

FINAL REPORT

STUDY TITLE

**REPEATED DOSE (90-DAY) ORAL TOXICITY STUDY BY GAVAGE WITH
ENZYME PREPARATION OF *BACILLUS AMYLOLIQUEFACIENS*
CONTAINING AMYLOMALTASE ACTIVITY IN WISTAR RATS**

STUDY No: G6597

STUDY DIRECTOR: Mr. P. M. SATHISH

STUDY COMPLETED ON: 28 September 2010

SPONSOR

DSM FOOD SPECIALTIES
PO BOX 1, 2600 MA DELFT
THE NETHERLANDS

TEST FACILITY

TOXICOLOGY
DEPARTMENT OF SAFETY ASSESSMENT
ADVINUS THERAPEUTICS PRIVATE LIMITED
POST BOX No. 5813, PLOT Nos. 21 & 22
PEENYA II PHASE, BANGALORE - 560 058
INDIA

STATEMENT OF CONFIDENTIALITY

The report contains **confidential** and **proprietary** information of DSM Food Specialties, PO Box 1, 2600 MA Delft, The Netherlands, which will not be disclosed to anyone except the employees of this company or to persons authorised by law or judicial judgement, without an expressed or a written approval of DSM Food Specialties, PO Box 1, 2600 MA Delft, The Netherlands.

STATEMENT OF GLP COMPLIANCE

The Study No.: G6597 was performed according to OECD Principles of Good Laboratory Practice for the testing of chemicals as specified by International [C (97) 186/Final] Legislation. This study was conducted in accordance with the standard operating procedures of Advinus Therapeutics Private Limited and the mutually agreed study plan signed by Study Director on 09 September 2009 and Monitoring Scientist on 18 September 2009. In addition study plan was amended once, Amendment No. 1 signed by the Study Director on 14 September 2010 and Monitoring Scientist on 27 September 2010.

DECLARATION

The Study Director hereby declares that the work was performed under his supervision and in accordance with the described procedures. It is assured that the reported results faithfully represent the raw data obtained during the experimental work. No circumstances have been left unreported which may have affected the quality or integrity of the data or which might have a potential bearing on the validity and reproducibility of this study.

The Study Director accepts overall responsibility for the technical conduct of the study as well as the interpretation, analysis, documentation and reporting of the results.



Mr. P. M. Sathish
Study Director

28 September 2010
Date

QUALITY ASSURANCE STATEMENT


Study No.: G6597, entitled " Repeated dose (90-Day) oral toxicity study by gavage with enzyme preparation of *Bacillus amyloliquefaciens* containing amylomaltase activity in Wistar Rats " has been inspected in accordance with the OECD Principles of Good Laboratory Practice for the testing of chemicals as specified by International [C (97) 186/Final] Legislation.

This study was inspected and findings reported to Management and Study Director on the dates shown below:

| INSPECTION DATE | PHASE | REPORTING DATE |
|--------------------------------|--|-------------------|
| | Initiation phase | |
| 31.08.2009 | Study plan review | 31.08.2009 |
| 14.09.2010 | Review of Amendment No. 1 to Study plan | 14.09.2010 |
| | In-life phase | |
| 15.09.2009 | Body weights, cage change, test item preparation and administration as oral gavage | 22.09.2009 |
| 06.10.2009 | Body weight and feed input (4 th week) | 12.10.2009 |
| 17.10.2009 | Test item administration as oral gavage on day 33 | 20.10.2009 |
| 23.10.2009 | Sampling of dose formulations for a.i. analysis | 26.10.2009 |
| 14.12.2009 | Blood collection and Necropsy | 21.12.2009 |
| | Reporting phase | |
| 18.02.2010 to 26.02.2010 | Draft report review | 26.02.2010 |
| 22.09.2010 to 23.09.2010 | Final report review | 23.09.2010 |

Inspections were performed according to the Standard Operating Procedures of the test facility's Quality Assurance Unit. The report was inspected against the approved study plan and pertinent raw data and accurately reflects the raw data.

Date: 28 Sept, 2010 -


(Mr. SATISH MURTHY.V)
 Head, GLP Section
 Quality Assurance Unit
 Advinus Therapeutics Private Limited, Bangalore

LIST OF COMMONLY USED ABBREVIATIONS AND SYMBOLS

| | | | |
|---------|---------------------------------------|----------|--|
| Alb | Albumin | M | Male |
| A.I. | Active Ingredient | m | metre |
| ALT | Alanine aminotransferase | MCH | Mean Corpuscular Haemoglobin |
| ALP | Alkaline phosphatase | MCHC | Mean Corpuscular Haemoglobin Concentration |
| App | Appendix / Appendices | MCV | Mean Corpuscular Volume |
| Approx. | Approximately | mEq | milli Equivalent |
| APTT | Activated Partial Thromboplastin Time | mg | milligram |
| AST | Aspartate aminotransferase | mL | millilitre |
| A/G | Albumin/Globulin ratio | micro | microcytes |
| | | min | minute |
| Baso | Basophils | mm | millimetre |
| BUN | Blood Urea Nitrogen | mmol | millimole |
| Bwt | Body weight | Mono | Monocytes |
| | | | |
| Ca | Calcium | NA | Not Applicable |
| Cl | Chloride | Na | Sodium |
| Creat | Creatinine | NAD | No Abnormality Detected |
| | | Neut | Neutrophils |
| DLC | Differential Leukocyte Count | No. | Number |
| | | | |
| Eosi | Eosinophils | pg | picogram |
| EDTA | Ethylene Diamine Tetra Acetic Acid | Pi | Inorganic phosphorus |
| | | Plt | Platelets |
| F | Female | PT | Prothrombin Time |
| fl | Femtolitre | | |
| | | | |
| g | gram | RBC | Red Blood Corpuscles |
| G | Giga | rpm | revolutions per minute |
| G. | Group | Ref.App. | Reference Appendix |
| GGT | Gamma Glutamyl Transpeptidase | | |
| Glu | Fasting Glucose | s | seconds |
| Glob | Globulin | SD | Standard Deviation |
| | | | |
| H | Height | T | Tera |
| Hgb | Haemoglobin | T.Bil | Total Bilirubin |
| Hct | Haematocrit | T.Chol | Total Cholesterol |
| h | Hours | T.Pro | Total plasma protein |
| | | TOS | Total organic solids |
| K | Potassium | | |
| Kg | kilogram | U | Units |
| | | | |
| L | litre | W | Width |
| Lymp | Lymphocytes | WBC | White Blood Corpuscles |
| | | % | Percent |
| | | | |
| | | μmol | micromole |
| | | °C | Degree Celsius |
| | | °F | Degree Fahrenheit |
| | | μ | microns |

TABLE OF CONTENTS

| | |
|--|----|
| STUDY TITLE | 1 |
| STATEMENT OF CONFIDENTIALITY | 2 |
| STATEMENT OF GLP COMPLIANCE | 2 |
| DECLARATION | 2 |
| QUALITY ASSURANCE STATEMENT | 3 |
| LIST OF COMMONLY USED ABBREVIATIONS AND SYMBOLS | 4 |
| TABLE OF CONTENTS | 5 |
| 1. STUDY DETAILS | 10 |
| 2. STUDY PERSONNEL | 11 |
| 3. SUMMARY | 12 |
| 4. OBJECTIVE..... | 13 |
| 5. STUDY GUIDELINE | 13 |
| 6. MATERIALS AND METHODS | 13 |
| 6.1 Materials..... | 13 |
| 6.1.1 Test Item Information..... | 13 |
| 6.1.2 Test System | 14 |
| 6.2 Methods..... | 15 |
| 6.2.1 Performance of the Test | 15 |
| 6.2.1.1 Husbandry | 15 |
| 6.2.1.2 Dose Selection..... | 16 |
| 6.2.1.3 Grouping..... | 17 |
| 6.2.1.4 Group Allocation and Number of Animals | 17 |
| 6.2.1.5 Route of Administration and Justification | 17 |
| 6.2.1.6 Identity of the Test Item | 17 |
| 6.2.1.7 Justification for the Selection of Vehicle | 17 |
| 6.2.1.8 Stability of the Test Item | 18 |
| 6.2.1.9 Test item preparation and administration..... | 18 |
| 6.2.1.10 Dose Formulation analysis | 18 |
| 6.2.1.11 Treatment | 19 |
| 6.3 Observations..... | 19 |

| | | |
|----------|---|----|
| 6.3.1 | Physical and Clinical Examination, General Clinical Signs and Mortality .. | 19 |
| 6.3.2 | Body Weights and Food Intake | 25 |
| 6.3.3 | Clinical Laboratory Investigations | 25 |
| 6.3.4 | Pathology | 28 |
| 6.4 | STATISTICAL ANALYSES | 30 |
| 7. | RESULTS | 31 |
| 7.1 | Analyses of the Test Item in Dose Solutions | 31 |
| 7.2 | In-Life Data | 31 |
| 7.2.1 | Physical Examination, General Clinical Signs and Mortality | 31 |
| 7.2.2 | Ophthalmological Examination | 31 |
| 7.2.3 | Neurological Examination (Functional Observation Battery) | 31 |
| 7.2.4 | Body Weights and Net Weight Gains | 32 |
| 7.2.5 | Food Intake | 32 |
| 7.2.6 | Clinical pathology | 32 |
| 7.2.7 | Terminal Fasting Body Weights, Organ Weights and Organ Weight Ratios | 33 |
| 7.2.8 | Gross Pathology | 34 |
| 7.2.9 | Histopathology | 34 |
| 8. | DISCUSSION | 36 |
| 9. | CONCLUSION | 36 |
| 10. | REFERENCES | 37 |
| 11. | ARCHIVING | 39 |
| 12. | REPORT DISTRIBUTION | 39 |
| 13. | TABLES | 40 |
| TABLE 1. | Details of Experimental Layout, Treatment, Clinical Pathology investigations and Sacrifice Schedule | 41 |
| TABLE 2. | Summary of Physical and Ophthalmological Examination, General Clinical Signs and Mortality | 42 |
| TABLE 3. | Summary of Clinical Examination | 43 |
| TABLE 4. | Summary of Functional Observation Battery - Males | 44 |
| TABLE 5. | Summary of Functional Observation Battery - Females | 49 |
| TABLE 6. | Summary of Body Weights (g) - Males | 54 |

| | | |
|-----------|---|----|
| TABLE 7. | Summary of Body Weights (g) - Females..... | 55 |
| TABLE 8. | Summary of Cumulative Net Body Weight Gains - Males..... | 56 |
| TABLE 9. | Summary of Cumulative Net Body Weight Gains - Females | 57 |
| TABLE 10. | Summary of Food Intake (g/rat/day) - Males..... | 58 |
| TABLE 11. | Summary of Food Intake (g/rat/day) - Females | 59 |
| TABLE 12. | Summary of Haematological values - Males | 60 |
| TABLE 13. | Summary of Haematological values - Females..... | 62 |
| TABLE 14. | Summary of Clinical Chemistry values - Males | 64 |
| TABLE 15. | Summary of Clinical Chemistry values - Females..... | 65 |
| TABLE 16. | Summary of Clinical Analysis of Urine at Termination - Males | 66 |
| TABLE 17. | Summary of Clinical Analysis of Urine at Termination - Females | 67 |
| TABLE 18. | Urine Electrolytes Values - Males | 68 |
| TABLE 19. | Urine Electrolytes Values - Females..... | 69 |
| TABLE 20. | Summary of Terminal Fasting Body Weights and Organ Weights - Males | 70 |
| TABLE 21. | Summary of Terminal Fasting Body Weights and Organ Weight Ratios - Males | 71 |
| TABLE 22. | Summary of Terminal Fasting Body Weights and Organ Weights - Females | 72 |
| TABLE 23. | Summary of Terminal Fasting Body Weights and Organ Weight Ratios - Females | 73 |
| TABLE 24. | Summary of Gross Pathological Findings..... | 74 |
| TABLE 25. | Summary of Histopathological Findings | 75 |
| 14. | FIGURES | 83 |
| FIGURE 1. | Body Weight and Growth Curves - Males..... | 84 |
| FIGURE 2. | Body Weight and Growth Curves - Females | 84 |
| FIGURE 3. | Food Consumption Curves - Males | 85 |

| | |
|---|-----|
| FIGURE 4. Food Consumption Curves - Females | 85 |
| 15. APPENDICES | 86 |
| APPENDIX 1. Individual Clinical Signs, Detailed Clinical Examination, Mortality and Ophthalmological Examination - Males | 87 |
| APPENDIX 2. Individual Clinical Signs, Detailed Clinical Examination, Mortality and Ophthalmological Examination - Females..... | 88 |
| APPENDIX 3. Functional Observation Battery - Males | 89 |
| APPENDIX 4. Functional Observation Battery - Females | 99 |
| APPENDIX 5. Individual Body Weights (g) - Males | 109 |
| APPENDIX 6. Individual Body Weights (g) - Females..... | 111 |
| APPENDIX 7. Individual Cumulative Net Body Weight gains (g) - Males | 113 |
| APPENDIX 8. Individual Cumulative Net Body Weight gains (g) - Females | 115 |
| APPENDIX 9. Individual Food Intake (g/rat/day) - Males..... | 117 |
| APPENDIX 10. Individual Food Intake (g/rat/day) - Females | 118 |
| APPENDIX 11. Individual Haematological values - Males | 119 |
| APPENDIX 12. Individual Haematological values - Females..... | 123 |
| APPENDIX 13. Individual Clinical Chemistry Values - Males..... | 127 |
| APPENDIX 14. Individual Clinical Chemistry Values - Females | 129 |
| APPENDIX 15. Individual Clinical Analysis of Urine at Termination - Males | 131 |
| APPENDIX 16. Individual Clinical Analysis of Urine at Termination - Females.. | 133 |
| APPENDIX 17. Urine Electrolytes Values - Males | 135 |
| APPENDIX 18. Urine Electrolytes Values - Females..... | 136 |
| APPENDIX 19. Individual Terminal Fasting Body Weights and Organ Weights (g) - Males..... | 137 |
| APPENDIX 20. Individual Terminal Fasting Body Weights and Organ Weight Ratios (%) - Males | 139 |
| APPENDIX 21. Individual Terminal Fasting Body Weights and Organ Weights (g) - Females | 141 |

| | | |
|--------------|---|-----|
| APPENDIX 22. | Individual Terminal Fasting Body Weights and Organ Weight Ratios (%) - Females..... | 143 |
| APPENDIX 23. | Individual Gross Pathological and Histopathological Findings - Males..... | 145 |
| APPENDIX 24. | Individual Gross Pathological and Histopathological Findings - Females | 152 |
| APPENDIX 25. | Gavage Preparation Data | 158 |
| APPENDIX 26. | Batch Analysis Data..... | 161 |
| APPENDIX 27. | Certificate of Analysis | 162 |
| APPENDIX 28. | Deviations from Approved Study Plan..... | 163 |
| 16. | ANNEXURES..... | 164 |
| ANNEXURE 1. | Contaminant Analysis Report for Bedding Material (Paddy Husk) | 165 |
| ANNEXURE 2. | Analysis Report - Animal Diet Sample | 167 |
| ANNEXURE 3. | Feed Contaminant Analysis Report for Ssniff Rats/Mice Diet - Maintenance Meal..... | 168 |
| ANNEXURE 4. | Analysis Report -Water Sample..... | 170 |
| ANNEXURE 5. | Contaminant Analysis Report for Water Sample..... | 171 |
| ANNEXURE 6. | GLP Certificate - Germany | 173 |
| ANNEXURE 7. | GLP Certificate - The Netherlands | 174 |
| ANNEXURE 8. | GLP Certificate - India..... | 175 |
| ANNEXURE 9. | Historical Data | 176 |

1. STUDY DETAILS

| | |
|--------------------------------|--|
| Study Title | : Repeated dose (90-Day) oral toxicity study by gavage with enzyme preparation of <i>Bacillus amyloliquefaciens</i> containing amylomaltase activity in Wistar Rats |
| Test Item | : Enzyme preparation of <i>Bacillus amyloliquefaciens</i> containing amylomaltase activity |
| Study Number | : G6597 |
| Sponsor | : DSM Food Specialties PO box 1, 2600 MA Delft The Netherlands |
| Test Facility | : Toxicology Department of Safety Assessment Advinus Therapeutics Private Limited Post Box No. 5813, Plot Nos. 21 & 22 Peenya II Phase, Bangalore – 560 058 India |
| Study schedule | |
| • Study initiation date | : 09 September 2009 |
| • Experimental start date | : 10 September 2009 |
| • Acclimatisation | : Start: 10 September 2009 End: 14 September 2009 |
| • Treatment | : Start: 15 September 2009 End: 13 December 2009 |
| • Sacrifice | : 14 December 2009 |
| • Experiment completion date | : 27 January 2010 |
| • Draft report submission date | : 27 February 2010 |
| • Study completion date | : 28 September 2010 |

2. STUDY PERSONNEL

The following personnel participated in the conduct of the study.

| Name, Responsibility, Section / Department | Function | Sign and Date |
|---|---|--|
| Mr. P. M. SATHISH, M.Sc. Study Director, Toxicology Department of Safety Assessment | Overall in-charge for the conduct of the study and report preparation | <i>P. M. Sathish</i> 28 September 2010 |
| Dr. K.B. RAVI, M.V.Sc. Technical co-ordinator and Study Veterinarian, Toxicology Department of Safety Assessment | Assistance in conduct of the study, report preparation and Veterinary services | <i>K. B. Ravi</i> 24 Sept 10 |
| Mr. M. RANGANATHA, M.Sc. Assistant, Toxicology Department of Safety Assessment | Assistance in conduct of the study | <i>M. Ranganatha</i> 24 Sept 2010 |
| Mr. H. GANESHA, B.Sc. Assistant, Toxicology Department of Safety Assessment | Assistance in conduct of the study | <i>H. Ganesh</i> 24 Sept 2010 |
| Mr. M. RAMAKRISHNA BHAT, M.Sc. Laboratory Investigations, Laboratory Services Department of Safety Assessment | Analyst – Haematology & Clinical chemistry | <i>M. R. Bhat</i> 24 Sept 2010 |
| Mr. V.SARAVANAN, B.Pharm. Analytical Chemist Residue/Analytical Section | Analytical service | <i>V. Saravanan</i> 24 Sept. 2010 |
| Dr. LAKSHMISHA K.V, M.V.Sc. Pathologist, Pathology Department of Safety Assessment | Study Pathologist | <i>L. K. V. Lakshmisha</i> 24 Sept 2010 |
| Ms. SAIQA NAZHATH, M.Sc. Necropsy and Histotechniques, Department of Safety Assessment | Necropsy | <i>S. Nazhath</i> 24 Sept 2010 |
| Mr. P. JAYARAM, M.Sc. Electronic Data Processing Department of Safety Assessment | Data Analysis | <i>P. Jayaram</i> 24/09/2010 |
| Mr. C. PUNITH, B.Sc. Electronic Data Processing, Department of Safety Assessment | Pathology Data Entry, Data Analysis, Report Compilation & Documentation | <i>P. Punith</i> 24th Sept 2010 |
| Mr. L. SANTOSH, B.Com. Electronic Data Processing, Department of Safety Assessment | Data Entry, Data Analysis, Report Compilation & Documentation | <i>L. Santosh</i> 24 Sept 2010 |

3. SUMMARY

The test item, enzyme preparation of *Bacillus amyloliquefaciens* containing amylomaltase activity was tested for its toxicity potential when administered orally for 90 consecutive days to Wistar rats. The test item was dissolved in MilliQ water and administered by oral gavage at doses of 100, 300 and 1000 mg TOS /kg bwt/day to low (G2), mid (G3) and high dose (G4) groups of rats, respectively at a volume of 20 mL/kg bwt/day. The rats in the concurrent vehicle control group (G1) received MilliQ water (the vehicle) without the test item at a volume of 20 mL/kg bwt/day.

All the groups consisted of 10 male and 10 female rats. The identity of the test item was provided by the Sponsor by a Certificate of Analysis. As per the information provided in the Certificate of Analysis by the Sponsor, the test item preparations at concentrations of 91, 273 and 909 mg/mL and undiluted test item were stable at room temperature for 4 hours and also for 7 days when stored at 4°C.

The dose formulations were analysed for protein content on Days 1, 39 and 67 of the treatment period. Results of analysis showed that the mean concentrations were within ± 10 % variation against the nominal concentrations of 5.0, 15.0 and 50.0 mg/mL.

Rats were observed for mortality, clinical signs, physical abnormalities, eye abnormalities and functional (neurological) changes, changes in body weights and food consumption. Clinical pathology investigations (haematology, clinical chemistry and urinalysis) were performed at sacrifice. All rats were subjected to detailed necropsy at terminal sacrifice and specified organs were weighed. Histopathological examination was carried out on the preserved organs and tissues of the high dose and vehicle control groups and gross lesions from all rats in the study.

The results of the study indicated that the oral administration of test item Enzyme preparation of *Bacillus amyloliquefaciens* containing amylomaltase activity to Wistar rats at dose levels of 100, 300 and 1000 mg TOS/kg bwt/day did not cause any effect on general health and growth, body weight and food consumption. No treatment-related changes were observed in the functional observation tests, haematology, clinical chemistry, urinalysis, organ weights and organ weight ratios. Gross and histopathology examination did not reveal any treatment related changes.

In view of the results described above, no changes of toxicological significance were noted among the animals that received doses up to 1000 mg TOS/kg bwt/day or 18181.81 mg enzyme preparation /kg bwt/day, this dose level is considered to be the No Observed Adverse Effect Level (NOAEL) in Wistar rats, under the test conditions employed.

4. OBJECTIVE

The purpose of this repeated dose (90-day) oral toxicity study was to assess the systemic toxicity potential of the test item when administered orally by gavage to Wistar rats. This study was intended to provide information on important toxic effects, target organs and an estimate of the No Observed Adverse Effect Level (NOAEL).

5. STUDY GUIDELINE

The study was performed according to the following guideline:

- OECD Guideline No. 408 for testing of chemicals, "Repeated Dose 90-Day Oral Toxicity Study in Rodents" adopted on September 21, 1998.
- In compliance with Commission Directive 2001/59/EC of 6 August 2001 B.26. Subchronic Oral Toxicity Test: Repeated Dose 90-day Oral Toxicity Study in Rodents (No. L225 2001).

This study did not include recovery groups for the control and high dose groups.

6. MATERIALS AND METHODS

6.1 Materials

6.1.1 Test Item Information

(as furnished by the Sponsor)

| | |
|---|--|
| Test item | : Enzyme preparation of <i>Bacillus amyloliquefaciens</i> containing amylomaltase activity |
| Common Name (active ingredient) | : Meltamase |
| Name used in the report | : Enzyme preparation of <i>Bacillus amyloliquefaciens</i> containing amylomaltase activity |
| Chemical name (IUPAC) | : Amylomaltase 2.4.1.25 |
| Batch No. | : MEG.GRZ.0905 |
| Batch Manufactured by (Name and Address) | : DSM Nutritional Products Emil-Barell-Str 3 79639 Grenzach-Wyhlen |

Supplier (Name and Address) : DSM Food Specialties
PO box 1, 2600MA Delft
The Netherlands

Manufactured Date : February 2009

Expiry Date : January 2010

Purity as per Certificate of Analysis (TOS) : 5.50%

Physical appearance : Brown liquid

Storage conditions : Deep Frozen (-10 to -20°C)

Note: 1. The test item was received in good condition at the test facility on 17.06.2009 and 05.10.2009.
2. Test Item code by Test Facility: D03-08.

6.1.2 Test System

Species : Wistar rats - HsdCpb: WU rats
conventionally bred (In-house random bred)

Source : Toxicology
Department of Safety Assessment
Advinus Therapeutics Private Limited
Bangalore 560 058, India

Justification for the selection of species : Rat is the standard rodent species used for toxicity assessment and also recommended by various regulatory authorities.

No. of Groups : 4 groups:
Vehicle control (G1)
Low dose (G2)
Mid dose (G3)
High dose (G4)

No. of rats / group : 20 rats (10 males + 10 females)
Total number of rats - 40 males + 40 females

Date of birth : 06.08.2009

Age at treatment : 5-6 weeks

| | | | |
|---|---|---|-------------------|
| Mean body weights (g) | : | <u>Males</u> | <u>Females</u> |
| Mean \pm SD at the start of treatment | | G1: 130.83 \pm 10.84 | 108.74 \pm 4.49 |
| | | G2: 131.07 \pm 10.56 | 110.12 \pm 5.10 |
| | | G3: 134.44 \pm 9.62 | 108.53 \pm 5.57 |
| | | G4: 134.63 \pm 8.66 | 110.31 \pm 5.48 |
| Identification | : | The animals were individually identified by accession numbers, cage cards and turmeric solution as permanent body marking. | |
| Acclimatization | : | After physical examination, for ascertaining good health and suitability for the study, the rats were acclimatized for five days before start of the treatment. Females used in the study were nulliparous and non-pregnant. During acclimatization, animals were temporarily identified using crystal violet solution as body marking. | |

6.2 Methods

6.2.1 Performance of the Test

6.2.1.1 Husbandry

Room Number

Laboratory Room No. SC-28

Conditions:

Rats were housed under standard laboratory conditions, air conditioned with adequate fresh air supply (13.9-14.4 air changes/hour). Environment: with temperature 20-24°C, relative humidity 64 -67%, with 12 hours light and 12 hours dark cycle.

The maximum and minimum temperature and relative humidity in the experimental room was recorded once daily. The relative humidity in the experimental room was calculated daily from dry and wet bulb temperature recordings.

Housing:

Two rats per sex per cage were housed in solid floor standard polysulfone cages (size: L 425 x B 266 x H 175 mm) with stainless steel top grill having

facilities for holding pelleted food and drinking water in polycarbonate bottle with stainless steel sipper tubes.

Bedding:

Steam sterilized clean paddy husk was used as bedding and changed along with the cage at least twice a week.

Contaminant analysis report of the bedding material (paddy husk) is presented in Annexure 1

Diet: *ad libitum*

Ssniff rats/mice pellet food - maintenance meal - manufactured by ssniff Spezialdiäten GmbH., Ferdinand-Gabriel-Weg 16, D-59494 Söest, Germany.

Analysis and contaminant analysis reports of Ssniff rats/mice diet – maintenance meal are given in Annexures 2 and 3, respectively.

Water: *ad libitum*

Deep bore-well water passed through activated charcoal filter and exposed to UV rays in Aquaguard on-line water filter-cum-purifier manufactured by Eureka Forbes Ltd., Mumbai - 400 001, India.

Analysis and contaminant analysis reports of water sample are given in Annexures 4 and 5, respectively.

6.2.1.2 Dose Selection

Three dose levels of 100 mg (G2), 300 mg (G3) and 1000 mg (G4) TOS /kg bwt/day have been selected for the study in consultation with the Sponsor. Since Total Organic Solids (TOS) = 5.50 % (Certificate of Analysis: TOS = Dry Matter-Ash), these levels correspond to 1818.18, 5454.54 and 18181.81 mg enzyme preparation /kg bwt/day.

The dose selection was supported by the repeated dose (14-day) oral toxicity study by gavage in Wistar rats (Study No.G6596), in which same doses were used. The results of the 14-day study were taken into account when selecting the dose levels for this 90-day study.

In addition to the test doses, a concurrent vehicle control group was included.

6.2.1.3 Grouping

Grouping was done a day prior to initiation of treatment by body weight stratification and distribution as follows: the rats procured for the study were weighed and segregated depending upon body weight ranges. Males in the range of 111-150 g and females in the range of 91-120 g were selected for the study. Rats were randomly distributed to all groups to attain group mean body weights not varying $\pm 20\%$ for each sex. The rats which were not selected or with extreme body weights were discarded under deep Isoflurane Anesthesia.

6.2.1.4 Group Allocation and Number of Animals

The selected male and female rats were assigned to vehicle control and different treatment groups as shown below:

| Group No. | Group | Colour of cage card | Doses in TOS (mg/kg bwt/day) | Concentration (mg TOS /mL) | Dose volume (mL/kg) | No. of rats | Sex | Rat Numbers | |
|-----------|-----------------|---------------------|------------------------------|----------------------------|---------------------|-------------|-----|-------------|--------|
| | | | | | | | | From | To |
| G1 | Vehicle control | White | 0 | 0 | 20 | 10 | M | Ri3931 | Ri3940 |
| | | | | | | 10 | F | Ri3971 | Ri3980 |
| G2 | Low dose | Yellow | 100 | 5 | 20 | 10 | M | Ri3941 | Ri3950 |
| | | | | | | 10 | F | Ri3981 | Ri3990 |
| G3 | Mid dose | Green | 300 | 15 | 20 | 10 | M | Ri3951 | Ri3960 |
| | | | | | | 10 | F | Ri3991 | Ri4000 |
| G4 | High dose | Pink | 1000 | 50 | 20 | 10 | M | Ri3961 | Ri3970 |
| | | | | | | 10 | F | Ri4001 | Ri4010 |

6.2.1.5 Route of Administration and Justification

Oral by gavage, dose is expressed as mg TOS/kg bwt/day. Oral route was chosen as this is a potential route of human exposure.

6.2.1.6 Identity of the Test Item

The identity of the test item was provided by the study Sponsor by a Certificate of Analysis. The responsibility for the correct identity, stability test results and the purity of the test item rests with the Sponsor. The test item was not authenticated at the test facility.

6.2.1.7 Justification for the Selection of Vehicle

Since the test item is an enzyme in an aqueous solution and based on the experience of previous studies conducted with similar test item at this test facility, "MilliQ" water was chosen as vehicle to prepare the dose solution.

6.2.1.8 Stability of the Test Item

As per the information provided in the Certificate of Analysis by the Sponsor, the test item preparations at concentrations of 91, 273 and 909 mg/mL and undiluted test item were stable at room temperature for 4 hours and also for 7 days when stored at 4°C.

6.2.1.9 Test item preparation and administration

The dose formulations were prepared on the first day of the treatment and at 3–4 day intervals thereafter (within the stability period). Refer Appendix 25.

The test item was thawed to room temperature, aliquoted and pH of the test item solution was recorded using pre-calibrated pH meter. The pH of the unfrozen test item solution was adjusted to 6.90 to 7.10 using sodium bicarbonate solution.

The test material enzyme preparation of *Bacillus amyloliquefaciens* containing amylomaltase activity has a Total Organic Solid content of 5.50 %. While taking the test item for dose preparations, a correction factor of 100/5.50 was applied to the test item weight, so that all the doses were based on the TOS content.

To prepare the test item solutions, 22.73 (G2), 68.18 (G3) and 227.27 (G4) mL test item was separately measured and volume was made up to 250.0 mL with “MilliQ” water to get the desired test item concentrations of 5 (90.9), 15 (272.7) and 50 (909.1) mg TOS/mL (mg enzyme preparation/mL) for low, mid and high dose groups respectively. The dose volume administered to each rat was at an equivolume of 20.0 mL/kg bwt throughout the study.

The prepared dose solutions were made into required number of aliquots, depending on daily requirement. The remaining aliquots were stored at 2 - 8 °C for 3-4 days and were used daily. The rats in the vehicle control group were administered “MilliQ” water at a volume of 20.0 mL/kg bwt/day.

The dose volume was calculated for individual animal on the first day of the treatment and was adjusted according to the body weights recorded during subsequent intervals of the treatment period.

The test item volume, volume of the test item prepared and administered varied depending on the body weights of the rats recorded during different intervals of treatment period and was recorded in the raw data.

6.2.1.10 Dose Formulation analysis

Dose solutions prepared on 15 September 2009 (Day 1), 23 October 2009 (Day 39) and 20 November 2009 (Day 67) were analysed for protein content by Micro-Kjeldahl method. The determination of protein content in enzyme samples was as follows: the total nitrogen content in the sample was

determined by digesting the sample with concentrated sulphuric acid and digestion mixture. A known volume of digested sample was distilled by using Micro-Kjeldahl distillation unit and the total nitrogen content was calculated. The protein content was calculated from the total nitrogen content in the sample by multiplying the total nitrogen content with a factor of 6.25.

6.2.1.11 Treatment

The dose solutions were administered orally by gavage to the rats of the specific groups daily at approximately same time each day for 90 consecutive days. Similarly, the vehicle was administered to rats in the vehicle control group for 90 consecutive days.

6.3 Observations

6.3.1 Physical and Clinical Examination, General Clinical Signs and Mortality

a. Physical/Detailed Clinical Examination

Physical and clinical examination was carried out prior to the initiation of treatment and once weekly thereafter during treatment period except for week 13 where the examination was done on day 5.

During detailed clinical examination, all rats were observed for changes in skin and fur, eyes, mucous membrane, occurrence of secretions and excretions, autonomic activity, changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypies and bizarre behaviour.

b. General Clinical Signs and Mortality

Clinical signs were observed once daily. All animals were observed for morbidity and mortality twice daily.

c. Ophthalmological Examination

Ophthalmological examination for all animals was carried out by trained veterinarian with an ophthalmoscope on the last day of acclimatization and on Day 90, prior to sacrifice. Mydriasis was induced before examination using 1% Tropicamide.

d. Neurological Examination

The following neurological examinations were conducted on Days 88 to 90 of the treatment period for all the dose group animals.

i. Home cage observations

The rats were observed in their home cages and while opening the cages, for:

- a. Absence or presence of convulsions
- b. Absence or presence of tremors
- c. Palpebral (eyelid) closure of the eyelids
 - 1 = wide open
 - 2 = slightly drooping
 - 3 = drooping eyelids (half closed)
 - 4 = completely shut

ii. Handling observations

Rats were removed from the cage and then observed for the following reactions:

a. Ease of removal from the cage:

- 1 = Very easy: rat sits quietly, allows investigator to pick it up
- 2 = Easy: with or without vocalization, without resistance or slight resistance to being picked up
- 3 = Moderately difficult: rat rears, after following investigator's hand
- 4 = Difficult: runs around cage, is hard to grab, with or without vocalization
- 5 = Very difficult: tail and throat rattles with or without vocalization, may attack hand

b. Ease of handling rat in hand:

- 1 = No resistance, rat is easy to handle
- 2 = Slight resistance: at being handled, with or without vocalization
- 3 = Moderate resistance: rat may be tense or rigid in hand, with or without vocalization
- 4 = High resistance: squirming/twisting the body, attempting to bite, with or without vocalization

c. Lacrimation:

If lacrimation is observed, then its severity i.e., whether it is slight or severe was recorded

d. Red deposits:

Rats were observed for presence or absence of red deposits around the eyes, nose and mouth

- e. Crusty deposits:
Rats were observed for presence or absence of crusty deposits around the eyes, nose and mouth
- f. Salivation:
Rats were observed for presence or absence of salivation. If salivation is present, then its severity i.e., slight or severe (active salivation/drooling) was recorded
- g. Fur appearance:
 - 1 = Normal: Clean and groomed
 - 2 = Slightly soiled
 - 3 = Very soiled/crusty
- h. Piloerection:
If piloerection is present, then its severity i.e., whether it is slight or severe was recorded
- i. Palpebral (eyelid) closure was observed for whether the eyelids were:
 - 1 = wide open
 - 2 = slightly drooping
 - 3 = drooping eyelids (half closed)
 - 4 = completely shut
- j. Respiratory character:
 - 1 = Normal respiratory character
 - 2 = Rales: abnormal sound accompanying breathing
 - 3 = Retching: repeated unavailing attempts to vomit
 - 4 = Dyspnoeic: laboured or difficult breathing
 - 5 = Gasping: short of breath, breathes with an open mouth
- k. Eye prominence:
 - 1 = Normal
 - 2 = Exophthalmus: protrusion of eye ball
 - 3 = Enophthalmus: retraction of eye ball in to the orbital cavity
- l. Muscle tone:
Musculature of the limbs was palpated between the thumb and forefinger to confirm whether the muscle was:
 - 1 = Firm but not hard (normal)
 - 2 = Soft and flabby
 - 3 = Tense and hard

iii. Open field observations

To carry out open field observations, the rat was placed in an open field arena (Dimension L850 x B580 x H200 mm) and evaluated over a 2-minute observation period for:

a. Mobility:

Scoring was done within 30 seconds of placing the rat in open field arena and the rat's mobility scored as:

1 = Normal

2 = Moderately impaired

3 = Totally impaired, locomotion impossible

b. Backing:

The number of times the rat stepped backward over a 2-minute period in an open field arena was recorded.

c. Gait:

The gait of the rat was rated as:

1 = Normal, head horizontal, abdomen just above surface, slight up and down movement with each step

2 = Walks on tiptoes

3 = Body drags, abdomen makes contact with surface, body sways

4 = Hind limbs splayed or dragging, unable to support weight

5 = Hunched body, bottom up, nose held down, arched back

6 = Ataxia, excessive sway, rocks or lurches as the rat proceeds forward

d. Convulsions:

Rats were observed for the presence or absence of convulsions

e. Tremors:

Rats were observed for the presence or absence of tremors

f. Arousal:

Rats were observed to assess whether arousal was:

1 = Very low: stupor, coma, little or no responsiveness

2 = Low: some what stuporous

3 = Normal: alert, exploratory movements

4 = Moderately high: slight excitement, tense, excited sudden darting or freezing

5 = Very high: hyper alert, excited, sudden bouts of running or body movements

g. Rearing:

Recorded the number of times the rat rears back on its hind legs and stands up with both front paws raised off the surface over the 2-minute observation period in open field arena.

h. Urination:

Number of pools of urine were counted in the open field arena

i. Defecation:

Number of fecal boli were counted in the open field arena

j. Stereotypies:

Rats were observed for:

1. Repetitive circling: The presence or absence of repetitive circling

2. Excessive grooming: The number of times the rat grooms itself over a 2-minute period. Grooming included wiping/rubbing face and head with fore paws, scratching head or body with hind paws and biting the fur

iv. Sensory observations

The following tests were performed in the open field arena:

a. Startle response (Auditory response):

A finger click was produced directly above the rat's head and the response was recorded:

1 = No reactions

2 = Normal reaction (rat flinches or flicks ear)

3 = Exaggerated reaction (rat jumps, flips)

b. Touch response (Tactile response):

The rump was touched with a finger tip and the reaction was recorded.

1 = No reaction

2 = Rat slowly turned, walked away

3 = More energetic response than (2), may include vocalization

4 = Freezes, actual muscle contraction

5 = Bizarre reaction - jumps, bites or attacks

c. Pupil response (Visual response):

Using a torch, light was shone into one of the eyes of the rat while the other eye was shielded from the light. The response of the pupil i.e. absence or presence of constriction of the pupil was recorded. The procedure was repeated with the other eye.

d. Response to nociceptive stimuli:

The tail was gently pressed with a pair of forceps and the response was recorded.

1 = No reaction

2 = Rat turned or walked away

3 = More energetic than (2), may include vocalization

4 = Freezes, actual muscle contraction

5 = Bizarre reaction - jumps, attacks or bites

e. Righting reflex:

The rat was

1. Placed on its back, to observe whether it turned over immediately or not

2. Dropped upside down from a height of 40 cm above the examination table to check whether it landed on its feet

v. Neuromuscular observations

a. Grip strength:

The grip strength of the fore and hind limbs was determined using the Digital Force Measurement Instrument (Chatillon grip strength apparatus). Each rat was allowed to grip the T-shaped bar with the paws of the fore or hind limbs. Recorded memory was tared using the zero key. The rat was then pulled back gently until the grip was released. The displayed readings were recorded. Three readings each, for the fore and hind limbs were recorded.

b. Motor activity:

UGO Basile Multiple Activity Cage Model No. 7445 was used to study the activity of rats over a 10-minute period. Activity was recorded by the instrument on thermal print-out paper.

The values for the horizontal and vertical activity were summed up and presented in the Tables 4 and 5.

c. Landing foot splay:

The heel pad of the hind feet of each rat was painted with ink and the rat was dropped on to a sheet of white blotting paper from a height of 30 cm above the table. The distance (in centimetres) between the centres of the back of the heel prints was measured. Three readings were recorded for each rat.

vi. Physiological observations

a. Body temperature (°C):

A thermometer was inserted into the rectum and the displayed temperature was recorded after the completion of equilibration (beep sound).

Note: Except for landing foot splay, grip strength and body temperature, neurological evaluation of individual rat was recorded in the form of scores (e.g. 0, 1, 2, 3).

6.3.2 Body Weights and Food Intake

a. Body weights:

Individual body weights were recorded on the first day of treatment before the test item administration and at weekly intervals except for week 13 where the body weights were recorded on day 5.

Fasted body weights were recorded prior to necropsy on Day 91.

b. Food intake:

Food consumption was monitored at weekly intervals. The food output was subtracted from the food input and the resultant value was divided by the number of rats per cage to determine the food intake/rat/week and was divided by the number of days to obtain food consumption g/rat/day. The food spillage was weighed and recorded at each food output recording session and during cage change and added to food output data for the calculation of food consumption.

6.3.3 Clinical Laboratory Investigations

a. Blood collection:

At the end of the treatment period, all surviving rats were fasted overnight (water allowed) and blood was collected on Day 91 from the abdominal aorta under isoflurane anaesthesia. An aliquot of blood was collected in tubes containing 3.2% sodium citrate solution for determination of Coagulation parameters and the remaining blood was collected into EDTA and heparinized tubes for haematology and clinical chemistry respectively.

After haematology analysis, whole blood samples were discarded. Following clinical chemistry analysis, the remaining plasma samples were frozen till the data was reviewed by the Study Director.

b. Haematology:

The following haematological parameters were determined using ADVIA 2120 haematology system (Bayer Health Care LLC, USA).

| Sl. No. | Parameter | Abbreviations | Units |
|---------|--|---------------|-----------|
| 1 | Absolute and percentage Reticulocytes | Retic | T/L and % |
| 2 | Haematocrit | HCT | L/L |
| 3 | Haemoglobin | HGB | g/L |
| 4 | Mean Corpuscular Haemoglobin | MCH | pg |
| 5 | Mean Corpuscular Haemoglobin Concentration | MCHC | g/L |
| 6 | Mean Corpuscular Volume | MCV | fL |
| 7 | Mean Platelet Volume | MPV | fL |
| 8 | Platelets | Plat | G/L |
| 9 | Red Blood Corpuscles | RBC | T/L |
| 10 | White Blood Corpuscles | WBC | G/L |
| 11 | Absolute and percentage differential leukocyte count # | DLC @ | T/L and % |

#: Additionally blood smears were prepared from the haematology (K₂EDTA tube) sample. The blood smears were stained by Wright's stain (solution). However these blood smears were not subjected to differential leukocyte count by conventional microscopy and were discarded.

@: Differential Leukocyte parameters and their respective abbreviations are: Neutrophils (Neut), Lymphocytes (Lymph), Monocytes (Mono), Eosinophils (Eos) and Basophils (Baso).

Coagulation:

Blood samples collected for coagulation analysis were centrifuged at 5000 rpm for 5 minutes for separation of plasma. Prothrombin time (PT) and Activated partial thromboplastin time (APTT) analysis were carried out with plasma using STart-4 coagulation analyser (Diagnostica stago, 92600 Asnieres, France).

c. Clinical chemistry:

Plasma was separated in a refrigerated centrifuge at 5000 rpm for 10 minutes and analysed using Roche/Hitachi 902 (Hitachi High-Technologies Corporation, Tokyo, Japan) Automatic Analyser for the following parameters:

| Sl. No. | Parameter (Abbreviation) | Abbreviations | Units |
|---------|--------------------------|---------------|--------|
| 1 | Glucose | Glu | mmol/L |
| 2 | Total Bilirubin | T.Bil | μmol/L |
| 3 | Creatinine | Creat | μmol/L |
| 4 | Inorganic phosphorous | Pi | mmol/L |
| 5 | Total plasma protein | T.Pro | g/L |

| Sl. No. | Parameter (Abbreviation) | Abbreviations | Units |
|---------|-------------------------------|---------------|--------|
| 6 | Albumin | Alb | g/L |
| 7 | Globulin [calculated values] | Glob | g/L |
| 8 | Albumin/Globulin ratio | A/G Ratio | - |
| 9 | Gamma Glutamyl Transpeptidase | GGT | U/L |
| 10 | Blood Urea Nitrogen | BUN | mmol/L |
| 11 | Alanine Amino Transferase | ALT | U/L |
| 12 | Aspartate Amino Transferase | AST | U/L |
| 13 | Alkaline phosphatase | ALP | U/L |
| 14 | Total Cholesterol | T.Chol | mmol/L |
| 15 | Calcium | Ca | mmol/L |
| 16 | Chloride | Cl | mEq/L |
| 17 | Sodium | Na | mEq/L |
| 18 | Potassium | K | mEq/L |

d. Urinalysis:

Urine was collected from all surviving rats prior to sacrifice. For urine collection, the rats were placed over-night in specially fabricated cages (water allowed) and the next morning, the collected urine was sent to Laboratory Services, Department of Safety Assessment, Advinus Therapeutics Private Limited, for analysis.

Urine was analysed for:

| Sr. No. | Parameter |
|---------|-----------------------------------|
| 1 | Specific gravity** |
| 2 | Leukocytes* |
| 3 | Nitrite* |
| 4 | pH* |
| 5 | Proteins* |
| 6 | Glucose* |
| 7 | Ketone bodies* |
| 8 | Urobilinogen* |
| 9 | Bilirubin* |
| 10 | Erythrocytes* |
| 11 | Appearance (colour and clarity) # |
| 12 | Volume # |
| 13 | Electrolytes (Cl, K, Na) |

*: Analyzed using Combur¹⁰ test-UX strips using Urilux[®] Reflectance Photometer (Roche Diagnostics GmbH., Germany)

** : Analysed using Refractometry

: Recorded manually

Urine was also subjected to microscopic examination for sediments such as crystals, epithelial cells and casts.

6.3.4 Pathology

a. Necropsy:

All rats in the study were subjected to gross necropsy and the findings were recorded. The rats were fasted overnight (water allowed), weighed, anaesthetized with isoflurane and exsanguinated and were subjected to detailed necropsy.

b. Tissue collection

On completion of the gross pathology examination the tissues and organs noted below were collected and weighed from all animals. Organ to the body weight ratio (%) was calculated by using the fasting body weight.

The tissues from all rats will be preserved in 10% buffered neutral formalin:

| Tissue | Organ Weights | Collection/ Preservation | Microscopic Examination |
|--|---------------|--------------------------|-------------------------|
| Adrenals | X | X | X |
| All gross lesions | | X | X |
| Aorta | | X | X |
| Bone marrow smear ** | | X | X** |
| Brain-Cerebrum, cerebellum and medulla | X | X | X |
| Cecum | | X | X |
| Colon | | X | X |
| Duodenum | | X | X |
| Epididymides | X | X | X |
| Eyes* with optic nerve | | X | X |
| Mammary gland | | X | X |
| Femur bone with distal joint*** | | X | X |
| Femoral muscle | | X | X |
| Heart | X | X | X |
| Ileum with Peyer's patches | | X | X |
| Jejunum | | X | X |
| Kidneys | X | X | X |
| Lacrimal glands | | X | X |
| Larynx | | X | X |
| Liver | X | X | X |
| Lungs (with bronchi and bronchioles)# | | X | X |
| Mandibular lymph nodes | | X | X |
| Mesenteric lymph nodes | | X | X |
| Oesophagus | | X | X |
| Ovaries | X | X | X |
| Oviducts | | X | X |
| Pancreas | | X | X |

| Tissue | Organ Weights | Collection/ Preservation | Microscopic Examination |
|--|---------------|--------------------------|-------------------------|
| Pituitary | X\$ | X | X |
| Prostate | X | X | X |
| Rectum | | X | X |
| Salivary glands | | X | X |
| Sciatic nerves | | X | X |
| Seminal vesicles and coagulating glands | | X | X |
| Skin | | X | X |
| Spinal cord at 3 levels - cervical, mid thoracic and lumbar. | | X | X |
| Spleen | X | X | X |
| Sternum with marrow*** | | X | X |
| Stomach | | X | X |
| Testes@ | X | X | X |
| Thymus | X | X | X |
| Thyroid with Parathyroids | X\$ | X | X |
| Tongue | | X | X |
| Trachea | | X | X |
| Ureters | | X | X |
| Urinary bladder | | X | X |
| Uterus with cervix | X | X | X |
| Vagina | | X | X |

*: Collected in Davidson's fluid

#: Inflated with fixative and then immersed in formalin

@: Collected in modified Davidson's fluid

X: Activity performed

**: Bone marrow smears were collected from all animals, fixed in methanol and stained with Giemsa stain. Evaluation of the bone marrow smears was not performed as there were no histopathological changes in the evaluated tissues.

***: decalcified prior to sectioning

\$: Weighed one day after Formalin fixation

c. Organ weights

The following organs were weighed from all rats; thymus, epididymides, brain, heart, adrenals, testes, prostate, ovaries, uterus with cervix, spleen, liver, and kidneys. Pituitary and thyroid (with parathyroid) were weighed one day after formalin fixation. The organ weight ratios as percentage of body weight determined and presented in the report.

d. Histopathology

Histopathology examination was carried out on the preserved organs of vehicle control and high dose group animals. In addition, all gross lesions from all the animals were examined microscopically.

The tissues were processed for routine paraffin embedding and 5 micron sections were stained with Harris/Mayer's Haematoxylin Eosin stain. Unused tissues will be archived.

6.4 STATISTICAL ANALYSES

Results of statistical analysis have been reported in the form of Mean \pm SD, sample size and standard error of the mean.

The statistical analysis of the experimental data were carried out using the in-house developed and validated package in Excel and also using licensed copies of SYSTAT Statistical package ver.12.0. All quantitative variables like neuromuscular observation, body temperature, body weight, net weight gain, food consumption, clinical pathology investigation (Haematology and Clinical Chemistry) and organ weights and organ weight ratios data were compared by Bartlett's test for homogeneity of variances within the group before performing a One-factor ANOVA modelling by treatment groups. When the data were found to be non-optimal (non-normal or heteroschedastic), ANOVA were done using suitable transformation. Comparison of means between treatment groups and control group was done using Dunnett's 't' test when the overall treatment, 'F' test is found to be significant.

All analyses and comparisons were evaluated at the 5% ($P \leq 0.05$) level. Statistically significant differences ($P \leq 0.05$), indicated by the aforementioned tests were designated by the superscripts throughout the report as stated below:

+/-: Significantly higher (+)/lower (-) than the control group

7. RESULTS

Details of experimental layout, treatment, clinical pathology investigations and sacrifice schedule are furnished in Table 1.

7.1 Analyses of the Test Item in Dose Solutions

Refer Appendix 26.

The mean analyzed test item concentrations were within the acceptance criteria of $\pm 10\%$ as against the nominal concentrations of 5.0, 15.0 and 50.0 mg/mL for low, mid and high dose groups respectively.

7.2 In-Life Data

7.2.1 Physical Examination, General Clinical Signs and Mortality

Refer Table 2 and 3, Appendices 1 and 2

No clinical signs or mortality were observed at any of the tested dose levels.

7.2.2 Ophthalmological Examination

Refer Table 2, Appendices 1 and 2

Ophthalmological examination did not reveal any eye abnormalities.

7.2.3 Neurological Examination (Functional Observation Battery)

Refer Table 4 and 5, Appendices 3 and 4

Neurological examinations including functional tests, conducted on male and female rats, revealed the following findings:

There were no treatment-related changes observed in home cage, handling, open field and sensory observations. The observed incidences of rearing, urination and defecation were within the normal range and were randomly distributed among the groups.

Neuromuscular Observations:

Males

There were no treatment-related changes observed in neuromuscular parameters except a statistically significant higher body temperature at high dose when compared to vehicle control group. The observed statistical

significance is marginal and with in the historical control data range and hence, considered as incidental finding.

Females

The neuromuscular observations revealed statistically significant higher vertical motor activity score at low dose, vertical and total motor activity score at mid dose and lower hind limb grip strength values at mid dose when compared to vehicle control group. These statistical significant changes were considered incidental and not treatment related as similar changes were not observed at the high dose.

7.2.4 Body Weights and Net Weight Gains

Refer Tables 6 to 9, Appendices 5 to 8, Figures 1 and 2

No significant changes were observed in the mean body weights and net weight gains at any of the tested doses in either sex.

7.2.5 Food Intake

Refer Table 10 and 11, Appendix 9 and 10, Figures 3 and 4

A statistically significant lower food consumption was observed in the low and high dose group males on weeks 12 and 5 respectively, when compared to control group.

Since the percentage of decrease is minimal and as there were no significant changes on other weeks of the treatment period, the observed lower food consumption was considered an incidental finding.

No differences were observed in females.

7.2.6 Clinical pathology

Refer Tables 12 to 15, Appendices 11 to 14

Hematology:

Following alterations in different parameters were observed.

- Increase in APTT values at mid dose group males
- Decrease in basophil percentage at high dose group males
- Increase in PT values at low dose group females
- Increase in neutrophil percentage at high dose group females
- Decrease in reticulocyte count at low dose group females

Clinical chemistry:

Following alterations in different parameters were observed.

- Increase in sodium levels at low and high dose group males
- Increase in chloride level at high dose group males
- Decrease in AG ratios at mid and high dose group females

The changes observed in hematology and clinical chemistry parameters in the treated animals were either minimal in nature or were within the range of historical control data and were considered toxicologically insignificant.

Refer Tables 16 to 19, Appendices 15 to 18

Urinanalysis:

Following alterations in different urine parameters were observed.

- Increase in number of incidences for bilirubin, ketone bodies and urobilinogen at the high dose group
- Increase in number of incidences for bilirubin, ketone bodies and urobilinogen at the high dose group females

Since there were no associated significant changes observed in the plasma total bilirubin and liver microscopically, the observed variations in the urine bilirubin/urobilinogen in both sexes were considered as incidental finding and not related to treatment.

The observed variations/incidences in ketone bodies in males and females were not associated with significant decrease in plasma glucose levels; hence they were considered as incidental finding and not related to treatment.

The difference observed in the volume of urine in the mid dose group females is not a significant change as the increase is only one fold and the values are within the range of historical control data.

Thus, there were no test item-related changes observed in any of the urine parameters analyzed.

7.2.7 Terminal Fasting Body Weights, Organ Weights and Organ Weight Ratios

Refer Tables 20 to 23, Appendices 19 to 22

There were no significant differences in the terminal fasting body weights in both males and females except for a statistically significant decrease in relative weight of thyroid (21%) in the mid dose group females. This was considered incidental, as the values were within the historical control data.

Thus, there were no test item related changes in terminal fasting body weights, organ weights and organ weight ratios in both males and females.

7.2.8 Gross Pathology

Refer Table 24, Appendices 23 and 24

Thymus petechiae observed at different dose groups were microscopically confirmed as hemorrhage. Mandibular lymph node discoloration and enlargement observed at different dose groups were microscopically confirmed as hemorrhage and lymphoid hyperplasia respectively. Hepatodiaphragmatic nodule observed at 100 mg/kg dose female was not associated with any microscopic change. Dilated uterus grossly was microscopically confirmed to be the same.

None of the gross lesions observed could be attributed to treatment as they were randomly distributed across the groups and hence considered incidental.

7.2.9 Histopathology

Refer Table 25, Appendices 23 and 24

Following table summarizes the microscopic findings in both the sex groups.

| TISSUE OBSERVATIONS | MALES | | | | FEMALES | | | |
|--------------------------------------|-------|----|----|----|---------|----|----|----|
| | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| RECTUM | | | | | | | | |
| Nematode | 0 | - | - | 3 | 1 | - | - | 0 |
| PANCREAS | | | | | | | | |
| Inflammation-chronic | 0 | - | - | 0 | 1 | - | - | 0 |
| Increased acinar cell apoptosis | 0 | - | - | 1 | 0 | - | - | 0 |
| LIVER | | | | | | | | |
| Chronic inflammatory focus(i) | 0 | - | - | 3 | 1 | 0 | 0 | 1 |
| LUNGS | | | | | | | | |
| Inflammatory focus(i) | 0 | - | - | 2 | 0 | - | - | 0 |
| Perivascular leukocytic infiltration | 1 | - | - | 0 | 0 | - | - | 0 |
| Increased alveolar macrophages | 2 | - | - | 1 | 1 | - | - | 1 |
| HEART | | | | | | | | |
| Inflammatory focus(i) | 0 | - | - | 1 | 0 | - | - | 0 |
| MANDIBULAR LYMPH NODES | | | | | | | | |
| Hemorrhage | 6 | 2 | 6 | 4 | 4 | 2 | 1 | 5 |
| Lymphoid hyperplasia | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 |
| Plasma cell hyperplasia | 3 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| PROSTATE | | | | | | | | |
| Lymphocytic infiltration | 2 | - | - | 2 | NA | NA | NA | NA |
| Cell debris in lumen | 0 | - | - | 1 | NA | NA | NA | NA |
| UTERUS WITH CERVIX | | | | | | | | |
| Dilatation | NA | NA | NA | NA | 0 | - | - | 1 |
| THYROID | | | | | | | | |

| | | | | | | | | |
|---------------------------|---|---|---|---|---|---|---|---|
| Ectopic thymus | 0 | - | - | 1 | 1 | - | - | 1 |
| ADRENALS | | | | | | | | |
| Accessory cortical tissue | 1 | - | - | 0 | 1 | - | - | 0 |
| THYMUS | | | | | | | | |
| Hemorrhage | 4 | 1 | - | 4 | 2 | - | 1 | 1 |
| Epithelial cyst(s) | 0 | 0 | - | 0 | 2 | - | 0 | 3 |
| KIDNEYS | | | | | | | | |
| Dilatation of pelvis | 1 | - | - | 0 | 0 | - | - | 0 |

The hemorrhages observed in thymus and lymph node are agonal in nature, caused likely at the time of sacrifice, attributed to euthanasia or dissection of tissues. In the absence of other inflammatory change and dose correlation, hemorrhages in thymus and lymph node were not treatment related.

None of the other microscopic findings could be attributed to treatment as they were within the range of historical control data and considered incidental.

8. DISCUSSION

The purpose of repeated dose (90-day) oral toxicity study was to assess the systemic toxic potential of the test item when administered orally by gavage to rats. This study was intended to provide information on important toxic effects, target organs and an estimate of the No Observed Adverse Effect Level (NOAEL).

This study consisted of one control (G1 – 0 mg/kg) and three treatment groups viz, low (G2 – 100 mg TOS /kg), mid (G3 – 300 mg TOS /kg) and high dose (G4 – 1000 mg TOS /kg). Each group consisted of 10 male and 10 female rats. The control and treated groups were administered "MilliQ" water and test item mixed solutions respectively by oral gavage once daily for 90 consecutive days.

Animals from all the groups were observed for clinical signs, physical abnormalities, changes in body weights and food consumption. Laboratory investigations on haematology, clinical chemistry and urinalysis were performed at sacrifice. The rats were subjected to detailed necropsy at terminal sacrifice. The protocol tissues from control and high dose groups were subjected to histopathological examination.

There were no treatment-related findings in daily observation, body weights, food consumption, haematology, clinical chemistry, terminal fasting body weights, organ weights and their ratios, gross and histopathology findings.

9. CONCLUSION

In view of the results described above, no changes of toxicological significance were noted among the animals that received doses up to 1000 mg TOS/kg bwt/day or 18181.81 mg enzyme preparation /kg bwt/day, this dose level is considered to be the No Observed Adverse Effect Level (NOAEL) in Wistar rats, under the test conditions employed.

10. REFERENCES

1. Glucose (Glu) mmol/l:

GOD-POD method: Trinder. P., Ann Clin Biochem., 6:24, 1969.

2. Blood Urea Nitrogen (BUN) mmol/l:

Urease-GLDH method: Tiffany et al., Clin Chem., 18:829, 1972.

3. Total Plasma Protein (Tot.Pro.) g/l:

Biuret method: Doumas et al., Clin Chem., 27:1642, 1981.

4. Aspartate Amino transferase (AST) U/l:

Infinity AST reagent based on recommendations of IFCC : IFCC method for AST J Clin Chem Clin Biochem., 24:497-510, 1986.

5. Alanine Amino transferase (ALT) U/l:

Infinity ALT reagent based on recommendations of IFCC : IFCC Expert panel on enzymes part 3 J Clin Chem Clin Biochem., 24:481-495, 1986.

6. Gamma Glutamyl Transpeptidase (GGT) U/l:

Szasz G., Persijn JP., et al.,: New substrates for measuring γ -glutamyl-transpeptidase activity J Clin Chem Clin Biochem., 12:228, 1973.

7. Total Bilirubin (Tot. Bil) μ mol/l:

Walters MI., Gerade HW: An ultramicro method for the determination of conjugated and total bilirubin in serum or plasma; Microchem J., 15:231, 1970.

8. Creatinine (Creat) μ mol/l:

Jaffe's kinetic method: Fabing DL, Ertingshausen G: Automated reaction rate method for determination of serum Creatinine with the "Centrifichem"; Clin Chem., 17:696, 1971.

9. Chloride (Cl) mmol/L:

Tietz NW. Clinical guide to Laboratory Tests. Philadelphian Pa: WB Saunders Co; 1983 : 110, 398, 446. Kaplan L, Pesce A. Clinical Chemistry theory, analysis and correlation. St. Louis, Mo: CV Mosby Co; 1984:1061, 1077.

10. Albumin (Alb) g/l:

Bromocresol-green method: Doumas B.T., et al.; In standard methods of Clin Chem Vol 7, (175-189), 1972 Academic Press, Chicago, USA

11. Inorganic Phosphorus (Pi) mmol/l:

Molybdate Method: Daly JA, Ertingshausen G; Direct method for determining inorganic phosphorus in serum with the "Centrifichem"; Clin Chem., 18:263, 1972.

12. Total Cholesterol (Chol) mmol/l:

CHOD-POD method: Allain CC, PoonLS, Chan CSG, Richmond W and Fu PC; Clin Chem., 20:470-475, 1974; Roeschlau P, Bernt E and Gruber WA., J Clin Chem Clin Biochem., 12:226, 1974.

13. Sodium (Na): mEq/l:

Using ion sensitive electrode principle (indirect potentiometry).

14. Potassium (K): mEq/l:

Using ion sensitive electrode principle (indirect potentiometry).

15. In compliance with Commission Directive 2001/59/EC of 6 August 2001 B.26. Subchronic Oral Toxicity Test: Repeated Dose 90-day Oral Toxicity Study in Rodents (No. L225 2001).

16. OECD Principles of Good Laboratory Practice (as revised in 1997), Environmental Directorate, Organisation for Economic Co-operation and Development, Paris 1998.

17. Levene H. 1960. Robust tests for equality of variances. In: Olkin I, Ghurye SG, Hoeffding W, Madow WG, Mann HB, editors. Contributions to probability and statistics. Stanford (CA): Stanford University Press. P 278-292.

18. Non Parametric Statistics in Behavioral Science Sidney Seigel and N.J.Castallan, McGraw Hill Publishing.

19. Shapiro SS, Wilk MB. 1965. An analysis of variance test for normality (complete samples). Biometrika 52(3-4): 591-611.

11. ARCHIVING

Advinus will archive at the archives of the test facility the following for 15 years after completion of the study: study plan, raw data, draft and final reports. A sample of the test item was sent to the archives from the test item stores before the first dispensing. This sample shall be stored for a period of 2 years from the date of this final report or till next GLP inspection, whichever is later, however not beyond 15 years. All tissue specimens will be archived for 5 years, blocks and slides will be archived for 12 years after which these will be handed over to the Sponsor or preserved longer at the cost of the sponsor.

12. REPORT DISTRIBUTION

Sponsor : One signed final report in original (Copy Nos. 1/2) and a soft copy in PDF format.
Archives : One signed final report in original (Copy No. 2/2).

A copy of the report to the sponsor on CD will be sent as PDF file for use by the Sponsor. The test facility does not archive such PDF file, and only the hard copy retained at the test facility is final for records / verification / inspection of the study.

13. TABLES

TABLE 1. Details of Experimental Layout, Treatment, Clinical Pathology investigations and Sacrifice Schedule

| Group No. | Dose (mg TOS/kg bwt/day) | No. of rats per group | | Treatment period (days) | Pathology | | | | Sacrifice (91 st day) |
|-----------|--------------------------|-----------------------|---------|-------------------------|-------------|--------------------|------------|-----------------------------------|----------------------------------|
| | | Males | Females | | Haematology | Clinical Chemistry | Urinalysis | Gross pathology and Organ weights | |
| G1 | 0 | 10 | 10 | 90 | + | + | + | + | + |
| G2 | 100 | 10 | 10 | 90 | + | + | + | + | + |
| G3 | 300 | 10 | 10 | 90 | + | + | + | + | + |
| G4 | 1000 | 10 | 10 | 90 | + | + | + | + | + |

+: Yes -: Not done

TABLE 2. Summary of Physical and Ophthalmological Examination, General Clinical Signs and Mortality

| PARAMETERS | Sex | Refer Appendices 1 and 2 | | | | | | | |
|---------------------------------|-------------|--------------------------|-----|-----|------|---------|-----|-----|------|
| | | Males | | | | Females | | | |
| | | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| | | 0 | 100 | 300 | 1000 | 0 | 100 | 300 | 1000 |
| | No. of rats | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 1. GENERAL AFFECTIONS | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2. NEUROLOGICAL AFFECTIONS | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3. RESPIRATORY AFFECTIONS | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4. EYE AFFECTIONS | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5. GASTRO INTESTINAL AFFECTIONS | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6. SKIN AFFECTIONS | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7. UROGENITAL AFFECTIONS | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 8. MORTALITY | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

TABLE 3. Summary of Clinical Examination

| | | Refer Appendices 1 and 2 | | | | | | | |
|--|--|--------------------------|-----|-----|------|---------|-----|-----|------|
| | | DOSING PERIOD | | | | | | | |
| PARAMETERS | | Males | | | | Females | | | |
| Group No. | | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| Dose(mg TOS/kg bwt/day) | | 0 | 100 | 300 | 1000 | 0 | 100 | 300 | 1000 |
| No. of rats | | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 1. Skin and Fur | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2. Eyes | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3. Mucous membrane | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4. Occurrence of secretions and excretions | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| a. Salivation | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| b. Urine staining | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| c. Fecal staining or diarrhoea | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| d. Nasal discharge | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5. Autonomic activity | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| a. Lacrimation | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| b. Piloerection | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| c. Pupil size or pupillary response | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| d. Unusual respiratory pattern | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6. Response to handling | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7. Changes in gait | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 8. Posture | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 9. Clonic or Tonic movements | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10. Stereotypies | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| a. Repetitive circling | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| b. Excessive grooming | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 11. Bizarre behaviour | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| a. Self mutilation | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| b. Walking backwards | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

TABLE 4. Summary of Functional Observation Battery - Males

Refer Appendix: 3

| Group No. Dose (mg TOS/kg bwt/day) | No. of rats | Home cage observations | | | Handling observations | | | | | |
|--|-------------------|------------------------|----------------|--------------------------|--------------------------------------|---|--------------------|-------------------------------|------|-------|
| | | <u>Convulsions</u> | <u>Tremors</u> | <u>Palpebral closure</u> | <u>Ease of removal from the cage</u> | <u>Ease of handling animal in hand</u> | <u>Lacrimation</u> | <u>No Red deposits around</u> | | |
| | | Absent | Absent | Eyelids wide open | Very easy | No resistance, animal is easy to handle | None | Eyes | Nose | Mouth |
| G1 0 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

TABLE 4 contd. Summary of Functional Observation Battery - Males

| Group No. Dose (mg TOS/kg bwt/day) | No. of rats | Handling observations contd. | | | | | | | | | | Refer Appendix: 3 | |
|--|-------------------|----------------------------------|------|-------|-------------------|-----------------------|---------------------|--------------------------|------------------------------|-----------------------|-------------------------------------|-------------------|--|
| | | <u>No Crusty Deposits around</u> | | | <u>Salivation</u> | <u>Fur Appearance</u> | <u>Piloerection</u> | <u>Palpebral closure</u> | <u>Respiratory character</u> | <u>Eye Prominence</u> | <u>Muscle tone</u> | | |
| | | Eyes | Nose | Mouth | Normal | Normal | None | Eyelids wide open | Normal | Normal | Muscle is firm but not hard(normal) | | |
| G1 0 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| G2 100 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| G3 300 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| G4 1000 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |

TABLE 4 contd. Summary of Functional Observation Battery - Males

Refer Appendix: 3

| Group No. Dose (mg TOS/kg bwt/day) | No. of rats | Open field observations | | | | | | | | |
|--|-------------------|---------------------------|----------------------------|-----------------------|------------------------------|--------------------------|--------------------------|----------------------------|------------------------------|-------------------------------|
| | | <u>Mobility</u> Normal | <u>Backing</u> (counts) | <u>Gait</u> Normal | <u>Convulsions</u> Absent | <u>Tremors</u> Absent | <u>Arousal</u> Normal | <u>Rearing</u> (counts) | <u>Urination</u> (counts) | <u>Defecation</u> (counts) |
| G1 0 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 29 | 6 | 5 |
| G2 100 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 31 | 5 | 5 |
| G3 300 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 33 | 7 | 4 |
| G4 1000 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 27 | 5 | 5 |

TABLE 4 contd. Summary of Functional Observation Battery - Males

Refer Appendix: 3

| Group No. Dose (mg TOS/kg bwt/day) | No. of rats | Open field observations contd. | | Sensory observations | | | | | | |
|--|-------------------|--------------------------------|--------------------------------|----------------------|--------------------------------------|----------------|---------------------------------|-------------------------------------|-------------------|--------------------|
| | | Stereotypies | | Startle response | Touch response | Pupil response | Response to Nociceptive stimuli | | Righting reflex | |
| | | Repetitive circling Absent | Excessive Grooming (counts) | Normal reaction | Animal slowly turned, walked away | present | Animal turned or walked away | More energetic response than (2) | Onback Present | Dropped Present |
| G1 0 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 0 | 10 | 10 |
| G2 100 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 0 | 10 | 10 |
| G3 300 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 0 | 10 | 10 |
| G4 1000 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 0 | 10 | 10 |

TABLE 4 contd. Summary of Functional Observation Battery - Males

Refer Appendix: 3

| Group No. Dose (mg TOS/kg bwt/day) | | Neuromuscular observations | | Horizontal score | Vertical score | Motor activity score Total | Hind limb foot splay (cms) Average | Physiological Observation Body temperature (°C) |
|--|------|----------------------------|-----------------------|---------------------|-------------------|-------------------------------|---------------------------------------|---|
| | | Grip strength (kg) | | | | | | |
| | | Fore limbs Average | Hind limbs Average | | | | | |
| G1 0 | Mean | 0.989 | 0.537 | 970.4 | 747.1 | 1717.5 | 7.27 | 37.09 |
| | SD | 0.026 | 0.051 | 271.59 | 151.69 | 406.37 | 0.25 | 0.48 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 0.981 | 0.551 | 1027.4 | 788.6 | 1816.0 | 7.37 | 37.15 |
| | SD | 0.045 | 0.047 | 240.31 | 194.95 | 429.61 | 0.25 | 0.37 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 0.963 | 0.554 | 1165.0 | 942.2 | 2107.2 | 7.28 | 37.28 |
| | SD | 0.036 | 0.053 | 112.24 | 196.65 | 269.34 | 0.16 | 0.25 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 0.975 | 0.524 | 1150.9 | 886.5 | 2037.4 | 7.26 | 37.56 |
| | SD | 0.038 | 0.049 | 179.8 | 111.86 | 264.28 | 0.13 | 0.28 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

N: No. of observations

+ : Significantly higher (+) than the Control Group

TABLE 5. Summary of Functional Observation Battery - Females

Refer Appendix 4

| Group No. Dose (mg TOS/kg bwt/day) | No. of rats | Home cage observations | | | | Handling observations | | | | |
|---|-------------------|------------------------|----------------|--------------------------|--------------------------------------|---|--------------------|-------------------------------|------|-------|
| | | <u>Convulsions</u> | <u>Tremors</u> | <u>Palpebral closure</u> | <u>Ease of removal from the cage</u> | <u>Ease of handling animal in hand</u> | <u>Lacrimation</u> | <u>No Red deposits around</u> | | |
| | | Absent | Absent | Eyelids wide open | Very easy | No resistance, animal is easy to handle | None | Eyes | Nose | Mouth |
| G1 0 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

TABLE 5 contd. Summary of Functional Observation Battery - Females

| Group No. Dose (mg TOS/kg bwt/day) | No. of rats | Handling observations contd. | | | | | | | | | | Refer Appendix 4 | |
|--|-------------------|----------------------------------|------|-------|-------------------|-----------------------|---------------------|--------------------------|------------------------------|-----------------------|-------------------------------------|------------------|--|
| | | <u>No Crusty Deposits around</u> | | | <u>Salivation</u> | <u>Fur Appearance</u> | <u>Piloerection</u> | <u>Palpebral closure</u> | <u>Respiratory character</u> | <u>Eye Prominence</u> | <u>Muscle tone</u> | | |
| | | Eyes | Nose | Mouth | Normal | Normal | None | Eyelids wide open | Normal | Normal | Muscle is firm but not hard(normal) | | |
| G1 0 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| G2 100 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| G3 300 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |
| G4 1000 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | | |

TABLE 5 contd. Summary of Functional Observation Battery - Females

| Group No. Dose (mg TOS/kg bwt/day) | No. of rats | Open field observations | | | | | | | | | Refer Appendix 4 |
|--|-------------------|---------------------------|----------------------------|-----------------------|------------------------------|--------------------------|--------------------------|----------------------------|------------------------------|-------------------------------|------------------|
| | | <u>Mobility</u> Normal | <u>Backing</u> (counts) | <u>Gait</u> Normal | <u>Convulsions</u> Absent | <u>Tremors</u> Absent | <u>Arousal</u> Normal | <u>Rearing</u> (counts) | <u>Urination</u> (counts) | <u>Defecation</u> (counts) | |
| G1 0 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 33 | 5 | 6 | |
| G2 100 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 38 | 5 | 6 | |
| G3 300 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 37 | 8 | 3 | |
| G4 1000 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 36 | 9 | 5 | |

TABLE 5 contd. Summary of Functional Observation Battery - Females

Refer Appendix 4

| Group No. Dose (mg TOS/kg bwt/day) | No. of rats | Open field observations contd. | | Sensory observations | | | | | | |
|--|-------------------|--------------------------------|--------------------------------|----------------------|--------------------------------------|----------------|---------------------------------|-------------------------------------|-------------------|--------------------|
| | | Stereotypies | | Startle response | Touch response | Pupil response | Response to Nociceptive stimuli | | Righting reflex | |
| | | Repetitive circling Absent | Excessive Grooming (counts) | Normal reaction | Animal slowly turned, walked away | present | Animal turned or walked away | More energetic response than (2) | Onback Present | Dropped Present |
| G1 0 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 0 | 10 | 10 |
| G2 100 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 0 | 10 | 10 |
| G3 300 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 0 | 10 | 10 |
| G4 1000 | 10 | 10 | 0 | 10 | 10 | 10 | 10 | 0 | 10 | 10 |

TABLE 5 contd. Summary of Functional Observation Battery - Females

Refer Appendix 4

Relat. Appendix 4

| Group No. Dose (mg TOS/kg bwt/day) | | Neuromuscular observations | | Horizontal score | Vertical Score | Motor activity score Total | Hind limb foot splay (cms) Average | Physiological Observation Body temperature (°C) |
|--|------|----------------------------|-----------------------|---------------------|-------------------|-------------------------------|---------------------------------------|---|
| | | Grip strength (kg) | | | | | | |
| | | Fore limbs Average | Hind limbs Average | | | | | |
| G1 0 | Mean | 0.976 | 0.529 | 995.6 | 809.6 | 1805.2 | 5.93 | 37.43 |
| | SD | 0.03 | 0.065 | 264.15 | 138.33 | 382.83 | 0.32 | 0.36 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 0.937 | 0.528 | 1154.0 | 991.1 | 2145.1 | 5.83 | 37.54 |
| | SD | 0.03 | 0.045 | 156.26 | 127.62 | 248.29 | 0.35 | 0.39 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 0.933 | - | 1245.4 | 1073.1 | 2318.5 | 5.96 | 37.66 |
| | SD | 0.064 | 0.039 | 177.92 | 179.74 | 310.22 | 0.41 | 0.39 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 0.934 | 0.496 | 1201.6 | 908.6 | 2110.2 | 6.14 | 37.52 |
| | SD | 0.043 | 0.041 | 245.62 | 161.21 | 371.75 | 0.39 | 0.51 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

N: No. of observations

+ / - : Significantly higher (+) / lower (-) than the Control Group

TABLE 6. Summary of Body Weights (g) - Males

| Group No. Dose (mg TOS/kg bwt/day) | | Refer Appendix 5 | | | | | | | | | | | | | |
|--|------|------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | Weeks | | | | | | | | | | | | | |
| | | \$ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G1 0 | Mean | 130.83 | 169.07 | 209.29 | 244.29 | 271.07 | 291.01 | 307.52 | 321.64 | 333.75 | 342.53 | 347.08 | 354.73 | 364.37 | 373.85 |
| | SD | 10.84 | 14.43 | 17.54 | 21.87 | 25.94 | 30.13 | 34.37 | 36.21 | 35.06 | 38.70 | 40.50 | 42.19 | 40.56 | 45.36 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 131.07 | 171.48 | 210.94 | 240.77 | 262.92 | 282.14 | 298.88 | 312.57 | 324.84 | 334.07 | 340.54 | 342.84 | 349.24 | 358.15 |
| | SD | 10.56 | 13.45 | 16.29 | 18.83 | 20.93 | 22.76 | 24.24 | 24.10 | 23.66 | 24.56 | 24.58 | 23.50 | 23.53 | 21.27 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 134.44 | 171.89 | 212.12 | 242.72 | 266.64 | 290.78 | 309.58 | 325.45 | 337.18 | 350.71 | 357.22 | 363.44 | 372.01 | 376.75 |
| | SD | 9.62 | 11.45 | 16.48 | 23.10 | 20.53 | 23.11 | 27.90 | 29.36 | 30.53 | 30.89 | 34.29 | 35.82 | 37.28 | 37.67 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 134.63 | 171.98 | 213.13 | 242.83 | 267.65 | 286.17 | 303.49 | 318.45 | 327.41 | 338.21 | 345.48 | 347.29 | 354.61 | 359.27 |
| | SD | 8.66 | 9.77 | 11.81 | 10.40 | 12.66 | 12.11 | 14.94 | 17.31 | 19.44 | 21.05 | 21.39 | 23.34 | 23.00 | 22.89 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

\$: Initial ; n: No. of Counts;

TABLE 7. Summary of Body Weights (g) - Females

| Group No. Dose (mg TOS/kg bwt/day) | | Refer Appendix 6 | | | | | | | | | | | | | |
|--|------|------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | Weeks | | | | | | | | | | | | | |
| | | \$ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G1 0 | Mean | 108.74 | 129.67 | 146.02 | 161.52 | 173.76 | 182.34 | 189.63 | 197.80 | 201.83 | 206.08 | 208.55 | 212.47 | 216.51 | 220.62 |
| | SD | 4.49 | 7.84 | 7.95 | 9.27 | 8.69 | 10.33 | 9.83 | 9.89 | 8.79 | 11.42 | 11.21 | 10.32 | 10.04 | 11.93 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 110.12 | 129.01 | 148.62 | 163.62 | 176.50 | 185.52 | 194.60 | 201.19 | 206.75 | 212.84 | 216.06 | 219.06 | 221.73 | 225.49 |
| | SD | 5.10 | 6.06 | 6.65 | 7.38 | 9.75 | 9.30 | 8.68 | 10.97 | 12.42 | 11.12 | 11.01 | 12.43 | 12.99 | 13.56 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 108.53 | 127.34 | 147.31 | 162.71 | 174.86 | 184.03 | 192.24 | 200.13 | 206.23 | 215.67 | 218.47 | 221.29 | 226.08 | 227.01 |
| | SD | 5.57 | 5.92 | 6.91 | 8.87 | 8.57 | 8.24 | 9.85 | 12.90 | 13.69 | 12.20 | 12.88 | 14.30 | 15.22 | 14.63 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 110.31 | 130.41 | 149.41 | 165.03 | 178.32 | 185.88 | 192.51 | 200.41 | 204.93 | 212.78 | 215.24 | 217.42 | 220.76 | 221.58 |
| | SD | 5.48 | 5.32 | 5.23 | 5.65 | 7.29 | 7.30 | 7.81 | 7.16 | 6.77 | 7.06 | 8.33 | 7.64 | 8.85 | 7.58 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

\$: Initial ; n: No. of Counts;

TABLE 8. Summary of Cumulative Net Body Weight Gains - Males

| Group No. Dose (mg TOS/kg bwt/day) | | Refer Appendix 7 | | | | | | | | | | | | |
|--|------|------------------|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | Weeks | | | | | | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G1 0 | Mean | 38.24 | 78.47 | 113.47 | 140.24 | 160.18 | 176.69 | 190.81 | 202.92 | 211.71 | 216.25 | 223.91 | 233.55 | 243.02 |
| | SD | 4.45 | 8.85 | 14.16 | 17.69 | 21.84 | 26.14 | 28.06 | 26.70 | 30.70 | 32.72 | 42.17 | 36.62 | 40.92 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 40.41 | 79.87 | 109.70 | 131.85 | 151.07 | 167.81 | 181.50 | 193.78 | 203.00 | 209.47 | 211.77 | 218.17 | 227.09 |
| | SD | 22.40 | 25.63 | 28.19 | 30.09 | 32.28 | 33.07 | 32.55 | 32.05 | 33.37 | 33.25 | 31.64 | 29.85 | 29.06 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 37.45 | 77.68 | 108.28 | 132.20 | 156.34 | 175.14 | 191.01 | 202.74 | 216.27 | 222.77 | 228.99 | 237.57 | 242.31 |
| | SD | 3.17 | 9.69 | 16.05 | 12.91 | 16.32 | 22.09 | 22.97 | 24.44 | 24.86 | 27.98 | 30.27 | 31.34 | 32.01 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 37.36 | 78.51 | 108.21 | 133.02 | 151.54 | 168.86 | 183.82 | 192.79 | 203.58 | 210.85 | 212.67 | 219.98 | 224.65 |
| | SD | 4.13 | 6.43 | 6.66 | 9.79 | 9.41 | 12.42 | 15.23 | 18.41 | 19.72 | 19.90 | 23.65 | 22.71 | 22.32 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

SD: Standard Deviation; n: No. of Counts;

TABLE 9. Summary of Cumulative Net Body Weight Gains - Females

| Group No. Dose (mg TOS/kg bwt/day) | | Refer Appendix 8 | | | | | | | | | | | | |
|--|------|------------------|-------|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|--------|
| | | Weeks | | | | | | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G1 0 | Mean | 20.94 | 37.28 | 52.79 | 65.03 | 73.61 | 80.89 | 89.06 | 93.10 | 97.35 | 99.81 | 103.73 | 107.78 | 111.88 |
| | SD | 3.96 | 4.43 | 5.51 | 6.11 | 6.72 | 6.85 | 6.92 | 6.16 | 8.42 | 8.54 | 7.51 | 8.33 | 10.14 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 18.89 | 38.50 | 53.50 | 66.38 | 75.40 | 84.48 | 91.07 | 96.64 | 102.72 | 105.94 | 108.94 | 111.61 | 115.37 |
| | SD | 2.75 | 4.71 | 5.53 | 8.12 | 8.14 | 8.57 | 10.02 | 12.12 | 10.98 | 10.97 | 12.04 | 12.74 | 13.71 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 18.81 | 38.79 | 54.18 | 66.34 | 75.50 | 83.71 | 91.60 | 97.70 | 107.14 | 109.95 | 112.76 | 117.56 | 118.48 |
| | SD | 2.72 | 3.24 | 5.88 | 6.12 | 5.57 | 8.29 | 12.35 | 12.00 | 11.09 | 12.06 | 13.44 | 14.59 | 13.89 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 20.10 | 39.10 | 54.72 | 68.01 | 75.56 | 82.20 | 90.09 | 94.61 | 102.47 | 104.92 | 107.10 | 110.44 | 111.26 |
| | SD | 2.47 | 4.11 | 4.88 | 6.29 | 6.13 | 7.67 | 6.97 | 7.47 | 7.30 | 7.94 | 6.73 | 7.90 | 8.02 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

SD: Standard Deviation; n: No. of Counts;

TABLE 10. Summary of Food Intake (g/rat/day) - Males

| | | Refer Appendix 9 | | | | | | | | | | | | |
|--|------|------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Group No. Dose (mg TOS/kg bwt/day) | | Weeks | | | | | | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G1 0 | Mean | 18.01 | 20.67 | 22.83 | 22.80 | 22.61 | 22.46 | 21.37 | 20.71 | 20.95 | 20.05 | 20.53 | 20.57 | 19.74 |
| | SD | 1.28 | 1.39 | 1.74 | 1.82 | 1.69 | 1.75 | 1.83 | 1.43 | 1.91 | 1.86 | 1.18 | 1.48 | 3.33 |
| | n | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| G2 100 | Mean | 17.72 | 20.14 | 20.89 | 20.90 | 21.28 | 21.24 | 20.31 | 19.16 | 19.57 | 18.50 | 18.91 | 18.44 | 19.60 |
| | SD | 0.20 | 0.38 | 0.99 | 1.42 | 1.29 | 1.00 | 0.64 | 1.11 | 0.84 | 1.05 | 0.80 | 0.90 | 0.82 |
| | n | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| G3 300 | Mean | 18.12 | 20.13 | 21.48 | 21.34 | 22.83 | 22.12 | 21.66 | 21.40 | 20.67 | 20.22 | 20.75 | 21.24 | 20.68 |
| | SD | 0.63 | 1.22 | 1.35 | 1.08 | 1.52 | 1.61 | 1.91 | 1.71 | 1.64 | 1.16 | 1.63 | 1.21 | 1.57 |
| | n | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| G4 1000 | Mean | 17.88 | 20.21 | 21.46 | 21.26 | 19.77 | 20.02 | 20.10 | 20.72 | 18.87 | 18.53 | 18.28 | 18.80 | 19.00 |
| | SD | 0.32 | 0.56 | 0.99 | 1.07 | 0.39 | 1.31 | 1.76 | 2.16 | 1.55 | 1.63 | 2.01 | 1.06 | 1.86 |
| | n | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

n: No. of Cages;

- : Significantly lower (-) than the Control Group

TABLE 11. Summary of Food Intake (g/rat/day) - Females

| | | Refer Appendix 10 | | | | | | | | | | | | |
|--|------|-------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Group No. Dose (mg TOS/kg bwt/day) | | Weeks | | | | | | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G1 0 | Mean | 13.77 | 13.89 | 15.13 | 15.15 | 15.57 | 15.87 | 15.14 | 14.77 | 15.89 | 15.54 | 15.80 | 15.98 | 15.69 |
| | SD | 0.81 | 0.53 | 0.71 | 0.45 | 0.63 | 0.36 | 0.98 | 0.75 | 1.21 | 1.11 | 1.31 | 1.46 | 0.78 |
| | n | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| G2 100 | Mean | 13.42 | 14.32 | 15.14 | 15.17 | 15.40 | 14.87 | 14.87 | 15.43 | 15.37 | 14.94 | 15.57 | 15.23 | 15.80 |
| | SD | 0.43 | 0.46 | 0.37 | 0.40 | 0.46 | 0.61 | 0.24 | 0.36 | 0.74 | 0.50 | 0.38 | 0.62 | 0.72 |
| | n | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| G3 300 | Mean | 13.66 | 14.62 | 15.48 | 15.59 | 15.16 | 14.08 | 14.64 | 15.10 | 15.38 | 15.01 | 15.55 | 15.59 | 14.69 |
| | SD | 0.65 | 0.89 | 0.98 | 1.23 | 1.79 | 1.21 | 1.11 | 1.56 | 0.65 | 1.03 | 1.14 | 1.05 | 0.52 |
| | n | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| G4 1000 | Mean | 13.99 | 14.83 | 16.03 | 16.49 | 15.92 | 15.34 | 16.86 | 14.98 | 15.51 | 14.98 | 15.44 | 15.00 | 14.57 |
| | SD | 0.71 | 0.90 | 2.20 | 3.09 | 2.42 | 2.26 | 4.63 | 2.07 | 1.27 | 1.24 | 1.35 | 1.99 | 1.62 |
| | n | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

n: No. of Cages;

TABLE 12. Summary of Haematological values - Males

| Group No. Dose (mg TOS/kg bwt/day) | | Refer Appendix 11 | | | | | | | | | | | | | | |
|--|------|-------------------|------------|-----------|------------|------------|-----------|-------------|-------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| | | WBC G/l | RBC T/l | Hb g/l | Hct l/l | MCV f/l | MCH pg | MCHC g/l | Plat G/l | P.T. s | APTT s | Neut % | Lymp % | Mono % | Eosi % | Baso % |
| G1 0 | Mean | 5.95 | 8.86 | 153.7 | 0.462 | 52.20 | 17.36 | 332.7 | 1187.4 | 14.62 | 9.98 | 22.01 | 71.59 | 2.89 | 1.87 | 0.20 |
| | SD | 1.92 | 0.21 | 4.85 | 0.010 | 1.70 | 0.49 | 11.71 | 151.32 | 1.20 | 0.72 | 10.21 | 11.46 | 0.77 | 1.58 | 0.07 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 4.36 | 8.76 | 153.9 | 0.453 | 51.69 | 17.56 | 340.3 | 1052.5 | 15.13 | 11.28 | 25.16 | 68.62 | 3.01 | 2.26 | 0.17 |
| | SD | 2.29 | 0.31 | 2.92 | 0.017 | 2.06 | 0.51 | 11.24 | 160.92 | 1.01 | 1.02 | 5.28 | 5.7 | 1.04 | 0.84 | 0.07 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 4.90 | 9.03 | 156.5 | 0.468 | 51.88 | 17.37 | 335.2 | 1092.9 | 15.33 | 12.25 | 24.08 | 70.48 | 2.79 | 1.78 | 0.13 |
| | SD | 1.09 | 0.52 | 5.84 | 0.018 | 1.56 | 0.97 | 12.84 | 76.27 | 1.72 | 1.94 | 7.31 | 6.36 | 0.80 | 0.59 | 0.07 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 5.23 | 9.00 | 157.4 | 0.461 | 51.22 | 17.51 | 342.0 | 1103.4 | 15.48 | 10.32 | 22.93 | 71.61 | 3.13 | 1.56 | 0.09 |
| | SD | 1.02 | 0.37 | 4.12 | 0.018 | 1.74 | 0.66 | 10.43 | 79.91 | 1.68 | 1.70 | 8.07 | 8.06 | 0.93 | 0.86 | 0.06 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

SD: Standard Deviation; n: No. of Counts;

+ / - : Significantly higher (+) / lower (-) than the control group

TABLE 12 contd. Summary of Haematological values - Males

| Group No. Dose (mg TOS/kg bwt/day) | | Refer Appendix 11 | | | | | | |
|--|------|-------------------|-------------|-------------|-------------|-------------|--------------|------------|
| | | Neut G/l | Lymp G/l | Mono G/l | Eosi G/l | Baso G/l | Retic T/l | Retic % |
| G1 0 | Mean | 1.28 | 4.30 | 0.17 | 0.11 | 0.01 | 0.233 | 2.64 |
| | SD | 0.63 | 1.65 | 0.07 | 0.09 | 0.01 | 0.030 | 0.36 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 1.08 | 3.01 | 0.13 | 0.11 | 0.01 | 0.230 | 2.63 |
| | SD | 0.59 | 1.65 | 0.08 | 0.09 | 0.01 | 0.012 | 0.17 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 1.18 | 3.45 | 0.14 | 0.08 | 0.01 | 0.215 | 2.39 |
| | SD | 0.44 | 0.88 | 0.04 | 0.02 | 0.01 | 0.033 | 0.37 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 1.15 | 3.79 | 0.17 | 0.08 | 0.01 | 0.207 | 2.31 |
| | SD | 0.34 | 1.06 | 0.08 | 0.04 | 0.01 | 0.027 | 0.37 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

SD: Standard Deviation; n: No. of Counts;

TABLE 13. Summary of Haematological values - Females

| Group No. Dose (mg TOS/kg bwt/day) | | Refer Appendix 12 | | | | | | | | | | | | | | |
|--|------|-------------------|------------|-----------|------------|------------|-----------|-------------|-------------|--------------------|-----------|--------------------|-----------|-----------|-----------|-----------|
| | | WBC G/l | RBC T/l | Hb g/l | Hct l/l | MCV f/l | MCH pg | MCHC g/l | Plat G/l | P.T. s | APTT s | Neut % | Lymp % | Mono % | Eosi % | Baso % |
| G1 0 | Mean | 4.25 | 8.11 | 150.7 | 0.445 | 54.82 | 18.58 | 339.0 | 1127.0 | 13.75 | 10.34 | 17.78 | 76.88 | 2.90 | 1.50 | 0.10 |
| | SD | 1.44 | 0.34 | 5.66 | 0.013 | 1.65 | 0.71 | 8.97 | 65.86 | 0.48 | 0.64 | 2.56 | 3.40 | 1.05 | 0.89 | 0.07 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 5.10 | 8.09 | 150.9 | 0.443 | 54.75 | 18.67 | 340.8 | 1255.6 | 15.93 ⁺ | 11.91 | 18.49 | 76.39 | 2.73 | 1.53 | 0.11 |
| | SD | 1.59 | 0.32 | 5.47 | 0.019 | 1.46 | 0.44 | 8.22 | 103.23 | 1.55 | 2.73 | 4.20 | 5.04 | 0.96 | 0.53 | 0.10 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 4.48 | 8.35 | 151.3 | 0.451 | 54.00 | 18.14 | 336.1 | 1158.7 | 14.51 | 12.06 | 24.17 | 69.66 | 2.50 | 2.68 | 0.17 |
| | SD | 2.08 | 0.38 | 5.46 | 0.018 | 1.64 | 0.60 | 12.05 | 220.95 | 1.64 | 1.76 | 9.16 | 10.37 | 0.63 | 2.54 | 0.08 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 4.03 | 8.13 | 147.4 | 0.433 | 53.34 | 18.15 | 339.9 | 1214.3 | 15.18 | 12.30 | 24.48 ⁺ | 69.96 | 2.71 | 1.88 | 0.16 |
| | SD | 2.26 | 0.47 | 6.36 | 0.018 | 1.51 | 0.58 | 3.81 | 77.73 | 1.65 | 2.55 | 6.01 | 6.42 | 0.66 | 0.96 | 0.08 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

SD: Standard Deviation; n: No. of Counts;

⁺ : Significantly higher (+) than the control group

TABLE 13 contd. Summary of Haematological values - Females

| Group No. Dose (mg TOS/kg bwt/day) | | Refer Appendix 12 | | | | | | |
|--|------|-------------------|-------------|-------------|-------------|-------------|--------------|------------|
| | | Neut G/l | Lymp G/l | Mono G/l | Eosi G/l | Baso G/l | Retic T/l | Retic % |
| G1 0 | Mean | 0.76 | 3.26 | 0.13 | 0.06 | 0.00 | 0.262 | 3.24 |
| | SD | 0.28 | 1.09 | 0.07 | 0.03 | 0.01 | 0.03 | 0.41 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 0.92 | 3.93 | 0.14 | 0.07 | 0.00 | - | 2.88 |
| | SD | 0.25 | 1.41 | 0.05 | 0.02 | 0.01 | 0.024 | 0.34 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 1.09 | 3.12 | 0.12 | 0.11 | 0.01 | 0.251 | 3.01 |
| | SD | 0.66 | 1.55 | 0.08 | 0.09 | 0.01 | 0.031 | 0.42 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 0.96 | 2.85 | 0.11 | 0.08 | 0.01 | 0.272 | 3.35 |
| | SD | 0.48 | 1.72 | 0.06 | 0.05 | 0.01 | 0.016 | 0.28 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

SD: Standard Deviation; n: No. of Counts;

- : Significantly lower (-) than the control group

TABLE 14. Summary of Clinical Chemistry values - Males

Refer Appendix 13

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Glu mmol/l | BUN mmol/l | T.Pro g/l | AST U/l | ALT U/l | ALP U/l | T.Bil μmol/l | Creat μmol/l | Alb g/l | Glob g/l | A/G | Pi mmol/l | Ca mmol/l | T.Chol mmol/l | Na mEq/l | K mEq/l | Cl mEq/l |
|---|---------|---------------|---------------|--------------|------------|------------|------------|-----------------|-----------------|------------|-------------|------|--------------|--------------|------------------|-------------|------------|-------------|
| G1 0 | Mean | 8.50 | 6.18 | 64.66 | 79.4 | 36.0 | 72.7 | 2.37 | 40.8 | 41.57 | 23.09 | 1.82 | 2.03 | 2.63 | 1.36 | 134.58 | 3.79 | 94.44 |
| | SD | 1.19 | 0.90 | 3.34 | 12.76 | 6.68 | 14.53 | 0.62 | 6.03 | 1.78 | 2.79 | 0.21 | 0.23 | 0.14 | 0.22 | 1.43 | 0.40 | 2.39 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 8.30 | 6.06 | 64.45 | 75.1 | 36.1 | 68.8 | 2.62 | 37.0 | 42.80 | 21.65 | 1.99 | 2.00 | 2.52 | 1.20 | 137.32 | 3.79 | 94.17 |
| | SD | 0.97 | 0.59 | 1.55 | 11.27 | 6.69 | 10.82 | 0.48 | 5.56 | 1.72 | 1.34 | 0.17 | 0.20 | 0.17 | 0.21 | 1.53 | 0.38 | 1.46 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 8.91 | 6.06 | 65.60 | 74.3 | 32.8 | 68.5 | 2.54 | 39.4 | 41.92 | 23.68 | 1.79 | 1.94 | 2.59 | 1.30 | 135.12 | 3.87 | 94.10 |
| | SD | 1.25 | 0.62 | 2.77 | 5.44 | 6.16 | 18.46 | 0.43 | 4.35 | 2.13 | 2.50 | 0.22 | 0.31 | 0.07 | 0.16 | 2.27 | 0.39 | 1.79 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 9.06 | 6.50 | 65.60 | 76.7 | 35.8 | 74.0 | 2.30 | 38.9 | 42.16 | 23.44 | 1.81 | 2.03 | 2.61 | 1.36 | 140.47 | 3.89 | 98.24 |
| | SD | 1.57 | 0.61 | 2.77 | 4.95 | 4.42 | 13.21 | 0.36 | 4.01 | 2.56 | 1.83 | 0.20 | 0.22 | 0.09 | 0.30 | 4.01 | 0.55 | 3.95 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

SD: Standard Deviation; n: No. of Counts;

+ : Significantly higher (+) than the control group

TABLE 15. Summary of Clinical Chemistry values - Females

Refer Appendix 14

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Glu mmol/l | BUN mmol/l | T.Pro g/l | AST U/l | ALT U/l | ALP U/l | T.Bil μmol/l | Creat μmol/l | Alb g/l | Glob g/l | A/G | Pi mmol/l | Ca mmol/l | T.Chol mmol/l | Na mEq/l | K mEq/l | Cl mEq/l |
|---|---------|---------------|---------------|--------------|------------|------------|------------|-----------------|-----------------|------------|-------------|------|--------------|--------------|------------------|-------------|------------|-------------|
| G1 0 | Mean | 9.59 | 6.41 | 66.08 | 77.9 | 26.2 | 43.5 | 2.96 | 42.9 | 47.78 | 18.30 | 2.69 | 1.69 | 2.63 | 1.21 | 135.22 | 3.58 | 94.46 |
| | SD | 1.70 | 0.85 | 3.90 | 9.86 | 3.77 | 14.59 | 1.04 | 5.00 | 5.22 | 2.62 | 0.64 | 0.27 | 0.16 | 0.42 | 4.44 | 0.44 | 3.37 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 8 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 8.37 | 6.84 | 67.06 | 73.7 | 26.4 | 42.2 | 2.73 | 46.3 | 46.97 | 20.09 | 2.37 | 1.77 | 2.55 | 1.33 | 136.02 | 3.59 | 94.98 |
| | SD | 1.19 | 0.55 | 4.22 | 8.56 | 4.93 | 7.98 | 0.48 | 5.38 | 3.39 | 2.57 | 0.33 | 0.21 | 0.10 | 0.30 | 4.65 | 0.48 | 3.38 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 8.63 | 6.05 | 65.26 | 72.5 | 24.9 | 46.0 | 2.57 | 42.2 | 44.71 | 20.55 | 2.20 | 1.77 | 2.52 | 1.32 | 135.95 | 3.91 | 94.66 |
| | SD | 1.18 | 0.60 | 3.10 | 4.22 | 3.00 | 11.09 | 0.73 | 3.71 | 2.72 | 2.06 | 0.29 | 0.18 | 0.08 | 0.23 | 3.79 | 0.63 | 5.26 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 9.86 | 6.07 | 66.23 | 76.6 | 28.0 | 43.6 | 2.77 | 42.7 | 45.18 | 21.05 | 2.17 | 1.66 | 2.58 | 1.40 | 135.49 | 3.77 | 95.43 |
| | SD | 1.12 | 0.55 | 2.63 | 14.96 | 10.3 | 11.31 | 0.45 | 5.87 | 2.13 | 2.05 | 0.27 | 0.21 | 0.11 | 0.17 | 5.15 | 0.53 | 5.12 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 8 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

SD: Standard Deviation; n: No. of Counts;

- : Significantly lower (-) than the control group

TABLE 16. Summary of Clinical Analysis of Urine at Termination - Males

| Group No. Dose (mg TOS/kg bwt/day) | No. of rats | Volume* (ml) | Refer Appendix 15 | |
|--|-------------------|-----------------|----------------------|-----|
| | | | Specific* gravity | pH* |
| G1 0 | 10 | 10.5 | 1.023 | 8.9 |
| G2 100 | 10 | 6.3 | 1.026 | 8.9 |
| G3 300 | 10 | 10.5 | 1.017 | 8.9 |
| G4 1000 | 10 | 8.0 | 1.020 | 9.0 |

Note: *:1) These parameters are reported as averages of observed values.

TABLE 17. Summary of Clinical Analysis of Urine at Termination - Females

| Group No. Dose (mg TOS/kg bwt/day) | No. of rats | Volume* (ml) | Refer Appendix 16 | |
|--|-------------------|-----------------|----------------------|-----|
| | | | Specific* gravity | pH* |
| G1 0 | 10 | 7.3 | 1.017 | 8.2 |
| G2 100 | 10 | 7.7 | 1.020 | 8.7 |
| G3 300 | 10 | 14.5 | 1.012 | 8.8 |
| G4 1000 | 10 | 7.3 | 1.016 | 8.9 |

Note: *: 1) These parameters are reported as averages of observed values.

TABLE 18. Urine Electrolytes Values - Males

| Refer Appendix 17 | | | | | |
|---------------------|------|--|-------|--------|--------|
| Group No. | | | Na | K | Cl |
| Dose | | | mEq/l | mEq/l | mEq/l |
| (mg TOS/kg bwt/day) | | | | | |
| G1 | Mean | | 57.30 | 120.67 | 71.86 |
| 0 | SD | | 55.35 | 107.31 | 61.93 |
| | n | | 10 | 10 | 10 |
| | | | | | |
| G2 | Mean | | 80.65 | 188.30 | 117.43 |
| 100 | SD | | 110.7 | 142.87 | 81.98 |
| | n | | 10 | 10 | 10 |
| | | | | | |
| G3 | Mean | | 34.91 | 137.86 | 111.17 |
| 300 | SD | | 16.92 | 66.48 | 57.42 |
| | n | | 10 | 10 | 10 |
| | | | | | |
| G4 | Mean | | 56.60 | 112.87 | 142.98 |
| 1000 | SD | | 34.52 | 54.23 | 66.40 |
| | n | | 10 | 10 | 10 |

n: No. of Counts;

TABLE 19. Urine Electrolytes Values - Females

| | | Refer Appendix 18 | | | |
|-----------|---------------------|-------------------|-------|--------|--------|
| Group No. | Dose | | Na | K | Cl |
| | (mg TOS/kg bwt/day) | | mEq/l | mEq/l | mEq/l |
| G1 | Mean | | 35.20 | 108.84 | 73.64 |
| 0 | SD | | 27.54 | 43.57 | 52.62 |
| | n | | 10 | 10 | 10 |
| | | | | | |
| G2 | Mean | | 41.19 | 113.53 | 72.36 |
| 100 | SD | | 31.67 | 85.61 | 48.06 |
| | n | | 10 | 10 | 10 |
| | | | | | |
| G3 | Mean | | 32.50 | 68.31 | 99.45 |
| 300 | SD | | 39.79 | 56.12 | 112.53 |
| | n | | 10 | 10 | 10 |
| | | | | | |
| G4 | Mean | | 26.36 | 103.94 | 78.62 |
| 1000 | SD | | 15.68 | 32.73 | 41.54 |
| | n | | 10 | 10 | 10 |

n: No. of Counts;

TABLE 20. Summary of Terminal Fasting Body Weights and Organ Weights - Males

| Group No. Dose (mg TOS/kg bwt/day) | | Fasting Bwt (g) | Organ weights (g) | | | | | | | | | | | Thyroid* |
|---|------|-----------------------|-------------------|--------|---------|-------|--------|--------|-------|-------|----------|----------|-----------|----------|
| | | | Adrenals | Testes | Kidneys | Liver | Thymus | Spleen | Heart | Brain | Prostate | Epididym | Pituitary | |
| G1 0 | Mean | 352.48 | 0.060 | 3.331 | 1.957 | 8.369 | 0.343 | 0.614 | 0.955 | 2.052 | 0.889 | 1.247 | 0.012 | 0.030 |
| | SD | 44.15 | 0.010 | 0.340 | 0.236 | 1.707 | 0.089 | 0.118 | 0.179 | 0.120 | 0.105 | 0.123 | 0.003 | 0.008 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 341.69 | 0.066 | 3.343 | 1.994 | 8.537 | 0.346 | 0.655 | 0.980 | 2.076 | 0.902 | 1.264 | 0.012 | 0.032 |
| | SD | 21.75 | 0.008 | 0.485 | 0.220 | 0.695 | 0.057 | 0.078 | 0.062 | 0.088 | 0.146 | 0.147 | 0.002 | 0.007 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 359.51 | 0.062 | 3.402 | 2.030 | 8.873 | 0.357 | 0.642 | 0.998 | 2.073 | 0.920 | 1.277 | 0.011 | 0.032 |
| | SD | 32.68 | 0.009 | 0.230 | 0.226 | 1.426 | 0.068 | 0.077 | 0.099 | 0.096 | 0.115 | 0.152 | 0.003 | 0.006 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 345.20 | 0.058 | 3.448 | 2.000 | 8.552 | 0.311 | 0.612 | 0.959 | 2.068 | 0.929 | 1.281 | 0.011 | 0.025 |
| | SD | 20.36 | 0.009 | 0.242 | 0.231 | 0.721 | 0.035 | 0.051 | 0.090 | 0.062 | 0.190 | 0.092 | 0.004 | 0.005 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

*: With parathyroids

TABLE 21. Summary of Terminal Fasting Body Weights and Organ Weight Ratios - Males

Refer Appendix 20

| Group No. Dose (mg TOS/kg bwt/day) | | Fasting Bwt (g) | Organ weight ratios (%) | | | | | | | | | | | |
|---|------|-----------------------|-------------------------|--------|---------|-------|--------|--------|-------|-------|----------|----------|-----------|----------|
| | | | Adrenals | Testes | Kidneys | Liver | Thymus | Spleen | Heart | Brain | Prostate | Epididym | Pituitary | Thyroid* |
| G1 0 | Mean | 352.48 | 0.017 | 0.955 | 0.558 | 2.381 | 0.097 | 0.176 | 0.271 | 0.591 | 0.254 | 0.357 | 0.004 | 0.009 |
| | SD | 44.15 | 0.003 | 0.124 | 0.055 | 0.391 | 0.024 | 0.035 | 0.038 | 0.085 | 0.032 | 0.040 | 0.001 | 0.002 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 341.69 | 0.019 | 0.978 | 0.583 | 2.501 | 0.101 | 0.192 | 0.287 | 0.610 | 0.264 | 0.370 | 0.004 | 0.010 |
| | SD | 21.75 | 0.002 | 0.126 | 0.044 | 0.170 | 0.015 | 0.017 | 0.020 | 0.052 | 0.043 | 0.040 | 0.001 | 0.002 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 359.51 | 0.017 | 0.953 | 0.565 | 2.455 | 0.099 | 0.179 | 0.278 | 0.580 | 0.258 | 0.357 | 0.003 | 0.009 |
| | SD | 32.68 | 0.003 | 0.109 | 0.039 | 0.207 | 0.017 | 0.011 | 0.014 | 0.048 | 0.039 | 0.043 | 0.001 | 0.002 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 345.2 | 0.017 | 1.003 | 0.579 | 2.477 | 0.090 | 0.178 | 0.278 | 0.601 | 0.268 | 0.372 | 0.003 | 0.007 |
| | SD | 20.36 | 0.002 | 0.098 | 0.056 | 0.149 | 0.010 | 0.016 | 0.019 | 0.032 | 0.048 | 0.036 | 0.001 | 0.002 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

*: With parathyroids

TABLE 22. Summary of Terminal Fasting Body Weights and Organ Weights - Females

Refer Appendix 21

| Group No. Dose (mg TOS/kg bwt/day) | | Fasting Bwt (g) | Organ weights (g) | | | | | | | | | | Thyroid* |
|---|------|-----------------------|-------------------|---------|---------|-------|--------|--------|-------|-------|--------------------------|-----------|----------|
| | | | Adrenals | Ovaries | Kidneys | Liver | Thymus | Spleen | Heart | Brain | Uterus with cervix | Pituitary | |
| G1 0 | Mean | 207.43 | 0.079 | 0.108 | 1.291 | 5.998 | 0.351 | 0.444 | 0.648 | 1.956 | 0.703 | 0.016 | 0.028 |
| | SD | 10.92 | 0.008 | 0.034 | 0.070 | 0.363 | 0.046 | 0.077 | 0.021 | 0.083 | 0.176 | 0.004 | 0.006 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 213.99 | 0.079 | 0.097 | 1.316 | 5.894 | 0.369 | 0.474 | 0.687 | 1.964 | 0.659 | 0.015 | 0.028 |
| | SD | 12.25 | 0.014 | 0.017 | 0.109 | 0.538 | 0.090 | 0.073 | 0.060 | 0.082 | 0.215 | 0.004 | 0.007 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 214.99 | 0.080 | 0.095 | 1.315 | 5.747 | 0.359 | 0.499 | 0.681 | 1.933 | 0.665 | 0.014 | 0.024 |
| | SD | 13.43 | 0.011 | 0.017 | 0.123 | 0.673 | 0.042 | 0.050 | 0.042 | 0.099 | 0.208 | 0.004 | 0.004 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 209.58 | 0.076 | 0.096 | 1.337 | 6.042 | 0.323 | 0.470 | 0.685 | 1.933 | 0.706 | 0.017 | 0.024 |
| | SD | 8.50 | 0.013 | 0.013 | 0.107 | 0.888 | 0.035 | 0.058 | 0.071 | 0.085 | 0.269 | 0.004 | 0.003 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

*: With parathyroids

TABLE 23. Summary of Terminal Fasting Body Weights and Organ Weight Ratios - Females

Refer Appendix 22

| Group No. Dose (mg TOS/kg bwt/day) | | Fasting Bwt (g) | Organ weight ratios (%) | | | | | | | | | | Thyroid* |
|---|------|-----------------------|-------------------------|---------|---------|-------|--------|--------|-------|-------|--------------------------|-----------|----------|
| | | | Adrenals | Ovaries | Kidneys | Liver | Thymus | Spleen | Heart | Brain | Uterus with cervix | Pituitary | |
| G1 0 | Mean | 207.43 | 0.038 | 0.052 | 0.623 | 2.892 | 0.169 | 0.214 | 0.313 | 0.946 | 0.341 | 0.008 | 0.014 |
| | SD | 10.92 | 0.005 | 0.017 | 0.017 | 0.097 | 0.020 | 0.031 | 0.017 | 0.073 | 0.095 | 0.002 | 0.003 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G2 100 | Mean | 213.99 | 0.037 | 0.045 | 0.615 | 2.756 | 0.172 | 0.222 | 0.321 | 0.920 | 0.307 | 0.007 | 0.013 |
| | SD | 12.25 | 0.006 | 0.007 | 0.030 | 0.209 | 0.038 | 0.033 | 0.023 | 0.059 | 0.094 | 0.002 | 0.003 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G3 300 | Mean | 214.99 | 0.037 | 0.044 | 0.611 | 2.671 | 0.168 | 0.234 | 0.317 | 0.901 | 0.308 | 0.007 | 0.011 |
| | SD | 13.43 | 0.005 | 0.008 | 0.030 | 0.245 | 0.023 | 0.031 | 0.014 | 0.052 | 0.087 | 0.002 | 0.001 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| G4 1000 | Mean | 209.58 | 0.037 | 0.046 | 0.638 | 2.878 | 0.154 | 0.224 | 0.327 | 0.923 | 0.338 | 0.008 | 0.011 |
| | SD | 8.50 | 0.005 | 0.007 | 0.040 | 0.365 | 0.013 | 0.027 | 0.029 | 0.050 | 0.131 | 0.002 | 0.001 |
| | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

*: With parathyroids

Values in the parenthesis includes % change

- : Significantly lower (-) than the control group

TABLE 24. Summary of Gross Pathological Findings

| PARAMETERS | Sex | Males | | | | Females | | | |
|---|--------------------------|-------|-----|-----|------|---------|-----|-----|------|
| | Group. No. | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| | Dose (mg TOS/kg bwt/day) | 0 | 100 | 300 | 1000 | 0 | 100 | 300 | 1000 |
| | No. of rats | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 1. No. dead during treatment/ No. of moribund sacrifice | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2. No. finally sacrificed | | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 3. No. examined for gross pathology | | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 4. No. showing gross pathology | | 4 | 3 | 6 | 4 | 2 | 4 | 3 | 3 |
| A. No. showing external pathology | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| B. No. showing visceral organ pathology | | 4 | 3 | 6 | 4 | 2 | 4 | 3 | 3 |
| 1. Thymus – petechiae | | 2 | 1 | 0 | 2 | 2 | 0 | 1 | 0 |
| 2. Mandibular lymph node - | | | | | | | | | |
| a. unilateral/bilateral – discoloration, red | | 2 | 2 | 5 | 2 | 0 | 2 | 1 | 2 |
| b. unilateral/bilateral – enlarged | | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 |
| 3. Liver – hepatodiaphragmatic, nodule – 0.8 cm | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 4. Uterus – dilatation | | NA | NA | NA | NA | 0 | 0 | 0 | 1 |

TABLE 25. Summary of Histopathological Findings

| Number in (): No. of tissues evaluated/group | | Refer Appendices 23 and 24 | | | | | | | |
|---|--------------------------|----------------------------|-----|-----|------|---------|-----|-----|------|
| TISSUE AND OBSERVATION | Sex | MALES | | | | FEMALES | | | |
| | Group No. | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| | Dose (mg TOS/kg bwt/day) | 0 | 100 | 300 | 1000 | 0 | 100 | 300 | 1000 |
| | No. of rats | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 3 | 6 | 10 | 10 | 4 | 3 | 10 |
| 1 | SALIVARY GLANDS | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 2 | ESOPHAGUS | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 3 | STOMACH | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 4 | DUODENUM | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 5 | JEJUNUM | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 6 | ILEUM WITH PEYER'S PATCH | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 7 | CECUM | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |

TABLE 25 contd. Summary of Histopathological Findings

| Number in (): No. of tissues evaluated/group | | Refer Appendices 23 and 24 | | | | | | | |
|---|--------------------------|----------------------------|-----|-----|------|---------|-----|-----|------|
| TISSUE AND OBSERVATION | Sex | MALES | | | | FEMALES | | | |
| | Group No. | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| | Dose (mg TOS/kg bwt/day) | 0 | 100 | 300 | 1000 | 0 | 100 | 300 | 1000 |
| | No. of rats | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 3 | 6 | 10 | 10 | 4 | 3 | 10 |
| 8 COLON | | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 9 RECTUM | | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| Nematode | | 0 | - | - | 3 | 1 | - | - | 0 |
| 10 PANCREAS | | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| Inflammation-chronic | | 0 | - | - | 0 | 1 | - | - | 0 |
| Increased acinar cell apoptosis | | 0 | - | - | 1 | 0 | - | - | 0 |
| 11 LIVER | | (10) | (-) | (-) | (10) | (10) | (1) | (-) | (10) |
| Chronic inflammatory focus(i) | | 0 | - | - | 3 | 1 | 0 | 0 | 1 |
| 12 LUNGS | | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| Inflammatory focus(i) | | 0 | - | - | 2 | 0 | - | - | 0 |
| Perivascular leukocytic infiltration | | 1 | - | - | 0 | 0 | - | - | 0 |
| Increased alveolar macrophages | | 2 | - | - | 1 | 1 | - | - | 1 |

TABLE 25 contd. Summary of Histopathological Findings

| Number in (): No. of tissues evaluated/group | | Refer Appendices 23 and 24 | | | | | | | |
|---|--------------------------|----------------------------|-----|-----|------|---------|-----|-----|------|
| TISSUE AND OBSERVATION | Sex | MALES | | | | FEMALES | | | |
| | Group No. | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| | Dose (mg TOS/kg bwt/day) | 0 | 100 | 300 | 1000 | 0 | 100 | 300 | 1000 |
| | No. of rats | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 3 | 6 | 10 | 10 | 4 | 3 | 10 |
| 13 | TRACHEA | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 14 | HEART | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| | Inflammatory focus(i) | 0 | - | - | 1 | 0 | - | - | 0 |
| 15 | AORTA | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 16 | SPLEEN | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 17 | MESENTERIC LYMPH NODES | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 18 | MANDIBULAR LYMPH NODES | (10) | (2) | (6) | (10) | (10) | (3) | (2) | (10) |
| | Hemorrhage | 6 | 2 | 6 | 4 | 4 | 2 | 1 | 5 |
| | Lymphoid hyperplasia | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 |
| | Plasma cell hyperplasia | 3 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |

TABLE 25 contd. Summary of Histopathological Findings

| Number in (): No. of tissues evaluated/group | | Refer Appendices 23 and 24 | | | | | | | |
|---|--------------------------|----------------------------|-----|-----|------|---------|-----|-----|------|
| TISSUE AND OBSERVATION | Sex | MALES | | | | FEMALES | | | |
| | Group No. | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| | Dose (mg TOS/kg bwt/day) | 0 | 100 | 300 | 1000 | 0 | 100 | 300 | 1000 |
| | No. of rats | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 3 | 6 | 10 | 10 | 4 | 3 | 10 |
| 19 | URETERS | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 20 | KIDNEYS | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| | Dilatation of pelvis | 1 | - | - | 0 | 0 | - | - | 0 |
| 21 | URINARY BLADDER | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 22 | TESTES | (10) | (-) | (-) | (10) | NA | NA | NA | NA |
| 23 | EPIDIDYIMIDES | (10) | (-) | (-) | (10) | NA | NA | NA | NA |
| 24 | PROSTATE | (10) | (-) | (-) | (10) | NA | NA | NA | NA |
| | Lymphocytic infiltration | 2 | - | - | 2 | NA | NA | NA | NA |
| | Cell debris in lumen | 0 | - | - | 1 | NA | NA | NA | NA |

TABLE 25 contd. Summary of Histopathological Findings

| Number in (): No. of tissues evaluated/group | | Refer Appendices 23 and 24 | | | | | | | |
|---|--------------------------|----------------------------|-----|-----|------|---------|-----|-----|------|
| TISSUE AND OBSERVATION | Sex | MALES | | | | FEMALES | | | |
| | Group No. | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| | Dose (mg TOS/kg bwt/day) | 0 | 100 | 300 | 1000 | 0 | 100 | 300 | 1000 |
| | No. of rats | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 3 | 6 | 10 | 10 | 4 | 3 | 10 |
| 25 | SEMINAL VESICLES | (10) | (-) | (-) | (10) | NA | NA | NA | NA |
| 26 | COAGULATING GLANDS | (10) | (-) | (-) | (10) | NA | NA | NA | NA |
| 27 | OVARIES | NA | NA | NA | NA | (10) | (-) | (-) | (10) |
| 28 | OVIDUCT | NA | NA | NA | NA | (10) | (-) | (-) | (10) |
| 29 | UTERUS WITH CERVIX | NA | NA | NA | NA | (10) | (-) | (-) | (10) |
| | Dilatation | NA | NA | NA | NA | 0 | - | - | 1 |
| 30 | VAGINA | NA | NA | NA | NA | (10) | (-) | (-) | (10) |
| 31 | THYROID | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| | Ectopic thymus | 0 | - | - | 1 | 1 | - | - | 1 |

TABLE 25 contd. Summary of Histopathological Findings

| Number in (): No. of tissues evaluated/group | | Refer Appendices 23 and 24 | | | | | | | |
|---|--------------------------------|----------------------------|-----|-----|------|---------|-----|-----|------|
| TISSUE AND OBSERVATION | Sex | MALES | | | | FEMALES | | | |
| | Group No. | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| | Dose (mg TOS/kg bwt/day) | 0 | 100 | 300 | 1000 | 0 | 100 | 300 | 1000 |
| | No. of rats | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 3 | 6 | 10 | 10 | 4 | 3 | 10 |
| 32 | PARATHYROID | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 33 | PITUITARY | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| | Tissue not fit for examination | 0 | - | - | 0 | 0 | - | - | 1 |
| 34 | ADRENALS | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| | Accessory cortical tissue | 1 | - | - | 0 | 1 | - | - | 0 |
| 35 | BRAIN-CEREBRUM | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 36 | BRAIN-CEREBELLUM | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 37 | BRAIN-MEDULLA/PONS | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 38 | SPINAL CORD | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 39 | SCIATIC NERVES | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |

TABLE 25 contd. Summary of Histopathological Findings

| Number in (): No. of tissues evaluated/group | | Refer Appendices 23 and 24 | | | | | | | |
|---|--------------------------|----------------------------|-----|-----|------|---------|-----|-----|------|
| TISSUE AND OBSERVATION | Sex | MALES | | | | FEMALES | | | |
| | Group No. | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| | Dose (mg TOS/kg bwt/day) | 0 | 100 | 300 | 1000 | 0 | 100 | 300 | 1000 |
| | No. of rats | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 3 | 6 | 10 | 10 | 4 | 3 | 10 |
| 40 | EYES WITH OPTIC NERVE | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 41 | SKIN | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 42 | TONGUE | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 43 | THYMUS | (10) | (1) | (-) | (10) | (10) | (-) | (1) | (10) |
| | Hemorrhage | 4 | 1 | - | 4 | 2 | - | 1 | 1 |
| | Epithelial cyst(s) | 0 | 0 | - | 0 | 2 | - | 0 | 3 |
| 44 | LARYNX | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 45 | MAMMARY GLAND | (5) | (-) | (-) | (5) | (10) | (-) | (-) | (10) |
| 46 | LACRIMAL GLANDS | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 47 | FEMORAL MUSCLE | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |

TABLE 25 contd. Summary of Histopathological Findings

| Number in (): No. of tissues evaluated/group | | Refer Appendices 23 and 24 | | | | | | | |
|---|--------------------------|----------------------------|-----|-----|------|---------|-----|-----|------|
| TISSUE AND OBSERVATION | Sex | MALES | | | | FEMALES | | | |
| | Group No. | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| | Dose (mg TOS/kg bwt/day) | 0 | 100 | 300 | 1000 | 0 | 100 | 300 | 1000 |
| | No. of rats | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 3 | 6 | 10 | 10 | 4 | 3 | 10 |
| 48 FEMUR WITH DISTAL JOINT | | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 49 STERNUM WITH MARROW | | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (10) |
| 50 BONE MARROW SMEAR | | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) |

14. FIGURES

FIGURE 1. Body Weight and Growth Curves - Males

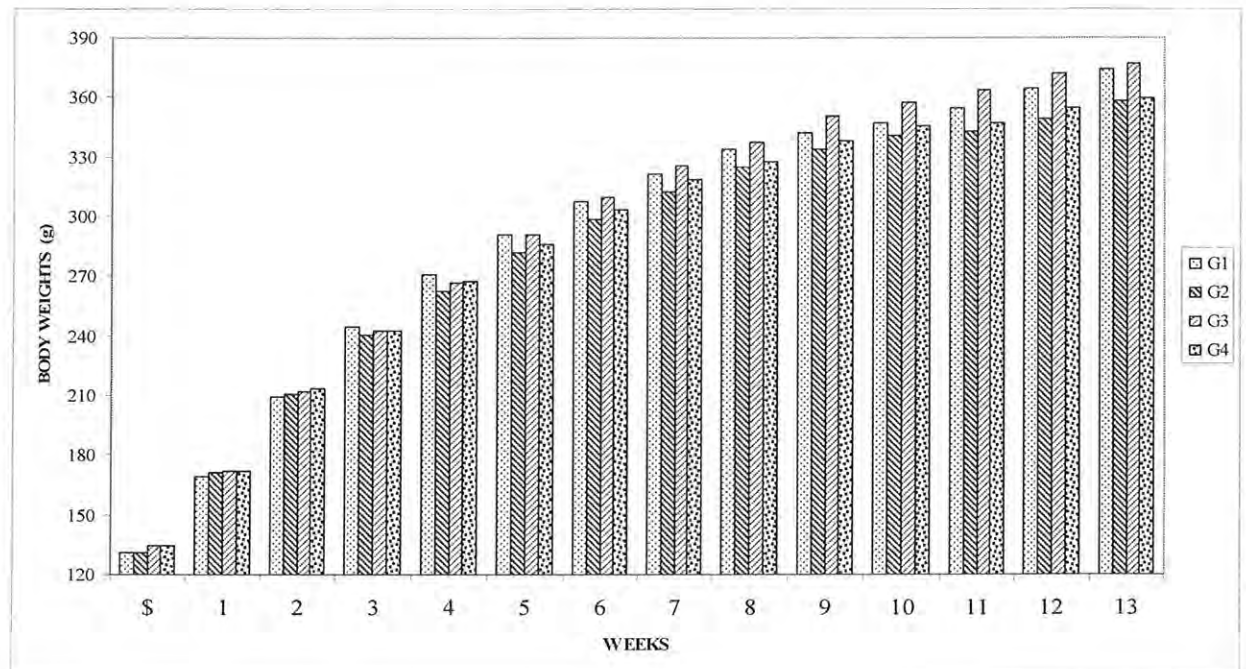


FIGURE 2. Body Weight and Growth Curves - Females

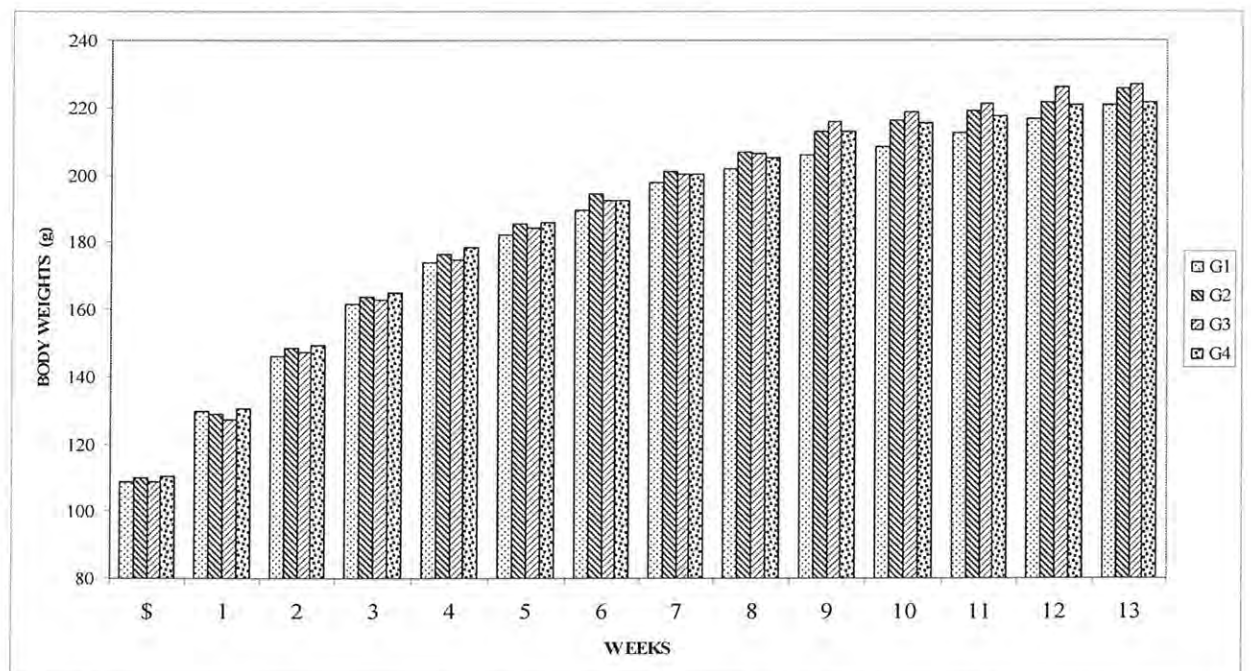


FIGURE 3. Food Consumption Curves - Males

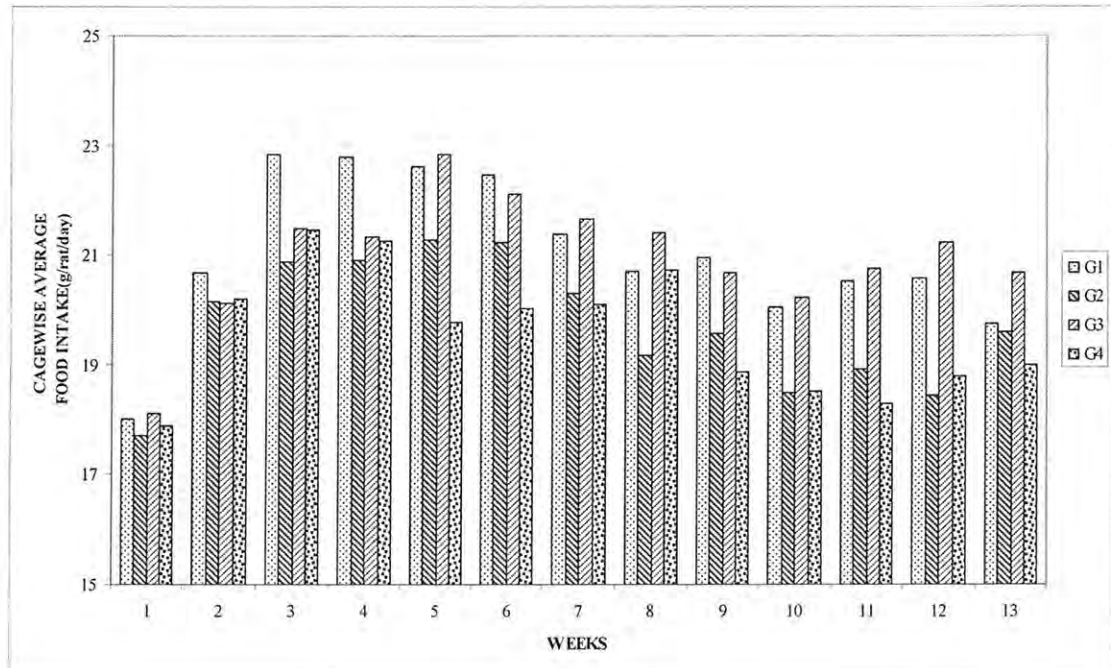
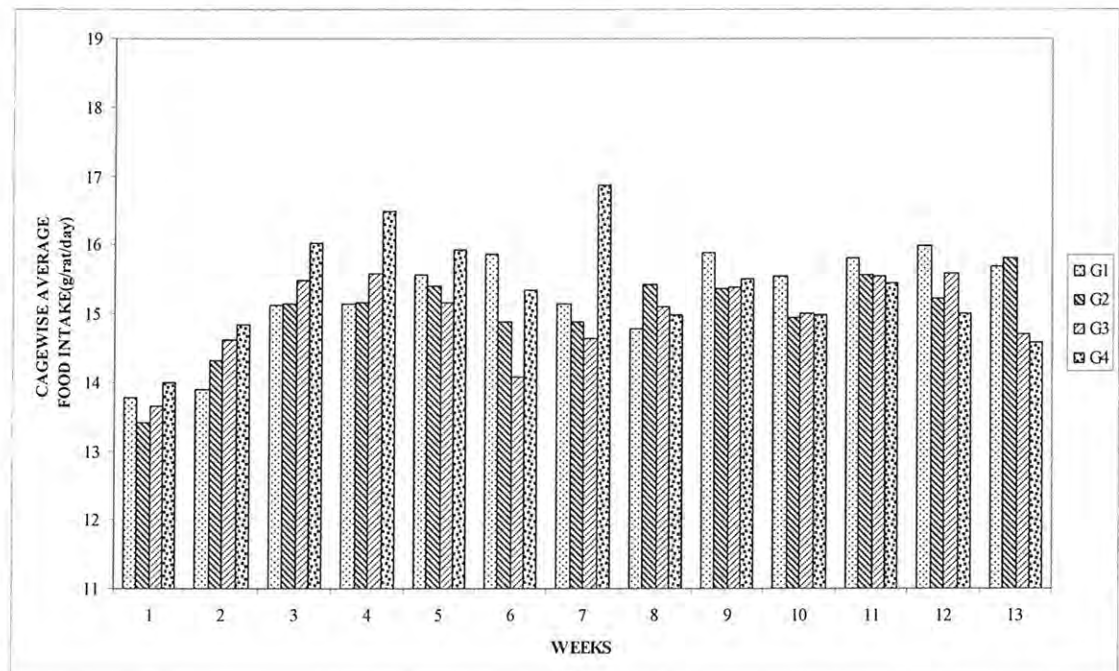


FIGURE 4. Food Consumption Curves - Females



15. APPENDICES

APPENDIX 1. Individual Clinical Signs, Detailed Clinical Examination, Mortality and Ophthalmological Examination - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Physical examination and general clinical signs | Clinical examination | Ophthalmological findings End of dosing period |
|--|------------|--|-------------------------|---|
| G1 0 | Ri3931 | NAD | NAD | NAD |
| | Ri3932 | NAD | NAD | NAD |
| | Ri3933 | NAD | NAD | NAD |
| | Ri3934 | NAD | NAD | NAD |
| | Ri3935 | NAD | NAD | NAD |
| | Ri3936 | NAD | NAD | NAD |
| | Ri3937 | NAD | NAD | NAD |
| | Ri3938 | NAD | NAD | NAD |
| | Ri3939 | NAD | NAD | NAD |
| | Ri3940 | NAD | NAD | NAD |
| G2 100 | Ri3941 | NAD | NAD | NAD |
| | Ri3942 | NAD | NAD | NAD |
| | Ri3943 | NAD | NAD | NAD |
| | Ri3944 | NAD | NAD | NAD |
| | Ri3945 | NAD | NAD | NAD |
| | Ri3946 | NAD | NAD | NAD |
| | Ri3947 | NAD | NAD | NAD |
| | Ri3948 | NAD | NAD | NAD |
| | Ri3949 | NAD | NAD | NAD |
| | Ri3950 | NAD | NAD | NAD |
| G3 300 | Ri3951 | NAD | NAD | NAD |
| | Ri3952 | NAD | NAD | NAD |
| | Ri3953 | NAD | NAD | NAD |
| | Ri3954 | NAD | NAD | NAD |
| | Ri3955 | NAD | NAD | NAD |
| | Ri3956 | NAD | NAD | NAD |
| | Ri3957 | NAD | NAD | NAD |
| | Ri3958 | NAD | NAD | NAD |
| | Ri3959 | NAD | NAD | NAD |
| | Ri3960 | NAD | NAD | NAD |
| G4 1000 | Ri3961 | NAD | NAD | NAD |
| | Ri3962 | NAD | NAD | NAD |
| | Ri3963 | NAD | NAD | NAD |
| | Ri3964 | NAD | NAD | NAD |
| | Ri3965 | NAD | NAD | NAD |
| | Ri3966 | NAD | NAD | NAD |
| | Ri3967 | NAD | NAD | NAD |
| | Ri3968 | NAD | NAD | NAD |
| | Ri3969 | NAD | NAD | NAD |
| | Ri3970 | NAD | NAD | NAD |

NAD: No Abnormality Detected

Note: Physical examination, ophthalmological examination during the acclimatization period and clinical examination of all rats prior to initiation of treatment did not reveal any abnormalities

APPENDIX 2. Individual Clinical Signs, Detailed Clinical Examination, Mortality and Ophthalmological Examination - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Physical examination and general clinical signs | Clinical examination | Ophthalmological findings End of dosing period |
|--|------------|--|-------------------------|---|
| G1 0 | Ri3971 | NAD | NAD | NAD |
| | Ri3972 | NAD | NAD | NAD |
| | Ri3973 | NAD | NAD | NAD |
| | Ri3974 | NAD | NAD | NAD |
| | Ri3975 | NAD | NAD | NAD |
| | Ri3976 | NAD | NAD | NAD |
| | Ri3977 | NAD | NAD | NAD |
| | Ri3978 | NAD | NAD | NAD |
| | Ri3979 | NAD | NAD | NAD |
| | Ri3980 | NAD | NAD | NAD |
| G2 100 | Ri3981 | NAD | NAD | NAD |
| | Ri3982 | NAD | NAD | NAD |
| | Ri3983 | NAD | NAD | NAD |
| | Ri3984 | NAD | NAD | NAD |
| | Ri3985 | NAD | NAD | NAD |
| | Ri3986 | NAD | NAD | NAD |
| | Ri3987 | NAD | NAD | NAD |
| | Ri3988 | NAD | NAD | NAD |
| | Ri3989 | NAD | NAD | NAD |
| | Ri3990 | NAD | NAD | NAD |
| G3 300 | Ri3991 | NAD | NAD | NAD |
| | Ri3992 | NAD | NAD | NAD |
| | Ri3993 | NAD | NAD | NAD |
| | Ri3994 | NAD | NAD | NAD |
| | Ri3995 | NAD | NAD | NAD |
| | Ri3996 | NAD | NAD | NAD |
| | Ri3997 | NAD | NAD | NAD |
| | Ri3998 | NAD | NAD | NAD |
| | Ri3999 | NAD | NAD | NAD |
| | Ri4000 | NAD | NAD | NAD |
| G4 1000 | Ri4001 | NAD | NAD | NAD |
| | Ri4002 | NAD | NAD | NAD |
| | Ri4003 | NAD | NAD | NAD |
| | Ri4004 | NAD | NAD | NAD |
| | Ri4005 | NAD | NAD | NAD |
| | Ri4006 | NAD | NAD | NAD |
| | Ri4007 | NAD | NAD | NAD |
| | Ri4008 | NAD | NAD | NAD |
| | Ri4009 | NAD | NAD | NAD |
| | Ri4010 | NAD | NAD | NAD |

NAD: No Abnormality Detected

Note: Physical examination, ophthalmological examination during the acclimatization period and clinical examination of all rats prior to initiation of treatment did not reveal any abnormalities

APPENDIX 3. Functional Observation Battery - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Home cage observations | | | Handling observations | | | | | | |
|---|------------|------------------------|-------------|--|---|--|--------------------------|---------------------------|---------------------------|---------------------------|--|
| | | Convulsions | Tremors | Palpebral closure | Ease of removal from the cage | Ease of handling animal in hand | Lacrimation | Red deposits around | | | |
| | | 1 = Absent | 1 = Absent | 1 = Eyelids wide open | 1 = Very easy | 1 = No resistance, animal is easy | 1 = None | Eyes | Nose | Mouth | |
| | | 2 = Present | 2 = Present | 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut | 2 = Easy 3 = Moderately difficult 4 = Difficult 5 = Very difficult | to handle 2 = Slight resistance 3 = Moderate resistance 4 = High resistance | 2 = Slight 3 = Severe | 1 = Absent 2 = Present | 1 = Absent 2 = Present | 1 = Absent 2 = Present | |
| G1 0 | Ri3931 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3932 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3933 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3934 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3935 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3936 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3937 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3938 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3939 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3940 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| G2 100 | Ri3941 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3942 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3943 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3944 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3945 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3946 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3947 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3948 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3949 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3950 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |

APPENDIX 3 contd. Functional Observation Battery - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Home cage observations | | | Handling observations | | | | Red deposits around | | |
|---|------------|------------------------|-------------|------------------------------------|-------------------------------|-----------------------------------|-------------|---|---------------------|-------------|-------------|
| | | Convulsions | Tremors | Palpebral closure | Ease of removal from the cage | Ease of handling animal in hand | Lacrimation | | Eyes | Nose | Mouth |
| | | 1 = Absent | 1 = Absent | 1 = Eyelids wide open | 1 = Very easy | 1 = No resistance, animal is easy | 1 = None | | 1 = Absent | 1 = Absent | 1 = Absent |
| | | 2 = Present | 2 = Present | 2 = Eyelids slightly drooping | 2 = Easy | to handle | 2 = Slight | | 2 = Present | 2 = Present | 2 = Present |
| | | | | 3 = Drooping eyelids (half closed) | 3 = Moderately difficult | 2 = Slight resistance | 3 = Severe | | | | |
| | | | | 4 = Eyelids completely shut | 4 = Difficult | 3 = Moderate resistance | | | | | |
| | | | | | 5 = Very difficult | 4 = High resistance | | | | | |
| G3 300 | Ri3951 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3952 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3953 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3954 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3955 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3956 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3957 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3958 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3959 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3960 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| G4 1000 | Ri3961 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3962 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3963 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3964 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3965 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3966 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3967 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3968 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3969 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3970 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

APPENDIX 3 contd. Functional Observation Battery - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Handling observations contd. | | | | | | | | | |
|---|------------|------------------------------|------|-------|---|--|--|---|--|--|--|
| | | Crusty Deposits around | | | Salivation 1= Normal 2 = Slight 3 = Severe | Fur Appearance 1= Normal 2 = Slightly soiled 3 = Very soiled, crusty | Piloerection 1 = None 2 = Slight 3 = Severe | Palpebral closure 1 = Eyelids wide open 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut | Respiratory character 1 = Normal 2 = Rales 3 = Retching 4 = Dyspnoeic 5 = Gasping | Eye Prominence 1 = Normal 2 = Exophthalmus 3 = Enophthalmus | Muscle tone 1 = Muscle is firm but not hard(normal) 2 = muscle is soft & flabby 3 = Muscle is tense & hard |
| | | Eyes | Nose | Mouth | | | | | | | |
| | | | | | | | | | | | |
| G1 0 | Ri3931 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3932 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3933 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3934 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3935 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3936 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3937 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3938 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3939 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3940 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| G2 100 | Ri3941 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3942 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3943 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3944 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3945 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3946 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3947 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3948 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3949 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3950 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

APPENDIX 3 contd. Functional Observation Battery - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Handling observations contd. | | | | | | | | | |
|---|------------|------------------------------|---------------------------|---------------------------|--|--|--|---|--|--|--|
| | | Crusty Deposits around | | | Salivation 1 = Normal 2 = Slight 3 = Severe | Fur Appearance 1= Normal 2 = Slightly soiled 3 = Very soiled, crusty | Piloerection 1 = None 2 = Slight 3 = Severe | Palpebral closure 1 = Eyelids wide open 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut | Respiratory character 1 = Normal 2 = Rales 3 = Retching 4 = Dyspnoeic 5 = Gasping | Eye Prominence 1 = Normal 2 = Exophthalmus 3 = Enophthalmus | Muscle tone 1 = Muscle is firm but not hard(normal) 2 = muscle is soft & flabby 3 = Muscle is tense & hard |
| | | Eyes | Nose | Mouth | | | | | | | |
| | | 1 = Absent 2 = Present | 1 = Absent 2 = Present | 1 = Absent 2 = Present | | | | | | | |
| G3 300 | Ri3951 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3952 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3953 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3954 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3955 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3956 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3957 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3958 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3959 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3960 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| G4 1000 | Ri3961 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3962 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3963 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3964 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3965 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3966 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3967 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3968 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3969 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3970 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

APPENDIX 3 contd. Functional Observation Battery - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Open field observations | | | | | | | | |
|--|------------|--|---------------------|---|--|--------------------------------------|--|---------------------|-----------------------|------------------------|
| | | Mobility 1 = Normal 2 = Moderately impaired 3 = Totally impaired locomotion impossible | Backing (counts) | Gait 1 = Normal 2 = Walks on tiptoes 3 = Body drags 4 = Hindlimbs splayed 5 = Hunched body 6 = Ataxia | Convulsions 1 = Absent 2 = Present | Tremors 1 = Absent 2 = Present | Arousal 1 = Very low 2 = Low 3 = Normal 4 = Moderately high 5 = Very high | Rearing (counts) | Urination (counts) | Defecation (counts) |
| G1 0 | Ri3931 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 1 | 0 |
| | Ri3932 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3933 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 1 |
| | Ri3934 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 0 |
| | Ri3935 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3936 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 1 | 0 |
| | Ri3937 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 0 | 1 |
| | Ri3938 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 1 |
| | Ri3939 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 0 |
| | Ri3940 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 1 | 0 |
| G2 100 | Ri3941 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 1 | 0 |
| | Ri3942 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 0 |
| | Ri3943 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 1 |
| | Ri3944 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 0 |
| | Ri3945 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 0 | 1 |
| | Ri3946 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 1 | 1 |
| | Ri3947 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 0 |
| | Ri3948 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 0 | 1 |
| | Ri3949 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 0 |
| | Ri3950 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |

APPENDIX 3 contd. Functional Observation Battery - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Open field observations | | | | | | | | |
|--|------------|--|---------------------|---|--|--------------------------------------|--|---------------------|-----------------------|------------------------|
| | | Mobility 1 = Normal 2 = Moderately impaired 3 = Totally impaired locomotion impossible | Backing (counts) | Gait 1 = Normal 2 = Walks on tiptoes 3 = Body drags 4 = Hindlimbs splayed 5 = Hunched body 6 = Ataxia | Convulsions 1 = Absent 2 = Present | Tremors 1 = Absent 2 = Present | Arousal 1 = Very low 2 = Low 3 = Normal 4 = Moderately high 5 = Very high | Rearing (counts) | Urination (counts) | Defecation (counts) |
| G3 300 | Ri3951 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 0 |
| | Ri3952 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3953 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 0 |
| | Ri3954 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 1 |
| | Ri3955 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 0 | 0 |
| | Ri3956 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 0 |
| | Ri3957 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 0 |
| | Ri3958 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 1 |
| | Ri3959 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 0 |
| | Ri3960 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 1 |
| G4 1000 | Ri3961 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 1 | 0 |
| | Ri3962 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3963 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3964 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 0 | 0 |
| | Ri3965 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 0 |
| | Ri3966 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 0 | 1 |
| | Ri3967 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 0 |
| | Ri3968 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 0 | 1 |
| | Ri3969 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 0 |
| | Ri3970 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 1 | 1 |

APPENDIX 3 contd. Functional Observation Battery - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Open field observations contd. | | Sensory observations | | | | | |
|---|------------|---|-----------------------------------|---|--|---|--|---|--------------------|
| | | Stereotypies | | Startle response 1 = No reaction 2 = Normal reaction 3 = Exaggerated reaction | Touch response 1 = No reaction 2 = Animal slowly turned, walked away 3 = More energetic response than (2) 4 = Freezes, actual muscle contraction 5 = Bizarre reaction | Pupil response 1 = No pupil response 2 = Pupil response present | Response to Nociceptive stimuli 1 = No reaction 2 = Animal turned or walked away 3 = More energetic response than (2) 4 = Freezes, actual muscle contraction 5 = Bizarre reaction | Righting reflex | |
| | | Repetitive circling 1 = Absent 2 = Present | Excessive Grooming (counts) | | | | | 1 = Present, 2 = Slow, 3 = Absent | On back Dropped |
| | | | | | | | | | |
| G1 0 | Ri3931 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3932 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3933 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3934 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3935 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3936 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3937 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3938 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3939 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3940 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| G2 100 | Ri3941 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3942 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3943 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3944 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3945 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3946 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3947 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3948 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3949 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3950 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |

APPENDIX 3 contd. Functional Observation Battery - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Open field observations contd. | | Sensory observations | | | | | |
|---|------------|--------------------------------|-----------------------|---|--|---|---|----------------------------|----------------------|
| | | Stereotypies | | Startle response | Touch response | Pupil response | Response to Nociceptive stimuli | Righting reflex | |
| | | Repetitive circling | Excessive Grooming | 1 = No reaction 2 = Normal reaction 3 = Exaggerated reaction | 1 = No reaction 2 = Animal slowly turned, walked away 3 = More energetic response than (2) 4 = Freezes, actual muscle contraction 5 = Bizarre reaction | 1 = No pupil response 2 = Pupil response present | 1 = No reaction 2 = Animal turned or walked away 3 = More energetic response than (2) 4 = Freezes, actual muscle contraction 5 = Bizarre reaction | 1 = Present, 3 = Absent | 2 = Slow, Dropped |
| | | 1 = Absent 2 = Present | (counts) | | | | | On back | |
| G3 300 | Ri3951 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3952 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3953 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3954 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3955 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3956 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3957 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3958 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3959 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3960 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| G4 1000 | Ri3961 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3962 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3963 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3964 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3965 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3966 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3967 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3968 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3969 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3970 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |

APPENDIX 3 contd. Functional Observation Battery - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Neuromuscular observations | | | | | | | | | | | | | | Physiological observation Body Temperature (°C) | |
|--|------------|----------------------------|-------|-------|-------|------------|-------|-------|-------|---------------------------|-----|-----|-----|----------------------|----------|---|------|
| | | Grip strength (kg) | | | | | | | | | | | | | | | |
| | | Fore limbs | | | | Hind limbs | | | | Hind limb foot splay (cm) | | | | Motor activity score | | | |
| | | R1 | R2 | R3 | Avg | R1 | R2 | R3 | Avg | R1 | R2 | R3 | Avg | Horizontal | Vertical | Total | |
| G1 0 | Ri3931 | 0.947 | 0.966 | 1.001 | 0.971 | 0.445 | 0.472 | 0.456 | 0.458 | 7.3 | 7.0 | 7.6 | 7.3 | 750 | 522 | 1272 | 36.8 |
| | Ri3932 | 0.968 | 1.018 | 0.989 | 0.992 | 0.569 | 0.406 | 0.570 | 0.515 | 6.5 | 8.0 | 7.3 | 7.3 | 1246 | 966 | 2212 | 37.1 |
| | Ri3933 | 1.078 | 0.966 | 0.948 | 0.997 | 0.530 | 0.551 | 0.569 | 0.550 | 7.5 | 6.8 | 7.6 | 7.3 | 775 | 707 | 1482 | 36.3 |
| | Ri3934 | 1.038 | 1.049 | 0.989 | 1.025 | 0.604 | 0.637 | 0.618 | 0.620 | 7.4 | 7.3 | 8.0 | 7.6 | 785 | 639 | 1424 | 36.8 |
| | Ri3935 | 0.977 | 1.001 | 1.005 | 0.994 | 0.468 | 0.571 | 0.580 | 0.540 | 7.2 | 7.2 | 8.0 | 7.5 | 632 | 555 | 1187 | 37.5 |
| | Ri3936 | 1.010 | 1.009 | 0.999 | 1.006 | 0.478 | 0.506 | 0.508 | 0.497 | 7.1 | 7.2 | 7.1 | 7.1 | 771 | 727 | 1498 | 37.2 |
| | Ri3937 | 1.044 | 1.001 | 0.948 | 0.998 | 0.514 | 0.549 | 0.472 | 0.512 | 7.0 | 6.9 | 7.3 | 7.1 | 941 | 836 | 1777 | 37.4 |
| | Ri3938 | 1.009 | 0.984 | 1.016 | 1.003 | 0.603 | 0.460 | 0.480 | 0.514 | 7.1 | 7.8 | 6.3 | 7.1 | 1422 | 862 | 2284 | 37.5 |
| | Ri3939 | 0.894 | 1.008 | 1.039 | 0.980 | 0.483 | 0.639 | 0.524 | 0.549 | 6.2 | 7.5 | 6.8 | 6.8 | 1119 | 720 | 1839 | 37.8 |
| | Ri3940 | 0.937 | 0.926 | 0.918 | 0.927 | 0.649 | 0.526 | 0.676 | 0.617 | 7.4 | 7.8 | 7.5 | 7.6 | 1263 | 937 | 2200 | 36.5 |
| G2 100 | Ri3941 | 0.898 | 0.888 | 1.008 | 0.931 | 0.662 | 0.629 | 0.455 | 0.582 | 7.4 | 7.3 | 8.0 | 7.6 | 795 | 540 | 1335 | 37.2 |
| | Ri3942 | 0.934 | 0.924 | 0.959 | 0.939 | 0.611 | 0.658 | 0.530 | 0.600 | 6.5 | 7.2 | 7.3 | 7.0 | 950 | 671 | 1621 | 36.9 |
| | Ri3943 | 0.972 | 0.837 | 0.995 | 0.935 | 0.444 | 0.599 | 0.428 | 0.490 | 7.8 | 7.4 | 7.6 | 7.6 | 1160 | 955 | 2115 | 37.0 |
| | Ri3944 | 1.006 | 1.009 | 1.020 | 1.012 | 0.585 | 0.606 | 0.601 | 0.597 | 7.3 | 8.1 | 6.5 | 7.3 | 854 | 661 | 1515 | 37.4 |
| | Ri3945 | 1.010 | 1.019 | 1.020 | 1.016 | 0.421 | 0.621 | 0.594 | 0.545 | 6.3 | 6.8 | 7.9 | 7.0 | 1123 | 979 | 2102 | 37.6 |
| | Ri3946 | 1.035 | 1.039 | 1.032 | 1.035 | 0.550 | 0.570 | 0.420 | 0.513 | 7.9 | 8.0 | 7.2 | 7.7 | 599 | 470 | 1069 | 37.4 |
| | Ri3947 | 0.996 | 1.035 | 1.030 | 1.020 | 0.513 | 0.623 | 0.471 | 0.536 | 7.1 | 7.3 | 7.4 | 7.3 | 1409 | 1021 | 2430 | 36.4 |
| | Ri3948 | 1.011 | 0.988 | 1.006 | 1.002 | 0.511 | 0.596 | 0.527 | 0.545 | 7.5 | 7.4 | 7.6 | 7.5 | 959 | 770 | 1729 | 36.8 |
| | Ri3949 | 1.001 | 1.020 | 0.998 | 1.006 | 0.611 | 0.420 | 0.426 | 0.486 | 7.0 | 7.4 | 7.2 | 7.2 | 1195 | 933 | 2128 | 37.3 |
| | Ri3950 | 0.918 | 0.937 | 0.896 | 0.917 | 0.568 | 0.690 | 0.598 | 0.619 | 7.5 | 7.4 | 7.5 | 7.5 | 1230 | 886 | 2116 | 37.5 |

R: Reading

APPENDIX 3 contd. Functional Observation Battery - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Neuromuscular observations | | | | | | | | | | | | Physiological observation | | | |
|--|------------|----------------------------|-------|-------|-------|------------|-------|-------|-------|---------------------------|-----|-----|-----|------------------------------|----------|-------|-----------------------------|
| | | Grip strength (kg) | | | | | | | | | | | | | | | |
| | | Fore limbs | | | | Hind limbs | | | | Hind limb foot splay (cm) | | | | Motor activity score | | | |
| | | R1 | R2 | R3 | Avg | R1 | R2 | R3 | Avg | R1 | R2 | R3 | Avg | Horizontal | Vertical | Total | Body Temperature (°C) |
| G3 300 | Ri3951 | 1.006 | 1.005 | 0.996 | 1.002 | 0.639 | 0.662 | 0.635 | 0.645 | 7.4 | 7.3 | 6.8 | 7.2 | 1228 | 1267 | 2495 | 37.4 |
| | Ri3952 | 0.950 | 1.030 | 0.994 | 0.991 | 0.536 | 0.578 | 0.568 | 0.561 | 6.5 | 7.0 | 7.5 | 7.0 | 1067 | 706 | 1773 | 37.4 |
| | Ri3953 | 1.015 | 1.005 | 0.998 | 1.006 | 0.620 | 0.592 | 0.473 | 0.562 | 7.5 | 7.8 | 6.5 | 7.3 | 1154 | 772 | 1926 | 37.5 |
| | Ri3954 | 1.026 | 0.819 | 0.821 | 0.923 | 0.571 | 0.574 | 0.587 | 0.577 | 6.8 | 7.4 | 7.3 | 7.2 | 1154 | 849 | 2003 | 37.4 |
| | Ri3955 | 1.006 | 0.936 | 0.898 | 0.947 | 0.496 | 0.673 | 0.496 | 0.555 | 7.5 | 7.2 | 7.4 | 7.4 | 1150 | 1146 | 2296 | 36.9 |
| | Ri3956 | 0.979 | 0.967 | 0.883 | 0.943 | 0.440 | 0.421 | 0.444 | 0.435 | 7.3 | 7.5 | 6.5 | 7.1 | 964 | 700 | 1664 | 36.8 |
| | Ri3957 | 0.988 | 1.008 | 1.010 | 1.002 | 0.486 | 0.550 | 0.600 | 0.545 | 7.1 | 7.3 | 7.4 | 7.3 | 1287 | 1061 | 2348 | 37.4 |
| | Ri3958 | 0.888 | 0.898 | 1.001 | 0.929 | 0.519 | 0.498 | 0.568 | 0.528 | 7.3 | 7.5 | 7.8 | 7.5 | 1216 | 844 | 2060 | 37.1 |
| | Ri3959 | 0.912 | 0.974 | 0.849 | 0.912 | 0.657 | 0.537 | 0.585 | 0.593 | 7.2 | 7.3 | 7.4 | 7.3 | 1080 | 1096 | 2176 | 37.5 |
| | Ri3960 | 1.004 | 0.966 | 0.944 | 0.971 | 0.561 | 0.584 | 0.472 | 0.539 | 7.5 | 7.1 | 7.8 | 7.5 | 1350 | 981 | 2331 | 37.4 |
| G4 1000 | Ri3961 | 1.006 | 0.849 | 0.989 | 0.948 | 0.628 | 0.588 | 0.461 | 0.559 | 6.8 | 7.0 | 7.2 | 7.0 | 1543 | 1092 | 2635 | 37.0 |
| | Ri3962 | 0.917 | 0.834 | 0.935 | 0.895 | 0.475 | 0.426 | 0.523 | 0.475 | 7.1 | 7.4 | 7.3 | 7.3 | 1241 | 877 | 2118 | 37.5 |
| | Ri3963 | 1.015 | 1.018 | 1.016 | 1.016 | 0.425 | 0.472 | 0.521 | 0.473 | 7.0 | 7.2 | 7.2 | 7.1 | 1115 | 764 | 1879 | 37.8 |
| | Ri3964 | 1.046 | 0.865 | 0.972 | 0.961 | 0.452 | 0.484 | 0.546 | 0.494 | 6.8 | 7.4 | 7.8 | 7.3 | 1043 | 897 | 1940 | 37.4 |
| | Ri3965 | 1.007 | 1.046 | 0.989 | 1.014 | 0.626 | 0.616 | 0.525 | 0.589 | 7.4 | 7.2 | 7.5 | 7.4 | 1080 | 812 | 1892 | 37.5 |
| | Ri3966 | 1.006 | 0.839 | 1.006 | 0.950 | 0.553 | 0.614 | 0.502 | 0.556 | 7.2 | 7.4 | 7.3 | 7.3 | 919 | 753 | 1672 | 37.6 |
| | Ri3967 | 0.958 | 1.016 | 0.993 | 0.989 | 0.466 | 0.483 | 0.526 | 0.492 | 7.5 | 7.3 | 7.4 | 7.4 | 955 | 996 | 1951 | 37.4 |
| | Ri3968 | 0.955 | 0.916 | 1.046 | 0.972 | 0.649 | 0.577 | 0.566 | 0.597 | 7.3 | 7.4 | 7.4 | 7.4 | 1178 | 831 | 2009 | 37.6 |
| | Ri3969 | 1.052 | 0.929 | 1.006 | 0.996 | 0.474 | 0.484 | 0.448 | 0.469 | 6.8 | 7.5 | 7.4 | 7.2 | 1149 | 837 | 1986 | 38.0 |
| | Ri3970 | 0.991 | 1.019 | 1.027 | 1.012 | 0.500 | 0.441 | 0.659 | 0.533 | 7.5 | 7.3 | 6.8 | 7.2 | 1286 | 1006 | 2292 | 37.8 |

R: Reading

APPENDIX 4. Functional Observation Battery - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Home cage observations | | | Handling observations | | | | | | |
|---|------------|--|--|--|---|--|---|---------------------------|---------------------------|---------------------------|--|
| | | Convulsions 1 = Absent 2 = Present | Tremors 1 = Absent 2 = Present | Palpebral closure 1 = Eyelids wide open 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut | Ease of removal from the cage 1 = Very easy 2 = Easy 3 = Moderately difficult 4 = Difficult 5 = Very difficult | Ease of handling animal in hand 1 = No resistance, animal is easy to handle 2 = Slight resistance 3 = Moderate resistance 4 = High resistance | Lacrimation 1 = None 2 = Slight 3 = Severe | Red deposits around | | | |
| | | | | | | | | Eyes | Nose | Mouth | |
| | | | | | | | | 1 = Absent 2 = Present | 1 = Absent 2 = Present | 1 = Absent 2 = Present | |
| G1 0 | Ri3971 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3972 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3973 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3974 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3975 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3976 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3977 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3978 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3979 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3980 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| G2 100 | Ri3981 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3982 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3983 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3984 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3985 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3986 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3987 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3988 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3989 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | Ri3990 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |

APPENDIX 4 contd. Functional Observation Battery - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Home cage observations | | | Handling observations | | | | | |
|---|------------|------------------------|-------------|--|---|---|--------------------------|---------------------------|---------------------------|---------------------------|
| | | Convulsions | Tremors | Palpebral closure | Ease of removal from the cage | Ease of handling animal in hand | Lacrimation | Red deposits around | | |
| | | 1 = Absent | 1 = Absent | 1 = Eyelids wide open | 1 = Very easy | 1 = No resistance, animal is easy | 1 = None | Eyes | Nose | Mouth |
| | | 2 = Present | 2 = Present | 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut | 2 = Easy 3 = Moderately difficult 4 = Difficult 5 = Very difficult | 2 = Slight resistance 3 = Moderate resistance 4 = High resistance | 2 = Slight 3 = Severe | 1 = Absent 2 = Present | 1 = Absent 2 = Present | 1 = Absent 2 = Present |
| G3 300 | Ri3991 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3992 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3993 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3994 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3995 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3996 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3997 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3998 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3999 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4000 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| G4 1000 | Ri4001 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4002 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4003 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4004 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4005 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4006 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4007 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4008 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4009 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4010 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

APPENDIX 4 contd. Functional Observation Battery - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Handling observations contd. | | | | | | | | | |
|---|------------|------------------------------|---------------------------|---------------------------|--------------------------|----------------------------------|--------------------------|--|--|--|---|
| | | Crusty Deposits around | | | Salivation | Fur Appearance | Piloerection | Palpebral closure | Respiratory character | Eye Prominence | Muscle tone |
| | | Eyes | Nose | Mouth | 1= Normal | 1= Normal 2 = Slightly soiled | 1 = None | 1 = Eyelids wide open 2 = Eyelids slightly drooping | 1 = Normal 2 = Rales | 1 = Normal 2 = Exophthalmus 3 = Enophthalmus | 1 = Muscle is firm but not hard(normal) 2 = muscle is soft & flabby 3 = Muscle is tense & hard |
| | | 1 = Absent 2 = Present | 1 = Absent 2 = Present | 1 = Absent 2 = Present | 2 = Slight 3 = Severe | 3 = Very soiled, crusty | 2 = Slight 3 = Severe | 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut | 3 = Retching 4 = Dyspnoeic 5 = Gasping | | |
| G1 0 | Ri3971 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3972 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3973 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3974 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3975 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3976 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3977 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3978 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3979 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3980 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| G2 100 | Ri3981 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3982 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3983 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3984 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3985 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3986 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3987 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3988 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3989 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3990 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

APPENDIX 4 contd. Functional Observation Battery - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Handling observations contd. | | | | | | | | | |
|---|------------|------------------------------|---------------------------|---------------------------|--------------------------|-----------------------------------|--------------------------|--|---|--|---|
| | | Crusty Deposits around | | | Salivation | Fur Appearance | Piloerection | Palpebral closure | Respiratory character | Eye Prominence | Muscle tone |
| | | Eyes | Nose | Mouth | 1 = Normal | 1 = Normal 2 = Slightly soiled | 1 = None | 1 = Eyelids wide open 2 = Eyelids slightly drooping | 1 = Normal 2 = Rales 3 = Retching 4 = Dyspnoeic 5 = Gasping | 1 = Normal 2 = Exophthalmus 3 = Enophthalmus | 1 = Muscle is firm but not hard(normal) 2 = muscle is soft & flabby 3 = Muscle is tense & hard |
| | | 1 = Absent 2 = Present | 1 = Absent 2 = Present | 1 = Absent 2 = Present | 2 = Slight 3 = Severe | 3 = Very soiled, crusty | 2 = Slight 3 = Severe | 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut | | | |
| G3 300 | Ri3991 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3992 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3993 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3994 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3995 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3996 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3997 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3998 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri3999 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4000 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| G4 1000 | Ri4001 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4002 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4003 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4004 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4005 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4006 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4007 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4008 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4009 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Ri4010 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

APPENDIX 4 contd. Functional Observation Battery - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Open field observations | | | | | | | | |
|--|------------|--|---------------------|---|--|--------------------------------------|--|---------------------|-----------------------|------------------------|
| | | Mobility 1 = Normal 2 = Moderately impaired 3 = Totally impaired locomotion impossible | Backing (counts) | Gait 1 = Normal 2 = Walks on tiptoes 3 = Body drags 4 = Hindlimbs splayed 5 = Hunched body 6 = Ataxia | Convulsions 1 = Absent 2 = Present | Tremors 1 = Absent 2 = Present | Arousal 1 = Very low 2 = Low 3 = Normal 4 = Moderately high 5 = Very high | Rearing (counts) | Urination (counts) | Defecation (counts) |
| G1 0 | Ri3971 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3972 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 0 |
| | Ri3973 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3974 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 0 | 1 |
| | Ri3975 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 0 |
| | Ri3976 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3977 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 0 |
| | Ri3978 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3979 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 1 |
| | Ri3980 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 0 |
| G2 100 | Ri3981 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 0 |
| | Ri3982 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3983 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 0 | 1 |
| | Ri3984 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 0 |
| | Ri3985 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3986 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 0 |
| | Ri3987 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3988 | 1 | 0 | 1 | 1 | 1 | 3 | 5 | 1 | 1 |
| | Ri3989 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 1 |
| | Ri3990 | 1 | 0 | 1 | 1 | 1 | 3 | 5 | 0 | 0 |

APPENDIX 4 contd. Functional Observation Battery - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Open field observations | | | | | | | | |
|--|------------|--|---------------------|---|--|--------------------------------------|--|---------------------|-----------------------|------------------------|
| | | Mobility 1 = Normal 2 = Moderately impaired 3 = Totally impaired locomotion impossible | Backing (counts) | Gait 1 = Normal 2 = Walks on tiptoes 3 = Body drags 4 = Hindlimbs splayed 5 = Hunched body 6 = Ataxia | Convulsions 1 = Absent 2 = Present | Tremors 1 = Absent 2 = Present | Arousal 1 = Very low 2 = Low 3 = Normal 4 = Moderately high 5 = Very high | Rearing (counts) | Urination (counts) | Defecation (counts) |
| G3 300 | Ri3991 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 0 |
| | Ri3992 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 1 |
| | Ri3993 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 2 | 0 |
| | Ri3994 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 2 | 0 |
| | Ri3995 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 0 |
| | Ri3996 | 1 | 0 | 1 | 1 | 1 | 3 | 5 | 1 | 1 |
| | Ri3997 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 0 | 1 |
| | Ri3998 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 0 | 0 |
| | Ri3999 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 0 |
| | Ri4000 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 0 |
| G4 1000 | Ri4001 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 1 |
| | Ri4002 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 2 | 0 |
| | Ri4003 | 1 | 0 | 1 | 1 | 1 | 3 | 5 | 2 | 1 |
| | Ri4004 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 2 | 1 |
| | Ri4005 | 1 | 0 | 1 | 1 | 1 | 3 | 2 | 0 | 0 |
| | Ri4006 | 1 | 0 | 1 | 1 | 1 | 3 | 5 | 0 | 1 |
| | Ri4007 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 1 | 0 |
| | Ri4008 | 1 | 0 | 1 | 1 | 1 | 3 | 4 | 0 | 1 |
| | Ri4009 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 1 | 0 |
| | Ri4010 | 1 | 0 | 1 | 1 | 1 | 3 | 3 | 0 | 0 |

APPENDIX 4 contd. Functional Observation Battery - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Open field observations contd. | | Sensory observations | | | | | |
|---|------------|--------------------------------|-----------------------------------|---|--|---|---|----------------------------|----------------------|
| | | Stereotypies | | Startle response | Touch response | Pupil response | Response to Nociceptive stimuli | Righting reflex | |
| | | Repetitive circling | Excessive Grooming (counts) | 1 = No reaction 2 = Normal reaction 3 = Exaggerated reaction | 1 = No reaction 2 = Animal slowly turned, walked away 3 = More energetic response than (2) 4 = Freezes, actual muscle contraction 5 = Bizarre reaction | 1 = No pupil response 2 = Pupil response present | 1 = No reaction 2 = Animal turned or walked away 3 = More energetic response than (2) 4 = Freezes, actual muscle contraction 5 = Bizarre reaction | 1 = Present, 3 = Absent | 2 = Slow, Dropped |
| | | 1 = Absent 2 = Present | | | | | | On back | |
| G1 0 | Ri3971 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3972 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3973 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3974 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3975 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3976 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3977 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3978 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3979 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3980 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| G2 100 | Ri3981 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3982 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3983 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3984 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3985 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3986 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3987 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3988 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3989 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |
| | Ri3990 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 |

APPENDIX 4 contd. Functional Observation Battery - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Open field observations contd. | | Sensory observations | | | | | | |
|---|------------|---|-----------------------------------|---|--|---|---|----------------------------|----------------------|--|
| | | Stereotypies | | Startle response | Touch response | Pupil response | Response to Nociceptive stimuli | Righting reflex | | |
| | | Repetitive circling 1 = Absent 2 = Present | Excessive Grooming (counts) | 1 = No reaction 2 = Normal reaction 3 = Exaggerated reaction | 1 = No reaction 2 = Animal slowly turned, walked away 3 = More energetic response than (2) 4 = Freezes, actual muscle contraction 5 = Bizarre reaction | 1 = No pupil response 2 = Pupil response present | 1 = No reaction 2 = Animal turned or walked away 3 = More energetic response than (2) 4 = Freezes, actual muscle contraction 5 = Bizarre reaction | 1 = Present, 3 = Absent | 2 = Slow, Dropped | |
| G3 300 | Ri3991 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri3992 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri3993 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri3994 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri3995 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri3996 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri3997 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri3998 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri3999 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri4000 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| G4 1000 | Ri4001 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri4002 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri4003 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri4004 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri4005 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri4006 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri4007 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri4008 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri4009 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |
| | Ri4010 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 1 | |

APPENDIX 4 contd. Functional Observation Battery - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Neuromuscular observations | | | | | | | | | | | | | | | Physiological observation Body Temperature (°C) |
|--|------------|----------------------------|-------|-------|-------|------------|-------|-------|-------|---------------------------|-----|-----|-----|----------------------|----------|-------|---|
| | | Grip strength (kg) | | | | | | | | | | | | | | | |
| | | Fore limbs | | | | Hind limbs | | | | Hind limb foot splay (cm) | | | | Motor activity score | | | |
| | | R1 | R2 | R3 | Avg | R1 | R2 | R3 | Avg | R1 | R2 | R3 | Avg | Horizontal | Vertical | Total | |
| G1 0 | Ri3971 | 1.010 | 0.933 | 1.008 | 0.984 | 0.566 | 0.492 | 0.591 | 0.550 | 6.2 | 5.3 | 5.8 | 5.8 | 863 | 663 | 1526 | 37.5 |
| | Ri3972 | 0.980 | 0.953 | 1.001 | 0.978 | 0.533 | 0.440 | 0.447 | 0.473 | 6.1 | 6.3 | 6.4 | 6.3 | 745 | 759 | 1504 | 37.8 |
| | Ri3973 | 0.833 | 0.940 | 1.007 | 0.927 | 0.406 | 0.527 | 0.463 | 0.465 | 4.9 | 5.8 | 5.8 | 5.5 | 1191 | 834 | 2025 | 37.6 |
| | Ri3974 | 0.981 | 0.992 | 1.001 | 0.991 | 0.656 | 0.646 | 0.541 | 0.614 | 5.0 | 6.2 | 6.3 | 5.8 | 482 | 668 | 1150 | 37.0 |
| | Ri3975 | 1.008 | 1.001 | 0.989 | 0.999 | 0.486 | 0.586 | 0.596 | 0.556 | 5.2 | 6.1 | 6.3 | 5.9 | 1170 | 821 | 1991 | 37.6 |
| | Ri3976 | 0.986 | 0.887 | 0.888 | 0.920 | 0.496 | 0.555 | 0.666 | 0.572 | 6.2 | 6.3 | 7.0 | 6.5 | 834 | 766 | 1600 | 36.9 |
| | Ri3977 | 0.998 | 1.006 | 0.972 | 0.992 | 0.472 | 0.502 | 0.453 | 0.476 | 6.5 | 6.3 | 5.9 | 6.2 | 1381 | 1127 | 2508 | 38.0 |
| | Ri3978 | 1.007 | 1.040 | 0.972 | 1.006 | 0.639 | 0.624 | 0.602 | 0.622 | 5.3 | 5.8 | 5.4 | 5.5 | 1068 | 759 | 1827 | 37.6 |
| | Ri3979 | 0.994 | 0.986 | 1.005 | 0.995 | 0.489 | 0.593 | 0.502 | 0.528 | 5.6 | 6.0 | 6.2 | 5.9 | 1045 | 752 | 1797 | 37.2 |
| | Ri3980 | 1.006 | 0.983 | 0.902 | 0.964 | 0.443 | 0.449 | 0.414 | 0.435 | 6.1 | 5.2 | 6.3 | 5.9 | 1177 | 947 | 2124 | 37.1 |
| G2 100 | Ri3981 | 0.884 | 0.886 | 0.936 | 0.902 | 0.572 | 0.566 | 0.628 | 0.589 | 6.2 | 6.5 | 5.0 | 5.9 | 1373 | 1150 | 2523 | 38.0 |
| | Ri3982 | 1.005 | 0.952 | 0.881 | 0.946 | 0.578 | 0.573 | 0.436 | 0.529 | 5.7 | 5.0 | 5.1 | 5.3 | 1265 | 1113 | 2378 | 38.1 |
| | Ri3983 | 0.968 | 0.944 | 0.969 | 0.960 | 0.436 | 0.456 | 0.469 | 0.454 | 6.0 | 6.2 | 6.0 | 6.1 | 1198 | 1055 | 2253 | 37.6 |
| | Ri3984 | 0.889 | 0.976 | 0.836 | 0.900 | 0.443 | 0.548 | 0.570 | 0.520 | 5.2 | 5.2 | 5.9 | 5.4 | 1030 | 1080 | 2110 | 37.1 |
| | Ri3985 | 0.851 | 0.998 | 1.017 | 0.955 | 0.417 | 0.487 | 0.546 | 0.483 | 6.1 | 6.3 | 6.4 | 6.3 | 1152 | 897 | 2049 | 37.2 |
| | Ri3986 | 0.940 | 0.909 | 0.911 | 0.920 | 0.618 | 0.586 | 0.494 | 0.566 | 6.2 | 6.5 | 6.2 | 6.3 | 945 | 1044 | 1989 | 37.5 |
| | Ri3987 | 0.996 | 0.909 | 1.001 | 0.969 | 0.446 | 0.601 | 0.498 | 0.515 | 7.0 | 5.2 | 5.8 | 6.0 | 1320 | 1003 | 2323 | 37.2 |
| | Ri3988 | 0.816 | 0.876 | 0.989 | 0.894 | 0.498 | 0.572 | 0.609 | 0.560 | 5.9 | 5.3 | 5.6 | 5.6 | 1222 | 987 | 2209 | 37.6 |
| | Ri3989 | 0.888 | 0.999 | 0.969 | 0.952 | 0.499 | 0.486 | 0.486 | 0.490 | 5.6 | 5.7 | 5.7 | 5.7 | 1138 | 827 | 1965 | 37.1 |
| | Ri3990 | 1.001 | 1.003 | 0.898 | 0.967 | 0.568 | 0.572 | 0.596 | 0.579 | 5.8 | 5.6 | 5.8 | 5.7 | 897 | 755 | 1652 | 38.0 |

R: Reading

APPENDIX 4 contd. Functional Observation Battery - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Neuromuscular observations | | | | | | | | | | | | Physiological observation Body Temperature (°C) | | | |
|--|------------|----------------------------|-------|-------|-------|------------|-------|-------|-------|---------------------------|-----|-----|-----|---|----------|-------|------|
| | | Grip strength (kg) | | | | | | | | | | | | | | | |
| | | Fore limbs | | | | Hind limbs | | | | Hind limb foot splay (cm) | | | | Motor activity score | | | |
| | | R1 | R2 | R3 | Avg | R1 | R2 | R3 | Avg | R1 | R2 | R3 | Avg | Horizontal | Vertical | Total | |
| G3 300 | Ri3991 | 0.981 | 0.851 | 0.986 | 0.939 | 0.447 | 0.484 | 0.616 | 0.516 | 6.2 | 6.3 | 6.5 | 6.3 | 991 | 1109 | 2100 | 37.5 |
| | Ri3992 | 0.830 | 0.860 | 0.910 | 0.867 | 0.401 | 0.458 | 0.396 | 0.418 | 6.5 | 6.2 | 6.3 | 6.3 | 1039 | 905 | 1944 | 38.0 |
| | Ri3993 | 0.900 | 0.882 | 0.902 | 0.895 | 0.507 | 0.470 | 0.416 | 0.464 | 5.0 | 5.2 | 5.4 | 5.2 | 1239 | 1315 | 2554 | 37.5 |
| | Ri3994 | 0.932 | 0.958 | 1.036 | 0.975 | 0.405 | 0.419 | 0.534 | 0.453 | 6.0 | 5.2 | 5.2 | 5.5 | 1650 | 1358 | 3008 | 37.6 |
| | Ri3995 | 0.904 | 0.896 | 0.851 | 0.884 | 0.456 | 0.447 | 0.406 | 0.436 | 6.1 | 6.2 | 5.8 | 6.0 | 1254 | 1048 | 2302 | 37.6 |
| | Ri3996 | 0.810 | 0.815 | 0.825 | 0.817 | 0.460 | 0.500 | 0.498 | 0.486 | 6.2 | 5.3 | 6.5 | 6.0 | 1222 | 1158 | 2380 | 37.2 |
| | Ri3997 | 0.986 | 1.015 | 0.999 | 1.000 | 0.425 | 0.600 | 0.586 | 0.537 | 6.1 | 5.2 | 5.1 | 5.5 | 1341 | 1061 | 2402 | 37.9 |
| | Ri3998 | 0.889 | 0.981 | 1.008 | 0.959 | 0.418 | 0.596 | 0.494 | 0.503 | 6.0 | 5.5 | 7.0 | 6.2 | 1188 | 843 | 2031 | 38.1 |
| | Ri3999 | 1.004 | 0.978 | 0.976 | 0.986 | 0.428 | 0.421 | 0.441 | 0.430 | 6.1 | 6.5 | 6.3 | 6.3 | 1264 | 829 | 2093 | 38.2 |
| | Ri4000 | 1.010 | 1.011 | 0.998 | 1.006 | 0.489 | 0.523 | 0.436 | 0.483 | 6.2 | 6.3 | 6.4 | 6.3 | 1266 | 1105 | 2371 | 37.0 |
| G4 1000 | Ri4001 | 0.901 | 0.832 | 0.926 | 0.886 | 0.534 | 0.515 | 0.571 | 0.540 | 6.4 | 6.5 | 6.0 | 6.3 | 1122 | 804 | 1926 | 37.4 |
| | Ri4002 | 1.018 | 1.017 | 0.823 | 0.953 | 0.466 | 0.478 | 0.457 | 0.467 | 7.0 | 6.5 | 6.5 | 6.7 | 1149 | 866 | 2015 | 38.6 |
| | Ri4003 | 0.908 | 0.937 | 0.912 | 0.919 | 0.519 | 0.443 | 0.490 | 0.484 | 6.2 | 6.3 | 6.4 | 6.3 | 1227 | 889 | 2116 | 37.4 |
| | Ri4004 | 0.983 | 0.961 | 1.010 | 0.985 | 0.421 | 0.463 | 0.425 | 0.436 | 7.0 | 6.3 | 6.2 | 6.5 | 975 | 705 | 1680 | 37.1 |
| | Ri4005 | 0.941 | 0.931 | 1.016 | 0.963 | 0.423 | 0.514 | 0.571 | 0.503 | 6.2 | 6.3 | 6.2 | 6.2 | 840 | 949 | 1789 | 37.4 |
| | Ri4006 | 0.955 | 0.877 | 0.875 | 0.902 | 0.473 | 0.468 | 0.451 | 0.464 | 6.2 | 6.3 | 6.4 | 6.3 | 1065 | 835 | 1900 | 37.5 |
| | Ri4007 | 1.020 | 0.824 | 0.801 | 0.882 | 0.545 | 0.512 | 0.517 | 0.525 | 6.2 | 6.2 | 6.3 | 6.2 | 1248 | 1088 | 2336 | 37.2 |
| | Ri4008 | 1.040 | 0.973 | 0.970 | 0.994 | 0.429 | 0.488 | 0.453 | 0.457 | 6.5 | 5.0 | 5.2 | 5.6 | 1739 | 1205 | 2944 | 37.5 |
| | Ri4009 | 0.963 | 0.810 | 0.898 | 0.890 | 0.539 | 0.555 | 0.458 | 0.517 | 5.3 | 5.6 | 5.5 | 5.5 | 1252 | 715 | 1967 | 36.9 |
| | Ri4010 | 1.049 | 0.895 | 0.941 | 0.962 | 0.588 | 0.601 | 0.508 | 0.566 | 6.0 | 5.5 | 5.8 | 5.8 | 1399 | 1030 | 2429 | 38.2 |

R: Reading

APPENDIX 5. Individual Body Weights (g) - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Weeks | | | | | | | | | | | | | |
|--|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | \$ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G1 0 | Ri3931 | 113.26 | 143.60 | 181.48 | 212.04 | 224.94 | 239.19 | 244.93 | 257.66 | 275.73 | 281.12 | 285.99 | 390.53 | 306.48 | 303.27 |
| | Ri3932 | 119.08 | 154.73 | 184.75 | 212.19 | 235.77 | 247.12 | 260.93 | 270.38 | 280.78 | 283.32 | 285.82 | 285.97 | 297.49 | 299.48 |
| | Ri3933 | 140.57 | 177.17 | 223.63 | 256.85 | 290.54 | 308.85 | 331.24 | 345.70 | 367.51 | 373.55 | 379.34 | 295.43 | 333.26 | 349.35 |
| | Ri3934 | 123.04 | 156.63 | 190.01 | 222.99 | 247.20 | 263.32 | 280.07 | 293.31 | 305.60 | 312.41 | 313.49 | 321.09 | 396.82 | 418.01 |
| | Ri3935 | 122.09 | 159.90 | 208.93 | 245.09 | 277.25 | 300.63 | 318.16 | 336.00 | 346.66 | 357.35 | 362.83 | 374.29 | 380.82 | 387.48 |
| | Ri3936 | 135.61 | 174.90 | 216.11 | 247.27 | 275.07 | 297.15 | 307.74 | 318.03 | 328.24 | 334.53 | 335.90 | 340.52 | 361.06 | 368.86 |
| | Ri3937 | 139.99 | 180.08 | 215.40 | 247.93 | 279.40 | 301.80 | 315.83 | 330.18 | 348.42 | 357.04 | 358.09 | 367.08 | 368.68 | 376.03 |
| | Ri3938 | 138.39 | 178.67 | 221.06 | 256.04 | 285.39 | 307.77 | 330.02 | 349.12 | 349.80 | 355.29 | 361.26 | 368.90 | 375.05 | 387.87 |
| | Ri3939 | 145.48 | 189.80 | 230.68 | 272.86 | 298.36 | 323.84 | 343.41 | 360.17 | 371.10 | 387.47 | 395.39 | 402.09 | 411.43 | 424.61 |
| | Ri3940 | 130.77 | 175.23 | 220.88 | 269.67 | 296.76 | 320.45 | 342.88 | 355.80 | 363.63 | 383.25 | 392.65 | 401.43 | 412.64 | 423.55 |
| G2 100 | Ri3941 | 117.31 | 185.95 | 231.28 | 255.41 | 276.40 | 298.77 | 318.31 | 323.12 | 335.95 | 346.87 | 356.33 | 361.76 | 369.46 | 380.75 |
| | Ri3942 | 131.38 | 167.21 | 210.17 | 240.36 | 258.07 | 282.88 | 298.83 | 314.66 | 327.49 | 332.00 | 337.18 | 343.14 | 353.39 | 360.45 |
| | Ri3943 | 131.61 | 168.86 | 207.76 | 234.54 | 257.56 | 278.59 | 290.74 | 307.37 | 321.60 | 330.01 | 333.20 | 337.99 | 346.17 | 354.70 |
| | Ri3944 | 136.32 | 175.30 | 213.96 | 251.73 | 285.39 | 297.59 | 323.53 | 338.56 | 349.70 | 357.86 | 365.49 | 371.54 | 374.18 | 382.73 |
| | Ri3945 | 131.45 | 153.23 | 189.37 | 222.44 | 250.06 | 266.22 | 278.16 | 291.85 | 306.22 | 318.81 | 331.48 | 337.04 | 344.24 | 346.54 |
| | Ri3946 | 117.50 | 192.97 | 235.94 | 271.97 | 294.11 | 318.57 | 337.45 | 355.01 | 367.57 | 379.54 | 386.89 | 384.30 | 391.06 | 395.85 |
| | Ri3947 | 147.62 | 150.12 | 184.51 | 207.42 | 229.53 | 241.02 | 256.26 | 270.78 | 283.25 | 291.80 | 298.23 | 306.84 | 333.62 | 334.02 |
| | Ri3948 | 118.60 | 176.62 | 220.13 | 255.53 | 281.03 | 300.25 | 310.55 | 322.56 | 329.53 | 344.29 | 345.00 | 336.30 | 329.39 | 346.98 |
| | Ri3949 | 135.39 | 179.39 | 213.89 | 240.88 | 258.71 | 278.12 | 294.81 | 306.35 | 320.61 | 326.02 | 329.28 | 327.78 | 311.61 | 338.95 |
| | Ri3950 | 143.50 | 165.17 | 202.38 | 227.44 | 238.34 | 259.41 | 280.17 | 295.42 | 306.52 | 313.48 | 322.31 | 321.73 | 339.30 | 340.57 |

\$: Initial

APPENDIX 5 contd. Individual Body Weights (g) - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Weeks | | | | | | | | | | | | | |
|--|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | \$ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G3 300 | Ri3951 | 128.92 | 163.91 | 202.38 | 230.40 | 263.20 | 297.03 | 321.63 | 346.16 | 360.56 | 380.99 | 386.43 | 404.61 | 408.95 | 416.82 |
| | Ri3952 | 120.34 | 157.35 | 204.37 | 240.01 | 257.65 | 281.15 | 294.56 | 311.99 | 323.37 | 332.27 | 333.16 | 341.74 | 351.55 | 356.91 |
| | Ri3953 | 148.53 | 190.29 | 238.43 | 279.37 | 300.64 | 331.53 | 317.99 | 375.26 | 388.72 | 400.56 | 404.57 | 410.34 | 420.59 | 421.08 |
| | Ri3954 | 143.19 | 177.47 | 223.41 | 250.23 | 276.02 | 297.21 | 357.94 | 334.20 | 340.57 | 356.10 | 368.00 | 371.83 | 384.00 | 390.81 |
| | Ri3955 | 136.56 | 176.90 | 221.92 | 255.24 | 272.07 | 303.69 | 328.89 | 343.65 | 356.82 | 369.62 | 390.57 | 395.43 | 405.88 | 412.53 |
| | Ri3956 | 132.65 | 170.52 | 208.27 | 242.56 | 258.09 | 276.08 | 292.57 | 309.05 | 328.97 | 336.10 | 346.76 | 351.44 | 359.07 | 365.61 |
| | Ri3957 | 136.65 | 175.38 | 215.75 | 246.76 | 269.76 | 294.14 | 311.19 | 325.22 | 334.85 | 349.86 | 348.35 | 349.95 | 360.29 | 362.48 |
| | Ri3958 | 120.16 | 151.91 | 188.93 | 195.41 | 229.77 | 249.44 | 259.41 | 268.13 | 274.55 | 290.25 | 287.49 | 292.60 | 295.94 | 298.42 |
| | Ri3959 | 144.88 | 181.63 | 228.69 | 264.01 | 291.62 | 309.52 | 328.34 | 338.50 | 348.17 | 362.05 | 370.77 | 376.78 | 388.47 | 391.55 |
| | Ri3960 | 132.53 | 173.50 | 189.04 | 223.23 | 247.61 | 267.98 | 283.26 | 302.38 | 315.21 | 329.28 | 336.05 | 339.63 | 345.33 | 351.29 |
| G4 1000 | Ri3961 | 118.41 | 161.17 | 199.51 | 234.43 | 262.12 | 279.45 | 299.86 | 313.21 | 326.12 | 332.90 | 340.66 | 342.42 | 350.48 | 355.54 |
| | Ri3962 | 132.64 | 171.52 | 213.47 | 235.94 | 258.88 | 277.81 | 288.39 | 307.92 | 316.71 | 326.11 | 343.52 | 348.27 | 350.84 | 355.35 |
| | Ri3963 | 137.67 | 175.68 | 216.27 | 244.34 | 266.23 | 290.95 | 303.98 | 321.33 | 328.80 | 337.73 | 343.43 | 351.35 | 349.43 | 356.72 |
| | Ri3964 | 147.14 | 189.26 | 228.17 | 256.69 | 283.65 | 294.43 | 313.20 | 325.72 | 330.81 | 334.76 | 341.91 | 319.78 | 342.22 | 351.44 |
| | Ri3965 | 132.69 | 166.61 | 203.38 | 236.17 | 262.10 | 282.46 | 298.09 | 313.36 | 318.08 | 329.12 | 333.55 | 340.52 | 348.15 | 356.62 |
| | Ri3966 | 127.39 | 163.78 | 195.95 | 225.63 | 246.41 | 264.79 | 276.97 | 288.48 | 297.79 | 306.63 | 308.16 | 314.59 | 319.78 | 324.03 |
| | Ri3967 | 132.70 | 161.04 | 220.04 | 246.46 | 272.11 | 289.21 | 313.95 | 332.74 | 342.66 | 354.35 | 364.68 | 373.87 | 380.06 | 381.73 |
| | Ri3968 | 145.58 | 184.88 | 232.54 | 259.95 | 289.67 | 310.01 | 331.41 | 351.75 | 365.54 | 381.88 | 388.21 | 391.06 | 398.71 | 404.79 |
| | Ri3969 | 130.60 | 168.19 | 208.67 | 246.68 | 274.34 | 292.02 | 309.55 | 325.85 | 341.06 | 355.90 | 358.41 | 359.01 | 371.86 | 372.27 |
| | Ri3970 | 141.44 | 177.68 | 213.32 | 242.03 | 260.94 | 280.56 | 299.49 | 304.14 | 306.57 | 322.67 | 332.23 | 332.06 | 334.54 | 334.25 |

APPENDIX 6. Individual Body Weights (g) - Females

| Group No. | Dose | Weeks | | | | | | | | | | | | | |
|---------------------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| (mg TOS/kg bwt/day) | Rat No. | \$ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G1 0 | Ri3971 | 110.20 | 130.91 | 144.98 | 163.95 | 174.50 | 183.71 | 187.00 | 197.85 | 204.44 | 203.79 | 206.85 | 212.47 | 214.91 | 216.59 |
| | Ri3972 | 110.85 | 130.88 | 149.01 | 164.39 | 173.35 | 190.70 | 204.74 | 213.54 | 211.91 | 223.10 | 229.05 | 227.77 | 233.84 | 240.66 |
| | Ri3973 | 108.89 | 125.91 | 142.83 | 157.05 | 167.17 | 173.70 | 180.25 | 191.22 | 192.27 | 197.66 | 200.49 | 202.77 | 206.26 | 208.61 |
| | Ri3974 | 105.34 | 125.53 | 138.28 | 154.96 | 172.15 | 177.79 | 187.05 | 194.29 | 199.68 | 201.36 | 199.76 | 209.86 | 219.38 | 226.64 |
| | Ri3975 | 114.01 | 140.04 | 154.00 | 167.23 | 176.14 | 187.37 | 194.57 | 198.82 | 200.80 | 206.79 | 209.36 | 211.90 | 213.16 | 217.83 |
| | Ri3976 | 107.84 | 133.97 | 151.06 | 166.59 | 184.69 | 183.54 | 191.81 | 195.53 | 206.76 | 210.56 | 213.21 | 212.13 | 221.12 | 219.15 |
| | Ri3977 | 101.48 | 117.98 | 138.94 | 149.76 | 162.00 | 171.78 | 179.60 | 187.68 | 188.00 | 187.86 | 191.94 | 197.22 | 198.91 | 199.71 |
| | Ri3978 | 104.76 | 120.71 | 135.55 | 149.55 | 163.37 | 170.82 | 180.44 | 191.74 | 198.03 | 203.09 | 206.99 | 210.19 | 215.41 | 222.47 |
| | Ri3979 | 107.26 | 127.96 | 144.16 | 161.34 | 174.31 | 179.07 | 184.02 | 190.19 | 198.77 | 200.68 | 203.75 | 208.61 | 213.80 | 218.80 |
| | Ri3980 | 116.73 | 142.83 | 161.38 | 180.41 | 189.93 | 204.94 | 206.78 | 217.12 | 217.67 | 225.93 | 224.09 | 231.73 | 228.35 | 235.74 |
| G2 100 | Ri3981 | 107.37 | 127.32 | 152.46 | 170.50 | 186.07 | 194.41 | 203.89 | 212.18 | 221.36 | 224.19 | 225.16 | 227.96 | 232.86 | 241.14 |
| | Ri3982 | 117.50 | 132.96 | 150.00 | 165.96 | 176.63 | 187.15 | 194.74 | 200.55 | 205.91 | 211.66 | 209.37 | 212.28 | 217.05 | 219.78 |
| | Ri3983 | 107.52 | 126.63 | 145.17 | 158.91 | 173.42 | 179.59 | 190.04 | 196.82 | 205.38 | 210.56 | 221.03 | 226.00 | 226.82 | 231.29 |
| | Ri3984 | 106.39 | 127.01 | 149.55 | 163.92 | 174.55 | 189.30 | 200.39 | 207.59 | 211.28 | 222.71 | 225.63 | 225.55 | 229.16 | 235.78 |
| | Ri3985 | 102.33 | 116.67 | 137.03 | 151.50 | 163.85 | 173.97 | 181.84 | 187.57 | 196.32 | 200.03 | 201.09 | 204.12 | 208.16 | 211.59 |
| | Ri3986 | 117.45 | 135.30 | 154.72 | 168.42 | 183.01 | 191.81 | 197.47 | 206.32 | 208.93 | 216.98 | 221.50 | 226.21 | 225.43 | 227.34 |
| | Ri3987 | 109.43 | 132.01 | 151.88 | 163.99 | 178.07 | 186.26 | 193.95 | 198.17 | 205.28 | 215.40 | 218.51 | 220.92 | 221.12 | 223.75 |
| | Ri3988 | 106.55 | 123.29 | 138.22 | 154.57 | 164.44 | 176.35 | 193.74 | 190.58 | 194.45 | 202.80 | 203.53 | 205.13 | 207.87 | 209.99 |
| | Ri3989 | 112.09 | 132.26 | 149.78 | 162.13 | 169.63 | 174.49 | 181.47 | 189.91 | 188.45 | 194.85 | 202.76 | 202.60 | 203.36 | 207.20 |
| | Ri3990 | 114.54 | 136.63 | 157.38 | 176.30 | 195.28 | 201.87 | 208.48 | 222.19 | 230.18 | 229.18 | 232.01 | 239.83 | 245.48 | 247.02 |

APPENDIX 6 contd. Individual Body Weights (g) - Females

| Group No. Dose (mg TOS/kg bwt/day)) | Rat No. | Weeks | | | | | | | | | | | | | |
|---|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | \$ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G3 300 | Ri3991 | 103.27 | 119.29 | 138.08 | 148.36 | 165.54 | 175.45 | 187.73 | 196.84 | 202.42 | 210.74 | 211.78 | 213.62 | 221.20 | 221.98 |
| | Ri3992 | 116.44 | 137.18 | 161.04 | 179.15 | 191.31 | 199.85 | 212.39 | 222.82 | 228.63 | 235.19 | 237.44 | 242.12 | 244.06 | 245.07 |
| | Ri3993 | 109.22 | 129.04 | 150.07 | 168.10 | 183.13 | 188.48 | 202.17 | 207.05 | 216.61 | 216.00 | 223.89 | 225.44 | 229.14 | 233.13 |
| | Ri3994 | 113.74 | 131.16 | 151.75 | 165.71 | 175.34 | 185.76 | 183.15 | 179.20 | 197.77 | 207.52 | 210.12 | 212.43 | 217.52 | 217.92 |
| | Ri3995 | 104.54 | 119.52 | 140.74 | 160.09 | 170.61 | 181.76 | 182.40 | 193.97 | 201.34 | 208.98 | 211.12 | 211.57 | 220.71 | 219.82 |
| | Ri3996 | 111.39 | 131.35 | 147.73 | 161.90 | 172.41 | 178.52 | 187.79 | 191.13 | 192.55 | 205.59 | 205.93 | 210.28 | 210.33 | 212.64 |
| | Ri3997 | 106.42 | 129.16 | 149.08 | 169.65 | 182.17 | 191.03 | 190.68 | 203.69 | 203.37 | 210.67 | 218.00 | 221.16 | 230.41 | 231.62 |
| | Ri3998 | 98.99 | 120.45 | 139.75 | 152.08 | 163.34 | 173.15 | 182.44 | 188.01 | 185.32 | 202.97 | 204.46 | 206.40 | 205.51 | 206.96 |
| | Ri3999 | 106.55 | 126.27 | 143.91 | 157.90 | 169.83 | 177.71 | 198.97 | 213.73 | 224.08 | 238.19 | 242.57 | 249.82 | 256.65 | 254.81 |
| | Ri4000 | 114.71 | 129.93 | 150.97 | 164.12 | 174.94 | 188.60 | 194.67 | 204.83 | 210.22 | 220.85 | 219.42 | 220.06 | 225.31 | 226.11 |
| G4 1000 | Ri4001 | 111.81 | 130.57 | 151.08 | 170.13 | 187.51 | 197.51 | 210.51 | 215.82 | 215.53 | 228.49 | 233.49 | 233.70 | 233.64 | 235.65 |
| | Ri4002 | 110.34 | 131.24 | 151.36 | 160.08 | 174.75 | 179.58 | 186.41 | 197.24 | 203.17 | 213.45 | 215.22 | 215.07 | 224.94 | 223.28 |
| | Ri4003 | 121.10 | 143.33 | 163.10 | 178.69 | 193.74 | 199.41 | 200.72 | 208.84 | 212.68 | 219.09 | 226.05 | 227.97 | 234.87 | 229.87 |
| | Ri4004 | 101.15 | 125.59 | 146.62 | 163.57 | 175.96 | 184.36 | 190.94 | 197.67 | 209.65 | 215.01 | 215.80 | 211.70 | 220.59 | 225.08 |
| | Ri4005 | 112.28 | 132.65 | 147.90 | 163.31 | 174.63 | 180.68 | 185.28 | 193.64 | 199.46 | 209.19 | 207.94 | 211.27 | 210.99 | 211.28 |
| | Ri4006 | 106.84 | 128.59 | 147.84 | 160.91 | 168.72 | 178.26 | 185.05 | 192.34 | 192.50 | 204.16 | 206.71 | 210.35 | 206.29 | 210.83 |
| | Ri4007 | 111.05 | 130.97 | 148.53 | 165.73 | 176.05 | 183.03 | 189.70 | 197.05 | 201.32 | 207.84 | 212.09 | 218.53 | 217.04 | 221.47 |
| | Ri4008 | 108.94 | 126.02 | 146.89 | 164.96 | 176.43 | 188.90 | 191.25 | 203.45 | 208.30 | 212.98 | 211.27 | 213.97 | 218.86 | 219.45 |
| | Ri4009 | 104.86 | 124.40 | 145.70 | 162.62 | 181.02 | 181.85 | 192.21 | 199.12 | 202.54 | 206.20 | 211.57 | 217.37 | 219.89 | 219.03 |
| | Ri4010 | 114.77 | 130.75 | 145.12 | 160.31 | 174.38 | 185.18 | 193.03 | 198.91 | 204.11 | 211.38 | 212.24 | 214.22 | 220.45 | 219.82 |

APPENDIX 7. Individual Cumulative Net Body Weight gains (g) - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Weeks | | | | | | | | | | | | |
|--|---------|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G1 0 | Ri3931 | 30.34 | 68.22 | 98.78 | 111.68 | 125.93 | 131.67 | 144.40 | 162.47 | 167.86 | 172.73 | 277.27 | 193.22 | 190.01 |
| | Ri3932 | 35.65 | 65.67 | 93.11 | 116.69 | 128.04 | 141.85 | 151.30 | 161.70 | 164.24 | 166.74 | 166.89 | 178.41 | 180.40 |
| | Ri3933 | 36.60 | 83.06 | 116.28 | 149.97 | 168.28 | 190.67 | 205.13 | 226.94 | 232.98 | 238.77 | 154.86 | 192.69 | 208.78 |
| | Ri3934 | 33.59 | 66.97 | 99.95 | 124.16 | 140.28 | 157.03 | 170.27 | 182.56 | 189.37 | 190.45 | 198.05 | 273.78 | 294.97 |
| | Ri3935 | 37.81 | 86.84 | 123.00 | 155.16 | 178.54 | 196.07 | 213.91 | 224.57 | 235.26 | 240.74 | 252.20 | 258.73 | 265.39 |
| | Ri3936 | 39.29 | 80.50 | 111.66 | 139.46 | 161.54 | 172.13 | 182.42 | 192.63 | 198.92 | 200.29 | 204.91 | 225.45 | 233.25 |
| | Ri3937 | 40.09 | 75.41 | 107.94 | 139.41 | 161.81 | 175.84 | 190.19 | 208.43 | 217.05 | 218.10 | 227.09 | 228.69 | 236.04 |
| | Ri3938 | 40.28 | 82.67 | 117.65 | 147.00 | 169.38 | 191.63 | 210.73 | 211.41 | 216.90 | 222.87 | 230.51 | 236.66 | 249.48 |
| | Ri3939 | 44.32 | 85.20 | 127.38 | 152.88 | 178.36 | 197.93 | 214.69 | 225.62 | 241.99 | 249.91 | 256.61 | 265.95 | 279.13 |
| | Ri3940 | 44.46 | 90.11 | 138.90 | 165.99 | 189.68 | 212.11 | 225.03 | 232.86 | 252.48 | 261.88 | 270.66 | 281.87 | 292.78 |
| G2 100 | Ri3941 | 68.64 | 113.97 | 138.10 | 159.09 | 181.46 | 201.00 | 205.81 | 218.64 | 229.56 | 239.02 | 244.45 | 252.15 | 263.44 |
| | Ri3942 | 35.83 | 78.79 | 108.98 | 126.69 | 151.50 | 167.45 | 183.28 | 196.11 | 200.62 | 205.80 | 211.76 | 222.01 | 229.07 |
| | Ri3943 | 37.25 | 76.15 | 102.93 | 125.95 | 146.98 | 159.13 | 175.76 | 189.99 | 198.40 | 201.59 | 206.38 | 214.56 | 223.09 |
| | Ri3944 | 38.98 | 77.64 | 115.41 | 149.07 | 161.27 | 187.21 | 202.24 | 213.38 | 221.54 | 229.17 | 235.22 | 237.86 | 246.41 |
| | Ri3945 | 21.78 | 57.92 | 90.99 | 118.61 | 134.77 | 146.71 | 160.40 | 174.77 | 187.36 | 200.03 | 205.59 | 212.79 | 215.09 |
| | Ri3946 | 75.47 | 118.44 | 154.47 | 176.61 | 201.07 | 219.95 | 237.51 | 250.07 | 262.04 | 269.39 | 266.80 | 273.56 | 278.35 |
| | Ri3947 | 2.50 | 36.89 | 59.80 | 81.91 | 93.40 | 108.64 | 123.16 | 135.63 | 144.18 | 150.61 | 159.22 | 186.00 | 186.40 |
| | Ri3948 | 58.02 | 101.53 | 136.93 | 162.43 | 181.65 | 191.95 | 203.96 | 210.93 | 225.69 | 226.40 | 217.70 | 210.79 | 228.38 |
| | Ri3949 | 44.00 | 78.50 | 105.49 | 123.32 | 142.73 | 159.42 | 170.96 | 185.22 | 190.63 | 193.89 | 192.39 | 176.22 | 203.56 |
| | Ri3950 | 21.67 | 58.88 | 83.94 | 94.84 | 115.91 | 136.67 | 151.92 | 163.02 | 169.98 | 178.81 | 178.23 | 195.80 | 197.07 |

APPENDIX 7 contd. Individual Cumulative Net Body Weight gains (g) - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Weeks | | | | | | | | | | | | |
|--|---------|-------|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G3 300 | Ri3951 | 34.99 | 73.46 | 101.48 | 134.28 | 168.11 | 192.71 | 217.24 | 231.64 | 252.07 | 257.51 | 275.69 | 280.03 | 287.90 |
| | Ri3952 | 37.01 | 84.03 | 119.67 | 137.31 | 160.81 | 174.22 | 191.65 | 203.03 | 211.93 | 212.82 | 221.40 | 231.21 | 236.57 |
| | Ri3953 | 41.76 | 89.90 | 130.84 | 152.11 | 183.00 | 169.46 | 226.73 | 240.19 | 252.03 | 256.04 | 261.81 | 272.06 | 272.55 |
| | Ri3954 | 34.28 | 80.22 | 107.04 | 132.83 | 154.02 | 214.75 | 191.01 | 197.38 | 212.91 | 224.81 | 228.64 | 240.81 | 247.62 |
| | Ri3955 | 40.34 | 85.36 | 118.68 | 135.51 | 167.13 | 192.33 | 207.09 | 220.26 | 233.06 | 254.01 | 258.87 | 269.32 | 275.97 |
| | Ri3956 | 37.87 | 75.62 | 109.91 | 125.44 | 143.43 | 159.92 | 176.40 | 196.32 | 203.45 | 214.11 | 218.79 | 226.42 | 232.96 |
| | Ri3957 | 38.73 | 79.10 | 110.11 | 133.11 | 157.49 | 174.54 | 188.57 | 198.20 | 213.21 | 211.70 | 213.30 | 223.64 | 225.83 |
| | Ri3958 | 31.75 | 68.77 | 75.25 | 109.61 | 129.28 | 139.25 | 147.97 | 154.39 | 170.09 | 167.33 | 172.44 | 175.78 | 178.26 |
| | Ri3959 | 36.75 | 83.81 | 119.13 | 146.74 | 164.64 | 183.46 | 193.62 | 203.29 | 217.17 | 225.89 | 231.90 | 243.59 | 246.67 |
| | Ri3960 | 40.97 | 56.51 | 90.70 | 115.08 | 135.45 | 150.73 | 169.85 | 182.68 | 196.75 | 203.52 | 207.10 | 212.80 | 218.76 |
| G4 1000 | Ri3961 | 42.76 | 81.10 | 116.02 | 143.71 | 161.04 | 181.45 | 194.80 | 207.71 | 214.49 | 222.25 | 224.01 | 232.07 | 237.13 |
| | Ri3962 | 38.88 | 80.83 | 103.30 | 126.24 | 145.17 | 155.75 | 175.28 | 184.07 | 193.47 | 210.88 | 215.63 | 218.20 | 222.71 |
| | Ri3963 | 38.01 | 78.60 | 106.67 | 128.56 | 153.28 | 166.31 | 183.66 | 191.13 | 200.06 | 205.76 | 213.68 | 211.76 | 219.05 |
| | Ri3964 | 42.12 | 81.03 | 109.55 | 136.51 | 147.29 | 166.06 | 178.58 | 183.67 | 187.62 | 194.77 | 172.64 | 195.08 | 204.30 |
| | Ri3965 | 33.92 | 70.69 | 103.48 | 129.41 | 149.77 | 165.40 | 180.67 | 185.39 | 196.43 | 200.86 | 207.83 | 215.46 | 223.93 |
| | Ri3966 | 36.39 | 68.56 | 98.24 | 119.02 | 137.40 | 149.58 | 161.09 | 170.40 | 179.24 | 180.77 | 187.20 | 192.39 | 196.64 |
| | Ri3967 | 28.34 | 87.34 | 113.76 | 139.41 | 156.51 | 181.25 | 200.04 | 209.96 | 221.65 | 231.98 | 241.17 | 247.36 | 249.03 |
| | Ri3968 | 39.30 | 86.96 | 114.37 | 144.09 | 164.43 | 185.83 | 206.17 | 219.96 | 236.30 | 242.63 | 245.48 | 253.13 | 259.21 |
| | Ri3969 | 37.59 | 78.07 | 116.08 | 143.74 | 161.42 | 178.95 | 195.25 | 210.46 | 225.30 | 227.81 | 228.41 | 241.26 | 241.67 |
| | Ri3970 | 36.24 | 71.88 | 100.59 | 119.50 | 139.12 | 158.05 | 162.70 | 165.13 | 181.23 | 190.79 | 190.62 | 193.10 | 192.81 |

APPENDIX 8. Individual Cumulative Net Body Weight gains (g) - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Weeks | | | | | | | | | | | | |
|--|---------|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G1 0 | Ri3971 | 20.71 | 34.78 | 53.75 | 64.30 | 73.51 | 76.80 | 87.65 | 94.24 | 93.59 | 96.65 | 102.27 | 104.71 | 106.39 |
| | Ri3972 | 20.03 | 38.16 | 53.54 | 62.50 | 79.85 | 93.89 | 102.69 | 101.06 | 112.25 | 118.20 | 116.92 | 122.99 | 129.81 |
| | Ri3973 | 17.02 | 33.94 | 48.16 | 58.28 | 64.81 | 71.36 | 82.33 | 83.38 | 88.77 | 91.60 | 93.88 | 97.37 | 99.72 |
| | Ri3974 | 20.19 | 32.94 | 49.62 | 66.81 | 72.45 | 81.71 | 88.95 | 94.34 | 96.02 | 94.42 | 104.52 | 114.04 | 121.30 |
| | Ri3975 | 26.03 | 39.99 | 53.22 | 62.13 | 73.36 | 80.56 | 84.81 | 86.79 | 92.78 | 95.35 | 97.89 | 99.15 | 103.82 |
| | Ri3976 | 26.13 | 43.22 | 58.75 | 76.85 | 75.70 | 83.97 | 87.69 | 98.92 | 102.72 | 105.37 | 104.29 | 113.28 | 111.31 |
| | Ri3977 | 16.50 | 37.46 | 48.28 | 60.52 | 70.30 | 78.12 | 86.20 | 86.52 | 86.38 | 90.46 | 95.74 | 97.43 | 98.23 |
| | Ri3978 | 15.95 | 30.79 | 44.79 | 58.61 | 66.06 | 75.68 | 86.98 | 93.27 | 98.33 | 102.23 | 105.43 | 110.65 | 117.71 |
| | Ri3979 | 20.70 | 36.90 | 54.08 | 67.05 | 71.81 | 76.76 | 82.93 | 91.51 | 93.42 | 96.49 | 101.35 | 106.54 | 111.54 |
| | Ri3980 | 26.10 | 44.65 | 63.68 | 73.20 | 88.21 | 90.05 | 100.39 | 100.94 | 109.20 | 107.36 | 115.00 | 111.62 | 119.01 |
| G2 100 | Ri3981 | 19.95 | 45.09 | 63.13 | 78.70 | 87.04 | 96.52 | 104.81 | 113.99 | 116.82 | 117.79 | 120.59 | 125.49 | 133.77 |
| | Ri3982 | 15.46 | 32.50 | 48.46 | 59.13 | 69.65 | 77.24 | 83.05 | 88.41 | 94.16 | 91.87 | 94.78 | 99.55 | 102.28 |
| | Ri3983 | 19.11 | 37.65 | 51.39 | 65.90 | 72.07 | 82.52 | 89.30 | 97.86 | 103.04 | 113.51 | 118.48 | 119.30 | 123.77 |
| | Ri3984 | 20.62 | 43.16 | 57.53 | 68.16 | 82.91 | 94.00 | 101.20 | 104.89 | 116.32 | 119.24 | 119.16 | 122.77 | 129.39 |
| | Ri3985 | 14.34 | 34.70 | 49.17 | 61.52 | 71.64 | 79.51 | 85.24 | 93.99 | 97.70 | 98.76 | 101.79 | 105.83 | 109.26 |
| | Ri3986 | 17.85 | 37.27 | 50.97 | 65.56 | 74.36 | 80.02 | 88.87 | 91.48 | 99.53 | 104.05 | 108.76 | 107.98 | 109.89 |
| | Ri3987 | 22.58 | 42.45 | 54.56 | 68.64 | 76.83 | 84.52 | 88.74 | 95.85 | 105.97 | 109.08 | 111.49 | 111.69 | 114.32 |
| | Ri3988 | 16.74 | 31.67 | 48.02 | 57.89 | 69.80 | 87.19 | 84.03 | 87.90 | 96.25 | 96.98 | 98.58 | 101.32 | 103.44 |
| | Ri3989 | 20.17 | 37.69 | 50.04 | 57.54 | 62.40 | 69.38 | 77.82 | 76.36 | 82.76 | 90.67 | 90.51 | 91.27 | 95.11 |
| | Ri3990 | 22.09 | 42.84 | 61.76 | 80.74 | 87.33 | 93.94 | 107.65 | 115.64 | 114.64 | 117.47 | 125.29 | 130.94 | 132.48 |

APPENDIX 8 contd. Individual Cumulative Net Body Weight gains (g) - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Weeks | | | | | | | | | | | | |
|--|---------|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| G3 300 | Ri3991 | 16.02 | 34.81 | 45.09 | 62.27 | 72.18 | 84.46 | 93.57 | 99.15 | 107.47 | 108.51 | 110.35 | 117.93 | 118.71 |
| | Ri3992 | 20.74 | 44.60 | 62.71 | 74.87 | 83.41 | 95.95 | 106.38 | 112.19 | 118.75 | 121.00 | 125.68 | 127.62 | 128.63 |
| | Ri3993 | 19.82 | 40.85 | 58.88 | 73.91 | 79.26 | 92.95 | 97.83 | 107.39 | 106.78 | 114.67 | 116.22 | 119.92 | 123.91 |
| | Ri3994 | 17.42 | 38.01 | 51.97 | 61.60 | 72.02 | 69.41 | 65.46 | 84.03 | 93.78 | 96.38 | 98.69 | 103.78 | 104.18 |
| | Ri3995 | 14.98 | 36.20 | 55.55 | 66.07 | 77.22 | 77.86 | 89.43 | 96.80 | 104.44 | 106.58 | 107.03 | 116.17 | 115.28 |
| | Ri3996 | 19.96 | 36.34 | 50.51 | 61.02 | 67.13 | 76.40 | 79.74 | 81.16 | 94.20 | 94.54 | 98.89 | 98.94 | 101.25 |
| | Ri3997 | 22.74 | 42.66 | 63.23 | 75.75 | 84.61 | 84.26 | 97.27 | 96.95 | 104.25 | 111.58 | 114.74 | 123.99 | 125.20 |
| | Ri3998 | 21.46 | 40.76 | 53.09 | 64.35 | 74.16 | 83.45 | 89.02 | 86.33 | 103.98 | 105.47 | 107.41 | 106.52 | 107.97 |
| | Ri3999 | 19.72 | 37.36 | 51.35 | 63.28 | 71.16 | 92.42 | 107.18 | 117.53 | 131.64 | 136.02 | 143.27 | 150.10 | 148.26 |
| | Ri4000 | 15.22 | 36.26 | 49.41 | 60.23 | 73.89 | 79.96 | 90.12 | 95.51 | 106.14 | 104.71 | 105.35 | 110.60 | 111.40 |
| G4 1000 | Ri4001 | 18.76 | 39.27 | 58.32 | 75.70 | 85.70 | 98.70 | 104.01 | 103.72 | 116.68 | 121.68 | 121.89 | 121.83 | 123.84 |
| | Ri4002 | 20.90 | 41.02 | 49.74 | 64.41 | 69.24 | 76.07 | 86.90 | 92.83 | 103.11 | 104.88 | 104.73 | 114.60 | 112.94 |
| | Ri4003 | 22.23 | 42.00 | 57.59 | 72.64 | 78.31 | 79.62 | 87.74 | 91.58 | 97.99 | 104.95 | 106.87 | 113.77 | 108.77 |
| | Ri4004 | 24.44 | 45.47 | 62.42 | 74.81 | 83.21 | 89.79 | 96.52 | 108.50 | 113.86 | 114.65 | 110.55 | 119.44 | 123.93 |
| | Ri4005 | 20.37 | 35.62 | 51.03 | 62.35 | 68.40 | 73.00 | 81.36 | 87.18 | 96.91 | 95.66 | 98.99 | 98.71 | 99.00 |
| | Ri4006 | 21.75 | 41.00 | 54.07 | 61.88 | 71.42 | 78.21 | 85.50 | 85.66 | 97.32 | 99.87 | 103.51 | 99.45 | 103.99 |
| | Ri4007 | 19.92 | 37.48 | 54.68 | 65.00 | 71.98 | 78.65 | 86.00 | 90.27 | 96.79 | 101.04 | 107.48 | 105.99 | 110.42 |
| | Ri4008 | 17.08 | 37.95 | 56.02 | 67.49 | 79.96 | 82.31 | 94.51 | 99.36 | 104.04 | 102.33 | 105.03 | 109.92 | 110.51 |
| | Ri4009 | 19.54 | 40.84 | 57.76 | 76.16 | 76.99 | 87.35 | 94.26 | 97.68 | 101.34 | 106.71 | 112.51 | 115.03 | 114.17 |
| | Ri4010 | 15.98 | 30.35 | 45.54 | 59.61 | 70.41 | 78.26 | 84.14 | 89.34 | 96.61 | 97.47 | 99.45 | 105.68 | 105.05 |

APPENDIX 9. Individual Food Intake (g/rat/day) - Males

| Group No. Dose (mg TOS/kg bwt/day) | | Weeks | | | | | | | | | | | | | |
|--|--------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Rat No. | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13* | |
| G1 0 | Ri3931 | Ri3932 | 16.62 | 18.84 | 20.89 | 20.49 | 21.90 | 20.30 | 19.23 | 18.85 | 18.92 | 18.04 | 19.39 | 19.18 | 14.35 |
| | Ri3933 | Ri3934 | 17.65 | 19.89 | 21.73 | 22.27 | 20.49 | 21.70 | 20.32 | 20.29 | 20.17 | 18.59 | 19.85 | 19.06 | 19.64 |
| | Ri3935 | Ri3936 | 17.25 | 20.54 | 22.37 | 22.27 | 22.04 | 21.82 | 20.78 | 20.49 | 20.91 | 20.15 | 20.63 | 21.75 | 20.49 |
| | Ri3937 | Ri3938 | 18.63 | 21.83 | 23.96 | 23.55 | 23.93 | 23.93 | 22.99 | 21.15 | 20.66 | 20.71 | 20.30 | 20.52 | 20.80 |
| | Ri3939 | Ri3940 | 19.88 | 22.23 | 25.20 | 25.40 | 24.71 | 24.56 | 23.54 | 22.79 | 24.07 | 22.74 | 22.46 | 22.35 | 23.43 |
| G2 100 | Ri3941 | Ri3942 | 17.98 | 20.61 | 22.02 | 19.99 | 21.31 | 21.06 | 19.92 | 18.06 | 19.40 | 17.69 | 18.61 | 19.06 | 20.34 |
| | Ri3943 | Ri3944 | 17.52 | 19.76 | 21.52 | 21.72 | 21.48 | 21.21 | 20.45 | 19.09 | 19.35 | 19.06 | 19.18 | 19.09 | 20.10 |
| | Ri3945 | Ri3946 | 17.87 | 20.45 | 19.42 | 22.77 | 23.29 | 22.89 | 21.33 | 19.95 | 20.93 | 19.98 | 20.07 | 19.09 | 20.15 |
| | Ri3947 | Ri3948 | 17.55 | 20.11 | 20.86 | 20.85 | 19.96 | 20.21 | 19.70 | 18.11 | 18.64 | 17.39 | 17.89 | 17.83 | 18.62 |
| | Ri3949 | Ri3950 | 17.66 | 19.78 | 20.63 | 19.16 | 20.37 | 20.81 | 20.14 | 20.57 | 19.53 | 18.39 | 18.81 | 17.15 | 18.80 |
| G3 300 | Ri3951 | Ri3952 | 17.27 | 20.62 | 20.56 | 22.85 | 24.36 | 23.92 | 23.01 | 23.38 | 22.17 | 20.09 | 22.44 | 22.07 | 21.81 |
| | Ri3953 | Ri3954 | 18.17 | 21.10 | 23.30 | 21.06 | 24.43 | 22.91 | 23.25 | 21.58 | 21.92 | 21.17 | 20.77 | 21.69 | 20.99 |
| | Ri3955 | Ri3956 | 18.79 | 20.87 | 22.02 | 19.92 | 22.58 | 22.92 | 22.86 | 22.71 | 21.06 | 21.47 | 21.95 | 22.34 | 22.46 |
| | Ri3957 | Ri3958 | 17.74 | 19.97 | 19.81 | 21.07 | 21.24 | 20.63 | 19.28 | 19.65 | 18.13 | 18.59 | 18.27 | 19.39 | 18.85 |
| | Ri3959 | Ri3960 | 18.63 | 18.08 | 21.69 | 21.82 | 21.52 | 20.21 | 19.89 | 19.66 | 20.07 | 19.77 | 20.31 | 20.70 | 19.27 |
| G4 1000 | Ri3961 | Ri3962 | 18.24 | 20.50 | 20.77 | 21.31 | 19.99 | 20.11 | 20.64 | 20.57 | 18.32 | 19.52 | 18.84 | 18.77 | 18.73 |
| | Ri3963 | Ri3964 | 18.22 | 20.38 | 22.05 | 20.80 | 20.23 | 20.59 | 20.09 | 23.72 | 17.73 | 17.60 | 15.82 | 17.99 | 20.11 |
| | Ri3965 | Ri3966 | 17.68 | 19.57 | 20.89 | 20.40 | 19.78 | 19.15 | 18.06 | 19.43 | 18.52 | 17.48 | 21.21 | 18.90 | 18.40 |
| | Ri3967 | Ri3968 | 17.59 | 20.91 | 22.93 | 23.08 | 19.18 | 21.82 | 22.69 | 21.78 | 21.60 | 20.91 | 18.37 | 20.51 | 21.36 |
| | Ri3969 | Ri3970 | 17.65 | 19.71 | 20.66 | 20.73 | 19.66 | 18.43 | 19.00 | 18.11 | 18.19 | 17.13 | 17.18 | 17.84 | 16.42 |

* : Calculated for 5 days

APPENDIX 10. Individual Food Intake (g/rat/day) - Females

| Group No. Dose (mg TOS/kg bwt/day) | | Weeks | | | | | | | | | | | | | |
|--|--------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Rat No. | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13* | |
| G1 0 | Ri3971 | Ri3972 | 13.71 | 13.81 | 15.17 | 15.58 | 15.73 | 16.18 | 15.79 | 15.76 | 16.86 | 15.54 | 15.83 | 18.10 | 16.03 |
| | Ri3973 | Ri3974 | 13.92 | 14.45 | 15.95 | 14.72 | 15.94 | 16.29 | 16.17 | 15.37 | 17.50 | 17.28 | 18.03 | 16.90 | 16.74 |
| | Ri3975 | Ri3976 | 14.77 | 14.22 | 15.02 | 15.29 | 15.49 | 15.67 | 13.62 | 13.98 | 15.05 | 14.43 | 14.69 | 14.98 | 14.61 |
| | Ri3977 | Ri3978 | 12.51 | 13.05 | 14.03 | 14.63 | 14.54 | 15.76 | 14.99 | 14.39 | 14.78 | 15.73 | 15.42 | 14.78 | 15.57 |
| | Ri3979 | Ri3980 | 13.94 | 13.93 | 15.49 | 15.54 | 16.16 | 15.43 | 15.15 | 14.36 | 15.25 | 14.72 | 15.05 | 15.15 | 15.48 |
| G2 100 | Ri3981 | Ri3982 | 12.91 | 15.10 | 15.70 | 15.64 | 15.94 | 15.64 | 14.82 | 15.72 | 14.72 | 14.72 | 15.29 | 14.73 | 15.45 |
| | Ri3983 | Ri3984 | 13.70 | 14.12 | 14.89 | 14.92 | 15.79 | 15.07 | 15.01 | 15.65 | 16.59 | 15.77 | 16.22 | 16.11 | 16.98 |
| | Ri3985 | Ri3986 | 13.90 | 14.31 | 15.34 | 14.64 | 15.34 | 14.08 | 14.66 | 14.91 | 14.96 | 14.80 | 15.39 | 14.63 | 15.58 |
| | Ri3987 | Ri3988 | 13.05 | 13.90 | 14.81 | 15.25 | 14.94 | 15.11 | 15.21 | 15.68 | 15.54 | 14.96 | 15.56 | 15.59 | 15.91 |
| | Ri3989 | Ri3990 | 13.55 | 14.19 | 14.97 | 15.41 | 14.97 | 14.46 | 14.67 | 15.19 | 15.04 | 14.45 | 15.37 | 15.07 | 15.10 |
| G3 300 | Ri3991 | Ri3992 | 13.72 | 14.57 | 15.31 | 15.83 | 15.82 | 15.90 | 16.02 | 14.34 | 15.75 | 14.67 | 15.65 | 15.77 | 14.60 |
| | Ri3993 | Ri3994 | 14.66 | 15.98 | 17.12 | 17.48 | 17.61 | 13.50 | 13.43 | 17.51 | 15.96 | 16.58 | 16.84 | 16.89 | 15.28 |
| | Ri3995 | Ri3996 | 12.87 | 13.53 | 14.51 | 14.19 | 14.53 | 13.46 | 13.73 | 13.90 | 14.28 | 13.73 | 13.70 | 13.96 | 13.91 |
| | Ri3997 | Ri3998 | 13.65 | 14.74 | 15.31 | 15.52 | 15.13 | 12.88 | 14.54 | 13.93 | 15.37 | 14.87 | 15.65 | 15.59 | 15.02 |
| | Ri3999 | Ri4000 | 13.41 | 14.27 | 15.13 | 14.95 | 12.71 | 14.68 | 15.47 | 15.84 | 15.52 | 15.21 | 15.89 | 15.76 | 14.64 |
| G4 1000 | Ri4001 | Ri4002 | 14.49 | 15.11 | 15.30 | 15.32 | 14.88 | 15.52 | 16.11 | 16.32 | 16.70 | 16.22 | 16.49 | 15.07 | 15.02 |
| | Ri4003 | Ri4004 | 14.97 | 16.15 | 19.73 | 21.87 | 18.20 | 15.20 | 15.49 | 17.17 | 17.00 | 16.17 | 16.41 | 16.93 | 14.81 |
| | Ri4005 | Ri4006 | 13.58 | 13.73 | 14.02 | 14.02 | 13.27 | 12.96 | 13.70 | 12.32 | 14.29 | 13.91 | 14.12 | 12.43 | 12.98 |
| | Ri4007 | Ri4008 | 13.63 | 14.81 | 16.12 | 15.95 | 18.75 | 18.96 | 24.94 | 15.78 | 15.13 | 15.05 | 16.38 | 16.91 | 16.92 |
| | Ri4009 | Ri4010 | 13.27 | 14.35 | 15.00 | 15.30 | 14.48 | 14.05 | 14.05 | 13.32 | 14.42 | 13.56 | 13.82 | 13.65 | 13.10 |

* : Calculated for 5 days

APPENDIX 11. Individual Haematological values - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | WBC G/l | RBC T/l | Hb g/l | Hct l/l | MCV f/l | MCH pg | MCHC g/l | Plat G/l | P.T. s | APTT s | Neut % | Lymp % | Mono % | Eosi % | Baso % |
|---|---------|------------|------------|-----------|------------|------------|-----------|-------------|-------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| G1 0 | Ri3931 | 5.11 | 8.93 | 157 | 0.460 | 51.5 | 17.5 | 340 | 1145 | 13.0 | 9.8 | 14.7 | 77.5 | 4.2 | 1.4 | 0.2 |
| | Ri3932 | 6.58 | 8.48 | 147 | 0.457 | 54.0 | 17.4 | 322 | 1107 | 13.7 | 8.4 | 15.9 | 79.8 | 2.7 | 0.7 | 0.1 |
| | Ri3933 | 4.32 | 9.01 | 152 | 0.448 | 49.8 | 16.8 | 338 | 1120 | 13.7 | 10.9 | 26.0 | 62.3 | 3.9 | 2.3 | 0.2 |
| | Ri3934 | 5.11 | 8.83 | 157 | 0.454 | 51.4 | 17.8 | 346 | 1153 | 13.9 | 10.6 | 14.2 | 80.1 | 3.0 | 1.1 | 0.2 |
| | Ri3935 | 9.77 | 8.95 | 154 | 0.474 | 53.0 | 17.2 | 325 | 1560 | 15.1 | 10.2 | 17.3 | 77.3 | 3.0 | 1.0 | 0.3 |
| | Ri3936 | 5.83 | 8.72 | 150 | 0.450 | 51.6 | 17.2 | 334 | 1246 | 16.7 | 9.8 | 12.5 | 82.8 | 2.4 | 1.3 | 0.2 |
| | Ri3937 | 4.44 | 8.58 | 153 | 0.473 | 55.1 | 17.9 | 324 | 1119 | 15.3 | 10.6 | 33.9 | 62.4 | 1.5 | 1.7 | 0.1 |
| | Ri3938 | 4.10 | 9.19 | 154 | 0.462 | 50.2 | 16.8 | 334 | 1260 | 16.3 | 10.2 | 16.9 | 77.8 | 2.7 | 1.3 | 0.2 |
| | Ri3939 | 5.46 | 9.01 | 164 | 0.466 | 51.7 | 18.2 | 351 | 988 | 14.1 | 9.9 | 44.0 | 46.4 | 2.4 | 6.2 | 0.2 |
| | Ri3940 | 8.79 | 8.87 | 149 | 0.476 | 53.7 | 16.8 | 313 | 1176 | 14.4 | 9.4 | 24.7 | 69.5 | 3.1 | 1.7 | 0.3 |
| G2 100 | Ri3941 | 2.23 | 8.43 | 149 | 0.447 | 53.0 | 17.6 | 333 | 1119 | 16.1 | 12.8 | 22.6 | 70.9 | 3.3 | 2.0 | 0.2 |
| | Ri3942 | 3.44 | 8.71 | 151 | 0.424 | 48.7 | 17.3 | 356 | 1016 | 16.9 | 10.6 | 26.6 | 69.1 | 1.8 | 1.9 | 0.3 |
| | Ri3943 | 3.97 | 8.67 | 158 | 0.445 | 51.3 | 18.3 | 356 | 1124 | 14.1 | 10.3 | 31.7 | 64.2 | 1.3 | 2.2 | 0.1 |
| | Ri3944 | 7.62 | 8.31 | 152 | 0.466 | 56.1 | 18.3 | 326 | 625 | 15.5 | 13.3 | 31.4 | 59.6 | 3.8 | 4.5 | 0.2 |
| | Ri3945 | 8.65 | 8.83 | 156 | 0.465 | 52.7 | 17.6 | 335 | 1194 | 13.3 | 11.5 | 19.9 | 75.4 | 1.8 | 1.9 | 0.1 |
| | Ri3946 | 4.11 | 8.82 | 153 | 0.444 | 50.3 | 17.3 | 345 | 1107 | 14.5 | 11.1 | 27.4 | 64.9 | 4.4 | 2.2 | 0.2 |
| | Ri3947 | 2.31 | 8.85 | 155 | 0.455 | 51.4 | 17.5 | 340 | 1056 | 15.1 | 10.7 | 27.0 | 65.7 | 3.9 | 2.5 | 0.2 |
| | Ri3948 | 5.86 | 8.62 | 154 | 0.449 | 52.1 | 17.9 | 344 | 1175 | 15.6 | 10.3 | 17.4 | 76.1 | 3.7 | 1.4 | 0.1 |
| | Ri3949 | 3.24 | 9.43 | 158 | 0.489 | 51.8 | 16.7 | 323 | 1028 | 15.2 | 11.3 | 18.3 | 75.5 | 3.1 | 1.9 | 0.2 |
| | Ri3950 | 2.20 | 8.96 | 153 | 0.444 | 49.5 | 17.1 | 345 | 1081 | 15.0 | 10.9 | 29.3 | 64.8 | 3.0 | 2.1 | 0.1 |

APPENDIX 11 contd. Individual Haematological values - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Neut G/l | Lymp G/l | Mono G/l | Eosi G/l | Baso G/l | Retic T/l | Retic % |
|--|---------|-------------|-------------|-------------|-------------|-------------|--------------|------------|
| G1 0 | Ri3931 | 0.75 | 3.96 | 0.21 | 0.07 | 0.01 | 0.203 | 2.28 |
| | Ri3932 | 1.05 | 5.25 | 0.18 | 0.04 | 0.01 | 0.205 | 2.42 |
| | Ri3933 | 1.12 | 2.69 | 0.17 | 0.10 | 0.01 | 0.235 | 2.61 |
| | Ri3934 | 0.73 | 4.09 | 0.15 | 0.06 | 0.01 | 0.196 | 2.22 |
| | Ri3935 | 1.69 | 7.55 | 0.29 | 0.10 | 0.03 | 0.231 | 2.58 |
| | Ri3936 | 0.73 | 4.83 | 0.14 | 0.08 | 0.01 | 0.290 | 3.32 |
| | Ri3937 | 1.50 | 2.77 | 0.07 | 0.07 | 0.00 | 0.275 | 3.20 |
| | Ri3938 | 0.69 | 3.19 | 0.11 | 0.05 | 0.01 | 0.234 | 2.55 |
| | Ri3939 | 2.40 | 2.53 | 0.13 | 0.34 | 0.01 | 0.220 | 2.44 |
| | Ri3940 | 2.17 | 6.11 | 0.28 | 0.15 | 0.03 | 0.244 | 2.75 |
| G2 100 | Ri3941 | 0.50 | 1.58 | 0.07 | 0.05 | 0.00 | 0.240 | 2.85 |
| | Ri3942 | 0.92 | 2.38 | 0.06 | 0.07 | 0.01 | 0.221 | 2.54 |
| | Ri3943 | 1.26 | 2.55 | 0.05 | 0.09 | 0.00 | 0.238 | 2.75 |
| | Ri3944 | 2.39 | 4.54 | 0.29 | 0.35 | 0.02 | 0.226 | 2.71 |
| | Ri3945 | 1.72 | 6.52 | 0.16 | 0.17 | 0.01 | 0.253 | 2.86 |
| | Ri3946 | 1.13 | 2.67 | 0.18 | 0.09 | 0.01 | 0.232 | 2.63 |
| | Ri3947 | 0.62 | 1.52 | 0.09 | 0.06 | 0.00 | 0.207 | 2.34 |
| | Ri3948 | 1.02 | 4.46 | 0.22 | 0.08 | 0.01 | 0.221 | 2.57 |
| | Ri3949 | 0.59 | 2.45 | 0.10 | 0.06 | 0.01 | 0.229 | 2.43 |
| | Ri3950 | 0.65 | 1.43 | 0.07 | 0.05 | 0.00 | 0.231 | 2.58 |

APPENDIX 11 contd. Individual Haematological values - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | WBC G/l | RBC T/l | Hb g/l | Hct l/l | MCV f/l | MCH pg | MCHC g/l | Plat G/l | P.T. s | APTT s | Neut % | Lymp % | Mono % | Eosi % | Baso % |
|---|---------|------------|------------|-----------|------------|------------|-----------|-------------|-------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| G3 300 | Ri3951 | 4.65 | 9.06 | 166 | 0.482 | 53.2 | 18.3 | 344 | 1151 | 18.1 | 10.0 | 21.9 | 72.7 | 2.7 | 1.8 | 0.2 |
| | Ri3952 | 3.91 | 8.84 | 163 | 0.460 | 52.0 | 18.4 | 354 | 1156 | 13.5 | 9.5 | 17.1 | 76.1 | 3.5 | 2.0 | 0.2 |
| | Ri3953 | 3.84 | 8.70 | 158 | 0.467 | 53.6 | 18.2 | 339 | 1231 | 12.5 | 15.2 | 29.9 | 64.0 | 2.8 | 2.7 | 0.2 |
| | Ri3954 | 5.22 | 9.42 | 159 | 0.471 | 50.1 | 16.8 | 337 | 1065 | 14.9 | 14.7 | 35.4 | 61.2 | 1.8 | 1.2 | 0.1 |
| | Ri3955 | 5.01 | 9.00 | 152 | 0.453 | 50.4 | 16.9 | 336 | 1016 | 16.4 | 14.4 | 35.0 | 61.8 | 1.5 | 1.0 | 0.1 |
| | Ri3956 | 4.42 | 9.87 | 155 | 0.500 | 50.6 | 15.7 | 311 | 1016 | 17.0 | 12.0 | 18.5 | 74.4 | 3.6 | 2.3 | 0.1 |
| | Ri3957 | 4.19 | 8.28 | 149 | 0.447 | 54.0 | 18.0 | 333 | 1032 | 16.6 | 12.2 | 19.7 | 75.9 | 2.4 | 1.3 | 0.0 |
| | Ri3958 | 4.39 | 9.69 | 155 | 0.488 | 50.4 | 16.0 | 319 | 1009 | 15.6 | 11.9 | 17.8 | 74.9 | 4.1 | 2.3 | 0.2 |
| | Ri3959 | 5.92 | 9.03 | 160 | 0.460 | 51.0 | 17.7 | 348 | 1139 | 14.4 | 11.5 | 27.9 | 66.6 | 2.6 | 2.1 | 0.1 |
| | Ri3960 | 7.41 | 8.36 | 148 | 0.447 | 53.5 | 17.7 | 331 | 1114 | 14.3 | 11.1 | 17.6 | 77.2 | 2.9 | 1.1 | 0.1 |
| G4 1000 | Ri3961 | 4.74 | 8.58 | 158 | 0.444 | 51.8 | 18.4 | 355 | 1194 | 18.2 | 9.8 | 22.2 | 73.8 | 2.5 | 0.9 | 0.1 |
| | Ri3962 | 3.90 | 8.98 | 163 | 0.484 | 53.9 | 18.1 | 336 | 1145 | 17.8 | 8.1 | 31.9 | 63.8 | 1.9 | 1.8 | 0.0 |
| | Ri3963 | 6.23 | 8.90 | 159 | 0.459 | 51.5 | 17.9 | 346 | 1109 | 14.6 | 10.6 | 11.6 | 83.7 | 2.8 | 0.9 | 0.0 |
| | Ri3964 | 4.88 | 8.43 | 154 | 0.439 | 52.1 | 18.3 | 351 | 1108 | 14.2 | 14.4 | 22.8 | 72.5 | 2.7 | 1.2 | 0.1 |
| | Ri3965 | 5.26 | 9.51 | 158 | 0.484 | 50.9 | 16.6 | 327 | 1080 | 13.6 | 8.4 | 23.8 | 67.9 | 4.7 | 3.2 | 0.1 |
| | Ri3966 | 5.10 | 8.79 | 149 | 0.442 | 50.3 | 16.9 | 336 | 977 | 13.2 | 10.1 | 39.4 | 55.2 | 3.1 | 1.3 | 0.1 |
| | Ri3967 | 6.03 | 9.24 | 156 | 0.472 | 51.1 | 16.9 | 331 | 1052 | 16.1 | 10.7 | 16.8 | 77.8 | 3.7 | 0.8 | 0.1 |
| | Ri3968 | 4.74 | 9.25 | 158 | 0.440 | 47.6 | 17.0 | 358 | 1238 | 16.4 | 10.5 | 23.6 | 70.1 | 2.4 | 3.0 | 0.2 |
| | Ri3969 | 4.17 | 8.79 | 156 | 0.466 | 53.0 | 17.8 | 336 | 1005 | 15.6 | 9.9 | 22.4 | 72.8 | 2.9 | 1.2 | 0.1 |
| | Ri3970 | 7.27 | 9.50 | 163 | 0.475 | 50.0 | 17.2 | 344 | 1126 | 15.1 | 10.7 | 14.8 | 78.5 | 4.6 | 1.3 | 0.1 |

APPENDIX 11 contd. Individual Haematological values - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Neut G/l | Lymp G/l | Mono G/l | Eosi G/l | Baso G/l | Retic T/l | Retic % |
|--|---------|-------------|-------------|-------------|-------------|-------------|--------------|------------|
| G3 300 | Ri3951 | 1.02 | 3.38 | 0.12 | 0.08 | 0.01 | 0.295 | 3.26 |
| | Ri3952 | 0.67 | 2.98 | 0.14 | 0.08 | 0.01 | 0.242 | 2.74 |
| | Ri3953 | 1.15 | 2.46 | 0.11 | 0.10 | 0.01 | 0.205 | 2.36 |
| | Ri3954 | 1.85 | 3.20 | 0.10 | 0.06 | 0.00 | 0.207 | 2.20 |
| | Ri3955 | 1.76 | 3.10 | 0.08 | 0.05 | 0.00 | 0.198 | 2.20 |
| | Ri3956 | 0.82 | 3.28 | 0.16 | 0.10 | 0.01 | 0.215 | 2.18 |
| | Ri3957 | 0.83 | 3.18 | 0.10 | 0.06 | 0.00 | 0.200 | 2.42 |
| | Ri3958 | 0.78 | 3.29 | 0.18 | 0.10 | 0.01 | 0.202 | 2.08 |
| | Ri3959 | 1.65 | 3.94 | 0.15 | 0.12 | 0.01 | 0.214 | 2.37 |
| | Ri3960 | 1.30 | 5.72 | 0.22 | 0.08 | 0.00 | 0.172 | 2.06 |
| G4 1000 | Ri3961 | 1.05 | 3.50 | 0.12 | 0.04 | 0.01 | 0.240 | 2.80 |
| | Ri3962 | 1.24 | 2.49 | 0.07 | 0.07 | 0.00 | 0.206 | 2.29 |
| | Ri3963 | 0.72 | 5.22 | 0.17 | 0.05 | 0.00 | 0.183 | 2.06 |
| | Ri3964 | 1.11 | 3.54 | 0.13 | 0.06 | 0.00 | 0.250 | 2.96 |
| | Ri3965 | 1.25 | 3.57 | 0.24 | 0.17 | 0.00 | 0.172 | 1.81 |
| | Ri3966 | 2.01 | 2.81 | 0.16 | 0.07 | 0.01 | 0.184 | 2.10 |
| | Ri3967 | 1.01 | 4.69 | 0.22 | 0.05 | 0.01 | 0.196 | 2.12 |
| | Ri3968 | 1.12 | 3.32 | 0.11 | 0.14 | 0.01 | 0.190 | 2.05 |
| | Ri3969 | 0.93 | 3.03 | 0.12 | 0.05 | 0.01 | 0.235 | 2.67 |
| | Ri3970 | 1.08 | 5.70 | 0.34 | 0.09 | 0.01 | 0.214 | 2.26 |

APPENDIX 12. Individual Haematological values - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | WBC G/l | RBC T/l | Hb g/l | Hct l/l | MCV f/l | MCH pg | MCHC g/l | Plat G/l | P.T. s | APTT s | Neut % | Lymp % | Mono % | Eosi % | Baso % |
|--|---------|------------|------------|-----------|------------|------------|-----------|-------------|-------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| G1 0 | Ri3971 | 6.39 | 7.90 | 153 | 0.433 | 54.8 | 19.3 | 353 | 1095 | 14.8 | 9.8 | 19.4 | 75.9 | 2.2 | 1.2 | 0.1 |
| | Ri3972 | 4.67 | 7.62 | 150 | 0.434 | 56.9 | 19.7 | 346 | 1265 | 14.0 | 9.7 | 20.1 | 74.9 | 2.7 | 1.4 | 0.1 |
| | Ri3973 | 2.68 | 8.30 | 144 | 0.434 | 52.2 | 17.4 | 332 | 1081 | 13.9 | 9.6 | 19.6 | 75.6 | 2.8 | 1.1 | 0.1 |
| | Ri3974 | 4.35 | 8.19 | 153 | 0.448 | 54.7 | 18.6 | 341 | 1034 | 14.1 | 10.6 | 13.9 | 82.8 | 2.0 | 0.7 | 0.2 |
| | Ri3975 | 2.53 | 8.28 | 148 | 0.450 | 54.3 | 17.9 | 329 | 1132 | 13.6 | 11.4 | 20.0 | 73.3 | 2.6 | 3.7 | 0.1 |
| | Ri3976 | 3.90 | 8.24 | 155 | 0.461 | 55.9 | 18.9 | 337 | 1059 | 13.4 | 10.7 | 19.6 | 75.2 | 2.9 | 1.4 | 0.1 |
| | Ri3977 | 2.44 | 7.48 | 139 | 0.426 | 56.9 | 18.5 | 326 | 1123 | 13.8 | 11.2 | 13.0 | 83.2 | 1.9 | 1.2 | 0.0 |
| | Ri3978 | 4.05 | 8.54 | 152 | 0.448 | 52.5 | 17.8 | 339 | 1151 | 13.3 | 10.5 | 18.0 | 76.3 | 3.2 | 1.2 | 0.0 |
| | Ri3979 | 6.25 | 8.30 | 157 | 0.448 | 54.0 | 18.9 | 351 | 1171 | 13.2 | 10.1 | 17.5 | 77.3 | 3.1 | 0.8 | 0.2 |
| | Ri3980 | 5.24 | 8.29 | 156 | 0.465 | 56.0 | 18.8 | 336 | 1159 | 13.4 | 9.8 | 16.7 | 74.3 | 5.6 | 2.3 | 0.1 |
| G2 100 | Ri3981 | 6.41 | 7.72 | 142 | 0.419 | 54.3 | 18.4 | 339 | 1337 | 17.2 | 9.2 | 20.6 | 74.7 | 3.0 | 0.8 | 0.2 |
| | Ri3982 | 8.68 | 8.07 | 149 | 0.446 | 55.2 | 18.5 | 335 | 1327 | 15.0 | 8.9 | 12.4 | 84.3 | 1.9 | 0.8 | 0.2 |
| | Ri3983 | 4.16 | 7.51 | 146 | 0.431 | 57.4 | 19.4 | 338 | 1339 | 17.9 | 15.0 | 18.4 | 77.5 | 2.1 | 1.4 | 0.0 |
| | Ri3984 | 6.25 | 8.26 | 153 | 0.451 | 54.7 | 18.5 | 338 | 1432 | 14.8 | 14.4 | 21.1 | 73.9 | 2.3 | 1.6 | 0.1 |
| | Ri3985 | 3.88 | 8.32 | 155 | 0.453 | 54.5 | 18.6 | 341 | 1214 | 14.9 | 8.2 | 17.2 | 76.3 | 3.2 | 2.2 | 0.0 |
| | Ri3986 | 5.15 | 7.81 | 148 | 0.409 | 52.3 | 19.0 | 363 | 1165 | 13.1 | 9.4 | 16.7 | 75.8 | 4.7 | 1.4 | 0.1 |
| | Ri3987 | 4.11 | 8.23 | 156 | 0.460 | 55.9 | 18.9 | 338 | 1212 | 17.8 | 15.0 | 17.0 | 78.6 | 2.1 | 1.8 | 0.1 |
| | Ri3988 | 4.60 | 8.14 | 146 | 0.432 | 53.0 | 18.0 | 339 | 1234 | 15.3 | 12.0 | 15.6 | 80.9 | 1.8 | 1.1 | 0.1 |
| | Ri3989 | 4.21 | 8.32 | 159 | 0.464 | 55.8 | 19.2 | 343 | 1221 | 16.9 | 13.7 | 17.7 | 76.9 | 2.3 | 2.2 | 0.3 |
| | Ri3990 | 3.51 | 8.54 | 155 | 0.465 | 54.4 | 18.2 | 334 | 1075 | 16.4 | 13.3 | 28.2 | 65.0 | 3.9 | 2.0 | 0.0 |

APPENDIX 12 contd. Individual Haematological values - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Neut G/l | Lymp G/l | Mono G/l | Eosi G/l | Baso G/l | Retic T/l | Retic % |
|--|---------|-------------|-------------|-------------|-------------|-------------|--------------|------------|
| G1 0 | Ri3971 | 1.24 | 4.85 | 0.14 | 0.08 | 0.01 | 0.255 | 3.23 |
| | Ri3972 | 0.94 | 3.50 | 0.13 | 0.06 | 0.00 | 0.266 | 3.49 |
| | Ri3973 | 0.52 | 2.02 | 0.07 | 0.03 | 0.00 | 0.277 | 3.33 |
| | Ri3974 | 0.61 | 3.60 | 0.09 | 0.03 | 0.01 | 0.284 | 3.47 |
| | Ri3975 | 0.51 | 1.85 | 0.07 | 0.09 | 0.00 | 0.205 | 2.48 |
| | Ri3976 | 0.77 | 2.94 | 0.12 | 0.05 | 0.00 | 0.224 | 2.72 |
| | Ri3977 | 0.32 | 2.03 | 0.05 | 0.03 | 0.00 | 0.286 | 3.82 |
| | Ri3978 | 0.73 | 3.09 | 0.13 | 0.05 | 0.00 | 0.267 | 3.13 |
| | Ri3979 | 1.10 | 4.83 | 0.19 | 0.05 | 0.01 | 0.305 | 3.68 |
| | Ri3980 | 0.87 | 3.89 | 0.29 | 0.12 | 0.01 | 0.253 | 3.05 |
| G2 100 | Ri3981 | 1.32 | 4.79 | 0.19 | 0.05 | 0.01 | 0.277 | 3.59 |
| | Ri3982 | 1.07 | 7.32 | 0.16 | 0.07 | 0.01 | 0.237 | 2.93 |
| | Ri3983 | 0.76 | 3.22 | 0.09 | 0.06 | 0.00 | 0.240 | 3.20 |
| | Ri3984 | 1.32 | 4.62 | 0.15 | 0.10 | 0.01 | 0.216 | 2.62 |
| | Ri3985 | 0.67 | 2.96 | 0.12 | 0.09 | 0.00 | 0.243 | 2.92 |
| | Ri3986 | 0.86 | 3.90 | 0.24 | 0.07 | 0.00 | 0.216 | 2.77 |
| | Ri3987 | 0.70 | 3.23 | 0.08 | 0.08 | 0.00 | 0.207 | 2.51 |
| | Ri3988 | 0.72 | 3.72 | 0.08 | 0.05 | 0.00 | 0.224 | 2.76 |
| | Ri3989 | 0.74 | 3.24 | 0.10 | 0.09 | 0.01 | 0.205 | 2.46 |
| | Ri3990 | 0.99 | 2.28 | 0.14 | 0.07 | 0.00 | 0.262 | 3.06 |

APPENDIX 12 contd. Individual Haematological values - Females

| Group No. | Dose | | WBC | RBC | Hb | Hct | MCV | MCH | MCHC | Plat | P.T. | APTT | Neut | Lymp | Mono | Eosi | Baso |
|---------------------|---------|------|------|-----|-------|------|------|-----|------|------|------|------|------|------|------|------|------|
| (mg TOS/kg bwt/day) | Rat No. | G/l | T/l | g/l | l/l | f/l | pg | g/l | G/l | s | s | % | % | % | % | % | % |
| G3 300 | Ri3991 | 3.89 | 8.30 | 153 | 0.430 | 51.8 | 18.4 | 355 | 1068 | 14.7 | 15.5 | 27.3 | 67.4 | 2.6 | 1.3 | 0.3 | |
| | Ri3992 | 2.75 | 7.79 | 140 | 0.433 | 55.6 | 17.9 | 323 | 1125 | 13.7 | 12.3 | 20.7 | 74.5 | 2.4 | 1.8 | 0.0 | |
| | Ri3993 | 6.80 | 8.68 | 156 | 0.469 | 54.0 | 18.0 | 333 | 1164 | 16.8 | 12.3 | 16.6 | 78.9 | 2.6 | 0.8 | 0.2 | |
| | Ri3994 | 9.27 | 9.03 | 157 | 0.486 | 53.8 | 17.3 | 322 | 1215 | 12.3 | 11.1 | 24.5 | 69.5 | 3.4 | 1.5 | 0.2 | |
| | Ri3995 | 3.44 | 8.43 | 148 | 0.464 | 55.1 | 17.6 | 319 | 1173 | 12.9 | 8.3 | 29.0 | 64.7 | 2.6 | 2.3 | 0.2 | |
| | Ri3996 | 4.98 | 8.72 | 155 | 0.451 | 51.7 | 17.8 | 343 | 936 | 16.9 | 12.5 | 45.5 | 46.5 | 2.4 | 5.2 | 0.1 | |
| | Ri3997 | 3.64 | 8.32 | 153 | 0.439 | 52.7 | 18.4 | 349 | 1523 | 13.2 | 12.1 | 14.9 | 80.7 | 1.9 | 1.3 | 0.1 | |
| | Ri3998 | 4.17 | 8.01 | 156 | 0.455 | 56.8 | 19.5 | 344 | 1218 | 15.7 | 11.6 | 14.0 | 79.8 | 3.6 | 1.3 | 0.2 | |
| | Ri3999 | 3.12 | 7.96 | 146 | 0.436 | 54.8 | 18.4 | 336 | 744 | 15.4 | 12.7 | 26.5 | 62.0 | 1.8 | 9.0 | 0.2 | |
| | Ri4000 | 2.70 | 8.26 | 149 | 0.444 | 53.7 | 18.1 | 337 | 1421 | 13.5 | 12.2 | 22.7 | 72.6 | 1.7 | 2.3 | 0.2 | |
| G4 1000 | Ri4001 | 2.78 | 7.91 | 148 | 0.436 | 55.2 | 18.7 | 338 | 1224 | 16.5 | 11.8 | 19.4 | 74.8 | 3.2 | 1.5 | 0.3 | |
| | Ri4002 | 3.15 | 7.91 | 149 | 0.430 | 54.3 | 18.8 | 347 | 1257 | 13.7 | 11.4 | 26.3 | 67.5 | 2.1 | 3.7 | 0.2 | |
| | Ri4003 | 4.14 | 7.95 | 147 | 0.426 | 53.6 | 18.5 | 344 | 1378 | 13.4 | 15.8 | 22.6 | 73.2 | 1.7 | 1.7 | 0.2 | |
| | Ri4004 | 1.95 | 7.85 | 143 | 0.425 | 54.1 | 18.2 | 336 | 1127 | 16.7 | 15.3 | 20.6 | 73.4 | 2.6 | 2.4 | 0.1 | |
| | Ri4005 | 5.70 | 8.37 | 145 | 0.430 | 51.4 | 17.4 | 338 | 1197 | 16.3 | 14.9 | 23.0 | 72.4 | 2.5 | 1.0 | 0.2 | |
| | Ri4006 | 2.16 | 8.21 | 149 | 0.441 | 53.8 | 18.2 | 338 | 1167 | 15.8 | 14.4 | 19.7 | 75.0 | 2.8 | 1.3 | 0.2 | |
| | Ri4007 | 1.90 | 7.50 | 137 | 0.401 | 53.5 | 18.3 | 342 | 1188 | 17.5 | 10.5 | 31.2 | 63.8 | 3.0 | 0.5 | 0.0 | |
| | Ri4008 | 3.33 | 7.82 | 143 | 0.424 | 54.3 | 18.3 | 337 | 1267 | 15.5 | 10.1 | 38.2 | 55.1 | 3.4 | 2.4 | 0.1 | |
| | Ri4009 | 8.78 | 8.82 | 161 | 0.468 | 53.1 | 18.2 | 343 | 1232 | 13.0 | 9.6 | 20.3 | 75.3 | 2.0 | 1.4 | 0.2 | |
| | Ri4010 | 6.37 | 9.00 | 152 | 0.451 | 50.1 | 16.9 | 336 | 1106 | 13.4 | 9.2 | 23.5 | 69.1 | 3.8 | 2.9 | 0.1 | |

APPENDIX 12 contd. Individual Haematological values - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Neut G/l | Lymp G/l | Mono G/l | Eosi G/l | Baso G/l | Retic T/l | Retic % |
|--|---------|-------------|-------------|-------------|-------------|-------------|--------------|------------|
| G3 300 | Ri3991 | 1.06 | 2.62 | 0.10 | 0.05 | 0.01 | 0.249 | 3.00 |
| | Ri3992 | 0.57 | 2.05 | 0.07 | 0.05 | 0.00 | 0.280 | 3.59 |
| | Ri3993 | 1.13 | 5.36 | 0.18 | 0.05 | 0.01 | 0.209 | 2.41 |
| | Ri3994 | 2.27 | 6.44 | 0.31 | 0.14 | 0.02 | 0.244 | 2.71 |
| | Ri3995 | 1.00 | 2.23 | 0.09 | 0.08 | 0.01 | 0.305 | 3.62 |
| | Ri3996 | 2.27 | 2.32 | 0.12 | 0.26 | 0.00 | 0.223 | 2.56 |
| | Ri3997 | 0.54 | 2.94 | 0.07 | 0.05 | 0.00 | 0.289 | 3.48 |
| | Ri3998 | 0.58 | 3.33 | 0.15 | 0.06 | 0.01 | 0.237 | 2.96 |
| | Ri3999 | 0.83 | 1.94 | 0.06 | 0.28 | 0.00 | 0.238 | 2.99 |
| | Ri4000 | 0.61 | 1.96 | 0.05 | 0.06 | 0.00 | 0.232 | 2.81 |
| G4 1000 | Ri4001 | 0.54 | 2.08 | 0.09 | 0.04 | 0.01 | 0.242 | 3.07 |
| | Ri4002 | 0.83 | 2.13 | 0.06 | 0.12 | 0.00 | 0.281 | 3.56 |
| | Ri4003 | 0.94 | 3.03 | 0.07 | 0.07 | 0.01 | 0.272 | 3.43 |
| | Ri4004 | 0.40 | 1.43 | 0.05 | 0.05 | 0.00 | 0.261 | 3.33 |
| | Ri4005 | 1.31 | 4.13 | 0.14 | 0.06 | 0.01 | 0.270 | 3.22 |
| | Ri4006 | 0.43 | 1.62 | 0.06 | 0.03 | 0.00 | 0.270 | 3.29 |
| | Ri4007 | 0.59 | 1.21 | 0.06 | 0.01 | 0.00 | 0.302 | 4.02 |
| | Ri4008 | 1.27 | 1.83 | 0.11 | 0.08 | 0.00 | 0.264 | 3.38 |
| | Ri4009 | 1.78 | 6.61 | 0.18 | 0.12 | 0.02 | 0.272 | 3.09 |
| | Ri4010 | 1.50 | 4.40 | 0.24 | 0.18 | 0.01 | 0.283 | 3.15 |

APPENDIX 13. Individual Clinical Chemistry Values - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Glu mmol/l | BUN mmol/l | T.Pro g/l | AST U/l | ALT U/l | ALP U/l | GGT* U/l | T.Bil* μmol/l | Creat μmol/l | Alb g/l | Glob g/l | A/G | Pi mmol/l | Ca mmol/l | T.Chol mmol/l | Na mEq/l | K mEq/l | Cl mEq/l |
|---|---------|---------------|---------------|--------------|------------|------------|------------|-------------|------------------|-----------------|------------|-------------|------|--------------|--------------|------------------|-------------|------------|-------------|
| G1 0 | Ri3931 | 7.84 | 6.74 | 64.6 | 71 | 28 | 77 | 0 | 3.14 | 37 | 42.5 | 22.1 | 1.92 | 2.29 | 2.49 | 1.21 | 135.7 | 3.69 | 94.3 |
| | Ri3932 | 8.53 | 7.15 | 62.7 | 79 | 40 | 96 | 0 | 2.26 | 30 | 42.8 | 19.9 | 2.15 | 2.12 | 2.58 | 1.60 | 134.0 | 3.29 | 95.7 |
| | Ri3933 | 7.94 | 5.00 | 63.4 | 67 | 30 | 49 | 0 | 3.60 | 46 | 42.9 | 20.5 | 2.09 | 2.12 | 2.78 | 1.83 | 135.1 | 3.63 | 94.0 |
| | Ri3934 | 11.21 | 7.04 | 65.9 | 111 | 48 | 71 | 0 | 2.67 | 51 | 42.3 | 23.6 | 1.79 | 1.68 | 2.67 | 1.25 | 134.5 | 3.64 | 93.4 |
| | Ri3935 | 7.62 | 6.68 | 69.6 | 79 | 38 | 77 | 0 | 2.16 | 45 | 40.4 | 29.2 | 1.38 | 2.45 | 2.73 | 1.38 | 133.9 | 4.47 | 92.2 |
| | Ri3936 | 7.37 | 5.56 | 61.0 | 79 | 38 | 61 | 0 | 1.92 | 45 | 39.2 | 21.8 | 1.80 | 1.95 | 2.53 | 1.25 | 135.4 | 3.88 | 96.9 |
| | Ri3937 | 8.68 | 7.17 | 67.0 | 78 | 36 | 73 | 0 | 1.74 | 40 | 42.5 | 24.5 | 1.73 | 2.04 | 2.59 | 1.37 | 136.0 | 4.51 | 95.6 |
| | Ri3938 | 8.53 | 5.27 | 65.6 | 65 | 25 | 79 | 0 | 1.92 | 37 | 41.2 | 24.4 | 1.69 | 1.85 | 2.81 | 1.07 | 135.0 | 3.53 | 95.7 |
| | Ri3939 | 7.54 | 4.95 | 58.6 | 80 | 39 | 55 | 0 | 1.78 | 40 | 38.2 | 20.4 | 1.87 | 1.77 | 2.39 | 1.20 | 135.2 | 3.59 | 97.3 |
| | Ri3940 | 9.78 | 6.23 | 68.2 | 85 | 38 | 89 | 0 | 2.51 | 37 | 43.7 | 24.5 | 1.78 | 2.06 | 2.76 | 1.39 | 131.0 | 3.70 | 89.3 |
| G2 100 | Ri3941 | 7.72 | 5.84 | 61.8 | 69 | 36 | 72 | 0 | 2.67 | 38 | 41.4 | 20.4 | 2.03 | 1.94 | 2.53 | 1.00 | 135.0 | 3.76 | 93.5 |
| | Ri3942 | 7.96 | 5.84 | 63.2 | 69 | 38 | 63 | 0 | 1.65 | 31 | 38.8 | 24.4 | 1.59 | 2.23 | 2.58 | 0.95 | 138.0 | 4.04 | 92.1 |
| | Ri3943 | 10.03 | 6.44 | 65.7 | 91 | 44 | 66 | 0 | 1.93 | 39 | 44.8 | 20.9 | 2.14 | 2.23 | 2.45 | 1.15 | 137.1 | 3.94 | 94.2 |
| | Ri3944 | 9.40 | 6.57 | 65.7 | 90 | 42 | 72 | 0 | 2.18 | 39 | 43.7 | 22.0 | 1.99 | 2.09 | 2.41 | 1.21 | 136.2 | 4.32 | 95.8 |
| | Ri3945 | 8.88 | 6.64 | 65.3 | 72 | 31 | 59 | 0 | 2.77 | 35 | 42.5 | 22.8 | 1.86 | 2.29 | 2.66 | 0.90 | 137.5 | 3.82 | 96.3 |
| | Ri3946 | 8.25 | 5.29 | 64.3 | 63 | 29 | 67 | 0 | 3.21 | 29 | 43.2 | 21.1 | 2.05 | 1.89 | 2.57 | 1.23 | 139.0 | 3.27 | 93.7 |
| | Ri3947 | 7.30 | 6.02 | 62.3 | 78 | 30 | 90 | 0 | 3.44 | 45 | 42.4 | 19.9 | 2.13 | 1.96 | 2.14 | 1.26 | 137.6 | 4.35 | 94.8 |
| | Ri3948 | 7.37 | 5.92 | 65.1 | 69 | 30 | 83 | 0 | 2.33 | 31 | 43.0 | 22.1 | 1.95 | 1.76 | 2.49 | 1.35 | 139.7 | 3.38 | 94.4 |
| | Ri3949 | 7.18 | 6.93 | 66.5 | 89 | 48 | 60 | 0 | 2.37 | 45 | 44.2 | 22.3 | 1.98 | 1.75 | 2.57 | 1.27 | 138.0 | 3.38 | 91.8 |
| | Ri3950 | 8.95 | 5.10 | 64.6 | 61 | 33 | 56 | 0 | 2.64 | 38 | 44.0 | 20.6 | 2.14 | 1.90 | 2.78 | 1.63 | 135.1 | 3.65 | 95.1 |

*: LLOQ - GGT: 3U/l, and T Bil: 1.71μmol/l

Values below Lower limit of Quantification (LLOQ) are not considered for statistical analysis.

APPENDIX 13 contd. Individual Clinical Chemistry Values - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Glu mmol/l | BUN mmol/l | T.Pro g/l | AST U/l | ALT U/l | ALP U/l | GGT* U/l | T.Bil* μmol/l | Creat μmol/l | Alb g/l | Glob g/l | A/G | Pi mmol/l | Ca mmol/l | T.Chol mmol/l | Na mEq/l | K mEq/l | Cl mEq/l |
|---|---------|---------------|---------------|--------------|------------|------------|------------|-------------|------------------|-----------------|------------|-------------|------|--------------|--------------|------------------|-------------|------------|-------------|
| G3 300 | Ri3951 | 7.36 | 4.91 | 67.3 | 87 | 40 | 91 | 0 | 1.84 | 37 | 42.2 | 25.1 | 1.68 | 2.25 | 2.68 | 1.34 | 137.4 | 3.80 | 95.9 |
| | Ri3952 | 9.56 | 5.76 | 65.5 | 69 | 28 | 91 | 0 | 3.12 | 34 | 42.3 | 23.2 | 1.82 | 2.11 | 2.54 | 1.40 | 135.5 | 3.51 | 93.1 |
| | Ri3953 | 11.74 | 6.30 | 64.9 | 69 | 32 | 80 | 0 | 2.22 | 40 | 43.8 | 21.1 | 2.08 | 1.55 | 2.66 | 1.49 | 136.4 | 4.17 | 92.3 |
| | Ri3954 | 9.15 | 5.40 | 62.7 | 75 | 36 | 72 | 0 | 2.40 | 40 | 39.9 | 22.8 | 1.75 | 1.92 | 2.56 | 1.14 | 135.5 | 3.47 | 94.3 |
| | Ri3955 | 8.70 | 6.32 | 68.7 | 78 | 31 | 68 | 0 | 2.16 | 36 | 39.5 | 29.2 | 1.35 | 1.99 | 2.62 | 1.38 | 135.4 | 3.62 | 92.7 |
| | Ri3956 | 9.36 | 6.75 | 65.8 | 73 | 31 | 64 | 0 | 2.22 | 42 | 44.7 | 21.1 | 2.12 | 2.41 | 2.62 | 1.24 | 137.6 | 4.02 | 91.8 |
| | Ri3957 | 8.92 | 6.57 | 62.3 | 77 | 32 | 62 | 0 | 2.87 | 43 | 40.6 | 21.7 | 1.87 | 1.92 | 2.47 | 1.55 | 131.0 | 4.75 | 93.7 |
| | Ri3958 | 7.46 | 5.52 | 71.0 | 70 | 20 | 26 | 0 | 3.04 | 48 | 45.1 | 25.9 | 1.74 | 1.37 | 2.60 | 1.06 | 131.8 | 3.90 | 97.7 |
| | Ri3959 | 8.90 | 6.48 | 63.0 | 72 | 37 | 62 | 0 | 2.76 | 34 | 39.2 | 23.8 | 1.65 | 2.07 | 2.51 | 1.16 | 136.9 | 3.57 | 94.9 |
| | Ri3960 | 7.99 | 6.56 | 64.8 | 73 | 41 | 69 | 0 | 2.80 | 40 | 41.9 | 22.9 | 1.83 | 1.82 | 2.60 | 1.24 | 133.7 | 3.85 | 94.6 |
| G4 1000 | Ri3961 | 8.76 | 6.03 | 68.6 | 75 | 41 | 73 | 0 | 1.78 | 34 | 43.2 | 25.4 | 1.70 | 1.81 | 2.58 | 1.40 | 138.1 | 3.61 | 96.1 |
| | Ri3962 | 8.38 | 7.49 | 66.0 | 74 | 32 | 81 | 0 | 2.37 | 39 | 41.9 | 24.1 | 1.74 | 2.42 | 2.58 | 1.46 | 143.5 | 3.33 | 98.3 |
| | Ri3963 | 9.02 | 6.94 | 64.0 | 72 | 36 | 56 | 0 | 2.46 | 36 | 42.9 | 21.1 | 2.03 | 2.01 | 2.63 | 1.57 | 140.7 | 4.95 | 104.9 |
| | Ri3964 | 9.17 | 6.41 | 61.8 | 86 | 34 | 59 | 0 | 2.80 | 35 | 40.2 | 21.6 | 1.86 | 2.12 | 2.66 | 1.29 | 135.5 | 3.78 | 93.5 |
| | Ri3965 | 7.83 | 6.05 | 68.4 | 82 | 41 | 104 | 0 | 2.58 | 42 | 46.4 | 22.0 | 2.11 | 2.28 | 2.71 | 1.07 | 142.0 | 3.43 | 100.3 |
| | Ri3966 | 13.37 | 6.03 | 65.5 | 72 | 35 | 80 | 0 | 2.19 | 43 | 40.3 | 25.2 | 1.60 | 1.95 | 2.62 | 1.06 | 148.0 | 4.59 | 102.8 |
| | Ri3967 | 8.26 | 7.16 | 64.3 | 76 | 32 | 71 | 0 | 1.83 | 35 | 38.9 | 25.4 | 1.53 | 2.18 | 2.52 | 1.39 | 143.4 | 3.37 | 100.0 |
| | Ri3968 | 8.58 | 5.55 | 65.3 | 72 | 34 | 74 | 0 | 2.07 | 41 | 40.5 | 24.8 | 1.63 | 1.75 | 2.48 | 1.23 | 141.1 | 3.99 | 98.1 |
| | Ri3969 | 8.91 | 6.46 | 62.0 | 82 | 30 | 69 | 0 | 1.44 | 38 | 41.0 | 21.0 | 1.95 | 1.78 | 2.52 | 1.10 | 135.5 | 3.59 | 92.2 |
| | Ri3970 | 8.28 | 6.90 | 70.1 | 76 | 43 | 73 | 0 | 2.61 | 46 | 46.3 | 23.8 | 1.95 | 1.98 | 2.78 | 2.06 | 136.9 | 4.29 | 96.2 |

*: LLOQ - GGT: 3U/l, and T Bil: 1.71μmol/l

Values below Lower limit of Quantification (LLOQ) are not considered for statistical analysis.

APPENDIX 14. Individual Clinical Chemistry Values - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Glu mmol/l | BUN mmol/l | T.Pro g/l | AST U/l | ALT U/l | ALP U/l | GGT* U/l | T.Bil* μmol/l | Creat μmol/l | Alb g/l | Glob g/l | A/G | Pi mmol/l | Ca mmol/l | T.Chol mmol/l | Na mEq/l | K mEq/l | Cl mEq/l |
|---|---------|---------------|---------------|--------------|------------|------------|------------|-------------|------------------|-----------------|------------|-------------|------|--------------|--------------|------------------|-------------|------------|-------------|
| G1 0 | Ri3971 | 10.03 | 5.45 | 64.2 | 91 | 28 | 45 | 0 | 2.55 | 53 | 48.7 | 15.5 | 3.14 | 1.65 | 2.60 | 1.55 | 133.5 | 3.57 | 93.1 |
| | Ri3972 | 11.30 | 7.27 | 65.8 | 67 | 25 | 35 | 0 | 1.92 | 39 | 44.6 | 21.2 | 2.10 | 1.62 | 2.49 | 1.49 | 132.7 | 3.53 | 93.8 |
| | Ri3973 | 8.12 | 5.92 | 69.9 | 69 | 28 | 29 | 0 | 4.68 | 41 | 55.5 | 14.4 | 3.85 | 1.94 | 2.80 | 0.54 | 130.2 | 3.32 | 90.6 |
| | Ri3974 | 11.66 | 7.60 | 66.0 | 83 | 24 | 40 | 0 | 1.36 | 46 | 43.0 | 23.0 | 1.87 | 1.13 | 2.39 | 1.38 | 131.0 | 3.39 | 90.6 |
| | Ri3975 | 11.30 | 5.82 | 65.4 | 71 | 25 | 51 | 0 | 2.39 | 49 | 46.4 | 19.0 | 2.44 | 1.40 | 2.58 | 1.35 | 136.9 | 3.49 | 92.0 |
| | Ri3976 | 6.91 | 6.12 | 61.4 | 74 | 23 | 37 | 0 | 1.59 | 39 | 42.7 | 18.7 | 2.28 | 1.72 | 2.65 | 0.86 | 132.2 | 3.08 | 97.5 |
| | Ri3977 | 11.02 | 5.37 | 60.2 | 73 | 20 | 53 | 0 | 2.50 | 41 | 43.0 | 17.2 | 2.5 | 1.66 | 2.59 | 1.29 | 145.3 | 3.40 | 101.3 |
| | Ri3978 | 8.27 | 6.29 | 72.8 | 70 | 28 | 29 | 0 | 3.68 | 37 | 56.5 | 16.3 | 3.47 | 1.99 | 2.95 | 0.50 | 136.2 | 3.79 | 95.1 |
| | Ri3979 | 7.97 | 7.69 | 70.0 | 88 | 27 | 38 | 0 | 4.07 | 43 | 52.1 | 17.9 | 2.91 | 2.01 | 2.68 | 1.66 | 135.8 | 3.52 | 93.5 |
| | Ri3980 | 9.33 | 6.59 | 65.1 | 93 | 34 | 78 | 0 | 1.89 | 41 | 45.3 | 19.8 | 2.29 | 1.76 | 2.56 | 1.52 | 138.4 | 4.71 | 97.1 |
| G2 100 | Ri3981 | 10.20 | 6.89 | 71.3 | 59 | 20 | 34 | 0 | 3.41 | 43 | 48.2 | 23.1 | 2.09 | 1.86 | 2.61 | 1.37 | 134.0 | 3.53 | 94.2 |
| | Ri3982 | 9.01 | 6.10 | 72.4 | 75 | 26 | 41 | 0 | 3.12 | 46 | 49.6 | 22.8 | 2.18 | 1.38 | 2.48 | 1.82 | 130.2 | 2.85 | 91.1 |
| | Ri3983 | 7.12 | 7.16 | 64.5 | 79 | 25 | 37 | 0 | 2.30 | 50 | 45.0 | 19.5 | 2.31 | 1.58 | 2.64 | 1.27 | 135.2 | 3.84 | 95.1 |
| | Ri3984 | 9.05 | 7.21 | 65.6 | 69 | 23 | 51 | 0 | 2.33 | 46 | 41.5 | 24.1 | 1.72 | 1.92 | 2.56 | 1.37 | 131.2 | 3.31 | 94.6 |
| | Ri3985 | 6.34 | 6.72 | 67.4 | 75 | 31 | 36 | 0 | 2.54 | 42 | 47.0 | 20.4 | 2.30 | 1.76 | 2.64 | 1.26 | 133.7 | 3.26 | 93.6 |
| | Ri3986 | 7.98 | 6.49 | 59.5 | 69 | 23 | 33 | 0 | 2.79 | 46 | 43.0 | 16.5 | 2.61 | 1.75 | 2.44 | 1.34 | 140.1 | 3.61 | 88.9 |
| | Ri3987 | 8.93 | 7.72 | 67.3 | 91 | 29 | 47 | 0 | 1.85 | 44 | 47.4 | 19.9 | 2.38 | 2.01 | 2.47 | 0.97 | 135.2 | 4.40 | 96.2 |
| | Ri3988 | 9.09 | 6.79 | 71.5 | 80 | 37 | 44 | 1 | 2.89 | 42 | 52.8 | 18.7 | 2.82 | 1.59 | 2.71 | 1.84 | 143.1 | 3.31 | 97.3 |
| | Ri3989 | 8.86 | 5.96 | 62.1 | 71 | 27 | 58 | 0 | 3.18 | 44 | 45.3 | 16.8 | 2.70 | 1.75 | 2.43 | 1.03 | 134.0 | 4.30 | 98.4 |
| | Ri3990 | 7.09 | 7.37 | 69.0 | 69 | 23 | 41 | 0 | 2.93 | 60 | 49.9 | 19.1 | 2.61 | 2.08 | 2.55 | 1.05 | 143.5 | 3.46 | 100.4 |

*: LLOQ - GGT: 3U/l, and T Bil: 1.71μmol/l

Values below Lower limit of Quantification (LLOQ) are not considered for Statistical Analysis.

APPENDIX 14 contd. Individual Clinical Chemistry Values - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Glu mmol/l | BUN mmol/l | T.Pro g/l | AST U/l | ALT U/l | ALP U/l | GGT* U/l | T.Bil* μmol/l | Creat μmol/l | Alb g/l | Glob g/l | A/G | Pi mmol/l | Ca mmol/l | T.Chol mmol/l | Na mEq/l | K mEq/l | Cl mEq/l |
|---|---------|---------------|---------------|--------------|------------|------------|------------|-------------|------------------|-----------------|------------|-------------|------|--------------|--------------|------------------|-------------|------------|-------------|
| G3 300 | Ri3991 | 8.40 | 6.73 | 70.3 | 75 | 23 | 34 | 0 | 3.05 | 49 | 48.2 | 22.1 | 2.18 | 1.63 | 2.55 | 0.84 | 143.8 | 5.05 | 106.7 |
| | Ri3992 | 6.08 | 5.35 | 66.8 | 80 | 21 | 30 | 0 | 4.04 | 42 | 49.3 | 17.5 | 2.82 | 1.64 | 2.62 | 1.27 | 130.3 | 4.77 | 86.1 |
| | Ri3993 | 8.36 | 5.79 | 66.5 | 73 | 22 | 36 | 0 | 1.94 | 37 | 42.7 | 23.8 | 1.79 | 1.79 | 2.45 | 1.63 | 138.5 | 4.13 | 91.8 |
| | Ri3994 | 10.11 | 6.89 | 65.6 | 78 | 25 | 45 | 1 | 1.78 | 44 | 42.8 | 22.8 | 1.88 | 1.59 | 2.42 | 1.42 | 133.0 | 4.12 | 94.0 |
| | Ri3995 | 9.76 | 5.50 | 64.9 | 71 | 24 | 46 | 0 | 2.93 | 42 | 44.3 | 20.6 | 2.15 | 1.96 | 2.54 | 1.22 | 135.6 | 3.70 | 94.2 |
| | Ri3996 | 8.69 | 5.51 | 61.6 | 73 | 27 | 58 | 0 | 2.15 | 42 | 42.7 | 18.9 | 2.26 | 1.75 | 2.46 | 1.52 | 134.7 | 3.71 | 93.2 |
| | Ri3997 | 9.69 | 5.62 | 63.0 | 69 | 27 | 46 | 0 | 2.96 | 40 | 42.3 | 20.7 | 2.04 | 1.91 | 2.52 | 1.11 | 134.4 | 3.34 | 98.6 |
| | Ri3998 | 8.91 | 5.79 | 60.3 | 68 | 30 | 50 | 0 | 2.07 | 38 | 41.8 | 18.5 | 2.26 | 2.13 | 2.52 | 1.27 | 139.6 | 3.31 | 92.8 |
| | Ri3999 | 8.79 | 6.69 | 64.7 | 71 | 22 | 67 | 0 | 2.25 | 47 | 45.8 | 18.9 | 2.42 | 1.65 | 2.48 | 1.55 | 135.2 | 3.06 | 93.9 |
| | Ri4000 | 7.54 | 6.59 | 68.9 | 67 | 28 | 48 | 0 | 1.68 | 41 | 47.2 | 21.7 | 2.18 | 1.60 | 2.68 | 1.33 | 134.4 | 3.92 | 95.3 |
| G4 1000 | Ri4001 | 10.44 | 6.56 | 63.7 | 90 | 42 | 39 | 0 | 1.29 | 36 | 41.1 | 22.6 | 1.82 | 1.94 | 2.70 | 1.38 | 131.3 | 3.54 | 90.4 |
| | Ri4002 | 9.17 | 5.53 | 62.8 | 65 | 20 | 36 | 0 | 3.17 | 47 | 42.6 | 20.2 | 2.11 | 1.71 | 2.45 | 1.15 | 133.7 | 4.79 | 99.3 |
| | Ri4003 | 10.99 | 6.38 | 68.6 | 73 | 24 | 56 | 0 | 1.87 | 39 | 46.5 | 22.1 | 2.10 | 1.31 | 2.49 | 1.29 | 132.7 | 3.18 | 92.9 |
| | Ri4004 | 11.43 | 7.00 | 66.2 | 113 | 51 | 65 | 0 | 2.86 | 53 | 43.7 | 22.5 | 1.94 | 1.71 | 2.51 | 1.30 | 144.6 | 3.81 | 100.0 |
| | Ri4005 | 9.44 | 6.10 | 66.8 | 72 | 22 | 35 | 0 | 3.01 | 49 | 45.5 | 21.3 | 2.14 | 1.72 | 2.53 | 1.32 | 145.1 | 4.36 | 106.7 |
| | Ri4006 | 9.02 | 5.82 | 65.0 | 71 | 26 | 28 | 0 | 2.82 | 38 | 45.7 | 19.3 | 2.37 | 1.75 | 2.58 | 1.41 | 132.8 | 3.20 | 92.2 |
| | Ri4007 | 10.93 | 5.53 | 67.2 | 69 | 28 | 52 | 0 | 2.34 | 35 | 47.2 | 20.0 | 2.36 | 1.45 | 2.56 | 1.65 | 130.7 | 3.64 | 92.4 |
| | Ri4008 | 7.69 | 6.68 | 62.7 | 81 | 22 | 47 | 0 | 2.89 | 42 | 45.9 | 16.8 | 2.73 | 1.47 | 2.52 | 1.31 | 133.4 | 3.23 | 95.6 |
| | Ri4009 | 9.73 | 5.71 | 69.5 | 64 | 20 | 42 | 2 | 3.17 | 45 | 45.5 | 24.0 | 1.90 | 1.99 | 2.68 | 1.53 | 135.6 | 4.15 | 93.7 |
| | Ri4010 | 9.80 | 5.43 | 69.8 | 68 | 25 | 36 | 0 | 1.14 | 43 | 48.1 | 21.7 | 2.22 | 1.59 | 2.80 | 1.68 | 135.0 | 3.75 | 91.1 |

*: LLOQ - GGT: 3U/l, and T Bil: 1.71μmol/l

Values below Lower limit of Quantification (LLOQ) are not considered for Statistical Analysis.

APPENDIX 15. Individual Clinical Analysis of Urine at Termination - Males

| Group No. Dose (mg TOS/kg bwt/day) | Animal No. | Volume (ml) | Appearance | | Glucose mmol/l | Bilirubin | Ketone | | pH | Proteins g/l | Urobilinogen μmol/l | Nitrite | Erythrocytes Ery/μL | Leukocytes Leu/ μL | Microscopic Findings | | | | | |
|---|---------------|----------------|------------|---------|-------------------|-----------|------------------|---------------------|------|-----------------|------------------------|----------|------------------------|-----------------------|----------------------|---|---|---------------------|---|-------|
| | | | | | | | Bodies mmol/l | Specific gravity | | | | | | | Crystals | | | Epithelial Cells | | Casts |
| | | | Colour | Clarity | | | | | | | | | | | a | b | c | d | | |
| G1 0 | Ri3931 | 5.0 | Brown | Clear | Negative | Small | 3.9 | 1.036 | 8.5 | ≥3.0 | 16 | Positive | Negative | Ca 500 | 3+ | - | - | - | - | - |
| | Ri3932 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.029 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Ca 500 | 3+ | - | - | - | - | - |
| | Ri3933 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.039 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Ca 500 | 3+ | - | - | - | - | - |
| | Ri3934 | 15.0 | Other | Clear | Negative | Negative | Negative | 1.005 | 8.5 | 0.3 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - |
| | Ri3935 | 10.0 | Orange | Clear | Negative | Negative | 1.5 | 1.016 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3936 | 25.0 | Orange | Clear | Negative | Negative | Trace | 1.005 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - |
| | Ri3937 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.032 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Ca 500 | 2+ | - | - | - | - | - |
| | Ri3938 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.029 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3939 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.039 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3940 | 25.0 | Other | Clear | Negative | Negative | Negative | 1.004 | ≥9.0 | 0.3 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - |
| G2 100 | Ri3941 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.014 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - |
| | Ri3942 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.028 | 8.5 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3943 | 5.0 | Orange | Clear | Negative | Small | 3.9 | 1.045 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Ca 500 | 2+ | - | - | - | - | - |
| | Ri3944 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.034 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Ca 500 | 1+ | - | - | - | - | - |
| | Ri3945 | 5.0 | Orange | Clear | Negative | Negative | Trace | 1.011 | ≥9.0 | 1.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - |
| | Ri3946 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.028 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3947 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.025 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3948 | 5.0 | Brown | Clear | Negative | Negative | Trace | 1.048 | ≥9.0 | 1.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - |
| | Ri3949 | 7.5 | Orange | Clear | Negative | Small | 1.5 | 1.016 | 8.5 | 1.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - |
| | Ri3950 | 15.0 | Orange | Clear | Negative | Negative | Trace | 1.009 | 8.5 | 1.0 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - |

a : Phosphates b: Calcium Carbonate/Oxalate c: Urates/Uric acid d: Hippuric Acid

1+: Occasional/Few in entire slide 2+: Moderate/Few in each field 3+: Large number in each field

Note: For pH average calculations, the values equal to and above 9.0 are considered as 9.0 only.

| Bilirubin | | Ketone bodies | | Proteins | | Erythrocytes | | Leukocytes | | Urobilinogen | |
|-----------|---------|---------------|------------|----------|------------------|--------------|------------|------------|-----------|--------------|-----|
| 1. | Small | 1. | 0 to trace | 1. | Negative / trace | 1. | 0 to trace | 1. | Negative | 1. | 3.2 |
| | Minimal | 2. | 1.5 | 2. | 0.3 | | Minimal | 2. | 15 | 2. | 16 |
| | | 3. | 3.9 | 3. | 1.0 | | Moderate | 3. | 70 | 3. | 33 |
| | | | | 4. | ≥3.0 | | High | 4. | 125 / 500 | | |
| | | | | | | | | | High | | |

APPENDIX 15 contd. Individual Clinical Analysis of Urine at Termination - Males

| Group No. Dose (mg TOS/kg bwt/day) | Animal No. | Volume (ml) | Appearance | | Glucose mmol/l | Bilirubin | Ketone | | pH | Proteins g/l | Urobilinogen μmol/l | Nitrite | Erythrocytes Ery/μL | Leukocytes Leu/ μL | Microscopic Findings | | | | | |
|---|---------------|----------------|------------|---------|-------------------|-----------|------------------|---------------------|------|-----------------|------------------------|----------|------------------------|-----------------------|----------------------|--------|---------|---|-----------|-------|
| | | | | | | | Bodies mmol/l | Specific gravity | | | | | | | Crystals | | | | Epithelia | Casts |
| | | | Colour | Clarity | | | | | | | | | | | mmol/l | mmol/l | gravity | | a | |
| G3 300 | Ri3951 | 15.0 | Brown | Clear | Negative | Small | Trace | 1.014 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3952 | 10.0 | Other | Clear | Negative | Small | Trace | 1.014 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3953 | 20.0 | Orange | Clear | Negative | Negative | Trace | 1.010 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - |
| | Ri3954 | 10.0 | Orange | Clear | Negative | Moderate | 3.9 | 1.036 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Ca 500 | 1+ | - | - | - | - | - |
| | Ri3955 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.018 | 8.5 | ≥3.0 | 16 | Positive | Negative | Negative | 3+ | - | - | - | - | - |
| | Ri3956 | 20.0 | Orange | Clear | Negative | Small | Negative | 1.010 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - |
| | Ri3957 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.020 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3958 | 7.5 | Yellow | Clear | Negative | Negative | Negative | 1.014 | 8.5 | 0.3 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - |
| | Ri3959 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.021 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - |
| | Ri3960 | 7.5 | Orange | Clear | Negative | Negative | 1.5 | 1.014 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| G4 1000 | Ri3961 | 7.5 | Yellow | Clear | Negative | Small | 1.5 | 1.020 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 1+ | - | - | - | - | - |
| | Ri3962 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.017 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3963 | 5.0 | Orange | Clear | Negative | Moderate | 1.5 | 1.019 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3964 | 5.0 | Orange | Clear | Negative | Small | 1.5 | 1.028 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 1+ | - | - | - | - | - |
| | Ri3965 | 10.0 | Orange | Clear | Negative | Small | Trace | 1.018 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3966 | 7.5 | Orange | Clear | Negative | Small | 1.5 | 1.022 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 3+ | - | - | - | - | - |
| | Ri3967 | 10.0 | Orange | Clear | 5.5 mmol/L | Small | 1.5 | 1.018 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - |
| | Ri3968 | 5.0 | Orange | Clear | Negative | Moderate | 1.5 | 1.021 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Ca 500 | 1+ | - | - | - | - | - |
| | Ri3969 | 15.0 | Orange | Clear | Negative | Small | 1.5 | 1.015 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - |
| | Ri3970 | 10.0 | Orange | Clear | Negative | Small | 1.5 | 1.017 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 1+ | - | - | - | - | - |

a : Phosphates

b: Calcium Carbonate/Oxalate

c: Urates/Uric acid

d: Hippuric Acid

1+: Occasional/Few in entire slide

2+: Moderate/Few in each field

3+: Large number in each field

Note: For pH average calculations, the values equal to and above 9.0 are considered as 9.0 only.

| Bilirubin | | | | Ketone bodies | | | | Proteins | | | | Erythrocytes | | | | Leukocytes | | | | Urobilinogen | | | |
|-----------|---------|---|---------|---------------|------------|---|-----------------------|----------|------------------|---|----------|--------------|------------|---|--------------------------------|------------|-----------|---|----------|--------------|-----|---|----------|
| 1. | Small | : | Minimal | 1. | 0 to trace | : | Negative / Negligible | 1. | Negative / trace | : | Normal | 1. | 0 to trace | : | Negative / Negligible / Normal | 1. | Negative | : | Normal | 1. | 3.2 | : | Normal |
| | Glucose | : | Minimal | 2. | 1.5 | : | Minimal | 2. | 0.3 | : | Minimal | 2. | 25 | : | Minimal | 2. | 15 | : | Minimal | 2. | 16 | : | Minimal |
| 1. | 5.5 | : | Minimal | 3. | 3.9 | : | Moderate | 3. | 1.0 | : | Moderate | 3. | 80 | : | Moderate | 3. | 70 | : | Moderate | 3. | 33 | : | Moderate |
| | | : | | 4. | ≥3.0 | : | High | 4. | ≥3.0 | : | High | 4. | 200 | : | High | 4. | 125 / 500 | : | High | | | : | |

APPENDIX 16. Individual Clinical Analysis of Urine at Termination - Females

| Group No. Dose (mg TOS/kg bwt/day) | Animal No. | Volume (ml) | Appearance | | Glucose mmol/l | Bilirubin | Ketone | | pH | Proteins g/l | Urobilinogen μmol/l | Nitrite | Erythrocytes Ery/μL | Leukocytes Leu/ μL | Microscopic Findings | | | | | | |
|---|---------------|----------------|------------|---------|-------------------|-----------|------------------|---------------------|------|-----------------|------------------------|----------|------------------------|-----------------------|----------------------|---|---|---|------------------|-------|--|
| | | | | | | | Bodies mmol/l | Specific gravity | | | | | | | Crystals | | | | Epithelial Cells | Casts | |
| | | | Colour | Clarity | | | | | | | | | | | a | b | c | d | | | |
| G1 0 | Ri3971 | 10.0 | Orange | Clear | Negative | Small | Trace | 1.019 | ≥9.0 | 1.0 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - | |
| | Ri3972 | 7.5 | Yellow | Clear | Negative | Negative | Negative | 1.016 | 8.5 | 1.0 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - | |
| | Ri3973 | 10.0 | Orange | Clear | Negative | Negative | Negative | 1.008 | ≥9.0 | 1.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri3974 | 5.0 | Orange | Clear | Negative | Negative | Trace | 1.025 | 7.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - | |
| | Ri3975 | 5.0 | Yellow | Clear | Negative | Negative | Negative | 1.014 | 5.0 | Negative | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri3976 | 5.0 | Orange | Clear | Negative | Negative | Negative | 1.021 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - | |
| | Ri3977 | 10.0 | Yellow | Clear | Negative | Small | Trace | 1.006 | 8.5 | ≥3.0 | 16 | Positive | Negative | Negative | 3+ | - | - | - | - | - | |
| | Ri3978 | 5.0 | Orange | Clear | Negative | Small | Trace | 1.017 | 8.5 | ≥3.0 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - | |
| | Ri3979 | 10.0 | Orange | Clear | Negative | Negative | Negative | 1.013 | ≥9.0 | 1.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri3980 | 5.0 | Orange | Clear | Negative | Negative | Negative | 1.028 | 8.5 | 1.0 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - | |
| G2 100 | Ri3981 | 7.5 | Orange | Clear | Negative | Small | Trace | 1.016 | 8.5 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri3982 | 12.0 | Orange | Clear | Negative | Small | Negative | 1.008 | 8.5 | ≥3.0 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - | |
| | Ri3983 | 10.0 | Orange | Clear | Negative | Small | Trace | 1.014 | 8.5 | ≥3.0 | 16 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri3984 | 10.0 | Orange | Clear | Negative | Small | Trace | 1.020 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri3985 | 5.0 | Brown | Clear | Negative | Negative | Negative | 1.042 | ≥9.0 | 1.0 | 3.2 | Negative | Negative | Negative | 1+ | - | - | - | - | - | |
| | Ri3986 | 5.0 | Orange | Clear | Negative | Small | Trace | 1.022 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri3987 | 5.0 | Orange | Clear | Negative | Negative | Trace | 1.021 | 8.5 | ≥3.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - | |
| | Ri3988 | 7.5 | Orange | Clear | Negative | Negative | Negative | 1.032 | ≥9.0 | 1.0 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - | |
| | Ri3989 | 5.0 | Orange | Clear | Negative | Negative | Negative | 1.015 | 8.5 | 1.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - | |
| | Ri3990 | 10.0 | Orange | Clear | Negative | Negative | Trace | 1.011 | 8.5 | 1.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |

a : Phosphates

b: Calcium Carbonate/Oxalate

c: Urates/Uric acid

d: Hippuric Acid

1+: Occasional/Few in entire slide

2+: Moderate/Few in each field

3+: Large number in each field

Note: For pH average calculations, the values equal to and above 9.0 are considered as 9.0 only.

| Bilirubin | | | Ketone bodies | | | Proteins | | | Erythrocytes | | | Leukocytes | | | Urobilinogen | | |
|-----------|---------|---|---------------|------------|---|----------|------------------|---|--------------|------------|---|------------|-----------|---|--------------|-----|---|
| 1. | Small | : | 1. | 0 to trace | : | 1. | Negative / trace | : | 1. | 0 to trace | : | 1. | Negative | : | 1. | 3.2 | : |
| | Minimal | : | 2. | 1.5 | : | 2. | 0.3 | : | 2. | 25 | : | 2. | 15 | : | 2. | 16 | : |
| | | : | 3. | 3.9 | : | 3. | 1.0 | : | 3. | 80 | : | 3. | 70 | : | 3. | 33 | : |
| | | : | | | : | 4. | ≥3.0 | : | 4. | 200 | : | 4. | 125 / 500 | : | | | : |
| | | : | | | : | | | : | | | : | | High | : | | | : |

APPENDIX 16 contd. Individual Clinical Analysis of Urine at Termination - Females

| Group No. Dose (mg TOS/kg bwt/day) | Animal No. | Volume (ml) | Appearance | | Glucose mmol/l | Bilirubin | Ketone Bodies mmol/l | Specific gravity | pH | Proteins g/l | Urobilinogen μmol/l | Nitrite | Erythrocytes Ery/μL | Leukocytes Leu/ μL | Microscopic Findings | | | | | | |
|---|---------------|----------------|------------|---------|-------------------|-----------|----------------------------|---------------------|------|-----------------|------------------------|----------|------------------------|-----------------------|----------------------|---|---|---|---------------------|---|-------|
| | | | | | | | | | | | | | | | Crystals | | | | Epithelial Cells | | Casts |
| | | | Colour | Clarity | | | | | | | | | | | a | b | c | d | | | |
| G3 300 | Ri3991 | 25.0 | Orange | Clear | Negative | Negative | Negative | 1.007 | ≥9.0 | 1.0 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - | |
| | Ri3992 | 15.0 | Orange | Clear | Negative | Negative | Negative | 1.009 | ≥9.0 | 1.0 | 3.2 | Negative | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri3993 | 15.0 | Orange | Clear | Negative | Negative | Negative | 1.006 | 8.5 | ≥3.0 | 16 | Positive | Negative | Negative | 3+ | - | - | - | - | - | |
| | Ri3994 | 5.0 | Orange | Clear | Negative | Negative | Negative | 1.013 | 8.5 | 0.3 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - | |
| | Ri3995 | 5.0 | Orange | Clear | Negative | Small | Trace | 1.020 | 8.5 | ≥3.0 | 16 | Positive | Negative | Negative | 1+ | - | - | - | - | - | |
| | Ri3996 | 5.0 | Orange | Clear | Negative | Small | Trace | 1.021 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 1+ | - | - | - | - | - | |
| | Ri3997 | 20.0 | Orange | Clear | Negative | Negative | Negative | 1.006 | ≥9.0 | 1.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - | |
| | Ri3998 | 15.0 | Orange | Clear | Negative | Negative | Negative | 1.007 | ≥9.0 | 0.3 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri3999 | 20.0 | Orange | Clear | Negative | Negative | Negative | 1.006 | ≥9.0 | 0.3 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri4000 | 20.0 | Orange | Clear | Negative | Negative | Negative | 1.024 | 8.5 | 0.3 | 3.2 | Positive | Negative | Negative | 3+ | - | - | - | - | - | |
| G4 1000 | Ri4001 | 5.0 | Yellow | Clear | Negative | Small | Trace | 1.026 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri4002 | 7.5 | Orange | Clear | Negative | Small | Trace | 1.018 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri4003 | 5.0 | Orange | Clear | Negative | Moderate | Trace | 1.022 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 1+ | - | - | - | - | - | |
| | Ri4004 | 7.5 | Orange | Clear | Negative | Moderate | 1.5 | 1.018 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Ca 500 | 2+ | - | - | - | - | - | |
| | Ri4005 | 5.0 | Orange | Clear | Negative | Small | Trace | 1.016 | ≥9.0 | ≥3.0 | 16 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri4006 | 15.0 | Orange | Clear | Negative | Negative | Negative | 1.009 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 2+ | - | - | - | - | - | |
| | Ri4007 | 7.5 | Orange | Clear | Negative | Negative | Negative | 1.010 | ≥9.0 | 1.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - | |
| | Ri4008 | 7.5 | Orange | Clear | Negative | Negative | Negative | 1.009 | 8.5 | 1.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - | |
| | Ri4009 | 5.0 | Orange | Clear | Negative | Small | Negative | 1.011 | 8.5 | ≥3.0 | 16 | Positive | Negative | Negative | 3+ | - | - | - | - | - | |
| | Ri4010 | 7.5 | Orange | Clear | Negative | Small | Negative | 1.017 | ≥9.0 | ≥3.0 | 3.2 | Positive | Negative | Negative | 1+ | - | - | - | - | - | |

a : Phosphates b: Calcium Carbonate/Oxalate c: Urates/Uric acid d: Hippuric Acid

1+: Occasional/Few in entire slide 2+: Moderate/Few in each field 3+: Large number in each field

Note: For pH average calculations, the values equal to and above 9.0 are considered as 9.0 only.

| Bilirubin | | | Ketone bodies | | | Proteins | | | Erythrocytes | | | Leukocytes | | | Urobilinogen | | |
|-----------|-------|-----------|---------------|------------|-------------------------|----------|------------------|------------|--------------|------------|----------------------------------|------------|-----------|------------|--------------|-----|------------|
| 1. | Small | : Minimal | 1. | 0 to trace | : Negative / Negligible | 1. | Negative / trace | : Normal | 1. | 0 to trace | : Negative / Negligible / Normal | 1. | Negative | : Normal | 1. | 3.2 | : Normal |
| | | | 2. | 1.5 | : Minimal | 2. | 0.3 | : Minimal | 2. | 25 | : Minimal | 2. | 15 | : Minimal | 2. | 16 | : Minimal |
| | | | 3. | 3.9 | : Moderate | 3. | 1.0 | : Moderate | 3. | 80 | : Moderate | 3. | 70 | : Moderate | 3. | 33 | : Moderate |
| | | | | | | 4. | ≥3.0 | : High | 4. | 200 | : High | 4. | 125 / 500 | : High | | | |

APPENDIX 17. Urine Electrolytes Values - Males

| Group No. | | | | |
|---------------------|---------|-------|--------|-------|
| Dose | | Na | K | Cl |
| (mg TOS/kg bwt/day) | Rat No. | mEq/l | mEq/l | mEq/l |
| G1 0 | Ri3931 | 154.8 | 202.65 | 124.8 |
| | Ri3932 | 70.5 | 227.73 | 85.2 |
| | Ri3933 | 46.6 | 226.09 | 76.9 |
| | Ri3934 | 6.6 | 29.21 | 7.2 |
| | Ri3935 | 14.2 | 125.69 | 53.6 |
| | Ri3936 | 5.6 | 28.50 | 8.7 |
| | Ri3937 | 104.6 | 48.58 | 209.9 |
| | Ri3938 | 129.4 | 4.73 | 86.4 |
| | Ri3939 | 36.3 | 291.33 | 51.9 |
| | Ri3940 | 4.4 | 22.22 | 14.0 |
| G2 100 | Ri3941 | 18.4 | 130.84 | 83.8 |
| | Ri3942 | 56.4 | 224.91 | 62.1 |
| | Ri3943 | 99.0 | 370.98 | 139.2 |
| | Ri3944 | 378.0 | 17.34 | 272.7 |
| | Ri3945 | 15.8 | 70.28 | 42.7 |
| | Ri3946 | 29.1 | 262.32 | 75.3 |
| | Ri3947 | 58.2 | 185.90 | 142.6 |
| | Ri3948 | 118.2 | 458.34 | 243.9 |
| | Ri3949 | 24.3 | 104.88 | 65.5 |
| | Ri3950 | 9.1 | 57.24 | 46.5 |
| G3 300 | Ri3951 | 28.5 | 109.81 | 226.0 |
| | Ri3952 | 35.5 | 108.96 | 156.6 |
| | Ri3953 | 12.1 | 77.95 | 61.4 |
| | Ri3954 | 71.1 | 284.40 | 106.8 |
| | Ri3955 | 52.1 | 163.14 | 168.6 |
| | Ri3956 | 20.7 | 74.20 | 62.3 |
| | Ri3957 | 27.8 | 175.10 | 128.6 |
| | Ri3958 | 35.6 | 85.63 | 67.7 |
| | Ri3959 | 24.2 | 104.90 | 59.0 |
| | Ri3960 | 41.5 | 194.46 | 74.7 |
| G4 1000 | Ri3961 | 128.0 | 5.63 | 89.1 |
| | Ri3962 | 94.2 | 157.34 | 277.7 |
| | Ri3963 | 66.5 | 151.96 | 168.7 |
| | Ri3964 | 46.6 | 28.23 | 170.6 |
| | Ri3965 | 41.4 | 138.49 | 153.3 |
| | Ri3966 | 54.6 | 163.11 | 196.3 |
| | Ri3967 | 68.5 | 112.70 | 149.0 |
| | Ri3968 | 28.3 | 141.93 | 88.6 |
| | Ri3969 | 18.9 | 103.08 | 74.9 |
| | Ri3970 | 19.0 | 126.26 | 61.6 |

APPENDIX 18. Urine Electrolytes Values - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Na mEq/l | K mEq/l | Cl mEq/l |
|--|---------|-------------|------------|-------------|
| G1 0 | Ri3971 | 23.1 | 119.86 | 30.6 |
| | Ri3972 | 69.8 | 132.94 | 121.6 |
| | Ri3973 | 7.8 | 59.71 | 32.8 |
| | Ri3974 | 59.0 | 174.95 | 87.0 |
| | Ri3975 | 15.0 | 85.58 | 50.6 |
| | Ri3976 | 40.4 | 112.60 | 67.8 |
| | Ri3977 | 2.8 | 40.91 | 8.6 |
| | Ri3978 | 30.2 | 129.49 | 100.7 |
| | Ri3979 | 19.6 | 72.02 | 49.8 |
| | Ri3980 | 84.3 | 160.30 | 186.9 |
| G2 100 | Ri3981 | 114.1 | 5.65 | 108.0 |
| | Ri3982 | 3.6 | 32.86 | 26.4 |
| | Ri3983 | 23.9 | 86.89 | 113.6 |
| | Ri3984 | 38.7 | 104.94 | 41.6 |
| | Ri3985 | 68.1 | 302.37 | 176.4 |
| | Ri3986 | 25.4 | 136.13 | 57.6 |
| | Ri3987 | 49.7 | 114.49 | 69.0 |
| | Ri3988 | 26.1 | 200.76 | 42.3 |
| | Ri3989 | 47.2 | 89.26 | 69.2 |
| | Ri3990 | 15.1 | 61.92 | 19.5 |
| G3 300 | Ri3991 | 7.6 | 21.43 | 20.1 |
| | Ri3992 | 10.2 | 63.76 | 27.8 |
| | Ri3993 | 126.8 | 4.78 | 80.1 |
| | Ri3994 | 11.4 | 68.24 | 94.7 |
| | Ri3995 | 30.7 | 93.13 | 340.0 |
| | Ri3996 | 36.1 | 128.06 | 241.9 |
| | Ri3997 | 10.7 | 47.77 | 21.5 |
| | Ri3998 | 8.6 | 41.52 | 11.3 |
| | Ri3999 | 5.6 | 24.35 | 10.5 |
| | Ri4000 | 77.3 | 190.08 | 146.6 |
| G4 1000 | Ri4001 | 40.2 | 120.60 | 50.6 |
| | Ri4002 | 19.2 | 112.33 | 51.1 |
| | Ri4003 | 53.2 | 138.22 | 132.5 |
| | Ri4004 | 20.1 | 131.50 | 107.5 |
| | Ri4005 | 32.0 | 105.03 | 114.3 |
| | Ri4006 | 10.2 | 57.94 | 43.1 |
| | Ri4007 | 30.8 | 89.20 | 91.7 |
| | Ri4008 | 1.7 | 41.55 | 11.4 |
| | Ri4009 | 40.0 | 137.52 | 128.5 |
| | Ri4010 | 16.2 | 105.49 | 55.5 |

APPENDIX 19. Individual Terminal Fasting Body Weights and Organ Weights (g) - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Fasting Bwt (g) | Organ weights (g) | | | | | | | | | | | |
|---|---------|-----------------------|-------------------|--------|---------|--------|--------|--------|-------|-------|----------|----------|-----------|----------|
| | | | Adrenals | Testes | Kidneys | Liver | Thymus | Spleen | Heart | Brain | Prostate | Epididym | Pituitary | Thyroid* |
| G1 0 | Ri3931 | 281.41 | 0.049 | 3.154 | 1.525 | 6.981 | 0.293 | 0.594 | 0.780 | 2.046 | 0.684 | 1.118 | 0.015 | 0.031 |
| | Ri3932 | 284.73 | 0.059 | 3.162 | 1.915 | 6.755 | 0.245 | 0.549 | 0.790 | 1.959 | 0.881 | 1.149 | 0.008 | 0.021 |
| | Ri3933 | 318.43 | 0.074 | 3.135 | 1.830 | 8.795 | 0.421 | 0.688 | 0.966 | 2.219 | 0.933 | 1.290 | 0.008 | 0.032 |
| | Ri3934 | 384.66 | 0.050 | 2.742 | 1.837 | 6.265 | 0.308 | 0.408 | 0.731 | 1.832 | 0.997 | 1.149 | 0.015 | 0.030 |
| | Ri3935 | 367.18 | 0.063 | 3.120 | 1.940 | 9.193 | 0.371 | 0.625 | 0.900 | 1.980 | 0.848 | 1.174 | 0.016 | 0.032 |
| | Ri3936 | 354.97 | 0.057 | 3.471 | 1.842 | 6.950 | 0.165 | 0.481 | 0.831 | 2.012 | 0.857 | 1.139 | 0.012 | 0.020 |
| | Ri3937 | 360.69 | 0.046 | 3.312 | 2.006 | 9.546 | 0.389 | 0.623 | 1.074 | 2.039 | 0.986 | 1.311 | 0.013 | 0.024 |
| | Ri3938 | 365.27 | 0.060 | 3.842 | 2.181 | 8.699 | 0.430 | 0.720 | 1.061 | 2.173 | 0.889 | 1.370 | 0.014 | 0.044 |
| | Ri3939 | 402.59 | 0.071 | 3.585 | 2.082 | 8.552 | 0.435 | 0.635 | 1.159 | 2.200 | 0.780 | 1.281 | 0.007 | 0.043 |
| | Ri3940 | 404.84 | 0.073 | 3.782 | 2.407 | 11.955 | 0.368 | 0.820 | 1.262 | 2.061 | 1.031 | 1.493 | 0.011 | 0.026 |
| G2 100 | Ri3941 | 361.91 | 0.073 | 3.997 | 2.423 | 9.408 | 0.377 | 0.771 | 1.008 | 1.933 | 0.905 | 1.408 | 0.014 | 0.019 |
| | Ri3942 | 344.39 | 0.054 | 2.583 | 1.746 | 7.485 | 0.317 | 0.616 | 0.904 | 2.091 | 0.769 | 1.397 | 0.015 | 0.033 |
| | Ri3943 | 337.75 | 0.067 | 3.151 | 1.967 | 8.988 | 0.391 | 0.624 | 0.961 | 2.233 | 1.182 | 1.164 | 0.014 | 0.034 |
| | Ri3944 | 366.63 | 0.062 | 3.387 | 2.092 | 8.989 | 0.439 | 0.638 | 1.055 | 2.080 | 1.022 | 1.307 | 0.014 | 0.031 |
| | Ri3945 | 337.76 | 0.075 | 2.915 | 1.890 | 8.125 | 0.317 | 0.625 | 0.916 | 1.987 | 0.909 | 1.029 | 0.011 | 0.033 |
| | Ri3946 | 377.82 | 0.080 | 3.919 | 2.274 | 9.372 | 0.351 | 0.808 | 1.055 | 2.092 | 0.830 | 1.318 | 0.010 | 0.029 |
| | Ri3947 | 309.65 | 0.063 | 2.735 | 1.706 | 7.636 | 0.257 | 0.601 | 0.922 | 2.127 | 0.650 | 1.044 | 0.012 | 0.025 |
| | Ri3948 | 336.91 | 0.062 | 3.667 | 1.912 | 8.370 | 0.356 | 0.552 | 0.959 | 2.096 | 0.943 | 1.247 | 0.008 | 0.036 |
| | Ri3949 | 327.68 | 0.062 | 3.461 | 1.981 | 8.071 | 0.268 | 0.671 | 0.948 | 1.979 | 0.835 | 1.456 | 0.013 | 0.041 |
| | Ri3950 | 316.42 | 0.063 | 3.613 | 1.949 | 8.930 | 0.390 | 0.646 | 1.067 | 2.143 | 0.975 | 1.269 | 0.011 | 0.041 |

*: With parathyroids

APPENDIX 19 contd. Individual Terminal Fasting Body Weights and Organ Weights (g) - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Fasting Bwt (g) | Organ weights (g) | | | | | | | | | | | |
|---|---------|-----------------------|-------------------|--------|---------|--------|--------|--------|-------|-------|----------|----------|-----------|----------|
| | | | Adrenals | Testes | Kidneys | Liver | Thymus | Spleen | Heart | Brain | Prostate | Epididym | Pituitary | Thyroid* |
| G3 300 | Ri3951 | 377.94 | 0.066 | 3.162 | 2.369 | 10.227 | 0.313 | 0.739 | 1.073 | 2.123 | 1.136 | 1.356 | 0.013 | 0.034 |
| | Ri3952 | 341.90 | 0.056 | 3.331 | 1.995 | 7.673 | 0.381 | 0.565 | 0.943 | 1.847 | 0.911 | 1.319 | 0.010 | 0.033 |
| | Ri3953 | 403.37 | 0.062 | 3.440 | 2.161 | 11.169 | 0.465 | 0.713 | 1.166 | 2.163 | 1.033 | 1.171 | 0.017 | 0.034 |
| | Ri3954 | 374.58 | 0.069 | 3.392 | 2.186 | 8.620 | 0.396 | 0.662 | 0.996 | 2.082 | 0.797 | 1.335 | 0.013 | 0.023 |
| | Ri3955 | 391.65 | 0.050 | 3.467 | 2.228 | 9.917 | 0.317 | 0.689 | 1.074 | 2.138 | 0.940 | 1.179 | 0.010 | 0.034 |
| | Ri3956 | 351.17 | 0.058 | 3.222 | 1.685 | 8.979 | 0.391 | 0.590 | 0.955 | 2.094 | 0.766 | 1.315 | 0.008 | 0.038 |
| | Ri3957 | 348.79 | 0.077 | 3.565 | 2.021 | 8.870 | 0.365 | 0.567 | 1.063 | 2.049 | 0.865 | 1.421 | 0.009 | 0.026 |
| | Ri3958 | 290.34 | 0.057 | 3.500 | 1.712 | 6.134 | 0.246 | 0.527 | 0.834 | 2.031 | 0.952 | 1.097 | 0.008 | 0.023 |
| | Ri3959 | 377.72 | 0.073 | 3.875 | 2.103 | 9.243 | 0.274 | 0.734 | 0.987 | 2.181 | 0.814 | 1.533 | 0.013 | 0.038 |
| | Ri3960 | 337.68 | 0.053 | 3.061 | 1.838 | 7.897 | 0.419 | 0.631 | 0.885 | 2.020 | 0.990 | 1.041 | 0.013 | 0.041 |
| G4 1000 | Ri3961 | 339.54 | 0.058 | 3.642 | 2.125 | 8.165 | 0.316 | 0.681 | 0.935 | 2.068 | 0.986 | 1.304 | 0.011 | 0.020 |
| | Ri3962 | 345.72 | 0.047 | 3.580 | 2.224 | 9.341 | 0.241 | 0.610 | 1.007 | 2.016 | 1.020 | 1.120 | 0.009 | 0.025 |
| | Ri3963 | 345.31 | 0.061 | 3.761 | 2.103 | 8.484 | 0.337 | 0.562 | 0.962 | 2.136 | 0.892 | 1.343 | 0.011 | 0.031 |
| | Ri3964 | 335.18 | 0.065 | 3.503 | 2.060 | 8.043 | 0.353 | 0.638 | 1.030 | 2.075 | 0.860 | 1.410 | 0.013 | 0.027 |
| | Ri3965 | 343.71 | 0.058 | 2.980 | 1.617 | 7.722 | 0.297 | 0.540 | 0.934 | 2.083 | 0.606 | 1.165 | 0.020 | 0.032 |
| | Ri3966 | 314.58 | 0.057 | 3.357 | 1.611 | 7.493 | 0.264 | 0.552 | 0.772 | 1.958 | 0.845 | 1.301 | 0.007 | 0.027 |
| | Ri3967 | 363.30 | 0.070 | 3.336 | 1.969 | 8.682 | 0.328 | 0.674 | 0.931 | 2.184 | 1.257 | 1.244 | 0.010 | 0.025 |
| | Ri3968 | 385.17 | 0.070 | 3.503 | 2.314 | 9.794 | 0.320 | 0.634 | 1.128 | 2.044 | 1.168 | 1.376 | 0.012 | 0.017 |
| | Ri3969 | 358.09 | 0.042 | 3.158 | 2.002 | 9.035 | 0.343 | 0.580 | 0.953 | 2.047 | 0.750 | 1.219 | 0.010 | 0.020 |
| | Ri3970 | 321.37 | 0.053 | 3.660 | 1.973 | 8.756 | 0.312 | 0.648 | 0.942 | 2.068 | 0.901 | 1.325 | 0.007 | 0.022 |

*: With parathyroids

APPENDIX 20. Individual Terminal Fasting Body Weights and Organ Weight Ratios (%) - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Fasting Bwt (g) | Organ weight ratios (%) | | | | | | | | | | | |
|---|---------|-----------------------|-------------------------|--------|---------|-------|--------|--------|-------|-------|----------|----------|-----------|----------|
| | | | Adrenals | Testes | Kidneys | Liver | Thymus | Spleen | Heart | Brain | Prostate | Epididym | Pituitary | Thyroid* |
| G1 0 | Ri3931 | 281.41 | 0.017 | 1.121 | 0.542 | 2.481 | 0.104 | 0.211 | 0.277 | 0.727 | 0.243 | 0.397 | 0.005 | 0.011 |
| | Ri3932 | 284.73 | 0.021 | 1.111 | 0.673 | 2.372 | 0.086 | 0.193 | 0.277 | 0.688 | 0.309 | 0.404 | 0.003 | 0.007 |
| | Ri3933 | 318.43 | 0.023 | 0.985 | 0.575 | 2.762 | 0.132 | 0.216 | 0.303 | 0.697 | 0.293 | 0.405 | 0.003 | 0.010 |
| | Ri3934 | 384.66 | 0.013 | 0.713 | 0.478 | 1.629 | 0.080 | 0.106 | 0.190 | 0.476 | 0.259 | 0.299 | 0.004 | 0.008 |
| | Ri3935 | 367.18 | 0.017 | 0.850 | 0.528 | 2.504 | 0.101 | 0.170 | 0.245 | 0.539 | 0.231 | 0.320 | 0.004 | 0.009 |
| | Ri3936 | 354.97 | 0.016 | 0.978 | 0.519 | 1.958 | 0.046 | 0.136 | 0.234 | 0.567 | 0.241 | 0.321 | 0.003 | 0.006 |
| | Ri3937 | 360.69 | 0.013 | 0.918 | 0.556 | 2.647 | 0.108 | 0.173 | 0.298 | 0.565 | 0.273 | 0.363 | 0.004 | 0.007 |
| | Ri3938 | 365.27 | 0.016 | 1.052 | 0.597 | 2.382 | 0.118 | 0.197 | 0.290 | 0.595 | 0.243 | 0.375 | 0.004 | 0.012 |
| | Ri3939 | 402.59 | 0.018 | 0.890 | 0.517 | 2.124 | 0.108 | 0.158 | 0.288 | 0.546 | 0.194 | 0.318 | 0.002 | 0.011 |
| | Ri3940 | 404.84 | 0.018 | 0.934 | 0.595 | 2.953 | 0.091 | 0.203 | 0.312 | 0.509 | 0.255 | 0.369 | 0.003 | 0.006 |
| G2 100 | Ri3941 | 361.91 | 0.020 | 1.104 | 0.670 | 2.600 | 0.104 | 0.213 | 0.279 | 0.534 | 0.250 | 0.389 | 0.004 | 0.005 |
| | Ri3942 | 344.39 | 0.016 | 0.750 | 0.507 | 2.173 | 0.092 | 0.179 | 0.262 | 0.607 | 0.223 | 0.406 | 0.004 | 0.010 |
| | Ri3943 | 337.75 | 0.020 | 0.933 | 0.582 | 2.661 | 0.116 | 0.185 | 0.285 | 0.661 | 0.350 | 0.345 | 0.004 | 0.010 |
| | Ri3944 | 366.63 | 0.017 | 0.924 | 0.571 | 2.452 | 0.120 | 0.174 | 0.288 | 0.567 | 0.279 | 0.356 | 0.004 | 0.008 |
| | Ri3945 | 337.76 | 0.022 | 0.863 | 0.560 | 2.406 | 0.094 | 0.185 | 0.271 | 0.588 | 0.269 | 0.305 | 0.003 | 0.010 |
| | Ri3946 | 377.82 | 0.021 | 1.037 | 0.602 | 2.481 | 0.093 | 0.214 | 0.279 | 0.554 | 0.220 | 0.349 | 0.003 | 0.008 |
| | Ri3947 | 309.65 | 0.020 | 0.883 | 0.551 | 2.466 | 0.083 | 0.194 | 0.298 | 0.687 | 0.210 | 0.337 | 0.004 | 0.008 |
| | Ri3948 | 336.91 | 0.018 | 1.088 | 0.568 | 2.484 | 0.106 | 0.164 | 0.285 | 0.622 | 0.280 | 0.370 | 0.002 | 0.011 |
| | Ri3949 | 327.68 | 0.019 | 1.056 | 0.605 | 2.463 | 0.082 | 0.205 | 0.289 | 0.604 | 0.255 | 0.444 | 0.004 | 0.013 |
| | Ri3950 | 316.42 | 0.020 | 1.142 | 0.616 | 2.822 | 0.123 | 0.204 | 0.337 | 0.677 | 0.308 | 0.401 | 0.003 | 0.013 |

*: With parathyroids

APPENDIX 20 contd. Individual Terminal Fasting Body Weights and Organ Weight Ratios (%) - Males

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Fasting Bwt (g) | Organ weight ratios (%) | | | | | | | | | | | |
|---|---------|-----------------------|-------------------------|--------|---------|-------|--------|--------|-------|-------|----------|----------|-----------|----------|
| | | | Adrenals | Testes | Kidneys | Liver | Thymus | Spleen | Heart | Brain | Prostate | Epididym | Pituitary | Thyroid* |
| G3 300 | Ri3951 | 377.94 | 0.017 | 0.837 | 0.627 | 2.706 | 0.083 | 0.196 | 0.284 | 0.562 | 0.301 | 0.359 | 0.003 | 0.009 |
| | Ri3952 | 341.90 | 0.016 | 0.974 | 0.584 | 2.244 | 0.111 | 0.165 | 0.276 | 0.540 | 0.266 | 0.386 | 0.003 | 0.010 |
| | Ri3953 | 403.37 | 0.015 | 0.853 | 0.536 | 2.769 | 0.115 | 0.177 | 0.289 | 0.536 | 0.256 | 0.290 | 0.004 | 0.008 |
| | Ri3954 | 374.58 | 0.018 | 0.906 | 0.584 | 2.301 | 0.106 | 0.177 | 0.266 | 0.556 | 0.213 | 0.356 | 0.003 | 0.006 |
| | Ri3955 | 391.65 | 0.013 | 0.885 | 0.569 | 2.532 | 0.081 | 0.176 | 0.274 | 0.546 | 0.240 | 0.301 | 0.003 | 0.009 |
| | Ri3956 | 351.17 | 0.017 | 0.918 | 0.480 | 2.557 | 0.111 | 0.168 | 0.272 | 0.596 | 0.218 | 0.374 | 0.002 | 0.011 |
| | Ri3957 | 348.79 | 0.022 | 1.022 | 0.579 | 2.543 | 0.105 | 0.163 | 0.305 | 0.587 | 0.248 | 0.407 | 0.003 | 0.007 |
| | Ri3958 | 290.34 | 0.020 | 1.205 | 0.590 | 2.113 | 0.085 | 0.182 | 0.287 | 0.700 | 0.328 | 0.378 | 0.003 | 0.008 |
| | Ri3959 | 377.72 | 0.019 | 1.026 | 0.557 | 2.447 | 0.073 | 0.194 | 0.261 | 0.577 | 0.216 | 0.406 | 0.003 | 0.010 |
| | Ri3960 | 337.68 | 0.016 | 0.906 | 0.544 | 2.339 | 0.124 | 0.187 | 0.262 | 0.598 | 0.293 | 0.308 | 0.004 | 0.012 |
| G4 1000 | Ri3961 | 339.54 | 0.017 | 1.073 | 0.626 | 2.405 | 0.093 | 0.201 | 0.275 | 0.609 | 0.290 | 0.384 | 0.003 | 0.006 |
| | Ri3962 | 345.72 | 0.014 | 1.036 | 0.643 | 2.702 | 0.070 | 0.176 | 0.291 | 0.583 | 0.295 | 0.324 | 0.003 | 0.007 |
| | Ri3963 | 345.31 | 0.018 | 1.089 | 0.609 | 2.457 | 0.098 | 0.163 | 0.279 | 0.619 | 0.258 | 0.389 | 0.003 | 0.009 |
| | Ri3964 | 335.18 | 0.019 | 1.045 | 0.615 | 2.400 | 0.105 | 0.190 | 0.307 | 0.619 | 0.257 | 0.421 | 0.004 | 0.008 |
| | Ri3965 | 343.71 | 0.017 | 0.867 | 0.470 | 2.247 | 0.086 | 0.157 | 0.272 | 0.606 | 0.176 | 0.339 | 0.006 | 0.009 |
| | Ri3966 | 314.58 | 0.018 | 1.067 | 0.512 | 2.382 | 0.084 | 0.175 | 0.245 | 0.622 | 0.269 | 0.414 | 0.002 | 0.009 |
| | Ri3967 | 363.30 | 0.019 | 0.918 | 0.542 | 2.390 | 0.090 | 0.186 | 0.256 | 0.601 | 0.346 | 0.342 | 0.003 | 0.007 |
| | Ri3968 | 385.17 | 0.018 | 0.909 | 0.601 | 2.543 | 0.083 | 0.165 | 0.293 | 0.531 | 0.303 | 0.357 | 0.003 | 0.004 |
| | Ri3969 | 358.09 | 0.012 | 0.882 | 0.559 | 2.523 | 0.096 | 0.162 | 0.266 | 0.572 | 0.209 | 0.340 | 0.003 | 0.006 |
| | Ri3970 | 321.37 | 0.016 | 1.139 | 0.614 | 2.725 | 0.097 | 0.202 | 0.293 | 0.643 | 0.280 | 0.412 | 0.002 | 0.007 |

*: With parathyroids

APPENDIX 21. Individual Terminal Fasting Body Weights and Organ Weights (g) - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Fasting Bwt (g) | Organ weights (g) | | | | | | | | | | |
|---|---------|-----------------------|-------------------|---------|---------|-------|--------|--------|-------|-------|-----------------------|-----------|----------|
| | | | Adrenals | Ovaries | Kidneys | Liver | Thymus | Spleen | Heart | Brain | Uterus with cervix | Pituitary | Thyroid* |
| G1 0 | Ri3971 | 207.54 | 0.079 | 0.098 | 1.249 | 6.114 | 0.352 | 0.415 | 0.639 | 1.990 | 0.736 | 0.013 | 0.034 |
| | Ri3972 | 227.26 | 0.071 | 0.098 | 1.430 | 6.624 | 0.412 | 0.532 | 0.676 | 1.963 | 0.704 | 0.022 | 0.029 |
| | Ri3973 | 199.91 | 0.068 | 0.071 | 1.313 | 5.997 | 0.377 | 0.422 | 0.653 | 1.876 | 1.054 | 0.017 | 0.032 |
| | Ri3974 | 202.08 | 0.092 | 0.128 | 1.234 | 6.132 | 0.256 | 0.340 | 0.661 | 2.001 | 0.779 | 0.015 | 0.027 |
| | Ri3975 | 209.84 | 0.082 | 0.093 | 1.300 | 5.648 | 0.377 | 0.415 | 0.653 | 1.844 | 0.509 | 0.019 | 0.016 |
| | Ri3976 | 205.99 | 0.077 | 0.150 | 1.263 | 5.823 | 0.408 | 0.574 | 0.613 | 1.885 | 0.451 | 0.014 | 0.024 |
| | Ri3977 | 191.07 | 0.076 | 0.099 | 1.197 | 5.413 | 0.331 | 0.358 | 0.663 | 2.004 | 0.873 | 0.012 | 0.022 |
| | Ri3978 | 205.57 | 0.092 | 0.179 | 1.256 | 5.894 | 0.340 | 0.441 | 0.653 | 2.004 | 0.696 | 0.009 | 0.032 |
| | Ri3979 | 201.03 | 0.084 | 0.084 | 1.292 | 5.847 | 0.313 | 0.418 | 0.612 | 2.111 | 0.588 | 0.017 | 0.029 |
| | Ri3980 | 224.01 | 0.072 | 0.079 | 1.379 | 6.484 | 0.347 | 0.529 | 0.661 | 1.880 | 0.639 | 0.020 | 0.034 |
| G2 100 | Ri3981 | 230.00 | 0.075 | 0.101 | 1.395 | 6.451 | 0.412 | 0.508 | 0.679 | 1.918 | 1.146 | 0.017 | 0.029 |
| | Ri3982 | 210.66 | 0.077 | 0.094 | 1.334 | 6.606 | 0.283 | 0.600 | 0.691 | 1.985 | 0.533 | 0.015 | 0.023 |
| | Ri3983 | 217.47 | 0.085 | 0.135 | 1.421 | 5.775 | 0.548 | 0.437 | 0.673 | 1.875 | 0.876 | 0.014 | 0.035 |
| | Ri3984 | 220.86 | 0.074 | 0.106 | 1.239 | 5.467 | 0.483 | 0.428 | 0.645 | 1.917 | 0.471 | 0.012 | 0.023 |
| | Ri3985 | 197.27 | 0.084 | 0.092 | 1.221 | 5.613 | 0.343 | 0.406 | 0.640 | 1.826 | 0.550 | 0.014 | 0.023 |
| | Ri3986 | 216.53 | 0.065 | 0.082 | 1.280 | 5.237 | 0.334 | 0.400 | 0.658 | 1.963 | 0.592 | 0.009 | 0.035 |
| | Ri3987 | 217.29 | 0.075 | 0.090 | 1.381 | 6.103 | 0.335 | 0.518 | 0.773 | 2.067 | 0.440 | 0.022 | 0.030 |
| | Ri3988 | 205.69 | 0.072 | 0.075 | 1.256 | 5.891 | 0.289 | 0.389 | 0.645 | 2.060 | 0.577 | 0.012 | 0.022 |
| | Ri3989 | 194.04 | 0.071 | 0.086 | 1.139 | 5.180 | 0.274 | 0.494 | 0.647 | 1.970 | 0.763 | 0.022 | 0.023 |
| | Ri3990 | 230.13 | 0.116 | 0.112 | 1.498 | 6.618 | 0.386 | 0.560 | 0.816 | 2.056 | 0.642 | 0.017 | 0.041 |

*: With parathyroids

APPENDIX 21 contd. Individual Terminal Fasting Body Weights and Organ Weights (g) - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Fasting Bwt (g) | Organ weights (g) | | | | | | | | | | Thyroid* |
|---|---------|-----------------------|-------------------|---------|---------|-------|--------|--------|-------|-------|-----------------------|-----------|----------|
| | | | Adrenals | Ovaries | Kidneys | Liver | Thymus | Spleen | Heart | Brain | Uterus with cervix | Pituitary | |
| G3 300 | Ri3991 | 205.02 | 0.069 | 0.073 | 1.157 | 5.044 | 0.367 | 0.506 | 0.649 | 1.931 | 0.553 | 0.017 | 0.025 |
| | Ri3992 | 227.48 | 0.085 | 0.082 | 1.324 | 5.145 | 0.287 | 0.488 | 0.683 | 1.947 | 1.034 | 0.020 | 0.025 |
| | Ri3993 | 218.44 | 0.087 | 0.074 | 1.307 | 6.025 | 0.419 | 0.501 | 0.660 | 1.939 | 1.024 | 0.016 | 0.030 |
| | Ri3994 | 209.38 | 0.072 | 0.088 | 1.307 | 6.065 | 0.401 | 0.429 | 0.700 | 1.901 | 0.498 | 0.010 | 0.024 |
| | Ri3995 | 206.07 | 0.058 | 0.086 | 1.272 | 4.991 | 0.361 | 0.484 | 0.653 | 1.892 | 0.533 | 0.011 | 0.019 |
| | Ri3996 | 207.55 | 0.082 | 0.109 | 1.345 | 6.206 | 0.378 | 0.623 | 0.719 | 2.106 | 0.610 | 0.008 | 0.023 |
| | Ri3997 | 218.52 | 0.083 | 0.123 | 1.391 | 6.004 | 0.387 | 0.461 | 0.694 | 1.968 | 0.739 | 0.019 | 0.024 |
| | Ri3998 | 195.15 | 0.087 | 0.104 | 1.119 | 4.861 | 0.328 | 0.515 | 0.619 | 1.745 | 0.498 | 0.009 | 0.017 |
| | Ri3999 | 242.60 | 0.097 | 0.104 | 1.565 | 6.748 | 0.354 | 0.480 | 0.766 | 2.045 | 0.664 | 0.015 | 0.025 |
| | Ri4000 | 219.70 | 0.076 | 0.107 | 1.359 | 6.381 | 0.305 | 0.507 | 0.666 | 1.855 | 0.496 | 0.016 | 0.023 |
| G4 1000 | Ri4001 | 227.79 | 0.101 | 0.073 | 1.427 | 6.614 | 0.351 | 0.563 | 0.734 | 2.045 | 0.538 | 0.019 | 0.029 |
| | Ri4002 | 206.52 | 0.069 | 0.113 | 1.453 | 5.527 | 0.262 | 0.421 | 0.725 | 2.047 | 0.638 | 0.023 | 0.026 |
| | Ri4003 | 220.40 | 0.094 | 0.099 | 1.502 | 7.500 | 0.390 | 0.454 | 0.731 | 1.837 | 0.535 | 0.017 | 0.023 |
| | Ri4004 | 206.36 | 0.076 | 0.114 | 1.403 | 5.854 | 0.301 | 0.391 | 0.628 | 1.852 | 0.435 | 0.014 | 0.021 |
| | Ri4005 | 201.75 | 0.074 | 0.085 | 1.261 | 6.049 | 0.316 | 0.533 | 0.671 | 1.983 | 0.717 | 0.016 | 0.022 |
| | Ri4006 | 199.00 | 0.073 | 0.103 | 1.181 | 4.569 | 0.290 | 0.469 | 0.525 | 1.910 | 0.590 | 0.010 | 0.022 |
| | Ri4007 | 208.33 | 0.066 | 0.092 | 1.318 | 7.083 | 0.344 | 0.459 | 0.746 | 1.933 | 1.023 | 0.018 | 0.026 |
| | Ri4008 | 209.57 | 0.069 | 0.094 | 1.223 | 5.601 | 0.334 | 0.401 | 0.738 | 1.930 | 0.554 | 0.016 | 0.022 |
| | Ri4009 | 208.98 | 0.060 | 0.088 | 1.263 | 5.184 | 0.313 | 0.482 | 0.635 | 1.989 | 1.320 | 0.012 | 0.026 |
| | Ri4010 | 207.10 | 0.082 | 0.103 | 1.340 | 6.436 | 0.324 | 0.530 | 0.721 | 1.801 | 0.711 | 0.020 | 0.025 |

*: With parathyroids

APPENDIX 22. Individual Terminal Fasting Body Weights and Organ Weight Ratios (%) - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Fasting Bwt (g) | Organ weight ratios (%) | | | | | | | | | | |
|---|---------|-----------------------|-------------------------|---------|---------|-------|--------|--------|-------|-------|-----------------------|-----------|----------|
| | | | Adrenals | Ovaries | Kidneys | Liver | Thymus | Spleen | Heart | Brain | Uterus with cervix | Pituitary | Thyroid* |
| G1 0 | Ri3971 | 207.54 | 0.038 | 0.047 | 0.602 | 2.946 | 0.170 | 0.200 | 0.308 | 0.959 | 0.355 | 0.006 | 0.016 |
| | Ri3972 | 227.26 | 0.031 | 0.043 | 0.629 | 2.915 | 0.181 | 0.234 | 0.297 | 0.864 | 0.310 | 0.010 | 0.013 |
| | Ri3973 | 199.91 | 0.034 | 0.036 | 0.657 | 3.000 | 0.189 | 0.211 | 0.327 | 0.938 | 0.527 | 0.009 | 0.016 |
| | Ri3974 | 202.08 | 0.046 | 0.063 | 0.611 | 3.034 | 0.127 | 0.168 | 0.327 | 0.990 | 0.385 | 0.007 | 0.013 |
| | Ri3975 | 209.84 | 0.039 | 0.044 | 0.620 | 2.692 | 0.180 | 0.198 | 0.311 | 0.879 | 0.243 | 0.009 | 0.008 |
| | Ri3976 | 205.99 | 0.037 | 0.073 | 0.613 | 2.827 | 0.198 | 0.279 | 0.298 | 0.915 | 0.219 | 0.007 | 0.012 |
| | Ri3977 | 191.07 | 0.040 | 0.052 | 0.626 | 2.833 | 0.173 | 0.187 | 0.347 | 1.049 | 0.457 | 0.006 | 0.012 |
| | Ri3978 | 205.57 | 0.045 | 0.087 | 0.611 | 2.867 | 0.165 | 0.215 | 0.318 | 0.975 | 0.339 | 0.004 | 0.016 |
| | Ri3979 | 201.03 | 0.042 | 0.042 | 0.643 | 2.909 | 0.156 | 0.208 | 0.304 | 1.050 | 0.292 | 0.008 | 0.014 |
| | Ri3980 | 224.01 | 0.032 | 0.035 | 0.616 | 2.895 | 0.155 | 0.236 | 0.295 | 0.839 | 0.285 | 0.009 | 0.015 |
| G2 100 | Ri3981 | 230.00 | 0.033 | 0.044 | 0.607 | 2.805 | 0.179 | 0.221 | 0.295 | 0.834 | 0.498 | 0.007 | 0.013 |
| | Ri3982 | 210.66 | 0.037 | 0.045 | 0.633 | 3.136 | 0.134 | 0.285 | 0.328 | 0.942 | 0.253 | 0.007 | 0.011 |
| | Ri3983 | 217.47 | 0.039 | 0.062 | 0.653 | 2.656 | 0.252 | 0.201 | 0.309 | 0.862 | 0.403 | 0.006 | 0.016 |
| | Ri3984 | 220.86 | 0.034 | 0.048 | 0.561 | 2.475 | 0.219 | 0.194 | 0.292 | 0.868 | 0.213 | 0.005 | 0.010 |
| | Ri3985 | 197.27 | 0.043 | 0.047 | 0.619 | 2.845 | 0.174 | 0.206 | 0.324 | 0.926 | 0.279 | 0.007 | 0.012 |
| | Ri3986 | 216.53 | 0.030 | 0.038 | 0.591 | 2.419 | 0.154 | 0.185 | 0.304 | 0.907 | 0.273 | 0.004 | 0.016 |
| | Ri3987 | 217.29 | 0.035 | 0.041 | 0.636 | 2.809 | 0.154 | 0.238 | 0.356 | 0.951 | 0.202 | 0.010 | 0.014 |
| | Ri3988 | 205.69 | 0.035 | 0.036 | 0.611 | 2.864 | 0.141 | 0.189 | 0.314 | 1.002 | 0.281 | 0.006 | 0.011 |
| | Ri3989 | 194.04 | 0.037 | 0.044 | 0.587 | 2.670 | 0.141 | 0.255 | 0.333 | 1.015 | 0.393 | 0.011 | 0.012 |
| | Ri3990 | 230.13 | 0.050 | 0.049 | 0.651 | 2.876 | 0.168 | 0.243 | 0.355 | 0.893 | 0.279 | 0.007 | 0.018 |

*: With parathyroids

APPENDIX 22 contd. Individual Terminal Fasting Body Weights and Organ Weight Ratios (%) - Females

| Group No. Dose (mg TOS/kg bwt/day) | Rat No. | Fasting Bwt (g) | Organ weight ratios (%) | | | | | | | | | | Thyroid* |
|---|---------|-----------------------|-------------------------|---------|---------|-------|--------|--------|-------|-------|-----------------------|-----------|----------|
| | | | Adrenals | Ovaries | Kidneys | Liver | Thymus | Spleen | Heart | Brain | Uterus with cervix | Pituitary | |
| G3 300 | Ri3991 | 205.02 | 0.034 | 0.036 | 0.564 | 2.460 | 0.179 | 0.247 | 0.317 | 0.942 | 0.270 | 0.008 | 0.012 |
| | Ri3992 | 227.48 | 0.037 | 0.036 | 0.582 | 2.262 | 0.126 | 0.215 | 0.300 | 0.856 | 0.455 | 0.009 | 0.011 |
| | Ri3993 | 218.44 | 0.040 | 0.034 | 0.598 | 2.758 | 0.192 | 0.229 | 0.302 | 0.888 | 0.469 | 0.007 | 0.014 |
| | Ri3994 | 209.38 | 0.034 | 0.042 | 0.624 | 2.897 | 0.192 | 0.205 | 0.334 | 0.908 | 0.238 | 0.005 | 0.011 |
| | Ri3995 | 206.07 | 0.028 | 0.042 | 0.617 | 2.422 | 0.175 | 0.235 | 0.317 | 0.918 | 0.259 | 0.005 | 0.009 |
| | Ri3996 | 207.55 | 0.040 | 0.053 | 0.648 | 2.990 | 0.182 | 0.300 | 0.346 | 1.015 | 0.294 | 0.004 | 0.011 |
| | Ri3997 | 218.52 | 0.038 | 0.056 | 0.637 | 2.748 | 0.177 | 0.211 | 0.318 | 0.901 | 0.338 | 0.009 | 0.011 |
| | Ri3998 | 195.15 | 0.045 | 0.053 | 0.573 | 2.491 | 0.168 | 0.264 | 0.317 | 0.894 | 0.255 | 0.005 | 0.009 |
| | Ri3999 | 242.60 | 0.040 | 0.043 | 0.645 | 2.782 | 0.146 | 0.198 | 0.316 | 0.843 | 0.274 | 0.006 | 0.010 |
| | Ri4000 | 219.70 | 0.035 | 0.049 | 0.619 | 2.904 | 0.139 | 0.231 | 0.303 | 0.844 | 0.226 | 0.007 | 0.010 |
| G4 1000 | Ri4001 | 227.79 | 0.044 | 0.032 | 0.626 | 2.904 | 0.154 | 0.247 | 0.322 | 0.898 | 0.236 | 0.008 | 0.013 |
| | Ri4002 | 206.52 | 0.033 | 0.055 | 0.704 | 2.676 | 0.127 | 0.204 | 0.351 | 0.991 | 0.309 | 0.011 | 0.013 |
| | Ri4003 | 220.40 | 0.043 | 0.045 | 0.681 | 3.403 | 0.177 | 0.206 | 0.332 | 0.833 | 0.243 | 0.008 | 0.010 |
| | Ri4004 | 206.36 | 0.037 | 0.055 | 0.680 | 2.837 | 0.146 | 0.189 | 0.304 | 0.897 | 0.211 | 0.007 | 0.010 |
| | Ri4005 | 201.75 | 0.037 | 0.042 | 0.625 | 2.998 | 0.157 | 0.264 | 0.333 | 0.983 | 0.355 | 0.008 | 0.011 |
| | Ri4006 | 199.00 | 0.037 | 0.052 | 0.593 | 2.296 | 0.146 | 0.236 | 0.264 | 0.960 | 0.296 | 0.005 | 0.011 |
| | Ri4007 | 208.33 | 0.032 | 0.044 | 0.633 | 3.400 | 0.165 | 0.220 | 0.358 | 0.928 | 0.491 | 0.009 | 0.012 |
| | Ri4008 | 209.57 | 0.033 | 0.045 | 0.584 | 2.673 | 0.159 | 0.191 | 0.352 | 0.921 | 0.264 | 0.008 | 0.010 |
| | Ri4009 | 208.98 | 0.029 | 0.042 | 0.604 | 2.481 | 0.150 | 0.231 | 0.304 | 0.952 | 0.632 | 0.006 | 0.012 |
| | Ri4010 | 207.10 | 0.040 | 0.050 | 0.647 | 3.108 | 0.156 | 0.256 | 0.348 | 0.870 | 0.343 | 0.010 | 0.012 |

*: With parathyroids

APPENDIX 23. Individual Gross Pathological and Histopathological Findings - Males

| Group No. | Rat No. | Dose (mg TOS/kg bwt/day) | Gross | Microscopic |
|-----------|---------|--------------------------|--|---|
| G1 | Ri3931 | 0 | NAD | EYES WITH OPTIC NERVE(X8): Tissue present no change |
| G1 | Ri3932 | 0 | NAD | MAMMARY GLAND: Tissue not present MANDIBULAR LYMPH NODES: Hemorrhage 1-bilateral |
| G1 | Ri3933 | 0 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red | THYMUS: Hemorrhage 1 PROSTATE: Lymphocytic infiltration 1 MANDIBULAR LYMPH NODES: Hemorrhage 2-bilateral |
| G1 | Ri3934 | 0 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red | LUNGS: Increased alveolar macrophages 1 BRAIN-MEDULLA/PONS(X17): Tissue present no change EYES WITH OPTIC NERVE(X8): Tissue present no change MANDIBULAR LYMPH NODES: Hemorrhage 1-unilateral Plasma cell hyperplasia 1-bilateral |

1: Minimal, 2: Mild, 3: Moderate, 4: Severe

X8: Lens not present

X17: Pons not present

NAD: No Abnormality Detected

contd.

APPENDIX 23 contd. Individual Gross Pathological and Histopathological Findings - Males

| Group No. | Rat No. | Dose (mg TOS/kg bwt/day) | Gross | Microscopic |
|-----------|---------|--------------------------|---|---|
| G1 | Ri3939 | 0 | MANDIBULAR LYMPH NODE(Unilateral): Enlarged - 0.6 cm THYMUS: Petechiae | KIDNEYS: Dilatation of pelvis 1-unilateral THYMUS: Hemorrhage 1 BRAIN-MEDULLA/PONS(X17): Tissue present no change MANDIBULAR LYMPH NODES: Plasma cell hyperplasia 1-unilateral |
| G1 | Ri3940 | 0 | THYMUS: Petechiae | THYMUS: Hemorrhage 2 PROSTATE: Lymphocytic infiltration 1 BRAIN-MEDULLA/PONS(X17): Tissue present no change EYES WITH OPTIC NERVE(X8): Tissue present no change MAMMARY GLAND: Tissue not present |
| G2 | Ri3941 | 100 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red | MANDIBULAR LYMPH NODES: Hemorrhage 2-bilateral |
| G2 | Ri3942 | 100 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red | MANDIBULAR LYMPH NODES: Hemorrhage 2-bilateral |
| G2 | Ri3943 | 100 | THYMUS: Petechiae | THYMUS: Hemorrhage 1 |
| G2 | Ri3944 | 100 | NAD | Tissues not examined |

1: Minimal, 2: Mild, 3: Moderate, 4: Severe

X8: Lens not present

X17: Pons not present

NAD: No Abnormality Detected

contd.

CONFIDENTIAL

APPENDIX 23 contd. Individual Gross Pathological and Histopathological Findings - Males

| Group No. | Rat No. | Dose (mg TOS/kg bwt/day) | Gross | Microscopic |
|-----------|---------|--------------------------|---|---|
| G2 | Ri3945 | 100 | NAD | Tissues not examined |
| G2 | Ri3946 | 100 | NAD | Tissues not examined |
| G2 | Ri3947 | 100 | NAD | Tissues not examined |
| G2 | Ri3948 | 100 | NAD | Tissues not examined |
| G2 | Ri3949 | 100 | NAD | Tissues not examined |
| G2 | Ri3950 | 100 | NAD | Tissues not examined |
| G3 | Ri3951 | 300 | NAD | Tissues not examined |
| G3 | Ri3952 | 300 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red | MANDIBULAR LYMPH NODES: Hemorrhage 2-bilateral |
| G3 | Ri3953 | 300 | MANDIBULAR LYMPH NODE(Unilateral): Discoloration, Red | MANDIBULAR LYMPH NODES: Hemorrhage 1-unilateral |
| G3 | Ri3954 | 300 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red | MANDIBULAR LYMPH NODES: Hemorrhage 1-bilateral |

1: Minimal, 2: Mild, 3: Moderate, 4: Severe

NAD: No Abnormality Detected

contd.

CONFIDENTIAL

APPENDIX 23 contd. Individual Gross Pathological and Histopathological Findings - Males

| Group No. | Rat No. | Dose (mg TOS/kg bwt/day) | Gross | Microscopic |
|-----------|---------|--------------------------|---|--|
| G3 | Ri3955 | 300 | MANDIBULAR LYMPH NODE(Unilateral): Enlarged - 0.5 cm | MANDIBULAR LYMPH NODES: Lymphoid hyperplasia 1-unilateral Hemorrhage 1 |
| G3 | Ri3956 | 300 | MANDIBULAR LYMPH NODE(Unilateral): Discoloration, Red | MANDIBULAR LYMPH NODES: Hemorrhage 2-bilateral |
| G3 | Ri3957 | 300 | NAD | Tissues not examined |
| G3 | Ri3958 | 300 | NAD | Tissues not examined |
| G3 | Ri3959 | 300 | NAD | Tissues not examined |
| G3 | Ri3960 | 300 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red | MANDIBULAR LYMPH NODES: Hemorrhage 1-bilateral |
| G4 | Ri3961 | 1000 | MANDIBULAR LYMPH NODE(Unilateral): Discoloration, Red | LIVER: Chronic inflammatory focus(i) 1 THYMUS: Hemorrhage 1 PROSTATE: Lymphocytic infiltration 1 |

1: Minimal, 2: Mild, 3: Moderate, 4: Severe

NAD: No Abnormality Detected

contd.

APPENDIX 23 contd. Individual Gross Pathological and Histopathological Findings - Males

| Group No. | Rat No. | Dose (mg TOS/kg bwt/day) | Gross | Microscopic |
|-----------|---------|--------------------------|-------------------|--|
| G4 | Ri3961 | 1000 | | BRAIN-MEDULLA/PONS(X17): Tissue present no change MAMMARY GLAND: Tissue not present MANDIBULAR LYMPH NODES: Hemorrhage 1-bilateral |
| G4 | Ri3962 | 1000 | NAD | RECTUM: Nematode PITUITARY(X20): Tissue present no change MANDIBULAR LYMPH NODES: Hemorrhage 1-bilateral |
| G4 | Ri3963 | 1000 | NAD | LIVER: Chronic inflammatory focus(i) 1 PARATHYROID(X2): Tissue present no change BRAIN-MEDULLA/PONS(X17): Tissue present no change EYES WITH OPTIC NERVE(X8): Tissue present no change |
| G4 | Ri3964 | 1000 | THYMUS: Petechiae | LIVER: Chronic inflammatory focus(i) 1 LUNGS: Increased alveolar macrophages 1 PANCREAS: Increased acinar cell apoptosis 1 THYMUS: Hemorrhage 2 THYROID: Ectopic thymus PROSTATE: Lymphocytic infiltration 1 MANDIBULAR LYMPH NODES: Hemorrhage 1-unilateral |

1: Minimal, 2: Mild, 3: Moderate, 4: Severe

X17: Pons not present

X8: Lens not present

X2: One organ not present

X20: Pars nervosa not present

NAD: No Abnormality Detected

contd.

CONFIDENTIAL

APPENDIX 23 contd. Individual Gross Pathological and Histopathological Findings - Males

| Group No. | Rat No. | Dose (mg TOS/kg bwt/day) | Gross | Microscopic |
|-----------|---------|--------------------------|--|---|
| G4 | Ri3965 | 1000 | NAD | MAMMARY GLAND: Tissue not present |
| G4 | Ri3966 | 1000 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red MANDIBULAR LYMPH NODE(Unilateral): Enlarged - 1.0 cm | MAMMARY GLAND: Tissue not present MANDIBULAR LYMPH NODES: Hemorrhage 2-bilateral Lymphoid hyperplasia 1-unilateral |
| G4 | Ri3967 | 1000 | NAD | LUNGS: Inflammatory focus(i) 2 THYMUS: Hemorrhage 1 MAMMARY GLAND: Tissue not present |
| G4 | Ri3968 | 1000 | NAD | LUNGS: Inflammatory focus(i) 1 RECTUM: Nematode PROSTATE: Cell debris in lumen BRAIN-MEDULLA/PONS(X17): Tissue present no change |
| G4 | Ri3969 | 1000 | NAD | HEART: Inflammatory focus(i) 1 MAMMARY GLAND: Tissue not present |
| G4 | Ri3970 | 1000 | THYMUS: Petechiae | RECTUM: Nematode THYMUS: Hemorrhage 2 PITUITARY(X20): Tissue present no change |

contd.

1: Minimal, 2: Mild, 3: Moderate, 4: Severe
X17: Pons not present
X20: Pars nervosa not present
NAD: No Abnormality Detected

APPENDIX 24. Individual Gross Pathological and Histopathological Findings - Females

| Group No. | Rat No. | Dose (mg TOS/kg bwt/day) | Gross | Microscopic |
|-----------|---------|--------------------------|-------------------|---|
| G1 | Ri3971 | 0 | NAD | PARATHYROID(X2): Tissue present no change EYES WITH OPTIC NERVE(X2): Tissue present no change |
| G1 | Ri3972 | 0 | THYMUS: Petechiae | THYMUS: Hemorrhage 2 Epithelial cyst(s) EYES WITH OPTIC NERVE(X6): Tissue present no change MANDIBULAR LYMPH NODES: Hemorrhage 1-bilateral |
| G1 | Ri3973 | 0 | THYMUS: Petechiae | LIVER: Chronic inflammatory focus(i) 1 THYMUS: Hemorrhage 1 MANDIBULAR LYMPH NODES: Hemorrhage 1-bilateral |
| G1 | Ri3974 | 0 | NAD | LUNGS: Increased alveolar macrophages 1 THYROID: Ectopic thymus MANDIBULAR LYMPH NODES: Hemorrhage 1-unilateral |
| G1 | Ri3975 | 0 | NAD | PARATHYROID(X2): Tissue present no change |

1: Minimal, 2: Mild, 3: Moderate, 4: Severe

X2: One organ not present

X6: Optic nerve not present

NAD: No Abnormality Detected

contd.

APPENDIX 24 contd. Individual Gross Pathological and Histopathological Findings - Females

| Group No. | Rat No. | Dose (mg TOS/kg bwt/day) | Gross | Microscopic |
|-----------|---------|--------------------------|--|---|
| G1 | Ri3976 | 0 | NAD | RECTUM: Nematode EYES WITH OPTIC NERVE(X8): Tissue present no change |
| G1 | Ri3977 | 0 | NAD | PANCREAS: Inflammation-chronic 1 PITUITARY(X20): Tissue present no change MANDIBULAR LYMPH NODES: Hemorrhage 1-unilateral |
| G1 | Ri3978 | 0 | NAD | THYMUS: Epithelial cyst(s) PARATHYROID(X2): Tissue present no change PITUITARY(X20): Tissue present no change |
| G1 | Ri3979 | 0 | NAD | ADRENALS: Accessory cortical tissue |
| G1 | Ri3980 | 0 | NAD | PARATHYROID(X2): Tissue present no change |
| G2 | Ri3981 | 100 | MANDIBULAR LYMPH NODE(Unilateral): Enlarged - 1.0 cm | MANDIBULAR LYMPH NODES: Lymphoid hyperplasia 1-unilateral |

contd.

1: Minimal, 2: Mild, 3: Moderate, 4: Severe

X8: Lens not present

X20: Pars nervosa not present

X2: One organ not present

NAD: No Abnormality Detected

CONFIDENTIAL

APPENDIX 24 contd. Individual Gross Pathological and Histopathological Findings - Females

| Group No. | Rat No. | Dose (mg TOS/kg bwt/day) | Gross | Microscopic |
|-----------|---------|--------------------------|--|---|
| G2 | Ri3982 | 100 | LIVER: Hepatodiaphragmatic - Nodule - 0.8 cm | LIVER: Tissue present no change |
| G2 | Ri3983 | 100 | NAD | Tissues not examined |
| G2 | Ri3984 | 100 | NAD | Tissues not examined |
| G2 | Ri3985 | 100 | NAD | Tissues not examined |
| G2 | Ri3986 | 100 | NAD | Tissues not examined |
| G2 | Ri3987 | 100 | NAD | Tissues not examined |
| G2 | Ri3988 | 100 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red | MANDIBULAR LYMPH NODES: Hemorrhage 2-unilateral |
| G2 | Ri3989 | 100 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red | MANDIBULAR LYMPH NODES: Hemorrhage 2-unilateral |
| G2 | Ri3990 | 100 | NAD | Tissues not examined |
| G3 | Ri3991 | 300 | MANDIBULAR LYMPH NODE(Bilateral): Enlarged - 0.6 cm | MANDIBULAR LYMPH NODES: Plasma cell hyperplasia 1-bilateral |

1: Minimal, 2: Mild, 3: Moderate, 4: Severe

contd.

NAD: No Abnormality Detected

CONFIDENTIAL

APPENDIX 24 contd. Individual Gross Pathological and Histopathological Findings - Females

| Group No. | Rat No. | Dose (mg TOS/kg bwt/day) | Gross | Microscopic |
|-----------|---------|--------------------------|--|--|
| G3 | Ri3992 | 300 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red | MANDIBULAR LYMPH NODES: Hemorrhage 2-bilateral |
| G3 | Ri3993 | 300 | NAD | Tissues not examined |
| G3 | Ri3994 | 300 | NAD | Tissues not examined |
| G3 | Ri3995 | 300 | THYMUS: Petechiae | THYMUS: Hemorrhage 2 |
| G3 | Ri3996 | 300 | NAD | Tissues not examined |
| G3 | Ri3997 | 300 | NAD | Tissues not examined |
| G3 | Ri3998 | 300 | NAD | Tissues not examined |
| G3 | Ri3999 | 300 | NAD | Tissues not examined |
| G3 | Ri4000 | 300 | NAD | Tissues not examined |

1: Minimal, 2: Mild, 3: Moderate, 4: Severe

contd.

NAD: No Abnormality Detected

APPENDIX 24 contd. Individual Gross Pathological and Histopathological Findings - Females

| Group No. | Rat No. | Dose (mg TOS/kg bwt/day) | Gross | Microscopic |
|-----------|---------|--------------------------|-------|---|
| G4 | Ri4001 | 1000 | NAD | PARATHYROID(S)(X2): Tissue present no change MANDIBULAR LYMPH NODES: Hemorrhage 1-unilateral Lymphoid hyperplasia 1-unilateral |
| G4 | Ri4002 | 1000 | NAD | EYES WITH OPTIC NERVE(X8): Tissue present no change MANDIBULAR LYMPH NODES: Hemorrhage 1-unilateral |
| G4 | Ri4003 | 1000 | NAD | THYMUS: Epithelial cyst(s) PITUITARY: Tissue not fit for examination THYROID: Ectopic thymus BRAIN-MEDULLA/PONS(X17): Tissue present no change EYES WITH OPTIC NERVE(X8): Tissue present no change |
| G4 | Ri4004 | 1000 | NAD | LUNGS: Increased alveolar macrophages 1 THYMUS: Epithelial cyst(s) PARATHYROID(S)(X2): Tissue present no change BRAIN-MEDULLA/PONS(X17): Tissue present no change EYES WITH OPTIC NERVE(X8): Tissue present no change |

1: Minimal, 2: Mild, 3: Moderate, 4: Severe

X2: One organ not present

X8: Lens not present

X17: Pons not present

X8: Lens not present

NAD: No Abnormality Detected

contd.

CONFIDENTIAL

APPENDIX 24 contd. Individual Gross Pathological and Histopathological Findings - Females

| Group No. | Rat No. | Dose (mg TOS/kg bwt/day) | Gross | Microscopic |
|-----------|---------|--------------------------|--|---|
| G4 | Ri4005 | 1000 | NAD | EYES WITH OPTIC NERVE(X8): Tissue present no change |
| G4 | Ri4006 | 1000 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red | THYMUS: Hemorrhage 1 ADRENALS(X2): Tissue present no change EYES WITH OPTIC NERVE(X8&X6): Tissue present no change MANDIBULAR LYMPH NODES: Hemorrhage 1-bilateral |
| G4 | Ri4007 | 1000 | MANDIBULAR LYMPH NODE(Bilateral): Discoloration, Red | MANDIBULAR LYMPH NODES: Hemorrhage 2-bilateral |
| G4 | Ri4008 | 1000 | NAD | PITUITARY(X20): Tissue present no change EYES WITH OPTIC NERVE(X8&X6): Tissue present no change |
| G4 | Ri4009 | 1000 | UTERUS: Dilatation | UTERUS WITH CERVIX: Dilatation 1 BRAIN-MEDULLA/PONS(X17): Tissue present no change EYES WITH OPTIC NERVE(X8): Tissue present no change MANDIBULAR LYMPH NODES: Hemorrhage 1-bilateral |
| G4 | Ri4010 | 1000 | NAD | LIVER: Chronic inflammatory focus(i) 1 THYMUS: Epithelial cyst(s) PARATHYROID(X2): Tissue present no change BRAIN-MEDULLA/PONS(X17): Tissue present no change EYES WITH OPTIC NERVE(X6): Tissue present no change |

contd.

1: Minimal, 2: Mild, 3: Moderate, 4: Severe
X2: One organ not present X6: Optic nerve not present X20: Pars nervosa not present
X8: Lens not present X17: Pons not present
NAD: No Abnormality Detected

APPENDIX 25. Gavage Preparation Data

| Date of mixing | Group No. | Dose (mg TOS/kg bwt/day) | Test Item (mL) | Total volume made up with "MilliQ" water (mL) |
|----------------|-----------|--------------------------|----------------|---|
| 15.09.2009 | G1 | 0 | 0.0 | 250 |
| | G2 | 100 | 22.73 | 250 |
| | G3 | 300 | 68.18 | 250 |
| | G4 | 1000 | 227.27 | 250 |
| 18.09.2009 | G1 | 0 | 0.0 | 150 |
| | G2 | 100 | 13.64 | 150 |
| | G3 | 300 | 40.91 | 150 |
| | G4 | 1000 | 136.36 | 150 |
| 22.09.2009 | G1 | 0 | 0.0 | 200 |
| | G2 | 100 | 18.18 | 200 |
| | G3 | 300 | 54.55 | 200 |
| | G4 | 1000 | 181.82 | 200 |
| 25.09.2009 | G1 | 0 | 0.0 | 260 |
| | G2 | 100 | 23.64 | 260 |
| | G3 | 300 | 70.91 | 260 |
| | G4 | 1000 | 236.36 | 260 |
| 29.09.2009 | G1 | 0 | 0.0 | 230 |
| | G2 | 100 | 20.91 | 230 |
| | G3 | 300 | 62.73 | 230 |
| | G4 | 1000 | 209.1 | 230 |
| 02.10.2009 | G1 | 0 | 0.0 | 310 |
| | G2 | 100 | 28.18 | 310 |
| | G3 | 300 | 84.55 | 310 |
| | G4 | 1000 | 281.82 | 310 |
| 06.10.2009 | G1 | 0 | 0.0 | 270 |
| | G2 | 100 | 24.55 | 270 |
| | G3 | 300 | 73.64 | 270 |
| | G4 | 1000 | 245.45 | 270 |
| 09.10.2009 | G1 | 0 | 0.0 | 360 |
| | G2 | 100 | 32.73 | 360 |
| | G3 | 300 | 98.18 | 360 |
| | G4 | 1000 | 327.27 | 360 |
| 13.10.2009 | G1 | 0 | 0.0 | 300 |
| | G2 | 100 | 27.27 | 300 |
| | G3 | 300 | 81.82 | 300 |
| | G4 | 1000 | 272.73 | 300 |
| 16.10.2009 | G1 | 0 | 0.0 | 400 |
| | G2 | 100 | 36.36 | 400 |
| | G3 | 300 | 109.1 | 400 |
| | G4 | 1000 | 363.64 | 400 |
| 20.10.2009 | G1 | 0 | 0.0 | 300 |
| | G2 | 100 | 27.27 | 300 |
| | G3 | 300 | 81.82 | 300 |
| | G4 | 1000 | 272.73 | 300 |

APPENDIX 25 contd. Gavage Preparation Data

| Date of mixing | Group No. | Dose (mg TOS/kg bwt/day) | Test Item (mL) | Total volume made up with "MilliQ" water (mL) |
|----------------|-----------|--------------------------|----------------|---|
| 23.10.2009 | G1 | 0 | 0.0 | 450 |
| | G2 | 100 | 40.91 | 450 |
| | G3 | 300 | 122.73 | 450 |
| | G4 | 1000 | 409.09 | 450 |
| 27.10.2009 | G1 | 0 | 0.0 | 325 |
| | G2 | 100 | 29.55 | 325 |
| | G3 | 300 | 88.64 | 325 |
| | G4 | 1000 | 295.45 | 325 |
| 30.10.2009 | G1 | 0 | 0.0 | 430 |
| | G2 | 100 | 39.09 | 430 |
| | G3 | 300 | 117.27 | 430 |
| | G4 | 1000 | 390.91 | 430 |
| 03.11.2009 | G1 | 0 | 0.0 | 350 |
| | G2 | 100 | 31.82 | 350 |
| | G3 | 300 | 95.45 | 350 |
| | G4 | 1000 | 318.18 | 350 |
| 06.11.2009 | G1 | 0 | 0.0 | 450 |
| | G2 | 100 | 40.91 | 450 |
| | G3 | 300 | 122.73 | 450 |
| | G4 | 1000 | 409.09 | 450 |
| 10.11.2009 | G1 | 0 | 0.0 | 375 |
| | G2 | 100 | 34.09 | 375 |
| | G3 | 300 | 102.27 | 375 |
| | G4 | 1000 | 340.91 | 375 |
| 13.11.2009 | G1 | 0 | 0.0 | 450 |
| | G2 | 100 | 40.91 | 450 |
| | G3 | 300 | 122.73 | 450 |
| | G4 | 1000 | 409.09 | 450 |
| 17.11.2009 | G1 | 0 | 0.0 | 350 |
| | G2 | 100 | 31.82 | 350 |
| | G3 | 300 | 95.45 | 350 |
| | G4 | 1000 | 318.18 | 350 |
| 20.11.2009 | G1 | 0 | 0.0 | 500 |
| | G2 | 100 | 45.46 | 500 |
| | G3 | 300 | 136.36 | 500 |
| | G4 | 1000 | 454.55 | 500 |
| 24.11.2009 | G1 | 0 | 0.0 | 375 |
| | G2 | 100 | 34.09 | 375 |
| | G3 | 300 | 102.27 | 375 |
| | G4 | 1000 | 340.91 | 375 |
| 27.11.2009 | G1 | 0 | 0.0 | 470 |
| | G2 | 100 | 42.73 | 470 |
| | G3 | 300 | 128.18 | 470 |
| | G4 | 1000 | 427.27 | 470 |

APPENDIX 25 contd. Gavage Preparation Data

| Date of mixing | Group No. | Dose (mg TOS/kg bwt/day) | Test Item (mL) | Total volume made up with "MilliQ" water (mL) |
|----------------|-----------|--------------------------|----------------|---|
| 01.12.2009 | G1 | 0 | 0.0 | 375 |
| | G2 | 100 | 34.09 | 375 |
| | G3 | 300 | 102.27 | 375 |
| | G4 | 1000 | 340.91 | 375 |
| 04.12.2009 | G1 | 0 | 0.0 | 480 |
| | G2 | 100 | 43.64 | 480 |
| | G3 | 300 | 130.91 | 480 |
| | G4 | 1000 | 436.36 | 480 |
| 08.12.2009 | G1 | 0 | 0.0 | 400 |
| | G2 | 100 | 36.36 | 400 |
| | G3 | 300 | 109.09 | 400 |
| | G4 | 1000 | 363.64 | 400 |
| 11.12.2009 | G1 | 0 | 0.0 | 480 |
| | G2 | 100 | 43.64 | 480 |
| | G3 | 300 | 130.91 | 480 |
| | G4 | 1000 | 436.36 | 480 |

APPENDIX 26. Batch Analysis Data

| Date | Batch No. | Group | Nominal concentration (mg/mL) | Mean protein content in the sample (mg/mL) | Test item concentration in samples (mg/mL) | Analysed concentration of test item as TOS |
|------------|-----------|-------|-------------------------------|--|--|--|
| 15.09.2009 | I | G1 | 0.0 | 0.0 | 0.0 | 0.0 |
| | | G2 | 5.0 | 2.02 | 91.8 | 5.05 |
| | | G3 | 15.0 | 5.98 | 271.8 | 14.95 |
| | | G4 | 50.0 | 20.04 | 910.9 | 50.10 |
| 23.10.2009 | II | G1 | 0.0 | 0.0 | 0.0 | 0.0 |
| | | G2 | 5.0 | 1.98 | 90.00 | 4.95 |
| | | G3 | 15.0 | 6.04 | 274.5 | 15.1 |
| | | G4 | 50.0 | 19.98 | 908.2 | 49.95 |
| 20.11.2009 | III | G1 | 0.0 | 0.0 | 0.0 | 0.0 |
| | | G2 | 5.0 | 2.03 | 92.42 | 5.08 |
| | | G3 | 15.0 | 6.01 | 273.04 | 15.03 |
| | | G4 | 50.0 | 20.02 | 910.15 | 50.05 |


$$\text{Test item concentration in the sample (mg/mL)} = \frac{\text{Mean protein content in the sample (mg/mL)} \times 100}{\text{Per cent protein content in the test item}}$$

$$\text{Analysed concentration of test item as TOS (mg/mL)} = \text{Test item concentration in the sample (mg/mL)} \times \% \text{ TOS} / 100$$

NOTE: % protein content in the test item is 2.20 % (w/w) and % TOS is 5.50 as furnished by the Sponsor in the Certificate of Analysis.

APPENDIX 27. Certificate of Analysis

DSM Food Specialties B.V.
R&D/REG

DSM 

Page 1 of 1

| CERTIFICATE OF ANALYSIS | | | |
|---|--|---------|--------|
| Name of the product | Mellamase | | |
| Batch no. | MEL GRZ 0005 | | |
| Status | ccUF for toxicity study | | |
| Date of manufacture | February 2009 | | |
| Date of expiration | 12 months (provisionally) , extended 4 months | | |
| Active component | Amylomaltase or 4- α -glucanotransferase | | |
| Date of issue | 29 October 2009, updated 17 August 2010 | | |
| Parameter | Method | Unit | Result |
| Characterization data | | | |
| Amylomaltase activity | B1903 | ATU / g | 2150 |
| Dry Matter | 60485 | % (w/w) | 6.76 |
| Ash | 60328 | % (w/w) | 1.26 |
| TOS | Calculation | % (w/w) | 6.50 |
| Proteins by Kjeldahl Nitrogen x 6.25 | B1804 | % (w/w) | 2.20 |
| Stability data; > 90% residual activity | | | |
| Stability at 4°C, undiluted | B1903 | Days | 7 |
| Stability at 4°C, 91 mg / ml | B1903 | Days | 7 |
| Stability at 4°C, 273 mg / ml | B1903 | Days | 7 |
| Stability at 4°C, 909 mg / ml | B1903 | Days | 7 |
| Stability at RT, undiluted | B1903 | Hours | 4 |
| Stability at RT, 91 mg / ml | B1903 | Hours | 4 |
| Stability at RT, 273 mg / ml | B1903 | Hours | 4 |
| Stability at RT, 909 mg / ml | B1903 | Hours | 4 |
| Signature R&D QESH | Remarks (if any) CoA drafted for toxicity study Analyses performed under GLP | | |

APPENDIX 28. Deviations from Approved Study Plan


Study No.: G6597

Study Title: Repeated dose (90-Day) oral toxicity study by gavage with enzyme preparation of *Bacillus amyloliquefaciens* containing amylomaltase activity in Wistar Rats

Test Item Code: D03-08

| AS IN STUDY PLAN | DEVIATION FROM STUDY PLAN |
|--|--|
| 1. STUDY DETAILS (Page 4/24) | STUDY DETAILS |
| Study Schedule Study completion : Latest by May/June 2010 | Study Schedule Study completion: The study could not be completed by June 2010. |
| Justification: Delay in the finalization of the report | |
| Impact of Deviation: None, This will not affect the out come of the study or interpretation of the results. | |

Date: 28 September 2010



(Mr. P.M. Sathish)
Study Director

16. ANNEXURES

ANNEXURE 1. Contaminant Analysis Report for Bedding Material (Paddy Husk)

LUFA-ITL GmbH

Dr.-Helt-Str. 6, 24107 Kiel, Germany
Tel.: +49(0431)1228-0, Fax: +49(0431)1228-498
eMail: zentrale@lufa-itl.de

LUFA - ITL Dr.-Helt-Str. 6, 24107 Kiel

ADVINUS THERAPEUTICS PRIVATE LIMITED
PEENYA INDUSTRIAL AREA
0 BANGALORE-560 058
INDIEN

AGROLAB
Laborgruppe
www.agrolab.de



Date 26.02.2009
Customer no. 1209576
Page 1 of 2

TEST REPORT

Sample No. 651329

Order No.
Sample Arrival
Sample code

582713

11.02.2009

Sample 6 Bedding material - Paddy Husk
data of sampling: 23.01.2009
batch-no.: PH-19

Sample packing

plastic bag

Mycotoxins

| Unit | Result | Declaration | Substance | Method |
|-------|--------|-------------|-----------|-----------------------------|
| µg/kg | 2,2 | | OM | HPLC-VDLUFA Bd. III, 16.1.4 |
| µg/kg | <1,0 | | OM | HPLC-VDLUFA Bd. III, 16.1.4 |
| µg/kg | <1,0 | | OM | HPLC-VDLUFA Bd. III, 16.1.4 |
| µg/kg | <1,0 | | OM | HPLC-VDLUFA Bd. III, 16.1.4 |

PCB

| | | | | |
|---------|-------|--------|----|----------------------------|
| PCB 28 | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| PCB 52 | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| PCB 101 | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| PCB 118 | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| PCB 138 | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| PCB 153 | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| PCB 180 | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |

Organochlorous-Pesticides GC-Multiresidueanalysis

| | | | | |
|-------------------------|-------|--------|----|----------------------------|
| Aldrin | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Dieldrin | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Endrin | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Chlorodane alpha | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Chlorodane gamma | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Chlorodane-oxy | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Endosulfan alpha | mg/kg | 0,011 | OM | acc. to §64 LFGB L00.00-34 |
| Endosulfan beta | mg/kg | 0,038 | OM | acc. to §64 LFGB L00.00-34 |
| Endosulfansulfat | mg/kg | 0,037 | OM | acc. to §64 LFGB L00.00-34 |
| HCB (Hexachlorobenzene) | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| epsilon-HCH | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| HCH-alpha | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| HCH-beta | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| HCH-delta | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| HCH-gamma (gammexane) | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Heptachlor | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Heptachloropoxide-cis | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Heptachloropoxide-trans | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| o,p-DDD | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |



ANNEXURE 1 contd. Contaminant Analysis Report for Bedding Material (Paddy Husk)

LUFA-ITL GmbH

Dr.-Hell-Str. 6, 24107 Kiel, Germany
Tel.: +49(0431)1228-0, Fax: +49(0431)1228-498
eMail: zentrale@lufa-itl.de

AGROLAB
Laborgruppe
www.agrolab.de



Date 26.02.2009
Customer no. 1209576
Page 2 of 2

Sample No. 651329

| | Unit | Result Declaration | Substance | Method |
|--|-------|--------------------|-----------|----------------------------|
| o,p-DDE | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| o,p-DDT | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| p,p-DDD | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| p,p-DDE | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| p,p-DDT | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Methoxychlor | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Quintozene | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Tecnazene | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Tetradifon | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Nitrofen | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Organo-Phosphorous Pesticides GC-Multiresidueanalysis | | | | |
| Bromphos (-methyl) | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Bromphos-ethyl | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Chlorfenvinphos | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Chlorpyrifos | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Chlorpyrifos-methyl | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Chlorthion | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Diazinone | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Dichlorvos | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Dimethoate | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Ethion | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Fenitrothion | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Fenthion | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Malathion | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Mecarbame | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Methidathion | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Parathion-ethyl | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Parathion-methyle | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Pirimiphos-ethyle | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Pirimiphos-methyle | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Profenofos | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Sulfotep | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |

Explanation: "<", n.d.: not detected, below limit of detection.
The actual limit of detection can be different to the standard value for a particular analysis due to matrix effects or insufficient sample volume.
Remark: OM=original matter, DM=dry matter

LUFA - ITL Dr. Reutter, Tel. 0431/1228-230

This electronically transmitted report was checked and released. It's in accordance with the requirements of DIN EN ISO/IEC 17025:2005 for simplified reports and valid without signature.

Copies

ADVINUS THERAPEUTICS PRIVATE LIMITED

The analytical results are valid for the delivered sample material only. The testing period is the time between the receipt of the sample and the reporting date. Validation of results is not possible for samples of unknown origin.



ANNEXURE 2. Analysis Report - Animal Diet Sample

ADVINUS THERAPEUTICS PRIVATE LIMITED
21 & 22, PEENYA INDUSTRIAL AREA, II PHASE
BANGALORE - 560 058

ANALYSIS REPORT - ANIMAL DIET SAMPLE

From: Analytical R & D Department
Advinus, Bangalore-560 058

To: Department of Safety Assessment
Advinus, Bangalore-560 058

Our Ref. No.: WC/TFS/1995

Date: 10/09/2009

Sample Details: Name : Complete diet for Rat/ Mice Maintenance
Sampling Date: 06/08/2009

Batch No. : 8582500

Supplier : Ssniff Spezialdiaten, GmbH, Germany.

Manufacturer: Ssniff Spezialdiaten, GmbH, Germany.

ANALYSIS RESULTS
(Analysis on "as is basis")

| Sl. No. | Parameter | (%) |
|---------|---------------------------|------|
| 1. | Moisture | 8.1 |
| 2. | Crude protein (N x 6.25) | 20.0 |
| 3. | Crude fat (Ether extract) | 3.8 |
| 4. | Crude fibre | 4.3 |
| 5. | Total ash | 7.9 |
| 6. | Acid insoluble ash | 0.8 |
| 7. | Nitrogen free extract | 55.9 |
| 8. | Calcium (Ca) | 1.0 |
| 9. | Phosphorus (P) | 0.8 |


14/09/09
Analytical R&D Department.

ANNEXURE 3. Feed Contaminant Analysis Report for Ssniff Rats/Mice Diet - Maintenance Meal

LUFA-ITL GmbH

Dr.-Hell-Str. 6, 24107 Kiel, Germany
Tel.: +49(0431)1228-0, Fax: +49(0431)1228-498
eMail: zentrale@lufa-itl.de

LUFA - ITL Dr.-Hell-Str. 6, 24107 Kiel

ADVINUS THERAPEUTICS PRIVATE LIMITED
PEENYA INDUSTRIAL AREA
0 BANGALORE-560 058
INDIEN

AGROLAB
Laborgruppe
www.agrolab.de



Date 26.02.2009
Customer no. 1209576
Page 1 of 2

TEST REPORT

Sample No. 651325

Order No.

582713

Sample Arrival

11.02.2009

Sample code

Sample 2 Complete diet for rats/mice maintenance meal
data of sampling: 21.01.2009
batch-no.: 8291275

Sample packing

plastic bag

| | Unit | Result | Declaration | Substance | Method |
|--|-------|--------|-------------|-----------|-----------------------------|
| Mycotoxins | | | | | |
| Aflatoxine B1 | µg/kg | <1,0 | | OM | HPLC-VDLUFA Bd. III, 16.1.4 |
| Aflatoxine B2 | µg/kg | <1,0 | | OM | HPLC-VDLUFA Bd. III, 16.1.4 |
| Aflatoxine G1 | µg/kg | <1,0 | | OM | HPLC-VDLUFA Bd. III, 16.1.4 |
| Aflatoxine G2 | µg/kg | <1,0 | | OM | HPLC-VDLUFA Bd. III, 16.1.4 |
| PCB | | | | | |
| PCB 28 | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| PCB 52 | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| PCB 101 | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| PCB 118 | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| PCB 138 | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| PCB 153 | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| PCB 180 | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| Organochlorous-Pesticides GC-Multiresidueanalysis | | | | | |
| Aldrin | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| Dieldrin | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| Endrin | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| Chlorodane alpha | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| Chlorodane gamma | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| Chlorodane-oxy | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| Endosulfan alpha | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| Endosulfan beta | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| Endosulfansulfat | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| HCB (Hexachlorobenzene) | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| epsilon-HCH | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| HCH-alpha | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| HCH-beta | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| HCH-delta | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| HCH-gamma (gammexane) | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| Heptachlor | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| Heptachlorepoxyde-cis | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| Heptachlorepoxyde-trans | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |
| o,p-DDD | mg/kg | <0,005 | | OM | acc. to §64 LFGB L00.00-34 |



ANNEXURE 3 contd. Feed Contaminant Analysis Report for Ssniff Rats/Mice Diet - Maintenance Meal

LUFA-ITL GmbH

Dr.-Hell-Str. 6, 24107 Kiel, Germany
Tel.: +49(0431)1228-0, Fax: +49(0431)1228-498
eMail: zentrale@lufa-itl.de

AGROLAB
Laborgruppe
www.agrolab.de



Date 26.02.2009
Customer no. 1209576
Page 2 of 2

Sample No. 651325

| | Unit | Result Declaration | Substance | Method |
|--------------|-------|--------------------|-----------|----------------------------|
| o,p-DDE | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| o,p-DDT | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| p,p-DDD | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| p,p-DDE | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| p,p-DDT | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Methoxychlor | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Quintozene | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Tecnazene | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Tetradifon | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |
| Nitrofen | mg/kg | <0,005 | OM | acc. to §64 LFGB L00.00-34 |

Organo-Phosphorous Pesticides GC-Multiresidueanalysis

| | | | | |
|---------------------|-------|--------|----|----------------------------|
| Bromophos (-methyl) | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Bromophos-ethyl | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Chlorfenvinphos | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Chlorpyrifos | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Chlorpyrifos-methyl | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Chlorthion | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Diazinone | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Dichlorvos | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Dimethoate | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Ethion | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Fenitrothione | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Fenthion | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Malathion | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Mecarbame | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Methidathion | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Parathion-ethyl | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Parathion-methyl | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Phosphor-ethyl | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Pirimiphos-methyl | mg/kg | 0,38 | OM | acc. to §64 LFGB L00.00-34 |
| Profenofos | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |
| Sulfotep | mg/kg | <0,010 | OM | acc. to §64 LFGB L00.00-34 |

Explanation: "<", n.d.: not detected, below limit of detection.

The actual limit of detection can be different to the standard value for a particular analysis due to matrix effects or insufficient sample volume.

Remark: OM=original matter, DM=dry matter

LUFA - ITL Dr. Reutter, Tel. 0431/1228-230

This electronically transmitted report was checked and released. It's in accordance with the requirements of DIN EN ISO/IEC 17025:2005 for simplified reports and valid without signature.

Copies

ADVINUS THERAPEUTICS PRIVATE LIMITED

The analytical results are valid for the delivered sample material only. The testing period is the time between the receipt of the sample and the reporting date. Validation of results is not possible for samples of unknown origin.



ANNEXURE 4. Analysis Report -Water Sample

ADVINUS THERAPEUTICS PRIVATE LIMITED
21 & 22, PEENYA INDUSTRIAL AREA, II PHASE
BANGALORE 560 058

ANALYSIS REPORT - WATER SAMPLE

From: Analytical R&D Department To: Department of Safety Assessment.
Advinus, Bangalore-560 058 Advinus, Bangalore-560 058

Our Ref. No: WC/TWS/239 Date: 14/10/2009

Sample Details: Source of Collection: Outlet of the Aquaguard (At use point)

Date of Collection: 09/09/2009

ANALYSIS RESULTS

| Sl. No. | Parameter | Content | Sl. No. | Parameter | Content (ppm) |
|---------|--|------------|---------|-----------------------------------|---------------|
| 1. | Colour | Colourless | 12. | Total hardness as CaCO_3 | 223 |
| 2. | Odour | Odourless | 13. | Calcium as Ca^{2+} | 38 |
| 3. | Turbidity | Clear | 14. | Magnesium as Mg^{2+} | 30 |
| 4. | PH | 7.82 | 15. | Chlorides as Cl^- | 281 |
| 5. | Electrical Conductivity, dSm^{-1} | 1.326 | 16. | Sulphates as SO_4^{2-} | 71 |
| 6. | Total solids, (ppm) | 944 | 17. | Carbonates as CO_3^{2-} | NIL |
| 7. | Suspended solids, (ppm) | 14 | 18. | Bicarbonates as HCO_3^- | 310 |
| 8. | Dissolved solids, (ppm) | 930 | 19. | Sodium as Na | 156 |
| 9. | Dissolved oxygen (ppm) | 4.5 | 20. | Potassium as K | 1.9 |
| 10. | Biochemical Oxygen Demand 5 days at 20°C , (ppm) | 2.0 | | | |
| 11. | Chemical Oxygen Demand (ppm) | 8.2 | | | |

[Signature] 14/10/2009
Analytical R&D Department

ANNEXURE 5. Contaminant Analysis Report for Water Sample



UCL Umwelt Control Labor GmbH · Postfach 2063 · 44510 Lünen

ADVINUS THERAPEUTICS PRIVATE LIMITED
- Herr Dr. Shivaram -
No. 21&22 Phasel 2 Peenya Industrial Area
560058 BANGALORE
INDIEN

Wertemitteilung

Auftragsnummer : 09-02877
Verantwortlicher : Dipl.-Chem. Jelena Spanig
Telefon : 02306/2409-9302
Freigabe Bericht : 19.02.2009
Prüfzeitraum : 12.02.2009 - 19.02.2009
Berichtsnummer : 09-02877/1

| Water sample for analysis | | | Proben-Nr.: | 09-02877-001 |
|-----------------------------|---------|----------|-------------------|----------------------------|
| Water | | | Eingangsdatum: | 12.02.2009 |
| Analysenparameter | Einheit | Ergebnis | Best. - Grenze | Methode |
| PCB | | | | |
| PCB-028 | µg/l | n.n. | 0,02 | DIN 38407 F2 |
| PCB-052 | µg/l | n.n. | 0,02 | DIN 38407 F2 |
| PCB-101 | µg/l | n.n. | 0,02 | DIN 38407 F2 |
| PCB-138 | µg/l | n.n. | 0,02 | DIN 38407 F2 |
| PCB-153 | µg/l | n.n. | 0,02 | DIN 38407 F2 |
| PCB-180 | µg/l | n.n. | 0,02 | DIN 38407 F2 |
| Summe PCB 028-180 | µg/l | n.n. | 0,02 | DIN 38407 F2 |
| PCB ges. | µg/l | n.n. | 0,1 | DIN 38407 F2 |
| Organochlorpestizide | | | | |
| Hexachlorbenzol (HCB) | µg/l | < 0,001 | | DIN 38407 Teil 2,FV |
| Aldrin | µg/l | < 0,001 | | DIN EN ISO 11369 F12,FV |
| o,p-DDD | µg/l | < 0,001 | | DIN EN ISO 11369 F12,FV |
| p,p-DDD | µg/l | < 0,001 | | DIN EN ISO 11369 F12,FV |
| o,p-DDE | µg/l | < 0,001 | | DIN EN ISO 11369 F12,FV |
| p,p-DDE | µg/l | < 0,001 | | DIN EN ISO 11369 F12,FV |
| o,p-DDT | µg/l | < 0,001 | | DIN EN ISO 11369 F12,FV |
| p,p-DDT | µg/l | < 0,001 | | DIN EN ISO 11369 F12,FV |
| Dieldrin | µg/l | < 0,001 | | DIN EN ISO 11369 F12,FV |
| alpha-Endosulfan | µg/l | < 0,001 | | DIN EN ISO 11369 F12,FV |
| beta-Endosulfan | µg/l | < 0,001 | | DIN EN ISO 11369 F12,FV |
| Endrin | µg/l | < 0,001 | | DIN EN ISO 11369 F12,FV |
| alpha-HCH | µg/l | < 0,001 | | DIN 38407 - F2,FV |

ANNEXURE 5 contd. Contaminant Analysis Report for Water Sample

09-02877

19.02.2009

Seite 2 von 2

20090424-1858205



| Water sample for analysis | | | Proben-Nr.: | 09-02877-001 |
|--|---------|----------|----------------------------|--------------|
| Water | | | Eingangsdatum: | 12.02.2009 |
| Analysenparameter | Einheit | Ergebnis | Best. - Methode Grenze | |
| Organochlorpestizide | | | | |
| beta-HCH | µg/l | < 0,001 | DIN 38407 - F2,FV | |
| gamma-HCH (Lindan) | µg/l | < 0,001 | DIN 38407 - F2, FV | |
| delta-HCH | µg/l | < 0,001 | DIN 38407 - F2,FV | |
| Heptachlor | µg/l | < 0,001 | DIN EN ISO 11369 F12,FV | |
| cis-Heptachlorepoxyd | µg/l | < 0,001 | DIN EN ISO 11369 F12,FV | |
| trans-Heptachlorepoxyd | µg/l | < 0,001 | DIN EN ISO 11369 F12,FV | |
| Methoxychlor | µg/l | < 0,001 | DIN EN ISO 11369 F12,FV | |
| n.n. = kleiner Bestimmungsgrenze n.b. = nicht bestimmbar - = nicht bestimmt * = nicht akkreditiert FV = Fremdvergabe | | | | |


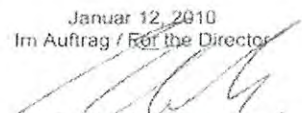
Mit freundlichen Grüßen

UCL GmbH

i. A. Cordula Althaus

Dipl.-Lab.Chem. Cordula Althaus

ANNEXURE 6. GLP Certificate - Germany

| | |
|---|---|
| <p>Bundesinstitut für Risikobewertung / Federal Institute for Risk Assessment</p> |  |
| <p>GUTE LABORPRAXIS / GOOD LABORATORY PRACTICE</p> <p>(gemäß / according to § 19b Abs.2 Nr.3 Chemikaliengesetz / Chemical Act)</p> <p>Eine GLP-Inspektion wurde durchgeführt in / A GLP inspection was carried out at</p> | |
| <p><u>Prüfeinrichtung / Test facility</u></p> <p>Advinus Therapeutics Private Limited 21& 22 Phase II, Peenya Industrial Area Bangalore – 560 058, INDIA</p> | |
| <p><u>Prüfkategorien / Area of Expertise</u></p> | |
| <ul style="list-style-type: none"> • Prüfungen zur Bestimmung der physikalisch-chemischen Eigenschaften und Gehaltsbestimmungen / Physical-chemical testing • Prüfungen zur Bestimmung der toxikologischen Eigenschaften / Toxicity studies • Prüfungen zur Bestimmung der erbgutverändernden Eigenschaften (<i>in vitro</i>, <i>in vivo</i>) / Mutagenicity studies • Ökotoxikologische Prüfungen zur Bestimmung der Auswirkungen auf aquatische und terrestrische Organismen / Environmental toxicity studies on aquatic and terrestrial organisms • Prüfungen zum Verhalten im Boden im Wasser und in der Luft; Bioakkumulation / Studies on behaviour in soil, water and air; bioaccumulation • Prüfungen zur Bestimmung von Rückständen / Residue studies • Analytische Prüfungen an biologischen Materialien / Analytical and clinical chemistry testing • sonstige Prüfungen – Bioanalytik, Pharmakokinetik, Sicherheitspharmakologie / other studies - bioanalytics, pharmacokinetics and safety pharmacology | |
| <p><u>Datum der Inspektion / Date of Inspection</u></p> <p>July 07 - 10, 2009</p> | |
| <p>Auf der Grundlage des Inspektionsberichtes und der Besprechung über zu erfolgende Maßnahmen wird hiermit bestätigt, dass in dieser Prüfeinrichtung die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können / Based on the inspection report and the discussion of follow up activities it can be confirmed, that the test facility is able to conduct the aforementioned studies in compliance with the Principles of GLP.</p> <p>Eine Überprüfung dieser GLP-Bestätigung ist spätestens drei Jahre nach der o. g. Inspektion zu beantragen. Ohne diesen Antrag wird nach Ablauf der Frist die Prüfeinrichtung aus dem deutschen GLP-Überwachungsprogramm genommen und diese GLP-Bestätigung verliert ihre Gültigkeit. / Verification of this GLP Certificate has to be applied three years after the above mentioned inspection at the latest. Elapsing this term, the test facility will be taken out of the German GLP Monitoring Programme and this GLP Certificate becomes invalid.</p> | |
| <p>Januar 12, 2010 Im Auftrag / For the Director</p>  <p>Dr. H.-W. Hembeck GLP-Bundesstelle / GLP Federal Bureau</p> <p><small>– Bundesinstitut für Risikobewertung / Federal Institute for Risk Assessment Thielallee 88-92, 14195 Berlin - GERMANY</small></p> | |

ANNEXURE 7. GLP Certificate - The Netherlands



voedsel en waren autoriteit

ENDORSEMENT OF COMPLIANCE

WITH THE OECD PRINCIPLES OF
GOOD LABORATORY PRACTICE

Pursuant to the Netherlands GLP Compliance Monitoring Programme and according to Directive 2004/9/EC the conformity with the OECD Principles of GLP was assessed on 4 – 7 May 2009 at

Advinus Therapeutics Private Limited
21 & 22 Phase II, Peenya Industrial Area
Bangalore - 560 058 INDIA

It is herewith confirmed that the afore-mentioned test facility is currently operating in compliance with the OECD Principles of Good Laboratory Practice in the following areas of expertise: physical-chemical testing, toxicity studies, mutagenicity studies, environmental studies on aquatic and terrestrial animals, and analytical and clinical chemistry.




The Hague, 27 August 2009

Dr Th. Helder, DVM

Manager GLP Compliance Monitoring Program

Food and Consumer Product Safety Authority (VWA)
Prinses Beatrixlaan 2, 2595 AL Den Haag
Postbus 19506, 2500 CM Den Haag, The Netherlands

ANNEXURE 8. GLP Certificate - India



NATIONAL GLP COMPLIANCE MONITORING AUTHORITY

GOOD LABORATORY PRACTICE

GLP CERTIFICATE

GLP Inspection was carried out at Advinus Therapeutics Private Limited, Plot Nos. 21 & 22, Phase-II, Post Box No. 5813, Peenya Industrial Area, Bangalore-560 058, India in the following areas of expertise:

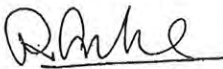
- physical-chemical testing
- toxicity studies
- mutagenicity studies
- environmental toxicity studies on aquatic & terrestrial organisms
- studies on behaviour in water, soil and air, bioaccumulation
- residue studies
- analytical and clinical chemistry testing

Based on the Inspection Report and the follow-up actions taken by the test facility, it is confirmed that the test facility is capable of conducting the above-mentioned tests/studies in compliance with OECD Principles of Good Laboratory Practice (GLP) and Norms, as adopted by the National GLP Compliance Monitoring Authority.

This GLP Certificate is valid for a period of three years from November 7, 2008 subject to the condition that the test facility complies with the Terms & Conditions of the National GLP Compliance Monitoring Authority's Document Number GLP-101.

Certificate No.: GLP/C-019

Issue Date : 24-12-2008



(R.SAHA)
Head

National GLP Compliance Monitoring Authority
Department of Science & Technology
Technology Bhavan New Delhi-110016

ANNEXURE 9. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.4: Haematological Values

Species : RATS
 Strain : Wistar
 Sex : Males
 Age : 18-21 Weeks
 No. of Studies : 9
 Time period : 2005-2009

| Parameter | WBC | RBC | Hb | Hct | MCV | MCH | MCHC | Plat | P.T. |
|---------------------|-------|-------|--------|------|-------|-------|--------|---------|-------|
| Unit | G/l | T/l | g/l | l/l | fl | pg | g/l | G/l | s |
| N | 95 | 95 | 95 | 95 | 95 | 95 | 95 | 95 | 95 |
| Mean | 7.12 | 8.95 | 162.40 | 0.46 | 51.14 | 18.18 | 356.01 | 983.02 | 15.82 |
| SD | 2.26 | 0.62 | 8.47 | 0.04 | 1.94 | 0.90 | 21.82 | 183.53 | 1.39 |
| 95% SD Range (Low) | 2.69 | 7.74 | 145.80 | 0.38 | 47.33 | 16.42 | 313.25 | 623.30 | 13.09 |
| 95% SD Range (High) | 11.55 | 10.17 | 179.00 | 0.54 | 54.95 | 19.94 | 398.77 | 1342.74 | 18.55 |

HD-33 (90-OGR)/Edition 10/2009
 Page 8/47

CONFIDENTIAL

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.4 contd.: Haematological Values

Species : RATS
 Strain : Wistar
 Sex : Males
 Age : 18-21 Weeks
 No. of Studies : 9
 Time period : 2005-2009

| Parameter | APTT | Neut | Lymp | Mono | Eosi | LUC | Baso | Retic | Retic |
|---------------------|-------|-------|-------|-------|-------|------|-------|-------|-------|
| Unit | s | % | % | % | % | % | % | % | T/1 |
| N | 10 | 95 | 95 | 95 | 95 | 20 | 95 | 25 | 10 |
| Mean | 12.95 | 21.92 | 73.95 | 1.74 | 2.04 | 0.24 | 0.13 | 0.93 | 0.18 |
| SD | 2.06 | 8.13 | 8.71 | 0.99 | 1.24 | 0.10 | 0.11 | 0.92 | 0.02 |
| 95% SD Range (Low) | 8.92 | 5.99 | 56.88 | -0.20 | -0.39 | 0.03 | -0.09 | -0.87 | 0.13 |
| 95% SD Range (High) | 16.98 | 37.85 | 91.02 | 3.68 | 4.47 | 0.45 | 0.36 | 2.73 | 0.23 |

HD-33 (90-OGR)/Edition 10/2009
 Page 9/47

G6597-90-OGR
 Copy No. 1/2

Page 177/207

CONFIDENTIAL

21 & 22, Peenya, Phase II, Bangalore- 560 058, India.

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.4 contd.: Haematological Values

Species : RATS
 Strain : Wistar
 Sex : Females
 Age : 18-21 Weeks
 No. of Studies : 9
 Time period : 2005-2009

| Parameter | WBC | RBC | Hb | Hct | MCV | MCH | MCHC | Plat | P.T. |
|---------------------|------|------|--------|------|-------|-------|--------|---------|-------|
| Unit | G/l | T/l | g/l | l/l | fl | pg | g/l | G/l | s |
| N | 95 | 95 | 95 | 95 | 95 | 95 | 95 | 95 | 95 |
| Mean | 4.51 | 8.08 | 155.64 | 0.43 | 53.59 | 19.32 | 361.44 | 1004.49 | 15.80 |
| SD | 2.01 | 0.61 | 7.90 | 0.04 | 2.37 | 1.22 | 30.53 | 138.19 | 1.28 |
| 95% SD Range (Low) | 0.57 | 6.89 | 140.15 | 0.35 | 48.96 | 16.94 | 301.60 | 733.64 | 13.28 |
| 95% SD Range (High) | 8.46 | 9.28 | 171.13 | 0.51 | 58.23 | 21.70 | 421.29 | 1275.35 | 18.31 |

HD-33 (90-OGR)/Edition 10/2009
 Page 10/47

G6597-90-OGR
 Copy No. 1/2

Page 178/207

CONFIDENTIAL

21 & 22, Peenya, Phase II, Bangalore- 560 058, India.

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.4 contd.: Haematological Values

Species : RATS
 Strain : Wistar
 Sex : Females
 Age : 18-21 Weeks
 No. of Studies : 9
 Time period : 2005-2009

| Parameter | APTT | Neut | Lymp | Mono | Eosi | LUC | Baso | Retic | Retic |
|---------------------|-------|-------|-------|-------|-------|------|-------|-------|-------|
| Unit | s | % | % | % | % | % | % | % | T/1 |
| N | 10 | 95 | 95 | 95 | 95 | 20 | 95 | 25 | 10 |
| Mean | 10.47 | 18.54 | 77.45 | 1.53 | 2.14 | 0.20 | 0.12 | 1.28 | 0.24 |
| SD | 1.21 | 7.86 | 8.69 | 0.79 | 1.31 | 0.10 | 0.12 | 1.34 | 0.05 |
| 95% SD Range (Low) | 8.09 | 3.14 | 60.43 | -0.02 | -0.44 | 0.00 | -0.11 | -1.35 | 0.13 |
| 95% SD Range (High) | 12.85 | 33.95 | 94.47 | 3.07 | 4.71 | 0.40 | 0.35 | 3.91 | 0.34 |

HD-33 (90-OGR)/Edition 10/2009
 Page 11/47

G6597-90-OGR
 Copy No. 1/2

Page 179/207

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.5: Clinical Chemistry Values

Species : RATS
 Strain : Wistar
 Sex : Males
 Age : 18-21 Weeks
 No. of Studies : 9
 Time period : 2005-2009

| Parameter | Glu | BUN | Urea | Tot.Pro | AST | ALT | ALP | GGT | T.Bil | Alb | Glob |
|---------------------|--------|--------|--------|---------|--------|-------|--------|-------|--------|-------|-------|
| Unit | mmol/l | mmol/l | mmol/l | g/l | U/l | U/l | U/l | U/l | mmol/l | g/l | g/l |
| N | 95 | 95 | 95 | 95 | 95 | 95 | 25 | 80 | 95 | 95 | 25 |
| Mean | 7.99 | 2.76 | 5.91 | 66.52 | 71.77 | 44.91 | 86.84 | 1.94 | 2.98 | 38.87 | 27.84 |
| SD | 1.97 | 0.53 | 1.13 | 3.12 | 20.10 | 22.76 | 19.46 | 2.57 | 1.11 | 4.75 | 6.78 |
| 95% SD Range (Low) | 4.13 | 1.73 | 3.70 | 60.40 | 32.38 | 0.30 | 48.70 | -3.10 | 0.81 | 29.56 | 14.56 |
| 95% SD Range (High) | 11.84 | 3.79 | 8.12 | 72.64 | 111.16 | 89.51 | 124.98 | 6.98 | 5.15 | 48.19 | 41.12 |

HD-33 (90-OGR)/Edition 10/2009
 Page 12/47

G6597-90-OGR
 Copy No. 1/2

Page 180/207

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.5 contd.: Clinical Chemistry Values

Species : RATS
 Strain : Wistar
 Sex : Males
 Age : 18-21 Weeks
 No. of Studies : 9
 Time period : 2005-2009

| Parameter | A/G | Pi | Ca | CK | Chol | Trig | Na | K | Cl | Creat |
|---------------------|------|------|--------|--------|--------|--------|--------|-------|--------|--------|
| Unit | | g/l | mmol/l | U/l | mmol/l | mmol/l | mEq/l | mEq/l | mmol/l | μmol/L |
| N | 10 | 95 | 95 | 10 | 95 | 25 | 95 | 95 | 80 | 95 |
| Mean | 2.37 | 1.78 | 2.70 | 185.60 | 1.88 | 1.39 | 145.32 | 4.05 | 98.23 | 46.21 |
| SD | 0.33 | 0.36 | 0.13 | 67.37 | 0.52 | 0.73 | 8.10 | 0.51 | 6.54 | 7.14 |
| 95% SD Range (Low) | 1.73 | 1.07 | 2.43 | 53.55 | 0.87 | -0.05 | 129.44 | 3.06 | 85.42 | 32.23 |
| 95% SD Range (High) | 3.01 | 2.49 | 2.96 | 317.65 | 2.89 | 2.83 | 161.20 | 5.04 | 111.05 | 60.20 |

HD-33 (90-OGR)/Edition 10/2009
 Page 13/47

G6597-90-OGR
 Copy No. 1/2

Page 181/207

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.5 contd.: Clinical Chemistry Values

Species : RATS
 Strain : Wistar
 Sex : Females
 Age : 18-21 Weeks
 No. of Studies : 9
 Time period : 2005-2009

| Parameter | Glu | BUN | Urea | Tot.Pro | AST | ALT | ALP | GGT | T.Bil | Alb | Glob |
|---------------------|--------|--------|--------|---------|-------|-------|-------|-------|--------|-------|-------|
| Unit | mmol/l | mmol/l | mmol/l | g/l | U/l | U/l | U/l | U/l | mmol/l | g/l | g/l |
| N | 95 | 95 | 95 | 95 | 95 | 95 | 25 | 80 | 95 | 95 | 25 |
| Mean | 6.89 | 2.95 | 6.32 | 68.34 | 69.43 | 35.88 | 53.20 | 1.86 | 3.07 | 42.98 | 24.29 |
| SD | 1.12 | 0.75 | 1.61 | 4.30 | 10.73 | 9.58 | 16.28 | 2.43 | 1.29 | 6.42 | 6.19 |
| 95% SD Range (Low) | 4.70 | 1.48 | 3.16 | 59.91 | 48.40 | 17.12 | 21.29 | -2.90 | 0.54 | 30.40 | 12.15 |
| 95% SD Range (High) | 9.08 | 4.43 | 9.49 | 76.77 | 90.46 | 54.65 | 85.11 | 6.62 | 5.60 | 55.57 | 36.43 |

HD-33 (90-OGR)/Edition 10/2009
 Page 14/47

G6597-90-OGR
 Copy No. 1/2

Page 182/207

CONFIDENTIAL

21 & 22, Peenya, Phase II, Bangalore- 560 058, India.

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.5 contd.: Clinical Chemistry Values

Species : RATS
 Strain : Wistar
 Sex : Females
 Age : 18-21 Weeks
 No. of Studies : 9
 Time period : 2005-2009

| Parameter | A/G | Pi | Ca | CK | Chol | Trig | Na | K | Cl | Creat |
|---------------------|------|------|--------|--------|--------|--------|--------|-------|--------|--------|
| Unit | | g/l | mmol/l | U/l | mmol/l | mmol/l | mEq/l | mEq/l | mmol/l | μmol/L |
| N | 10 | 95 | 95 | 10 | 95 | 25 | 95 | 95 | 80 | 95 |
| Mean | 3.16 | 1.34 | 2.68 | 226.90 | 1.63 | 0.51 | 142.03 | 3.76 | 100.13 | 50.21 |
| SD | 0.35 | 0.36 | 0.13 | 86.35 | 0.40 | 0.16 | 9.40 | 0.48 | 8.18 | 7.38 |
| 95% SD Range (Low) | 2.47 | 0.65 | 2.43 | 57.66 | 0.85 | 0.20 | 123.62 | 2.82 | 84.09 | 35.74 |
| 95% SD Range (High) | 3.85 | 2.04 | 2.93 | 396.14 | 2.41 | 0.81 | 160.45 | 4.70 | 116.16 | 64.68 |

HD-33 (90-OGR)/Edition 10/2009
 Page 15/47

G6597-90-OGR
 Copy No. 1/2

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.6: Clinical Analysis of Urine

Species : RATS
Strain : Wistar
Sex : Males
Age : 18-21 Weeks
No. of Studies: 10
Time period : 2005-2009

| Study No. | No. of rats | Volume in mL | Leukocytes* | Nitrite* | pH S | Protein* | Glucose* | Ketone Bodies* | Urobilinogen* | Bilirubin* | Erythrocytes* | Specific gravity S | Microscopic Findings |
|-----------|---------------|--------------|-------------|----------|------|----------|----------|----------------|---------------|------------|---------------|--------------------|----------------------|
| 4270 | Not evaluated | | | | | | | | | | | | |
| G4742 | Not evaluated | | | | | | | | | | | | |
| 4495 | 15 | 15.3 | 1 | 8 | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 1.017 | NPS |
| 4010 | 15 | 10.0 | 15 | 7 | 8.1 | 14 | 4 | 0 | 0 | 0 | 4 | 1.015 | NPS |
| G4903 | Not evaluated | | | | | | | | | | | | |
| G4839 | Not evaluated | | | | | | | | | | | | |
| G4897 | 10 | 5.6 | 4 | 5 | 8.9 | 4 | 0 | 4 | 0 | 0 | 0 | 1.018 | NPS |
| G4894 | 10 | 2.3 | 8 | 4 | 9 | 0 | 0 | 8 | 0 | 0 | 0 | 1.017 | NPS |
| G4963 | Not evaluated | | | | | | | | | | | | |
| G5239 | 10 | 15.4 | 2 | 8 | 8.6 | 2 | 0 | 2 | 1 | 0 | 0 | 1.016 | NPS |

NPS : Not of Pathological Significance
\$: Mean values

* Incidences of parameters measured

#: Values less than or equal to 3.2 µmol/L were not considered for counting of incidences

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.6 contd. Clinical Analysis of Urine

Species : RATS
Strain : Wistar
Sex : Females
Age : 18-21 Weeks
No. of Studies: 10
Time period : 2005-2009

| Study No. | No. of rats | Volume in mL S | Leukocytes* | Nitrite* | pH S | Protein* | Glucose* | Ketone Bodies* | Urobilinogen* # | Bilirubin* | Erythrocytes* | Specific gravity S | Microscopic Findings |
|-----------|---------------|----------------|-------------|----------|------|----------|----------|----------------|-----------------|------------|---------------|--------------------|----------------------|
| 4270 | Not evaluated | | | | | | | | | | | | |
| G4742 | Not evaluated | | | | | | | | | | | | |
| 4495 | 15 | 18.8 | 0 | 14 | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 1.017 | NPS |
| 4010 | 15 | 9.7 | 5 | 8 | 7.9 | 1 | 5 | 0 | 0 | 0 | 5 | 1.015 | NPS |
| G4903 | Not evaluated | | | | | | | | | | | | |
| G4839 | Not evaluated | | | | | | | | | | | | |
| G4897 | 10 | 11.9 | 0 | 7 | 9.0 | 0 | 0 | 0 | 0 | 0 | 1 | 1.015 | NPS |
| G4894 | 10 | 3.8 | 3 | 4 | 8 | 3 | 0 | 1 | 0 | 0 | 0 | 1.017 | NPS |
| G4963 | Not evaluated | | | | | | | | | | | | |
| G5239 | 10 | 6.8 | 2 | 5 | 8.6 | 1 | 0 | 0 | 0 | 0 | 0 | 1.017 | NPS |

NPS : Not of Pathological Significance
S: Mean values

*: Incidences of parameters measured

#: Values less than or equal to 3.2 µmol/L were not considered for counting of incidences

HD-33 (90-OGR)/Edition 10/2009
Page 17/47

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | MALES | | | | | | | | | |
|---------------------------------------|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 1 SALIVARY GLAND | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Vacuolation | | 0 | 3 | 0 | 0 | 0 | 4 | 3 | 5 | 7 | 0 |
| Increased mast cells | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| Lymphocytic infiltration | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Perivascular lymphocytic infiltration | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Adenitis | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| 2 ESOPHAGUS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 3 STOMACH | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Epithelial vacuolation-nonglandular | | 0 | 0 | 0 | 0 | 3 | 0 | 2 | 1 | 0 | 1 |
| Focal mucosal necrosis-glandular | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Cystic gland(s) | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Distended glands | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Cyst-glandular stomach | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Distended glands-glandular stomach | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

HD-33 (90-OGR)/Edition 10/2009
Page 26/47

CONFIDENTIAL

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | MALES | | | | | | | | | |
|------------------------------|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 4 DUODENUM | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 5 JEJUNUM | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 6 ILEUM (WITH PEYER'S PATCH) | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 7 CECUM | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 8 COLON | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Nematode | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 9 RECTUM | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Parasite(s) | | 2 | 0 | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| Nematode | | 0 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 3 | 0 |

HD-33 (90-OGR)/Edition 10/2009
Page 27/47

G6597-90-OGR
Copy No. 1/2

Page 187/207

CONFIDENTIAL

21 & 22, Peenya, Phase II, Bangalore- 560 058, India.

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | MALES | | | | | | | | | |
|---------------------------------|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 10 PANCREAS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Lymphocytic infiltration | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Acinar cell vacuolation | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Lobular atrophy | | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 |
| Inflammation | | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Atrophy-acinar cells | | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Inflammation-chronic | | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vasculitis | | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 11 LIVER | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Lymphocytic infiltration | | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Portal lymphocytic infiltration | | 0 | 1 | 0 | 0 | 0 | 2 | 3 | 1 | 3 | 2 |
| Hepatocyte vacuolation | | 0 | 1 | 0 | 0 | 0 | 5 | 0 | 1 | 3 | 0 |
| Chronic inflammatory focus(i) | | 0 | 0 | 0 | 0 | 6 | 6 | 5 | 9 | 6 | 8 |
| Hepatocyte degeneration-focal | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Focal fatty change | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Necrobiotic focus(i) | | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Extralobation | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

HD-33 (90-OGR)/Edition 10/2009

Page 28/47

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | MALES | | | | | | | | | |
|--|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 12 LUNGS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Perivascular lymphocytic infiltration | | 0 | 6 | 0 | 0 | 0 | 1 | 9 | 0 | 1 | 0 |
| Mineralisation blood vessels | | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Pneumonic focus(i) | | 0 | 4 | 3 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| Osseous metaplasia | | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 |
| Hemorrhage | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 0 |
| Mineralisation-pulmonary vessels | | 0 | 0 | 0 | 0 | 0 | 8 | 1 | 0 | 5 | 0 |
| Thrombus | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Vasculitis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Increased macrophages | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 4 |
| Alveolar macrophages | | 0 | 4 | 0 | 0 | 1 | 1 | 8 | 0 | 0 | 0 |
| Lymphocytic infiltration/Perivascular lymphocytic infiltration | | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Chronic pleuritis | | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lymphocytic infiltration | | 2 | 0 | 6 | 2 | 0 | 0 | 0 | 0 | 0 | 1 |
| 13 TRACHEA | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Cystic gland(s) | | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| Distended glands | | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Lymphocytic infiltration-submucosa | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 14 LARYNX | | (10) | (10) | (-) | (-) | (10) | (10) | (10) | (-) | (-) | (-) |

HD-33 (90-OGR)/Edition 10/2009
Page 29/47

CONFIDENTIAL

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | MALES | | | | | | | | | |
|-------------------------------|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 15 PHARYNX | | (10) | (10) | (-) | (-) | (10) | (10) | (10) | (-) | (-) | (-) |
| 16 NOSE | | (10) | (10) | (-) | (-) | (10) | (10) | (10) | (-) | (-) | (-) |
| 17 HEART | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Chronic inflammatory focus(i) | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Lymphocytic infiltration | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 18 AORTA | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 19 SPLEEN | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Increased hemosiderosis | | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| 20 MESENTERIC LYMPH NODES | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Cystic space(s) | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Increased mast cells | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| Edema | | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

HD-33 (90-OGR)/Edition 10/2009
Page 30/47

G6597-90-OGR
Copy No. 1/2

Page 190/207

CONFIDENTIAL

21 & 22, Peenya, Phase II, Bangalore- 560 058, India.

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | MALES | | | | | | | | | |
|-------------------------------------|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 21 MANDIBULAR LYMPH NODE | | (-) | (1) | (-) | (-) | (1) | (2) | (2) | (-) | (-) | (10) |
| Lymphoid hyperplasia | | - | 0 | - | - | 0 | 2 | 0 | - | - | 3 |
| Hemorrhage | | - | 1 | - | - | 1 | 0 | 2 | - | - | 1 |
| 22 AXILLARY LYMPH NODE | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (-) |
| Lymphoid hyperplasia | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | - |
| Increased mast cells | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | - |
| 23 KIDNEYS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Lymphocytic infiltration | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Mineralisation | | 3 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Dilatation of pelvis | | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| Basophilic tubules | | 2 | 2 | 0 | 1 | 0 | 2 | 1 | 2 | 0 | 1 |
| Focal inflammation | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Urothelial hyperplasia | | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Proteinaceous material in tubules | | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 1 | 0 | 0 |
| Nephropathy | | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 |
| Hyaline droplets-tubular epithelium | | 0 | 0 | 0 | 0 | 1 | 0 | 5 | 0 | 0 | 0 |
| Hyaline casts | | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 |
| Glomerulosclerosis | | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |

HD-33 (90-OGR)/Edition 10/2009
Page 31/47

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | MALES | | | | | | | | | |
|---|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 24 URINARY BLADDER | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Lymphocytic infiltration-submucosa | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| 25 TESTES | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Degenerative changes-seminiferous tubules | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 26 EPIDIDYMIDES | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Lymphocytic infiltration | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Cellular debris in duct lumen | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Leukocytic infiltration-epididymal fat | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 27 PROSTATE | | (10) | (10) | (15) | (15) | (9) | (10) | (10) | (10) | (10) | (10) |
| Lymphocytic infiltration | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 4 |
| Suppurative exudate in the lumen | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| Focal atrophy | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 28 SEMINAL VESICLES | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |

HD-33 (90-OGR)/Edition 10/2009
Page 32/47

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | MALES | | | | | | | | | |
|--------------------------------|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 29 COAGULATING GLANDS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 30 THYROIDS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Ectopic thymus | | 2 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 1 | 0 |
| Ultimobranchial cyst | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 |
| 31 PARATHYROIDS | | (10) | (-) | (14) | (15) | (9) | (9) | (10) | (10) | (10) | (10) |
| 32 PITUITARY | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Eosinophilic vacuoles | | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 2 | 0 | 0 |
| Cyst(s) | | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cyst(s)-pars distalis | | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 0 |
| Cyst like structure | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Focal hyperplasia | | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 33 ADRENALS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Accessory cortical tissue | | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 2 | 0 | 0 |
| Accessory adrenal | | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Increased cortical vacuolation | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

HD-33 (90-OGR)/Edition 10/2009
Page 33/47

CONFIDENTIAL

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | MALES | | | | | | | | | |
|-----------------------------------|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 34 BRAIN-CEREBRUM | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 35 BRAIN-CEREBELLUM | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 36 BRAIN-MEDULLA / PONS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 37 SPINAL CORD | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 38 SCIATIC NERVES | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 39 EYES WITH RETINA & OPTIC NERVE | | (10) | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (-) | (-) |
| Retinal atrophy | | 0 | 1 | - | - | 0 | 0 | - | - | - | - |
| 40 EYES WITH OPTIC NERVE | | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (10) |
| Extraocular inflammation | | - | - | - | - | - | - | - | - | - | 1 |

HD-33 (90-OGR)/Edition 10/2009
Page 34/47

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | MALES | | | | | | | | | |
|---------------------------|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 41 EYES | | (-) | (-) | (15) | (15) | (-) | (-) | (-) | (-) | (-) | (-) |
| Retinal atrophy | | - | - | 1 | 0 | - | - | - | - | - | - |
| 42 SKIN | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Epidermal hyperplasia | | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| Parakeratosis | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 43 TONGUE | | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (10) |
| 44 THYMUS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Epithelial hyperplasia | | 0 | 1 | 0 | 0 | 3 | 4 | 2 | 0 | 2 | 0 |
| Hemorrhage | | 0 | 4 | 0 | 1 | 0 | 0 | 2 | 2 | 5 | 4 |
| Epithelial cyst(s) | | 0 | 1 | 0 | 0 | 2 | 1 | 2 | 0 | 1 | 1 |
| Ectopic parathyroid | | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| Histiocytosis | | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 2 | 0 | 0 |
| Involution | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 45 MAMMARY GLAND | | NA | NA | (-) | (-) | (-) | (-) | (-) | (-) | (10) | (7) |

HD-33 (90-OGR)/Edition 10/2009
Page 35/47

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | MALES | | | | | | | | | |
|----------------------------|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-CGR | 90-OGR | 90-OGR | 90-OGR | 90-CGR | 90-OGR | 90-OGR | 90-CGR | 90-OGR | 90-CGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 46 LACRIMAL GLANDS | | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (10) |
| Lymphocytic infiltration | | - | - | - | - | - | - | - | - | - | 1 |
| Inflammation | | - | - | - | - | - | - | - | - | - | 1 |
| 47 MUSCLE FEMORAL | | (-) | (-) | (15) | (15) | (-) | (-) | (-) | (-) | (-) | (-) |
| 48 BONE (FEMUR) WITH JOINT | | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (10) | (10) | (10) |
| 49 STERNUM WITH MARROW | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 50 BONE MARROW (SMEAR) | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Increased mast cells | | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | FEMALES | | | | | | | | | |
|-------------------------------------|----------------------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 1 SALIVARY GLAND | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Vacuolation | | 0 | 4 | 0 | 0 | 0 | 1 | 0 | 1 | 5 | 0 |
| Lymphocytic infiltration | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Squamous metaplasia-ducts | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 2 ESOPHAGUS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Granulomatous inflammation | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| 3 STOMACH | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Epithelial vacuolation-nonglandular | | 0 | 2 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| Cystic gland(s) | | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Erosion-nonglandular focal | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Erosion-nonglandular | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Epithelial hyperplasia-nonglandular | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Cyst-glandular stomach | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Distended glands-glandular stomach | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Keratin cyst | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

HD-33 (90-OGR)/Edition 10/2009
Page 37/47

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | FEMALES | | | | | | | | | |
|--|---------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No.of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No.of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 4 DUODENUM Ectopic pancreas | | (10) 1 | (10) 0 | (15) 0 | (15) 0 | (10) 0 | (10) 0 | (10) 0 | (10) 0 | (10) 0 | (10) 0 |
| 5 JEJUNUM | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 6 ILEUM (WITH PEYER'S PATCH) Lymphoid hyperplasia | | (10) 1 | (10) 0 | (15) 0 | (15) 1 | (10) 0 | (10) 0 | (10) 0 | (10) 0 | (10) 0 | (10) 0 |
| 7 CECUM | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 8 COLON Parasite(s) | | (10) 1 | (10) 0 | (15) 0 | (15) 0 | (10) 0 | (10) 0 | (10) 0 | (10) 0 | (10) 0 | (10) 0 |
| 9 RECTUM Parasite(s) | | (10) 1 | (10) 0 | (15) 2 | (15) 2 | (10) 0 | (10) 0 | (10) 0 | (10) 0 | (10) 0 | (10) 0 |

HD-33 (90-OGR)/Edition 10/2009
Page 38/47

G6597-90-OGR
Copy No. 1/2

Page 198/207

CONFIDENTIAL

21 & 22, Peenya, Phase II, Bangalore- 560 058, India.

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | FEMALES | | | | | | | | | |
|---------------------------|---------------------------------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| No. of rats examined | | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 10 | PANCREAS | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| | Increased acinar cell apoptosis | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | Lymphocytic infiltration | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| | Focal inflammation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | Fibrosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 |
| | Acinar cell vacuolation | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Leukocytic infiltration | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Lobular atrophy | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | Vacuolation | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 11 | LIVER | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| | Lymphocytic infiltration | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Portal lymphocytic infiltration | 0 | 5 | 0 | 0 | 0 | 0 | 3 | 0 | 2 | 6 |
| | Hepatocyte vacuolation | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Chronic inflammatory focus(1) | 0 | 4 | 0 | 0 | 10 | 6 | 7 | 9 | 3 | 8 |
| | Portal leukocytic infiltration | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Focal necrosis | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Necrobiotic focus(i) | 3 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |

HD-33 (90-OGR)/Edition 10/2009
Page 39/47

CONFIDENTIAL

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | FEMALES | | | | | | | | | |
|---------------------------------------|---------------------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No.of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No.of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 12 LUNGS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Perivascular lymphocytic infiltration | | 0 | 5 | 0 | 0 | 4 | 2 | 2 | 0 | 0 | 0 |
| Mineralisation blood vessels | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 |
| Pneumonic focus(i) | | 0 | 1 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Leukocytic infiltration | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Hemorrhage | | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Mineralisation-pulmonary vessels | | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 1 | 0 |
| Increased macrophages | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 |
| Cholesterol crystals | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 |
| Alveolar macrophages | | 0 | 1 | 0 | 0 | 1 | 3 | 4 | 0 | 1 | 0 |
| Chronic pleuritis | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Lymphocytic infiltration | | 2 | 0 | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mineralisation | | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 13 TRACHEA | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Cystic gland(s) | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 14 LARYNX | | (10) | (10) | (-) | (-) | (10) | (9) | (10) | (-) | (-) | (-) |
| 15 PHARYNX | | (10) | (10) | (-) | (-) | (10) | (10) | (10) | (-) | (-) | (-) |

HD-33 (90-OGR)/Edition 10/2009

Page 40/47

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | FEMALES | | | | | | | | | |
|---------------------------|----------------------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 16 NOSE | | (10) | (10) | (-) | (-) | (10) | (10) | (10) | (-) | (-) | (-) |
| 17 HEART | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Inflammatory focus(i) | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| 18 AORTA | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 19 SPLEEN | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Increased hemosiderosis | | 0 | 5 | 2 | 1 | 0 | 6 | 0 | 8 | 7 | 4 |
| 20 MESENTERIC LYMPH NODES | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Lymphoid hyperplasia | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Cystic space(s) | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Increased mast cells | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Edema | | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 21 MANDIBULAR LYMPH NODE | | (-) | (-) | (-) | (1) | (-) | (-) | (-) | (-) | (-) | (10) |
| Lymphoid hyperplasia | | - | - | - | 1 | - | - | - | - | - | 3 |

IID-33 (90-OGR)/Edition 10/2009
Page 41/47

CONFIDENTIAL

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | FEMALES | | | | | | | | | |
|--|----------------------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 22 AXILLARY LYMPH NODE | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (-) |
| Lymphoid hyperplasia | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | - |
| 23 KIDNEYS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Lymphocytic infiltration | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Mineralisation | | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 2 | 0 | 0 |
| Dilatation of pelvis | | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 2 | 0 | 1 |
| Basophilic tubules | | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 |
| Urothelial hyperplasia | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Proteinaceous material in tubules | | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 |
| Suburothelial lymphocytic infiltration | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Nephropathy | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Mineralisation-corticomedullary junction | | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| Suburothelial leucocytic infiltration | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Hyaline casts | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Glomerulosclerosis | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Pyelitis | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 24 URINARY BLADDER | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Lymphocytic infiltration | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

HD-33 (90-OGR)/Edition 10/2009

Page 42/47

G6597-90-OGR

Copy No. 1/2

Page 202/207

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | FEMALES | | | | | | | | | |
|-------------------------------|---------------------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No.of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No.of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 25 OVARIES WITH OVIDUCTS | | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (10) | (10) | (-) |
| 26 OVARIES | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (-) | (-) | (10) |
| Cyst(s) | | 1 | 0 | 0 | 0 | 0 | 0 | 0 | - | - | 0 |
| Inflammatory exudate in lumen | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | - | - | 0 |
| Luteal cyst(s) | | 1 | 0 | 0 | 2 | 0 | 0 | 0 | - | - | 0 |
| Follicular cyst(s) | | 0 | 0 | 0 | 1 | 0 | 0 | 0 | - | - | 0 |
| 27 UTERUS (WITH CERVIX) | | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (10) |
| Dilatation | | - | - | - | - | - | - | - | - | - | 5 |
| 28 UTERUS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (-) |
| Dilatation | | 3 | 4 | 2 | 3 | 4 | 2 | 0 | 2 | 4 | - |
| Cystic gland(s) | | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | - |
| Squamous metaplasia | | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | - |

HD-33 (90-OGR)/Edition 10/2009
Page 43/47

G6597-90-OGR
Copy No. 1/2

Page 203/207

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | FEMALES | | | | | | | | | |
|---------------------------------|----------------------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 29 THYROIDS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Ectopic thymus | | 2 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 0 |
| Ultimobranchial cyst | | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Lymphocytic infiltration | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Embryonic remnants | | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 PARATHYROIDS | | (10) | (-) | (15) | (15) | (7) | (8) | (10) | (10) | (10) | (10) |
| Connective tissue proliferation | | 0 | - | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| 31 PITUITARY | | (10) | (10) | (15) | (15) | (10) | (10) | (9) | (10) | (10) | (10) |
| Cyst(s) | | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Cyst(s)-pars intermedia | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 32 ADRENALS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Accessory cortical tissue | | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 1 | 0 |
| Accessory adrenal | | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| Hypertrophy-zona glomerulosa | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Increased cortical vacuolation | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

HD-33 (90-OGR)/Edition 10/2009
Page 44/47

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | FEMALES | | | | | | | | | |
|---------------------------------------|----------------------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 33 BRAIN-CEREBRUM | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 34 BRAIN-CEREBELLUM | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 35 BRAIN-MEDULLA / PONS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 36 SPINAL CORD | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| 37 SCIATIC NERVES | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Perivascular lymphocytic infiltration | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 38 EYES WITH RETINA & OPTIC NERVE | | (10) | (10) | (-) | (-) | (10) | (10) | (-) | (-) | (-) | (-) |
| Retinal atrophy | | 0 | 2 | - | - | 0 | 0 | - | - | - | - |
| 39 EYES WITH OPTIC NERVE | | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (10) |

HD-33 (90-OGR)/Edition 10/2009
Page 45/47

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | FEMALES | | | | | | | | | |
|---------------------------------|---------------------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No.of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No.of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 40 EYES | | (-) | (-) | (15) | (15) | (-) | (-) | (-) | (-) | (-) | (-) |
| 41 SKIN | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Epidermal hyperplasia | | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 42 TONGUE | | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (10) |
| 43 THYMUS | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (10) | (10) |
| Epithelial hyperplasia | | 1 | 3 | 0 | 0 | 1 | 4 | 5 | 2 | 0 | 2 |
| Hemorrhage | | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Epithelial cyst(s) | | 0 | 6 | 2 | 0 | 8 | 6 | 7 | 2 | 4 | 4 |
| Ectopic parathyroid | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Histiocytosis | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Cyst with eosinophilic crystals | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Pigmentation | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Granulomatous inflammation | | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

ANNEXURE 9 contd. Historical Data

HISTORICAL DATA – 33

90-DAY REPEATED DOSE ORAL TOXICITY STUDY BY GAVAGE IN WISTAR RATS

33.9 contd.: Histopathological Findings

| TISSUE AND OBSERVATION | Sex | FEMALES | | | | | | | | | |
|----------------------------|----------------------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | Study No. | 4270 | G4742 | 4495 | 4010 | G4903 | G4839 | G4963 | G4894 | G4897 | G5239 |
| | Study code | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR | 90-OGR |
| | Age of rats | 21 W | 19 W | 21 W | 18 W | 18 W | 21 W | 19 W | 19 W | 21 W | 20 W |
| | No. of rats | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| | No. of rats examined | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 |
| 44 MAMMARY GLAND | | NA | (10) | (15) | (-) | (10) | (9) | (9) | (10) | (10) | (10) |
| 45 LACRIMAL GLANDS | | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (10) |
| Lymphocytic infiltration | | - | - | - | - | - | - | - | - | - | 2 |
| Inflammation | | - | - | - | - | - | - | - | - | - | 1 |
| 46 MUSCLE FEMORAL | | (-) | (-) | (15) | (15) | (-) | (-) | (-) | (-) | (-) | (-) |
| 47 BONE (FEMUR) WITH JOINT | | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (10) | (10) | (10) |
| 48 STERNUM WITH MARROW | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (8) | (10) |
| Cystic space(s) | | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 49 BONE MARROW (SMEAR) | | (10) | (10) | (15) | (15) | (10) | (10) | (10) | (10) | (8) | (10) |
| Increased mast cells | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |