |

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**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 04, 200 MG/KG**

ANIMAL NUMBER :

56 57 58 59 60  
MK1 MK1 MK1 MK1 MK1

|                       | 56  | 57  | 58  | 59    | 60  |
|-----------------------|-----|-----|-----|-------|-----|
|                       | MK1 | MK1 | MK1 | MK1   | MK1 |
| THYROID GLAND         | +G  | +G  | +G  | +G    | +G  |
| - Pigment storage     | 3.  | 3.  | 3.  | 2.    | 2.  |
| - Incr. vacuolation   | 1.  | 2.  | 2.  | 1.    | 2.  |
| - Follic. hypertrophy | 1.  | 2.  | 1.  | 1.    | 1.  |
| .....                 |     |     |     |       |     |
| PARATHYROID GLANDS    | -   | -   | ( - | 0 ( - |     |
| .....                 |     |     |     |       |     |

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TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

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**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 04, 200 MG/KG**

ANIMAL NUMBER :

|                        | 106 | 107 | 108 | 109  | 110  | 111 | 112 | 113  | 114 | 115 |
|------------------------|-----|-----|-----|------|------|-----|-----|------|-----|-----|
|                        | FKO | FKO | FKO | FKO  | FKO  | FKO | FKO | FKO  | FKO | FKO |
| CEREBRUM               | -   | -   | -   | -    | -    | -   | -   | -    | -   | -   |
| CEREBELLUM             | -   | -   | -   | -    | -    | -   | -   | -    | -   | -   |
| MEDULLA OBLONGATA      | -   | -   | -   | -    | -    | -   | -   | -    | -   | -   |
| PONS                   | -   | -   | -   | -    | -    | -   | -   | -    | -   | -   |
| SPINAL CORD, CERVIC.   | -   | -   | -   | -    | -    | -   | -   | -    | -   | -   |
| SPINAL CORD, THORAC.   | -   | -   | -   | -    | -    | -   | -   | -    | -   | -   |
| SPINAL CORD, LUMBAR    | -   | -   | -   | -    | -    | -   | -   | -    | -   | -   |
| SCIATIC NERVES         | ( - | ( - | ( - | ( +  | ( +  | ( - | ( - | ( +  | ( - | ( - |
| - Axonal degeneration  | .   | .   | .   | ( 1. | ( 1. | .   | .   | ( 1. | .   | .   |
| HEART                  | -   | -   | -   | -    | -    | -   | -   | -    | +   | -   |
| - Myocardial fibrosis  | .   | .   | .   | .    | .    | .   | .   | .    | 2.  | .   |
| AORTA                  | -   | -   | -   | -    | -    | -   | -   | -    | -   | -   |
| TRACHEA                | +   | +   | -   | +    | -    | -   | -   | -    | -   | -   |
| - Glandular dilation   | 1.  | 1.  | .   | .    | .    | .   | .   | .    | .   | .   |
| - Mononuclear foci     | .   | .   | .   | 1.   | .    | .   | .   | .    | .   | .   |
| LUNGS                  | -   | +   | -   | -    | -    | -   | -   | +    | +   | +   |
| - Vasc. mineralization | .   | .   | .   | .    | .    | .   | .   | 1.   | .   | .   |
| - Alveolar macrophages | .   | 2*  | .   | .    | .    | .   | .   | .    | 1.  | 1.  |
| ESOPHAGUS              | -   | -   | -   | -    | -    | -   | -   | -    | -   | -   |
| STOMACH                | +   | +   | +   | +    | -    | +   | +   | +    | +   | -   |
| - Hyaline inclusions   | 1.  | 1.  | 1.  | 1.   | .    | 1.  | .   | 1.   | 1.  | .   |
| - Epithelial cyst(s)   | .   | .   | .   | .    | .    | .   | 1.  | .    | .   | .   |
| DUODENUM               | -   | -   | -   | -    | -    | -   | -   | -    | -   | -   |
| JEJUNUM                | -   | -   | -   | -    | -    | -   | -   | -    | -   | -   |

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 SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
 DATE : 19-JUL-05  
 PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)**  
 DOSE GROUP : 04, 200 MG/KG

ANIMAL NUMBER :

|                         | 106  | 107  | 108  | 109  | 110  | 111  | 112  | 113  | 114  | 115  |
|-------------------------|------|------|------|------|------|------|------|------|------|------|
|                         | FKO  | FKO  | FKO  | FKO  | FKO  | FKO  | FKO  | FKO  | FKO  | FKO  |
| PEYERS PATCHES JEJ.     | -    | -    | -    | -    | -    | -    | -    | +    | -    | -    |
| - Mineralization        | .    | .    | .    | .    | .    | .    | .    | 1.   | .    | .    |
| ILEUM                   | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| PEYERS PATCHES ILEUM    | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| CECUM                   | -    | -    | -    | -    | -    | -    | -    | -    | +G   | -    |
| - Hemorrhage            | .    | .    | .    | .    | .    | .    | .    | .    | 3.   | .    |
| COLON                   | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| RECTUM                  | -    | -    | -    | -    | -*   | -    | -    | -    | -    | -    |
| LIVER                   | +    | +    | +    | -    | -    | +    | +    | -    | -    | +    |
| - Fatty change          | .    | 1.   | 1.   | .    | .    | .    | .    | .    | .    | .    |
| - Inflammatory foci     | 1.   | .    | 1.   | .    | .    | 1.   | 1.   | .    | .    | 2.   |
| - Hepatoc. hypertrophy  | 2.   | .    | .    | .    | .    | .    | .    | .    | .    | .    |
| PANCREAS                | -    | -    | -    | -    | -    | -    | -    | -*   | -    | +    |
| - Acinar atrophy        | .    | .    | .    | .    | .    | .    | .    | .    | .    | 1.   |
| KIDNEYS                 | +    | +    | +    | +    | +    | +    | +    | +    | +    | +    |
| - Tubular mineraliz.    | ( 1. | .    | ( 1. | .    | .    | ( 1. | .    | 1.   | .    | 1.   |
| - Inflammatory foci     | .    | ( 1. | .    | .    | ( 1. | .    | ( 1. | ( 1. | .    | .    |
| - Tubulus cell swell.   | 2.   | 2.   | 1.   | 2.   | 2.   | 2.   | 2.   | 2.   | 3.   | .    |
| - Pigment tubul. cells  | 1.   | ( 1. | 1.   | 1.   | 1.   | 2.   | 1.   | 1.   | 1.   | .    |
| - Tubular basophilia    | ( 1. | ( 1. | .    | ( 1. | .    | 1.   | .    | 1.   | 2*   | .    |
| - Pigment basoph. cells | ( 1. | ( 1. | .    | ( 1. | .    | 1.   | .    | 1.   | 2*   | .    |
| - Pigment. tubul. casts | .    | .    | .    | .    | .    | .    | .    | .    | ( 1. | .    |
| URINARY BLADDER         | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| OVARIES                 | -    | -    | -    | +G   | -    | -    | -    | +    | +G   | +    |
| - Rete ovarii           | .    | .    | .    | .    | .    | .    | .    | .    | .    | ( P. |
| - Bursa cyst            | .    | .    | .    | ( P. | .    | .    | .    | .    | ( P. | .    |
| - Interst. c. hyperpl.  | .    | .    | .    | ( 2. | .    | .    | .    | ( 2. | .    | .    |

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SPONSOR : WELLA AG

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DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 04, 200 MG/KG**

ANIMAL NUMBER :

|                            | 106<br>FKO | 107<br>FKO | 108<br>FKO | 109<br>FKO | 110<br>FKO | 111<br>FKO | 112<br>FKO | 113<br>FKO | 114<br>FKO | 115<br>FKO |
|----------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| <b>UTERUS</b>              | -          | -          | -          | -          | -          | +G         | -          | +          | -          | -          |
| - Luminal dilation         | .          | .          | .          | .          | .          | P.         | .          | P.         | .          | .          |
| <b>VAGINA</b>              | +          | +          | +          | +          | +          | +          | +          | +          | +          | +          |
| - Proestrus                | .          | .          | .          | .          | .          | .          | .          | P.         | .          | .          |
| - Estrus                   | P.         | .          | .          | P.         | .          | P.         | .          | .          | P.         | .          |
| - Metestrus                | .          | P.         | .          | .          | P.         | .          | P.         | .          | .          | .          |
| - Diestrus                 | .          | .          | P.         | .          | .          | .          | .          | .          | .          | P.         |
| - Luminal plugs            | .          | 2.         | .          | .          | .          | .          | .          | .          | .          | 1.         |
| <b>PITUITARY GLAND</b>     | -          | -          | -          | -          | -          | -          | -          | -          | -          | -          |
| <b>THYROID GLAND</b>       | +G         | +G         | +G         | +G         | +G         | +G         | +G         | +G         | +G         | +G         |
| - Ultimobranchial cyst     | .          | .          | .          | .          | .          | .          | ( P.       | ( P.       | .          | .          |
| - Pigment storage          | 2.         | 2.         | 2.         | 2.         | 2.         | 3.         | 2.         | 3.         | 2.         | 2*         |
| - Incr. vacuolation        | .          | .          | .          | 1.         | .          | 2.         | .          | .          | 1.         | .          |
| - Follic. hypertrophy      | 1.         | .          | .          | 1.         | .          | 1.         | .          | 1.         | 1.         | ( 1.       |
| <b>PARATHYROID GLANDS</b>  | ( -        | ( -        | -          | -          | ( -        | -          | ( -        | -          | -          | -          |
| <b>ADRENAL CORTICES</b>    | -          | -          | -          | -          | -          | -          | -          | -          | -          | -          |
| <b>ADRENAL MEDULLAS</b>    | -          | -          | -          | -          | -          | -          | -          | -          | -          | -          |
| <b>SPLEEN</b>              | +          | +          | +          | +          | +          | +          | +          | +          | +          | +          |
| - Extram. hemopoiesis      | 1.         | 2.         | 3.         | 3.         | 1.         | 1.         | 2.         | 3.         | 2.         | .          |
| - Hemosiderin              | 2.         | 3.         | 3.         | 2.         | 1.         | 2.         | 1.         | 3.         | 2.         | 2.         |
| <b>BONE MARROW, FEMUR</b>  | +          | -          | +          | +          | +          | +          | +          | +          | +          | +          |
| - Fatty replacement        | 1.         | .          | .          | 1.         | 1.         | 1.         | 1.         | 1.         | 1.         | .          |
| - Incr. erythropoiesis     | .          | .          | 1.         | .          | .          | .          | .          | 1.         | .          | 1.         |
| <b>THYMUS</b>              | +          | +          | +          | -          | -          | -          | -          | +          | +          | +          |
| - Cyst(s)                  | P.         | P.         | P.         | .          | .          | .          | .          | P.         | P.         | P.         |
| <b>MESENT. LYMPH NODE</b>  | -          | -          | -          | -          | -          | -          | -          | -          | -          | -          |
| <b>MANDIB. LYMPH NODES</b> | ( -        | ( -        | ( -        | ( -        | ( -        | ( -        | ( +        | ( -        | ( -        | ( -        |
| - Hemorrhage               | .          | .          | .          | .          | .          | .          | ( 1.       | .          | .          | .          |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
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**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 04, 200 MG/KG**

ANIMAL NUMBER :

|                     | 106  | 107  | 108  | 109  | 110  | 111  | 112  | 113  | 114  | 115  |
|---------------------|------|------|------|------|------|------|------|------|------|------|
|                     | FKO  | FKO  | FKO  | FKO  | FKO  | FKO  | FKO  | FKO  | FKO  | FKO  |
| SUBLINGUAL GLANDS   | -    | -    | -    | -    | -    | -    | -    | ( -  | -    | -    |
| MANDIBULAR GLANDS   | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| MAMMARY GLAND AREA  | -    | -    | -    | -    | -    | -    | +    | -    | -    | +    |
| - Lobular alveoli   | .    | .    | .    | .    | .    | .    | P.   | .    | .    | P.   |
| SKIN/SUBCUTIS       | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| EYES                | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| RETROORBITAL TISSUE | +    | +    | +    | +    | +    | +    | +    | +    | +    | +    |
| - Hemorrhage        | ( 1. | ( 1. | ( 1. | ( 1. | ( 2. | ( 1. | ( 1. | ( 1. | .    | ( 2. |
| - Inflammation      | ( 1. | ( 1. | ( 1. | .    | .    | .    | .    | .    | ( 1. | ( 1. |
| OPTIC NERVES        | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  
DOSE GROUP : 04, 200 MG/KG**

ANIMAL NUMBER :

116 117 118 119 120  
FK1 FK1 FK1 FK1 FK1

|                        | 116 | 117 | 118 | 119  | 120 |
|------------------------|-----|-----|-----|------|-----|
|                        | FK1 | FK1 | FK1 | FK1  | FK1 |
| UTERUS                 | +G  | '   | '   | '    | '   |
| - Luminal dilation     | P.  |     |     |      |     |
| .....                  |     |     |     |      |     |
| THYROID GLAND          | +G  | +   | +G  | +G   | +G  |
| - Pigment storage      | 3.  | 2.  | 3.  | 2.   | 3.  |
| - Incr. vacuolation    | 1.  | 1.  | .   | .    | 1.  |
| - Follic. hypertrophy  | 1.  | 1.  | 1.  | ( 1. | 1.  |
| .....                  |     |     |     |      |     |
| PARATHYROID GLANDS     | -   | ( - | ( - | ( -  | ( - |
| .....                  |     |     |     |      |     |
| SKIN/SUBCUTIS          | +G  | '   | '   | +G   | -G  |
| - Hair follic. atrophy | 2.  |     |     | 1.   | .   |
| .....                  |     |     |     |      |     |

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ANIMAL HEADING DATA  
DOSE GROUP : 01, 0 MG/KG

| ANIMAL NUMBER | SEX M/F | DEFINED STATE | AND FINAL OF NECROPSY | TEST DAYS | FIRST DAY UNDER TEST | AND LAST DAY UNDER TEST | DATE OF NECROPSY |
|---------------|---------|---------------|-----------------------|-----------|----------------------|-------------------------|------------------|
| 1             | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05               | 17-FEB-05        |
| 2             | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05               | 17-FEB-05        |
| 3             | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05               | 17-FEB-05        |
| 4             | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05               | 17-FEB-05        |
| 5             | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05               | 17-FEB-05        |
| 6             | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05               | 17-FEB-05        |
| 7             | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05               | 17-FEB-05        |
| 8             | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05               | 17-FEB-05        |
| 9             | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05               | 17-FEB-05        |
| 10            | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05               | 17-FEB-05        |
| 11            | M       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05               | 16-FEB-05        |
| 12            | M       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05               | 16-FEB-05        |
| 13            | M       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05               | 16-FEB-05        |
| 14            | M       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05               | 16-FEB-05        |
| 15            | M       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05               | 16-FEB-05        |
| 61            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05               | 18-FEB-05        |
| 62            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05               | 18-FEB-05        |
| 63            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05               | 18-FEB-05        |
| 64            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05               | 18-FEB-05        |
| 65            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05               | 18-FEB-05        |
| 66            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05               | 18-FEB-05        |
| 67            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05               | 18-FEB-05        |
| 68            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05               | 18-FEB-05        |
| 69            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05               | 18-FEB-05        |
| 70            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05               | 18-FEB-05        |
| 71            | F       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05               | 16-FEB-05        |
| 72            | F       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05               | 16-FEB-05        |
| 73            | F       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05               | 16-FEB-05        |
| 74            | F       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05               | 16-FEB-05        |
| 75            | F       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05               | 16-FEB-05        |



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SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 01, 0 MG/KG MALE

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108 \* ANIMAL NO. : 1  
.....

**\* NECROPSY FINDINGS**

MANDIBULAR LYMPH NODES:  
01: FOCUS/FOCI, D=1 MM, ISOLATED, DARK RED.  
NO OTHER NECROPSY OBSERVATIONS NOTED

**\* MICROSCOPIC FINDINGS**

SCIATIC NERVES:  
Only one of paired organs examined/present  
-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1  
HEART:  
-Inflammatory cell foci, right ventricle, grade 2  
LUNGS:  
-Alveolar macrophages, focal/multifocal, grade 1  
STOMACH:  
-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1  
LIVER:  
-Fatty change, predominantly zone 1, grade 1  
-Inflammatory cell focus/foci, grade 1  
KIDNEYS:  
-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1  
-Tubular basophilia, focal/multifocal, bilateral, grade 1  
TESTES:  
(rete tubuli cut bilaterally)  
-Tubular vacuolation, focal/multifocal, unilateral, grade 1  
PARATHYROID GLANDS:  
Tissue not present for histologic examination  
SPLEEN:  
-Hemosiderin storage, grade 1

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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 01, 0 MG/KG MALE

CONT./FF. ANIMAL NO. : 1

**THYMUS:**

- Cyst(s), focal/multifocal
- Hemorrhage, focal/multifocal, grade 1

**MANDIBULAR LYMPH NODES:**

- Only one of paired organs examined/present
- No microscopic finding corresponding to necropsy observation no. 01.

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

**\* STATE AT NECROPSY: K0**

DAYS ON TEST : 108

\* ANIMAL NO. : 2

**\* NECROPSY FINDINGS**

NO NECROPSY OBSERVATIONS NOTED.

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

- Only one of paired organs examined/present

**HEART:**

- Inflammatory cell foci, left ventricle, grade 1

**TRACHEA:**

- Glandular dilation, submucosa, grade 1

**STOMACH:**

- Hyperkeratosis, parakeratotic, grade 1
- Hyaline inclusions, epithelium, limiting ridge, multifocal, grade 1

**PEYER'S PATCHES (JEJUNUM):**

- Mineralization, grade 1

**LIVER:**

- Inflammatory cell focus/foci, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

MALE

CONT./FF. ANIMAL NO. : 2

KIDNEYS:

- Hyaline droplets, proximal tubulus epithelium, multifocal, bilateral, grade 2  
Grade 1 in contra lateral organ.
- Inflammatory cell focus/foci, interstitial, unilateral, grade 1

PARATHYROID GLANDS:

Tissue not present for histologic examination

SPLEEN:

- Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

- Fatty replacement, grade 2

THYMUS:

- Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

- Hemorrhage, unilateral, grade 2
- Inflammation, due to blood sampling, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 3

\* NECROPSY FINDINGS

KIDNEYS:

01: LEFT SIDE: PELVIC DILATION.

NO OTHER NECROPSY OBSERVATIONS NOTED

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

MALE

CONT./FF. ANIMAL NO. : 3

.....

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present  
-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

**HEART:**

-Inflammatory cell foci, left ventricle and septum, grade 1

**LUNGS:**

-Alveolar macrophages, focal/multifocal, grade 1

**STOMACH:**

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1  
-Mucosal hyperplasia, superficial, pars glandularis, focal,  
grade 1

**PEYER'S PATCHES (JEJUNUM):**

-Mineralization, grade 1

**RECTUM:**

-Luminal dilation

**LIVER:**

-Hemopoietic cell focus/foci, grade 1

**KIDNEYS:**

-Pelvic dilation, unilateral  
This finding corresponds to necropsy observation no: 01.  
-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1  
-Inflammatory cell focus/foci, interstitial, unilateral,  
grade 1

**TESTES:**

(rete tubulus cut unilaterally)  
-Tubular vacuolation, focal/multifocal, bilateral, grade 1  
-Tubular degeneration, focal/multifocal, bilateral, grade 1  
-Spermatid retention, focal, unilateral, grade 1

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, 0 MG/KG

MALE

CONT./FF. ANIMAL NO. : 3

SPLEEN:

- Extramedullary hemopoiesis, grade 1
- Hemosiderin storage, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

- Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 4

\* NECROPSY FINDINGS

EXORBITAL LACRIMAL GLANDS:

01: BOTH SIDES: FOCUS/FOCI, D=1 MM, SEVERAL, GRAY WHITE.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

- Vascular mineralization, focal/multifocal, grade 1

STOMACH:

- Epithelial vacuolation, limiting ridge, grade 1
- Hyaline inclusions, epithelium, limiting ridge, multifocal, grade 1

LIVER:

- Inflammatory cell focus/foci, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, 0 MG/KG

MALE

CONT./FF. ANIMAL NO. : 4

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

TESTES:

(rete tubulus cut unilaterally)

PARATHYROID GLANDS:

Only one of paired organs examined/present

ADRENAL CORTICES:

-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 2

SPLEEN:

-Hemosiderin storage, grade 2

THYMUS:

-Cyst(s), focal/multifocal

-Hemorrhage, focal/multifocal, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

EXORBITAL LACRIMAL GLANDS:

-Harderian gland change, multifocal, bilateral, grade 2  
Grade 1 in contra lateral organ.

This finding corresponds to necropsy observation no: 01.

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 01, 0 MG/KG MALE

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108 \* ANIMAL NO. : 5  
.....

**\* NECROPSY FINDINGS**

**LUNGS:**

01: LEFT LOBE: FOCUS/FOCI, D=2 MM, ISOLATED, REDDISH.  
NO OTHER NECROPSY OBSERVATIONS NOTED

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**TRACHEA:**

-Mononuclear cell focus/foci, submucosa, grade 1

**LUNGS:**

No microscopic finding corresponding to necropsy observation no. 01.

-Vascular mineralization, focal/multifocal, grade 1

**STOMACH:**

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

**LIVER:**

-Fatty change, predominantly zone 1, grade 1

**KIDNEYS:**

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

-Inflammatory cell focus/foci, interstitial, unilateral,  
grade 1

-Tubular basophilia, focal/multifocal, bilateral, grade 1

**TESTES:**

(rete tubuli cut unilaterally)

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

**SPLEEN:**

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, 0 MG/KG

MALE

CONT./FF. ANIMAL NO. : 5

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: KO

DAYS ON TEST : 108

\* ANIMAL NO. : 6

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

-Alveolar hemorrhage, focal/multifocal, grade 1

LIVER:

-Fatty change, predominantly zone 1, grade 1

-Inflammatory cell focus/foci, grade 1

-Peribiliary inflammation, focal/multifocal, grade 1

TESTES:

-Tubular vacuolation, focal/multifocal, bilateral, grade 2

Grade 1 in contra lateral organ.

-Tubular degeneration, focal/multifocal, bilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present



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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, 0 MG/KG

MALE

CONT./FF. ANIMAL NO. : 6

SPLEEN:

- Extramedullary hemopoiesis, grade 1
- Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

- Fatty replacement, grade 1

THYMUS:

- Starry sky, (= increased tingible body macrophages), grade 2  
foamy, at cortico-medullary junction

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 7

\* NECROPSY FINDINGS

KIDNEYS:

01: RIGHT SIDE: PELVIC DILATION.

SEMINAL VESICLES:

01: BOTH SIDES: FOCUS/FOCI, D=1 MM, ISOLATED, DARK RED.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

HEART:

- Inflammatory cell foci, left/right ventricle + septum, grade 2

LUNGS:

- Vascular mineralization, focal/multifocal, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, 0 MG/KG MALE

CONT./FF. ANIMAL NO. : 7

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

RECTUM:

-Luminal nematodes, focal/multifocal, grade 2

LIVER:

-Fatty change, predominantly zone 1, grade 1

-Inflammatory cell focus/foci, grade 1

-Hepatocellular hypertrophy, grade 1

KIDNEYS:

-Pelvic dilation, unilateral

This finding corresponds to necropsy observation no: 01.

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

-Tubular basophilia, focal/multifocal, bilateral, grade 1

SEMINAL VESICLES:

No microscopic finding corresponding to necropsy observation no. 01.

SPLEEN:

-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

MALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 8

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

HEART:

-Inflammatory cell foci, septum, grade 1

TRACHEA:

-Glandular dilation, submucosa, grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

STOMACH:

-Hyperkeratosis, grade 1

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 2

PEYER'S PATCHES (JEJUNUM):

Tissue not present for histologic examination

LIVER:

-Fatty change, predominantly zone 1, grade 1

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

-Inflammatory cell focus/foci, interstitial, bilateral, grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

SEMINAL VESICLES:

-Fibrosis, submucosal, focal, unilateral, grade 1

PITUITARY GLAND:

-Hypertrophy/plasia, chromophobic cells, focal/multifocal,  
grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

MALE

CONT./FF. ANIMAL NO. : 8

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

-Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 9

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

-Alveolar macrophages, focal/multifocal, grade 1

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 2

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DOSE GROUP : 01, 0 MG/KG

MALE

CONT./FF. ANIMAL NO. : 9

PEYER'S PATCHES (JEJUNUM):

-Mineralization, grade 1

LIVER:

-Inflammatory cell focus/foci, grade 2

KIDNEYS:

-Tubular mineralization, focal/multifocal, bilateral, grade 1

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

TESTES:

(rete tubulus cut unilaterally)

ADRENAL CORTICES:

-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

-Increased erythropoiesis, grade 1

THYMUS:

-Hemorrhage, focal/multifocal, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

-Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

MALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 10

\* NECROPSY FINDINGS

STOMACH:

01: MUCOSA, FUNDUS: FOCUS/FOCI, D=4 MM, REDDISH.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

STOMACH:

No microscopic finding corresponding to necropsy observation no. 01.

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

LIVER:

-Fatty change, predominantly zone 1, grade 1

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

TESTES:

(rete tubulus cut unilaterally)

-Tubular vacuolation, focal/multifocal, bilateral, grade 1

-Spermatid retention, focal, unilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

ADRENAL CORTICES:

-Capsular fibrosis, focal, unilateral, grade 1

-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 2

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

MALE

CONT./FF. ANIMAL NO. : 10

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

OPTIC NERVES:

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 11

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Follicular cell hypertrophy, bilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

Organ examined, no pathologic findings noted

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

MALE

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 12

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

PARATHYROID GLANDS:

Only one of paired organs examined/present  
NO MICROSCOPIC FINDINGS NOTED.

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 13

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Thymic remnant, unilateral

PARATHYROID GLANDS:

Organ examined, no pathologic findings noted



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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

MALE

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 14

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Follicular cell hypertrophy, bilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

Organ examined, no pathologic findings noted

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 15

\* NECROPSY FINDINGS

KIDNEYS:

01: LEFT SIDE: PELVIC DILATION.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

KIDNEYS:

Only one of paired organs examined/present

-Pelvic dilation, unilateral

This finding corresponds to necropsy observation no: 01.

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
unilateral, grade 1

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TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 01, 0 MG/KG

MALE

CONT./FF. ANIMAL NO. : 15

.....  
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

FEMALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 61

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

TRACHEA:

-Glandular dilation, submucosa, grade 1

ESOPHAGUS:

-Mononuclear cell focus/foci, muscularis, outer layer, grade 1

STOMACH:

-Epithelial vacuolation, limiting ridge, grade 2

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 2

-Epithelial cyst(s), focal/multifocal, pars glandularis,  
grade 1

PEYER'S PATCHES (JEJUNUM):

-Mineralization, grade 1

LIVER:

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Tubular mineralization, focal/multifocal, unilateral, grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

UTERUS:

-Luminal dilation, (cyclic change)

VAGINA:

-Estrus

SPLEEN:

-Hemosiderin storage, grade 2

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 61

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

SUBLINGUAL GLANDS:

-Serous metaplasia, focal, unilateral, grade 1

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

-Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 62

\* NECROPSY FINDINGS

LUNGS:

01: FOCUS/FOCI, D=2 MM, SEVERAL, GRAY WHITE.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

LUNGS:

No microscopic finding corresponding to necropsy observation no. 01.

-Vascular mineralization, focal/multifocal, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 62

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

KIDNEYS:

-Tubular mineralization, focal/multifocal, bilateral, grade 1

VAGINA:

-Diestrus

SPLEEN:

-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: KO

DAYS ON TEST : 109

\* ANIMAL NO. : 63

\* NECROPSY FINDINGS

UTERUS:

01: RIGHT HORN: DISCOLORATION, DARK RED.

NO OTHER NECROPSY OBSERVATIONS NOTED

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 63

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**LUNGS:**

- Vascular mineralization, focal/multifocal, grade 1
- Osseous metaplasia, focal/multifocal, grade 1
- Alveolar macrophages, focal/multifocal, grade 1  
foamy

**STOMACH:**

- Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

**LIVER:**

- Fatty change, predominantly zone 1, grade 1
- Inflammatory cell focus/foci, grade 1

**KIDNEYS:**

- Tubular mineralization, focal/multifocal, unilateral, grade 1

**OVARIES:**

- Corpus luteum cyst, unilateral, grade 1

**UTERUS:**

- Congestion, at uterus horn, unilaterally  
This finding corresponds to necropsy observation no: 01.

**VAGINA:**

- Metestrus

**THYROID GLAND (BOTH LOBES):**

- Thymic remnant, unilateral

**SPLEEN:**

- Hemosiderin storage, grade 1

**BONE MARROW (FEMUR):**

- Fatty replacement, grade 1

**THYMUS:**

- Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, 0 MG/KG

FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 109

\* ANIMAL NO. : 64

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LIVER:

- Fatty change, predominantly zone 1, grade 1
- Inflammatory cell focus/foci, grade 1

KIDNEYS:

- Pyelonephritis, lymphocytic, unilateral, grade 1

OVARIES:

- Rete ovarii (embrionic remnant), unilateral

UTERUS:

- Luminal dilation, (cyclic change)

VAGINA:

- Proestrus

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

- Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

- Fatty replacement, grade 2

THYMUS:

- Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

- Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 01, 0 MG/KG FEMALE

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 109 \* ANIMAL NO. : 65

**\* NECROPSY FINDINGS**

NO NECROPSY OBSERVATIONS NOTED.

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**TRACHEA:**

-Glandular dilation, submucosa, grade 2

**LUNGS:**

-Vascular mineralization, focal/multifocal, grade 1

**STOMACH:**

-Erosion, pars glandularis, focal, grade 1

**PANCREAS:**

hemorrhage and hemosiderin storage in adjacent lymph node

**UTERUS:**

-Luminal dilation, (cyclic change)

**VAGINA:**

-Proestrus

**SPLEEN:**

-Hemosiderin storage, grade 2

**BONE MARROW (FEMUR):**

-Fatty replacement, grade 1

**THYMUS:**

(moderate hemosiderin storage in adjacent lymph node)

-Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

-Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.



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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, 0 MG/KG FEMALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 66

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present  
-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

HEART:

-Myocardial fibrosis, septum, grade 1

LUNGS:

-Alveolar macrophages, focal/multifocal, grade 1

LIVER:

-Inflammatory cell focus/foci, grade 1

VAGINA:

-Diestrus

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Increased erythropoiesis, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

FEMALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 67

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present  
-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

TRACHEA:

-Glandular dilation, submucosa, grade 1

KIDNEYS:

-Pyelonephritis, unilateral, grade 1

VAGINA:

-Estrus

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

EYES:

(cutting artifact: unilaterally focal "loss" of retinal  
outer nuclear layer)

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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DATE : 19-JUL-05  
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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

FEMALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 68

\* NECROPSY FINDINGS

LUNGS:

01: DISCOLORATION, REDDISH.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

TRACHEA:

-Glandular dilation, submucosa, grade 1

-Mononuclear cell focus/foci, submucosa, grade 1

LUNGS:

(beginning autolysis)

-Congestion

This finding corresponds to necropsy observation no: 01.

-Vascular mineralization, focal/multifocal, grade 1

-Alveolar macrophages, focal/multifocal, grade 2  
foamy

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

LIVER:

(artifact: beginning autolysis)

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Tubular basophilia, focal/multifocal, unilateral, grade 1

VAGINA:

-Metestrus

SPLEEN:

-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 68

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: KO

DAYS ON TEST : 109

\* ANIMAL NO. : 69

\* NECROPSY FINDINGS

LUNGS:

01: FOCUS/FOCI, D=4 MM, SEVERAL, GRAY WHITE.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

No microscopic finding corresponding to necropsy observation no. 01.

-Vascular mineralization, focal/multifocal, grade 1

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

-Increased inflammatory infiltrate, submucosa, grade 1

VAGINA:

-Diestrus

SPLEEN:

-Hemosiderin storage, grade 2

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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 01, 0 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 69

**BONE MARROW (FEMUR):**

-Fatty replacement, grade 2

**THYMUS:**

-Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

**\* STATE AT NECROPSY: K0**

DAYS ON TEST : 109

\* ANIMAL NO. : 70

**\* NECROPSY FINDINGS**

NO NECROPSY OBSERVATIONS NOTED.

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**LUNGS:**

-Vascular mineralization, focal/multifocal, grade 1

**STOMACH:**

-Squamous hyperplasia, pars non-glandularis, grade 1

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

**KIDNEYS:**

-Tubular basophilia, focal/multifocal, unilateral, grade 1

**OVARIES:**

-Interstitial cell hyperplasia, bilateral, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 70

UTERUS:

- Luminal dilation, (cyclic change)
- Epithelial cyst(s), focal/multifocal

VAGINA:

- Proestrus

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

- Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

- Fatty replacement, grade 2

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

MAMMARY GLAND AREA:

- Lobular alveoli

EYES:

(cutting artifact: unilaterally focal "loss" of retinal  
outer nuclear layer)

RETROORBITAL TISSUE:

- Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 71

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 71

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

Organ examined, no pathologic findings noted

PARATHYROID GLANDS:

Tissue not present for histologic examination

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 72

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

Organ examined, no pathologic findings noted

PARATHYROID GLANDS:

Tissue not present for histologic examination

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 01, 0 MG/KG

FEMALE

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 73

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

PARATHYROID GLANDS:

Only one of paired organs examined/present  
NO MICROSCOPIC FINDINGS NOTED.

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 74

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

Organ examined, no pathologic findings noted  
PARATHYROID GLANDS:  
Tissue not present for histologic examination



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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 01, 0 MG/KG

FEMALE

**\* STATE AT NECROPSY: K1**

DAYS ON TEST : 107

\* ANIMAL NO. : 75

**\* NECROPSY FINDINGS**

**OVARIES:**

01: BOTH SIDES: DISCOLORATION, DARK RED.

**UTERUS:**

01: BOTH HORNS: DILATION, D=5 MM, CONTAINS WATERY FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

**\* MICROSCOPIC FINDINGS**

**OVARIES:**

-Congestion, bilateral

This finding corresponds to necropsy observation no: 01.

**UTERUS:**

-Luminal dilation, (cyclic change)

This finding corresponds to necropsy observation no: 01.

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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ANIMAL HEADING DATA  
DOSE GROUP : 02, 15 MG/KG

| ANIMAL NUMBER | SEX M/F | DEFINED STATE | AND FINAL OF NECROPSY | TEST DAYS | FIRST DAY UNDER TEST | LAST DAY UNDER TEST | DATE OF NECROPSY |
|---------------|---------|---------------|-----------------------|-----------|----------------------|---------------------|------------------|
| 16            | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 17            | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 18            | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 19            | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 20            | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 21            | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 22            | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 23            | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 24            | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 25            | M       | K0            | K0                    | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 26            | M       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 27            | M       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 28            | M       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 29            | M       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 30            | M       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 76            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 77            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 78            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 79            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 80            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 81            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 82            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 83            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 84            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 85            | F       | K0            | K0                    | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 86            | F       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 87            | F       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 88            | F       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 89            | F       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 90            | F       | K1            | K1                    | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |

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DATE : 19-JUL-05  
PathData®System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

MALE

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108

\* ANIMAL NO. : 16

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

TRACHEA:

-Mononuclear cell focus/foci, submucosa, grade 1

LIVER:

-Fatty change, predominantly zone 1, grade 1

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

-Tubular basophilia, focal/multifocal, bilateral, grade 1

ADRENAL CORTICES:

-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 2

Grade 1 in contra lateral organ.

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 02, 15 MG/KG MALE

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108 \* ANIMAL NO. : 17  
.....

\* NECROPSY FINDINGS

TESTES:

01: BOTH SIDES: REDUCED IN SIZE, D=17X10 MM.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

RECTUM:

-Luminal nematodes, focal/multifocal, grade 1

LIVER:

-Inflammatory cell focus/foci, grade 1

TESTES:

-Dilation of rete testis, unilateral

-Tubular degeneration, diffuse, end stage, bilateral, grade 5  
(probably due to efferent duct blockage)

This finding corresponds to necropsy observation no: 01.

-Inflammation, focal, peritubular, lympho-plasmacytic,  
unilateral, grade 2

EPIDIDYMIDES:

-Hypozoospermia, (grade 5 = Azoospermia), bilateral, grade 5

-Cellular debris, bilateral, grade 3

PROSTATE GLAND:

-Glandular atrophy, ventral lobe, grade 2

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

MALE

CONT./FF. ANIMAL NO. : 17

THYMUS:

-Hemorrhage, focal/multifocal, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

-Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 18

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

KIDNEYS:

-Pelvic dilation, unilateral

-Tubular basophilia, focal/multifocal, unilateral, grade 1

TESTES:

-Tubular vacuolation, focal/multifocal, unilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

ADRENAL CORTICES:

-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 2

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

MALE

CONT./FF. ANIMAL NO. : 18

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

SUBLINGUAL GLANDS:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 19

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

HEART:

-Inflammatory cell foci, right ventricle, grade 1

TRACHEA:

-Glandular dilation, submucosa, grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

-Alveolar macrophages, focal/multifocal, grade 1  
foamy

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

MALE

CONT./FF. ANIMAL NO. : 19

RECTUM:

-Luminal dilation

LIVER:

-Hemopoietic cell focus/foci, grade 1

KIDNEYS:

-Tubular basophilia, focal/multifocal, unilateral, grade 1

TESTES:

(rete tubuli cut unilaterally)

-Tubular vacuolation, focal/multifocal, bilateral, grade 1

-Tubular degeneration, focal/multifocal, unilateral, grade 1

EPIDIDYMIDES:

-Inflammatory cell focus/foci, interstitial, unilateral,  
grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

ADRENAL CORTICES:

-Accessory cortical tissue, unilateral

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 1

THYMUS:

-Cyst(s), focal/multifocal

-Hemorrhage, focal/multifocal, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

SUBLINGUAL GLANDS:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 02, 15 MG/KG

MALE

**\* STATE AT NECROPSY: KO**

DAYS ON TEST : 108

\* ANIMAL NO. : 20

**\* NECROPSY FINDINGS**

NO NECROPSY OBSERVATIONS NOTED.

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**STOMACH:**

- Epithelial vacuolation, limiting ridge, grade 1
- Hyaline inclusions, epithelium, limiting ridge, multifocal, grade 1

**LIVER:**

- Inflammatory cell focus/foci, grade 2

**KIDNEYS:**

- Hyaline droplets, proximal tubulus epithelium, multifocal, unilateral, grade 1
- Tubular basophilia, focal/multifocal, unilateral, grade 1

**TESTES:**

- Tubular hypoplasia, sertoli only tubulus(1), focal, unilateral, grade 1

**PITUITARY GLAND:**

- Hypertrophy/plasia, chromophobic cells, focal/multifocal, grade 1

**THYROID GLAND (BOTH LOBES):**

- Follicular cell hypertrophy, bilateral, grade 1

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

**SPLEEN:**

- Extramedullary hemopoiesis, grade 2
- Hemosiderin storage, grade 1

**THYMUS:**

- Cyst(s), focal/multifocal



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DOSE GROUP : 02, 15 MG/KG

MALE

CONT./FF. ANIMAL NO. : 20

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 21

\* NECROPSY FINDINGS

KIDNEYS:

01: LEFT SIDE: PELVIC DILATION.

SKIN/SUBCUTIS:

01: NOSE REGION, RIGHT SIDE: ESCHAR(S), D=3 MM.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

(parenchyma incompletely inflated)

-Vascular mineralization, focal/multifocal, grade 1

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

LIVER:

-Fatty change, zone 1 and 3, grade 2

-Inflammatory cell focus/foci, grade 2

-Peribiliary inflammation, focal/multifocal, grade 1

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DOSE GROUP : 02, 15 MG/KG

MALE

CONT./FF. ANIMAL NO. : 21

**KIDNEYS:**

No microscopic finding corresponding to necropsy observation no. 01.  
-Tubular basophilia, focal/multifocal, unilateral, grade 1

**PROSTATE GLAND:**

-Glandular hyperplasia, grade 1

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

**ADRENAL CORTICES:**

-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 1

**SPLEEN:**

-Extramedullary hemopoiesis, grade 1  
-Hemosiderin storage, grade 1

**BONE MARROW (FEMUR):**

-Fatty replacement, grade 2

**THYMUS:**

-Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present  
-Hemorrhage, unilateral, grade 1

**SKIN/SUBCUTIS:**

-Inflammation, subcutis, mixed-cellular, nose-region, grade 2  
This finding corresponds to necropsy observation no: 01.  
-Hemorrhage, subcutis and perifollicular sinus, nose region,  
grade 2

This finding corresponds to necropsy observation no: 01.

**RETROORBITAL TISSUE:**

-Hemorrhage, unilateral, grade 2

**OPTIC NERVES:**

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

MALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 22

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

- Vascular mineralization, focal/multifocal, grade 1
- Alveolar macrophages, focal/multifocal, grade 1

STOMACH:

- Hyperkeratosis, grade 1

KIDNEYS:

- Hyaline droplets, proximal tubulus epithelium, multifocal, bilateral, grade 2
- Tubular basophilia, focal/multifocal, unilateral, grade 1
- Pigment storage in vacuolar basophilic cells, brown, unilateral, grade 1

TESTES:

(rete tubulus cut unilaterally)

ADRENAL CORTICES:

- Accessory cortical tissue, unilateral
- Vacuolation, zona fasciculata/reticularis, multifocal, bilateral, grade 2

SPLEEN:

- Extramedullary hemopoiesis, grade 1

BONE MARROW (FEMUR):

- Fatty replacement, grade 1

THYMUS:

- Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

MALE

CONT./FF. ANIMAL NO. : 22

RETROORBITAL TISSUE:

- Hemorrhage, unilateral, grade 1
  - Inflammation, due to blood sampling, unilateral, grade 1
- ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108

\* ANIMAL NO. : 23

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

- Only one of paired organs examined/present
- Axonal degeneration, secondary, focal/multifocal, unilateral, grade 1

HEART:

- Inflammatory cell foci, grade 2
- Myocardial fibrosis, grade 1

LUNGS:

- Vascular mineralization, focal/multifocal, grade 1
- Alveolar macrophages, focal/multifocal, grade 1

STOMACH:

- Hyaline inclusions, epithelium, limiting ridge, multifocal, grade 1
- Epithelial cyst(s), focal/multifocal, pars glandularis, grade 1

LIVER:

- Fatty change, predominantly zone 1, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

MALE

CONT./FF. ANIMAL NO. : 23

**KIDNEYS:**

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

**PROSTATE GLAND:**

-Glandular hyperplasia, focal, ventral lobe, grade 1

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

**ADRENAL CORTICES:**

-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 2

**BONE MARROW (FEMUR):**

-Fatty replacement, grade 1

**THYMUS:**

-Hemorrhage, focal/multifocal, grade 1

**MESENTERIC LYMPH NODE:**

-Sinus dilation, grade 1

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

-Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108

\* ANIMAL NO. : 24

**\* NECROPSY FINDINGS**

NO NECROPSY OBSERVATIONS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

MALE

CONT./FF. ANIMAL NO. : 24

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present  
-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

RECTUM:

-Luminal dilation

LIVER:

-Inflammatory cell focus/foci, grade 2

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 3  
Grade 2 in contra lateral organ.  
-Tubular basophilia, focal/multifocal, unilateral, grade 1  
-Pigment storage in vacuolar basophilic cells, brown, unilateral,  
grade 1

PITUITARY GLAND:

-Hypertrophy/plasia, chromophobic cells, focal/multifocal,  
grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

-Extramedullary hemopoiesis, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2  
-Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 108

\* ANIMAL NO. : 25

\* NECROPSY FINDINGS

KIDNEYS:

01: LEFT SIDE: PELVIC DILATION.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

TRACHEA:

-Glandular dilation, submucosa, grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1  
-Alveolar hemorrhage, focal/multifocal, grade 1

STOMACH:

-Epithelial cyst(s), focal/multifocal, pars glandularis,  
grade 1

LIVER:

-Inflammatory cell focus/foci, grade 2  
-Peribiliary inflammation, focal/multifocal, grade 1

KIDNEYS:

-Pelvic dilation, unilateral

This finding corresponds to necropsy observation no: 01.

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

-Pigment storage in vacuolar basophilic cells, brown, unilateral,  
grade 1

TESTES:

(rete tubulus cut unilaterally)

SPLEEN:

-Hemosiderin storage, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

MALE

CONT./FF. ANIMAL NO. : 25

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K1  
DAYS ON TEST : 107

\* ANIMAL NO. : 26

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

\* STATE AT NECROPSY: K1  
DAYS ON TEST : 107

\* ANIMAL NO. : 27

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.



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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

MALE

CONT./FF. ANIMAL NO. : 27

\* MICROSCOPIC FINDINGS

PARATHYROID GLANDS:

Only one of paired organs examined/present  
NO MICROSCOPIC FINDINGS NOTED.

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 28

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

PARATHYROID GLANDS:

Only one of paired organs examined/present  
NO MICROSCOPIC FINDINGS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

MALE

\* STATE AT NECROPSY: K1  
DAYS ON TEST : 107

\* ANIMAL NO. : 29

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

\* STATE AT NECROPSY: K1  
DAYS ON TEST : 107

\* ANIMAL NO. : 30

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 76

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

HEART:

-Inflammatory cell foci, left ventricle, grade 1

LUNGS:

(parenchyma incompletely inflated)

PEYER'S PATCHES (JEJUNUM):

-Mineralization, grade 1

LIVER:

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Tubular mineralization, focal/multifocal, unilateral, grade 1

OVARIES:

-Interstitial cell hyperplasia, unilateral, grade 1

UTERUS:

-Luminal dilation, (cyclic change)

VAGINA:

-Proestrus

PARATHYROID GLANDS:

Tissue not present for histologic examination

ADRENAL CORTICES:

-Hemosiderin, unilateral, grade 1

-Hemopoietic focus/foci, unilateral, grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 3

-Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

-Increased erythropoiesis, grade 1

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 02, 15 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 76

**THYMUS:**

-Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

**\* STATE AT NECROPSY: K0**

DAYS ON TEST : 109

\* ANIMAL NO. : 77

**\* NECROPSY FINDINGS**

**UTERUS:**

01: BOTH HORNS: DILATION, D=5 MM.

NO OTHER NECROPSY OBSERVATIONS NOTED

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**TRACHEA:**

-Mononuclear cell focus/foci, submucosa, grade 2

**STOMACH:**

-Hyperkeratosis, grade 1

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

-Ulceration, focal, limiting ridge, grade 2

**LIVER:**

-Inflammatory cell focus/foci, grade 1

**PANCREAS:**

(focally beginning intravascular fibrin condensation, most  
likely intramortal artifact)

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 77

**KIDNEYS:**

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 1

**UTERUS:**

-Luminal dilation, (cyclic change)  
This finding corresponds to necropsy observation no: 01.

**VAGINA:**

-Estrus

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

**SPLEEN:**

-Hemosiderin storage, grade 2

**THYMUS:**

-Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

-Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: KO

DAYS ON TEST : 109

\* ANIMAL NO. : 78

**\* NECROPSY FINDINGS**

NO NECROPSY OBSERVATIONS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 78

.....

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**LUNGS:**

-Vascular mineralization, focal/multifocal, grade 1

**STOMACH:**

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

**PEYER'S PATCHES (JEJUNUM):**

Tissue not present for histologic examination

**LIVER:**

-Fatty change, predominantly zone 1, grade 1

**VAGINA:**

-Proestrus, late

**THYROID GLAND (BOTH LOBES):**

-Follicular cell hypertrophy, unilateral, grade 1

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

**SPLEEN:**

-Hemosiderin storage, grade 2

**BONE MARROW (FEMUR):**

-Fatty replacement, grade 1  
-Increased erythropoiesis, grade 1

**THYMUS:**

-Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

.....

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 109

\* ANIMAL NO. : 79

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

RECTUM:

-Luminal dilation

PANCREAS:

hemosiderin storage in adjacent lymph node

KIDNEYS:

-Cortical cyst, unilateral

-Pyelonephritis, bilateral, grade 1

OVARIES:

-Interstitial cell hyperplasia, bilateral, grade 2

-Atrophy, bilateral, grade 3

VAGINA:

-Diestrus

-Hypermucification, grade 2

THYROID GLAND (BOTH LOBES):

-Ultimobranchial cyst(s), focal/multifocal, unilateral

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

-Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 79

.....  
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 109

\* ANIMAL NO. : 80

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

LIVER:

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Pelvic dilation, unilateral

VAGINA:

-Diestrus

-Luminal plugs, consisting of neutrophiles and detritus,  
grade 1

SPLEEN:

-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 2



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DOSE GROUP : 02, 15 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 80

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

-Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 81

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

TRACHEA:

-Glandular dilation, submucosa, grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

LIVER:

-Inflammatory cell focus/foci, grade 1

UTERUS:

-Luminal dilation, (cyclic change)

VAGINA:

-Proestrus

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 81

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

**SPLEEN:**

- Extramedullary hemopoiesis, grade 1
- Hemosiderin storage, grade 1

**BONE MARROW (FEMUR):**

- Fatty replacement, grade 1
- Increased erythropoiesis, grade 1

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

- Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

**\* STATE AT NECROPSY: K0**

DAYS ON TEST : 109

\* ANIMAL NO. : 82

**\* NECROPSY FINDINGS**

NO NECROPSY OBSERVATIONS NOTED.

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**HEART:**

- Inflammatory cell foci, septum, grade 1

**LUNGS:**

- Vascular mineralization, focal/multifocal, grade 1

**STOMACH:**

- Hyaline inclusions, epithelium, limiting ridge, multifocal, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 82

PEYER'S PATCHES (JEJUNUM):

Tissue not present for histologic examination

LIVER:

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 1

-Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 1

OVARIES:

-Congestion, unilateral

-Interstitial cell hyperplasia, bilateral, grade 1

VAGINA:

-Estrus

PARATHYROID GLANDS:

Tissue not present for histologic examination

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 2

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 83

\* NECROPSY FINDINGS

UTERUS:

01: BOTH HORNS: DILATION, D=5 MM.

NO OTHER NECROPSY OBSERVATIONS NOTED

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 83

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

KIDNEYS:

-Tubulus cell swelling, vacuolar, corticomedullary junction, bilateral, grade 1

-Pigment storage in tubulus cells, brown, fine-granular, unilateral, grade 1

-Pyelonephritis, unilateral, grade 1

UTERUS:

-Luminal dilation, (cyclic change)

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Proestrus

PARATHYROID GLANDS:

Only one of paired organs examined/present

ADRENAL CORTICES:

-Hypertrophy, focal, clear cellular, unilateral, grade 2

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

-Increased erythropoiesis, grade 1

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 84

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

TRACHEA:

-Mononuclear cell focus/foci, submucosa, grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

-Alveolar macrophages, focal/multifocal, grade 1  
foamy

PEYER'S PATCHES (JEJUNUM):

Tissue not present for histologic examination

LIVER:

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Tubular mineralization, focal/multifocal, unilateral, grade 1

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 1

-Pigment storage in tubulus cells, brown, fine-granular,  
unilateral, grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

OVARIES:

-Interstitial cell hyperplasia, bilateral, grade 2

VAGINA:

-Diestrus

PARATHYROID GLANDS:

Tissue not present for histologic examination

SPLEEN:

-Hemosiderin storage, grade 2

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 84

**THYMUS:**

-Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

**\* STATE AT NECROPSY: K0**

DAYS ON TEST : 109

\* ANIMAL NO. : 85

**\* NECROPSY FINDINGS**

**LUNGS:**

01: FOCUS/FOCI, D=4 MM, SEVERAL, GRAY WHITE.

NO OTHER NECROPSY OBSERVATIONS NOTED

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**TRACHEA:**

-Glandular dilation, submucosa, grade 1

**LUNGS:**

No microscopic finding corresponding to necropsy observation no. 01.

**STOMACH:**

-Epithelial vacuolation, limiting ridge, grade 1

-Squamous hyperplasia, pars non-glandularis, grade 1

**LIVER:**

-Inflammatory cell focus/foci, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 85

PANCREAS:

-Basophilic focus/foci, grade 1

KIDNEYS:

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 1

-Pigment storage in tubulus cells, brown, fine-granular,  
unilateral, grade 1

VAGINA:

-Estrus

SPLEEN:

-Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

-Fatty replacement, grade 2

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

-Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 86

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 86

.....  
\* MICROSCOPIC FINDINGS

PARATHYROID GLANDS:

Only one of paired organs examined/present  
NO MICROSCOPIC FINDINGS NOTED.

.....  
\* STATE AT NECROPSY: K1  
DAYS ON TEST : 107

\* ANIMAL NO. : 87

.....  
\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Follicular cell hypertrophy, bilateral, grade 1

PARATHYROID GLANDS:

Organ examined, no pathologic findings noted

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

\* STATE AT NECROPSY: K1  
DAYS ON TEST : 107

\* ANIMAL NO. : 88

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

PARATHYROID GLANDS:

Only one of paired organs examined/present  
NO MICROSCOPIC FINDINGS NOTED.

\* STATE AT NECROPSY: K1  
DAYS ON TEST : 107

\* ANIMAL NO. : 89

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 02, 15 MG/KG

FEMALE

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 90

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

Organ examined, no pathologic findings noted

PARATHYROID GLANDS:

Tissue not present for histologic examination

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**ANIMAL HEADING DATA**  
DOSE GROUP : 03, 50 MG/KG

| ANIMAL NUMBER | SEX M/F | DEFINED STATE | AND FINAL OF NECROPSY | TEST DAYS | FIRST AND LAST DAY UNDER TEST | DATE OF NECROPSY |
|---------------|---------|---------------|-----------------------|-----------|-------------------------------|------------------|
| 31            | M       | K0            | K0                    | 108       | 01-NOV-04 16-FEB-05           | 17-FEB-05        |
| 32            | M       | K0            | K0                    | 108       | 01-NOV-04 16-FEB-05           | 17-FEB-05        |
| 33            | M       | K0            | K0                    | 108       | 01-NOV-04 16-FEB-05           | 17-FEB-05        |
| 34            | M       | K0            | K0                    | 108       | 01-NOV-04 16-FEB-05           | 17-FEB-05        |
| 35            | M       | K0            | K0                    | 108       | 01-NOV-04 16-FEB-05           | 17-FEB-05        |
| 36            | M       | K0            | K0                    | 108       | 01-NOV-04 16-FEB-05           | 17-FEB-05        |
| 37            | M       | K0            | K0                    | 108       | 01-NOV-04 16-FEB-05           | 17-FEB-05        |
| 38            | M       | K0            | K0                    | 108       | 01-NOV-04 16-FEB-05           | 17-FEB-05        |
| 39            | M       | K0            | K0                    | 108       | 01-NOV-04 16-FEB-05           | 17-FEB-05        |
| 40            | M       | K0            | K0                    | 108       | 01-NOV-04 16-FEB-05           | 17-FEB-05        |
| 41            | M       | K1            | K1                    | 107       | 01-NOV-04 15-FEB-05           | 16-FEB-05        |
| 42            | M       | K1            | K1                    | 107       | 01-NOV-04 15-FEB-05           | 16-FEB-05        |
| 43            | M       | K1            | K1                    | 107       | 01-NOV-04 15-FEB-05           | 16-FEB-05        |
| 44            | M       | K1            | K1                    | 107       | 01-NOV-04 15-FEB-05           | 16-FEB-05        |
| 45            | M       | K1            | K1                    | 107       | 01-NOV-04 15-FEB-05           | 16-FEB-05        |
| 91            | F       | K0            | K0                    | 109       | 01-NOV-04 17-FEB-05           | 18-FEB-05        |
| 92            | F       | K0            | K0                    | 109       | 01-NOV-04 17-FEB-05           | 18-FEB-05        |
| 93            | F       | K0            | K0                    | 109       | 01-NOV-04 17-FEB-05           | 18-FEB-05        |
| 94            | F       | K0            | K0                    | 109       | 01-NOV-04 17-FEB-05           | 18-FEB-05        |
| 95            | F       | K0            | K0                    | 109       | 01-NOV-04 17-FEB-05           | 18-FEB-05        |
| 96            | F       | K0            | K0                    | 109       | 01-NOV-04 17-FEB-05           | 18-FEB-05        |
| 97            | F       | K0            | K0                    | 109       | 01-NOV-04 17-FEB-05           | 18-FEB-05        |
| 98            | F       | K0            | K0                    | 109       | 01-NOV-04 17-FEB-05           | 18-FEB-05        |
| 99            | F       | K0            | K0                    | 109       | 01-NOV-04 17-FEB-05           | 18-FEB-05        |
| 100           | F       | K0            | K0                    | 109       | 01-NOV-04 17-FEB-05           | 18-FEB-05        |
| 101           | F       | K1            | K1                    | 107       | 01-NOV-04 15-FEB-05           | 16-FEB-05        |
| 102           | F       | K1            | K1                    | 107       | 01-NOV-04 15-FEB-05           | 16-FEB-05        |
| 103           | F       | K1            | K1                    | 107       | 01-NOV-04 15-FEB-05           | 16-FEB-05        |
| 104           | F       | K1            | K1                    | 107       | 01-NOV-04 15-FEB-05           | 16-FEB-05        |
| 105           | F       | K1            | K1                    | 107       | 01-NOV-04 15-FEB-05           | 16-FEB-05        |

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TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

MALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 31

\* NECROPSY FINDINGS

PANCREAS:

01: DISCOLORATION, DARK RED.

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

STOMACH:

(artifact: limiting ridge cut tangentially)

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

LIVER:

-Inflammatory cell focus/foci, grade 1

-Peribiliary inflammation, focal/multifocal, grade 1

PANCREAS:

(focally beginning intravascular fibrin condensation, most  
likely intramortal artifact)

-Congestion

This finding corresponds to necropsy observation no: 01.

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 2

-Tubular basophilia, focal/multifocal, unilateral, grade 1

-Pigment storage in vacuolar basophilic cells, brown, unilateral,  
grade 1

TESTES:

-Tubular degeneration, focal/multifocal, unilateral, grade 1

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DOSE GROUP : 03, 50 MG/KG

MALE

CONT./FF. ANIMAL NO. : 31

PROSTATE GLAND:

-Glandular hyperplasia, focal, ventral lobe, grade 1

PITUITARY GLAND:

-Hypertrophy/plasia, chromophobic cells, focal/multifocal,  
grade 1

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

-Follicular cell hypertrophy, bilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 32

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

NO OTHER NECROPSY OBSERVATIONS NOTED

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DOSE GROUP : 03, 50 MG/KG

MALE

CONT./FF. ANIMAL NO. : 32

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present  
-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

**HEART:**

-Myocardial fibrosis, heart tip, grade 1

**LUNGS:**

-Vascular mineralization, focal/multifocal, grade 1

**LIVER:**

-Inflammatory cell focus/foci, grade 1

**KIDNEYS:**

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1  
-Inflammatory cell focus/foci, interstitial, unilateral,  
grade 1  
-Tubular basophilia, focal/multifocal, bilateral, grade 1  
-Pigment storage in vacuolar basophilic cells, brown, unilateral,  
grade 1

**PROSTATE GLAND:**

-Inflammatory cell focus/foci, interstitial, ventral lobe,  
grade 1  
-Glandular hyperplasia, dorso-lateral lobe and ventral lobe,  
grade 1

**PITUITARY GLAND:**

-Cyst, pars distalis  
-Hypertrophy/plasia, chromophobic cells, focal/multifocal,  
grade 2

**THYROID GLAND (BOTH LOBES):**

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 1  
This finding corresponds to necropsy observation no: 01.  
-Follicular cell hypertrophy, bilateral, grade 1

**ADRENAL CORTICES:**

-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 2

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MALE

CONT./FF. ANIMAL NO. : 32

**SPLEEN:**

- Extramedullary hemopoiesis, grade 2
- Hemosiderin storage, grade 1

**THYMUS:**

- Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

- Hemorrhage, unilateral, grade 1

**OPTIC NERVES:**

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

**\* STATE AT NECROPSY: KO**

DAYS ON TEST : 108

\* ANIMAL NO. : 33

**\* NECROPSY FINDINGS**

NO NECROPSY OBSERVATIONS NOTED.

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

- Axonal degeneration, secondary, focal/multifocal, unilateral, grade 1

**HEART:**

- Inflammatory cell foci, left ventricle and septum, grade 1

**LUNGS:**

- Vascular mineralization, focal/multifocal, grade 1
- Osseous metaplasia, focal/multifocal, grade 1

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DOSE GROUP : 03, 50 MG/KG

MALE

CONT./FF. ANIMAL NO. : 33

STOMACH:

- Hyaline inclusions, epithelium, limiting ridge, multifocal, grade 1
- Epithelial cyst(s), focal/multifocal, pars glandularis, grade 1
- Cryptabscess(es), focal/multifocal, pars glandularis, grade 1

RECTUM:

- Luminal dilation

LIVER:

- Inflammatory cell focus/foci, grade 1

KIDNEYS:

- Tubular basophilia, focal/multifocal, unilateral, grade 1
- Pigment storage in vacuolar basophilic cells, brown, unilateral, grade 1

TESTES:

- (rete tubulus cut unilaterally)
- Tubular vacuolation, focal/multifocal, bilateral, grade 1

PITUITARY GLAND:

- Hypertrophy/plasia, chromophobic cells, focal/multifocal, grade 2

THYROID GLAND (BOTH LOBES):

- Pigment storage, cytoplasmic, brown, fine-granular, bilateral, grade 1
- Follicular cell hypertrophy, unilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

- Extramedullary hemopoiesis, grade 1
- Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

- Fatty replacement, grade 2

THYMUS:

- Cyst(s), focal/multifocal
- Hemorrhage, focal/multifocal, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present



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MALE

CONT./FF. ANIMAL NO. : 33

**RETROORBITAL TISSUE:**

- Hemorrhage, unilateral, grade 1
  - Inflammation, due to blood sampling, unilateral, grade 1
- ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: KO  
DAYS ON TEST : 108

\* ANIMAL NO. : 34

**\* NECROPSY FINDINGS**

**THYROID GLAND (BOTH LOBES):**

- 01: BOTH SIDES: DISCOLORATION, BLACK.
- NO OTHER NECROPSY OBSERVATIONS NOTED

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**TRACHEA:**

- Glandular dilation, submucosa, grade 1

**LUNGS:**

- Vascular mineralization, focal/multifocal, grade 1

**STOMACH:**

- Hyaline inclusions, epithelium, limiting ridge, multifocal, grade 1

**LIVER:**

- Inflammatory cell focus/foci, grade 1

**KIDNEYS:**

- Hyaline droplets, proximal tubulus epithelium, multifocal, bilateral, grade 1
- Tubular basophilia, focal/multifocal, bilateral, grade 1

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DOSE GROUP : 03, 50 MG/KG

MALE

CONT./FF. ANIMAL NO. : 34

**PITUITARY GLAND:**

-Hypertrophy/plasia, chromophobic cells, focal/multifocal,  
grade 2

**THYROID GLAND (BOTH LOBES):**

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 1

This finding corresponds to necropsy observation no: 01.

-Follicular cell hypertrophy, bilateral, grade 1

**ADRENAL CORTICES:**

-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 1

**SPLEEN:**

-Hemosiderin storage, grade 1

**BONE MARROW (FEMUR):**

-Fatty replacement, grade 1

**THYMUS:**

-Hemorrhage, focal/multifocal, grade 1

-Lymphoid atrophy, grade 1

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

-Hemorrhage, unilateral, grade 3

-Inflammation, due to blood sampling, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 108

\* ANIMAL NO. : 35

\* NECROPSY FINDINGS

KIDNEYS:

01: LEFT SIDE: PELVIC DILATION.

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

STOMACH:

-Hyperkeratosis, grade 2

-Epithelial vacuolation, limiting ridge, grade 1

-Squamous hyperplasia, pars non-glandularis, grade 1

PEYER'S PATCHES (JEJUNUM):

-Mineralization, grade 1

KIDNEYS:

-Pelvic dilation, unilateral

This finding corresponds to necropsy observation no: 01.

-Hyaline droplets, proximal tubulus epithelium, multifocal, bilateral, grade 2

Grade 1 in contra lateral organ.

-Tubular basophilia, focal/multifocal, bilateral, grade 1

-Pigment storage in vacuolar basophilic cells, brown, unilateral, grade 1

TESTES:

-Multinuclear giant cells, spermatidic, focal, unilateral, grade 1

PROSTATE GLAND:

-Inflammatory cell focus/foci, interstitial, grade 1

-Glandular hyperplasia, focal, ventral lobe, grade 1

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DOSE GROUP : 03, 50 MG/KG

MALE

CONT./FF. ANIMAL NO. : 35

COAGULATING GLANDS (ANTERIOR PROSTATE):

-Glandular atrophy, bilateral, grade 1

SEMINAL VESICLES:

-Glandular atrophy, with reduced secretal contents, bilateral,  
grade 1

PITUITARY GLAND:

-Hypertrophy/plasia, chromophobic cells, focal/multifocal,  
grade 2

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

-Extramedullary hemopoiesis, grade 1  
-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Decreased myelopoiesis, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

MALE

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108

\* ANIMAL NO. : 36

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):  
01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present  
-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

ESOPHAGUS:

-Mononuclear cell focus/foci, muscularis, outer layer, grade 2

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

LIVER:

-Fatty change, predominantly zone 1, grade 1  
-Bile duct proliferation, grade 1

PANCREAS:

-Acinar atrophy, focal/multifocal, grade 1

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 2  
-Tubular basophilia, focal/multifocal, unilateral, grade 1  
-Pigment storage in vacuolar basophilic cells, brown, unilateral,  
grade 1

TESTES:

(rete tubuli cut unilaterally)

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

MALE

CONT./FF. ANIMAL NO. : 36

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This finding corresponds to necropsy observation no: 01.  
-Follicular cell hypertrophy, bilateral, grade 1  
SPLEEN:  
-Extramedullary hemopoiesis, grade 1  
-Hemosiderin storage, grade 1  
BONE MARROW (FEMUR):  
-Fatty replacement, grade 2  
-Increased erythropoiesis, grade 1  
MANDIBULAR LYMPH NODES:  
Only one of paired organs examined/present  
RETROORBITAL TISSUE:  
-Hemorrhage, unilateral, grade 1  
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108

\* ANIMAL NO. : 37

.....

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):  
01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:  
Only one of paired organs examined/present  
HEART:  
-Myocardial fibrosis, left ventricle, grade 1  
STOMACH:  
-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

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MALE

CONT./FF. ANIMAL NO. : 37

RECTUM:

-Luminal dilation

LIVER:

-Inflammatory cell focus/foci, grade 1

-Peribiliary inflammation, focal/multifocal, grade 1

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 2

TESTES:

(rete tubuli cut bilaterally)

-Tubular vacuolation, focal/multifocal, unilateral, grade 1

PROSTATE GLAND:

-Glandular hyperplasia, focal, ventral lobe, grade 1

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 1

This finding corresponds to necropsy observation no: 01.

PARATHYROID GLANDS:

Only one of paired organs examined/present

ADRENAL CORTICES:

-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 2

Grade 1 in contra lateral organ.

SPLEEN:

-Extramedullary hemopoiesis, grade 2

-Hemosiderin storage, grade 2

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

-Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

MALE

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108

\* ANIMAL NO. : 38

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):  
01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

HEART:

-Inflammatory cell foci, left ventricle, grade 1

TRACHEA:

-Glandular dilation, submucosa, grade 2

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

-Alveolar macrophages, focal/multifocal, grade 1

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

LIVER:

-Fatty change, predominantly zone 1, grade 1

-Inflammatory cell focus/foci, grade 2

PANCREAS:

-Acinar atrophy, focal/multifocal, grade 2

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

TESTES:

(rete tubuli cut unilaterally)

-Tubular vacuolation, focal/multifocal, unilateral, grade 1

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

-Follicular cell hypertrophy, bilateral, grade 1



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MALE

CONT./FF. ANIMAL NO. : 38

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

-Increased erythropoiesis, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 39

\* NECROPSY FINDINGS

STOMACH:

01: MUCOSA, FUNDUS: FOCUS/FOCI, D=3 MM, ISOLATED, DARK RED.

SEMINAL VESICLES:

01: BOTH SIDES: FOCUS/FOCI, D=1 MM, SEVERAL, DARK RED.

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, ISOLATED, DARK RED.

NO OTHER NECROPSY OBSERVATIONS NOTED

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MALE

CONT./FF. ANIMAL NO. : 39

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

TRACHEA:

-Glandular dilation, submucosa, grade 1

LUNGS:

(parenchyma incompletely inflated)

-Vascular mineralization, focal/multifocal, grade 1

STOMACH:

No microscopic finding corresponding to necropsy observation no. 01.

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

-Epithelial cyst(s), focal/multifocal, pars glandularis,  
grade 1

LIVER:

-Inflammatory cell focus/foci, grade 1

PANCREAS:

-Basophilic focus/foci, grade 1

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

-Tubular basophilia, focal/multifocal, bilateral, grade 1

-Pigment storage in vacuolar basophilic cells, brown, bilateral,  
grade 1

TESTES:

(rete tubulus cut unilaterally)

-Inflammatory focus, perivascular, focal, lymphocytic,  
unilateral, grade 1

PROSTATE GLAND:

-Glandular hyperplasia, multifocal, ventral lobe, grade 2

SEMINAL VESICLES:

No microscopic finding corresponding to necropsy observation no. 01.

PITUITARY GLAND:

-Hypertrophy/plasia, chromophobic cells, focal/multifocal,  
grade 2

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

MALE

CONT./FF. ANIMAL NO. : 39

.....  
THYROID GLAND (BOTH LOBES):

- Thymic remnant, unilateral
- Pigment storage, cytoplasmic, brown, fine-granular, bilateral, grade 1  
This finding corresponds to necropsy observation no: 01.
- Increased vacuolation, cytoplasmic, follicular cell, bilateral, grade 1
- Follicular cell hypertrophy, bilateral, grade 1

SPLEEN:

- Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

- Fatty replacement, grade 1

THYMUS:

- Hemorrhage, focal/multifocal, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

SUBLINGUAL GLANDS:

Only one of paired organs examined/present

- Periductular fibrosis, focal, unilateral, grade 1

RETROORBITAL TISSUE:

- Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

.....  
\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 40

.....  
\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

MALE

CONT./FF. ANIMAL NO. : 40

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**STOMACH:**

- Epithelial vacuolation, limiting ridge, grade 1
- Hyaline inclusions, epithelium, limiting ridge, multifocal, grade 1

**LIVER:**

- Inflammatory cell focus/foci, grade 2
- Hepatocellular hypertrophy, grade 1

**KIDNEYS:**

- Tubular basophilia, focal/multifocal, bilateral, grade 1

**TESTES:**

- (rete tubuli cut unilaterally)
- Spermatid retention, focal, unilateral, grade 1
- Multinuclear giant cells, spermatidic, unilateral, grade 1

**PITUITARY GLAND:**

- Hypertrophy/plasia, chromophobic cells, focal/multifocal, grade 1

**THYROID GLAND (BOTH LOBES):**

- Pigment storage, cytoplasmic, brown, fine-granular, bilateral, grade 2

This finding corresponds to necropsy observation no: 01.

- Follicular cell hypertrophy, bilateral, grade 1

**SPLEEN:**

- Extramedullary hemopoiesis, grade 1
- Hemosiderin storage, grade 1

**MESENTERIC LYMPH NODE:**

- Hemorrhage, sinusoidal, grade 1

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

- Hemorrhage, unilateral, grade 2
- Inflammation, due to blood sampling, unilateral, grade 1

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DOSE GROUP : 03, 50 MG/KG

MALE

CONT./FF. ANIMAL NO. : 40

.....  
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K1  
DAYS ON TEST : 107

\* ANIMAL NO. : 41

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):  
01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):  
-Thymic remnant, bilateral  
-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 1  
This finding corresponds to necropsy observation no: 01.  
-Follicular cell hypertrophy, bilateral, grade 1  
PARATHYROID GLANDS:  
Organ examined, no pathologic findings noted

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

MALE

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 42

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1

-Follicular cell hypertrophy, bilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

Organ examined, no pathologic findings noted

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 43

\* NECROPSY FINDINGS

SEMINAL VESICLES:

01: BOTH SIDES: FOCUS/FOCI, ISOLATED, D=1 MM, REDDISH.

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 03, 50 MG/KG MALE

CONT./FF. ANIMAL NO. : 43

\* MICROSCOPIC FINDINGS

SEMINAL VESICLES:

-Hemorrhage, multifocal, submucosa, unilateral, grade 1  
This finding corresponds to necropsy observation no: 01.

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1

-Follicular cell hypertrophy, bilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 44

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

PARATHYROID GLANDS:

Organ examined, no pathologic findings noted

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

MALE

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 45

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 1

This finding corresponds to necropsy observation no: 01.

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1

-Follicular cell hypertrophy, bilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

Organ examined, no pathologic findings noted



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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

FEMALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 91

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, DARK RED.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

TRACHEA:

-Mononuclear cell focus/foci, submucosa, grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

-Alveolar macrophages, focal/multifocal, grade 1

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

KIDNEYS:

-Pelvic dilation, unilateral

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

-Pigment storage in vacuolar basophilic cells, brown, unilateral,  
grade 1

OVARIES:

-Interstitial cell hyperplasia, bilateral, grade 1

UTERUS:

-Luminal dilation, (cyclic change)

VAGINA:

-Proestrus

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

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DOSE GROUP : 03, 50 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 91

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

- Extramedullary hemopoiesis, grade 1
- Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

- Fatty replacement, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

- Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 92

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, DARK RED.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

- Vascular mineralization, focal/multifocal, grade 1

LIVER:

- Inflammatory cell focus/foci, grade 2

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DOSE GROUP : 03, 50 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 92

**KIDNEYS:**

-Pelvic dilation, unilateral

**UTERUS:**

-Luminal dilation, (cyclic change), unilateral

**VAGINA:**

-Estrus

**THYROID GLAND (BOTH LOBES):**

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 1

This finding corresponds to necropsy observation no: 01.

**ADRENAL CORTICES:**

-Vacuolation, zona glomerulosa, focal, unilateral, grade 2

**SPLEEN:**

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 1

**BONE MARROW (FEMUR):**

-Fatty replacement, grade 2

**THYMUS:**

-Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**SUBLINGUAL GLANDS:**

-Glandular atrophy, diffuse, bilateral, grade 1

**RETROORBITAL TISSUE:**

-Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

FEMALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 93

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, DARK RED.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LIVER:

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
unilateral, grade 1  
-Pigment storage in tubulus cells, brown, fine-granular,  
unilateral, grade 1

VAGINA:

-Diestrus  
-Luminal plugs, consisting of neutrophiles and detritus,  
grade 1

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2  
This finding corresponds to necropsy observation no: 01.

SPLEEN:

-Extramedullary hemopoiesis, grade 1  
-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 03, 50 MG/KG FEMALE

CONT./FF. ANIMAL NO. : 93

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: KO

DAYS ON TEST : 109

\* ANIMAL NO. : 94

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, DARK RED.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

STOMACH:

-Epithelial vacuolation, limiting ridge, grade 1

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

RECTUM:

-Luminal nematodes, focal/multifocal, grade 2

LIVER:

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 1

-Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

-Pigment storage in vacuolar basophilic cells, brown, unilateral,

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 94

.....

grade 1  
OVARIES:  
-Interstitial cell hyperplasia, unilateral, grade 1  
UTERUS:  
-Epithelial cyst(s), focal/multifocal  
filled with neutrophils  
VAGINA:  
-Diestrus  
-Luminal plugs, consisting of neutrophils and detritus,  
grade 1  
THYROID GLAND (BOTH LOBES):  
-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2  
This finding corresponds to necropsy observation no: 01.  
PARATHYROID GLANDS:  
Only one of paired organs examined/present  
SPLEEN:  
-Extramedullary hemopoiesis, grade 1  
-Hemosiderin storage, grade 1  
BONE MARROW (FEMUR):  
-Fatty replacement, grade 1  
THYMUS:  
-Cyst(s), focal/multifocal  
MANDIBULAR LYMPH NODES:  
Only one of paired organs examined/present  
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

FEMALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 95

\* NECROPSY FINDINGS

UTERUS:

01: BOTH HORNS: CONTAINS WATERY FLUID, D=10X5 MM.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present  
-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

LUNGS:

(parenchyma incompletely inflated)

STOMACH:

-Epithelial vacuolation, limiting ridge, grade 1  
-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

KIDNEYS:

-Tubular casts, unilateral, grade 2  
-Tubular basophilia, focal/multifocal, unilateral, grade 1

UTERUS:

-Luminal dilation, (cyclic change)  
This finding corresponds to necropsy observation no: 01.

VAGINA:

-Proestrus

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 3  
-Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

-Fatty replacement, grade 1  
-Increased erythropoiesis, grade 1

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DOSE GROUP : 03, 50 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 95

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 109

\* ANIMAL NO. : 96

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

-Alveolar macrophages, focal/multifocal, grade 1

LIVER:

-Inflammatory cell focus/foci, grade 1

-Peribiliary inflammation, focal/multifocal, grade 1

KIDNEYS:

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 1

-Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

-Pigment storage in vacuolar basophilic cells, brown, unilateral,  
grade 1



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DOSE GROUP : 03, 50 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 96

VAGINA:

-Estrus

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 2

-Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

MAMMARY GLAND AREA:

-Lobular alveoli

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 97

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, DARK RED.  
NO OTHER NECROPSY OBSERVATIONS NOTED

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DOSE GROUP : 03, 50 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 97

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present  
-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

LIVER:

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 1  
-Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 1

VAGINA:

-Metestrus

PITUITARY GLAND:

-Cyst, pars intermedia, focal/multifocal  
-Cyst, pars distalis

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2  
This finding corresponds to necropsy observation no: 01.

SPLEEN:

-Extramedullary hemopoiesis, grade 3  
-Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

-Fatty replacement, grade 1  
-Increased erythropoiesis, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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DOSE GROUP : 03, 50 MG/KG

FEMALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 98

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LIVER:

-Hemopoietic cell focus/foci, grade 1

OVARIES:

-Atrophy, bilateral, grade 2

VAGINA:

-Diestrus

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

Grade 1 in contra lateral organ.

SPLEEN:

-Extramedullary hemopoiesis, grade 2

-Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

-Increased erythropoiesis, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

FEMALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 99

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, DARK RED.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present  
-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

OVARIES:

-Rete ovarii (embrionic remnant), unilateral

VAGINA:

-Estrus

PITUITARY GLAND:

-Cyst, pars distalis

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

-Follicular cell hypertrophy, bilateral, grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 3

BONE MARROW (FEMUR):

-Fatty replacement, grade 2

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

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SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 03, 50 MG/KG FEMALE

CONT./FF. ANIMAL NO. : 99

.....  
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

**\* STATE AT NECROPSY: K0**

DAYS ON TEST : 109

\* ANIMAL NO. : 100

**\* NECROPSY FINDINGS**

**UTERUS:**

01: BOTH HORNS: DISCOLORATION, DARK RED.

**THYROID GLAND (BOTH LOBES):**

01: BOTH SIDES: DISCOLORATION, DARK RED.

NO OTHER NECROPSY OBSERVATIONS NOTED

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**LUNGS:**

-Alveolar macrophages, focal/multifocal, grade 1  
foamy

**KIDNEYS:**

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 1

-Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

**UTERUS:**

-Congestion, at uterus horn, unilaterally

This finding corresponds to necropsy observation no: 01.

**VAGINA:**

-Estrus

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 100

.....  
**THYROID GLAND (BOTH LOBES):**

- Thyroglossal duct cyst, unilateral
- Pigment storage, cytoplasmic, brown, fine-granular, bilateral, grade 1  
This finding corresponds to necropsy observation no: 01.
- Follicular cell hypertrophy, bilateral, grade 1

**SPLEEN:**

- Extramedullary hemopoiesis, grade 2
- Hemosiderin storage, grade 2

**BONE MARROW (FEMUR):**

- Fatty replacement, grade 1

**THYMUS:**

- Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

- Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

.....  
\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 101

.....  
\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 101

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

Grade 1 in contra lateral organ.

-Follicular cell hypertrophy, unilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

Organ examined, no pathologic findings noted

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 102

\* NECROPSY FINDINGS

OVARIES:

01: LEFT SIDE: DISCOLORATION, DARK RED.

UTERUS:

01: BOTH HORNS: DILATION, D=5 MM, CONTAINS WATERY FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

OVARIES:

Only one of paired organs examined/present

-Congestion, unilateral

This finding corresponds to necropsy observation no: 01.

UTERUS:

-Luminal dilation, (cyclic change)

This finding corresponds to necropsy observation no: 01.

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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 03, 50 MG/KG FEMALE

CONT./FF. ANIMAL NO. : 102

**THYROID GLAND (BOTH LOBES):**

- Thymic remnant, unilateral
- Pigment storage, cytoplasmic, brown, fine-granular, bilateral, grade 2
- Follicular cell hypertrophy, bilateral, grade 1

**PARATHYROID GLANDS:**

Organ examined, no pathologic findings noted

**\* STATE AT NECROPSY: K1**

DAYS ON TEST : 107

\* ANIMAL NO. : 103

**\* NECROPSY FINDINGS**

**UTERUS:**

01: BOTH HORNS: DILATION, D=8 MM, CONTAINS WATERY FLUID.  
NO OTHER NECROPSY OBSERVATIONS NOTED

**\* MICROSCOPIC FINDINGS**

**UTERUS:**

- Luminal dilation, (cyclic change)
- This finding corresponds to necropsy observation no: 01.

**THYROID GLAND (BOTH LOBES):**

- Pigment storage, cytoplasmic, brown, fine-granular, bilateral, grade 1
- Follicular cell hypertrophy, bilateral, grade 1

**PARATHYROID GLANDS:**

Only one of paired organs examined/present  
Organ examined, no pathologic findings noted



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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 03, 50 MG/KG

FEMALE

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 104

\* NECROPSY FINDINGS

UTERUS:

01: BOTH HORNS: DILATION, D=5 MM, CONTAINS WATERY FLUID.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

UTERUS:

-Luminal dilation, (cyclic change)

This finding corresponds to necropsy observation no: 01.

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

-Follicular cell hypertrophy, bilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

Organ examined, no pathologic findings noted

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 105

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 03, 50 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 105

.....

**\* MICROSCOPIC FINDINGS**

**THYROID GLAND (BOTH LOBES):**

- Thymic remnant, unilateral
- Pigment storage, cytoplasmic, brown, fine-granular, bilateral, grade 2

**PARATHYROID GLANDS:**

- Only one of paired organs examined/present
- Organ examined, no pathologic findings noted

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ANIMAL HEADING DATA  
DOSE GROUP : 04, 200 MG/KG

| ANIMAL NUMBER | SEX M/F | DEFINED STATE | AND FINAL NECROPSY | TEST DAYS | FIRST DAY UNDER TEST | LAST DAY UNDER TEST | DATE OF NECROPSY |
|---------------|---------|---------------|--------------------|-----------|----------------------|---------------------|------------------|
| 46            | M       | K0            | K0                 | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 47            | M       | K0            | K0                 | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 48            | M       | K0            | K0                 | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 49            | M       | K0            | K0                 | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 50            | M       | K0            | K0                 | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 51            | M       | K0            | K0                 | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 52            | M       | K0            | K0                 | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 53            | M       | K0            | K0                 | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 54            | M       | K0            | K0                 | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 55            | M       | K0            | K0                 | 108       | 01-NOV-04            | 16-FEB-05           | 17-FEB-05        |
| 56            | M       | K1            | K1                 | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 57            | M       | K1            | K1                 | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 58            | M       | K1            | K1                 | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 59            | M       | K1            | K1                 | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 60            | M       | K1            | K1                 | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 106           | F       | K0            | K0                 | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 107           | F       | K0            | K0                 | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 108           | F       | K0            | K0                 | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 109           | F       | K0            | K0                 | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 110           | F       | K0            | K0                 | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 111           | F       | K0            | K0                 | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 112           | F       | K0            | K0                 | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 113           | F       | K0            | K0                 | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 114           | F       | K0            | K0                 | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 115           | F       | K0            | K0                 | 109       | 01-NOV-04            | 17-FEB-05           | 18-FEB-05        |
| 116           | F       | K1            | K1                 | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 117           | F       | K1            | K1                 | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 118           | F       | K1            | K1                 | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 119           | F       | K1            | K1                 | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |
| 120           | F       | K1            | K1                 | 107       | 01-NOV-04            | 15-FEB-05           | 16-FEB-05        |

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

MALE

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108

\* ANIMAL NO. : 46

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):  
01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:  
Only one of paired organs examined/present  
LUNGS:  
-Vascular mineralization, focal/multifocal, grade 1  
STOMACH:  
-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1  
LIVER:  
-Inflammatory cell focus/foci, grade 1  
PITUITARY GLAND:  
-Cyst, pars nervosa  
THYROID GLAND (BOTH LOBES):  
-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 3  
This finding corresponds to necropsy observation no: 01.  
-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1  
-Follicular cell hypertrophy, bilateral, grade 2  
PARATHYROID GLANDS:  
Only one of paired organs examined/present  
SPLEEN:  
-Extramedullary hemopoiesis, grade 1  
-Hemosiderin storage, grade 3  
BONE MARROW (FEMUR):  
-Fatty replacement, grade 2  
-Increased erythropoiesis, grade 2

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DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 46

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108

\* ANIMAL NO. : 47

\* NECROPSY FINDINGS

KIDNEYS:

01: LEFT SIDE: PELVIC DILATION.

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

HEART:

-Myocardial inflammation, chronic, lympho-histiocytic, grade 2

-Myocardial fibrosis, grade 2

-Valvular endocardiosis, left atrio-ventricular valve, grade 1

TRACHEA:

-Glandular dilation, submucosa, grade 1

-Mononuclear cell focus/foci, submucosa, grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

-Alveolar macrophages, focal/multifocal, grade 1  
foamy

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 47

**STOMACH:**

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

**LIVER:**

-Fatty change, predominantly zone 1, grade 1  
-Inflammatory cell focus/foci, grade 1

**KIDNEYS:**

No microscopic finding corresponding to necropsy observation no. 01.  
-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 2  
-Inflammatory cell focus/foci, interstitial, unilateral,  
grade 1  
-Tubular basophilia, focal/multifocal, bilateral, grade 2  
Grade 1 in contra lateral organ.  
-Pigment storage in vacuolar basophilic cells, brown, bilateral,  
grade 1

**TESTES:**

(rete tubulus cut unilaterally)  
-Tubular hypoplasia, sertoli only tubulus(i), focal, unilateral,  
grade 1

**PITUITARY GLAND:**

-Cyst, pars distalis  
-Hypertrophy/plasia, chromophobic cells, focal/multifocal,  
grade 1

**THYROID GLAND (BOTH LOBES):**

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 4  
This finding corresponds to necropsy observation no: 01.  
-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 2  
-Follicular cell hypertrophy, bilateral, grade 2

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

**SPLEEN:**

-Extramedullary hemopoiesis, grade 2  
-Hemosiderin storage, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 47

**BONE MARROW (FEMUR):**

-Fatty replacement, grade 1

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS:**

-Inflammatory cell focus/foci, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

**\* STATE AT NECROPSY: K0**

DAYS ON TEST : 108

\* ANIMAL NO. : 48

**\* NECROPSY FINDINGS**

**THYROID GLAND (BOTH LOBES):**

01: BOTH SIDES: DISCOLORATION, BLACK.

NO OTHER NECROPSY OBSERVATIONS NOTED

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**TRACHEA:**

-Glandular dilation, submucosa, grade 1  
with inspissated contents

**LUNGS:**

-Vascular mineralization, focal/multifocal, grade 1  
-Alveolar macrophages, focal/multifocal, grade 1

**STOMACH:**

-Hyperkeratosis, grade 1

**PEYER'S PATCHES (JEJUNUM):**

Tissue not present for histologic examination

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DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 48

**LIVER:**

- Fatty change, predominantly zone 1, grade 2
- Inflammatory cell focus/foci, grade 1

**THYROID GLAND (BOTH LOBES):**

- Pigment storage, cytoplasmic, brown, fine-granular, bilateral, grade 4

This finding corresponds to necropsy observation no: 01.

- Follicular cell hypertrophy, bilateral, grade 2

**ADRENAL CORTICES:**

- Vacuolation, zona fasciculata/reticularis, multifocal, bilateral, grade 2

Grade 1 in contra lateral organ.

**SPLEEN:**

- Extramedullary hemopoiesis, grade 1
- Hemosiderin storage, grade 2

**BONE MARROW (FEMUR):**

- Fatty replacement, grade 1

**MESENTERIC LYMPH NODE:**

- Hemorrhage, sinusoidal, grade 1

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

- Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.



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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

MALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 49

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

LIVER:

-Inflammatory cell focus/foci, grade 1

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

-Pigment storage in vacuolar basophilic cells, brown, unilateral,  
grade 1

PITUITARY GLAND:

-Hypertrophy/plasia, chromophobic cells, focal/multifocal,  
grade 1

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 3

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 2

-Follicular cell hypertrophy, bilateral, grade 2

ADRENAL CORTICES:

-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 2

-Hemosiderin storage, grade 1

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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 49

**BONE MARROW (FEMUR):**

-Increased erythropoiesis, grade 1

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

**\* STATE AT NECROPSY: K0**

DAYS ON TEST : 108

\* ANIMAL NO. : 50

**\* NECROPSY FINDINGS**

NO NECROPSY OBSERVATIONS NOTED.

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**HEART:**

-Inflammatory cell foci, right ventricle, grade 1

**TRACHEA:**

-Glandular dilation, submucosa, grade 1

-Mononuclear cell focus/foci, submucosa, grade 2

**LUNGS:**

-Vascular mineralization, focal/multifocal, grade 1

**STOMACH:**

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

**RECTUM:**

-Luminal nematodes, focal/multifocal, grade 2

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 50

**LIVER:**

-Inflammatory cell focus/foci, grade 1

**KIDNEYS:**

-Hyaline droplets, proximal tubulus epithelium, multifocal, bilateral, grade 2

-Pigment storage in tubulus cells, brown, fine-granular, bilateral, grade 1

-Tubular basophilia, focal/multifocal, bilateral, grade 1

-Pigment storage in vacuolar basophilic cells, brown, bilateral, grade 1

-Pigmented tubular casts, brown, focal/multifocal, bilateral, grade 1

**TESTES:**

(rete tubulus cut unilaterally)

-Tubular vacuolation, focal/multifocal, bilateral, grade 1

-Multinuclear giant cells, spermatocytic, focal, unilateral, grade 1

**THYROID GLAND (BOTH LOBES):**

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral, grade 3

-Increased vacuolation, cytoplasmic, follicular cell, bilateral, grade 1

-Follicular cell hypertrophy, bilateral, grade 1

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

**SPLEEN:**

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 1

**THYMUS:**

-Hemorrhage, focal/multifocal, grade 1

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

-Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 108

\* ANIMAL NO. : 51

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

HEART:

-Inflammatory cell foci, septum, grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

STOMACH:

-Epithelial vacuolation, limiting ridge, grade 2

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 2

-Mucosal hyperplasia, superficial, pars glandularis, grade 2  
multifocal

LIVER:

-Fatty change, predominantly zone 1, grade 1

-Inflammatory cell focus/foci, grade 2

PANCREAS:

hemorrhage and hemosiderin storage in adjacent lymph node

-Acinar atrophy, focal/multifocal, grade 1

-Basophilic focus/foci, grade 1

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 1

-Inflammatory cell focus/foci, interstitial, unilateral,  
grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

-Pigment storage in vacuolar basophilic cells, brown, unilateral,  
grade 1

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DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 51

PROSTATE GLAND:

-Glandular atrophy, grade 2

SEMINAL VESICLES:

-Glandular atrophy, with reduced secretal contents, bilateral,  
grade 1

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 3

This finding corresponds to necropsy observation no: 01.

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1

ADRENAL CORTICES:

-Capsular fibrosis, focal, unilateral, grade 1

-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 2

-Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

-Increased erythropoiesis, grade 1

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

-Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

MALE

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108

\* ANIMAL NO. : 52

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):  
01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1  
-Epithelial cyst(s), focal/multifocal, pars glandularis,  
grade 1

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 2  
-Inflammatory cell focus/foci, interstitial, unilateral,  
grade 1  
-Tubular basophilia, focal/multifocal, bilateral, grade 2  
Grade 1 in contra lateral organ.  
-Pigment storage in vacuolar basophilic cells, brown, bilateral,  
grade 1

URINARY BLADDER:

-Mononuclear cell focus/foci, lymphocytic, submucosa, grade 1

TESTES:

(rete tubulus cut unilaterally)

PROSTATE GLAND:

-Inflammatory cell focus/foci, interstitial, ventral lobe,  
grade 1  
-Glandular hyperplasia, multifocal, ventral lobe, grade 2

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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 52

**PITUITARY GLAND:**

- Cyst, pars intermedia, focal/multifocal
- Hypertrophy/plasia, chromophobic cells, focal/multifocal, grade 1
- Fatty change, focal, grade 1

**THYROID GLAND (BOTH LOBES):**

- Pigment storage, cytoplasmic, brown, fine-granular, bilateral, grade 3  
This finding corresponds to necropsy observation no: 01.
- Increased vacuolation, cytoplasmic, follicular cell, bilateral, grade 1
- Follicular cell hypertrophy, bilateral, grade 1

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

**ADRENAL CORTICES:**

- Accessory cortical tissue, unilateral
- Vacuolation, zona fasciculata/reticularis, multifocal, bilateral, grade 1

**SPLEEN:**

- Extramedullary hemopoiesis, grade 2
- Hemosiderin storage, grade 1

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

- Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

MALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 53

\* NECROPSY FINDINGS

STOMACH:

01: MUCOSA, FUNDUS: FOCUS/FOCI, D=4 MM, ISOLATED, DARK RED.

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

THYMUS:

01: FOCUS/FOCI, D=2 MM, SEVERAL, DARK RED.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

- Vascular mineralization, focal/multifocal, grade 1
- Alveolar macrophages, focal/multifocal, grade 1

STOMACH:

- Hyperemia, pars glandularis, multifocal, superficial, grade 2  
This finding corresponds to necropsy observation no: 01.
- Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

COLON:

- Luminal nematodes, focal/multifocal, grade 1

LIVER:

- Inflammatory cell focus/foci, grade 1

KIDNEYS:

- Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 1
- Tubular basophilia, focal/multifocal, bilateral, grade 2  
Grade 1 in contra lateral organ.
- Pigment storage in vacuolar basophilic cells, brown, bilateral,  
grade 1
- Pigmented tubular casts, brown, focal/multifocal, bilateral,  
grade 1



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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 04, 200 MG/KG MALE

CONT./FF. ANIMAL NO. : 53

**PROSTATE GLAND:**

- Inflammatory cell focus/foci, nera ductus deferens, grade 1
- Glandular atrophy, grade 1

**PITUITARY GLAND:**

- Cyst, pars distalis
- Hypertrophy/plasia, chromophobic cells, focal/multifocal, grade 1

**THYROID GLAND (BOTH LOBES):**

- Pigment storage, cytoplasmic, brown, fine-granular, bilateral, grade 3  
This finding corresponds to necropsy observation no: 01.
- Increased vacuolation, cytoplasmic, follicular cell, bilateral, grade 2
- Follicular cell hypertrophy, bilateral, grade 1

**ADRENAL CORTICES:**

- Vacuolation, zona fasciculata/reticularis, multifocal, bilateral, grade 1

**SPLEEN:**

- Extramedullary hemopoiesis, grade 3
- Hemosiderin storage, grade 1

**THYMUS:**

No microscopic finding corresponding to necropsy observation no. 01.

**MESENTERIC LYMPH NODE:**

- Hemorrhage, sinusoidal, grade 1

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

- Hemorrhage, unilateral, grade 2
- Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 200 MG/KG

MALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 108

\* ANIMAL NO. : 54

\* NECROPSY FINDINGS

STOMACH:

01: MUCOSA, FUNDUS: FOCUS/FOCI, D=2 MM, ISOLATED, REDDISH.

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

(parenchyma incompletely inflated)

-Vascular mineralization, focal/multifocal, grade 1

-Alveolar hemorrhage, focal/multifocal, grade 1

-Alveolar macrophages, focal/multifocal, grade 1  
foamy

STOMACH:

-Hyperemia, pars glandularis, multifocal, superficial, grade 2

This finding corresponds to necropsy observation no: 01.

-Epithelial cyst(s), focal/multifocal, pars glandularis,  
grade 1

PEYER'S PATCHES (JEJUNUM):

-Mineralization, grade 1

RECTUM:

(linea anorectalis cut focally)

LIVER:

-Inflammatory cell focus/foci, grade 1

PANCREAS:

-Acinar atrophy, focal/multifocal, grade 1

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,  
bilateral, grade 2

-Tubular basophilia, focal/multifocal, bilateral, grade 1

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DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 54

.....

-Pigment storage in vacuolar basophilic cells, brown, bilateral,  
grade 1

TESTES:  
(rete tubuli cut unilaterally)

PROSTATE GLAND:  
-Glandular atrophy, grade 1

SEMINAL VESICLES:  
-Glandular atrophy, with reduced secretal contents, bilateral,  
grade 1

PITUITARY GLAND:  
-Hypertrophy/plasia, chromophobic cells, focal/multifocal,  
grade 1

THYROID GLAND (BOTH LOBES):  
-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 3  
This finding corresponds to necropsy observation no: 01.  
-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1  
-Follicular cell hypertrophy, bilateral, grade 1

PARATHYROID GLANDS:  
Only one of paired organs examined/present

ADRENAL CORTICES:  
-Vacuolation, zona fasciculata/reticularis, multifocal,  
unilateral, grade 1

SPLEEN:  
-Extramedullary hemopoiesis, grade 2  
-Hemosiderin storage, grade 2

THYMUS:  
-Cyst(s), focal/multifocal

MESENTERIC LYMPH NODE:  
-Hemorrhage, sinusoidal, grade 1

MANDIBULAR LYMPH NODES:  
Only one of paired organs examined/present

RETROORBITAL TISSUE:  
-Hemorrhage, unilateral, grade 1

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DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 54

.....  
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 108

\* ANIMAL NO. : 55

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):  
01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

- Vascular mineralization, focal/multifocal, grade 1
- Alveolar hemorrhage, focal/multifocal, grade 1
- Alveolar macrophages, focal/multifocal, grade 1

STOMACH:

- Hyaline inclusions, epithelium, limiting ridge, multifocal, grade 1

LIVER:

- Inflammatory cell focus/foci, grade 2

KIDNEYS:

- Hyaline droplets, proximal tubulus epithelium, multifocal, bilateral, grade 1
- Pigment storage in tubulus cells, brown, fine-granular, bilateral, grade 1
- Tubular basophilia, focal/multifocal, bilateral, grade 2  
Grade 1 in contra lateral organ.
- Pigment storage in vacuolar basophilic cells, brown, bilateral,

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 55

.....

grade 1  
-Pigmented tubular casts, brown, focal/multifocal, bilateral,  
grade 1  
PITUITARY GLAND:  
-Hypertrophy/plasia, chromophobic cells, focal/multifocal,  
grade 1  
THYROID GLAND (BOTH LOBES):  
-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2  
This finding corresponds to necropsy observation no: 01.  
-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1  
-Follicular cell hypertrophy, bilateral, grade 1  
PARATHYROID GLANDS:  
Only one of paired organs examined/present  
ADRENAL CORTICES:  
-Vacuolation, zona fasciculata/reticularis, multifocal,  
bilateral, grade 2  
SPLEEN:  
-Extramedullary hemopoiesis, grade 2  
-Hemosiderin storage, grade 2  
THYMUS:  
-Cyst(s), focal/multifocal  
MANDIBULAR LYMPH NODES:  
Only one of paired organs examined/present  
RETROORBITAL TISSUE:  
-Hemorrhage, unilateral, grade 1  
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

MALE

\* STATE AT NECROPSY: K1  
DAYS ON TEST : 107

\* ANIMAL NO. : 56

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):  
01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):  
-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 3  
This finding corresponds to necropsy observation no: 01.  
-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1  
-Follicular cell hypertrophy, bilateral, grade 1  
PARATHYROID GLANDS:  
Organ examined, no pathologic findings noted

\* STATE AT NECROPSY: K1  
DAYS ON TEST : 107

\* ANIMAL NO. : 57

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):  
01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 57

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 3

This finding corresponds to necropsy observation no: 01.

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 2

-Follicular cell hypertrophy, bilateral, grade 2

PARATHYROID GLANDS:

Organ examined, no pathologic findings noted

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 58

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 3

This finding corresponds to necropsy observation no: 01.

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 2

-Follicular cell hypertrophy, bilateral, grade 1

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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 04, 200 MG/KG

MALE

CONT./FF. ANIMAL NO. : 58

**PARATHYROID GLANDS:**

Only one of paired organs examined/present  
Organ examined, no pathologic findings noted

**\* STATE AT NECROPSY: K1**

DAYS ON TEST : 107

\* ANIMAL NO. : 59

**\* NECROPSY FINDINGS**

**THYROID GLAND (BOTH LOBES):**

01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

**\* MICROSCOPIC FINDINGS**

**THYROID GLAND (BOTH LOBES):**

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1

-Follicular cell hypertrophy, bilateral, grade 1

**PARATHYROID GLANDS:**

Tissue not present for histologic examination



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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

MALE

\* STATE AT NECROPSY: K1  
DAYS ON TEST : 107

\* ANIMAL NO. : 60

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):  
01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):  
-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2  
This finding corresponds to necropsy observation no: 01.  
-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 2  
-Follicular cell hypertrophy, bilateral, grade 1  
PARATHYROID GLANDS:  
Only one of paired organs examined/present  
Organ examined, no pathologic findings noted

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 109

\* ANIMAL NO. : 106

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, DARK RED.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

TRACHEA:

-Glandular dilation, submucosa, grade 1

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

LIVER:

-Inflammatory cell focus/foci, grade 1  
-Hepatocellular hypertrophy, grade 2

KIDNEYS:

-Tubular mineralization, focal/multifocal, unilateral, grade 1  
-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 2  
-Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 1  
-Tubular basophilia, focal/multifocal, unilateral, grade 1  
-Pigment storage in vacuolar basophilic cells, brown, unilateral,  
grade 1

VAGINA:

-Estrus

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

-Follicular cell hypertrophy, bilateral, grade 1

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DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 106

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

**SPLEEN:**

- Extramedullary hemopoiesis, grade 1
- Hemosiderin storage, grade 2

**BONE MARROW (FEMUR):**

- Fatty replacement, grade 1

**THYMUS:**

- Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

- Hemorrhage, unilateral, grade 1
- Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

**\* STATE AT NECROPSY: KO**

DAYS ON TEST : 109

\* ANIMAL NO. : 107

**\* NECROPSY FINDINGS**

**THYROID GLAND (BOTH LOBES):**

01: BOTH SIDES: DISCOLORATION, DARK RED.  
NO OTHER NECROPSY OBSERVATIONS NOTED

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**TRACHEA:**

- Glandular dilation, submucosa, grade 1

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DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 107

**LUNGS:**

-Alveolar macrophages, focal/multifocal, grade 2  
foamy

**STOMACH:**

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

**LIVER:**

-Fatty change, predominantly zone 1, grade 1

**KIDNEYS:**

-Inflammatory cell focus/foci, interstitial, unilateral,  
grade 1

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 2

-Pigment storage in tubulus cells, brown, fine-granular,  
unilateral, grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

-Pigment storage in vacuolar basophilic cells, brown, unilateral,  
grade 1

**VAGINA:**

-Metestrus

-Luminal plugs, consisting of neutrophiles and detritus,  
grade 2

**THYROID GLAND (BOTH LOBES):**

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

**PARATHYROID GLANDS:**

Only one of paired organs examined/present

**SPLEEN:**

-Extramedullary hemopoiesis, grade 2

-Hemosiderin storage, grade 3

**THYMUS:**

-Cyst(s), focal/multifocal

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 107

RETROORBITAL TISSUE:

- Hemorrhage, unilateral, grade 1
  - Inflammation, due to blood sampling, unilateral, grade 1
- ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 109

\* ANIMAL NO. : 108

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

- 01: BOTH SIDES: DISCOLORATION, DARK RED.
- NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

STOMACH:

- Hyaline inclusions, epithelium, limiting ridge, multifocal, grade 1

LIVER:

- Fatty change, predominantly zone 1, grade 1
- Inflammatory cell focus/foci, grade 1

KIDNEYS:

- Tubular mineralization, focal/multifocal, unilateral, grade 1
- Tubulus cell swelling, vacuolar, corticomedullary junction, bilateral, grade 1
- Pigment storage in tubulus cells, brown, fine-granular, bilateral, grade 1

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DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 108

VAGINA:

-Diestrus

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

SPLEEN:

-Extramedullary hemopoiesis, grade 3

-Hemosiderin storage, grade 3

BONE MARROW (FEMUR):

-Increased erythropoiesis, grade 1

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

-Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 109

\* NECROPSY FINDINGS

OVARIES:

01: RIGHT SIDE: WATERY CYST, D=10 MM.

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, DARK RED.

NO OTHER NECROPSY OBSERVATIONS NOTED

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 109

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present  
-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

TRACHEA:

-Mononuclear cell focus/foci, submucosa, grade 1

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

KIDNEYS:

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 2  
-Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 1  
-Tubular basophilia, focal/multifocal, unilateral, grade 1  
-Pigment storage in vacuolar basophilic cells, brown, unilateral,  
grade 1

OVARIES:

-Bursa cyst, unilateral  
This finding corresponds to necropsy observation no: 01.  
-Interstitial cell hyperplasia, unilateral, grade 2

VAGINA:

-Estrus

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2  
This finding corresponds to necropsy observation no: 01.  
-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1  
-Follicular cell hypertrophy, bilateral, grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 3  
-Hemosiderin storage, grade 2

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DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 109

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 110

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, DARK RED.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

RECTUM:

(anus cut additionally)

KIDNEYS:

-Inflammatory cell focus/foci, interstitial, unilateral,  
grade 1

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 2

-Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 1



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DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 110

VAGINA:

-Metestrus

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 111

\* NECROPSY FINDINGS

UTERUS:

01: BOTH HORNS: DILATION, D=5 MM, CONTAINS FLUID.

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

NO OTHER NECROPSY OBSERVATIONS NOTED

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DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 111

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**STOMACH:**

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

**LIVER:**

-Inflammatory cell focus/foci, grade 1

**KIDNEYS:**

-Tubular mineralization, focal/multifocal, unilateral, grade 1

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 2

-Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 2

-Tubular basophilia, focal/multifocal, bilateral, grade 1

-Pigment storage in vacuolar basophilic cells, brown, bilateral,  
grade 1

**UTERUS:**

-Luminal dilation, (cyclic change)

This finding corresponds to necropsy observation no: 01.

**VAGINA:**

-Estrus

**THYROID GLAND (BOTH LOBES):**

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 3

This finding corresponds to necropsy observation no: 01.

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 2

-Follicular cell hypertrophy, bilateral, grade 1

**SPLEEN:**

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 2

**BONE MARROW (FEMUR):**

-Fatty replacement, grade 1

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DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 111

**MANDIBULAR LYMPH NODES:**

Only one of paired organs examined/present

**RETROORBITAL TISSUE:**

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 109

\* ANIMAL NO. : 112

**\* NECROPSY FINDINGS**

**THYROID GLAND (BOTH LOBES):**

01: BOTH SIDES: DISCOLORATION, DARK RED.

NO OTHER NECROPSY OBSERVATIONS NOTED

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present

**STOMACH:**

-Epithelial cyst(s), focal/multifocal, pars glandularis,  
grade 1

**LIVER:**

-Inflammatory cell focus/foci, grade 1

**KIDNEYS:**

-Inflammatory cell focus/foci, interstitial, unilateral,  
grade 1

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 2

-Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 1

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DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 112

VAGINA:

-Metestrus

THYROID GLAND (BOTH LOBES):

-Ultimobranchial cyst(s), focal/multifocal, unilateral  
-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

-Extramedullary hemopoiesis, grade 2  
-Hemosiderin storage, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

-Hemorrhage, unilateral, grade 1

MAMMARY GLAND AREA:

-Lobular alveoli

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 113

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

NO OTHER NECROPSY OBSERVATIONS NOTED

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**TEXT OF GROSS AND MICROSCOPIC FINDINGS**

DOSE GROUP : 04, 200 MG/KG

**FEMALE**

CONT./FF. ANIMAL NO. : 113

**\* MICROSCOPIC FINDINGS**

**SCIATIC NERVES:**

Only one of paired organs examined/present  
-Axonal degeneration, secondary, focal/multifocal, unilateral,  
grade 1

**LUNGS:**

-Vascular mineralization, focal/multifocal, grade 1

**STOMACH:**

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

**PEYER'S PATCHES (JEJUNUM):**

-Mineralization, grade 1

**PANCREAS:**

(focally beginning intravascular fibrin condensation, most  
likely intramortal artifact)

**KIDNEYS:**

-Tubular mineralization, focal/multifocal, bilateral, grade 1  
-Inflammatory cell focus/foci, interstitial, unilateral,  
grade 1  
-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 2  
-Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 1  
-Tubular basophilia, focal/multifocal, bilateral, grade 1  
-Pigment storage in vacuolar basophilic cells, brown, bilateral,  
grade 1

**OVARIES:**

-Interstitial cell hyperplasia, unilateral, grade 2

**UTERUS:**

-Luminal dilation, (cyclic change)

**VAGINA:**

-Proestrus

**THYROID GLAND (BOTH LOBES):**

-Ultimobranchial cyst(s), focal/multifocal, unilateral  
-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 3

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TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 113

.....  
This finding corresponds to necropsy observation no: 01.  
-Follicular cell hypertrophy, bilateral, grade 1  
SPLEEN:  
-Extramedullary hemopoiesis, grade 3  
-Hemosiderin storage, grade 3  
BONE MARROW (FEMUR):  
-Fatty replacement, grade 1  
-Increased erythropoiesis, grade 1  
THYMUS:  
-Cyst(s), focal/multifocal  
MANDIBULAR LYMPH NODES:  
Only one of paired organs examined/present  
SUBLINGUAL GLANDS:  
Only one of paired organs examined/present  
RETROORBITAL TISSUE:  
-Hemorrhage, unilateral, grade 1  
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

\* STATE AT NECROPSY: K0  
DAYS ON TEST : 109

\* ANIMAL NO. : 114

.....  
\* NECROPSY FINDINGS

CECUM:  
01: MUCOSA: FOCUS/FOCI, D=20 MM, DARK RED.  
OVARIES:  
01: LEFT SIDE: WATERY CYST, D=10 MM.  
THYROID GLAND (BOTH LOBES):  
01: BOTH SIDES: DISCOLORATION, BLACK.  
NO OTHER NECROPSY OBSERVATIONS NOTED

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DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 114

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

HEART:

-Myocardial fibrosis, left ventricle, grade 2

LUNGS:

-Alveolar macrophages, focal/multifocal, grade 1

STOMACH:

-Hyaline inclusions, epithelium, limiting ridge, multifocal,  
grade 1

CECUM:

-Hemorrhage, submucosa, grade 3

This finding corresponds to necropsy observation no: 01.

KIDNEYS:

-Tubulus cell swelling, vacuolar, corticomedullary junction,  
bilateral, grade 3

-Pigment storage in tubulus cells, brown, fine-granular,  
bilateral, grade 1

-Tubular basophilia, focal/multifocal, bilateral, grade 2  
Grade 1 in contra lateral organ.

-Pigment storage in vacuolar basophilic cells, brown, bilateral,  
grade 2

Grade 1 in contra lateral organ.

-Pigmented tubular casts, brown, focal/multifocal, unilateral,  
grade 1

OVARIES:

-Bursa cyst, unilateral

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Estrus

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1

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DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 114

.....  
-Follicular cell hypertrophy, bilateral, grade 1

SPLEEN:

- Extramedullary hemopoiesis, grade 2
- Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

- Fatty replacement, grade 1

THYMUS:

- Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

RETROORBITAL TISSUE:

- Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

.....  
\* STATE AT NECROPSY: K0

DAYS ON TEST : 109

\* ANIMAL NO. : 115

.....  
\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

SCIATIC NERVES:

Only one of paired organs examined/present

LUNGS:

- Alveolar macrophages, focal/multifocal, grade 1

LIVER:

- Inflammatory cell focus/foci, grade 2



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DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 115

PANCREAS:

-Acinar atrophy, focal/multifocal, grade 1

KIDNEYS:

-Tubular mineralization, focal/multifocal, bilateral, grade 1

OVARIES:

-Rete ovarii (embrionic remnant), unilateral

VAGINA:

-Diestrus

-Luminal plugs, consisting of neutrophiles and detritus,  
grade 1

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

Grade 1 in contra lateral organ.

This finding corresponds to necropsy observation no: 01.

-Follicular cell hypertrophy, unilateral, grade 1

SPLEEN:

-Hemosiderin storage, grade 2

BONE MARROW (FEMUR):

-Increased erythropoiesis, grade 1

THYMUS:

-Cyst(s), focal/multifocal

MANDIBULAR LYMPH NODES:

Only one of paired organs examined/present

MAMMARY GLAND AREA:

-Lobular alveoli

RETROORBITAL TISSUE:

-Hemorrhage, unilateral, grade 2

-Inflammation, due to blood sampling, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 200 MG/KG FEMALE

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 116

.....

\* NECROPSY FINDINGS

UTERUS:

01: BOTH HORNS: DILATION, D=5 MM, CONTAINS WATERY FLUID.

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

SKIN/SUBCUTIS:

01: SHOULDER: ALOPECIA, ISOLATED, D=20 MM, SLIGHT.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

UTERUS:

-Luminal dilation, (cyclic change)

This finding corresponds to necropsy observation no: 01.

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 3

This finding corresponds to necropsy observation no: 01.

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1

-Follicular cell hypertrophy, bilateral, grade 1

PARATHYROID GLANDS:

Organ examined, no pathologic findings noted

SKIN/SUBCUTIS:

-Hair follicle atrophy, focal, shoulder region, grade 2

This finding corresponds to necropsy observation no: 01.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 200 MG/KG FEMALE

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 117

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1

-Follicular cell hypertrophy, bilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

Organ examined, no pathologic findings noted

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 118

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

NO OTHER NECROPSY OBSERVATIONS NOTED

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DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 118

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 3

This finding corresponds to necropsy observation no: 01.

-Follicular cell hypertrophy, bilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

Organ examined, no pathologic findings noted

\* STATE AT NECROPSY: K1

DAYS ON TEST : 107

\* ANIMAL NO. : 119

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

SKIN/SUBCUTIS:

01: SHOULDER: ALOPECIA, D=10 MM, SLIGHT.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 2

This finding corresponds to necropsy observation no: 01.

-Follicular cell hypertrophy, unilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

Organ examined, no pathologic findings noted

PATHOLOGY REPORT  
INDIVIDUAL ANIMAL DATA

PAGE : 242/ 242  
RCC : 857092

TEST ARTICLE : A084, WR 23081  
TEST SYSTEM : RAT, 90-DAY, ORAL (GAVAGE)  
SPONSOR : WELLA AG

PATHOL. NO.: 80076 NED  
DATE : 19-JUL-05  
PathData®System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS  
DOSE GROUP : 04, 200 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 119

SKIN/SUBCUTIS:

-Hair follicle atrophy, focal, shoulder region, grade 1  
This finding corresponds to necropsy observation no: 01.

\* STATE AT NECROPSY: K1  
DAYS ON TEST : 107

\* ANIMAL NO. : 120

\* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):

01: BOTH SIDES: DISCOLORATION, BLACK.

SKIN/SUBCUTIS:

01: SHOULDER: ALOPECIA, ISOLATED, D=10 MM, SLIGHT.  
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Pigment storage, cytoplasmic, brown, fine-granular, bilateral,  
grade 3

This finding corresponds to necropsy observation no: 01.

-Increased vacuolation, cytoplasmic, follicular cell, bilateral,  
grade 1

-Follicular cell hypertrophy, bilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

SKIN/SUBCUTIS:

No microscopic finding corresponding to necropsy observation no. 01.  
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

# **RCC Study Number 857092**

Repeated Dose 90-Day Oral Toxicity Study  
with

**2-Amino-4-Hydroxyethylaminoanisole  
Sulfate (A 80, WR 23081)**

in Wistar Rats

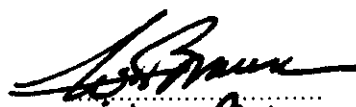
**Final Study Plan**



## SIGNATURES

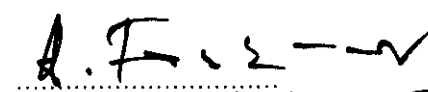
Study Director:

W. H. Braun

  
date: 25 Oct 2004

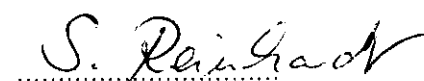
Test Facility Management:

Dr. H. Fankhauser

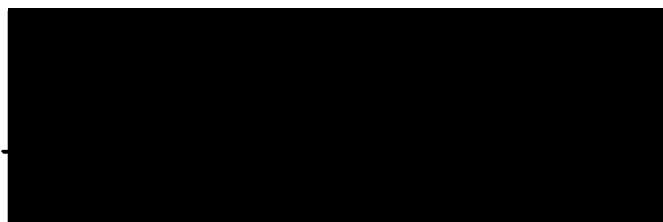
  
date: 25 October 2004

Lead Quality Assurance:

S. Reinhardt

  
date: 25-OCT-2004

Sponsor:



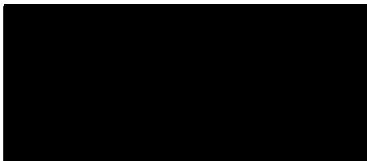
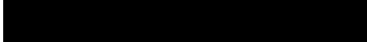
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## 1     **PREFACE**

### 1.1   **GENERAL**

|                      |   |
|----------------------|---|
| Title                | Repeated Dose 90-Day Oral Toxicity Study with 2-Amino-4-Hydroxyethylaminoaniso le Sulfate (A 80, WR 23081) in Wistar Rats   |
| Sponsor              |   |
| Monitoring Scientist |   |
| Test Facility        | RCC Ltd<br>Toxicology<br>CH – 4452 Itingen / Switzerland (a)<br>CH – 4414 Füllinsdorf / Switzerland (b)   |
| Test Site(s)         | RCC Ltd<br>Environmental Chemistry & Pharmanalytics<br>CH – 4452 Itingen / Switzerland (c)  |
| Lead QA              | RCC Ltd<br>Quality Assurance GLP<br>Toxicology<br>CH–4452 Itingen / Switzerland   |
| Test Site QAs        | RCC Ltd<br>Quality Assurance GLP<br>Environmental Chemistry & Pharmanalytics<br>CH–4452 Itingen / Switzerland<br>Contact person: D. Bürgin<br>(Responsible for test site c) |

### 1.2   **RESPONSIBILITIES**

#### **Study Personnel:**

|                           |                           |
|---------------------------|---------------------------|
| Study Director            | W. H. Braun (a)           |
| Deputy Study Director     | Dr. B. Damme (a)          |
| Laboratory Coordinator    | P. Althaus Ravenstijn (a) |
| Clinical Diagnostic       | Dr. P. Gretener (b)       |
| Necropsy/ Histotechnology | Dr. K. Weber (a)          |
| Pathology                 | Dr. K. Weber (a)          |

**Principal Investigators:**

Study Phase:

Analytical Chemistry                      Dr. D. Flade (c)

Thyroid Hormone                          Dr. R. Burri (c)

**Quality Assurance:**

Head of Lead QA                          I. Wüthrich

**1.3 SCHEDULE**

|                              |  |
|------------------------------|--|
| Experimental Starting Date   | 25 October 2004                                      |
| Experimental Completion Date | March/April 2005 (proposed)                          |
| Delivery of Animals          | 25 October 2004                                      |
| Acclimatization              | 25 to 31 October 2004                                |
| Administration/Treatment     | 01 November 2004 to 30/31 January / 01 February 2005 |
| Termination (Necropsy)       | 31 January to 02 February 2005                       |
| Draft Report                 | 18 April 2005 (proposed submission)                  |

**1.3.1 RCC – PROPOSED SUBMISSION DATES**

|                                      |               |
|--------------------------------------|---------------|
| Clinical Laboratory Investigations   | 01 April 2005 |
| Hormone Analysis                     | 01 April 2005 |
| Pathology                            | 01 April 2005 |
| Chemical Analysis of Formulations    | 01 April 2005 |
| QA-Audit of Draft Report (completed) | 22 May 2005   |

**1.4 GOOD LABORATORY PRACTICE**

This study will be performed in compliance with:

Swiss Ordinance relating to Good Laboratory Practice adopted February 2<sup>nd</sup>, 2000 [RS 813.016.5]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26<sup>th</sup>, 1997 by decision of the OECD Council [C (97)186/Final].

Each Principal Investigator (PI) will be responsible for compliance with his national GLP regulations for any work performed at his test site and for data provided to RCC for inclusion in the report. Any phase report provided by a PI should include a Statement of GLP Compliance signed by the PI and a Quality Assurance Statement signed by an authorized representative of the PI's Quality Assurance.

The test site Quality Assurance should inspect study-related work at their test site according to its own SOPs. They should report any inspection results in writing to the PI, test site management, study director, test facility management and the lead Quality Assurance.

## **1.5 ACCREDITATION**

"RCC Ltd, Toxicology" is accredited as testing laboratory for analysis in the fields of clinical laboratory investigations, hematology, coagulation and urine in accordance with the Standard ISO/IEC 17025 under accreditation number STS 085 by the Swiss Accreditation Service.

## **1.6 TEST GUIDELINES**

The study procedures described in this protocol conform to the following guidelines:

"Repeated Dose 90-Day Oral Toxicity Study in Rodents", OECD Guidelines for the testing of Chemicals, Section 4, Health Effects, Number 408, 21 September 1998.

## **1.7 ANIMAL WELFARE**

This study will be performed in an AAALAC-approved laboratory in accordance with the Swiss Animal Protection Law under license no. 27.

## **1.8 AMENDMENT AND DEVIATION PROCEDURES**

Amendments (planned changes) to the study plan will be issued and signed by the Study Director, and will become effective at the time of Study Director signature. The Sponsor will receive the original amendment, which must be signed and returned to RCC, and one copy. The amendment will be distributed (see Distribution) and added to all copies of the study plan.

Deviations (unplanned changes) to the study plan will be documented and maintained with the raw data. The report will reflect any deviations. The sponsor will be promptly informed of any relevant deviations from the study plan.

Each Principal Investigator will document deviations to the study plan, acknowledge and report them to the Study Director.

## **1.9 ARCHIVING**

RCC Ltd (CH-4452 Itingen / Switzerland) will retain the study plan, raw data, sample of test item(s), specimens (as long as the quality permits evaluation) and the final report of the present study for at least ten years. Wet tissue samples will be archived at RCC Ltd for a minimum of five years. Thereafter, in agreement with the Sponsor, these samples may be further archived at RCC Ltd or transferred to another GLP archive facility for the remainder of the prescribed period. No raw data or material pertaining to this study will be discarded without the Sponsor's prior written consent.

## 2      **PURPOSE**

The purpose of this oral toxicity study is to assess the cumulative toxicity of 2-Amino-4-Hydroxyethylaminoanisoole Sulfate (A 80, WR 23081) when administered to rats via gavage for a period of at least 13 weeks.

This study should provide a rational basis for risk assessment in man and should indicate potential target organs.

## 3      **MATERIALS AND METHODS**

General Remarks: Details of the materials and methods that are not specified in the subsequent sections of this study plan are contained in the appropriate RCC standard operating procedures.

### 3.1    **TEST SYSTEM**

|  |   |
|--|---|
| Test system                                      | Rat, HanBrl:WIST(SPF)   |
| Rationale  | Recognized by the international guidelines as a recommended test system.  |
| Source   | RCC Ltd<br>Laboratory Animal Services<br>CH-4414 Füllinsdorf / Switzerland  |
| Number of animals per group                      | 15 males; 15 females (Groups 1-4)   |
| Total number of animals                          | 60 males; 60 females  |
| Total number of animals ordered                  | will be listed in the raw data and report (reserve animals will be used as needed and their exchange and/or sacrifice will be documented in raw data) |
| Age at delivery                                  | Approximately 6 weeks   |
| Body weight and range at acclimatization/pretest | Males:        150 grams ( $\pm 20\%$ ),<br>Females:    125 grams ( $\pm 20\%$ ).  |
| Identification                                   | Cage card and individual ear tattoo   |
| Randomization                                    | Computer-generated random algorithm.  |
| Acclimatization                                  | Under test conditions after health examination. Only animals without any visible signs of illness will be used for the study.                         |

### 3.2 ALLOCATION

| Allocation  | Group 1    | Group 2   | Group 3   | Group 4   |
|-------------|------------|-----------|-----------|-----------|
| And         | 0          | 15        | 50        | 200       |
| Dose Levels | mg/kg/day* | mg/kg/day | mg/kg/day | mg/kg/day |
| Males A     | 1 - 10     | 16 - 25   | 31 - 40   | 46 - 55   |
| Males B     | 11 - 15    | 25 - 30   | 41 - 45   | 56 - 60   |
| Females A   | 61 - 70    | 76 - 85   | 91 - 100  | 106 - 115 |
| Females B   | 71 - 75    | 86 - 90   | 101 - 105 | 116 - 120 |

A - Toxicity testing (termination after 13 treatment weeks)

B - Hormone testing (termination after 13 treatment weeks)

\* - Control animals were treated with the vehicle only

### 3.3 HUSBANDRY

|               |  |
|---------------|--|
| Room number   | Will be documented in the raw data and added to the report. (Itingen)  |
| Conditions    | Standard Laboratory Conditions. Air-conditioned with 10-15 air changes per hour, and continuously monitored environment with target ranges for temperature $22 \pm 3^{\circ}\text{C}$ and for relative humidity between 40-70%. 12 hours fluorescent light/12 hours dark, music during the light period. |
| Accommodation | In groups of five in Makrolon type-4 cages with wire mesh tops and standardized softwood bedding ('Lignocel' Schill AG, CH-4132 MuttENZ/Switzerland).  |
| Diet          | Pelleted standard Kliba 3433 rat maintenance diet (Provimi Kliba AG, CH-4303 Kaiseraugst/Switzerland) <i>ad libitum</i> . Results of analyses for contaminants will be included in the report.   |
| Water         | Community tap-water, from Itingen <i>ad libitum</i> . Results of representative bacteriological, chemical and contaminant analyses will be included in the report.   |

### 3.4 TEST ITEM

|                        |   |
|------------------------|---|
| Identity               | 2-Amino-4-HydroxyethylaminoanisoLe Sulfate (A 80, WR 23081) |
| Description            | pale grey powder  |
| Batch number           | 57  |
| Purity                 | 99.6 % area% HPLC   |
| Stability of test item | Stable under storage conditions                             |

|                    |   |
|--------------------|---|
| Expiry date        | July 2005   |
| Storage conditions | at room temperature (15-25°C) in the original container away from direct sunlight |
| Safety precautions | Routine hygienic procedures (gloves, goggles, face mask)                          |

These data were provided by the sponsor.

### 3.5 ANALYTICAL STANDARD

|          |  |
|----------|--|
| Identity | 2-Amino-4-Hydroxyethylaminoaniso le Sulfate (A 80, WR 23081) (the test item will serve as its own analytical standard) |
|----------|--|

### 3.6 DOSE FORMULATION

**Dose levels are in terms of test item as supplied unless otherwise stated by the sponsor.**

|                               |        |
|-------------------------------|--------|
| Frequency of dose formulation | weekly |
|-------------------------------|--------|

The test item will be weighed into a tared glass beaker on a suitable precision balance and the vehicle added (weight:volume). The mixtures will be prepared using a magnetic stirrer or homogenizer, as appropriate.

Homogeneity of the test item in the vehicle will be maintained during the daily administration period using a magnetic stirrer.

#### 3.6.1 STORAGE OF DOSE FORMULATIONS

|                                |   |
|--------------------------------|---|
| Stability of dose formulations | for at least seven days; based upon information provided by the sponsor                         |
| Storage of dose formulations   | at room temperature (ca. 15-25°C) in glass beakers protected from light (i.e. in aluminum foil) |

#### 3.6.2 ANALYSIS OF DOSE FORMULATIONS

Concentration, homogeneity and stability (after 2 hours and 7 days) of the dose formulations will be determined in samples taken on the first day of treatment. Analyses will be performed by the Principal Investigator of the analytical phase (see Responsibilities, page 5), according to a HPLC analytical method supplied by the Sponsor. Details of the analytical method will be documented in the raw data generated by the Principal Investigator and the Principal Investigator will provide an analytical phase report. Concentration and homogeneity of the dose formulations will be determined in samples taken monthly during the treatment.

### 3.7 VEHICLE AND CONTROL ITEM

|          |                   |
|----------|-------------------|
| Identity | bidistilled water |
|----------|-------------------|

### 3.8 TREATMENT

|                                    |  |
|------------------------------------|--|
| Method                             | Oral, by gavage.   |
| Rationale                          | The oral route was selected as it is a possible route of human exposure during manufacture, handling and use of the test item.   |
| Daily dose levels                  | Group 1: 0 mg/kg body weight<br>Group 2: 15 mg/kg body weight<br>Group 3: 50 mg/kg body weight<br>Group 4: 200 mg/kg body weight<br><br>Dose levels are in terms of test item as supplied unless otherwise requested by the sponsor. |
| Rationale for dose level selection | The dose levels were provided by the sponsor.  |
| Frequency of administration        | Daily  |
| Dose volume                        | 10 ml/kg   |
| Duration of acclimatization period | 7 days   |
| Duration of treatment              | at least 13 weeks  |

### 3.9 OBSERVATIONS

The following observations will be recorded:

|                                |   |
|--------------------------------|---|
| Viability/mortality            | Twice daily   |
| General observations           | Once prior to first administration; once daily during the treatment and recovery periods  |
| Detailed clinical observations | Once before the first test item exposure and once weekly during weeks 1 – 12 (Allocation A)   |
| Ophthalmoscopy                 | At acclimatization: Once in all animals (Allocation A)<br>At week 13: in control and high dose animals (Allocation A)<br><br>The intermediate dose groups will also be examined at week 13 if test item-related changes are seen in the animals of the high dose group. |
| Food consumption               | Weekly  |
| Body weights                   | At least weekly during acclimatization and treatment periods.   |

### 3.9.1 FUNCTIONAL OBSERVATIONAL BATTERY

At week 13 (Allocation A), relevant parameters from a modified Irwin screen test will be performed on all rats. A description of all test parameters will be listed in the report. Any abnormal findings will be recorded and graded in severity.

Hind-forelimb grip strength measurement will be performed using a push-pull strain gauge (Mecmesin, AFG 25N).

Locomotor activity will be measured quantitatively. Decreased or increased activity will be recorded. Activity will be measured with an AMS Föhr Medical Instruments GmbH (FMI) and DeMeTec GmbH. Activity of the animals will be recorded for 10-minute intervals over a period of 60 minutes. These data and the total activity over 60 minutes will be reported.

## 4 CLINICAL LABORATORY INVESTIGATIONS

Blood samples will be drawn from the retro-orbital plexus from all rats per sex and group of Allocation A under light isoflurane anesthesia. The animals will be fasted in metabolism cages for approximately 18 hours before blood sampling but allowed access to water *ad libitum*. The samples will be collected early in the working day to reduce biological variation caused by circadian rhythms.

Blood and urine sampling:  
after 13 weeks (Allocation A)                      01/02 February 2005

### 4.1 HEMATOLOGY

The following hematology parameters will be determined:

|   |   |
|---|---|
| Erythrocyte count                           | Reticulocyte maturity index   |
| Hemoglobin                                  | Methemoglobin   |
| Hematocrit                                  | Heinz bodies (slides will be prepared but evaluated only if changes are seen in the methemoglobin levels) |
| Mean corpuscular volume                     | Total leukocyte count   |
| Red cell volume distribution width          | Differential leukocyte count  |
| Mean corpuscular hemoglobin                 | Coagulation:  |
| Mean corpuscular hemoglobin concentration   | Thromboplastin time   |
| Hemoglobin concentration distribution width | Activated partial thromboplastin time   |
| Platelet (thrombocyte) count                |   |
| Reticulocyte count                          |   |



## 4.2 CLINICAL BIOCHEMISTRY

The following clinical biochemistry parameters will be determined:

|                            |                            |
|----------------------------|----------------------------|
| Glucose                    | Creatine kinase            |
| Urea                       | Alkaline phosphatase       |
| Creatinine                 | Gamma-glutamyl-transferase |
| Bilirubin, total           | Sodium                     |
| Cholesterol, total         | Potassium                  |
| Triglycerides              | Chloride                   |
| Phospholipids              | Calcium                    |
| Aspartate aminotransferase | Phosphorus inorganic       |
| Alanine aminotransferase   | Protein, total             |
| Lactate dehydrogenase      | Protein, electrophoresis   |
| Glutamate dehydrogenase    | Albumin/Globulin ratio     |

## 4.3 URINALYSIS

The following urinalysis parameters will be determined:

|                                     |              |
|-------------------------------------|--------------|
| Volume (18 hours)                   | Glucose      |
| Specific gravity (relative density) | Ketones      |
| Color                               | Urobilinogen |
| Appearance                          | Bilirubin    |
| pH                                  | Blood        |
| Nitrite                             | Sediment     |
| Protein                             |              |

## 5 HORMONE ANALYSIS

Blood samples will be drawn from the retro-orbital plexus prior to scheduled necropsy for hormone analysis and placed on ice. After serum samples have been taken, they will be deep-frozen (ca.  $-80^{\circ}\text{C}$ ). Five (5) aliquots of 300  $\mu\text{l}$  serum each will be provided to Dr. R. Burri for the analysis of total  $T_3$ , total  $T_4$ , free  $T_3$ , free  $T_4$  and TSH, and the reported results will be provided to the study director for inclusion in the report.

Scheduled date of sampling:  
after 13 weeks

31 January 2005 (Allocation B)

## **6      PATHOLOGY**

### **6.1    NECROPSY**

All animals will be weighed and necropsied. Descriptions of all macroscopic abnormalities will be recorded. All animals surviving to the end of the observation period and all moribund animals will be anesthetized by intraperitoneal injection of pentobarbitone and killed by exsanguination.

Necropsy:

after 13 weeks (Allocation A)                      01/02 February 2005  
after 13 weeks (Allocation B)                      31 January 2005

From representative test item-related macroscopic findings photographs will be taken during the necropsy, if appropriate.

Samples of the following tissues and organs will be collected from all animals at necropsy and, unless otherwise indicated, fixed in neutral phosphate buffered 4% formaldehyde solution. Additional tissues (such as ear tattoo) will be retained in accordance with standard procedures but will not be processed or examined further.

|   |   |
|---|---|
| <b>Adrenal glands</b>                                       | Nasal cavity (turbinates)                                 |
| <b>Aorta</b>  | <b>Ovaries</b>  |
| Bone (sternum, femur including joint)                       | <b>Pancreas</b>   |
| <b>Bone marrow (femur)</b>                                  | <b>Pituitary gland</b>                                    |
| <b>Brain (generally 4 levels)</b>                           | <b>Prostate gland (incl. coagulating glands)</b>          |
| <b>Cecum</b>  | <b>Rectum</b>   |
| <b>Colon</b>  | <b>Salivary glands - mandibular, sublingual</b>           |
| <b>Duodenum</b>   | <b>Sciatic nerve</b>                                      |
| <b>Epididymides (fixed in Bouin's solution)</b>             | <b>Seminal vesicles</b>                                   |
| <b>Esophagus</b>  | Skeletal muscle   |
| Exorbital lacrimal glands                                   | <b>Skin</b>   |
| <b>Eyes with optic nerve (fixed in Davidson's solution)</b> | <b>Spinal cord - cervical, midthoracic, lumbar</b>        |
| Harderian gland (fixed in Davidson's solution)              | <b>Spleen</b>   |
| <b>Heart</b>  | <b>Stomach</b>  |
| <b>Ileum, with Peyer's patches</b>                          | <b>Testes (fixed in Bouin's solution)</b>                 |
| <b>Jejunum with Peyer's patches</b>                         | <b>Thymus</b>   |
| <b>Kidneys</b>  | <b>Thyroid (including parathyroid gland, if possible)</b> |
| Larynx  | Tongue  |
| Lacrimal gland, exorbital                                   | <b>Trachea</b>  |
| <b>Liver</b>  | <b>Urinary bladder, infused with formalin at necropsy</b> |
| <b>Lungs, infused with formalin at necropsy</b>             | <b>Uterus</b>   |
| <b>Lymph nodes - mesenteric, mandibular</b>                 | <b>Vagina</b>   |
| <b>Mammary gland area</b>                                   | <b>Gross lesions</b>                                      |

## 6.2 ORGAN WEIGHTS

The following organ weights will be recorded on the scheduled dates of necropsy listed and their organ to terminal body weight ratios as well as organ to brain weight ratios determined:

|                         |          |              |
|-------------------------|----------|--------------|
| Brain                   | Thymus   | Spleen       |
| Heart                   | Kidneys  | Testes       |
| Liver                   | Adrenals | Epididymides |
| Thyroids w/parathyroids | Uterus   | Ovaries      |

## 6.3 HISTOTECHNIQUE

All organ and tissue samples to be examined by the study pathologist (see Histopathology, below) will be processed, embedded and cut at an approximate thickness of 2-4 micrometers and stained with hematoxylin and eosin. Special stains will be used at the discretion of the study pathologist.

## 6.4 HISTOPATHOLOGY

Slides of all organs and tissues listed in boldface type (see Necropsy, above) that were collected at terminal sacrifice from the Allocation A animals of control and test item-treated groups, as well as thyroid glands of the Allocation B will be examined by the study pathologist. The same applies to all occurring gross lesions and to all animals that die spontaneously or must be terminated in extremis.

If microscopical tissue discoloration is observed which is considered likely to be a passive effect of the test item (for example, a dye stuff which causes discoloration but does not evoke an evident tissue reaction that could be of toxicological relevance), additional slides will be taken from only one male and one female of the each interim group to establish a no-effect level. These animals will be selected by the study director and the pathologist.

## 7 STATISTICAL ANALYSIS

The following statistical methods may be used to analyze ophthalmoscopy, grip strength, locomotor activity, body weight, organ weights and ratios, as well as:

- The Dunnett-test (many to one t-test) based on a pooled variance estimate will be applied if the variables can be assumed to follow a normal distribution for the comparison of the treated groups and the control groups for each sex.
- The Steel-test (many-one rank test) will be applied instead of the Dunnett-test when the data can not be assumed to follow a normal distribution.
- Fisher's exact-test will be applied to the macroscopic findings.
- Armitage/Cochran Trend Test for non-neoplastic lesions, if appropriate.

The following statistical methods may be used for statistical analysis of clinical laboratory data:

- Quantitative data will be analyzed by a one-way analysis of variance (ANOVA) when the variances are considered homogeneous according to Bartlett. Alternatively, if the variances are considered to be heterogeneous ( $p \leq 0.05$ ), a non-parametric Kruskal-Wallis test will be used. Treated groups will then be compared to the control groups using Dunnett's test if the ANOVA was significant at the 5% level and by Dunn's test in the case of a significant Kruskal-Wallis test ( $p \leq 0.05$ ).
- Ordinal data such as urine sediment will be analyzed using the Kruskal-Wallis test. If this test is significant ( $p \leq 0.05$ ), comparisons will be made between the control group and each of the treatment groups using Dunn's test.

Additional methods of statistical analysis will be used at the discretion of the statistician. The methods and the results will be described in the report.

References :

C.W. Dunnett: A Multiple Comparison Procedure for Comparing Several Treatments with a Control, J. Amer. Stat. Assoc. 50, 1096-1121 (1955).

S.C. Gad and C.S. Weil: Statistics and Experimental Design for Toxicologists. The Telford Press, Caldwell, New Jersey, 43-45 (1986).

W.H. Kruskal and W.A. Wallis: Use of ranks in one-criterion variance analysis. Journal of the American Statistical Association, 47, 583-621 (1952).

O.J. Dunn: Multiple comparisons using rank sums. Technometrics 6, 241-252 (1964).

R.G. Miller: Simultaneous Statistical Inference, Springer Verlag, New York (1981).

R.A. Fisher: Statistical Methods for Research Workers, Oliver and Boyd, Edinburgh (1950).

P. Armitage: Test for linear trends in proportions and frequencies. Biometrics 11, 375-386 (1955).

## **8        REPORTING**

A GLP-compliant draft report will be submitted to the sponsor for scientific review. Following receipt of the sponsor's comments, a QA-audited final report will be issued.

## 9      DISTRIBUTION

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# **RCC Study Number 857092**

Repeated Dose 90-Day Oral Toxicity Study  
with

**2-Amino-4-Hydroxyethylamino-  
anisole Sulfate (A084, WR 23081)**

in Wistar Rats

**Study Plan Amendment No. 1**


Date of Issue: 24-Nov-04  
Total Number of Pages: 9



## SIGNATURES


Study Director:

W. H. Braun

  
date: 24 Nov. 2004

Test Facility Management:

Dr. H. Fankhauser

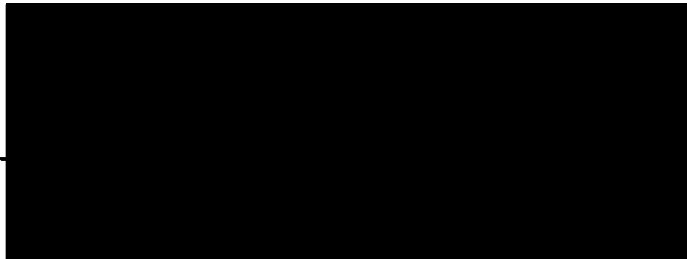
  
date: 22 November 2004

Lead Quality Assurance:

C. Zeugin

  
date: 24 Nov. 2004

Sponsor:



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**PAGE**

Entire study plan

**CONCERNING**

Test item name

**PRESENT**

Hydroxyethylaminoanisoole Sulfate (A 80, WR 23081)

**NEW**

Hydroxyethylaminoanisoole Sulfate (A084, WR 23081)

**REASON FOR THE ALTERATION**

Correction of typing error (note: this correction was already implemented in this document).

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**PAGE**

4

**CONCERNING**

Study Personnel

**PRESENT**

**Study Personnel:**

|                        |                           |
|------------------------|---------------------------|
| Laboratory Coordinator | P. Althaus Ravenstijn (a) |
|------------------------|---------------------------|

**NEW**

**Study Personnel:**

|                        |               |
|------------------------|---------------|
| Laboratory Coordinator | R. Sacher (a) |
|------------------------|---------------|

**REASON FOR THE ALTERATION**

Reallocation of personnel.

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**PAGE**

5

**CONCERNING**

Schedule

**PRESENT**

**1.3 SCHEDULE**

|                              |  |
|------------------------------|--|
| Experimental Starting Date   | 25 October 2004                                      |
| Experimental Completion Date | March/April 2005 (proposed)                          |
| Delivery of Animals          | 25 October 2004                                      |
| Acclimatization              | 25 to 31 October 2004                                |
| Administration/Treatment     | 01 November 2004 to 30/31 January / 01 February 2005 |
| Termination (Necropsy)       | 31 January to 02 February 2005                       |
| Draft Report                 | 18 April 2005 (proposed submission)                  |

**1.3.1 RCC – PROPOSED SUBMISSION DATES**

|                                      |               |
|--------------------------------------|---------------|
| Clinical Laboratory Investigations   | 01 April 2005 |
| Hormone Analysis                     | 01 April 2005 |
| Pathology                            | 01 April 2005 |
| Chemical Analysis of Formulations    | 01 April 2005 |
| QA-Audit of Draft Report (completed) | 22 May 2005   |

**NEW**

**1.3 SCHEDULE**

|                              |   |
|------------------------------|---|
| Experimental Starting Date   | 25 October 2004                         |
| Experimental Completion Date | March/April 2005 (proposed)             |
| Delivery of Animals          | 25 October 2004                         |
| Acclimatization              | 25 to 31 October 2004                   |
| Administration/Treatment     | 01 November 2004 to 15-17 February 2005 |
| Termination (Necropsy)       | 16 to 18 February 2005                  |
| Draft Report                 | 29 April 2005 (proposed submission)     |

### 1.3.1 RCC – PROPOSED SUBMISSION DATES

|                                      |               |
|--------------------------------------|---------------|
| Clinical Laboratory Investigations   | 18 April 2005 |
| Hormone Analysis                     | 18 April 2005 |
| Pathology                            | 18 April 2005 |
| Chemical Analysis of Formulations    | 18 April 2005 |
| QA-Audit of Draft Report (completed) | 03 June 2005  |

### REASON FOR THE ALTERATION

The treatment period was extended to compensate for marked degradation of the initial formulation.

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### PAGE

9

### CONCERNING

Dose Formulation

### PRESENT

Frequency of dose formulation      weekly

### NEW

Frequency of dose formulation      daily

### REASON FOR THE ALTERATION

Test item is insufficiently stable for weekly dose formulation.

---

---

### PAGE

9

### CONCERNING

Dose Formulation

### PRESENT

### 3.6.1 STORAGE OF DOSE FORMULATIONS

Stability of dose formulations      for at least seven days; based upon information provided by the sponsor

Storage of dose formulations      at room temperature (ca. 15-25°C) in glass beakers protected from light (i.e. in aluminum foil)

**NEW**

**3.6.1 STABILITY OF DOSE FORMULATIONS**

Stability of dose formulations at least 4 hours  
Preparation of dose formulations at room temperature (ca. 15-25°C) in glass beakers, thereafter protected from light (i.e. in aluminum foil)

**REASON FOR THE ALTERATION**

Test item is insufficiently stable for weekly dose formulation.

---

**PAGE**

9

**CONCERNING**

Dose Formulation

**PRESENT**

**3.6.2 ANALYSIS OF DOSE FORMULATIONS**

Concentration, homogeneity and stability (after 2 hours and 7 days) of the dose formulations will be determined in samples taken on the first day of treatment. Analyses will be performed by the Principal Investigator of the analytical phase (see Responsibilities, page 5), according to a HPLC analytical method supplied by the Sponsor. Details of the analytical method will be documented in the raw data generated by the Principal Investigator and the Principal Investigator will provide an analytical phase report. Concentration and homogeneity of the dose formulations will be determined in samples taken monthly during the treatment.

**NEW**

**3.6.2 ANALYSIS OF DOSE FORMULATIONS**

Concentration, homogeneity and stability (after 4 hours) of the dose formulations will be determined in samples taken on the first day of daily dose formulation (samples for 2 hours and 7 day analyses were taken earlier in the study). Analyses will be performed by the Principal Investigator of the analytical phase (see Responsibilities, page 5), according to a HPLC analytical method supplied by the Sponsor. Details of the analytical method will be documented in the raw data generated by the Principal Investigator and the Principal Investigator will provide an analytical phase report. Concentration and homogeneity of the dose formulations will be determined in samples taken monthly during the treatment.

**REASON FOR THE ALTERATION**

Test item is insufficiently stable for weekly dose formulation.

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**PAGE**

10

**CONCERNING**

**OBSERVATIONS**

**PRESENT**

Detailed clinical observations                      Once before the first test item exposure and once weekly during weeks 1 – 12 (Allocation A)

Ophthalmoscopy    At acclimatization: Once in all animals (Allocation A)  
At week 13: in control and high dose animals (Allocation A)

The intermediate dose groups will also be examined at week 13 if test item-related changes are seen in the animals of the high dose group.

**NEW**

Detailed clinical observations                      Once before the first test item exposure and once weekly during weeks 1 – 14 (Allocation A)

Ophthalmoscopy    At acclimatization: Once in all animals (Allocation A)  
After week 13: in control and high dose animals (Allocation A)

The intermediate dose groups will also be examined after week 13 if test item-related changes are seen in the animals of the high dose group.

**REASON FOR THE ALTERATION**

Adaptation of wording according to procedural change.

---

**PAGE**

11

**CONCERNING**

**FUNCTIONAL OBSERVATIONAL BATTERY**

**PRESENT**

At week 13 (Allocation A), relevant parameters from a modified Irwin screen test will be performed on all rats. A description of all test parameters will be listed in the report. Any abnormal findings will be recorded and graded in severity.

**NEW**

After week 14 (Allocation A), relevant parameters from a modified Irwin screen test will be performed on all rats. A description of all test parameters will be listed in the report. Any abnormal findings will be recorded and graded in severity.

**REASON FOR THE ALTERATION**

Adaptation of wording according to procedural change.

---

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**PAGE**

11

**CONCERNING**

CLINICAL LABORATORY DIAGNOSTICS

**PRESENT**

Blood and urine sampling:  
after 13 weeks (Allocation A)                      01/02 February 2005

**NEW**

Blood and urine sampling:  
after 15 weeks (Allocation A)                      17 February 2005

**REASON FOR THE ALTERATION**

Adaptation of wording according to procedural change.

---

---

**PAGE**

12

**CONCERNING**

HORMONE ANALYSIS

**PRESENT**

Scheduled date of sampling:  
after 13 weeks    31 January 2005 (Allocation B)

**NEW**

Scheduled date of sampling:  
after 15 weeks    16 February 2005 (Allocation B)

**REASON FOR THE ALTERATION**

Adaptation of wording according to procedural change.

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**PAGE**

13

**CONCERNING**

NECROPSY

**PRESENT**

Necropsy:

after 13 weeks (Allocation A)

01/02 February 2005

after 13 weeks (Allocation B)

31 January 2005

**NEW**

Necropsy:

after 15 weeks (Allocation A)

17/18 February 2005

after 15 weeks (Allocation B)

16 February 2005

**REASON FOR THE ALTERATION**

Adaptation of wording according to procedural change.

---

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# **RCC Study Number 857092**

Repeated Dose 90-Day Oral Toxicity Study  
with

**2-Amino-4-Hydroxyethylamino-  
anisole Sulfate (A084, WR 23081)**

in Wistar Rats

**Study Plan Amendment No. 2**

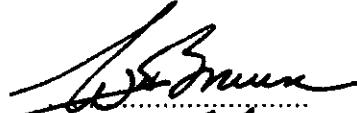
Date of Issue: 1-Mar-05  
Total Number of Pages: 4



## SIGNATURES

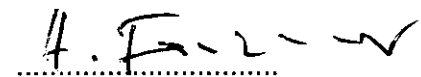
Study Director:

W. H. Braun

  
date: 01 Mar 2005


Test Facility Management:

Dr. H. Fankhauser

  
date: 01 March 2005

Lead Quality Assurance:

S. Reinhardt

  
date: 01-MAR-2005

Sponsor:





---

**PAGE**

4

**CONCERNING**

Study personnel

**PRESENT**

Pathology

Dr. K. Weber (a)

**NEW**

Pathology

Dr. D. Nehrbass (a)

**REASON FOR THE ALTERATION**

Re-allocation of study pathologist for capacity planning

---

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