

## FINAL REPORT

**Test Facility Study No. 20334125**

# Dose Range Finder for the Extended One Generation Reproductive Toxicity Study with Code 10 (SF-002) by Dietary Administration in Rats

**GLP**

## SPONSOR:

Kerry Inc.

3400 Millington Road Beloit

Wisconsin 53511 USA

## TEST FACILITY:

Charles River Laboratories Den Bosch BV Hambakenwetering 7

5231 DD ‘s-Hertogenbosch The Netherlands

Charles River Laboratories Den Bosch BV Nistelrooisebaan 3

5374 RE Schaijk The Netherlands

**Page 1 of 459**

# TABLE OF CONTENTS

[LIST OF TABLES 4](#_bookmark0)

[LIST OF APPENDICES 5](#_bookmark1)

[QUALITY ASSURANCE STATEMENT 6](#_bookmark2)

[COMPLIANCE STATEMENT AND REPORT APPROVAL 8](#_bookmark3)

1. [RESPONSIBLE PERSONNEL 9](#_bookmark4)
   1. [Test Facility 9](#_bookmark5)
2. [SUMMARY 10](#_bookmark6)
3. [INTRODUCTION 12](#_bookmark7)
4. [MATERIALS AND METHODS 13](#_bookmark8)
   1. [Test Materials 13](#_bookmark9)
      1. [Test Material Characterization 13](#_bookmark10)
      2. [Test Material 13](#_bookmark11)
      3. [Vehicle 14](#_bookmark12)
   2. [Study Design 14](#_bookmark13)
   3. [Deviations 15](#_bookmark14)
5. [COMPUTERIZED SYSTEMS 15](#_bookmark15)
6. [RETENTION AND DISPOSITION OF RECORDS, SAMPLES, AND](#_bookmark16) [SPECIMENS 16](#_bookmark16)
7. [RESULTS 17](#_bookmark17)
   1. [Diet Preparation Analyses 17](#_bookmark18)
      1. [Mortality 17](#_bookmark19)
      2. [Clinical Observations 17](#_bookmark20)
      3. [Body Weights and Body Weight Gains 17](#_bookmark21)
      4. [Food Consumption 18](#_bookmark22)
      5. [Test Material Intake 18](#_bookmark23)
      6. [Macroscopic Findings 18](#_bookmark24)
      7. [Organ Weights 19](#_bookmark25)
      8. [Histopathology 19](#_bookmark26)
   2. [Reproduction Data 19](#_bookmark27)
      1. [Estrous Cycle 19](#_bookmark28)
      2. [Mating Index 19](#_bookmark29)
      3. [Precoital Interval 19](#_bookmark30)
      4. [Number of Implantation Sites 20](#_bookmark31)
      5. [Fertility Index 20](#_bookmark32)
      6. [Pregnancy Index 20](#_bookmark33)
   3. [Developmental Data 20](#_bookmark34)
      1. [Gestation Index and Length 20](#_bookmark35)
      2. [Parturition/Maternal Care 20](#_bookmark36)
      3. [Post-Implantation Loss 20](#_bookmark37)
      4. [Litter Size 21](#_bookmark38)
      5. [Live Birth Index 21](#_bookmark39)
      6. [Viability Index 21](#_bookmark41)
      7. [Survival Index 21](#_bookmark43)
      8. [Clinical Signs 21](#_bookmark44)
      9. [Body Weights 22](#_bookmark45)
      10. [Sex Ratio 22](#_bookmark46)
      11. [Anogenital Distance 22](#_bookmark47)
      12. [Areola/Nipple Retention 22](#_bookmark48)
      13. [Macroscopic Findings 22](#_bookmark49)
8. [DISCUSSION 23](#_bookmark50)
9. [CONCLUSION 24](#_bookmark51)
10. [REPORT APPROVAL 25](#_bookmark52)

# LIST OF TABLES

[Table 1 Summary of Clinical Observations 26](#_bookmark53)

[Table 2 Summary of Body Weights 30](#_bookmark55)

[Table 3 Summary of Body Weight Gains 34](#_bookmark57)

[Table 4 Summary of Food Consumption 38](#_bookmark59)

[Table 5 Summary of Test Material Intake 42](#_bookmark61)

[Table 6 Summary of Organ Weights 46](#_bookmark63)

[Table 7 Summary of Macroscopic Pathology 48](#_bookmark65)

[Table 8 Summary of Microscopic Pathology 50](#_bookmark66)

[Table 9 Summary of Reproductive Performance 51](#_bookmark68)

[Table 10 Summary of Natural Delivery Observations 52](#_bookmark70)

[Table 11 Summary of Litter Observations 54](#_bookmark73)

[Table 12 Summary of Litter Mean Pup Body Weights 55](#_bookmark75)

[Table 13 Summary of Litter Mean Pup Physical Development 58](#_bookmark77)

# LIST OF APPENDICES

[Appendix 1 Last Amended Study Plan and Study Plan 59](#_bookmark79)

[Appendix 2 Test Material Characterization 122](#_bookmark143)

[Appendix 3 Diet Analysis Report 126](#_bookmark145)

[Appendix 4 Explanation Page 144](#_bookmark163)

[Appendix 5 Individual Mortality 146](#_bookmark164)

[Appendix 6 Individual Clinical Observations 154](#_bookmark166)

[Appendix 7 Individual Body Weights 167](#_bookmark168)

[Appendix 8 Individual Body Weight Gains 183](#_bookmark170)

[Appendix 9 Individual Food Consumption 199](#_bookmark172)

[Appendix 10 Individual Test Material Intake 215](#_bookmark174)

[Appendix 11 Indivudual Estrous Cycles 231](#_bookmark176)

[Appendix 12 Individual Organ Weights 248](#_bookmark177)

[Appendix 13 Individual Macroscopic and Microscopic Pathology 259](#_bookmark179)

[Appendix 14 Pathology Report 339](#_bookmark181)

[Appendix 15 Individual Reproductive Performance 348](#_bookmark197)

[Appendix 16 Individual Natural Delivery Observations 352](#_bookmark199)

[Appendix 17 Individual Litter Observations 360](#_bookmark201)

[Appendix 18 Individual Pup Clinical Observations 376](#_bookmark203)

[Appendix 19 Individual Litter Mean Pup Body Weights 380](#_bookmark205)

[Appendix 20 Individual Pup Body Weights 388](#_bookmark207)

[Appendix 21 Individual Litter Mean Pup Physical Development 404](#_bookmark209)

[Appendix 22 Individual Pup Physical Development 408](#_bookmark211)

[Appendix 23 Individual Pup Gross Pathology 435](#_bookmark213)

[Appendix 24 Historical Control Data 448](#_bookmark215)

## QUALITY ASSURANCE STATEMENT

This report was inspected by the Test Facility Quality Assurance Unit (QAU) according to the Standard Operating Procedure(s). The reported method and procedures were found to describe those used and the report reflects the raw data. The Test Facility inspection program was conducted in accordance with Standard Operating Procedure. During the on-site process inspections, procedures applicable to this type of study were inspected.

The dates of Quality Assurance inspections are given below.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Test Facility Study No.** | 20334125 |  | | |
|  |  | **Start** | **End** | **Reporting** |
|  |  | **Inspection** | **Inspection** | **date to TFM** |
| **Type of Inspections** | **Phase/Process** | **date** | **date** | **and SD\*** |
| **Study** |  |  |  |  |
|  | Final Study Plan | 31-May-2022 | 31-May-2022 | 01-Jun-2022 |
|  | Study Plan Amendment 01 | 13-Jun-2022 | 13-Jun-2022 | 13-Jun-2022 |
|  | Study Plan Amendment 02 | 14-Jun-2022 | 14-Jun-2022 | 15-Jun-2022 |
|  | Study Plan Amendment 03 | 13-Jul-2022 | 13-Jul-2022 | 13-Jul-2022 |
|  | Phase Report - Analytical |  |  |  |
|  | Chemistry | 24-Nov-2022 | 24-Nov-2022 | 24-Nov-2022 |
|  | Report - Materials and Methods | 24-Nov-2022 | 24-Nov-2022 | 30-Nov-2022 |
|  | Data Review - Formulations | 24-Nov-2022 | 29-Nov-2022 | 30-Nov-2022 |
|  | Data Review - Technical |  |  |  |
|  | Operations | 25-Nov-2022 | 25-Nov-2022 | 30-Nov-2022 |
|  | Data Review - Fetal Pathology | 25-Nov-2022 | 25-Nov-2022 | 30-Nov-2022 |
|  | Data Review - Necropsy | 25-Nov-2022 | 25-Nov-2022 | 30-Nov-2022 |
|  | Data Review - Histology | 28-Nov-2022 | 28-Nov-2022 | 30-Nov-2022 |
|  | Phase Report - Pathology | 28-Nov-2022 | 28-Nov-2022 | 30-Nov-2022 |
|  | Report - Results | 28-Nov-2022 | 29-Nov-2022 | 30-Nov-2022 |
|  | Study Plan Amendment 04 | 03-Feb-2023 | 03-Feb-2023 | 03-Feb-2023 |
|  | Final Report | 13-Mar-2023 | 13-Mar-2023 | 13-Mar-2023 |
| **Process** |  |  |  |  |
|  | **Analytical and physical chemistry** | 16-May-2022 | 31-May-2022 | 31-May-2022 |
|  |  | 25-Jul-2022 | 05-Aug-2022 | 05-Aug-2022 |
|  | Test Item Handling |  |  |  |
|  | Exposure |  |  |  |
|  | Observations/Measurements |  |  |  |
|  | Specimen Handling |  |  |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of Inspections Process** | **Phase/Process** | **Start Inspection date** | **End Inspection date** | **Reporting date to TFM and SD\*** |
|  | **Animal Facilities** | 24-Jun-2022 | 24-Jun-2022 | 24-Jun-2022 |
|  |  | 05-Jul-2022 | 26-Jul-2022 | 26-Jul-2022 |
|  |  | 04-Aug-2022 | 04-Aug-2022 | 25-Aug-2022 |
|  |  | 14-Sep-2022 | 28-Sep-2022 | 29-Sep-2022 |
|  |  | 04-Oct-2022 | 26-Oct-2022 | 28-Oct-2022 |
|  | Test Item Handling |  |  |  |
|  | Exposure |  |  |  |
|  | Observations/Measurements |  |  |  |
|  | Specimen Handling |  |  |  |
|  | **Fetal Pathology** | 09-May-2022 | 13-May-2022 | 16-May-2022 |
|  |  | 09-Aug-2022 | 22-Aug-2022 | 22-Aug-2022 |
|  | Observations/Measurements |  |  |  |
|  | Specimen Handling |  |  |  |
|  | **Histology** | 13-Jun-2022 | 23-Jun-2022 | 23-Jun-2022 |
|  |  | 08-Sep-2022 | 19-Sep-2022 | 19-Sep-2022 |
|  | Specimen Handling |  |  |  |
|  | **Necropsy** | 20-Jun-2022 | 30-Jun-2022 | 04-Jul-2022 |
|  |  | 14-Sep-2022 | 20-Sep-2022 | 20-Sep-2022 |
|  | Observations/Measurements |  |  |  |
|  | Specimen Handling |  |  |  |
|  | **Test Item Formulation** | 07-Jun-2022 | 07-Jun-2022 | 08-Jun-2022 |
|  |  | 15-Aug-2022 | 29-Aug-2022 | 29-Aug-2022 |
|  | Test Item Handling |  |  |  |
|  | **Test Item Receipt** | 13-Jun-2022 | 23-Jun-2022 | 24-Jun-2022 |
|  |  | 19-Sep-2022 | 21-Sep-2022 | 21-Sep-2022 |
|  | Test Item Handling |  |  |  |

\*TFM=Test Facility Management SD = Study Director

All electronic signatures appear at the end of this Report upon finalization.

## COMPLIANCE STATEMENT AND REPORT APPROVAL

The study was performed in accordance with the OECD Principles of Good Laboratory Practice as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA and EPA), Japan (MHLW, MAFF and METI), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

This study was conducted in accordance with the procedures described herein. All deviations authorized/acknowledged by the Study Director are documented in the Study Records. The report represents an accurate and complete record of the results obtained.

There were no deviations from the above regulations that affected the overall integrity of the study or the interpretation of the study results and conclusions.

All electronic signatures appear at the end of this Report at finalization.

## RESPONSIBLE PERSONNEL

### Test Facility

|  |  |  |  |
| --- | --- | --- | --- |
| **Role/Phase** | **Quality Assurance Unit** | **Name** | **Contact Information** |
| Study Director from 01 Feb  2023 onwards | Charles River | Daphne van den Oetelaar, MSc | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [daphne.vandenoetelaar@crl.com](mailto:daphne.vandenoetelaar@crl.com) |
| Study Director |  |  | Address as cited for Test Facility |
| from start study  onwards up to 01 | Charles River | Corina van den Heuvel, PhD | Tel: +31 73 640 6700  E-mail: |
| Feb 2023 |  |  | [corina.vandenheuvel@crl.com](mailto:corina.vandenheuvel@crl.com) |
| Test Facility Management | Charles River | Harry Emmen, MSc | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [harry.emmen@crl.com](mailto:harry.emmen@crl.com) |
| Test Facility QAU | Charles River | Lead QA | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [QADenBosch@crl.com](mailto:QADenBosch@crl.com) |
| **Individual Scientist (IS)** | | | |
| Analytical Chemistry | Charles River | Marc Baremans, MSc | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [marc.baremans@crl.com](mailto:marc.baremans@crl.com) |
| Microscopic Pathology | Charles River | Joost Lensen, PhD, CRP/TP | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [joost.lensen@crl.com](mailto:joost.lensen@crl.com) |

## SUMMARY

The objective of this study was to provide information for the selection of dose levels for an extended one-generation reproductive toxicity study in rats (Test Facility Study

No. 20334130).

The potential toxic effects of Code 10 (SF-002) when given *via* diet for a minimum of 28 days to Wistar Han rats were determined, and the potential to affect male and female

reproductive performance such as gonadal function, mating behavior, conception, parturition and early postnatal development was evaluated.

The dose levels in this study were selected to be 0, 12500, 25000 and 50000 ppm, based on information provided by the Sponsor (90-day repeated dose toxicity study with dietary administration of Code 10 (SF-002) in rats (Study number 2330/010)).

The study design was as follows:

Text Table 1 Experimental Design

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Group No.** | **Test Material Identification** | **Target Dose Level**  **(mg/kg bw/day)** | **Diet Concentration (ppm)a** | **Number of Animals** | |
| **Males** | **Females** |
| 1 | - | 0 | 0b | 10 | 10 |
| 2 | Code 10 (SF-002) | 800 | 12500 | 10 | 10 |
| 3 | Code 10 (SF-002) | 1600 | 25000 | 10 | 10 |
| 4 | Code 10 (SF-002) | 3300 | 50000 | 10 | 10 |

a Diet calculations were not corrected for purity.

b Powder rodent diet with propylene glycol, without test material.

Chemical analyses of dietary preparations were conducted once during the study to assess accuracy and homogeneity. Dietary analyses confirmed that diets were prepared accurately and homogenously.

The following parameters and end points were evaluated in this study: mortality/ moribundity, clinical signs, body weight and food consumption, test material intake, macroscopic examination, organ weights and microscopic examination.

In addition, the following reproduction/developmental parameters were determined: estrous cycle, mating, pregnancy and fertility indices, precoital time, number of implantation sites, gestation index and duration, viability and survival indices, parturition, maternal care, sex ratio and early postnatal pup development (mortality, clinical signs, body weights, anogenital distance, areola/nipple retention and macroscopic examination).

No adverse test material-related effects were observed in parental parameters up to 25000 ppm.

At 25000 ppm, non-adverse lower body weight (gain) was observed in males and females.

At 50000 ppm, non-adverse lower body weight (gain) correlating with lower food consumption was observed in males. Adverse lower body weight (gain) was observed in females, correlating with lower food consumption during the lactation phase. These differences were considered not to be dose-limiting.

No mortality and no test material-related changes were noted in any of the remaining parental parameters investigated in this study (i.e., clinical appearance, test material intake, macroscopic examination, organ weights, and microscopic examination).

No test material-related effects were observed in reproduction parameters up to the highest dose level tested (50000 ppm).

No test material-related changes were noted in any of the reproductive parameters investigated in this study (i.e., mating, pregnancy and fertility indices, precoital interval, number of implantations, estrous cycle, spermatogenic profiling, and histopathological examination of reproductive organs).

No adverse test material-related effects were observed in developmental parameters up to 25000 ppm.

At 25000 ppm non-adverse lower body weights were observed for male pups.

At 50000 ppm adverse lower pup body weights (both sexes) were observed. These differences were considered not to be dose-limiting.

No test material-related changes were noted in any of the remaining developmental parameters investigated in this study (i.e., gestation, viability and survival indices, gestation length, parturition, sex ratio, maternal care, litter size and early postnatal pup development consisting of mortality, clinical signs, body weight, anogenital distance, areola/nipple retention and macroscopic examination).

Based on the results of this dose range finding study for an extended one-generation reproductive toxicity study in rats (Test Facility Study No. 20334130), dose levels of up to 50000 ppm (corresponding to an actual test material intake of 3394 and 4737 mg/kg/day for males and females, respectively) were considered suitable for Wistar Han rats.

## INTRODUCTION

The objective of this study was to provide information for the selection of dose levels for an extended one-generation reproductive toxicity study in rats (Test Facility Study

No. 20334130).

The potential toxic effects of Code 10 (SF-002) when given *via* diet for a minimum of 28 days to Wistar Han rats were determined, and the potential to affect male and female

reproductive performance such as gonadal function, mating behavior, conception, parturition and early postnatal development was evaluated.

No specific guidelines are applicable, but the design is based on test guideline OECD

421. This study is needed to select dose levels for a subsequent extended one-generation reproduction toxicity study (EOGRTS; OECD guideline 443).

The last Study Plan Amendment and Study Plan are presented in [Appendix 1](#_bookmark80). Study Initiation Date: 30 May 2022

Initiation of Diet Administration: 14 Jun 2022

Completion of In-life: 15 Aug 2022

Experimental Start Date: 06 Jun 2022

Experimental Completion Date: 27 Oct 2022

All animal activities and necropsy were performed at the Schaijk location, the test material preparation was performed either at the Schaijk location or at 's-Hertogenbosch location (documented in the raw data). All other activities conducted by the Test Facility were performed at the ‘s-Hertogenbosch location.

## MATERIALS AND METHODS

### Test Materials

The terms “item” and “material” (i.e., test material, control item) are both used in this study report and do have the same meaning. Therefore, both terms can be used interchangeably.

### Test Material Characterization

The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the test material, and this information is available to the appropriate regulatory agencies should it be requested.

The Sponsor provided to the Test Facility documentation of the identity, strength, purity, composition, and stability for the test material.

Information about the purity and composition of the test material is not available since the test material is an UVCB (Substance of Unknown or Variable composition, Complex Reaction Products or Biological Materials). Since a sample relevant for the purpose of this study was tested, it was concluded that the study integrity was not affected by the omission of this information.

The characterization of the test material was conducted in a GMP environment. A Certificate of Analysis was provided to the Test Facility and is presented in [Appendix 2](#_bookmark144). An additional Certificate of Analysis was provided to the Test Facility and is also presented in [Appendix 2](#_bookmark144), showing that the test material was still suitable for use after the re-evaluation date.

### Test Material

Identification: Code 10 (SF-002) Batch (Lot) Number: 05591112

Expiry Date: 30 May 2023 (re-evaluation date)

Physical Description: Clear amber liquid

Purity/Composition: UVCB. See Certificate of Analysis issued 21

January 2022

Storage Conditions: At room temperature protected from light Additional information

Test Facility Test Material Number:

Purity/Composition Correction Factor:

213125/A

No correction factor required

Test Material Handling: Bulk containers of the test article WILL NOT be

subjected to mixing (i.e., inversion, vortexing, agitation or shaking) of the bulk test article prior to sampling for dose formulation preparation. The technician should pull from the center of the bulk container when removing aliquots and not scrape the sides or bottom of the bulk container.

Specific gravity / density: 1.086

Stability in powder diet: Stability for at least 10 days at room temperature

(15 to 25°C) under normal laboratory light conditions, in open containers is confirmed over the concentration range 500 to 50000 ppm, Project 20334112 (17 kg bulk).

### Vehicle

Identification: Propylene glycol (Merck, Darmstadt, Germany)

Specific gravity: 1.036

### Study Design

Text Table 2 Experimental Design

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Target** |  | **Number of** | |  | |
|  |  | **Dose Level** | **Diet** | **Animals** | | **Animal Numbers** | |
| **Group** | **Test Material** | **(mg/kg** | **Concentration** |  |  |  |  |
| **No.** | **identification** | **bw/day)** | **(ppm)a** | **Males** | **Females** | **Males** | **Females** |
| 1 | - | 0 | 0b | 10 | 10 | 01-10 | 41-50 |
| 2 | Code 10 (SF-002) | 800 | 12500 | 10 | 10 | 11-20 | 51-60 |
| 3 | Code 10 (SF-002) | 1600 | 25000 | 10 | 10 | 21-30 | 61-70 |
| 4 | Code 10 (SF-002) | 3300 | 50000 | 10 | 10 | 31-40 | 71-80 |

a Diet calculations were not corrected for purity.

b Powder rodent diet with propylene glycol, without test material.

The study was conducted in accordance with the Study Plan (Amendment) presented in [Appendix 1](#_bookmark80) with the following requirements and exceptions.

Text Table 3 Additional Study Plan Deliverables

|  |  |
| --- | --- |
| **Concerns** | **Requirement** |
| Source of Test System | Charles River Deutschland, Sulzfeld, Germany. |
| Age at Initiation of Dosing, weeks | Males: 11  Females: 12 |
| Body Weight Range at Initiation of Dosing | Males: 285 – 342 g males  Females: 187 – 241 g females |
| Number of Acclimation days | 6 |
| Number of Treatment days | Males: 28  Females: 43 - 63 |
| Environmental Conditions | The actual daily mean temperature during the study period was 19 to 22°C with an actual daily mean  relative humidity of 48 to 67%. |

### Deviations

All deviations that occurred during the study have been authorized/acknowledged by the Study Director, assessed for impact, and documented in the study records. All Study Plan deviations and those SOP deviations that could have impacted the quality or integrity of the study are listed below.

None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

Text Table 4 Deviations

|  |  |  |
| --- | --- | --- |
| **In-life Procedures** | | |
| **Study Plan Section No.** | **Deviation** | **Impact** |
| 10 | No cage side observation was performed for  Animal No. 53 (25000 ppm) on Day 4 of lactation. | No clinical observations were recorded for this animal throughout the treatment period.  Sufficient information available. |
| 10 and 11 | On the day of necropsy no detailed observation was performed for Animal  Nos. 59 (25000 ppm), 77 and 78 (50000 ppm).  On the day of necropsy, no pup clinical observations were performed for Litter Nos. 52 (25000 ppm) and 63 (50000 ppm). | Sufficient data was available from these animals during the in-life phase of the study, and from other animals in these groups. |

## COMPUTERIZED SYSTEMS

Computerized systems used in the study are listed below or presented in the appropriate Phase Report. All computerized systems used in the conduct of this study have been validated; when a particular system has not satisfied all requirements, appropriate administrative and procedural controls were implemented to assure the quality and integrity of data.

Text Table 5 Computerized Systems

|  |  |
| --- | --- |
| **System Name** | **Description of Data Collected and/or Analyzed** |
| Provantis® | In-life phase (Mortality; Clinical signs; Body weights; Food consumption; Estrous Stage Determination; Macroscopy; Organ weights; Reproduction parameters; Observations pups) data  collection |
| Dispense | Test material receipt, accountability and/or diet preparation  activities |
| REES Centron | Temperature and humidity (animal and laboratory facilities) data  collection |
| M-Files® | Reporting and collection of 21 CFR Part 11 compliant signature |

## RETENTION AND DISPOSITION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, documentation, Study Plan, retained samples and specimens, and Final Report(s) from this study were archived at the Test Facility at the finalization of the report. At least two years after issue of the Final Report, the Sponsor will be contacted, to determine the disposition of materials associated with the study.

Electronic data generated by the Test Facility were archived as noted above, except that data collected using Provantis and Dispense, files stored M-Files® (Study Plan (amendments) and reporting files) and study deviations were archived at the Charles River Laboratories facility location in Wilmington, Massachusetts, USA.

## RESULTS

### Diet Preparation Analyses

([Appendix 3](#_bookmark146)) Accuracy

The concentrations analyzed in the diets of Group 2 and Group 3 were agreement with target concentrations (i.e., mean sample concentration results were within or equal to 80-120% of target concentration).

For the diet of Group 4 prepared for use in Week 1, the mean recovery was 78% of target. An out of specification investigation was performed. No analytical reason was found for the low recovery. The accuracy of the Group 4 diet only showed a small deviation from the target range and was therefore considered acceptable for the purpose of this dose range finding study.

A small response at the retention time of the test material was observed in the chromatograms of the Group 1 diet prepared for use in Week 1.

Homogeneity

The diets of Group 2 and Group 4 were homogeneous (i.e., coefficient of variation

≤ 10.00%).

### Mortality

([Appendix 5](#_bookmark165))

No mortality occurred during the study period.

### Clinical Observations

([Table 1](#_bookmark54) and [Appendix 6](#_bookmark167))

No test material-related clinical signs were noted during daily detailed clinical observations.

Incidental findings noted during the treatment period occurred in the control group and/or within the range of background findings to be expected for rats of this age and strain which are housed and treated under the conditions in this study. At the incidence observed, these were considered not to be test material-related.

### Body Weights and Body Weight Gains

([Table](#_bookmark56) 2, [Table 3](#_bookmark58) and [Appendix](#_bookmark169) 7, [Appendix 8](#_bookmark171))

Body weights and body weight gain of treated animals remained in the same range as controls over the treatment period in males and females at 12500 ppm.

In males, body weight gain at 25000 and 50000 ppm was lower during the treatment period, resulting in a 4 and 8% lower body weight on Day 28, respectively, when compared to control (not statistically significant at 25000 ppm). At 25000 ppm, this was mainly due to lower body weight gain over Days 1-8 and 15-22, while at 50000 ppm, lower body weight gain was noted on all occasions (statistically significant over Days 1-8 and 15-22 only).

In females at 25000 ppm, body weights were comparable to control during the premating and gestation periods. During the lactation period, body weights were lower (down to 5% lower than control on Day 13, not statistically significant).

In females at 50000 ppm, lower body weight gain was noted during the premating period and over Days 4-7 and Days 11-14 of the gestation period (not statistically significant), but this did not result in lower body weights. During the second week of the lactation period, body weights were lower (statistically significant on Day 13 only, down to 11% lower than control on Day 13), with lower body weight gain from Day 1 onwards and body weight loss over Days 10-13.

### Food Consumption

([Table 4](#_bookmark60) and [Appendix 9](#_bookmark173))

Food consumption of treated animals was similar to the control level over the treatment period in males and females up to 25000 ppm.

In males at 50000 ppm, food consumption was lower over Days 1-8 (22% lower than control), which was mostly recovered over Days 8-15 and fully recovered over Days 15-22. Normal values for food consumption were noted during the rest of the treatment period.

In females, food consumption of treated animals was similar to the control level during the premating and the gestation period. During the lactation period, females at 50000 ppm had lower food consumption over Days 4-13 (down to 23% lower than control, only statistically significant over Days 10-13), resulting in a lower overall food consumption (16% lower than control).

### Test Material Intake

([Table 5](#_bookmark62) and [Appendix 10](#_bookmark175))

Mean daily test material intake over the study period was as follows:

Text Table 6 Test Material Intake

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Mean over means intake**  **[mg test material/kg body weight/day] (mean range indicated within brackets)** | | | | | |
|  | **Group No.** | 2 | | 3 | | 4 | |
| **Target dose level (mg test material/kg body weight/day)** | 800 | | 1600 | | 3300 | |
|  | |  | | | | | |
| **Sex** | **Study Period** |  | |  | |  | |
|  |  |  | |  | |  | |
| **Males** | Days 1-28 | 853 | (782-899) | 1712 | (1579-1830) | 3394 | (2982-3816) |
|  |  |  | |  | |  | |
|  | |  | | | | | |
| **Females** | Premating | 879 | (853-905) | 1849 | (1788-1909) | 3383 | (3312-3455) |
| Gestation | 986 | (906-1085) | 2009 | (1791-2189) | 3978 | (3431-4501) |
| Lactation | 1979 | (1525-2372) | 4054 | (3235-4670) | 7580 | (6231-8465) |
| *Mean of meansa* | 1212 | | 2494 | | 4737 | |

a Mean of means of all periods, weighed for number of measurement days/period: Females: ((14 x mean premating) + (20 x mean gestation) + (12 x mean lactation)) / 46

### Macroscopic Findings

([Table 8](#_bookmark67) and [Appendix 13](#_bookmark180))

There were no test material-related gross observations.

All of the recorded macroscopic findings were within the range of background gross observations encountered in rats of this age and strain.

### Organ Weights

([Table 6](#_bookmark64) and [Appendix 12](#_bookmark178))

There were no test material-related alterations in organ weights.

The testes and epididymides weights (relative to body weight) were statistically significantly higher at 50000 ppm, when compared to the control group but were considered to be the result of a test material-related effect on the final body weight which was statistically significantly lower.

### Histopathology

([Table 8](#_bookmark67) and [Appendix 13,](#_bookmark180) [Appendix 14](#_bookmark182))

There were no test material-related microscopic observations.

All of the recorded microscopic findings were within the range of background pathology encountered in rats of this age and strain. There was no test material-related alteration in the prevalence, severity, or histologic character of those incidental tissue alterations.

Reproductive performance

Stage dependent qualitative evaluation of spermatogenesis in the testis was performed. The testis revealed normal progression of the spermatogenic cycle and the expected cell associations and proportions in the various stages of spermatogenesis were present.

### Reproduction Data

### Estrous Cycle

([Appendix 10](#_bookmark175))

Length and regularity of the estrous cycle were considered not to have been affected by treatment with the test material.

Most females had regular cycles of 4 days. An irregular cycle was noted for Female No. 71 at 50000 ppm (with normal litter). Given their incidental nature and absence of an apparent correlation to pregnancy status, this finding did not indicate a relationship with treatment of the test material.

### Mating Index

([Table 9](#_bookmark69))

Mating index for females was considered not to be affected by treatment with the test material. One control female (No. 48) was not mated. This female was in continued di-estrous during the mating period.

The mating indices were 90, 100, 100 and 100% for the control, 12500, 25000 and 50000 ppm groups, respectively.

Note: Mating index is defined as the number of females with evidence of mating (or no confirmed mating date and pregnant) compared to the number of paired females (percentage).

### Precoital Interval

([Table 9](#_bookmark69) and [Appendix 15](#_bookmark198))

Precoital interval was considered not to be affected by treatment with the test material. Except for Female No. 43 (control), which was mated on Day 13, all females showed evidence of mating within 4 days.

### Number of Implantation Sites

([Table 10](#_bookmark71) and [Appendix 16](#_bookmark200))

Number of implantation sites was considered not to be affected by treatment with the test material.

Mean number of implantation sites was 13.2, 11.3, 13.0 and 12.1 for the control, 12500,

25000 and 50000 ppm groups, respectively.

### Fertility Index

([Table 9](#_bookmark69))

Fertility index for females was considered not to be affected by treatment with the test material. The fertility indices were 100, 90, 100 and 80% for the control, 12500, 25000 and 50000 ppm groups, respectively.

One female at 12500 ppm (No. 59) and two females at 50000 ppm (Nos. 77 and 78) were not pregnant. Female No. 77 did not show any body weight gain over the treatment period. Given the absence of any reproductive/developmental toxicity during the study, this was considered not to be related to treatment with the test material.

Note: Fertility index is defined as the number of pregnant females compared to the number of females with evidence of mating (percentage).

### Pregnancy Index

([Table 9](#_bookmark69))

Pregnancy index for females was considered not to be affected by treatment with the test material. The pregnancy indices were 90, 90, 100 and 80% for the control, 12500, 25000 and 50000 ppm groups, respectively.

Note: Pregnancy index is defined as the number of pregnant females compared to the number of paired females (percentage).

### Developmental Data

### Gestation Index and Length

([Table 10](#_bookmark71) and [Appendix 16](#_bookmark200))

Gestation index (females with living pups on Day 1 compared to the number of pregnant females) and duration of gestation were considered not to be affected by treatment with the test material. The gestation indices were 100% for all groups.

### Parturition/Maternal Care

No signs of difficult or prolonged parturition were noted among the pregnant females.

Examination of cage debris of pregnant females revealed no signs of abortion or premature birth. No deficiencies in maternal care were observed.

### Post-Implantation Loss

([Table 10](#_bookmark72) and [Appendix 16](#_bookmark200))

The total number of offspring born compared to the total number of uterine implantations was considered not to be affected by treatment with the test material.

Post-implantation loss was 12, 12, 8 and 7% for the control, 12500, 25000 and 50000 ppm groups, respectively.

For Female Nos. 70 and 71 (25000 and 50000 ppm, respectively), the number of pups was slightly higher than the number of implantations. This phenomenon is observed from time to time and is caused by normal resorption of these areas during the 14-16 days of lactation.

### Litter Size

([Table 10](#_bookmark71) and [Appendix 16](#_bookmark200))

Litter size was considered not affected by treatment with the test material.

Live litter sizes were 11.7, 9.9, 11.9 and 11.3 living pups/litter for the control, 12500, 25000 and 50000 ppm groups, respectively.

The lower mean number of living pups at 12500 ppm was considered related to the slightly lower number of implantation sites in this dose group. As a dose-related response was absent, this was regarded as not test material-related.

### Live Birth Index

([Table 10](#_bookmark71) and [Appendix 16](#_bookmark200))

The number of live offspring on Day 1 after littering compared to the total number of offspring born was considered not to be affected by treatment with the test material.

The live birth indices were 100, 100, 99 and 100% for the control, 12500, 25000 and 50000 ppm groups, respectively.

One pup at 25000 ppm was found dead at first litter check. Autolysis was recorded for this pup at necropsy. This dead pup was considered to be unrelated to treatment with the test material, since the mortality incidence did not show a dose-related trend and remained within the range considered normal for pups of this age.

### Viability Index

([Table 11](#_bookmark74) and [Appendix 17](#_bookmark202))

The number of live offspring on Day 4 before culling compared to the number of offspring on Day 1 was considered not affected by treatment with the test material.

Viability indices were 100, 99, 100 and 100% for the control, 12500, 25000 and 50000 ppm groups, respectively.

One pup at 12500 ppm was found dead on PND 4. This dead pup was cannibalized. Since the mortality incidence did not show a dose-related trend and remained within the range considered normal for pups of this age, this was considered unrelated to treatment with the test material.

### Survival Index

([Table 11](#_bookmark74) and [Appendix 17](#_bookmark202))

The number of live offspring on Day 13 after littering compared to the number of live offspring on Day 4 (after culling) was not affected by treatment with the test material. No pups were found dead/missing between lactation Days 5 and 13, resulting in a survival index of 100% for all groups.

### Clinical Signs

([Appendix 18](#_bookmark204))

No clinical signs occurred among pups surviving until scheduled necropsy that were considered to be related to treatment with the test material.

For one pup of Female No. 57 (12500 ppm) a pale skin was noted on PND 1. For one pup of Female No. 75 (50000 ppm) slight to moderate dehydration was suspected over PND 7-9. At the low incidence observed and as it recovered on PND 10, this was considered an isolated event unrelated to treatment with the test material. The nature and incidence of other clinical signs remained within the range considered normal for pups of this age, and were therefore considered not to be test material-related.

Note: Only days on which clinical signs were present between first and last litter check are presented in the table.

### Body Weights

([Table 12](#_bookmark76) and [Appendix 19](#_bookmark206), [Appendix 20](#_bookmark208))

Body weights of pups were considered not to be affected by treatment with the test material in males up to 12500 ppm and in females up to 25000 ppm.

In male pups at 25000 and 50000 ppm lower body weights were noted from PND 7 onwards. On PND 13 body weights at 25000 and 50000 ppm were 8 and 15% lower than control, respectively.

In female pups at 50000 ppm, body weights on PND 13 were 14% lower than control.

### Sex Ratio

([Table 11](#_bookmark74) and [Appendix 21](#_bookmark210))

Sex ratio was considered not to be affected by treatment with the test material.

### Anogenital Distance

([Table 13](#_bookmark78) and [Appendix 22](#_bookmark212))

Anogenital distance (absolute and corrected for body weight) in male and female pups was considered not to be affected by treatment with the test material.

### Areola/Nipple Retention

([Table 13](#_bookmark78) and [Appendix 22](#_bookmark212))

Treatment with the test material up to 50000 ppm had no effect on areola/nipple retention. For none of the examined male pups nipples were observed on PND 13.

### Macroscopic Findings

([Appendix 23](#_bookmark214))

No macroscopic findings were noted among pups surviving until scheduled necropsy.

For macroscopic findings observed in pups that died before scheduled necropsy, see Sections [7.3.5](#_bookmark40) and [7.3.6](#_bookmark42).

## DISCUSSION

Wistar Han rats were treated with Code 10 (SF-002) by daily dietary administration at dose levels of 12500, 25000 and 50000 ppm. The rats of the control group received similarly prepared powder diet with propylene glycol, without the test material.

For the diet of Group 4 prepared for use in Week 1, the mean recovery was 78% of target. Since the deviation from target range (80-120%) was only small, these results were considered acceptable for the purpose of this study, i.e., to select dose levels for an extended one-generation reproductive toxicity study.

*Parental results*

No adverse test material-related effects were observed in parental parameters up to 25000 ppm.

At 25000 ppm, lower body weight gains were observed in males over Days 1-8 and 15-22 of treatment resulting in a slightly lower body weight at the end of treatment. In females, a slightly lower body weight was noted on Day 13 of the lactation period. Considering the magnitude of change (< 10% lower compared to control), this was considered not adverse.

At 50000 ppm, lower body weight gains were observed in males throughout the treatment period, resulting in a lower body weight at the end of treatment. This correlated with a lower food consumption during the first week of treatment. Considering the magnitude of change (< 10% lower compared to control) and/or transient nature, this was considered not adverse. In females, lower body weight gain was noted during the premating period and over Days 4-7 and 11-14 of gestation, not resulting in lower body weights at the end of gestation.

Throughout the lactation period body weight gain was lower and body weights were lower mainly during the second week of lactation. This correlated with lower food consumption from Day 4 of lactation onwards. Considering the magnitude of change (> 10% lower body weight compared to control, during the lactation phase), this was regarded adverse in females at 50000 ppm, but it was considered not to be dose limiting.

*Reproductive results*

No test material-related effects were observed in reproduction parameters up to the highest dose level tested (50000 ppm).

*Developmental results*

No adverse test material-related effects were observed in developmental parameters up to 25000 ppm.

Lower body weights were observed in pups at 25000 ppm (males only) and 50000 ppm (both sexes). Considering the magnitude of change at 50000 ppm (> 10% lower compared to control) this was regarded as adverse at this dose level. These differences were considered not to be dose limiting.

The reproduction and developmental toxicity observed in this study occurred at dose levels associated with parental toxicity. This included lower mean body weights for females at the end of the lactation period, accompanied by a lower overall food consumption during the lactation period at 50000 ppm. It could not be excluded that this effect on body weight and food intake was related to the observed developmental toxicity. No developmental toxicity was observed at dose levels which were non-toxic to the parental animals.

## CONCLUSION

Based on the results of this dose range finding study for an extended one-generation reproductive toxicity study in rats (Test Facility Study No. 20334130), dose levels of up to 50000 ppm (corresponding to an actual test material intake of 3394 and 4737 mg/kg/day for males and females, respectively) were considered suitable for Wistar Han rats.

## REPORT APPROVAL

All electronic signatures appear at the end of this Report at finalization.

**Summary of Clinical Observations: F0 Generation - Males 20334125**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Observation Type: All Types  From Day 1 (Start Date) to 29 (Start Date) | 0  ppm Group 1 | Male  12500 25000  ppm ppm  Group 2 Group 3 | | 50000  ppm Group 4 |
| **Skin, Lesion, Scapular, Left** |  |  |  |  |
| Number of Animals Affected | 1 | 0 | 0 | 0 |
| Number of Times Recorded | 1 | 0 | 0 | 0 |
| % of Affected Animals | 10 | 0 | 0 | 0 |
| First to Last seen | 15 - 15 | - | - | - |

**Summary of Clinical Observations: F0 Generation - Premating 20334125**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Observation Type: All Types  From Day 1 (Start Date (A)) to -1 (Mating) | 0  ppm Group 1 | Female  12500 25000  ppm ppm  Group 2 Group 3 | | 50000  ppm Group 4 |
| **Skin, Lesion, Dorsal Cervical** |  |  |  |  |
| Number of Animals Affected | 0 | 0 | 0 | 1 |
| Number of Times Recorded | 0 | 0 | 0 | 4 |
| % of Affected Animals | 0 | 0 | 0 | 10 |
| First to Last seen | - | - | - | 8 - 12 |
| **Skin, Lesion, Ventral Cervical** |  |  |  |  |
| Number of Animals Affected | 0 | 0 | 0 | 1 |
| Number of Times Recorded | 0 | 0 | 0 | 1 |
| % of Affected Animals | 0 | 0 | 0 | 10 |
| First to Last seen | - | - | - | 5 - 5 |
| **Skin, Scab, Dorsal Cervical** |  |  |  |  |
| Number of Animals Affected | 0 | 0 | 0 | 1 |
| Number of Times Recorded | 0 | 0 | 0 | 7 |
| % of Affected Animals | 0 | 0 | 0 | 10 |
| First to Last seen | - | - | - | 6 - 16 |
| **Skin, Scab, Interscapular** |  |  |  |  |
| Number of Animals Affected | 0 | 0 | 1 | 0 |
| Number of Times Recorded | 0 | 0 | 2 | 0 |
| % of Affected Animals | 0 | 0 | 10 | 0 |
| First to Last seen | - | - | 11 - 12 | - |

**Summary of Clinical Observations: F0 Generation - Gestation 20334125**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Observation Type: All Types  From Day 0 (Mating (A)) to 0 (Littering) | 0  ppm Group 1 | Female  12500 25000  ppm ppm  Group 2 Group 3 | | 50000  ppm Group 4 |
| **Fur, Loss** |  |  |  |  |
| Number of Animals Affected | 0 | 0 | 0 | 1 |
| Number of Times Recorded | 0 | 0 | 0 | 13 |
| % of Affected Animals | 0 | 0 | 0 | 10 |
| First to Last seen | - | - | - | 10 - 23 |
| **Skin, Scab, Dorsal Cervical** |  |  |  |  |
| Number of Animals Affected | 0 | 0 | 0 | 1 |
| Number of Times Recorded | 0 | 0 | 0 | 26 |
| % of Affected Animals | 0 | 0 | 0 | 10 |
| First to Last seen | - | - | - | 0 - 22 |

**Summary of Clinical Observations: F0 Generation - Lactation 20334125**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Observation Type: All Types  From Day 1 (Littering (A)) to 16 (Littering) | 0  ppm Group 1 | Female  12500 25000  ppm ppm  Group 2 Group 3 | | 50000  ppm Group 4 |
| **Fur, Loss** |  |  |  |  |
| Number of Animals Affected | 1 | 0 | 0 | 1 |
| Number of Times Recorded | 3 | 0 | 0 | 2 |
| % of Affected Animals | 11 | 0 | 0 | 13 |
| First to Last seen | 1 - 3 | - | - | 1 - 2 |
| **Skin, Scab, Dorsal Cervical** |  |  |  |  |
| Number of Animals Affected | 0 | 0 | 0 | 1 |
| Number of Times Recorded | 0 | 0 | 0 | 5 |
| % of Affected Animals | 0 | 0 | 0 | 13 |
| First to Last seen | - | - | - | 4 - 7 |
| **Eyeball, Abnormal Size, Left** |  |  |  |  |
| Number of Animals Affected | 1 | 0 | 0 | 0 |
| Number of Times Recorded | 2 | 0 | 0 | 0 |
| % of Affected Animals | 11 | 0 | 0 | 0 |
| First to Last seen | 1 - 14 | - | - | - |

**Summary of Body Weights: F0 Generation - Males 20334125**

Bodyweight (g)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Sex: Male | | Day(s) Relative to Start Date | | | | |
| 1 | 8 | 15 | 22 | 28 |
| 0 | Mean | 311.6 | 346.5 | 367.3 | 382.0 | 395.2 |
| ppm | SD | 17.0 | 21.3 | 25.2 | 24.0 | 22.4 |
| Group 1 | N | 10 | 10 | 10 | 10 | 10 |
| 12500 | Mean | 315.7 | 344.9 | 366.6 | 377.5 | 391.5 |
| ppm | SD | 10.4 | 11.5 | 13.4 | 14.0 | 12.8 |
| Group 2 | N | 10 | 10 | 10 | 10 | 10 |
|  | %Diff | 1.3 | -0.5 | -0.2 | -1.2 | -0.9 |
| 25000 | Mean | 305.3 | 331.2 | 354.3 | 364.0 | 378.3 |
| ppm | SD | 9.1 | 10.8 | 14.2 | 17.5 | 19.6 |
| Group 3 | N | 10 | 10 | 10 | 10 | 10 |
|  | %Diff | -2.0 | -4.4 | -3.5 | -4.7 | -4.3 |
| 50000 | Mean | 312.3 | 321.6\*\* | 340.8\*\* | 351.0\*\* | 363.5\*\* |
| ppm | SD | 9.3 | 10.5 | 11.6 | 13.2 | 14.9 |
| Group 4 | N | 10 | 10 | 10 | 10 | 10 |
|  | %Diff | 0.2 | -7.2 | -7.2 | -8.1 | -8.0 |

Anova & Dunnett: \*\* = p ≤ 0.01

###### Summary of Body Weights: F0 Generation - Premating 20334125

Bodyweight (g)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Sex: Female | | Day(s) Relative to Start Date | | |
| 1 | 8 | 15 |
| 0 | Mean | 210.0 | 219.1 | 222.4 |
| ppm | SD | 10.9 | 11.1 | 9.7 |
| Group 1 | N | 10 | 10 | 10 |
| 12500 | Mean | 212.9 | 219.4 | 225.5 |
| ppm | SD | 10.5 | 13.2 | 10.2 |
| Group 2 | N | 10 | 10 | 10 |
|  | %Diff | 1.4 | 0.1 | 1.4 |
| 25000 | Mean | 208.6 | 215.1 | 220.9 |
| ppm | SD | 8.1 | 9.8 | 10.5 |
| Group 3 | N | 10 | 10 | 10 |
|  | %Diff | -0.7 | -1.8 | -0.7 |
| 50000 | Mean | 215.1 | 217.0 | 218.6 |
| ppm | SD | 14.3 | 14.4 | 14.3 |
| Group 4 | N | 10 | 10 | 10 |
|  | %Diff | 2.4 | -1.0 | -1.7 |

Anova & Dunnett

###### Summary of Body Weights: F0 Generation - Gestation 20334125

Bodyweight (g)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Sex: Female | | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 [G] | 4 [G] | 7 [G1] | 11 [G] | 14 [G] | 17 [G] | 20 [G] |
| 0 | Mean | 225.7 | 239.8 | 248.1 | 259.0 | 269.3 | 292.3 | 326.8 |
| ppm | SD | 13.9 | 12.6 | 10.5 | 12.2 | 14.5 | 14.4 | 17.6 |
| Group 1 | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 12500 | Mean | 225.9 | 241.1 | 249.4 | 261.1 | 269.9 | 292.9 | 323.0 |
| ppm | SD | 13.5 | 13.6 | 16.0 | 15.0 | 17.9 | 16.0 | 20.6 |
| Group 2 | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|  | %Diff | 0.1 | 0.6 | 0.5 | 0.8 | 0.2 | 0.2 | -1.2 |
| 25000 | Mean | 220.9 | 236.1 | 243.2 | 254.1 | 263.9 | 286.5 | 321.2 |
| ppm | SD | 9.7 | 11.4 | 8.9 | 12.1 | 12.8 | 15.2 | 17.4 |
| Group 3 | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
|  | %Diff | -2.1 | -1.5 | -2.0 | -1.9 | -2.0 | -2.0 | -1.7 |
| 50000 | Mean | 220.0 | 235.9 | 239.4 | 251.0 | 258.3 | 280.4 | 311.1 |
| ppm | SD | 15.8 | 19.9 | 18.4 | 22.3 | 21.3 | 23.0 | 25.4 |
| Group 4 | N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
|  | %Diff | -2.5 | -1.6 | -3.5 | -3.1 | -4.1 | -4.1 | -4.8 |

[G] - Anova & Dunnett

[G1] - Kruskal-Wallis & Dunn

###### Summary of Body Weights: F0 Generation - Lactation 20334125

Bodyweight (g)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Sex: Female | | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 [G] | 4 [G] | 7 [G] | 10 [G1] | 13 [G] |
| 0 | Mean | 250.8 | 267.6 | 281.4 | 290.8 | 294.9 |
| ppm | SD | 14.5 | 15.7 | 18.9 | 18.1 | 16.6 |
| Group 1 | N | 9 | 9 | 9 | 9 | 9 |
| 12500 | Mean | 255.6 | 266.7 | 279.3 | 289.6 | 297.6 |
| ppm | SD | 16.5 | 19.0 | 18.7 | 20.2 | 18.4 |
| Group 2 | N | 9 | 9 | 9 | 9 | 9 |
|  | %Diff | 1.9 | -0.3 | -0.8 | -0.4 | 0.9 |
| 25000 | Mean | 246.1 | 257.6 | 272.1 | 279.0 | 279.5 |
| ppm | SD | 14.3 | 13.9 | 15.1 | 10.4 | 14.6 |
| Group 3 | N | 10 | 10 | 10 | 10 | 10 |
|  | %Diff | -1.9 | -3.7 | -3.3 | -4.1 | -5.2 |
| 50000 | Mean | 243.9 | 252.4 | 260.6 | 263.8 | 261.8\*\* |
| ppm | SD | 19.4 | 20.5 | 21.1 | 24.3 | 24.3 |
| Group 4 | N | 8 | 8 | 8 | 8 | 8 |
|  | %Diff | -2.8 | -5.7 | -7.4 | -9.3 | -11.2 |

[G] - Anova & Dunnett: \*\* = p ≤ 0.01 [G1] - Kruskal-Wallis & Dunn

###### Summary of Body Weight Gains (g): F0 Generation - Males 20334125

Bodyweight Gain (Interval)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Sex: Male | | Day(s) Relative to Start Date | | | | | |
| 1 → 8 | 8 → 15 | 1 → 15 | 15 → 22 | 22 → 28 | 1 → 28 |
| 0 | Mean | 34.9 | 20.8 | 55.7 | 14.7 | 13.2 | 83.6 |
| ppm | SD | 6.3 | 6.4 | 10.3 | 4.1 | 5.1 | 11.0 |
| Group 1 | N | 10 | 10 | 10 | 10 | 10 | 10 |
| 12500 | Mean | 29.2 | 21.7 | 50.9 | 10.9 | 14.0 | 75.8 |
| ppm | SD | 5.4 | 4.2 | 7.2 | 4.0 | 3.7 | 8.5 |
| Group 2 | N | 10 | 10 | 10 | 10 | 10 | 10 |
| 25000 | Mean | 25.9\*\* | 23.1 | 49.0 | 9.7\* | 14.3 | 73.0 |
| ppm | SD | 4.7 | 4.6 | 8.9 | 3.8 | 4.0 | 14.2 |
| Group 3 | N | 10 | 10 | 10 | 10 | 10 | 10 |
| 50000 | Mean | 9.3\*\* | 19.2 | 28.5\*\* | 10.2\* | 12.5 | 51.2\*\* |
| ppm | SD | 5.7 | 7.6 | 11.1 | 3.9 | 4.6 | 13.0 |
| Group 4 | N | 10 | 10 | 10 | 10 | 10 | 10 |

Anova & Dunnett: \* = p ≤ 0.05; \*\* = p ≤ 0.01

###### Summary of Body Weight Gains (g): F0 Generation - Premating 20334125

Bodyweight Gain (Interval)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Sex: Female | | Day(s) Relative to Start Date | | |
| 1 → 8 | 8 → 15 | 1 → 15 |
| 0 | Mean | 9.1 | 3.3 | 12.4 |
| ppm | SD | 5.9 | 4.5 | 7.2 |
| Group 1 | N | 10 | 10 | 10 |
| 12500 | Mean | 6.5 | 6.1 | 12.6 |
| ppm | SD | 6.9 | 5.4 | 5.9 |
| Group 2 | N | 10 | 10 | 10 |
| 25000 | Mean | 6.5 | 5.8 | 12.3 |
| ppm | SD | 5.3 | 4.9 | 7.3 |
| Group 3 | N | 10 | 10 | 10 |
| 50000 | Mean | 1.9 | 1.6 | 3.5\* |
| ppm | SD | 5.3 | 3.0 | 6.2 |
| Group 4 | N | 10 | 10 | 10 |

Anova & Dunnett: \* = p ≤ 0.05

###### Summary of Body Weight Gains (g): F0 Generation - Gestation 20334125

Bodyweight Gain (Interval)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Sex: Female | | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 → 4 [G] | 4 → 7 [G] | 7 → 11 [G] | 11 → 14 [G] | 14 → 17 [G] | 17 → 20 [G1] | 0 → 20 [G] |
| 0 | Mean | 14.1 | 8.3 | 10.9 | 10.3 | 23.0 | 34.4 | 101.1 |
| ppm | SD | 6.0 | 3.0 | 3.3 | 4.7 | 3.4 | 5.4 | 14.9 |
| Group 1 | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 12500 | Mean | 15.2 | 8.3 | 11.7 | 8.8 | 23.0 | 30.1 | 97.1 |
| ppm | SD | 4.4 | 5.5 | 3.8 | 5.4 | 4.6 | 7.3 | 12.1 |
| Group 2 | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 25000 | Mean | 15.2 | 7.1 | 10.9 | 9.8 | 22.6 | 34.7 | 100.3 |
| ppm | SD | 4.7 | 3.6 | 3.8 | 2.9 | 4.6 | 4.6 | 11.8 |
| Group 3 | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 50000 | Mean | 15.9 | 3.5 | 11.6 | 7.3 | 22.1 | 30.8 | 91.1 |
| ppm | SD | 5.6 | 3.9 | 6.0 | 3.0 | 4.0 | 3.6 | 11.0 |
| Group 4 | N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

[G] - Anova & Dunnett

[G1] - Kruskal-Wallis & Dunn

###### Summary of Body Weight Gains (g): F0 Generation - Lactation 20334125

Bodyweight Gain (Interval)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Sex: Female | | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 → 4 [G] | 4 → 7 [G] | 7 → 10 [G] | 10 → 13 [G] | 1 → 13 [G1] |
| 0 | Mean | 16.8 | 13.9 | 9.3 | 4.1 | 44.1 |
| ppm | SD | 3.9 | 7.1 | 11.1 | 10.2 | 7.8 |
| Group 1 | N | 9 | 9 | 9 | 9 | 9 |
| 12500 | Mean | 11.1 | 12.7 | 10.2 | 8.0 | 42.0 |
| ppm | SD | 6.8 | 6.2 | 10.1 | 8.2 | 5.6 |
| Group 2 | N | 9 | 9 | 9 | 9 | 9 |
| 25000 | Mean | 11.5 | 14.5 | 6.9 | 0.5 | 33.4 |
| ppm | SD | 7.0 | 7.7 | 8.7 | 9.1 | 7.5 |
| Group 3 | N | 10 | 10 | 10 | 10 | 10 |
| 50000 | Mean | 8.5 | 8.3 | 3.1 | -2.0 | 17.9\*\* |
| ppm | SD | 7.3 | 6.0 | 5.9 | 8.9 | 11.5 |
| Group 4 | N | 8 | 8 | 8 | 8 | 8 |

[G] - Anova & Dunnett

[G1] - Kruskal-Wallis & Dunn: \*\* = p ≤ 0.01

###### Summary of Food Consumption: F0 Generation - Males 20334125

Daily Food Cons Per Animal (g)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sex: Male | | Day(s) Relative to Animal Start Date | | | |
| 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 |
| 0 | Mean | 24.2 | 25.4 | 26.4 | 24.1 |
| ppm | SD | 0.6 | 0.3 | 1.2 | 0.4 |
| Group 1 | N | 2 | 2 | 2 | 2 |
| 12500 | Mean | 23.7 | 24.7 | 25.8 | 24.1 |
| ppm | SD | 0.3 | 0.4 | 1.2 | 0.1 |
| Group 2 | N | 2 | 2 | 2 | 2 |
|  | %Diff | -1.8 | -3.0 | -2.5 | -0.2 |
| 25000 | Mean | 21.8 | 23.6 | 26.3 | 23.4 |
| ppm | SD | 0.3 | 0.7 | 1.6 | 0.9 |
| Group 3 | N | 2 | 2 | 2 | 2 |
|  | %Diff | -9.7 | -7.2 | -0.6 | -2.9 |
| 50000 | Mean | 18.9 | 23.2 | 26.4 | 23.4 |
| ppm | SD | 0.1 | 0.3 | 0.4 | 0.0 |
| Group 4 | N | 2 | 2 | 2 | 2 |
|  | %Diff | -21.8 | -8.9 | -0.2 | -2.9 |

###### Summary of Food Consumption: F0 Generation - Premating 20334125

Daily Food Cons Per Animal (g)

|  |  |  |  |
| --- | --- | --- | --- |
| Sex: Female | | Day(s) Relative to Animal Start Date | |
| 1 → 8 | 8 → 15 |
| 0 | Mean | 15.1 | 16.3 |
| ppm | SD | 0.4 | 0.2 |
| Group 1 | N | 2 | 2 |
| 12500 | Mean | 14.8 | 16.1 |
| ppm | SD | 0.6 | 0.7 |
| Group 2 | N | 2 | 2 |
|  | %Diff | -2.1 | -0.9 |
| 25000 | Mean | 15.2 | 16.6 |
| ppm | SD | 0.2 | 0.2 |
| Group 3 | N | 2 | 2 |
|  | %Diff | 0.6 | 2.4 |
| 50000 | Mean | 14.3 | 15.1 |
| ppm | SD | 0.7 | 0.6 |
| Group 4 | N | 2 | 2 |
|  | %Diff | -5.1 | -7.2 |

###### 29-Nov-2022 11:32:59

**Summary of Food Consumption: F0 Generation - Gestation 20334125**

Food Mean Daily Consumption (g/animal/day)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Sex: Female | | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | 0 → 20 |
| 0 | Mean | 18.78 | 19.78 | 20.50 | 20.37 | 22.78 | 21.96 | 20.59 |
| ppm | SD | 2.80 | 1.90 | 2.54 | 2.64 | 6.78 | 2.98 | 2.49 |
| Group 1 | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 12500 | Mean | 20.28 | 19.96 | 21.11 | 20.33 | 20.63 | 22.26 | 20.76 |
| ppm | SD | 2.76 | 1.60 | 1.51 | 1.33 | 2.85 | 1.54 | 1.38 |
| Group 2 | N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|  | %Diff | 7.99 | 0.94 | 2.98 | -0.18 | -9.43 | 1.35 | 0.81 |
| 25000 | Mean | 19.35 | 20.47 | 21.70 | 20.40 | 20.33 | 21.73 | 20.65 |
| ppm | SD | 1.92 | 0.67 | 2.39 | 1.89 | 1.50 | 1.30 | 1.00 |
| Group 3 | N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
|  | %Diff | 3.05 | 3.48 | 5.85 | 0.15 | -10.73 | -1.05 | 0.30 |
| 50000 | Mean | 20.53 | 19.92 | 20.47 | 18.29 | 21.46 | 20.29 | 20.19 |
| ppm | SD | 2.61 | 2.13 | 1.91 | 1.98 | 2.44 | 1.76 | 1.80 |
| Group 4 | N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
|  | %Diff | 9.34 | 0.70 | -0.15 | -10.20 | -5.79 | -7.61 | -1.92 |

Anova & Dunnett

###### 04-Oct-2022 00:49:12

**Summary of Food Consumption: F0 Generation - Lactation 20334125**

Food Mean Daily Consumption (g/animal/day)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Sex: Female | | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | 1 → 13 |
| 0 | Mean | 33.22 | 43.59 | 51.00 | 58.26 | 46.52 |
| ppm | SD | 4.12 | 5.96 | 7.30 | 11.74 | 6.47 |
| Group 1 | N | 9 | 9 | 9 | 9 | 9 |
| 12500 | Mean | 31.74 | 41.04 | 48.67 | 55.56 | 44.25 |
| ppm | SD | 2.99 | 3.42 | 5.20 | 3.14 | 2.76 |
| Group 2 | N | 9 | 9 | 9 | 9 | 9 |
|  | %Diff | -4.46 | -5.86 | -4.58 | -4.64 | -4.88 |
| 25000 | Mean | 32.60 | 41.20 | 48.57 | 52.13 | 43.63 |
| ppm | SD | 4.27 | 3.18 | 2.81 | 4.26 | 2.85 |
| Group 3 | N | 10 | 10 | 10 | 10 | 10 |
|  | %Diff | -1.87 | -5.49 | -4.77 | -10.51 | -6.22 |
| 50000 | Mean | 30.92 | 37.96 | 43.29 | 44.63 \*\* | 39.20 \*\* |
| ppm | SD | 3.00 | 3.62 | 6.60 | 6.55 | 4.48 |
| Group 4 | N | 8 | 8 | 8 | 8 | 8 |
|  | %Diff | -6.94 | -12.92 | -15.11 | -23.40 | -15.74 |

Anova & Dunnett: \*\* = p ≤ 0.01

###### Summary of Test Material Intake: F0 Generation - Males

**20334125**

Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Sex: Male | | Day(s) Relative to Animal Start Date | | | | |
| 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 | Mean |
| 0  ppm | Mean N | 0  2 | 0  2 | 0  2 | 0  2 | 0 |
| Group: 1 |  |  |  |  |  |  |
| 12500  ppm | Mean N | 899  2 | 866  2 | 865  2 | 782  2 | 853 |
| Group: 2 |  |  |  |  |  |  |
| 25000  ppm | Mean N | 1716  2 | 1722  2 | 1830  2 | 1579  2 | 1712 |
| Group: 3 |  |  |  |  |  |  |
| 50000  ppm | Mean N | 2982  2 | 3503  2 | 3816  2 | 3276  2 | 3394 |
| Group: 4 |  |  |  |  |  |  |

###### Summary of Test Material Intake: F0 Generation - Premating

**20334125**

Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Sex: Female | | Day(s) Relative to Animal Start Date | | |
| 1 → 8 | 8 → 15 | Mean |
| 0  ppm | Mean N | 0  2 | 0  2 | 0 |
| Group: 1 |  |  |  |  |
| 12500  ppm | Mean N | 853  2 | 905  2 | 879 |
| Group: 2 |  |  |  |  |
| 25000  ppm | Mean N | 1788  2 | 1909  2 | 1849 |
| Group: 3 |  |  |  |  |
| 50000  ppm | Mean N | 3312  2 | 3455  2 | 3383 |
| Group: 4 |  |  |  |  |

###### Summary of Test Material Intake: F0 Generation - Gestation

**20334125**

Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Sex: Female | | Day(s) Relative to Animal Mating Date | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | Mean |
| 0  ppm | Mean N | 0  9 | 0  9 | 0  9 | 0  9 | 0  9 | 0  9 | 0 |
| Group: 1 |  |  |  |  |  |  |  |  |
| 12500  ppm | Mean N | 1085  9 | 1016  9 | 1036  9 | 959  9 | 914  9 | 906  9 | 986 |
| Group: 2 |  |  |  |  |  |  |  |  |
| 25000  ppm | Mean N | 2117  10 | 2136  10 | 2189  10 | 1974  10 | 1848  10 | 1791  10 | 2009 |
| Group: 3 |  |  |  |  |  |  |  |  |
| 50000  ppm | Mean N | 4501  8 | 4189  8 | 4176  8 | 3592  8 | 3982  8 | 3431  8 | 3978 |
| Group: 4 |  |  |  |  |  |  |  |  |

###### Summary of Test Material Intake: F0 Generation - Lactation

**20334125**

Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Sex: Female | | Day(s) Relative to Animal Littering Date | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | Mean |
| 0  ppm | Mean N | 0  9 | 0  9 | 0  9 | 0  9 | 0 |
| Group: 1 |  |  |  |  |  |  |
| 12500  ppm | Mean N | 1525  9 | 1882  9 | 2137  9 | 2372  9 | 1979 |
| Group: 2 |  |  |  |  |  |  |
| 25000  ppm | Mean N | 3235  10 | 3893  10 | 4416  10 | 4670  10 | 4054 |
| Group: 3 |  |  |  |  |  |  |
| 50000  ppm | Mean N | 6231  8 | 7397  8 | 8228  8 | 8465  8 | 7580 |
| Group: 4 |  |  |  |  |  |  |

**04-Oct-2022 00:56:17**

###### Summary of Organ Weights: F0 Generation 20334125

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sex: Male  Day(s) Relative to Start Date | | 0  ppm Group 1 | 12500  ppm Group 2 | 25000  ppm Group 3 | 50000  ppm Group 4 |
| Terminal Body Weight (g) - [G] | Mean | 375.0 | 369.6 | 355.4 | 341.0 \*\* |
|  | SD | 24.1 | 13.5 | 17.6 | 15.0 |
|  | N | 10 | 10 | 10 | 10 |
|  | %Diff | - | -1.4 | -5.2 | -9.1 |
| Epididymis Weight (g) - [G] | Mean | 1.1105 | 1.0883 | 1.0793 | 1.1102 |
|  | SD | 0.1127 | 0.1023 | 0.0889 | 0.0578 |
|  | N | 10 | 10 | 10 | 10 |
|  | %Diff | - | -1.9991 | -2.8095 | -0.0270 |
| Epididymis (%bw) - [G] | Mean | 0.29596 | 0.29434 | 0.30442 | 0.32604 \* |
|  | SD | 0.02022 | 0.02380 | 0.02995 | 0.02059 |
|  | N | 10 | 10 | 10 | 10 |
|  | %Diff | - | -0.54473 | 2.86044 | 10.16497 |
| Testis Weight (g) - [G] | Mean | 3.6672 | 3.5157 | 3.5355 | 3.6905 |
|  | SD | 0.3138 | 0.3580 | 0.2153 | 0.2326 |
|  | N | 10 | 10 | 10 | 10 |
|  | %Diff | - | -4.1312 | -3.5913 | 0.6354 |
| Testis (%bw) - [G] | Mean | 0.97939 | 0.95143 | 0.99751 | 1.08377 \* |
|  | SD | 0.08016 | 0.09060 | 0.08359 | 0.07703 |
|  | N | 10 | 10 | 10 | 10 |
|  | %Diff | - | -2.85527 | 1.85002 | 10.65782 |

[G] - Anova & Dunnett: \* = p ≤ 0.05; \*\* = p ≤ 0.01

**04-Oct-2022 00:57:06**

###### Summary of Organ Weights: F0 Generation 20334125

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sex: Female  Day(s) Relative to Littering (Litter: A) | | 0  ppm Group 1 | 12500  ppm Group 2 | 25000  ppm Group 3 | 50000  ppm Group 4 |
| Terminal Body Weight (g) - [G] | Mean | 291.6 | 291.7 | 280.4 | 264.2 |
|  | SD | 24.3 | 32.1 | 12.3 | 28.5 |
|  | N | 10 | 10 | 10 | 10 |
|  | %Diff | - | 0.0 | -3.8 | -9.4 |

[G] - Kruskal-Wallis & Dunn

**27-Oct-2022 10:56:07**

**Summary of Macroscopic Pathology 20334125**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Removal Reason(s): TERMINAL EUTHANASIA  Summary: Incidence  Number of Animals: | 0  ppm Group 1 | Male  12500 25000  ppm ppm Group Group  2 3 | | 50000  ppm Group 4 | 0  ppm Group 1 | Female  12500 25000  ppm ppm Group Group  2 3 | | 50000  ppm Group 4 |
| 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **CERVIX** |  |  |  |  |  |  |  |  |
| Submitted | . | . | . | . | 10 | 10 | 10 | 10 |
| No Visible Lesions | . | . | . | . | 10 | 10 | 10 | 9 |
| Enlargement | . | . | . | . | 0 | 0 | 0 | 1 |
| Fluid accumulation, pale | . | . | . | . | 0 | 0 | 0 | 1 |
| **EPIDIDYMIS** |  |  |  |  |  |  |  |  |
| Submitted | 10 | 10 | 10 | 10 | . | . | . | . |
| No Visible Lesions | 10 | 10 | 10 | 10 | . | . | . | . |
| **GLAND, COAGULATING** |  |  |  |  |  |  |  |  |
| Submitted | 10 | 10 | 10 | 10 | . | . | . | . |
| No Visible Lesions | 10 | 10 | 10 | 10 | . | . | . | . |
| **GLAND, MAMMARY** |  |  |  |  |  |  |  |  |
| Submitted | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **GLAND, PARATHYROID** |  |  |  |  |  |  |  |  |
| Submitted | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **GLAND, PITUITARY** |  |  |  |  |  |  |  |  |
| Submitted | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **GLAND, PROSTATE** |  |  |  |  |  |  |  |  |
| Submitted | 10 | 10 | 10 | 10 | . | . | . | . |
| No Visible Lesions | 10 | 10 | 10 | 10 | . | . | . | . |
| **GLAND, SEMINAL VESICLE** |  |  |  |  |  |  |  |  |
| Submitted | 10 | 10 | 10 | 10 | . | . | . | . |
| No Visible Lesions | 10 | 10 | 10 | 10 | . | . | . | . |
| **GLAND, THYROID** |  |  |  |  |  |  |  |  |
| Submitted | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| No Visible Lesions | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **OVARY** |  |  |  |  |  |  |  |  |
| Submitted | . | . | . | . | 10 | 10 | 10 | 10 |
| No Visible Lesions | . | . | . | . | 10 | 10 | 10 | 10 |
| **SKIN** |  |  |  |  |  |  |  |  |
| Submitted | . | . | . | . | 0 | 0 | 0 | 1 |
| Thin hair coat; forelimb, left | . | . | . | . | . | . | . | 1 |

**27-Oct-2022 10:56:07**

**Summary of Macroscopic Pathology 20334125**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Removal Reason(s): TERMINAL EUTHANASIA  Summary: Incidence  Number of Animals: | 0  ppm Group 1 | Male  12500 25000  ppm ppm Group Group  2 3 | | 50000  ppm Group 4 | 0  ppm Group 1 | Female  12500 25000  ppm ppm Group Group  2 3 | | 50000  ppm Group 4 |
| 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **SKIN (Continued...)** |  |  |  |  |  |  |  |  |
| Thin hair coat; forelimb, right | . | . | . | . | . | . | . | 1 |
| **SPLEEN** |  |  |  |  |  |  |  |  |
| Submitted | 0 | 0 | 0 | 1 | . | . | . | . |
| Enlargement | . | . | . | 1 | . | . | . | . |
| **TESTIS** |  |  |  |  |  |  |  |  |
| Submitted | 10 | 10 | 10 | 10 | . | . | . | . |
| No Visible Lesions | 10 | 10 | 10 | 10 | . | . | . | . |
| **UTERUS** |  |  |  |  |  |  |  |  |
| Submitted | . | . | . | . | 10 | 10 | 10 | 10 |
| No Visible Lesions | . | . | . | . | 10 | 10 | 10 | 9 |
| Enlargement | . | . | . | . | 0 | 0 | 0 | 1 |
| Fluid accumulation, pale | . | . | . | . | 0 | 0 | 0 | 1 |
| **VAGINA** |  |  |  |  |  |  |  |  |
| Submitted | . | . | . | . | 10 | 10 | 10 | 10 |
| No Visible Lesions | . | . | . | . | 10 | 10 | 10 | 10 |

**27-Oct-2022 10:56:32**

**Summary of Microscopic Pathology 20334125**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence  Number of Animals: | 0  ppm Group 1 | Male 12500 25000  ppm ppm  Group Group  2 3 | | 50000  ppm Group 4 |
| 10 | 10 | 10 | 10 |
| **EPIDIDYMIS** |  |  |  |  |
| Examined | 10 | 0 | 0 | 10 |
| No Visible Lesions | 10 | . | . | 10 |
| **SPLEEN** |  |  |  |  |
| Examined | 0 | 0 | 0 | 1 |
| Congestion | . | . | . | 1 |
| .... mild | . | . | . | 1 |
| Hematopoietic cells, increased | . | . | . | 1 |
| .... mild | . | . | . | 1 |
| **TESTIS** |  |  |  |  |
| Examined | 10 | 0 | 0 | 10 |
| No Visible Lesions | 10 | . | . | 10 |

**02-Nov-2022 15:12:04**

**Summary of Reproductive Performance 20334125**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sex: Female  Day(s) Relative to Pairing (Litter: A) | | 0  ppm Group 1 | 12500  ppm Group 2 | 25000  ppm Group 3 | 50000  ppm Group 4 |
| Group Size - Females |  | 10 | 10 | 10 | 10 |
| Paired - Females | N+ve | 10 | 10 | 10 | 10 |
| Mated Females | N+ve | 9 | 10 | 10 | 10 |
| Pregnant | N+ve | 9 | 9 | 10 | 8 |
| Pre-coital Interval (Days) [k] | Mean | 4.0 | 2.3 | 2.5 | 3.0 |
|  | SD | 3.5 | 1.1 | 1.4 | 0.9 |
|  | N | 9 | 10 | 10 | 10 |
|  | %Diff | - | -42.5 | -37.5 | -25.0 |
| Pregnant No Confirmed Mating [f] | N+ve | 0 | 0 | 0 | 0 |
| Confirmed Mating Days 1-7 [f] | N+ve | 8 | 10 | 10 | 10 |
|  | % | 88.9 | 100.0 | 100.0 | 100.0 |
| Confirmed Mating Days 8-14 [f] | N+ve | 1 | 0 | 0 | 0 |
|  | % | 11.1 | 0.0 | 0.0 | 0.0 |
| Female Mating Index [f] | % | 90.0 | 100.0 | 100.0 | 100.0 |
|  | ProA | 9/10 | 10/10 | 10/10 | 10/10 |
| Female Fertility Index [f] | % | 100.0 | 90.0 | 100.0 | 80.0 |
|  | ProA | 9/9 | 9/10 | 10/10 | 8/10 |
| Female Pregnancy Index [f] | % | 90.0 | 90.0 | 100.0 | 80.0 |
|  | ProA | 9/10 | 9/10 | 10/10 | 8/10 |

[k] - Kruskal-Wallis & Dunn

[f] - Fisher's Exact

###### 14-Oct-2022 09:43:53

**Summary of Natural Delivery Observations: F0 Generation 20334125**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sex: Female  Day(s) Relative to Littering (Litter: A) | | 0  ppm Group 1 | 12500  ppm Group 2 | 25000  ppm Group 3 | 50000  ppm Group 4 |
| Group Size - Females |  | 10 | 10 | 10 | 10 |
| Number of Females Pregnant [k] | N+ve | 9 | 9 | 10 | 8 |
|  | % | 100.0 | 100.0 | 100.0 | 100.0 |
| Gestation Index [f] | % | 100.0 | 100.0 | 100.0 | 100.0 |
|  | ProA | 9/9 | 9/9 | 10/10 | 8/8 |
| Females Completing Delivery [f] | N+ve | 9 | 9 | 10 | 8 |
| Females with Liveborn [f] | N+ve | 9 | 9 | 10 | 8 |
| Female with no Liveborn Pups [f] | N+ve | 0 | 0 | 0 | 0 |
| Fem w/ Stillborn Pups [f] | N+ve | 0 | 0 | 1 | 0 |
| Stillborn Pups/Litter (%) [k] | Mean | 0.00 | 0.00 | 1.00 | 0.00 |
|  | SD | 0.00 | 0.00 | 3.16 | 0.00 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | - | - | - |
| Number Pups Stillborn | Mean | 0.0 | 0.0 | 0.1 | 0.0 |
|  | SD | 0.0 | 0.0 | 0.3 | 0.0 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | . | . | . | . |
| Number Live Newborn Pups [k] | Mean | 11.7 | 9.9 | 11.9 | 11.3 |
|  | SD | 1.7 | 1.8 | 2.2 | 1.8 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | -15.2 | 2.0 | -3.6 |
| Live Birth Index (%) [k] | Mean | 100.00 | 100.00 | 99.00 | 100.00 |
|  | SD | 0.00 | 0.00 | 3.16 | 0.00 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | 0.00 | -1.00 | 0.00 |
| Post-implant Loss/Litter (%) [k] | Mean | 11.77 | 11.94 | 7.66 | 7.29 |
|  | SD | 10.67 | 8.85 | 9.28 | 8.74 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | 1.48 | -34.90 | -38.07 |
| Implantation Sites - Total [k] | Mean | 13.2 | 11.3 | 13.0 | 12.1 |
|  | SD | 1.1 | 2.3 | 1.9 | 1.5 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | -14.3 | -1.7 | -8.3 |

[k] - Kruskal-Wallis & Dunn

[f] - Fisher's Exact

###### 14-Oct-2022 09:43:53

**Summary of Natural Delivery Observations: F0 Generation 20334125**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sex: Female  Day(s) Relative to Littering (Litter: A) | | 0  ppm Group 1 | 12500  ppm Group 2 | 25000  ppm Group 3 | 50000  ppm Group 4 |
| Gestation Length (Days) [k] | Mean | 21.7 | 21.8 | 21.5 | 21.6 |
|  | SD | 0.5 | 0.4 | 0.5 | 0.5 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | 0.5 | -0.8 | -0.2 |

[k] - Kruskal-Wallis & Dunn

###### 03-Nov-2022 10:40:19

**Summary of Litter Observations: F0 Generation 20334125**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sex: Female  Day(s) Relative to Littering (Litter: A) | | 0  ppm Group 1 | 12500  ppm Group 2 | 25000  ppm Group 3 | 50000  ppm Group 4 |
| Group Size - Females |  | 10 | 10 | 10 | 10 |
| Females with Liveborn | N+ve | 9 | 9 | 10 | 8 |
| Viability Index Birth-4 (%) [k] | Mean | 100.00 | 98.99 | 100.00 | 100.00 |
|  | SD | 0.00 | 3.03 | 0.00 | 0.00 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | -1.01 | 0.00 | 0.00 |
| Survival Index 4Postcull-13 (%) [k] | Mean | 100.00 | 100.00 | 100.00 | 100.00 |
|  | SD | 0.00 | 0.00 | 0.00 | 0.00 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | 0.00 | 0.00 | 0.00 |
| Live Male Pups/Litter (%) 1 [G] | Mean | 49.67 | 55.94 | 47.41 | 52.89 |
|  | SD | 19.09 | 18.17 | 19.71 | 10.53 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | 12.62 | -4.55 | 6.50 |
| Live Male Pups/Litter (%) 13 [G] | Mean | 48.61 | 53.37 | 47.50 | 48.44 |
|  | SD | 9.77 | 14.44 | 12.91 | 4.42 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | 9.80 | -2.29 | -0.36 |

[k] - Kruskal-Wallis & Dunn

[G] - Anova & Dunnett

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Sex: Female  Day(s) Relative to Littering (Litter: A) | | | 0  ppm Group 1 | 12500  ppm Group 2 | 25000  ppm Group 3 | 50000  ppm Group 4 |
| Mean Pup BW | 1 [G] | Mean | 6.64 | 6.95 | 6.32 | 6.64 |
| all |  | SD  N | 0.52  9 | 0.51  9 | 0.81  10 | 0.48  8 |
|  |  | %Diff | - | 4.67 | -4.90 | -0.11 |
|  | 4 [G1] | Mean | 10.01 | 10.73 | 9.45 | 9.72 |
|  |  | SD | 1.08 | 0.77 | 1.24 | 0.81 |
|  |  | N | 9 | 9 | 10 | 8 |
|  |  | %Diff | - | 7.22 | -5.57 | -2.90 |
|  | 7 [G1] | Mean | 17.05 | 17.44 | 15.76 | 15.59 \* |
|  |  | SD | 1.40 | 0.96 | 1.35 | 0.98 |
|  |  | N | 9 | 9 | 10 | 8 |
|  |  | %Diff | - | 2.29 | -7.55 | -8.55 |
|  | 13 [G1] | Mean | 31.80 | 32.51 | 29.74 | 27.20 \*\* |
|  |  | SD | 2.16 | 1.46 | 2.05 | 2.00 |
|  |  | N | 9 | 9 | 10 | 8 |
|  |  | %Diff | - | 2.22 | -6.48 | -14.48 |

[G] - Kruskal-Wallis & Dunn

[G1] - Anova & Dunnett: \* = p ≤ 0.05; \*\* = p ≤ 0.01

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Sex: Female  Day(s) Relative to Littering (Litter: A) | | | 0  ppm Group 1 | 12500  ppm Group 2 | 25000  ppm Group 3 | 50000  ppm Group 4 |
| Mean Pup BW | 1 [G] | Mean | 6.77 | 7.10 | 6.39 | 6.75 |
| males |  | SD  N | 0.52  9 | 0.57  9 | 0.77  10 | 0.51  8 |
|  |  | %Diff | - | 4.96 | -5.62 | -0.20 |
|  | 4 [G] | Mean | 10.11 | 10.88 | 9.49 | 9.86 |
|  |  | SD | 1.09 | 0.83 | 1.22 | 0.82 |
|  |  | N | 9 | 9 | 10 | 8 |
|  |  | %Diff | - | 7.64 | -6.12 | -2.46 |
|  | 7 [G] | Mean | 17.29 | 17.71 | 15.74 \* | 15.84 \* |
|  |  | SD | 1.37 | 1.02 | 1.23 | 0.96 |
|  |  | N | 9 | 9 | 10 | 8 |
|  |  | %Diff | - | 2.41 | -8.99 | -8.43 |
|  | 13 [G] | Mean | 32.17 | 32.83 | 29.75 \* | 27.48 \*\* |
|  |  | SD | 1.99 | 1.46 | 1.95 | 2.08 |
|  |  | N | 9 | 9 | 10 | 8 |
|  |  | %Diff | - | 2.04 | -7.54 | -14.57 |

[G] - Anova & Dunnett: \* = p ≤ 0.05; \*\* = p ≤ 0.01

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Sex: Female  Day(s) Relative to Littering (Litter: A) | | | 0  ppm Group 1 | 12500  ppm Group 2 | 25000  ppm Group 3 | 50000  ppm Group 4 |
| Mean Pup BW | 1 [G] | Mean | 6.50 | 6.78 | 6.26 | 6.49 |
| females |  | SD  N | 0.51  9 | 0.47  9 | 0.87  10 | 0.47  8 |
|  |  | %Diff | - | 4.32 | -3.67 | -0.03 |
|  | 4 [G1] | Mean | 9.93 | 10.55 | 9.40 | 9.56 |
|  |  | SD | 1.06 | 0.72 | 1.29 | 0.80 |
|  |  | N | 9 | 9 | 10 | 8 |
|  |  | %Diff | - | 6.21 | -5.31 | -3.75 |
|  | 7 [G1] | Mean | 16.81 | 17.07 | 15.74 | 15.40 |
|  |  | SD | 1.46 | 0.95 | 1.52 | 1.07 |
|  |  | N | 9 | 9 | 10 | 8 |
|  |  | %Diff | - | 1.55 | -6.33 | -8.36 |
|  | 13 [G1] | Mean | 31.45 | 32.09 | 29.75 | 27.03 \*\* |
|  |  | SD | 2.36 | 1.64 | 2.21 | 2.16 |
|  |  | N | 9 | 9 | 10 | 8 |
|  |  | %Diff | - | 2.02 | -5.42 | -14.06 |

[G] - Kruskal-Wallis & Dunn

[G1] - Anova & Dunnett: \*\* = p ≤ 0.01

###### Summary of Litter Mean Pup Physical Development: F1 Generation 20334125

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sex: Female  Day(s) Relative to Littering (Litter: A) | | 0  ppm Group 1 | 12500  ppm Group 2 | 25000  ppm Group 3 | 50000  ppm Group 4 |
| Mean Pup AGD males (mm) d1 [G] | Mean  SD | 2.78  0.35 | 2.82  0.24 | 2.70  0.34 | 2.67  0.27 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | 1.57 | -2.75 | -3.79 |
|  |
| Mean Pup AGD females (mm) d1 [G] | Mean  SD | 1.14  0.12 | 1.14  0.06 | 1.11  0.10 | 1.20  0.12 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | 0.64 | -2.46 | 5.52 |
|  |
| Mean Normalized Pup AGD m d1 [G] | Mean  SD | 1.470  0.174 | 1.470  0.126 | 1.458  0.152 | 1.415  0.123 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | 0.038 | -0.805 | -3.757 |
|  |
| Mean Normalized Pup AGD f d1 [G] | Mean  SD | 0.611  0.063 | 0.605  0.036 | 0.604  0.061 | 0.646  0.081 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | -0.824 | -1.034 | 5.874 |
|  |
| Mean Pup A/N Count males d13 [k] | Mean  SD | 0.0  0.0 | 0.0  0.0 | 0.0  0.0 | 0.0  0.0 |
|  | N | 9 | 9 | 10 | 8 |
|  | %Diff | - | - | - | - |

[G] - Anova & Dunnett

[k] - Kruskal-Wallis & Dunn



**STUDY PLAN AMENDMENT NO. 04**

**Test Facility Study No. 20334125**

### Dose Range Finder for the Extended One-Generation Reproductive Toxicity Study with Code 10 (SF-002) by Dietary Administration in Rats

###### GLP SPONSOR:

Kerry Inc.

3400 Millington Road Beloit

Wisconsin 53511 USA

###### TEST FACILITY:

Charles River Laboratories Den Bosch B.V. Hambakenwetering 7

5231 DD ‘s-Hertogenbosch The Netherlands

Charles River Laboratories Den Bosch B.V. Nistelrooise Baan 3

5374 RE Schaijk The Netherlands

**Page 1 of 31**

**SUMMARY OF CHANGES AND JUSTIFICATIONS**

**Study Plan effective date: 30 May 2022**

Note: When applicable, additions are indicated in bold underlined text and deletions are indicated in bold strikethrough text in the affected sections of the document.

|  |  |
| --- | --- |
| **Item or Section(s)** | **Justification** |
| **Amendment No. 1** | **Effective Date: 13 Jun 2022** |
| 2.Proposed Study Schedule | For logistical reasons, dosing will be initiated one day later (14 Jun 2022). The mating period will also be shifted to ensure a premating dosing period of 14 days. For the purpose of this DRF study, a one-day shorter total dosing time was considered not to affect the study outcome. |
| ATTACHMENT D | Updated Certificate of Analysis. |
| **Amendment No. 2** | **Effective Date: 14 Jun 2022** |
| 2.Proposed Study Schedule  6.2. Sample Collection and Analysis | As the pairing period was postponed with 1 day, start of delivery and all consecutive dates will also be 1 day later.  Sample collection dates during Week 1 of the study are adjusted accordingly. |
| 2.Proposed Study Schedule | Addition of estrous cycle determination in the study schedule (was already included in other parts of the study plan) and clarification of the location of activities. |
| 6.2.1. Analytical Method | Details on diet analysis added. |
| 10.2. Cohabitation/Mating Procedure – F0-Generation | Due to the 1-day postponement of initiation of the administration period and initiation of the pairing period, the pairing period will be 13 days instead of 14 days.  Selected males are not applicable in this study. |
| **Amendment No. 3** | **Effective Date: 12 Jul 2022** |
| 10. IN-LIFE PROCEDURES, OBSERVATIONS, AND  MEASUREMENTS –  F0-GENERATION | For logistical/practical reasons, an additional body weight and food consumption measurement will be scheduled on Lactation Day 10. |
| **Amendment No. 4** | **Effective Date: See date of Study Director approval** |
| 3. Sponsor | Change in Study Monitor per sponsor request |
| 4. Responsible Personnel | Due to temporary absence of the original Study Director, a new Study Director was appointed effective immediately. |

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 2

###### TABLE OF CONTENTS

[SUMMARY OF CHANGES AND JUSTIFICATIONS 2](#_bookmark81)

[TABLE OF CONTENTS 3](#_bookmark82)

1. [OBJECTIVE(S) 5](#_bookmark83)
2. [PROPOSED STUDY SCHEDULE 5](#_bookmark84)
3. [SPONSOR 6](#_bookmark85)
4. [RESPONSIBLE PERSONNEL 6](#_bookmark86)
5. [TEST MATERIALS 7](#_bookmark87)
6. [DIET PREPARATION AND ANALYSIS 9](#_bookmark88)
7. [TEST SYSTEM 10](#_bookmark89)
8. [HUSBANDRY 11](#_bookmark90)
9. [EXPERIMENTAL DESIGN 13](#_bookmark91)
10. [IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS – F0-](#_bookmark92) [GENERATION 14](#_bookmark92)
11. [IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS – F1-](#_bookmark93) [GENERATION 16](#_bookmark93)
12. [TERMINAL PROCEDURES – F0-GENERATION 17](#_bookmark94)
13. [HISTOLOGY AND MICROSCOPIC EVALUATION 19](#_bookmark95)
14. [TERMINAL PROCEDURES – F1-GENERATION 19](#_bookmark96)
15. [STATISTICAL ANALYSIS 20](#_bookmark98)
16. [COMPUTERIZED SYSTEMS 23](#_bookmark99)
17. [REGULATORY COMPLIANCE 24](#_bookmark100)
18. [QUALITY ASSURANCE 24](#_bookmark101)
19. [AMENDMENTS AND DEVIATIONS 24](#_bookmark102)
20. [RETENTION AND DISPOSITION OF RECORDS, SAMPLES AND](#_bookmark103)

[SPECIMENS 25](#_bookmark103)

1. [REPORTING 25](#_bookmark104)
2. [JUSTIFICATIONS AND GUIDELINES 25](#_bookmark105)
3. [ANIMAL WELFARE 26](#_bookmark106)

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 3

[AMENDMENT APPROVAL 27](#_bookmark107)

[ATTACHMENT A 28](#_bookmark108)

[ATTACHMENT B 29](#_bookmark109)

[ATTACHMENT C 30](#_bookmark110)

[ATTACHMENT D 31](#_bookmark111)

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 4

###### OBJECTIVE(S)

The objectives of this study is to provide information for the selection of dose levels for an extended one-generation reproductive toxicity study in rats (Test Facility Study

No. 20334130).

The potential toxic effects of Code 10 (SF-002) when given *via* diet for a minimum of 28 days to Wistar Han rats will be determined.

As this study serves as a dose range finding study, No Observed Adverse Effect Levels (NOAELs) will not be evaluated.

###### PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual applicable dates will be included in the Final Report.

Experimental Start Date: 08 Jun 2022

(First date of study-specific data collection; randomization)

Experimental Completion Date: 17 Nov 2022

(Last date data are collected from the study)

Animal Arrival: Males: 08 Jun 2022

Females: 08 Jun 2022 Initiation of Estrous Cycle Determination 14 Jun 2022 Initiation of Diet Administration: 14 Jun 2022

Initiation of Mating: 28 Jun 2022

Necropsy Male: 12 Jul 2022a

Delivery of Litters (PND 1): ≥ 20 Jul 2022

Measurement Anogenital Distance (PND 1): ≥ 20 Jul 2022

Culling of F1-Pups (PND 4):

Determination Areola/Nipple Retention (PND 13):

Necropsy Pups (PND 14-16):

Necropsy Females (PND 14-16):

≥ 23 Jul 2022

≥ 01 Aug 2022

≥ 02 Aug 2022

≥ 02 Aug 2022

Completion of In-life: 19 Aug 2022

(Last date of necropsy)

Unaudited Draft Report: 18 Nov 2022

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 5

Final Report Within 6 months after issuing the draft report (i.e., latest 18 May 2023)

PND = postnatal day

a Necropsy and blood sampling dates of any males used for an extension of the mating phase will be specified and approved in the study files by the Study Director.

All animal activities and necropsy will be performed at the Schaijk location, the test material preparation and sampling will be performed either at the Schaijk location or at

's-Hertogenbosch location (will be documented in the raw data) and all other activities will be performed at the ‘s-Hertogenbosch location.

###### SPONSOR

|  |  |  |
| --- | --- | --- |
| **Role** | **Name** | **Contact Information** |
| Sponsor Representative Name | Zeynep Ilkbahar | Address:  Kerry Inc.  Global Regulatory Affairs Lead – Taste Global Technology & Innovation Centre Millennium Park, Naas  Co. Kildare, Ireland W91W923 Mobile: +353 87 3593124  Landline: +353 45 931298  E-mail: [Zeynep.ilkbahar@kerry.com](mailto:Zeynep.ilkbahar@kerry.com) |
|  |  | Address: |
|  |  | **~~ToxStrategies, Inc.~~** |
|  |  | **~~PO Box~~** |
|  |  | **~~Saffron Walden~~** |
|  |  | **~~Essex CB10 9FJ~~** |
|  |  | **~~United Kingdom~~** |
|  |  | **~~Tel: + 1 (346) 348-2569~~** |
|  |  | **~~Mobile: +44 (0) 7825 291149~~** |
| Sponsor Study Monitor Name | **~~Anna Bottomley~~ Sara Hershberger** | [**~~E-mail: Abottomley@toxstrategies.com~~**](mailto:Abottomley@toxstrategies.com)  **ToxStrategies, LLC** |
|  |  | **23501 Cinco Ranch Blvd** |
|  |  | **Suite 226** |
|  |  | **Katy** |
|  |  | **Texas** |
|  |  | **Tel: +1 317 426 1989** |
|  |  | **Mob: +1 612 716 5140** |
|  |  | [**Email: shershberger@toxstrategies.com**](mailto:shershberger@toxstrategies.com) |

1. **RESPONSIBLE PERSONNEL**

|  |  |  |  |
| --- | --- | --- | --- |
| **Role/Phase** | **Quality Assurance Unit** | **Name** | **Contact Information** |
| **Study Director from 01 Feb 2023 onwards** | **Charles River** | **Daphne Peperkamp - van den Oetelaar, MSc** | **Address as cited for Test Facility Tel: +31 73 640 6700**  **E-mail:** [**daphne.vandenoetelaar@crl.com**](mailto:daphne.vandenoetelaar@crl.com) |

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 6

|  |  |  |  |
| --- | --- | --- | --- |
| **Role/Phase** | **Quality Assurance Unit** | **Name** | **Contact Information** |
| Study Director **from start study onwards up to 01 Feb 2023** | Charles River | Corina van den Heuvel, PhD | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [corina.vandenheuvel@crl.com](mailto:corina.vandenheuvel@crl.com) |
| Test Facility Management | Charles River | Harry Emmen, MSc | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [harry.emmen@crl.com](mailto:harry.emmen@crl.com) |
| Test Facility QAU | Charles River | Lead QA | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [QADenBosch@crl.com](mailto:QADenBosch@crl.com) |
| **Individual Scientist (IS)** | | | |
| Analytical Chemistry | Charles River | Marc Baremans, MSc | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [marc.baremans@crl.com](mailto:marc.baremans@crl.com) |
| Microscopic Pathology | Charles River | Joost Lensen, PhD, CRP/TP | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [joost.lensen@crl.com](mailto:joost.lensen@crl.com) |

Each IS is required to report all deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner for authorization/acknowledgement. Each IS will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report.

The IS Phase Report will include the following:

* A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

###### TEST MATERIALS

* 1. **Test Material Characterization**

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity, composition, and stability for the test material. A Certificate of Analysis or equivalent documentation may be provided for inclusion in the Final Report.

The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the test material, and this information is available to the appropriate regulatory agencies should it be requested.

###### Test Material Identification

* + 1. **Test Material**

Identification: Code 10 (SF-002) Batch (Lot) Number: 05591112

Expiry Date: 30 May 2023

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 7

Physical Description: Clear amber liquid

Purity/Composition: UVCB. See Certificate of Analysis issued 21

January 20221

Storage Conditions: At room temperature protected from light Additional information

Test Facility Test Material Number:

Purity/Composition Correction Factor:

213125/A

No correction factor required

Test Material Handling: Bulk containers of the test article WILL NOT be

subjected to mixing (i.e., inversion, vortexing, agitation or shaking) of the bulk test article prior to sampling for dose formulation preparation. The technician should pull from the center of the bulk container when removing aliquots and not scrape the sides or bottom of the bulk container.

Specific gravity / density: 1.086

Stability in powder diet: Stability for at least 10 days at room temperature

(15 to 25°C) under normal laboratory light conditions, in open containers is confirmed over the concentration range 500 to 50000 ppm, Project 20334112 (17 kg bulk)

###### Vehicle

Identification: Propylene glycol

Supplier: Documented in the Final Report

Specific Gravity: 1.036

###### Reserve Samples

For each batch (lot) of test material and if practically possible, a reserve sample will be collected and maintained under the appropriate storage conditions by the Test Facility.

###### Test and Control Material Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of test materials will be maintained.

###### Safety

The following safety instructions apply to this study:

* Standard safety precautions specified in Charles River Den Bosch procedures.

1 For Certificate of Analysis see [ATTACHMENT D.](#_bookmark111)

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 8

###### DIET PREPARATION AND ANALYSIS

* 1. **Preparation of Diet Containing Test Material**

The test material will be mixed first with propylene glycol to facilitate mixing of the test material with the food, and thereafter with the required amount of powder feed. Standard powder rodent diet (SM R/M-Z from SSNIFF® Spezialdiäten GmbH, Soest, Germany) will be used.

Diets will be prepared freshly for use at room temperature for a maximum of 10 days. Diets will be kept at room temperature until use, if not used on the day of preparation. Any remaining food left after filling the food hoppers may be stored at room temperature for a maximum of 10 days (stability is confirmed under Test Facility Study No. 20334112 (analytical Method Development and Validation Study)) for supplementing food during the respective food consumption measurement interval.

###### Sample Collection and Analysis

Diet preparation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

**Diet Preparation Sample Collection Schedule**

|  |  |  |  |
| --- | --- | --- | --- |
| **Occasion** | **Concentration (M)** | **Homogeneity (TMB)** | **Sampling Froma** |
| Week 1 of treatment: (range: 14 Jun 2022 –20  Jun 2022) | All groups  2 x approximately 5 g | Groups 2 and 4  2 x approximately  5 g | Diet batch |

M = sample collected from approximately Middle; TMB = sample collected from approximately Top, Middle and Bottom; t = time

a Sampling from diet batches that will be used in Week 1 of dosing.

All samples to be analyzed will be transferred (at room temperature) to the analytical laboratory at the Test Facility for same day analysis, where possible or stored for analysis within known diet stability period.

Residual samples will be discarded after completion of the sample analysis.

In addition, random back-up diet samples will be taken in Week 1 and stored at ≤-15ºC for possible future analysis. Remaining samples will be discarded after completion of the sample analysis.

###### Analytical Method

Analyses described below will be performed using a validated analytical procedure (Test Facility Study No. 20334112).

###### Concentration and Homogeneity Analysis

Storage Conditions: 18-22°C.

Acceptance Criteria: For concentration, mean sample concentration results within or equal to ± 20% of theoretical concentration.

For homogeneity, relative standard deviation (RSD) of concentrations of  10.00% for each group.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 9

###### Stability Analysis

Stability analyses performed previously in conjunction with the method development and validation study (Test Facility Study No. 20334112) demonstrated that the test material is stable in the diet when prepared and stored under the same conditions at concentrations bracketing those used in the present study. Stability data have been retained in the study records of No. 20334112.

###### TEST SYSTEM

Species: Rat.

Strain: Crl: WI(Han).

Animal Condition: Outbred, SPF-Quality.

Animal Supplier: Charles River Deutschland, Sulzfeld, Germany or Charles

River Laboratories France, L'Arbresle Cedex, France. Details will be documented in raw data and report.

Number of Males 40.

Number of Females 40 (nulliparous and non-pregnant).

Number of Pups Expected: Approximately 480 pups (40 litters x 12 pups).

Target Age at the Initiation of Administration:

Target Weight at the Initiation of Administration:

Males: approximately 10-12 weeks. Females: approximately 12-14 weeks.

Males: 250 to 350 g.

Females: 200 to 250 g.

The actual age and weight of animals received will be listed in the Final report.

###### Animal Identification

Method: Each animal will be identified using a subcutaneously implanted electronic identification chip that is implanted prior to start of the treatment period.

Pups will be identified on postnatal day (PND) 1. They will be randomized per litter and individually identified by means of subcutaneous injection of Indian ink. When general hair growth blurs the identification, the pups will be identified by tattoo on the feet.

Further identification marks may be applicable (e.g., tail mark with indelible ink), to be documented in the study file.

###### Environmental Acclimation

The animals will be allowed to acclimate to the Test Facility toxicology accommodation for at least 5 days before the commencement of administration.

###### Selection, Assignment, Replacement, and Disposition of Animals

Animals will be randomly assigned to groups at arrival. Males and females will be randomized separately. Animals in poor health will not be assigned to groups.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 10

At least upon receipt of the animals, a health inspection will be performed and any assigned animals considered unsuitable for use in the study will be replaced by alternate animals obtained from the same shipment and maintained under the same environmental conditions.

After initiation of administration, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-test material-related health issues, or similar circumstances. The alternate animals may be used as replacements on the study within 1 to 3 days.

The disposition of all animals will be documented in the study records.

On PND 4, eight pups from each litter of equal sex distribution (if possible) will be selected to reduce variability among the litters. The non-selected pups will be culled on PND 4. For more details see Section [11](#_bookmark93).

###### HUSBANDRY

* 1. **Housing**

Caging: On arrival and during the pre-mating period, animals will be group housed (up to 5 animals of the same sex and same dosing group together) in polycarbonate cages (Makrolon, MIV type, height 18 cm).

During the mating phase, males and females will be cohabitated on a 1:1 basis in Makrolon plastic cages (MIII type, height 18 cm).

During the post-mating phase, males will be housed in their home cage (Makrolon plastic cages, MIV type, height 18 cm) with a maximum of 5 males/cage. Females will be individually housed in Makrolon plastic cages (MIII type, height 18 cm).

During the lactation phase, females will be housed in Makrolon plastic cages (MIII type, height 18 cm). Pups will be housed with the dam.

Cages containing sterilized wooden fibers as bedding material (Lignocel S 8-15, JRS - J.Rettenmaier & Söhne GmbH + CO. KG, Rosenberg, Germany) equipped with water bottles.

These housing conditions will be maintained unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The room(s) in which the animals will be kept will be documented in the study records.

Animals will be separated during designated procedures/activities. Cage Identification: Color-coded cage card indicating at least Test Facility Study No.,

group, animal identification number.

###### Animal Enrichment

Animals will be socially housed for psychological/environmental enrichment and will be provided with materials such as devices for hiding in, paper and/or objects for chewing, except when interrupted by study procedures/activities.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 11

Results of analysis for contaminants are provided by the supplier and are on file at the Test Facility. It is considered that there are no known contaminants that would interfere with the objectives of the study.

###### Environmental Conditions

The target conditions for animal room environment will be as follows:

Temperature: 20 to 24°C.

Humidity: 40 to 70%.

Light Cycle: 12-hours light and 12-hours dark (may be interrupted for designated procedures).

Ventilation: At least 10 air changes per hour.

Any variations to these conditions will be evaluated and maintained in the raw data.

###### Food

Diet: SM R/M-Z from SSNIFF® Spezialdiäten GmbH, Soest, Germany

Type: Powder (alternate diet may be provided on individual animal basis as warranted as approved by the Study Director).

Procedure During the acclimatization period, animals will have free access to similarly prepared powder diet without the test material but with the vehicle.

The diet will be provided in stainless steel containers, covered by a stainless steel grid to prevent spillage.

The same diets remain in the food hopper for a maximum of 10 days.

Frequency: *Ad libitum*, except during designated procedures.

Analysis: Results of analysis for nutritional components and environmental contaminants are provided by the Supplier and are on file at the Test Facility. It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

###### Water

Type: Municipal tap water.

Frequency/Ration: Freely available to each animal via water bottles.

Analysis: Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility. It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

###### Veterinary Care

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. All

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 12

veterinary examinations and recommended therapeutic treatments, if any, will be documented in the study records.

In the event that animals show signs of illness or distress, the responsible veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director. All such actions will be properly documented in the study records and, when appropriate, by study plan amendment. Treatment of the animal(s) for minor injuries or ailments may be approved without prior consultation with the Sponsor Monitor and/or Sponsor Representative when such treatment does not impact fulfillment of the study objectives. If the condition of the animal(s) warrants significant therapeutic intervention or alterations in study procedures, the Sponsor Monitor and/or Sponsor Representative will be contacted, when possible, to discuss appropriate action. If the condition of the animal(s) is such that emergency measures must be taken, the Study Director and/or attending veterinarian will attempt to consult with the Sponsor Monitor and/or Sponsor Representative prior to responding to the medical crisis, but the Study Director and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor Monitor and/or Sponsor Representative will be fully informed of any such events.

###### EXPERIMENTAL DESIGN

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Group No.** | **Test Material Id.** | **Target Dose Level**  **(mg/kg bw/day)** | **Diet Concentration (ppm)a** | **Number of Animals** | | **Animal Numbers** | |
| **Males** | **Females** | **Males** | **Females** |
| 1 | - | 0 | 0b | 10 | 10 | 01-10 | 41-50 |
| 2 | Code 10 (SF-002) | 800 | 12500 | 10 | 10 | 11-20 | 51-60 |
| 3 | Code 10 (SF-002) | 1600 | 25000 | 10 | 10 | 21-30 | 61-70 |
| 4 | Code 10 (SF-002) | 3300 | 50000 | 10 | 10 | 31-40 | 71-80 |

Id.= identification.

a Diet calculations will not be corrected for purity.

b Powder rodent diet with propylene glycol, without test material.

* 1. **Administration of Test Material** Dose Route: Dietary exposure Treatment Frequency: *Ad libitum*

Treatment Duration: males: 7 days a week for a minimum of 28 days, including at least 2 weeks of treatment prior to mating and during the mating period (up to and including the day before scheduled necropsy).

females: 7 days a week for at least 14 days prior to mating (with the objective of covering at least two complete estrous cycles), the variable time to conception, the duration of pregnancy and at least 13 days after delivery, up to and including the day of scheduled necropsy.

Pups will not be treated directly but could potentially be exposed to the test material *in utero, via* maternal milk, or from exposure to maternal urine/feces, or spilled diet from the food hopper.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 13

Method: The first day of exposure will be designated as Day 1 (exception: Alternate animals used for replacement after Day 1 will assume the day of the animal being replaced).

The amount of test material incorporated in the diet will be kept at a constant level in terms of ppm, throughout one specified phase of the study period. After termination, the actual test material intake will be estimated based on the body weight and food consumption values.

The same diets remain in the food hopper for a maximum of 10 days.

###### IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS – F0-GENERATION

**General In-life Assessments – F0-Animals**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Population(s)** | **Frequency (minimum required)** | **Comments** |
| **Mortality** | All animals | At least twice daily beginning upon arrival through termination/release. Except on days of receipt and necropsy where frequency will be at least  once daily. | Animals will be observed within their cage unless necessary for identification or confirmation of possible findings. |
| **Cage Side Observations** | All animals | Once prior to first administration and at least once daily from start of administration onwards, up to the day prior to necropsy. | Animals will be observed within their cage unless necessary for identification or confirmation of possible findings.  For observations that cannot be attributed to an individual animal due to social housing (e.g., watery feces), the observation will be recorded to each animal in the socialized group. |
| **Detailed Clinical Observations** | All animals | Once before the first administration of the test material and weekly during the Treatment Period, and on the day of scheduled  necropsy. | Animals will be observed for clinical signs outside the home cage. |
| **Individual Body Weights** | All animals | On Day 1 of treatment (prior to administration) and at least weekly thereafter.  Mated females: on Days 0, 4, 7, 11, 14, 17, and 20 of  gestation and during lactation on PND 1, 4, 7, 10  and 13. | In order to monitor the health status animals may be weighed more often. This will be documented in the study raw data. |
| **Food Consumption** | All animals | At least weekly, except for males and females which are housed together for mating and for females without  evidence of mating. | Quantitatively measured per cage. |

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 14

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Population(s)** | **Frequency (minimum required)** | **Comments** |
|  |  | Mated females: on Days 0, 4, 7, 11, 14, 17, and 20 of  gestation and during lactation on PND 1, 4, 7, 10  and 13. |  |
| **Water Consumption** | All animals | Regular basis throughout the study. | Water consumption will be monitored by visual inspection of the water bottles. If inter group  differences are noted, consumption may be assessed by weight. |

###### Estrous Cycle Evaluations – F0-Generation

Frequency: Daily vaginal lavage will be performed for all females during the first 14 days of treatment and during mating until evidence of copulation is observed. Vaginal lavage will continue for those females with no evidence of copulation until termination of the mating period. End of Treatment - on the day of necropsy, a vaginal lavage will also be taken to determine the stage of estrus. This will be done for all females, except for females that have to be euthanized in extremis or die spontaneously.

Procedure: Estrous cycles will be evaluated by examining the vaginal cytology of samples obtained by serial vaginal lavage procedures.

###### Cohabitation/Mating Procedure – F0-Generation

Frequency: Daily, after a minimum of 14 days of treatment. The mating period will consist of a maximum of 13 consecutive days.

Procedure: Animals will be cohabitated on a 1:1 basis within the same treatment group, avoiding sibling mating. Detection of mating will be confirmed by evidence of sperm in the vaginal lavage or by the appearance of an intravaginal copulatory plug. This day will be designated Day 0 of gestation. Once mating has occurred, the males and females will be separated.

A maximum of 14 days will be allowed for mating, after which females who have not shown evidence of mating will be separated from their males. In case less than 9 females per group have shown evidence of mating, each non-mated female may be re-mated once with a male for a maximum of 7 days (if possible). A male of the same group having previously shown evidence of mating will be used for re-mating.

###### General Reproduction Data – F0-Generation

Frequency: Daily from the mating period onwards.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 15

Procedure: Male number paired with, mating date, confirmation of pregnancy, and delivery day will be recorded. Palpation may be used to aid in confirmation of pregnancy.

The females will be allowed to litter. Postnatal day (PND) 1 is defined as the day when a litter is found completed (i.e., membranes and placentas cleaned up, nest built and/or feeding of pups started). The day prior to PND 1 is considered to be the day when the female started to deliver and is defined as PND 0 and used for recording of delivery. Females that are littering will be left undisturbed.

Cage debris of pregnant females will be examined for evidence of premature delivery. Signs of difficult or prolonged parturition will be recorded, if applicable.

Deficiencies in maternal care, such as inadequate construction or cleaning of the nest, pups left scattered and cold, physical abuse of pups or apparently inadequate lactation or feeding, will be recorded, if applicable.

###### IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS – F1-GENERATION

**General In-life Assessments – F1-Animals**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Population(s)** | **Frequency (minimum required)** | **Comments** |
| **Mortality** | All pups | The number of live and dead pups will be determined on PND 1 and daily thereafter. | Pups will be observed within their cage unless necessary for identification or confirmation of  possible findings. |
| **Clinical Observations** | All pups | At least once daily, including the day of necropsy. | Only days on which clinical signs are present between the first and last  litter check will be given in the respective report tables. |
| **Individual Body Weights** | All pups | On PND 1, 4, 7, and 13. | Live pups will be individually weighed. |
| **Sex** | All pups | On PND 1 and 4. | Sex will be externally determined. |
| **Anogenital Distance** | All pups | On PND 1. | Anogenital distance (AGD) will be measured for all live pups. |
| **Areola/Nipple Retention** | All male pups in each litter | On PND 13. | Examination for the number of areola/nipples. |
| **Culling** | All litters | On PND 4. | To reduce variability among the litters, eight pups from each litter of equal sex distribution (if possible) will be selected. Selective elimination of pups, e.g. based upon body weight or AGD, will not be done. Whenever the number of male or female pups prevents having four  of each sex per litter, partial |

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 16

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Population(s)** | **Frequency (minimum required)** | **Comments** |
|  |  |  | adjustment (for example, five males  and three females) is acceptable. See also Section [14.3.](#_bookmark97) |

###### TERMINAL PROCEDURES – F0-GENERATION

**Terminal Procedures**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Group No.** | **No. of Animals** | | **Scheduled Euthanasia** | **Necropsy Procedures** | | | **Histology Processing** | **Microscopic Evaluation** |
| **M** | **F** | **Necropsy** | **Tissue Collection** | **Organ Weights** |
|  |  |  |  |  |  |  | Male testes and | Male testes and |
| 1 | ≤ 10 | ≤ 10 | **Males:** |  |  |  | epididymides | epididymides |
|  |  |  | after a minimum of 28  days of |  |  |  |  |  |
| 2 | ≤ 10 | ≤ 10 | - | - |
|  |  |  | administration | X | Xa | Xa |  |  |
|  |  |  | - | - |
| 3 | ≤ 10 | ≤ 10 | **Females:**  PND 14-16, or |  |  |  |  |  |
|  |  |  | failure to deliver |  |  |  |  |  |
| 4 | ≤ 10 | ≤ 10 | Male testes and epididymides | Male testes and epididymides |
| Unscheduled Deaths (sacrificed *in extremis* or found dead) | | | | X | X | - | - | - |
| Unscheduled Euthanasia Females with Total Litter Loss | | | | X | Xa | Xa | - | - |

X = Procedure to be conducted; - = Not applicable.

“Histology Processing”= embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

a See Tissue Collection and Preservation table in [ATTACHMENT C](#_bookmark110) for listing of tissues.

###### Unscheduled Deaths/Euthanasia – F0-Generation

If an animal dies on study, a necropsy will be conducted and specified tissues will be saved, but not weighed. If necessary, the animal will be refrigerated to minimize autolysis.

Animals may be euthanized for humane reasons as per Test Facility SOPs. These animals will be deeply anesthetized using isoflurane and subsequently exsanguinated. They will undergo necropsy, and specified tissues will be retained, but not weighed.

Females with total litter loss: Dams with no surviving pups will be euthanized within

24 hours after the last pup is found dead or missing.

They will undergo necropsy, will have a terminal body weight recorded and specified tissues will be weighed and retained. Females will not be fasted before necropsy.

The specified tissues which will be weighed and/or retained are mentioned in [ATTACHMENT C.](#_bookmark110)

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 17

###### Scheduled Euthanasia – F0-Generation

Animals surviving until scheduled euthanasia will have a terminal body weight recorded and will be deeply anesthetized using isoflurane and subsequently exsanguinated.

Scheduled necropsies are summarized below:

Males (which sire or fail to sire): Following completion of the mating period (a minimum

of 28 days of administration).

Females which deliver: PND 14-16.

Females which fail to deliver: With evidence of mating: Gestation Days 25-27.

Without evidence of mating: Approximately 24-26 days after the last day of the mating period.

All males surviving to scheduled necropsy will be fasted overnight with a maximum of 24 hours before necropsy. Water will be available. F0-females will not be fasted overnight.

The specified tissues which will be retained are mentioned in [ATTACHMENT C](#_bookmark110).

###### Necropsy – F0-Generation

All animals will be subjected to a full *post mortem* examination, with special attention being paid to the reproductive organs.

The numbers of former implantation sites will be recorded for all paired females.

Necropsy procedures will be performed by qualified personnel with appropriate training and experience in animal anatomy and gross pathology. A veterinary pathologist, or other suitably qualified person, will be available.

###### Organ weights – F0-Generation

The organs detailed in Section [12](#_bookmark94) and [ATTACHMENT C](#_bookmark110) tables will be weighed at necropsy for all scheduled euthanasia animals and females with total litter loss. Organ weights will not be recorded for animals found dead or euthanized in poor condition or *in extremis*. Paired organs will be weighed together. Organ weights as a percent of body weight (using the terminal body weight) will be calculated.

###### Tissue Collection and Preservation – F0-Generation

Representative samples of the tissues will be collected from all animals and preserved in 10% neutral buffered formalin or modified Davidson's solution as detailed in Test Facility SOPs, Section [12](#_bookmark94) and [ATTACHMENT C](#_bookmark110). Additional tissue samples may be collected to elucidate abnormal findings.

For females which fail to deliver a complete litter, uterine contents (i.e., any fetuses, placenta and implantation sites) will be fixed (if applicable), but will not be examined histopathologically in first instance.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 18

###### HISTOLOGY AND MICROSCOPIC EVALUATION

* 1. **Histology**

Tissues as detailed in Section [12](#_bookmark94) and [ATTACHMENT C](#_bookmark110) tables from F0-males will be embedded in paraffin, sectioned at a thickness of 2-4 micrometers, mounted on glass slides, and stained with hematoxylin and eosin.

###### Microscopic Evaluation

Tissues as detailed in Section [12](#_bookmark94) and [ATTACHMENT C](#_bookmark110) will be evaluated histopathologically by a board-certified toxicological pathologist with training and experience in laboratory animal pathology. Target tissues identified by the study pathologist during microscopic evaluation will be communicated to the Study Director; tissues will be evaluated and reported.

Special stains may be used at the discretion of the pathologist to further characterize lesions and changes identified during routine evaluation of individual animals. Any special stains will be documented in the individual animal data. Any additional stains or evaluations, if deemed necessary by the pathologist, may be added by Study Plan amendment following discussion with the Study Director and in consultation with the Sponsor. Efforts will be made to evaluate all Study Plan-required tissues microscopically; however, it is not always feasible for every Study Plan-required tissue to be present on every slide. Study Plan-required tissues that are not examined will be documented in the histopathology data and the impact of these missing tissues on the study will be documented in the Pathology Report.

Images may be generated for illustration of or consultation on histological observations. These images will not be used for data generation or interpretation, and will not be archived or included in the Final Report.

###### TERMINAL PROCEDURES – F1-GENERATION

* 1. **Method of Euthanasia – F1-Generation**

Pups younger than 7 days will be euthanized by decapitation.

All remaining pups (PND 7-16) will be euthanized by an intraperitoneal injection of sodium pentobarbital.

###### Unscheduled Deaths – F1-Generation

Recognizable fetuses of females that die spontaneously or are euthanized *in extremis* will be examined externally and sexed (both externally and internally, if possible). Live fetuses will be euthanized by decapitation.

Pups that die or are euthanized before scheduled termination will also be examined externally and sexed (both externally and internally, if possible). Pups found dead during the weekend can be fixed in identified containers containing 70% ethanol if not being subjected to necropsy on the same day. The stomach of pups not surviving to the scheduled necropsy date will be examined for the presence of milk, if possible. If possible, defects or cause of death will be evaluated.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 19

###### Scheduled Euthanasia – F1-Generation

On PND 4, the surplus pups will be euthanized by decapitation. Sex will be determined both externally and internally. Descriptions of all external abnormalities will be recorded.

All remaining pups will be euthanized on PND 14-16. Sex will be determined both externally and internally. Descriptions of all external abnormalities will be recorded. Particular attention will be paid to the external reproductive genitals to examine signs of altered development. No full histopathological examination will be performed, however, if any abnormalities will be observed during determination of sex, abnormalities may be collected and fixed in 10% buffered formalin at discretion of the Study Director.

###### STATISTICAL ANALYSIS

All statistical analyses will be performed within the respective study phase, unless otherwise noted. Numerical data collected on scheduled occasions will be summarized and statistically analyzed as indicated below according to sex and occasion or by litter.

###### Constructed Variables

* + 1. **Parental Variables**

Body Weight Changes: Males: Calculated between each scheduled interval as well

as overall premating period and overall dosing period.

Females: Premating period: Calculated between each scheduled interval through cohabitation as well as overall premating period until initiation of cohabitation.

Gestation and Lactation: Calculated between each scheduled interval as well as Gestation Day 0-20 and Lactation Day

1-13.

Food Consumption: Males: Calculated between each scheduled interval.

Females: Premating period: Calculated between each scheduled interval.

Gestation and Lactation: Calculated between each scheduled interval as well as Gestation Day 0-20 and Lactation Day

1-13.

Test Material Intake: Calculated as concentration of test material in diet (ppm)

against relative food consumption.

Organ Weight Relative to Body Weight:

Calculated against the terminal body weight.

Additional or alternative body weight or food consumption intervals may be evaluated to elucidate study results at the discretion of the Study Director.

###### Reproduction and Developmental Variables

The following parental indices and natural delivery/reproductive parameters will be reported, as appropriate:

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 20

Precoital time: Number of days between initiation of cohabitation and confirmation of mating.

Number of females with evidence of mating

Female Mating Index:

(or no confirmed mating date and pregnant) × 100% Number of females paired

Number of pregnant females

Female Fertility Index:

Female Pregnancy Index:

Number of females with evidence of mating (or no confirmed mating date and pregnant)

Number of pregnant females Number of females paired

× 100%

× 100%

Gestation Length: The gestation length is calculated from Gestation Day 0 to the day

the first pup is observed.

Number of females with live offspring

Gestation Index:

Live Birth Index:

Number of females pregnant Number of live newborn pups Number of newborn pups

× 100%

× 100%

Sex Ratio (% Males):

Number of live male pups Total number of live pups

× 100%

Viability Index:

(Day 4 after littering)

Survival Index (4Postcull- 13):

Post-Implantation Loss/Litter:

Normalized Anogenital Distance

Number of live pups on Day 4 (before culling)

× 100%

Number of live newborn pups

Number of live pups on Day 13 after littering

× 100%

Number live pups on Day 4 (after culling)

Number of implantation sites – total newborn pups

× 100%

Number of implantation sites

Anogenital Distance

3√Pup Body Weight

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 21

###### Statistics for Data Collected/Processed in Provantis

* + 1. **Descriptive Statistical Analyses**

Means, standard deviations (or % coefficient of variation or standard error, when deemed appropriate), percentages, numbers, and/or incidences will be reported as appropriate by dataset.

###### Inferential Statistical Methods

All statistical tests will be conducted at the 5% significance level. All pairwise comparisons will be conducted using two sided tests and will be reported at the 1% and 5% levels, unless otherwise noted.

The pairwise comparisons of interest are listed below:

|  |  |  |
| --- | --- | --- |
| Group 2 | vs. | Group 1 |
| Group 3 | vs. | Group 1 |
| Group 4 | vs. | Group 1 |

Analyses will be performed according to the matrix below when possible, but will exclude any group with less than 3 observations.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 22

**Statistical Matrix**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables for Inferential Analysis** | **Statistical Method** | | |
| **Parametric/ Non-parametric** | **Non-parametric** | **Incidence** |
| **General Data** | | | |
| Body Weighta | X | - | - |
| Body Weight Gainsa | X | - | - |
| Food Consumptiona | X | - | - |
| **Mating and Fertility** | | | |
| Pregnancy, Mating and Fertility indices | - | - | X |
| Precoital Intervalb | - | X | - |
| **Natural Delivery and Litter Data** | | | |
| Natural Delivery and Litter Observations (Proportional) (e.g., Pregnant, Females with  Liveborn, Gestation index) | - | - | X |
| Natural Delivery and Litter Observations (Count) (e.g., Gestation Length, Live Pups, Implantation Sites) | - | X | - |
| Litter Observations (Continuous) (e.g., Sex  Ratio, Males, Mean Litter Body Weights) | X | - | - |
| Anogenital Distance and Normalized Anogenital Distances (Litter Mean)c | X | - | - |
| Areola/Nipple Retention (Litter Mean) | - | X | - |
| Live Birth Index | - | X | - |
| **Organ Weights** | | | |
| Organ Weightsa | X | - | - |
| Organ Weight relative to Body Weighta | X | - | - |
| 1. Excludes animals not pregnant from the gestation phase summarization and statistical analysis. 2. Excludes animals with no confirmed mating date from summarization and statistical analysis. 3. Includes males and females separately, live pups only. The AGD is normalized to the cube root of body weight. | | | |

###### Parametric/Non-parametric

Levene’s test will be used to assess the homogeneity of group variances.

The groups will be compared using an overall one-way ANOVA F-test if Levene’s test is not significant or the Kruskal-Wallis test if it is significant. If the overall F-test or Kruskal-Wallis test is found to be significant, then pairwise comparisons will be conducted using Dunnett’s or Dunn’s test, respectively.

###### Non-parametric

The groups will be compared using an overall Kruskal-Wallis test. If the overall Kruskal- Wallis test is found to be significant, then the above pairwise comparisons will be conducted using Dunn’s test.

###### Incidence

A Fisher’s exact test will be used to conduct pairwise group comparisons of interest.

###### COMPUTERIZED SYSTEMS

The following computerized systems may be used in the study. The actual computerized systems used will be specified in the Final Report.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 23

**Computerized Systems**

|  |  |
| --- | --- |
| **System Name** | **Description of Data Collected and/or Analyzed** |
| Provantis® | In-life and post-mortem (mortality; clinical signs; body weights; food  consumption; clinical pathology; macroscopy; organ weights; histopathology; reproduction parameters; observations pups) data collection |
| REES Centron | Temperature and humidity (animal and laboratory facilities) data collection |
| Dispense | Test material receipt, accountability and/or formulation activities |
| Deviation Information Library | Deviations |
| M-Files® | Reporting and collection of 21 CFR Part 11 compliant signature |
| Cary WinUV | System control, data acquisition and integration (diet analysis) |
| Empower 3 database | System control, data acquisition and integration (diet analysis) |
| MassHunter GC/MS | System control, data acquisition and integration (diet analysis) |
| MassHunter ICP-MS/MS | System control, data acquisition and integration (diet analysis) |
| MassHunter ICP-MS | System control, data acquisition and integration (diet analysis) |
| MassLynx | System control, data acquisition and integration (diet analysis) |
| MSD Chemstation | System control, data acquisition and integration (diet analysis) |

Data for parameters not required by study plan, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by study plan and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

###### REGULATORY COMPLIANCE

The study will be performed in accordance with the OECD Principles of Good Laboratory Practice as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA and EPA), Japan (MHLW, MAFF and METI), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

###### QUALITY ASSURANCE

* 1. **Test Facility**

The Test Facility Quality Assurance Unit (QAU) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAU will review the Study Plan, conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

###### AMENDMENTS AND DEVIATIONS

Changes to the approved Study Plan shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary Study Plan changes in advance with the Sponsor. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 24

###### RETENTION AND DISPOSITION OF RECORDS, SAMPLES AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens and final report will be archived at finalization of the report. All materials generated by Charles River from this study will be transferred to a Charles River archive. At least two years after issue of the final report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Records to be maintained will include, but will not be limited to, documentation and data for the following:

* Study Plan, Study Plan amendments, and deviations
* Study schedule
* Study-related correspondence
* Test system receipt, health, and husbandry
* Test material receipt, identification, preparation, and analysis
* In-life measurements and observations

###### REPORTING

* Gross observations and related data
* Organ weight measurements
* Statistical analysis results

A comprehensive Draft Report will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft Report. The Final Report will be provided in Adobe Acrobat PDF format (hyperlinked and searchable). The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Test Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation.

Reports should be finalized within 6 months of issue of the Draft Report. If the Sponsor has not provided comments to the report within 6 months of draft issue, the report will be finalized by the Test Facility unless other arrangements are made by the Sponsor.

###### JUSTIFICATIONS AND GUIDELINES

* 1. **Justification of Test System and Number of Animals**

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models that do not use live animals currently do not exist.

The Wistar Han rat was chosen as the animal model for this study as it is an accepted rodent species for toxicity testing by regulatory agencies. Charles River Den Bosch has general and reproduction/developmental historical data in this species from the same strain and source. This animal model has been proven to be susceptible to the effects of reproductive toxicants.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 25

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the test material. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

###### Justification of Route and Dose Levels

The oral route of administration *via* dietary inclusion was selected because this is the intended route of human exposure.

The dose levels were selected based on information provided by the Sponsor (90 day repeated dose toxicity study with dietary administration of Code 10 (SF-002) in rats (Study number 2330/010)). Code 10 (SF-002) was incorporated in the feed at levels of 0.25, 1.25 and 5%.

This corresponded to an overall mean intake of 174, 1836 and 4211 mg/kg/day for males and 208, 2128 and 4948 mg/kg/day for females over the 13-week study duration. In this previous study 50,000 ppm was tolerated in-life, however, there was a reduction of body weight gain observed in males and females receiving 25,000 or 50,000 ppm. The high dose for this study 50,000 ppm has been chosen as it is expected that it will show some toxic effects (reduced body weight gain), but not death nor obvious suffering and is the maximum feasible dietary dose. The mid and low dose have been chosen at 25,000 ppm and 12,500 ppm to assess a graded responses to the test material and to further investigate possible dose levels for the planned definite extended one-generation reproductive toxicity study in rats.

###### Guidelines for Study

No specific guidelines are available for the present dose range-finding study (DRF study). The present study serves as a DRF study for a subsequent extended one-generation reproduction toxicity study (EOGRTS; OECD guideline 443).

###### ANIMAL WELFARE

This Study Plan was reviewed and agreed by the Animal Welfare Body of Charles River Laboratories Den Bosch B.V. within the framework of project license AVD2360020172866 (Appendix 2) approved by the Central Authority for Scientific Procedures on Animals (CCD) as required by the Dutch Act on Animal Experimentation (December 2014).

Animals showing pain, distress or discomfort, which is considered not transient in nature or is likely to become more severe, will be sacrificed for humane reasons based on OECD Guidance Document on humane endpoints (ENV/JM/MONO/ 2000/7). The circumstances of any death will be recorded in detail.

By approving this Study Plan, the Sponsor affirms that this study is required by a relevant government regulatory agency and that it does not unnecessarily duplicate any previous experiments.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 26

###### AMENDMENT APPROVAL

I hereby confirm that I am aware of all necessary information concerning the study including GLP compliance, study plan, amendments, deviations as allocated to me by management as replacement study director.

All electronic signatures appear at the end of the document upon finalization.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 27

###### ATTACHMENT A

**Distribution List**

**Electronic copies will be supplied unless otherwise specified below.**

**Version Recipient**

Original Study Director

1 Copy Sponsor Representative / Study Monitor

1 Copy QAU / Management

1 Copy Diet preparations

1 Copy Estrous Cycle Determination

1 Copy Necropsy

1 Copy Study Assistants

1 Copy Individual Scientist Analytical Chemistry

1 Copy Coordinating Biotechnician

Qaumailboxher; Tsfher;

Monique Brouwers; Her/necropsy; Sagit;

Marc Baremans;

HER-studyplansAFC@crl.com; Ruud Pigmans;

HER-DL-DIE-Schaijk@crl.com;

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 28

###### ATTACHMENT B

Test Facility Numbers for online data collection will be used as indicated below. All data will be reported under Test Facility Study No. 20334125.

Provantis: all data of the study

20334125

**Reference Number Online Data**

**Test Facility Study No.**

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 29

###### ATTACHMENT C

**Tissue Weighing, Collection, Processing and Evaluation Table**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Tissue** | **Weigha** | **Collect** | **Histology** | **Microscopic Evaluation** |
| Animal identification | - | $ | - | - |
| Cervix | - | $ | - | - |
| Epididymis | $ (2) | $ (2) | $ (2) | $ (2) |
| Gland, mammary | - | $ | - | - |
| Gland, parathyroid | - | $ (2) | - | - |
| Gland, pituitary | - | $ | - | - |
| Gland, prostate | - | $ | - | - |
| Gland, seminal vesicle including  coagulation gland and fluid | - | $ (2) | - | - |
| Gland, thyroid | - | $ (2) | - | - |
| Ovaries | - | $ (2) | - | - |
| Testes | $ (2) | $ (2) | $ (2) b | $ (2) b |
| Uterus | - | $ | - | - |
| Vagina | - | $ | - | - |

- = Not applicable; (1) = one side. (2) = both sides.

$ = Procedure to be conducted for all animals;

Macroscopic abnormalities in the organs listed and in other organs will be sampled at necropsy, processed for histology and examined microscopically.

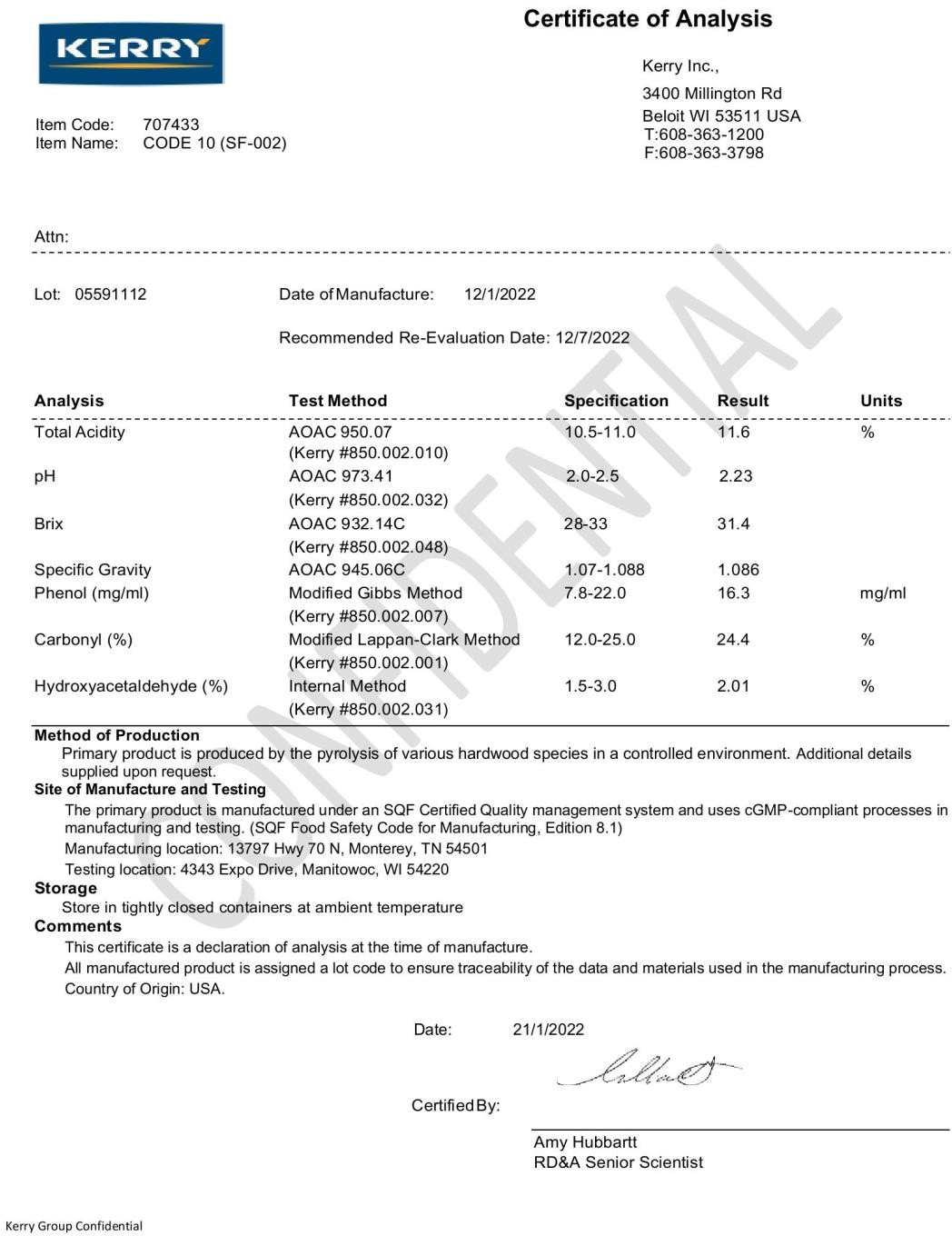
a Organ weights will not be determined for animals which die spontaneously or are sacrificed *in extremis*.

b For the testes of all males of Groups 1 and 4 detailed qualitative examination will be made, taking into account the tubular stages of the spermatogenic cycle. The examination will be conducted in order to identify treatment related effects such as missing germ cell layers or types, retained spermatids, multinucleate or apoptotic germ cells and sloughing of spermatogenic cells into the lumen. Any cell- or stage-specificity of testicular findings will be noted.

Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 30

###### ATTACHMENT D

**Certificate of Analysis**



Study Plan Amendment No. 04 Test Facility Study No. 20334125 Page 31



**Study Director Approval:**

I approve this document.

Name:

**van den Oetelaar, Daphne**

van den Oetelaar, Daphne

Electronically Signed in

01-Feb-2023 15:04:30 (UTC+00:00)

Timestamp

**SIGNATURE(S) FOR DOCUMENT: 20334125 - Study Plan Amend 04**



**TFM Approval-** I approve the Study Director identified in this document and management’s responsibility to the study as

**GLP:** defined by the relevant GLP.

Name:

**Van Dycke, Kirsten**

Van Dycke, Kirsten

Electronically Signed in

01-Feb-2023 15:03:25 (UTC+00:00)

Timestamp



**FINAL STUDY PLAN**

**Test Facility Study No. 20334125**

### Dose Range Finder for the Extended One-Generation Reproductive Toxicity Study with Code 10 (SF-002) by Dietary Administration in Rats

###### GLP SPONSOR:

Kerry Inc.

3400 Millington Road Beloit

Wisconsin 53511 USA

###### TEST FACILITY:

Charles River Laboratories Den Bosch B.V. Hambakenwetering 7

5231 DD ‘s-Hertogenbosch The Netherlands

Charles River Laboratories Den Bosch B.V. Nistelrooise Baan 3

5374 RE Schaijk The Netherlands

###### Page 1 of 30

**TABLE OF CONTENTS**

[TABLE OF CONTENTS 2](#_bookmark112)

1. [OBJECTIVE(S) 4](#_bookmark113)
2. [PROPOSED STUDY SCHEDULE 4](#_bookmark114)
3. [SPONSOR 5](#_bookmark115)
4. [RESPONSIBLE PERSONNEL 5](#_bookmark116)
5. [TEST MATERIALS 6](#_bookmark117)
6. [DIET PREPARATION AND ANALYSIS 7](#_bookmark118)
7. [TEST SYSTEM 8](#_bookmark119)
8. [HUSBANDRY 9](#_bookmark120)
9. [EXPERIMENTAL DESIGN 12](#_bookmark121)
10. [IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS – F0-](#_bookmark122) [GENERATION 12](#_bookmark122)
11. [IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS – F1-](#_bookmark123) [GENERATION 15](#_bookmark123)
12. [TERMINAL PROCEDURES – F0-GENERATION 15](#_bookmark124)
13. [HISTOLOGY AND MICROSCOPIC EVALUATION 17](#_bookmark125)
14. [TERMINAL PROCEDURES – F1-GENERATION 18](#_bookmark126)
15. [STATISTICAL ANALYSIS 18](#_bookmark128)
16. [COMPUTERIZED SYSTEMS 21](#_bookmark129)
17. [REGULATORY COMPLIANCE 22](#_bookmark130)
18. [QUALITY ASSURANCE 22](#_bookmark131)
19. [AMENDMENTS AND DEVIATIONS 22](#_bookmark132)
20. [RETENTION AND DISPOSITION OF RECORDS, SAMPLES AND](#_bookmark133)

[SPECIMENS 23](#_bookmark133)

1. [REPORTING 23](#_bookmark134)
2. [JUSTIFICATIONS AND GUIDELINES 23](#_bookmark135)
3. [ANIMAL WELFARE 24](#_bookmark136)

Test Facility Study No. 20334125

Page 2

[TEST FACILITY APPROVAL 25](#_bookmark137)

[SPONSOR APPROVAL 26](#_bookmark138)

[ATTACHMENT A 27](#_bookmark139)

[ATTACHMENT B 28](#_bookmark140)

[ATTACHMENT C 29](#_bookmark141)

[ATTACHMENT D 30](#_bookmark142)

Test Facility Study No. 20334125

Page 3

###### OBJECTIVE(S)

The objectives of this study is to provide information for the selection of dose levels for an extended one-generation reproductive toxicity study in rats (Test Facility Study

No. 20334130).

The potential toxic effects of Code 10 (SF-002) when given *via* diet for a minimum of 28 days to Wistar Han rats will be determined.

As this study serves as a dose range finding study, No Observed Adverse Effect Levels (NOAELs) will not be evaluated.

###### PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual applicable dates will be included in the Final Report.

Experimental Start Date: 08 Jun 2022

(First date of study-specific data collection; randomization)

Experimental Completion Date: 17 Nov 2022

(Last date data are collected from the study)

Animal Arrival: Males: 08 Jun 2022

Females: 08 Jun 2022

Initiation of Diet Administration: 13 Jun 2022

Initiation of Mating: 27 Jun 2022

Necropsy Male: 12 Jul 2022a

Delivery of Litters (PND 1): ≥ 19 Jul 2022

Measurement Anogenital Distance (PND 1): ≥ 19 Jul 2022

Culling of F1-Pups (PND 4):

Determination Areola/Nipple Retention (PND 13):

Necropsy Pups (PND 14-16):

Necropsy Females (PND 14-16):

≥ 22 Jul 2022

≥ 31 Jul 2022

≥ 01 Aug 2022

≥ 01 Aug 2022

Completion of In-life: 19 Aug 2022

(Last date of necropsy)

Unaudited Draft Report: 18 Nov 2022

Final Report Within 6 months after issuing the draft report (i.e., latest 18 May 2023)

Test Facility Study No. 20334125

Page 4

PND = postnatal day

a Necropsy and blood sampling dates of any males used for an extension of the mating phase will be specified and approved in the study files by the Study Director.

All animal activities and necropsy will be performed at the Schaijk location, the test material preparation and sampling will be performed either at the Schaijk location or at

's-Hertogenbosch location (will be documented in the raw data).

###### SPONSOR

|  |  |  |
| --- | --- | --- |
| **Role** | **Name** | **Contact Information** |
|  |  | Address: |
|  |  | Kerry Inc. |
|  |  | Global Regulatory Affairs Lead – Taste |
| Sponsor Representative Name | Zeynep Ilkbahar | Global Technology & Innovation Centre Millennium Park, Naas  Co. Kildare, Ireland W91W923 Mobile: +353 87 3593124 |
|  |  | Landline: +353 45 931298 |
|  |  | E-mail: [Zeynep.ilkbahar@kerry.com](mailto:Zeynep.ilkbahar@kerry.com) |
|  |  | Address: |
|  |  | ToxStrategies, Inc. |
|  |  | PO Box |
| Sponsor Study Monitor Name | Anna Bottomley | Saffron Walden Essex CB10 9FJ  United Kingdom |
|  |  | Tel: + 1 (346) 348-2569 |
|  |  | Mobile: +44 (0) 7825 291149 |
|  |  | E-mail: [Abottomley@toxstrategies.com](mailto:Abottomley@toxstrategies.com) |

1. **RESPONSIBLE PERSONNEL**

|  |  |  |  |
| --- | --- | --- | --- |
| **Role/Phase** | **Quality**  **Assurance Unit** | **Name** | **Contact Information** |
| Study Director | Charles River | Corina van den Heuvel, PhD | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [corina.vandenheuvel@crl.com](mailto:corina.vandenheuvel@crl.com) |
| Test Facility Management | Charles River | Harry Emmen, MSc | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [harry.emmen@crl.com](mailto:harry.emmen@crl.com) |
| Test Facility QAU | Charles River | Lead QA | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [QADenBosch@crl.com](mailto:QADenBosch@crl.com) |
| **Individual Scientist (IS)** | | | |
| Analytical Chemistry | Charles River | Marc Baremans, MSc | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [marc.baremans@crl.com](mailto:marc.baremans@crl.com) |

Test Facility Study No. 20334125

Page 5

|  |  |  |  |
| --- | --- | --- | --- |
| **Role/Phase** | **Quality Assurance Unit** | **Name** | **Contact Information** |
| Microscopic Pathology | Charles River | Joost Lensen, PhD, CRP/TP | Address as cited for Test Facility Tel: +31 73 640 6700  E-mail: [joost.lensen@crl.com](mailto:joost.lensen@crl.com) |

Each IS is required to report all deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner for authorization/acknowledgement. Each IS will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report.

The IS Phase Report will include the following:

* A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

###### TEST MATERIALS

* 1. **Test Material Characterization**

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity, composition, and stability for the test material. A Certificate of Analysis or equivalent documentation may be provided for inclusion in the Final Report.

The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the test material, and this information is available to the appropriate regulatory agencies should it be requested.

###### Test Material Identification

* + 1. **Test Material**

Identification: Code 10 (SF-002) Batch (Lot) Number: 05591112

Expiry Date: 30 May 2023

Physical Description: Clear amber liquid

Purity/Composition: UVCB. See Certificate of Analysis issued 21

January 20221

Storage Conditions: At room temperature protected from light Additional information

Test Facility Test Material Number:

Purity/Composition Correction Factor:

213125/A

No correction factor required

1 For Certificate of Analysis see [ATTACHMENT D.](#_bookmark142)

Test Facility Study No. 20334125

Page 6

Test Material Handling: Bulk containers of the test article WILL NOT be

subjected to mixing (i.e., inversion, vortexing, agitation or shaking) of the bulk test article prior to sampling for dose formulation preparation. The technician should pull from the center of the bulk container when removing aliquots and not scrape the sides or bottom of the bulk container.

Specific gravity / density: 1.086

Stability in powder diet: Stability for at least 10 days at room temperature

(15 to 25°C) under normal laboratory light conditions, in open containers is confirmed over the concentration range 500 to 50000 ppm, Project 20334112 (17 kg bulk)

###### Vehicle

Identification: Propylene glycol

Supplier: Documented in the Final Report

Specific Gravity: 1.036

###### Reserve Samples

For each batch (lot) of test material and if practically possible, a reserve sample will be collected and maintained under the appropriate storage conditions by the Test Facility.

###### Test and Control Material Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of test materials will be maintained.

###### Safety

The following safety instructions apply to this study:

* Standard safety precautions specified in Charles River Den Bosch procedures.

###### DIET PREPARATION AND ANALYSIS

* 1. **Preparation of Diet Containing Test Material**

The test material will be mixed first with propylene glycol to facilitate mixing of the test material with the food, and thereafter with the required amount of powder feed. Standard powder rodent diet (SM R/M-Z from SSNIFF® Spezialdiäten GmbH, Soest, Germany) will be used.

Diets will be prepared freshly for use at room temperature for a maximum of 10 days. Diets will be kept at room temperature until use, if not used on the day of preparation. Any remaining food left after filling the food hoppers may be stored at room temperature for a maximum of 10 days (stability is confirmed under Test Facility Study No. 20334112 (analytical Method Development and Validation Study)) for supplementing food during the respective food consumption measurement interval.

Test Facility Study No. 20334125

Page 7

###### Sample Collection and Analysis

Diet preparation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

**Diet Preparation Sample Collection Schedule**

|  |  |  |  |
| --- | --- | --- | --- |
| **Occasion** | **Concentration (M)** | **Homogeneity (TMB)** | **Sampling Froma** |
| Week 1 of treatment: (range: 13 Jun 2022 – 19  Jun 2022) | All groups  2 x approximately 5 g | Groups 2 and 4  2 x approximately  5 g | Diet batch |

M = sample collected from approximately Middle; TMB = sample collected from approximately Top, Middle and Bottom; t = time

a Sampling from diet batches that will be used in Week 1 of dosing.

All samples to be analyzed will be transferred (at room temperature) to the analytical laboratory at the Test Facility for same day analysis, where possible or stored for analysis within known diet stability period.

Residual samples will be discarded after completion of the sample analysis.

In addition, random back-up diet samples will be taken in Week 1 and stored at ≤-15ºC for possible future analysis. Remaining samples will be discarded after completion of the sample analysis.

###### Analytical Method

Concentration, homogeneity and stability analyses performed previously in conjunction with the method development and validation study (Test Facility Study No. 20334112) demonstrated that the test material is stable in the diet when prepared and stored under the same conditions at concentrations bracketing those used in the present study. Data have been retained in the study records of No. 20334112.

###### TEST SYSTEM

Species: Rat.

Strain: Crl: WI(Han).

Animal Condition: Outbred, SPF-Quality.

Animal Supplier: Charles River Deutschland, Sulzfeld, Germany or Charles

River Laboratories France, L'Arbresle Cedex, France. Details will be documented in raw data and report.

Number of Males 40.

Number of Females 40 (nulliparous and non-pregnant).

Number of Pups Expected: Approximately 480 pups (40 litters x 12 pups).

Target Age at the Initiation of Administration:

Target Weight at the Initiation of Administration:

Males: approximately 10-12 weeks. Females: approximately 12-14 weeks.

Males: 250 to 350 g.

Females: 200 to 250 g.

The actual age and weight of animals received will be listed in the Final report.

Test Facility Study No. 20334125

Page 8

###### Animal Identification

Method: Each animal will be identified using a subcutaneously implanted electronic identification chip that is implanted prior to start of the treatment period.

Pups will be identified on postnatal day (PND) 1. They will be randomized per litter and individually identified by means of subcutaneous injection of Indian ink. When general hair growth blurs the identification, the pups will be identified by tattoo on the feet.

Further identification marks may be applicable (e.g., tail mark with indelible ink), to be documented in the study file.

###### Environmental Acclimation

The animals will be allowed to acclimate to the Test Facility toxicology accommodation for at least 5 days before the commencement of administration.

###### Selection, Assignment, Replacement, and Disposition of Animals

Animals will be randomly assigned to groups at arrival. Males and females will be randomized separately. Animals in poor health will not be assigned to groups.

At least upon receipt of the animals, a health inspection will be performed and any assigned animals considered unsuitable for use in the study will be replaced by alternate animals obtained from the same shipment and maintained under the same environmental conditions.

After initiation of administration, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-test material-related health issues, or similar circumstances. The alternate animals may be used as replacements on the study within 1 to 3 days.

The disposition of all animals will be documented in the study records.

On PND 4, eight pups from each litter of equal sex distribution (if possible) will be selected to reduce variability among the litters. The non-selected pups will be culled on PND 4. For more details see Section [11](#_bookmark123).

###### HUSBANDRY

* 1. **Housing**

Caging: On arrival and during the pre-mating period, animals will be group housed (up to 5 animals of the same sex and same dosing group together) in polycarbonate cages (Makrolon, MIV type, height 18 cm).

During the mating phase, males and females will be cohabitated on a 1:1 basis in Makrolon plastic cages (MIII type, height 18 cm).

During the post-mating phase, males will be housed in their home cage (Makrolon plastic cages, MIV type, height 18 cm) with a maximum of 5 males/cage. Females will be individually housed in Makrolon plastic cages (MIII type, height 18 cm).

Test Facility Study No. 20334125

Page 9

During the lactation phase, females will be housed in Makrolon plastic cages (MIII type, height 18 cm). Pups will be housed with the dam.

Cages containing sterilized wooden fibers as bedding material (Lignocel S 8-15, JRS - J.Rettenmaier & Söhne GmbH + CO. KG, Rosenberg, Germany) equipped with water bottles.

These housing conditions will be maintained unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The room(s) in which the animals will be kept will be documented in the study records.

Animals will be separated during designated procedures/activities. Cage Identification: Color-coded cage card indicating at least Test Facility Study No.,

group, animal identification number.

###### Animal Enrichment

Animals will be socially housed for psychological/environmental enrichment and will be provided with materials such as devices for hiding in, paper and/or objects for chewing, except when interrupted by study procedures/activities.

Results of analysis for contaminants are provided by the supplier and are on file at the Test Facility. It is considered that there are no known contaminants that would interfere with the objectives of the study.

###### Environmental Conditions

The target conditions for animal room environment will be as follows:

Temperature: 20 to 24°C.

Humidity: 40 to 70%.

Light Cycle: 12-hours light and 12-hours dark (may be interrupted for designated procedures).

Ventilation: At least 10 air changes per hour.

Any variations to these conditions will be evaluated and maintained in the raw data.

###### Food

Diet: SM R/M-Z from SSNIFF® Spezialdiäten GmbH, Soest, Germany

Type: Powder (alternate diet may be provided on individual animal basis as warranted as approved by the Study Director).

Procedure During the acclimatization period, animals will have free access to similarly prepared powder diet without the test material but with the vehicle.

The diet will be provided in stainless steel containers, covered by a stainless steel grid to prevent spillage.

Test Facility Study No. 20334125

Page 10

The same diets remain in the food hopper for a maximum of 10 days.

Frequency: *Ad libitum*, except during designated procedures.

Analysis: Results of analysis for nutritional components and environmental contaminants are provided by the Supplier and are on file at the Test Facility. It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

###### Water

Type: Municipal tap water.

Frequency/Ration: Freely available to each animal via water bottles.

Analysis: Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility. It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

###### Veterinary Care

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations and recommended therapeutic treatments, if any, will be documented in the study records.

In the event that animals show signs of illness or distress, the responsible veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director. All such actions will be properly documented in the study records and, when appropriate, by study plan amendment. Treatment of the animal(s) for minor injuries or ailments may be approved without prior consultation with the Sponsor Monitor and/or Sponsor Representative when such treatment does not impact fulfillment of the study objectives. If the condition of the animal(s) warrants significant therapeutic intervention or alterations in study procedures, the Sponsor Monitor and/or Sponsor Representative will be contacted, when possible, to discuss appropriate action. If the condition of the animal(s) is such that emergency measures must be taken, the Study Director and/or attending veterinarian will attempt to consult with the Sponsor Monitor and/or Sponsor Representative prior to responding to the medical crisis, but the Study Director and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor Monitor and/or Sponsor Representative will be fully informed of any such events.

Test Facility Study No. 20334125

Page 11

###### EXPERIMENTAL DESIGN

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Group No.** | **Test Material Id.** | **Target Dose Level**  **(mg/kg bw/day)** | **Diet Concentration (ppm)a** | **Number of Animals** | | **Animal Numbers** | |
| **Males** | **Females** | **Males** | **Females** |
| 1 | - | 0 | 0b | 10 | 10 | 01-10 | 41-50 |
| 2 | Code 10 (SF-002) | 800 | 12500 | 10 | 10 | 11-20 | 51-60 |
| 3 | Code 10 (SF-002) | 1600 | 25000 | 10 | 10 | 21-30 | 61-70 |
| 4 | Code 10 (SF-002) | 3300 | 50000 | 10 | 10 | 31-40 | 71-80 |

Id.= identification.

a Diet calculations will not be corrected for purity.

b Powder rodent diet with propylene glycol, without test material.

* 1. **Administration of Test Material** Dose Route: Dietary exposure Treatment Frequency: *Ad libitum*

Treatment Duration: males: 7 days a week for a minimum of 28 days, including at least 2 weeks of treatment prior to mating and during the mating period (up to and including the day before scheduled necropsy).

females: 7 days a week for at least 14 days prior to mating (with the objective of covering at least two complete estrous cycles), the variable time to conception, the duration of pregnancy and at least 13 days after delivery, up to and including the day of scheduled necropsy.

Pups will not be treated directly but could potentially be exposed to the test material *in utero, via* maternal milk, or from exposure to maternal urine/feces, or spilled diet from the food hopper.

Method: The first day of exposure will be designated as Day 1 (exception: Alternate animals used for replacement after Day 1 will assume the day of the animal being replaced).

The amount of test material incorporated in the diet will be kept at a constant level in terms of ppm, throughout one specified phase of the study period. After termination, the actual test material intake will be estimated based on the body weight and food consumption values.

The same diets remain in the food hopper for a maximum of 10 days.

###### IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS – F0-GENERATION

**General In-life Assessments – F0-Animals**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Population(s)** | **Frequency (minimum required)** | **Comments** |
| **Mortality** | All animals | At least twice daily beginning upon arrival through termination/release. Except on days of receipt  and necropsy where | Animals will be observed within their cage unless necessary for identification or confirmation of possible findings. |

Test Facility Study No. 20334125

Page 12

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Population(s)** | **Frequency (minimum required)** | **Comments** |
|  |  | frequency will be at least  once daily. |  |
| **Cage Side Observations** | All animals | Once prior to first administration and at least once daily from start of administration onwards, up to the day prior to necropsy. | Animals will be observed within their cage unless necessary for identification or confirmation of possible findings.  For observations that cannot be attributed to an individual animal due to social housing (e.g., watery feces), the observation will be recorded to each animal in the socialized group. |
| **Detailed Clinical Observations** | All animals | Once before the first administration of the test material and weekly during the Treatment Period, and on the day of scheduled  necropsy. | Animals will be observed for clinical signs outside the home cage. |
| **Individual Body Weights** | All animals | On Day 1 of treatment (prior to administration) and at least weekly thereafter.  Mated females: on Days 0, 4, 7, 11, 14, 17, and 20 of  gestation and during lactation on PND 1, 4, 7,  and 13. | In order to monitor the health status animals may be weighed more often. This will be documented in the study raw data. |
| **Food Consumption** | All animals | At least weekly, except for males and females which are housed together for mating and for females without evidence of mating.  Mated females: on Days 0, 4, 7, 11, 14, 17, and 20 of  gestation and during lactation on PND 1, 4, 7,  and 13. | Quantitatively measured per cage. |
| **Water Consumption** | All animals | Regular basis throughout the study. | Water consumption will be monitored by visual inspection of the water bottles. If inter group  differences are noted, consumption may be assessed by weight. |

###### Estrous Cycle Evaluations – F0-Generation

Frequency: Daily vaginal lavage will be performed for all females during the first 14 days of treatment and during mating until evidence of copulation is observed. Vaginal lavage will continue for those females with no evidence of copulation until termination of the mating period. End of Treatment - on the day of necropsy, a vaginal lavage will also be taken to determine the stage of estrus. This will be

Test Facility Study No. 20334125

Page 13

done for all females, except for females that have to be euthanized in extremis or die spontaneously.

Procedure: Estrous cycles will be evaluated by examining the vaginal cytology of samples obtained by serial vaginal lavage procedures.

###### Cohabitation/Mating Procedure – F0-Generation

Frequency: Daily, after a minimum of 14 days of treatment. The mating period will consist of a maximum of 14 consecutive days.

Procedure: Animals will be cohabitated on a 1:1 basis within the same treatment group, avoiding sibling mating. Detection of mating will be confirmed by evidence of sperm in the vaginal lavage or by the appearance of an intravaginal copulatory plug. This day will be designated Day 0 of gestation. Once mating has occurred, the males and females will be separated.

A maximum of 14 days will be allowed for mating, after which females who have not shown evidence of mating will be separated from their males. In case less than 9 females per group have shown evidence of mating, each non-mated female may be re-mated once with a male for a maximum of 7 days (if possible). A male of the same group having previously shown evidence of mating

(non-selected male if possible, see Section [9](#_bookmark121)) will be used for re- mating.

###### General Reproduction Data – F0-Generation

Frequency: Daily from the mating period onwards.

Procedure: Male number paired with, mating date, confirmation of pregnancy, and delivery day will be recorded. Palpation may be used to aid in confirmation of pregnancy.

The females will be allowed to litter. Postnatal day (PND) 1 is defined as the day when a litter is found completed (i.e., membranes and placentas cleaned up, nest built and/or feeding of pups started). The day prior to PND 1 is considered to be the day when the female started to deliver and is defined as PND 0 and used for recording of delivery. Females that are littering will be left undisturbed.

Cage debris of pregnant females will be examined for evidence of premature delivery. Signs of difficult or prolonged parturition will be recorded, if applicable.

Deficiencies in maternal care, such as inadequate construction or cleaning of the nest, pups left scattered and cold, physical abuse of pups or apparently inadequate lactation or feeding, will be recorded, if applicable.

Test Facility Study No. 20334125

Page 14

###### IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS – F1-GENERATION

**General In-life Assessments – F1-Animals**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Population(s)** | **Frequency (minimum required)** | **Comments** |
| **Mortality** | All pups | The number of live and dead pups will be determined on PND 1 and daily thereafter. | Pups will be observed within their cage unless necessary for identification or confirmation of  possible findings. |
| **Clinical Observations** | All pups | At least once daily, including the day of necropsy. | Only days on which clinical signs are present between the first and last litter check will be given in the respective report tables. |
| **Individual Body Weights** | All pups | On PND 1, 4, 7, and 13. | Live pups will be individually weighed. |
| **Sex** | All pups | On PND 1 and 4. | Sex will be externally determined. |
| **Anogenital Distance** | All pups | On PND 1. | Anogenital distance (AGD) will be measured for all live pups. |
| **Areola/Nipple Retention** | All male pups in each litter | On PND 13. | Examination for the number of areola/nipples. |
| **Culling** | All litters | On PND 4. | To reduce variability among the litters, eight pups from each litter of equal sex distribution (if possible) will be selected. Selective elimination of pups, e.g. based upon body weight or AGD, will not be done. Whenever the number of male or female pups prevents having four of each sex per litter, partial adjustment (for example, five males and three females) is acceptable. See  also Section [14.3.](#_bookmark127) |

###### TERMINAL PROCEDURES – F0-GENERATION

**Terminal Procedures**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Group No.** | **No. of Animals** | | **Scheduled Euthanasia** | **Necropsy Procedures** | | | **Histology Processing** | **Microscopic Evaluation** |
| **M** | **F** | **Necropsy** | **Tissue Collection** | **Organ Weights** |
|  |  |  | **Males:** |  |  |  | Male testes and | Male testes and |
| 1 | ≤ 10 | ≤ 10 | after a minimum of 28 |  |  |  | epididymides | epididymides |
|  |  |  | days of administration | X | Xa | Xa |  |  |
| 2 | ≤ 10 | ≤ 10 | - | - |
|  |  |  | **Females:**  PND 14-16, or  failure to |  |  |  |  |  |
| 3 | ≤ 10 | ≤ 10 | - | - |
|  |  |  | deliver |  |  |  |  |  |

Test Facility Study No. 20334125

Page 15

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Group No.** | **No. of Animals** | | **Scheduled Euthanasia** | **Necropsy Procedures** | | | **Histology Processing** | **Microscopic Evaluation** |
| **M** | **F** | **Necropsy** | **Tissue Collection** | **Organ Weights** |
| 4 | ≤ 10 | ≤ 10 |  |  |  | Male testes and epididymides | Male testes and epididymides |
| Unscheduled Deaths (sacrificed *in extremis* or found dead) | | | | X | X | - | - | - |
| Unscheduled Euthanasia  Females with Total Litter Loss | | | | X | Xa | Xa | - | - |

X = Procedure to be conducted; - = Not applicable.

“Histology Processing”= embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

a See Tissue Collection and Preservation table in [ATTACHMENT C](#_bookmark141) for listing of tissues.

###### Unscheduled Deaths/Euthanasia – F0-Generation

If an animal dies on study, a necropsy will be conducted and specified tissues will be saved, but not weighed. If necessary, the animal will be refrigerated to minimize autolysis.

Animals may be euthanized for humane reasons as per Test Facility SOPs. These animals will be deeply anesthetized using isoflurane and subsequently exsanguinated. They will undergo necropsy, and specified tissues will be retained, but not weighed.

Females with total litter loss: Dams with no surviving pups will be euthanized within

24 hours after the last pup is found dead or missing.

They will undergo necropsy, will have a terminal body weight recorded and specified tissues will be weighed and retained. Females will not be fasted before necropsy.

The specified tissues which will be weighed and/or retained are mentioned in [ATTACHMENT C.](#_bookmark141)

###### Scheduled Euthanasia – F0-Generation

Animals surviving until scheduled euthanasia will have a terminal body weight recorded and will be deeply anesthetized using isoflurane and subsequently exsanguinated.

Scheduled necropsies are summarized below:

Males (which sire or fail to sire): Following completion of the mating period (a minimum

of 28 days of administration).

Females which deliver: PND 14-16.

Females which fail to deliver: With evidence of mating: Gestation Days 25-27.

Without evidence of mating: Approximately 24-26 days after the last day of the mating period.

All males surviving to scheduled necropsy will be fasted overnight with a maximum of 24 hours before necropsy. Water will be available. F0-females will not be fasted overnight.

The specified tissues which will be retained are mentioned in [ATTACHMENT C](#_bookmark141).

Test Facility Study No. 20334125

Page 16

###### Necropsy – F0-Generation

All animals will be subjected to a full *post mortem* examination, with special attention being paid to the reproductive organs.

The numbers of former implantation sites will be recorded for all paired females.

Necropsy procedures will be performed by qualified personnel with appropriate training and experience in animal anatomy and gross pathology. A veterinary pathologist, or other suitably qualified person, will be available.

###### Organ weights – F0-Generation

The organs detailed in Section [12](#_bookmark124) and [ATTACHMENT C](#_bookmark141) tables will be weighed at necropsy for all scheduled euthanasia animals and females with total litter loss. Organ weights will not be recorded for animals found dead or euthanized in poor condition or *in extremis*. Paired organs will be weighed together. Organ weights as a percent of body weight (using the terminal body weight) will be calculated.

###### Tissue Collection and Preservation – F0-Generation

Representative samples of the tissues will be collected from all animals and preserved in 10% neutral buffered formalin or modified Davidson's solution as detailed in Test Facility SOPs, Section [12](#_bookmark124) and [ATTACHMENT C](#_bookmark141). Additional tissue samples may be collected to elucidate abnormal findings.

For females which fail to deliver a complete litter, uterine contents (i.e., any fetuses, placenta and implantation sites) will be fixed (if applicable), but will not be examined histopathologically in first instance.

###### HISTOLOGY AND MICROSCOPIC EVALUATION

* 1. **Histology**

Tissues as detailed in Section [12](#_bookmark124) and [ATTACHMENT C](#_bookmark141) tables from F0-males will be embedded in paraffin, sectioned at a thickness of 2-4 micrometers, mounted on glass slides, and stained with hematoxylin and eosin.

###### Microscopic Evaluation

Tissues as detailed in Section [12](#_bookmark124) and [ATTACHMENT C](#_bookmark141) will be evaluated histopathologically by a board-certified toxicological pathologist with training and experience in laboratory animal pathology. Target tissues identified by the study pathologist during microscopic evaluation will be communicated to the Study Director; tissues will be evaluated and reported.

Special stains may be used at the discretion of the pathologist to further characterize lesions and changes identified during routine evaluation of individual animals. Any special stains will be documented in the individual animal data. Any additional stains or evaluations, if deemed necessary by the pathologist, may be added by Study Plan amendment following discussion with the Study Director and in consultation with the Sponsor. Efforts will be made to evaluate all Study Plan-required tissues microscopically; however, it is not always feasible for every Study Plan-required tissue to be present on every slide. Study Plan-required tissues

Test Facility Study No. 20334125

Page 17

that are not examined will be documented in the histopathology data and the impact of these missing tissues on the study will be documented in the Pathology Report.

Images may be generated for illustration of or consultation on histological observations. These images will not be used for data generation or interpretation, and will not be archived or included in the Final Report.

###### TERMINAL PROCEDURES – F1-GENERATION

* 1. **Method of Euthanasia – F1-Generation**

Pups younger than 7 days will be euthanized by decapitation.

All remaining pups (PND 7-16) will be euthanized by an intraperitoneal injection of sodium pentobarbital.

###### Unscheduled Deaths – F1-Generation

Recognizable fetuses of females that die spontaneously or are euthanized *in extremis* will be examined externally and sexed (both externally and internally, if possible). Live fetuses will be euthanized by decapitation.

Pups that die or are euthanized before scheduled termination will also be examined externally and sexed (both externally and internally, if possible). Pups found dead during the weekend can be fixed in identified containers containing 70% ethanol if not being subjected to necropsy on the same day. The stomach of pups not surviving to the scheduled necropsy date will be examined for the presence of milk, if possible. If possible, defects or cause of death will be evaluated.

###### Scheduled Euthanasia – F1-Generation

On PND 4, the surplus pups will be euthanized by decapitation. Sex will be determined both externally and internally. Descriptions of all external abnormalities will be recorded.

All remaining pups will be euthanized on PND 14-16. Sex will be determined both externally and internally. Descriptions of all external abnormalities will be recorded. Particular attention will be paid to the external reproductive genitals to examine signs of altered development. No full histopathological examination will be performed, however, if any abnormalities will be observed during determination of sex, abnormalities may be collected and fixed in 10% buffered formalin at discretion of the Study Director.

###### STATISTICAL ANALYSIS

All statistical analyses will be performed within the respective study phase, unless otherwise noted. Numerical data collected on scheduled occasions will be summarized and statistically analyzed as indicated below according to sex and occasion or by litter.

###### Constructed Variables

* + 1. **Parental Variables**

Body Weight Changes: Males: Calculated between each scheduled interval as well

as overall premating period and overall dosing period.

Females: Premating period: Calculated between each scheduled interval through cohabitation as well as overall

Test Facility Study No. 20334125

Page 18

premating period until initiation of cohabitation.

Gestation and Lactation: Calculated between each scheduled interval as well as Gestation Day 0-20 and Lactation Day

1-13.

Food Consumption: Males: Calculated between each scheduled interval.

Females: Premating period: Calculated between each scheduled interval.

Gestation and Lactation: Calculated between each scheduled interval as well as Gestation Day 0-20 and Lactation Day

1-13.

Test Material Intake: Calculated as concentration of test material in diet (ppm)

against relative food consumption.

Organ Weight Relative to Body Weight:

Calculated against the terminal body weight.

Additional or alternative body weight or food consumption intervals may be evaluated to elucidate study results at the discretion of the Study Director.

###### Reproduction and Developmental Variables

The following parental indices and natural delivery/reproductive parameters will be reported, as appropriate:

Precoital time: Number of days between initiation of cohabitation and confirmation of mating.

Number of females with evidence of mating

Female Mating Index:

(or no confirmed mating date and pregnant) × 100% Number of females paired

Number of pregnant females

Female Fertility Index:

Female Pregnancy Index:

Number of females with evidence of mating (or no confirmed mating date and pregnant)

Number of pregnant females Number of females paired

× 100%

× 100%

Gestation Length: The gestation length is calculated from Gestation Day 0 to the day

the first pup is observed.

Number of females with live offspring

Gestation Index:

Live Birth Index:

Number of females pregnant Number of live newborn pups Number of newborn pups

× 100%

× 100%

Test Facility Study No. 20334125

Page 19

Number of live male pups

Sex Ratio (% Males): × 100%

Total number of live pups

Viability Index:

(Day 4 after littering)

Survival Index (4Postcull- 13):

Post-Implantation Loss/Litter:

Normalized Anogenital Distance

Number of live pups on Day 4 (before culling)

× 100%

Number of live newborn pups

Number of live pups on Day 13 after littering

× 100%

Number live pups on Day 4 (after culling)

Number of implantation sites – total newborn pups

× 100%

Number of implantation sites

Anogenital Distance

3√Pup Body Weight

###### Statistics for Data Collected/Processed in Provantis

* + 1. **Descriptive Statistical Analyses**

Means, standard deviations (or % coefficient of variation or standard error, when deemed appropriate), percentages, numbers, and/or incidences will be reported as appropriate by dataset.

###### Inferential Statistical Methods

All statistical tests will be conducted at the 5% significance level. All pairwise comparisons will be conducted using two sided tests and will be reported at the 1% and 5% levels, unless otherwise noted.

The pairwise comparisons of interest are listed below:

|  |  |  |
| --- | --- | --- |
| Group 2 | vs. | Group 1 |
| Group 3 | vs. | Group 1 |
| Group 4 | vs. | Group 1 |

Analyses will be performed according to the matrix below when possible, but will exclude any group with less than 3 observations.

Test Facility Study No. 20334125

Page 20

**Statistical Matrix**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables for Inferential Analysis** | **Statistical Method** | | |
| **Parametric/ Non-parametric** | **Non-parametric** | **Incidence** |
| **General Data** | | | |
| Body Weighta | X | - | - |
| Body Weight Gainsa | X | - | - |
| Food Consumptiona | X | - | - |
| **Mating and Fertility** | | | |
| Pregnancy, Mating and Fertility indices | - | - | X |
| Precoital Intervalb | - | X | - |
| **Natural Delivery and Litter Data** | | | |
| Natural Delivery and Litter Observations (Proportional) (e.g., Pregnant, Females with  Liveborn, Gestation index) | - | - | X |
| Natural Delivery and Litter Observations (Count) (e.g., Gestation Length, Live Pups, Implantation Sites) | - | X | - |
| Litter Observations (Continuous) (e.g., Sex  Ratio, Males, Mean Litter Body Weights) | X | - | - |
| Anogenital Distance and Normalized Anogenital Distances (Litter Mean)c | X | - | - |
| Areola/Nipple Retention (Litter Mean) | - | X | - |
| Live Birth Index | - | X | - |
| **Organ Weights** | | | |
| Organ Weightsa | X | - | - |
| Organ Weight relative to Body Weighta | X | - | - |
| 1. Excludes animals not pregnant from the gestation phase summarization and statistical analysis. 2. Excludes animals with no confirmed mating date from summarization and statistical analysis. 3. Includes males and females separately, live pups only. The AGD is normalized to the cube root of body weight. | | | |

###### Parametric/Non-parametric

Levene’s test will be used to assess the homogeneity of group variances.

The groups will be compared using an overall one-way ANOVA F-test if Levene’s test is not significant or the Kruskal-Wallis test if it is significant. If the overall F-test or Kruskal-Wallis test is found to be significant, then pairwise comparisons will be conducted using Dunnett’s or Dunn’s test, respectively.

###### Non-parametric

The groups will be compared using an overall Kruskal-Wallis test. If the overall Kruskal- Wallis test is found to be significant, then the above pairwise comparisons will be conducted using Dunn’s test.

###### Incidence

A Fisher’s exact test will be used to conduct pairwise group comparisons of interest.

###### COMPUTERIZED SYSTEMS

The following computerized systems may be used in the study. The actual computerized systems used will be specified in the Final Report.

Test Facility Study No. 20334125

Page 21

**Computerized Systems**

|  |  |
| --- | --- |
| **System Name** | **Description of Data Collected and/or Analyzed** |
| Provantis® | In-life and post-mortem (mortality; clinical signs; body weights; food  consumption; clinical pathology; macroscopy; organ weights; histopathology; reproduction parameters; observations pups) data collection |
| REES Centron | Temperature and humidity (animal and laboratory facilities) data collection |
| Dispense | Test material receipt, accountability and/or formulation activities |
| Deviation Information Library | Deviations |
| M-Files® | Reporting and collection of 21 CFR Part 11 compliant signature |
| Cary WinUV | System control, data acquisition and integration (diet analysis) |
| Empower 3 database | System control, data acquisition and integration (diet analysis) |
| MassHunter GC/MS | System control, data acquisition and integration (diet analysis) |
| MassHunter ICP-MS/MS | System control, data acquisition and integration (diet analysis) |
| MassHunter ICP-MS | System control, data acquisition and integration (diet analysis) |
| MassLynx | System control, data acquisition and integration (diet analysis) |
| MSD Chemstation | System control, data acquisition and integration (diet analysis) |

Data for parameters not required by study plan, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by study plan and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

###### REGULATORY COMPLIANCE

The study will be performed in accordance with the OECD Principles of Good Laboratory Practice as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA and EPA), Japan (MHLW, MAFF and METI), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

###### QUALITY ASSURANCE

* 1. **Test Facility**

The Test Facility Quality Assurance Unit (QAU) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAU will review the Study Plan, conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

###### AMENDMENTS AND DEVIATIONS

Changes to the approved Study Plan shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary Study Plan changes in advance with the Sponsor. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

Test Facility Study No. 20334125

Page 22

###### RETENTION AND DISPOSITION OF RECORDS, SAMPLES AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens and final report will be archived at finalization of the report. All materials generated by Charles River from this study will be transferred to a Charles River archive. At least two years after issue of the final report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Records to be maintained will include, but will not be limited to, documentation and data for the following:

* Study Plan, Study Plan amendments, and deviations
* Study schedule
* Study-related correspondence
* Test system receipt, health, and husbandry
* Test material receipt, identification, preparation, and analysis
* In-life measurements and observations

###### REPORTING

* Gross observations and related data
* Organ weight measurements
* Statistical analysis results

A comprehensive Draft Report will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft Report. The Final Report will be provided in Adobe Acrobat PDF format (hyperlinked and searchable). The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Test Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation.

Reports should be finalized within 6 months of issue of the Draft Report. If the Sponsor has not provided comments to the report within 6 months of draft issue, the report will be finalized by the Test Facility unless other arrangements are made by the Sponsor.

###### JUSTIFICATIONS AND GUIDELINES

* 1. **Justification of Test System and Number of Animals**

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models that do not use live animals currently do not exist.

The Wistar Han rat was chosen as the animal model for this study as it is an accepted rodent species for toxicity testing by regulatory agencies. Charles River Den Bosch has general and reproduction/developmental historical data in this species from the same strain and source. This animal model has been proven to be susceptible to the effects of reproductive toxicants.

Test Facility Study No. 20334125

Page 23

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the test material. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

###### Justification of Route and Dose Levels

The oral route of administration *via* dietary inclusion was selected because this is the intended route of human exposure.

The dose levels were selected based on information provided by the Sponsor (90 day repeated dose toxicity study with dietary administration of Code 10 (SF-002) in rats (Study number 2330/010)). Code 10 (SF-002) was incorporated in the feed at levels of 0.25, 1.25 and 5%.

This corresponded to an overall mean intake of 174, 1836 and 4211 mg/kg/day for males and 208, 2128 and 4948 mg/kg/day for females over the 13-week study duration. In this previous study 50,000 ppm was tolerated in-life, however, there was a reduction of body weight gain observed in males and females receiving 25,000 or 50,000 ppm. The high dose for this study 50,000 ppm has been chosen as it is expected that it will show some toxic effects (reduced body weight gain), but not death nor obvious suffering and is the maximum feasible dietary dose. The mid and low dose have been chosen at 25,000 ppm and 12,500 ppm to assess a graded responses to the test material and to further investigate possible dose levels for the planned definite extended one-generation reproductive toxicity study in rats.

###### Guidelines for Study

No specific guidelines are available for the present dose range-finding study (DRF study). The present study serves as a DRF study for a subsequent extended one-generation reproduction toxicity study (EOGRTS; OECD guideline 443).

###### ANIMAL WELFARE

This Study Plan was reviewed and agreed by the Animal Welfare Body of Charles River Laboratories Den Bosch B.V. within the framework of project license AVD2360020172866 (Appendix 2) approved by the Central Authority for Scientific Procedures on Animals (CCD) as required by the Dutch Act on Animal Experimentation (December 2014).

Animals showing pain, distress or discomfort, which is considered not transient in nature or is likely to become more severe, will be sacrificed for humane reasons based on OECD Guidance Document on humane endpoints (ENV/JM/MONO/ 2000/7). The circumstances of any death will be recorded in detail.

By approving this Study Plan, the Sponsor affirms that this study is required by a relevant government regulatory agency and that it does not unnecessarily duplicate any previous experiments.

Test Facility Study No. 20334125

Page 24

###### TEST FACILITY APPROVAL

All electronic signatures appear at the end of the document upon finalization.

Test Facility Study No. 20334125

Page 25

###### SPONSOR APPROVAL

The Study Plan was approved by the Sponsor’s Study Monitor by e-mail on the date designated below. The correspondence giving approval will be archived, as appropriate with other Sponsor communications.

12 May 2022

Date of Sponsor Study Monitor’s Approval

Test Facility Study No. 20334125

Page 26

###### ATTACHMENT A

**Distribution List**

**Electronic copies will be supplied unless otherwise specified below.**

|  |  |  |
| --- | --- | --- |
| **Version** | **Recipient** |  |
| Original | Study Director |
| 1 Copy | Sponsor Representative / Study Monitor |
| 1 Copy | QAU / Management | Qaumailboxher; |
| 1 Copy | Diet preparations | Tsfher; |
| 1 Copy | Estrous Cycle Determination | Monique Brouwers; |
| 1 Copy | Necropsy | Her/necropsy; |
| 1 Copy | Study Assistants | Sagit; |
| 1 Copy | Individual Scientist Analytical Chemistry | Marc Baremans; |
| 1 Copy | Coordinating Biotechnician | [HER-studyplansAFC@crl.com;](mailto:HER-studyplansAFC@crl.com)  Ruud Pigmans; |
|  |  | HER-DL-DIE-Schaijk@crl.com; |

Test Facility Study No. 20334125

Page 27

###### ATTACHMENT B

Test Facility Numbers for online data collection will be used as indicated below. All data will be reported under Test Facility Study No. 20334125.

Provantis: all data of the study

20334125

**Reference Number Online Data**

**Test Facility Study No.**

Test Facility Study No. 20334125

Page 28

###### ATTACHMENT C

**Tissue Weighing, Collection, Processing and Evaluation Table**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Tissue** | **Weigha** | **Collect** | **Histology** | **Microscopic Evaluation** |
| Animal identification | - | $ | - | - |
| Cervix | - | $ | - | - |
| Epididymis | $ (2) | $ (2) | $ (2) | $ (2) |
| Gland, mammary | - | $ | - | - |
| Gland, parathyroid | - | $ (2) | - | - |
| Gland, pituitary | - | $ | - | - |
| Gland, prostate | - | $ | - | - |
| Gland, seminal vesicle including  coagulation gland and fluid | - | $ (2) | - | - |
| Gland, thyroid | - | $ (2) | - | - |
| Ovaries | - | $ (2) | - | - |
| Testes | $ (2) | $ (2) | $ (2) b | $ (2) b |
| Uterus | - | $ | - | - |
| Vagina | - | $ | - | - |

- = Not applicable; (1) = one side. (2) = both sides.

$ = Procedure to be conducted for all animals;

Macroscopic abnormalities in the organs listed and in other organs will be sampled at necropsy, processed for histology and examined microscopically.

a Organ weights will not be determined for animals which die spontaneously or are sacrificed *in extremis*.

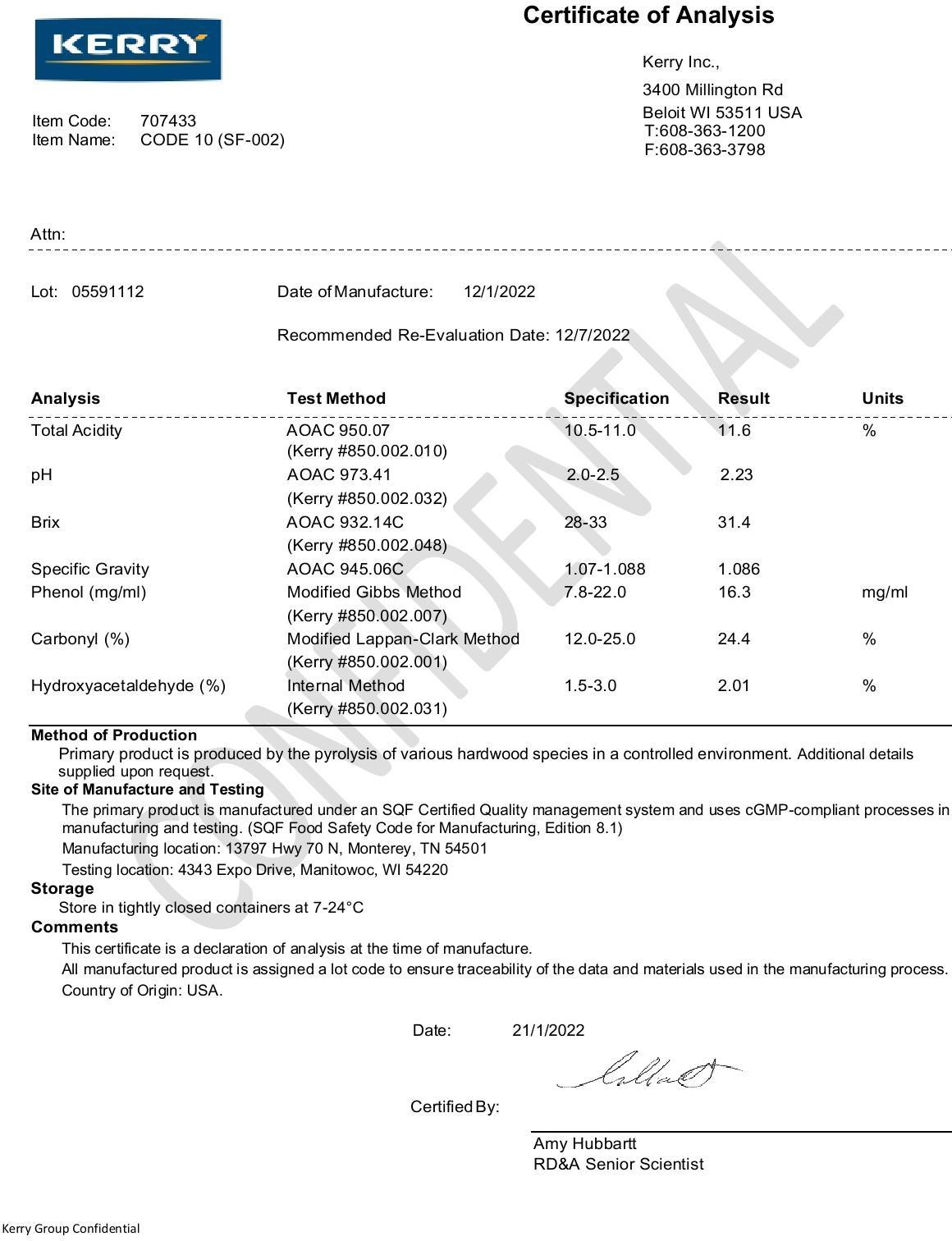
b For the testes of all males of Groups 1 and 4 detailed qualitative examination will be made, taking into account the tubular stages of the spermatogenic cycle. The examination will be conducted in order to identify treatment related effects such as missing germ cell layers or types, retained spermatids, multinucleate or apoptotic germ cells and sloughing of spermatogenic cells into the lumen. Any cell- or stage-specificity of testicular findings will be noted.

Test Facility Study No. 20334125

Page 29

###### ATTACHMENT D

**Certificate of Analysis**



Test Facility Study No. 20334125

Page 30



**Study Director Approval:**

I approve this document.

Name:

**Heuvel, Corina**

Heuvel, Corina

Electronically Signed in

30-May-2022 12:47:46 (UTC+00:00)

Timestamp

**SIGNATURE(S) FOR DOCUMENT: 20334125 - Final Study Plan**



**TFM Approval-** I approve the Study Director identified in this document and management’s responsibility to the study as

**GLP:** defined by the relevant GLP.

Name:

**Van Dycke, Kirsten**

Van Dycke, Kirsten

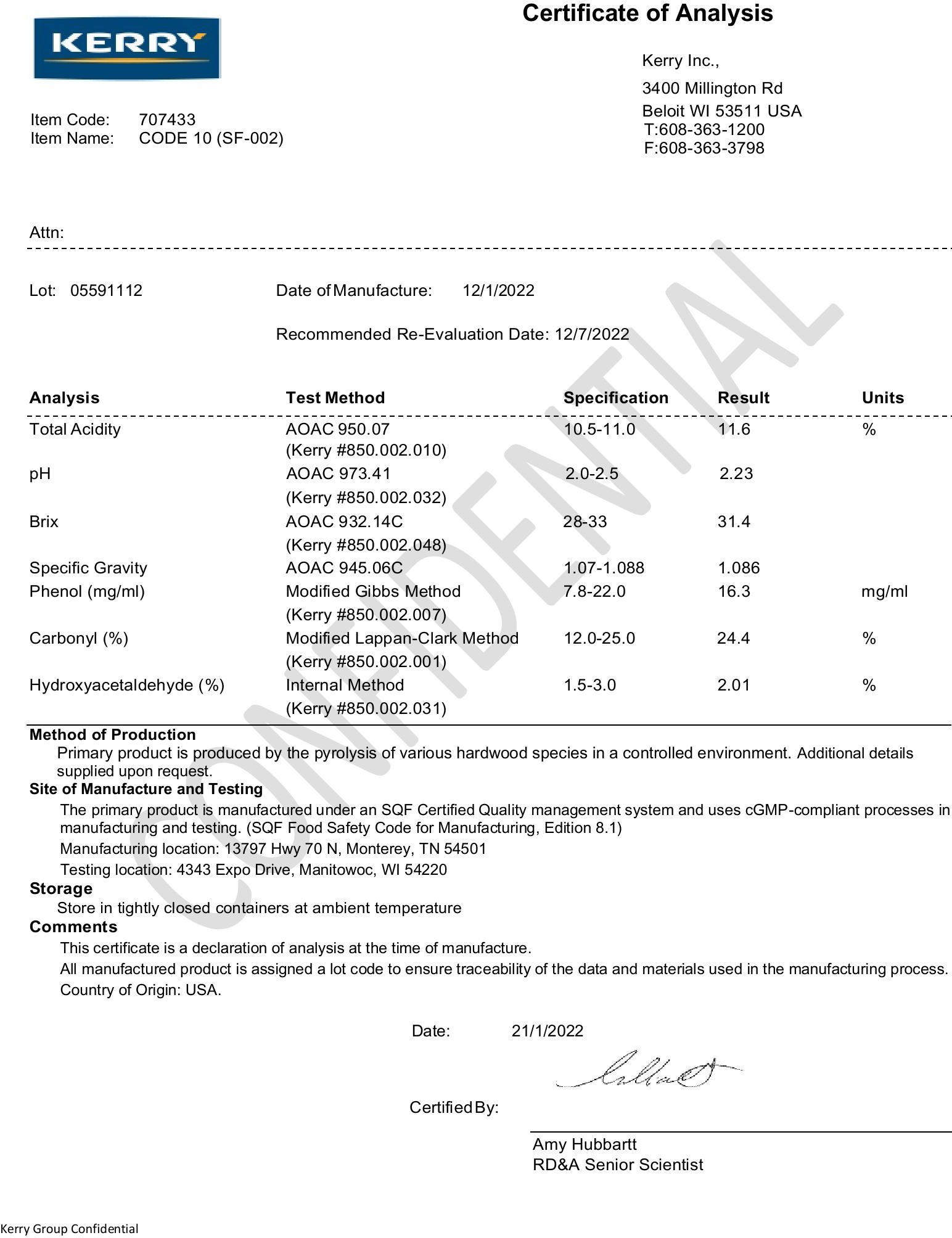
Electronically Signed in

30-May-2022 11:59:56 (UTC+00:00)

Timestamp

### Test Material Characterization

20334125



### Test Material Characterization

20334125



# Certificate of Analysis



**Appendix 2**

Item Code: Item Name:

707433

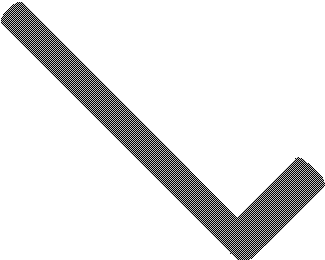
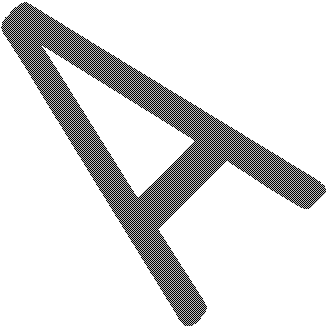
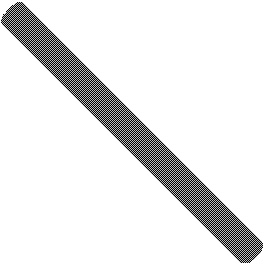
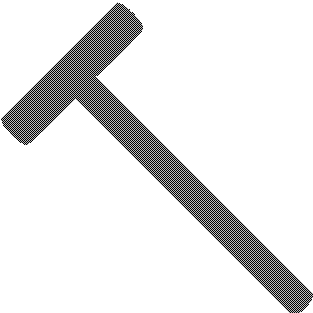
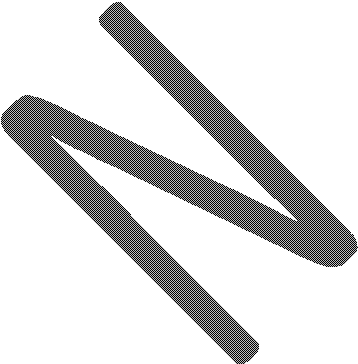
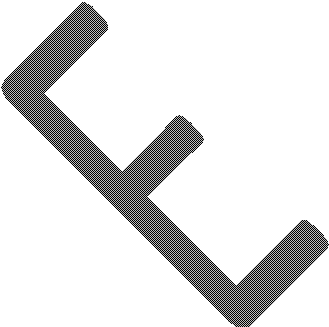
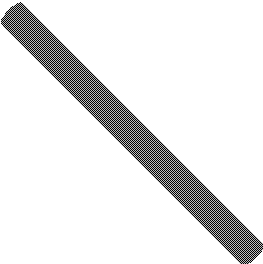
CODE 10 (SF-002)

Kerry Inc.,

3400 Millington Rd

Beloit WI 53511 USA T:608-363-1200 F:608-363-3798

Attn:



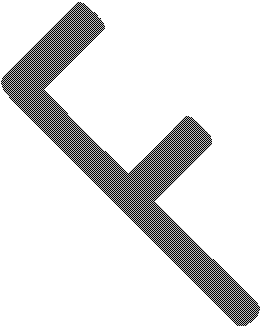
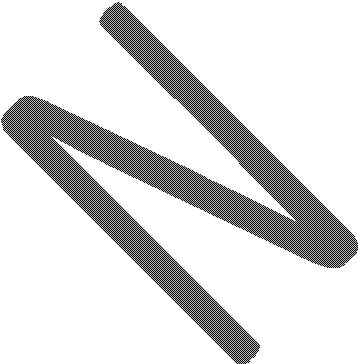
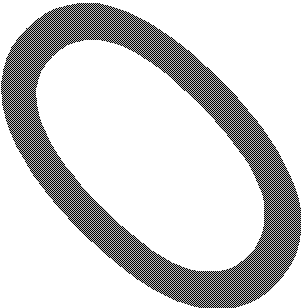
Lot: 05591112

Date of Manufacture: 12/01/2022

Recommended Re-Evaluation Date: 12/01/2024

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Analysis** | **Test Method** | **Specification** | **Result** | **Units** |
| Total Acidity | AOAC 950.07  (Kerry #850.002.010) | 10.5-11.0 | 11.0 | % |
| pH | AOAC 973.41 | 2.0-2.5 | 2.10 |  |
|  | (Kerry #850.002.032) |  |  |  |
| Brix | AOAC 932.14C | 28-33 | 29.7 |  |
|  | (Kerry #850.002.048) |  |  |  |
| Specific Gravity | AOAC 945.06C | 1.07-1.088 | 1.088 |  |
| Phenol (mg/ml) | Modified Gibbs Method | 7.8-22.0 | 13.2 | mg/ml |
|  | (Kerry #850.002.007) |  |  |  |
| Carbonyl (%) | Modified Lappan-Clark Method | 12.0-25.0 | 17.2 | % |
|  | (Kerry #850.002.001) |  |  |  |
| Hydroxyacetaldehyde (%) | Internal Method | 1.5-3.0 | 2.16 | % |
|  | (Kerry #850.002.031) |  |  |  |

**Method of Production**



Primary product is produced by the pyrolysis of various hardwood species in a controlled environment. Additional details supplied upon request.

**Site of Manufacture and Testing**

The primary product is manufactured under an SQF Certified Quality management system and uses cGMP-compliant processes in manufacturing and testing. (SQF Food Safety Code for Manufacturing, Edition 8.1)

Manufacturing location: 13797 Hwy 70 N, Monterey, TN 54501 Testing location: 4343 Expo Drive, Manitowoc, WI 54220

**Storage**

Store in tightly closed containers at 7-24°C

**Comments**

This certificate is a declaration of analysis at the time of manufacture.

All manufactured product is assigned a lot code to ensure traceability of the data and materials used in the manufacturing process. Country of Origin: USA.

Date: 08/12/2022



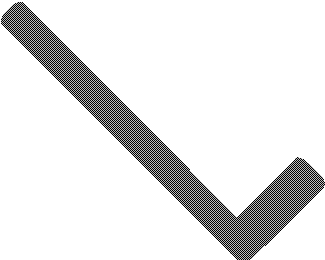
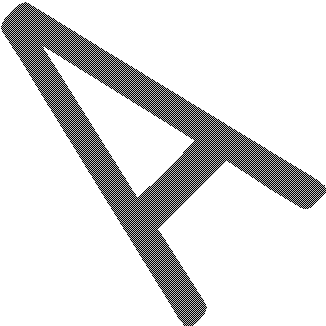
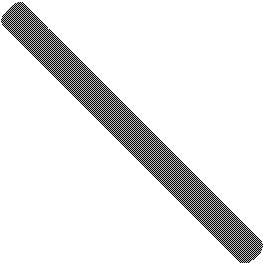
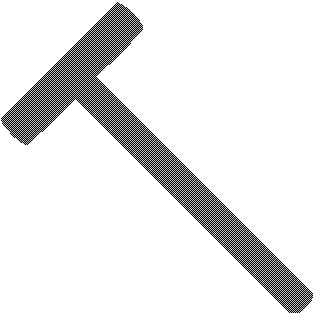
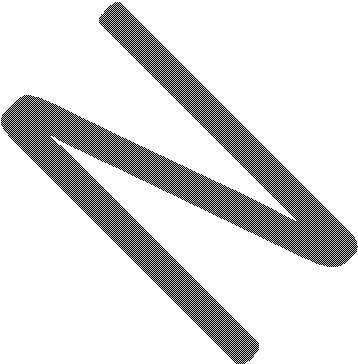
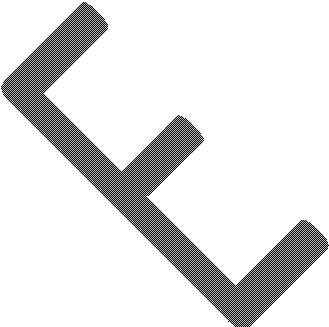
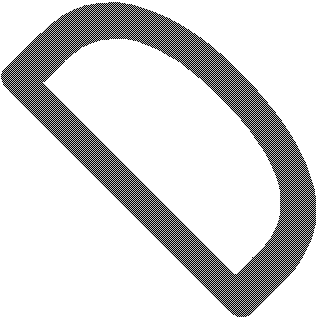
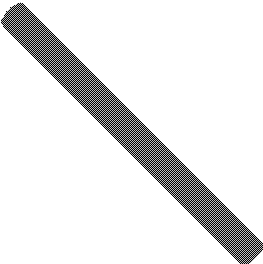
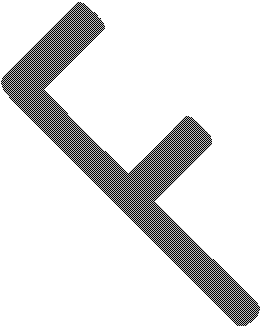
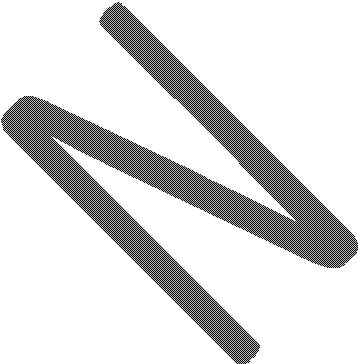
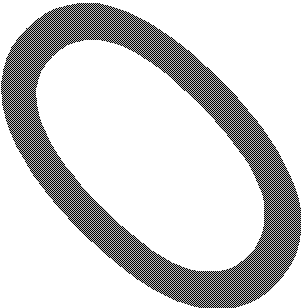
Certified By:

Amy Hubbartt

RD&A Senior Scientist

Kerry Group Confidential

### Appendix 2



Kerry Group Confidential

**FINAL REPORT**

**Study Phase: Analytical Chemistry**

**Test Facility Study No. 20334125**

**TEST FACILITY:**

Charles River Laboratories Den Bosch BV Hambakenwetering 7

5231 DD ‘s-Hertogenbosch The Netherlands

###### Page 1 of 17

**TABLE OF CONTENTS**

[LIST OF TABLES 2](#_bookmark147)

[LIST OF ADDENDUM 2](#_bookmark148)

[REPORT APPROVAL 3](#_bookmark149)

1. [SUMMARY 4](#_bookmark150)
2. [INTRODUCTION 5](#_bookmark151)
3. [MATERIALS AND METHODS 5](#_bookmark152)
4. [CONSTRUCTED VARIABLES 6](#_bookmark153)
5. [COMPUTERIZED SYSTEMS 7](#_bookmark154)
6. [RESULTS 7](#_bookmark155)
   1. [Calibration Curves 7](#_bookmark156)
   2. [Samples 7](#_bookmark157)
      1. [QC Samples 7](#_bookmark158)
      2. [Study Samples 7](#_bookmark159)

###### LIST OF TABLES

[Table 1 QC Samples 8](#_bookmark160)

[Table 2 Week 1: Accuracy and Homogeneity Test 8](#_bookmark161)

###### LIST OF ADDENDUM

[Addendum 1 Analytical procedure 9](#_bookmark162)

Test Facility Study No. 20334125 Page 2

Final Report

###### REPORT APPROVAL

All electronic signatures appear at the end of this Phase Report at finalization.

Test Facility Study No. 20334125 Page 3

Final Report

###### SUMMARY

The objective of the analytical study was to determine the accuracy of preparation and homogeneity of Code 10 (SF-002) in diets.

Accuracy

The concentrations analyzed in the diets of Group 2 and Group 3 were agreement with target concentrations (i.e. mean sample concentration results were within or equal to 80-120% of target concentration).

For the diet of Group 4 prepared for use in Week 1, the mean recovery was 78% of target. An out of specification investigation was performed. No analytical reason was found for the low recovery. Study results of the diet of Group 4, provide sufficient information and were therefore accepted for the purpose of this dose range finding study.

A small response at the retention time of the test material was observed in the chromatograms of the Group 1 diet prepared for use in Week 1.

Homogeneity

The diets of Group 2 and Group 4 were homogeneous (i.e. coefficient of variation ≤ 10.00%).

Test Facility Study No. 20334125 Page 4

Final Report

###### INTRODUCTION

For the work detailed in this phase report, the analytical phase start date was 06 Jun 2022, and the analytical phase completion date was 14 Jun 2022.

###### MATERIALS AND METHODS

Analysis was based on the analytical procedure validated for the test material in Test Facility Study No. 20334112.

General data concerning chemicals, reagents, preparation of study samples, stock solutions, calibration standards, and quality control samples (QCs) as well as the analytical methods and conditions are given in [Addendum 1](#_bookmark162).

Accuracy and homogeneity were determined for diets prepared for use during treatment.

Samples of approximately 60 g were taken from the diets. For determination of accuracy, samples were taken at the random position or at top, middle and bottom position (90%, 50% and 10% height). The samples taken at 90%, 50% and 10% height were also used for the determination of the homogeneity of the diets.

Calibration solutions were injected in duplicate. Test samples and QC samples were analyzed by single injection.

Test Facility Study No. 20334125 Page 5

Final Report

###### CONSTRUCTED VARIABLES

Response (R) [units] Peak area of the test material

Calibration curve R = a CN + b where:

CN nominal concentration [mg/L]

1. slope [units  L/mg]
2. intercept [units]

Analyzed concentration (CA) [ppm] CA = (R - b) × V × d

a w

where:

Recovery of QC samples [%]

Recovery of study samples [%]

w weight sample [g]

V volume extraction solvent [mL] d dilution factor

CA

CN × 100

where:

CN nominal concentration [ppm]

CA

CT × 100

where:

CT target concentration [ppm]

Maximum contribution  𝑅𝑏𝑙𝑎𝑛𝑐𝑜×𝑑𝑏𝑙𝑎𝑛𝑐𝑜 . 100%

𝑅𝑠𝑎𝑚𝑝𝑙𝑒×𝑑𝑠𝑎𝑚𝑝𝑙𝑒

where:

R response

d dilution factor

Concentration results of the diets were considered acceptable if mean sample concentration results were within or equal to 80-120% of target concentration. Homogeneity results were considered acceptable if the coefficient of variation was ≤ 10.00%.

Test Facility Study No. 20334125 Page 6

Final Report

###### COMPUTERIZED SYSTEMS

Computerized systems used in the phase are listed below. All computerized systems used in the conduct of this phase have been validated.

Text Table 1 Computerized Systems

|  |  |
| --- | --- |
| **System name** | **Description of Data Collected and/or Analyzed** |
| MassLynx | System control, data acquisition and processing |
| REES Centron | Temperature, relative humidity and/or atmospheric pressure monitoring |

###### RESULTS

* 1. **Calibration Curves**

The calibration curve was constructed using six concentration levels. For each level, duplicate responses were used. Linear regression analysis was performed using the least squares method with a 1/concentration2 weighting factor. The coefficient of correlation (r) was > 0.99.

###### Samples

* + 1. **QC Samples**

The results for the QC samples are given in [Table 1](#_bookmark160).

The mean recoveries of the QC samples were within the criterion range of 80-120%. It demonstrated that the analytical method was adequate for the determination of the test material in the study samples.

###### Study Samples

The results of the study samples are given in [Table 2](#_bookmark161). Accuracy

The concentrations analyzed in the diets of Group 2 and Group 3 were in agreement with target concentrations (i.e. mean sample concentration results were within or equal to

80-120% of target concentration).

For the diet of Group 4 prepared for use in Week 1, the mean recovery was 78% of target. An out of specification investigation was performed. No analytical reason was found for the low recovery. Study results of the diet of Group 4, provide sufficient information and were therefore accepted for the purpose of this dose range finding study.

A small response at the retention time of the test material was observed in the chromatograms of the Group 1 diet prepared for use in Week 1. The maximum contribution to the Group 2 samples was 0.074%.

Homogeneity

The diets of Group 2 and Group 4 were homogeneous (i.e. coefficient of variation ≤ 10.00%).

Test Facility Study No. 20334125 Page 7

Final Report

**Table 1 QC Samples**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Date of analysis** | **Concentration**  **[ppm]** | | | **Recovery**  **[%]** | |
| **Target** | **Nominal** | **Analyzed** | **Individual** | **Mean** |
| 14 Jun 2022 | 12500 | 13112 | 13434 | 102 | 102 |
|  |  | 13040 | 13026 | 100 |  |
|  |  | 13402 | 13735 | 102 |  |
|  | 50000 | 50802 | 44612 | 88 | 88 |
|  |  | 48112 | 42457 | 88 |  |
|  |  | 48313 | 41878 | 87 |  |

**Table 2**

**Week 1: Accuracy and Homogeneity Test**

14 Jun 2022

**Date of analysis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Group** | **Sample position** | **Concentration**  **[ppm]** | | **Recovery**  **[%]** | | **Coefficient of variation [%]** |
| **Target** | **Analyzed** | **Individual** | **Mean** |
| 1 | 50% height | 0  0 | 7.991  7.73 | n.a.  n.a. | n.a. | n.a. |
| 2 | 90% height | 12500 | 11028 | 88 | 89 | 1.7 |
|  |  | 12500 | 10799 | 86 |  |  |
|  | 50% height | 12500 | 11341 | 91 |  |  |
|  |  | 12500 | 11070 | 89 |  |  |
|  | 10% height | 12500 | 11027 | 88 |  |  |
|  |  | 12500 | 11218 | 90 |  |  |
| 3 | 50% height | 25000 | 21714 | 87 | 90 | n.a. |
|  |  | 25000 | 23413 | 94 |  |  |
| 4 | 90% height | 50000 | 38246 | 76 | 78 | 3.0 |
|  |  | 50000 | 38651 | 77 |  |  |
|  | 50% height | 50000 | 40995 | 82 |  |  |
|  |  | 50000 | 39706 | 79 |  |  |
|  | 10% height | 50000 | 37819 | 76 |  |  |
|  |  | 50000 | 39809 | 80 |  |  |

1 The maximum contribution to the Group 2 samples was 0.074%, taking the dilution factor into account.

n.a. Not applicable.

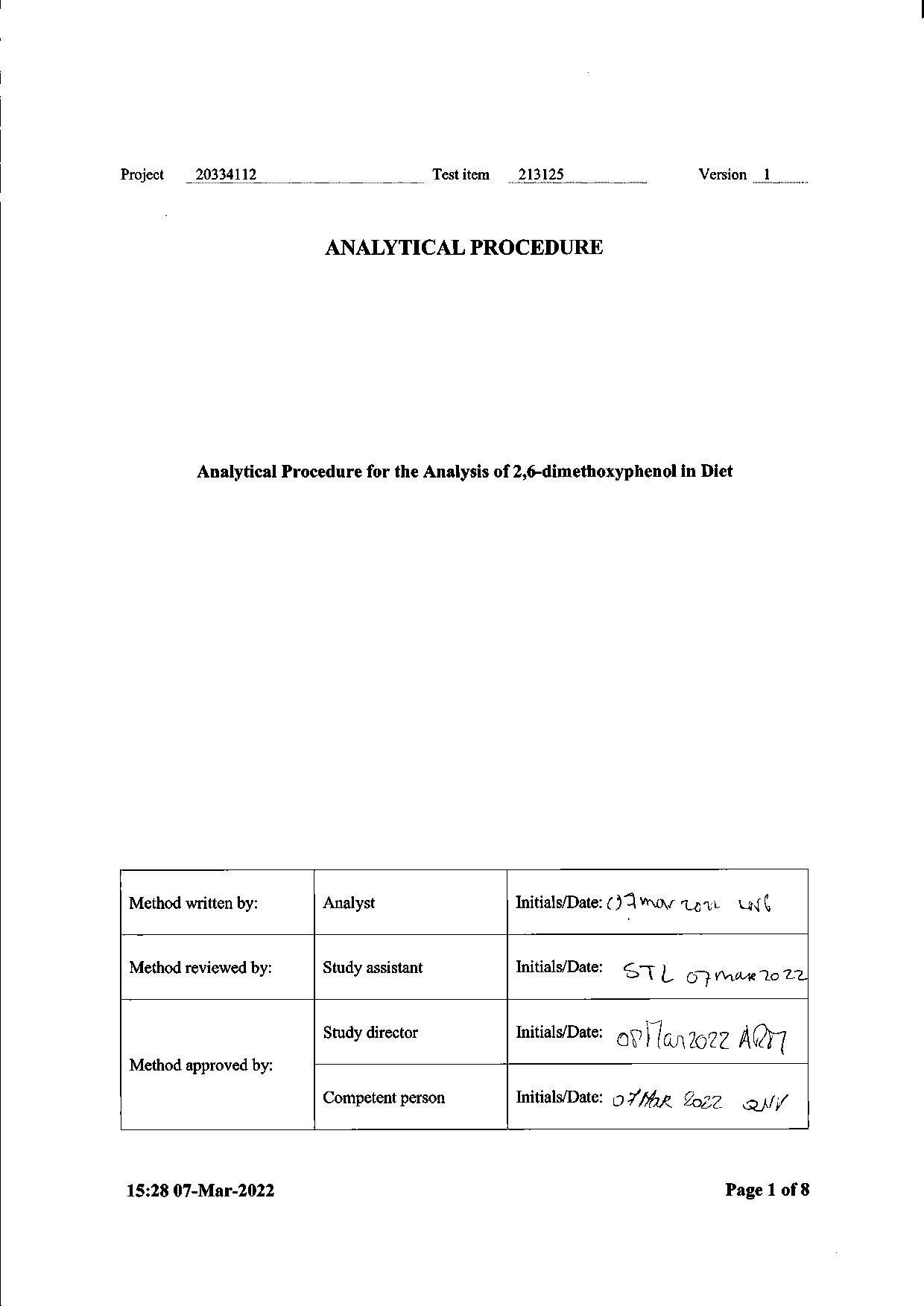
Test Facility Study No. 20334125 Page 8

Final Report

###### Addendum 1 Analytical procedure

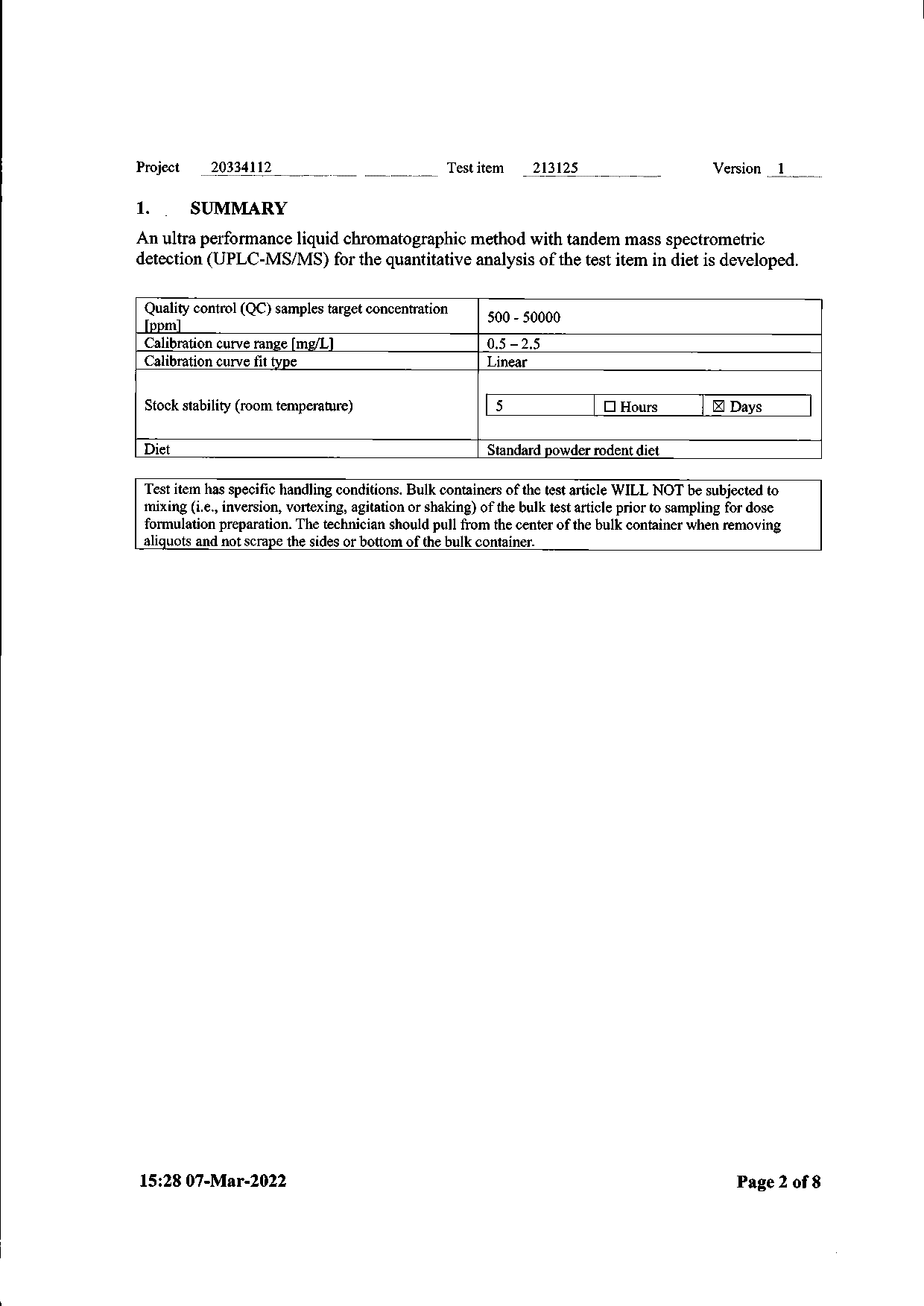
Test Facility Study No. 20334125 Page 9

Final Report



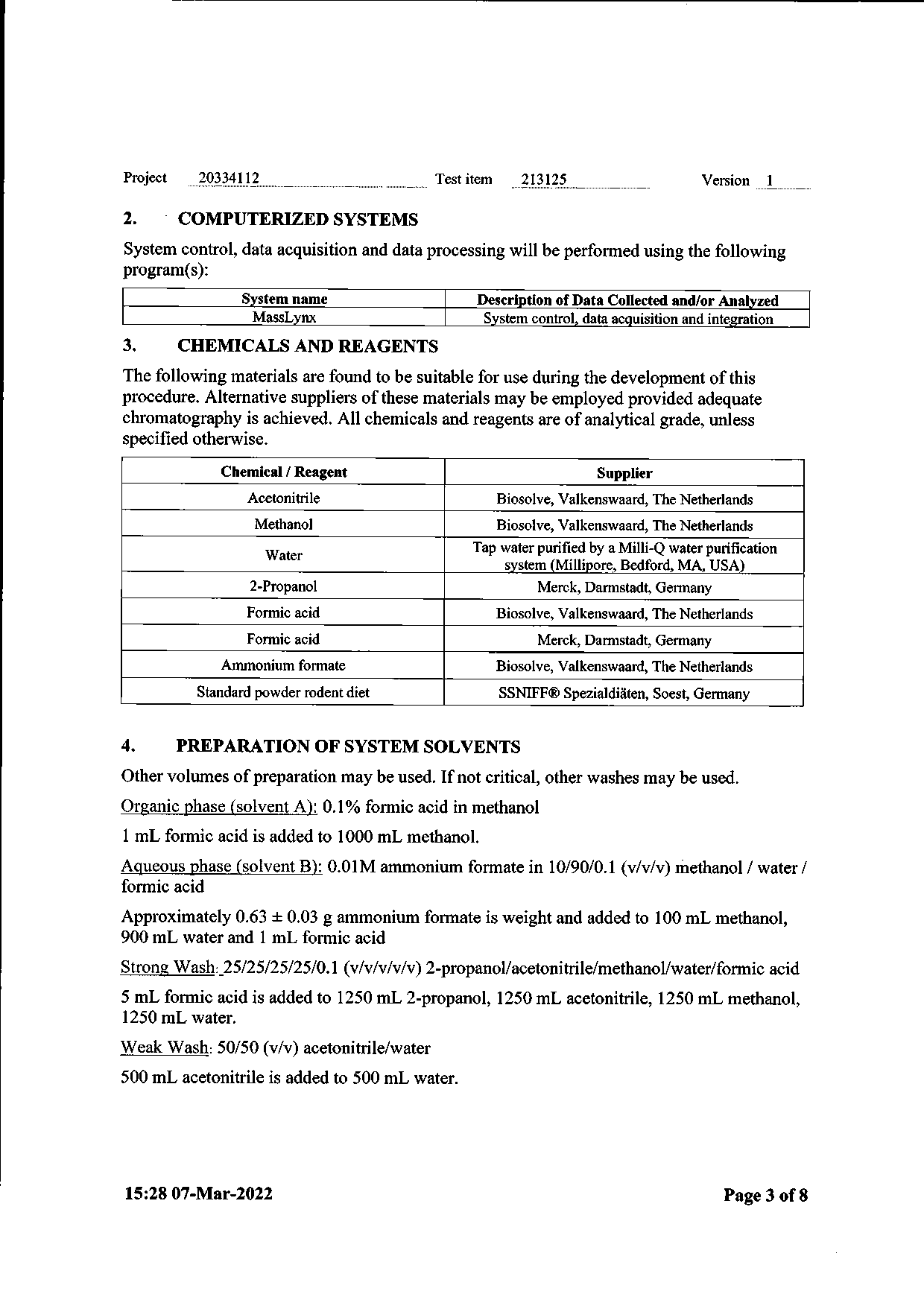
Final Report

Test Facility Study No. 20334125 Page 10



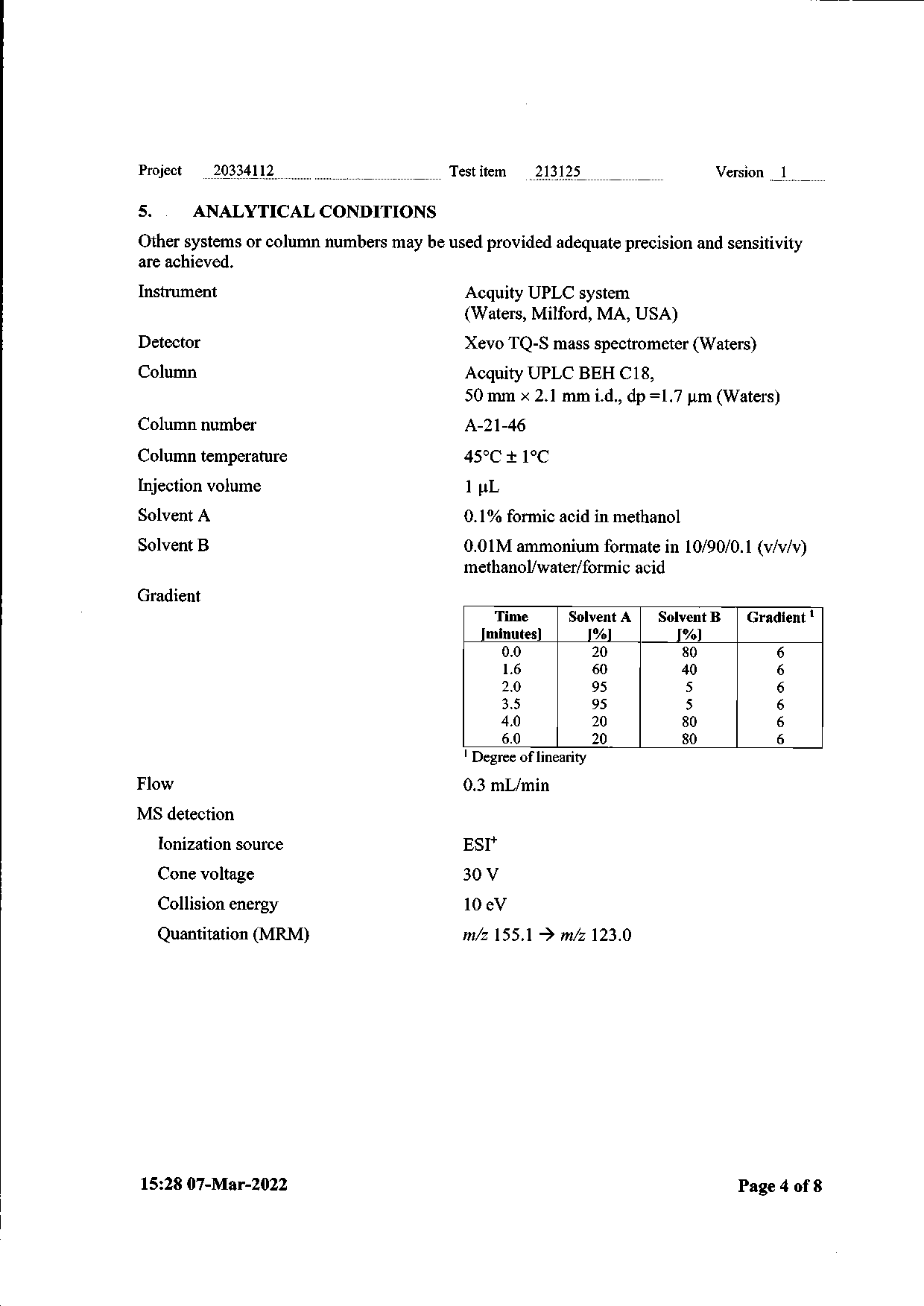
Final Report

Test Facility Study No. 20334125 Page 11



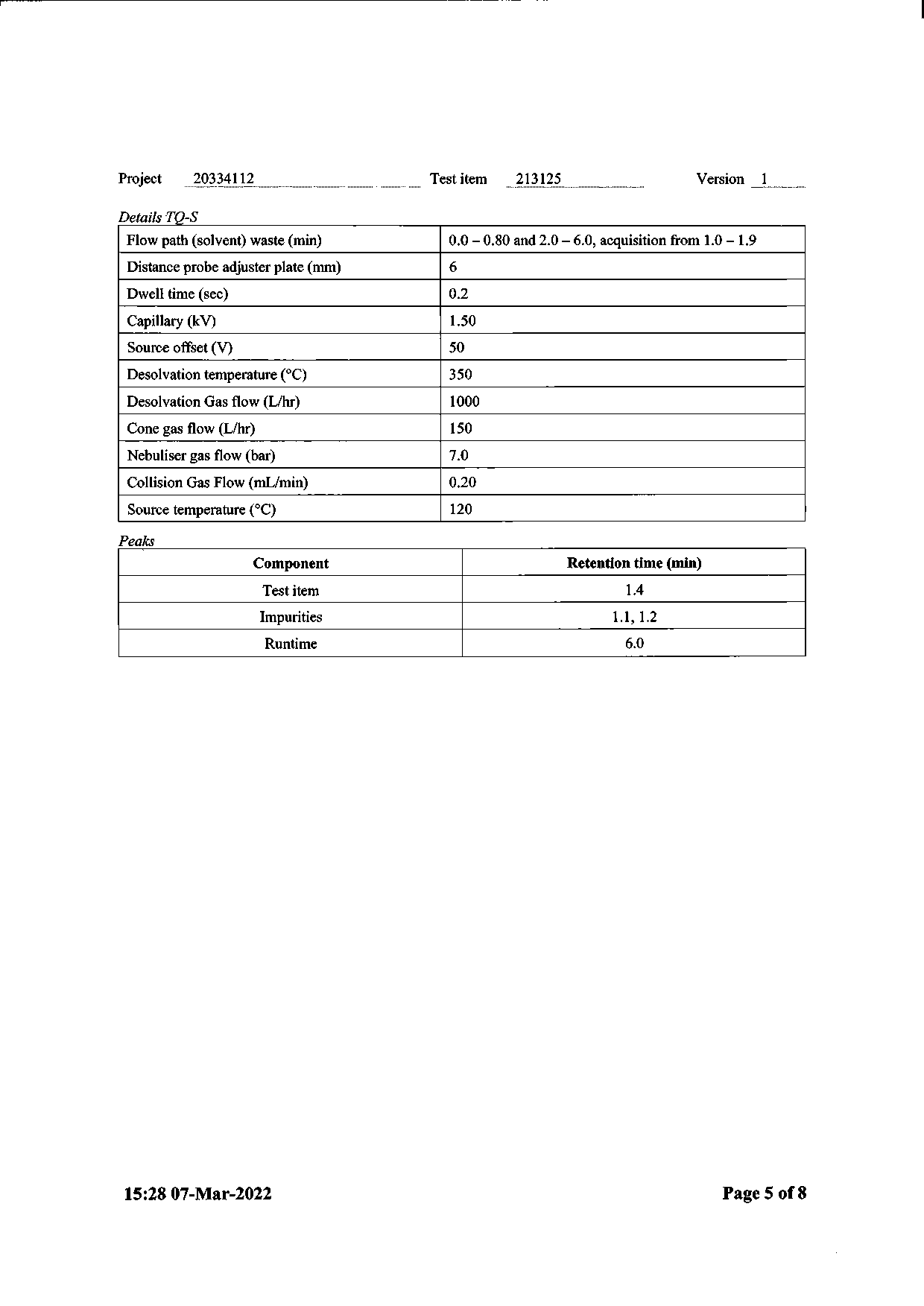
Final Report

Test Facility Study No. 20334125 Page 12



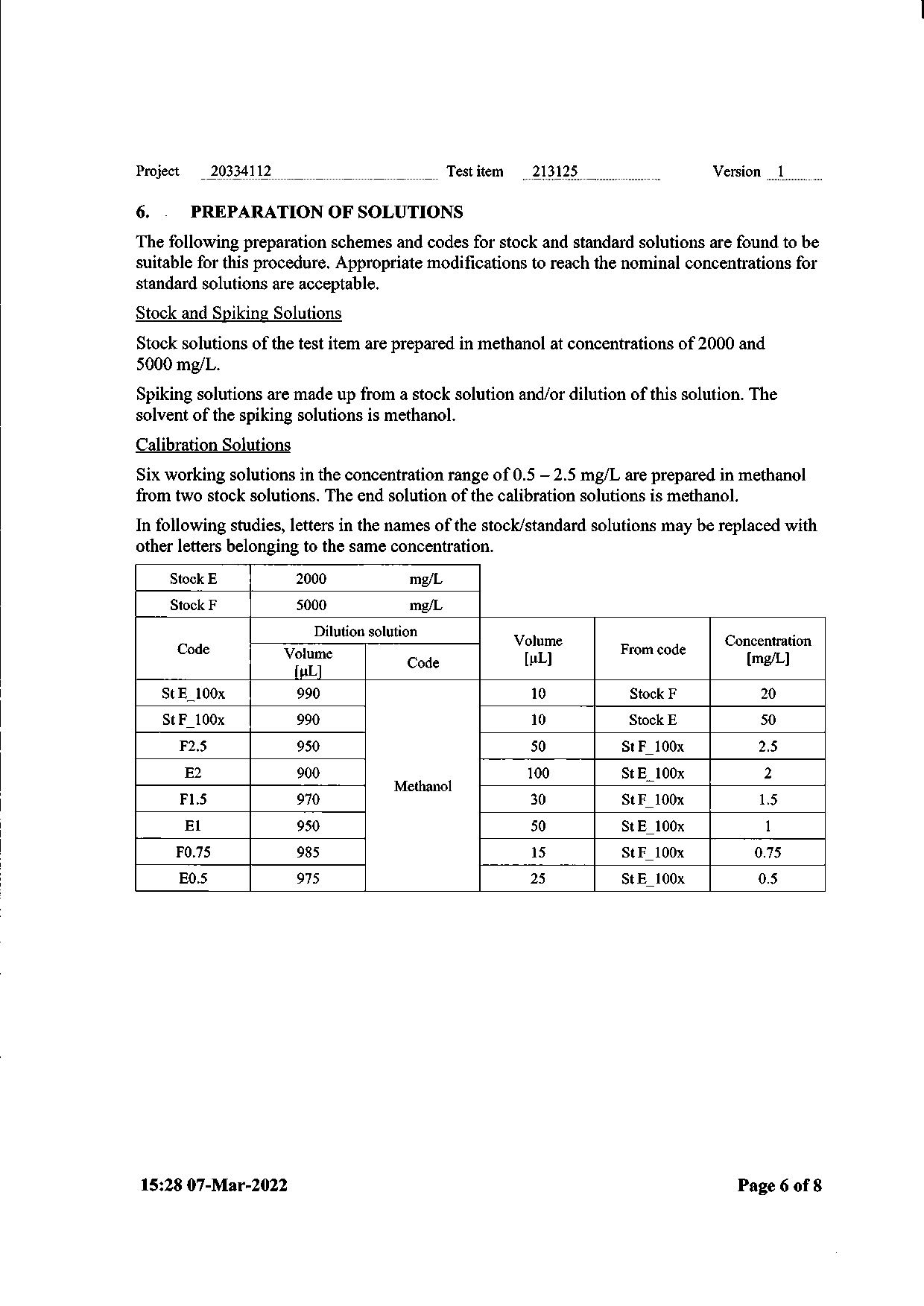
Final Report

Test Facility Study No. 20334125 Page 13



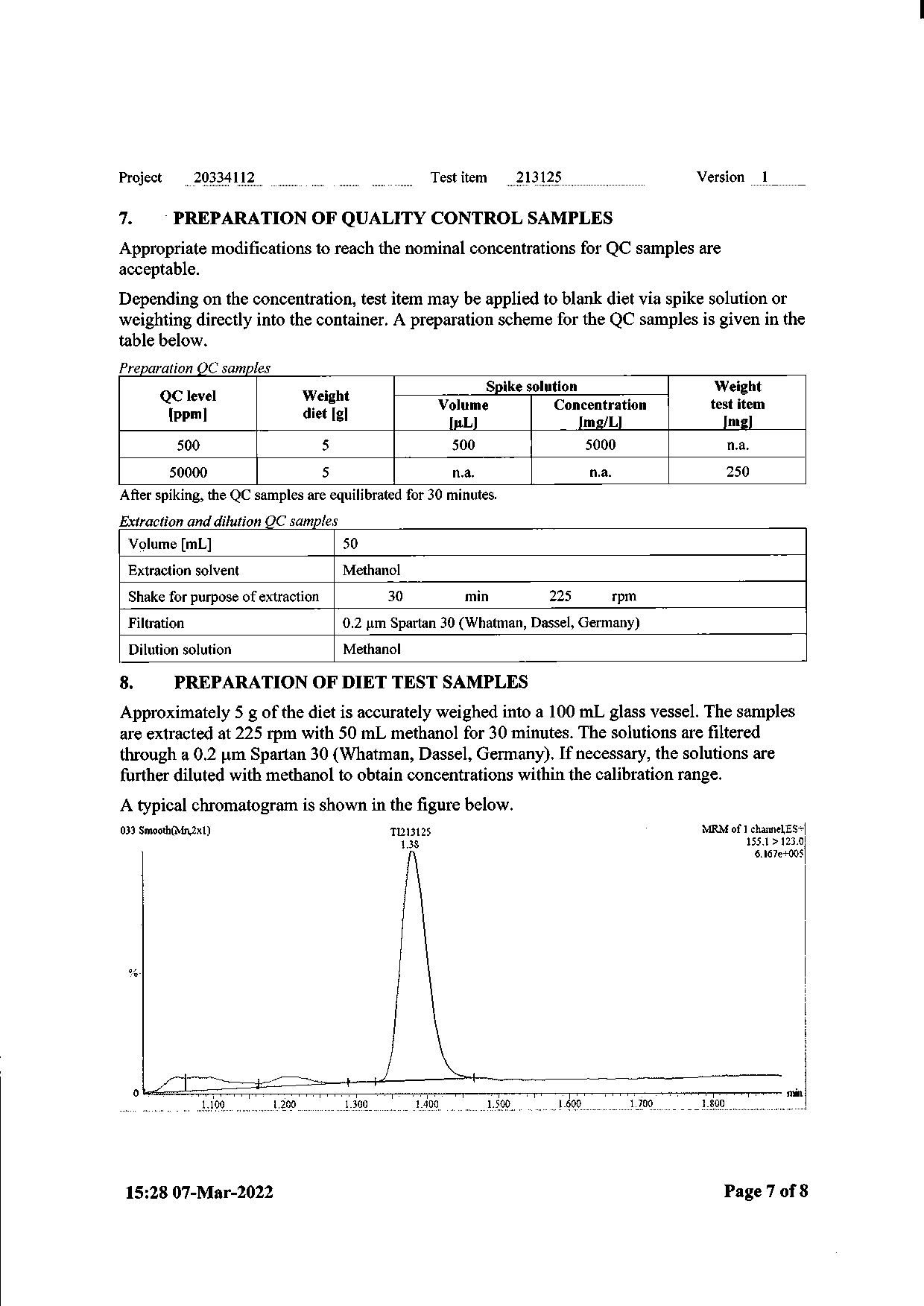
Final Report

Test Facility Study No. 20334125 Page 14



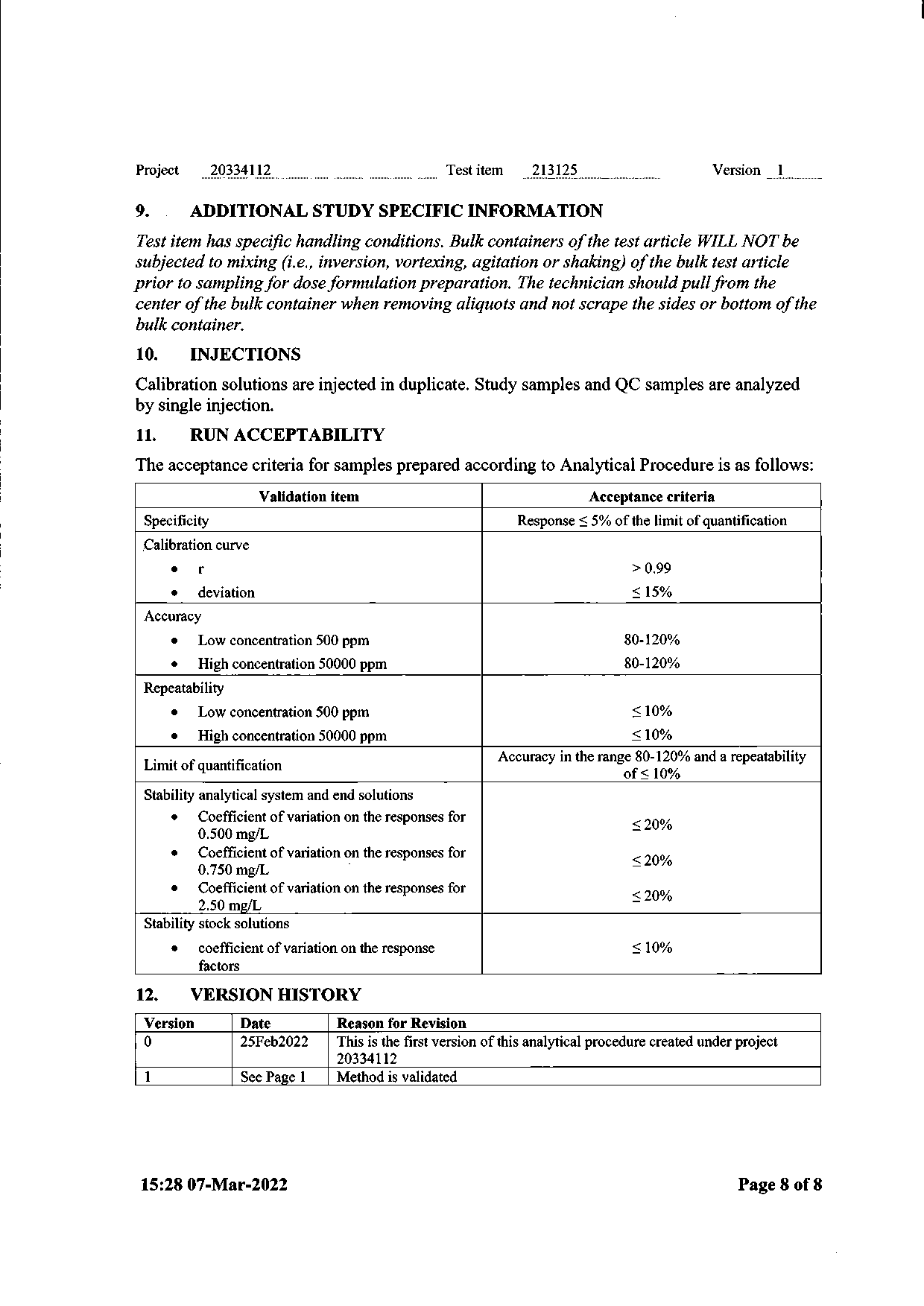
Final Report

Test Facility Study No. 20334125 Page 15



Final Report

Test Facility Study No. 20334125 Page 16



Final Report

Test Facility Study No. 20334125 Page 17

**SIGNATURE(S) FOR DOCUMENT: 20334125 - 20334125 Analytical Chemistry Final Report**



**Individual Scientist:**

I approve this document.

Name:

**Baremans, Marc**

Baremans, Marc

Electronically Signed in

14-Mar-2023 09:14:22 (UTC+00:00)

Timestamp

### Explanation Page

20334125

### General

|  |  |  |  |
| --- | --- | --- | --- |
| **Abbreviation** | **Description** | **Abbreviation** | **Description** |
| RC | Result Comment | M/m, F/f | Male, Female |
| Litter: A | First Litter | NP | Not Pregnant |
| ProA | Proportion Alpha | NM | Not Mated |

- / . No abnormality detected, animal not examined or deceased, collection not scheduled to be performed (unless otherwise listed below) or unable to calculate.

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed below may not be applicable to this report.

### Mortality

###### Abbreviation Description

TERM Terminal Euthanasia

### Clinical Observations

###### Abbreviation Description

CSO Cage Side Observation

DE Detailed Examination

Note: Only positive findings are presented: only time points and animals with at least one observation are presented in this appendix.

### Food Consumption

Note: At the start of period 22-28 Male Nos 3 and 8 were still in mating, therefore the number of animals in the cage is shown as n=4’.

### Estrous Cycles

|  |  |  |  |
| --- | --- | --- | --- |
| **Abbreviation** | **Description** | **Abbreviation** | **Description** |
| E | Estrus | M | Metestrus |
| D | Diestrus | P | Proestrus |
| RC | Regular Cycling | IC | Irregular Cycling |
| NC | Non-Cycling | ID | Insufficient Data |
| + | Sperm Positive | 1 | Plug in Animal |

/ Denotes the Start of Estrus Cycle

CD Diestrus >5 Consecutive Days

### Macroscopic and Microscopic Pathology

|  |  |  |  |
| --- | --- | --- | --- |
| **Abbreviation** | **Description** | **Abbreviation** | **Description** |
| C | Clinical Observation | M | Mass |
| E | Excluded | MPF | Major Pathological Finding |
| G | Gross Pathology | TGL | Trackable Gross Lesion |
| H | Histopathology | ? | Questionable |

**Natural Delivery**

###### Abbreviation Description

Fem Female

### Explanation Page

20334125

### Pup Body Weight

###### Abbreviation Description

PBWT Pup Body Weight

### Pup Physical Development

|  |  |  |  |
| --- | --- | --- | --- |
| **Abbreviation** | **Description** | **Abbreviation** | **Description** |
| A/N | Areola / Nipple Count | (Norm.) AGD | (Normalized) Anogenital Distance |
| NSCH | Not Scheduled to be Performed |  |  |

For the following pups, pup 5 of litter 75, the value was not within the expected range for the pertaining sex. However, since the sex was confirmed at necropsy, the AGD value determined for this animal on PND 1 was reported under that sex.

|  |  |  |  |
| --- | --- | --- | --- |
| **Dam** | **Pup Sex** | **Pup** | **Anogenital Distance (mm)** |
| 75 | f | 75-5 | 2.7 |

|  |  |  |  |
| --- | --- | --- | --- |
| 0  ppm Group 1 |  |  |  |
| Day of Death | Removal Date | Path Removal  Reason |
| 1 | 29 | 12-Jul-2022 | TERM |
| 2 | 29 | 12-Jul-2022 | TERM |
| 3 | 29 | 12-Jul-2022 | TERM |
| 4 | 29 | 12-Jul-2022 | TERM |
| 5 | 29 | 12-Jul-2022 | TERM |
| 6 | 29 | 12-Jul-2022 | TERM |
| 7 | 29 | 12-Jul-2022 | TERM |
| 8 | 29 | 12-Jul-2022 | TERM |
| 9 | 29 | 12-Jul-2022 | TERM |
| 10 | 29 | 12-Jul-2022 | TERM |

|  |  |  |  |
| --- | --- | --- | --- |
| 12500  ppm Group 2 |  |  |  |
| Day of Death | Removal Date | Path Removal  Reason |
| 11 | 29 | 12-Jul-2022 | TERM |
| 12 | 29 | 12-Jul-2022 | TERM |
| 13 | 29 | 12-Jul-2022 | TERM |
| 14 | 29 | 12-Jul-2022 | TERM |
| 15 | 29 | 12-Jul-2022 | TERM |
| 16 | 29 | 12-Jul-2022 | TERM |
| 17 | 29 | 12-Jul-2022 | TERM |
| 18 | 29 | 12-Jul-2022 | TERM |
| 19 | 29 | 12-Jul-2022 | TERM |
| 20 | 29 | 12-Jul-2022 | TERM |

|  |  |  |  |
| --- | --- | --- | --- |
| 25000  ppm Group 3 |  |  |  |
| Day of Death | Removal Date | Path Removal  Reason |
| 21 | 29 | 12-Jul-2022 | TERM |
| 22 | 29 | 12-Jul-2022 | TERM |
| 23 | 29 | 12-Jul-2022 | TERM |
| 24 | 29 | 12-Jul-2022 | TERM |
| 25 | 29 | 12-Jul-2022 | TERM |
| 26 | 29 | 12-Jul-2022 | TERM |
| 27 | 29 | 12-Jul-2022 | TERM |
| 28 | 29 | 12-Jul-2022 | TERM |
| 29 | 29 | 12-Jul-2022 | TERM |
| 30 | 29 | 12-Jul-2022 | TERM |

|  |  |  |  |
| --- | --- | --- | --- |
| 50000  ppm Group 4 |  |  |  |
| Day of Death | Removal Date | Path Removal  Reason |
| 31 | 29 | 12-Jul-2022 | TERM |
| 32 | 29 | 12-Jul-2022 | TERM |
| 33 | 29 | 12-Jul-2022 | TERM |
| 34 | 29 | 12-Jul-2022 | TERM |
| 35 | 29 | 12-Jul-2022 | TERM |
| 36 | 29 | 12-Jul-2022 | TERM |
| 37 | 29 | 12-Jul-2022 | TERM |
| 38 | 29 | 12-Jul-2022 | TERM |
| 39 | 29 | 12-Jul-2022 | TERM |
| 40 | 29 | 12-Jul-2022 | TERM |

Sex: Female Day(s): - Relative to Start Date

|  |  |  |  |
| --- | --- | --- | --- |
| 0  ppm Group 1 |  |  |  |
| Day of Death | Removal Date | Path Removal  Reason |
| 41 | 56 | 08-Aug-2022 | TERM |
| 42 | 56 | 08-Aug-2022 | TERM |
| 43 | 63 | 15-Aug-2022 | TERM |
| 44 | 53 | 05-Aug-2022 | TERM |
| 45 | 56 | 08-Aug-2022 | TERM |
| 46 | 53 | 05-Aug-2022 | TERM |
| 47 | 56 | 08-Aug-2022 | TERM |
| 48 | 52 | 04-Aug-2022 | TERM |
| 49 | 52 | 04-Aug-2022 | TERM |
| 50 | 53 | 05-Aug-2022 | TERM |

Sex: Female Day(s): - Relative to Start Date

|  |  |  |  |
| --- | --- | --- | --- |
| 12500  ppm Group 2 |  |  |  |
| Day of Death | Removal Date | Path Removal  Reason |
| 51 | 56 | 08-Aug-2022 | TERM |
| 52 | 51 | 03-Aug-2022 | TERM |
| 53 | 52 | 04-Aug-2022 | TERM |
| 54 | 53 | 05-Aug-2022 | TERM |
| 55 | 56 | 08-Aug-2022 | TERM |
| 56 | 53 | 05-Aug-2022 | TERM |
| 57 | 56 | 08-Aug-2022 | TERM |
| 58 | 52 | 04-Aug-2022 | TERM |
| 59 | 43 | 26-Jul-2022 | TERM |
| 60 | 53 | 05-Aug-2022 | TERM |

Sex: Female Day(s): - Relative to Start Date

|  |  |  |  |
| --- | --- | --- | --- |
| 25000  ppm Group 3 |  |  |  |
| Day of Death | Removal Date | Path Removal  Reason |
| 61 | 53 | 05-Aug-2022 | TERM |
| 62 | 56 | 08-Aug-2022 | TERM |
| 63 | 51 | 03-Aug-2022 | TERM |
| 64 | 52 | 04-Aug-2022 | TERM |
| 65 | 56 | 08-Aug-2022 | TERM |
| 66 | 52 | 04-Aug-2022 | TERM |
| 67 | 52 | 04-Aug-2022 | TERM |
| 68 | 56 | 08-Aug-2022 | TERM |
| 69 | 52 | 04-Aug-2022 | TERM |
| 70 | 56 | 08-Aug-2022 | TERM |

Sex: Female Day(s): - Relative to Start Date

|  |  |  |  |
| --- | --- | --- | --- |
| 50000  ppm Group 4 |  |  |  |
| Day of Death | Removal Date | Path Removal  Reason |
| 71 | 56 | 08-Aug-2022 | TERM |
| 72 | 56 | 08-Aug-2022 | TERM |
| 73 | 56 | 08-Aug-2022 | TERM |
| 74 | 53 | 05-Aug-2022 | TERM |
| 75 | 56 | 08-Aug-2022 | TERM |
| 76 | 56 | 08-Aug-2022 | TERM |
| 77 | 43 | 26-Jul-2022 | TERM |
| 78 | 43 | 26-Jul-2022 | TERM |
| 79 | 56 | 08-Aug-2022 | TERM |
| 80 | 53 | 05-Aug-2022 | TERM |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 0 | Observation Type: All Types | Day(s) Relative to Start Date | | | | | | |
| ppm |  | 15 |  |  |  |  |  |  |
| Group 1  Sex: Male |  | DE |
| 10 | Skin, Lesion, Scapular, Left, Slight | X | | | | | | |

X=Present

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 25000 | Observation Type: All Types | Day(s) Relative to Start Date (A) | | | | | | |
| ppm |  | 5 | 6 | 7 | 8 | 10 | 11 | 12 |
| Group 3  Sex: Female |  | CSO | CSO | CSO | DE | CSO | CSO | CSO |
| 61 | Skin, Scab, Interscapular | . | . | . | . | . | X | X |

X=Present

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 25000 | Observation Type: All Types | Day(s) Relative to Start Date (A) | | | | | | |
| ppm |  | 13 | 14 | 15 | 15 | 16 |  |  |
| Group 3  Sex: Female |  | CSO | CSO | CSO | DE | CSO |
| 61 | Skin, Scab, Interscapular | . | . | . | . | . |  |  |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000 | Observation Type: All Types | Day(s) Relative to Start Date (A) | | | | | | |
| ppm |  | 5 | 6 | 7 | 8 | 10 | 11 | 12 |
| Group 4  Sex: Female |  | CSO | CSO | CSO | DE | CSO | CSO | CSO |
| 80 | Skin, Lesion, Dorsal Cervical, Slight | . | . | . | X | X | X | X |
|  | Skin, Lesion, Ventral Cervical, Slight | X | . | . | . | . | . | . |
|  | Skin, Scab, Dorsal Cervical | . | X | X | . | . | . | . |

X=Present

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4  Sex: Female | Observation Type: All Types | Day(s) Relative to Start Date (A) | | | | | | |
| 13  CSO | 14  CSO | 15  CSO | 15  DE | 16  CSO |  |  |
| 80 | Skin, Lesion, Dorsal Cervical, Slight  Skin, Lesion, Ventral Cervical, Slight Skin, Scab, Dorsal Cervical | .  . X | .  . X | .  . X | .  . X | .  . X |  |  |

X=Present

###### Individual Clinical Observations: F0 Generation - Gestation 20334125

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000 | Observation Type: All Types | Day(s) Relative to Mating (A) | | | | | | |
| ppm |  | 0 | 1 | 2 | 3 | 4 | 5 | 5 |
| Group 4  Sex: Female |  | CSO | CSO | CSO | CSO | CSO | CSO | DE |
| 77 | Fur, Loss | . | . | . | . | . | . | . |
| 80 | Skin, Scab, Dorsal Cervical | X | X | X | X | X | X | X |

X=Present

###### Individual Clinical Observations: F0 Generation - Gestation 20334125

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000 | Observation Type: All Types | Day(s) Relative to Mating (A) | | | | | | |
| ppm |  | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Group 4  Sex: Female |  | CSO | CSO | CSO | CSO | CSO | CSO | CSO |
| 77 | Fur, Loss | . | . | . | . | 1 | 1 | 1 |
| 80 | Skin, Scab, Dorsal Cervical | X | X | X | X | X | X | X |

1=Slight; X=Present

###### Individual Clinical Observations: F0 Generation - Gestation 20334125

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000 | Observation Type: All Types | Day(s) Relative to Mating (A) | | | | | | |
| ppm |  | 12 | 13 | 14 | 15 | 16 | 17 | 18 |
| Group 4  Sex: Female |  | DE | CSO | CSO | CSO | CSO | CSO | CSO |
| 77 | Fur, Loss | . | 1 | 1 | 1 | 1 | 2 | . |
| 80 | Skin, Scab, Dorsal Cervical | X | X | X | X | X | X | X |

1=Slight; 2=Moderate; X=Present

###### Individual Clinical Observations: F0 Generation - Gestation 20334125

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000 | Observation Type: All Types | Day(s) Relative to Mating (A) | | | | | | |
| ppm |  | 18 | 19 | 19 | 20 | 21 | 22 | 23 |
| Group 4  Sex: Female |  | DE | CSO | DE | CSO | CSO | CSO | CSO |
| 77 | Fur, Loss | 1 | . | . | 1 | 1 | 1 | 1 |
| 80 | Skin, Scab, Dorsal Cervical | . | X | X | X | X | X | . |

1=Slight; X=Present

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 0 | Observation Type: All Types | Day(s) Relative to Littering (A) | | | | | | |
| ppm |  | 1 | 1 | 2 | 3 | 4 | 4 | 5 |
| Group 1  Sex: Female |  | CSO | DE | CSO | CSO | CSO | DE | CSO |
| 43 | Eyeball, Abnormal Size, Left, Enlarged | . | X | . | . | . | . | . |
| 46 | Fur, Loss, Slight | X | . | X | X | . | . | . |

X=Present

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 0 | Observation Type: All Types | Day(s) Relative to Littering (A) | | | | | | |
| ppm |  | 6 | 7 | 14 |  |  |  |  |
| Group 1  Sex: Female |  | CSO | CSO | DE |
| 43 | Eyeball, Abnormal Size, Left, Enlarged | . | . | X |  |  |  |  |
| 46 | Fur, Loss, Slight | . | . | . |  |  |  |  |

X=Present

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000 | Observation Type: All Types | Day(s) Relative to Littering (A) | | | | | | |
| ppm |  | 1 | 1 | 2 | 3 | 4 | 4 | 5 |
| Group 4  Sex: Female |  | CSO | DE | CSO | CSO | CSO | DE | CSO |
| 80 | Fur, Loss, Slight | X | . | X | . | . | . | . |
|  | Skin, Scab, Dorsal Cervical | . | . | . | . | X | X | X |

X=Present

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000 | Observation Type: All Types | Day(s) Relative to Littering (A) | | | | | | |
| ppm |  | 6 | 7 | 14 |  |  |  |  |
| Group 4  Sex: Female |  | CSO | CSO | DE |
| 80 | Fur, Loss, Slight | . | . | . |  |  |  |  |
|  | Skin, Scab, Dorsal Cervical | X | X | . |

X=Present

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Day(s) Relative to Start Date | | | | |
| 1 | 8 | 15 | 22 | 28 |
| 1 | 335 | 369 | 394 | 405 | 411 |
| 2 | 311 | 348 | 367 | 386 | 398 |
| 3 | 306 | 342 | 363 | 376 | 382 |
| 4 | 312 | 337 | 352 | 367 | 376 |
| 5 | 316 | 355 | 377 | 395 | 408 |
| 6 | 285 | 310 | 337 | 349 | 370 |
| 7 | 303 | 335 | 350 | 369 | 386 |
| 8 | 312 | 352 | 368 | 376 | 391 |
| 9 | 342 | 387 | 421 | 433 | 447 |
| 10 | 294 | 330 | 344 | 364 | 383 |
| Mean | 311.6 | 346.5 | 367.3 | 382.0 | 395.2 |
| SD | 17.0 | 21.3 | 25.2 | 24.0 | 22.4 |
| N | 10 | 10 | 10 | 10 | 10 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Day(s) Relative to Start Date | | | | |
| 1 | 8 | 15 | 22 | 28 |
| 11 | 309 | 338 | 357 | 363 | 375 |
| 12 | 304 | 322 | 338 | 352 | 372 |
| 13 | 324 | 352 | 378 | 389 | 397 |
| 14 | 321 | 346 | 371 | 389 | 403 |
| 15 | 315 | 347 | 371 | 385 | 400 |
| 16 | 311 | 344 | 372 | 384 | 401 |
| 17 | 302 | 333 | 355 | 360 | 376 |
| 18 | 325 | 357 | 378 | 388 | 405 |
| 19 | 311 | 349 | 364 | 376 | 387 |
| 20 | 335 | 361 | 382 | 389 | 399 |
| Mean | 315.7 | 344.9 | 366.6 | 377.5 | 391.5 |
| SD | 10.4 | 11.5 | 13.4 | 14.0 | 12.8 |
| N | 10 | 10 | 10 | 10 | 10 |
| %Diff | 1.3 | -0.5 | -0.2 | -1.2 | -0.9 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Day(s) Relative to Start Date | | | | |
| 1 | 8 | 15 | 22 | 28 |
| 21 | 305 | 332 | 358 | 368 | 382 |
| 22 | 291 | 311 | 330 | 332 | 342 |
| 23 | 318 | 343 | 363 | 374 | 382 |
| 24 | 296 | 316 | 332 | 338 | 351 |
| 25 | 308 | 339 | 366 | 375 | 398 |
| 26 | 311 | 339 | 365 | 379 | 395 |
| 27 | 305 | 336 | 365 | 380 | 395 |
| 28 | 318 | 337 | 358 | 370 | 385 |
| 29 | 305 | 336 | 364 | 374 | 390 |
| 30 | 296 | 323 | 342 | 350 | 363 |
| Mean | 305.3 | 331.2 | 354.3 | 364.0 | 378.3 |
| SD | 9.1 | 10.8 | 14.2 | 17.5 | 19.6 |
| N | 10 | 10 | 10 | 10 | 10 |
| %Diff | -2.0 | -4.4 | -3.5 | -4.7 | -4.3 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Day(s) Relative to Start Date | | | | |
| 1 | 8 | 15 | 22 | 28 |
| 31 | 318 | 328 | 334 | 342 | 350 |
| 32 | 307 | 317 | 341 | 353 | 364 |
| 33 | 323 | 322 | 337 | 352 | 361 |
| 34 | 312 | 325 | 343 | 353 | 373 |
| 35 | 294 | 301 | 331 | 337 | 344 |
| 36 | 306 | 323 | 346 | 362 | 372 |
| 37 | 327 | 343 | 369 | 381 | 395 |
| 38 | 310 | 322 | 340 | 343 | 356 |
| 39 | 311 | 318 | 341 | 350 | 370 |
| 40 | 315 | 317 | 326 | 337 | 350 |
| Mean | 312.3 | 321.6 | 340.8 | 351.0 | 363.5 |
| SD | 9.3 | 10.5 | 11.6 | 13.2 | 14.9 |
| N | 10 | 10 | 10 | 10 | 10 |
| %Diff | 0.2 | -7.2 | -7.2 | -8.1 | -8.0 |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Day(s) Relative to Start Date | | | | | | | | |
| 1 | 8 | 15 | 22 | 29 | 36 | 43 | 50 | 52 |
| 41 | 208 | 220 | 214 | - | - | - | - | - | - |
| 42 | 230 | 231 | 230 | - | - | - | - | - | - |
| 43 | 214 | 220 | 225 | 245 | - | - | - | - | - |
| 44 | 187 | 193 | 202 | - | - | - | - | - | - |
| 45 | 215 | 220 | 221 | - | - | - | - | - | - |
| 46 | 208 | 230 | 234 | - | - | - | - | - | - |
| 47 | 203 | 215 | 218 | - | - | - | - | - | - |
| 48 | 216 | 229 | 232 | 255 | 249 | 248 | 248 | 251 | 251 |
| 49 | 212 | 221 | 229 | - | - | - | - | - | - |
| 50 | 207 | 212 | 219 | - | - | - | - | - | - |
| Mean | 210.0 | 219.1 | 222.4 | 250.0 | 249.0 | 248.0 | 248.0 | 251.0 | 251.0 |
| SD | 10.9 | 11.1 | 9.7 | 7.1 | - | - | - | - | - |
| N | 10 | 10 | 10 | 2 | 1 | 1 | 1 | 1 | 1 |

|  |  |  |  |
| --- | --- | --- | --- |
| 12500  ppm Group 2 | Day(s) Relative to Start Date | | |
| 1 | 8 | 15 |
| 51 | 208 | 217 | 223 |
| 52 | 226 | 232 | 235 |
| 53 | 204 | 206 | 217 |
| 54 | 218 | 222 | 223 |
| 55 | 227 | 241 | 246 |
| 56 | 205 | 209 | 221 |
| 57 | 227 | 233 | 235 |
| 58 | 206 | 198 | 213 |
| 59 | 207 | 219 | 217 |
| 60 | 201 | 217 | 225 |
| Mean | 212.9 | 219.4 | 225.5 |
| SD | 10.5 | 13.2 | 10.2 |
| N | 10 | 10 | 10 |
| %Diff | 1.4 | 0.1 | 1.4 |

|  |  |  |  |
| --- | --- | --- | --- |
| 25000  ppm Group 3 | Day(s) Relative to Start Date | | |
| 1 | 8 | 15 |
| 61 | 206 | 213 | 220 |
| 62 | 218 | 224 | 222 |
| 63 | 196 | 201 | 212 |
| 64 | 214 | 230 | 242 |
| 65 | 196 | 205 | 209 |
| 66 | 214 | 210 | 222 |
| 67 | 209 | 220 | 225 |
| 68 | 209 | 214 | 213 |
| 69 | 205 | 207 | 211 |
| 70 | 219 | 227 | 233 |
| Mean | 208.6 | 215.1 | 220.9 |
| SD | 8.1 | 9.8 | 10.5 |
| N | 10 | 10 | 10 |
| %Diff | -0.7 | -1.8 | -0.7 |

|  |  |  |  |
| --- | --- | --- | --- |
| 50000  ppm Group 4 | Day(s) Relative to Start Date | | |
| 1 | 8 | 15 |
| 71 | 228 | 234 | 239 |
| 72 | 194 | 198 | 201 |
| 73 | 221 | 217 | 221 |
| 74 | 224 | 233 | 237 |
| 75 | 218 | 226 | 223 |
| 76 | 241 | 235 | 233 |
| 77 | 206 | 206 | 205 |
| 78 | 215 | 216 | 216 |
| 79 | 203 | 199 | 204 |
| 80 | 201 | 206 | 207 |
| Mean | 215.1 | 217.0 | 218.6 |
| SD | 14.3 | 14.4 | 14.3 |
| N | 10 | 10 | 10 |
| %Diff | 2.4 | -1.0 | -1.7 |

###### Individual Body Weights: F0 Generation - Gestation 20334125

Sex: Female Bodyweight (g)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 | 4 | 7 | 11 | 14 | 17 | 20 |
| 41 | 223 | 242 | 252 | 265 | 275 | 304 | 335 |
| 42 | 236 | 245 | 250 | 259 | 270 | 294 | 324 |
| 43 | 249 | 255 | 258 | 274 | 280 | 301 | 338 |
| 44 | 198 | 217 | 228 | 239 | 249 | 274 | 308 |
| 45 | 227 | 248 | 257 | 267 | 286 | 310 | 346 |
| 46 | 232 | 250 | 257 | 269 | 284 | 301 | 338 |
| 47 | 221 | 235 | 247 | 252 | 263 | 288 | 327 |
| 49 | 227 | 243 | 250 | 264 | 272 | 293 | 335 |
| 50 | 218 | 223 | 234 | 242 | 245 | 266 | 290 |
| Mean | 225.7 | 239.8 | 248.1 | 259.0 | 269.3 | 292.3 | 326.8 |
| SD | 13.9 | 12.6 | 10.5 | 12.2 | 14.5 | 14.4 | 17.6 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

###### Individual Body Weights: F0 Generation - Gestation 20334125

Sex: Female Bodyweight (g)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 | 4 | 7 | 11 | 14 | 17 | 20 |
| 51 | 222 | 243 | 251 | 267 | 273 | 297 | 339 |
| 52 | 235 | 250 | 271 | 281 | 287 | 308 | 331 |
| 53 | 210 | 230 | 235 | 244 | 251 | 270 | 294 |
| 54 | 230 | 239 | 248 | 258 | 275 | 303 | 337 |
| 55 | 247 | 258 | 267 | 272 | 287 | 307 | 343 |
| 56 | 218 | 232 | 242 | 259 | 264 | 287 | 322 |
| 57 | 242 | 263 | 268 | 280 | 295 | 312 | 344 |
| 58 | 209 | 222 | 229 | 240 | 246 | 278 | 300 |
| 59 NP | 219 E | 235 E | 242 E | 243 E | 237 E | 234 E | 238 E |
| 60 | 220 | 233 | 234 | 249 | 251 | 274 | 297 |
| Mean | 225.9 | 241.1 | 249.4 | 261.1 | 269.9 | 292.9 | 323.0 |
| SD | 13.5 | 13.6 | 16.0 | 15.0 | 17.9 | 16.0 | 20.6 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

E = Exclude

###### Individual Body Weights: F0 Generation - Gestation 20334125

Sex: Female Bodyweight (g)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 | 4 | 7 | 11 | 14 | 17 | 20 |
| 61 | 213 | 236 | 240 | 254 | 261 | 288 | 329 |
| 62 | 228 | 245 | 253 | 264 | 279 | 301 | 334 |
| 63 | 209 | 226 | 235 | 242 | 252 | 278 | 314 |
| 64 | 234 | 251 | 254 | 271 | 281 | 305 | 340 |
| 65 | 210 | 216 | 228 | 233 | 240 | 257 | 291 |
| 66 | 220 | 234 | 241 | 252 | 263 | 280 | 307 |
| 67 | 220 | 238 | 249 | 264 | 274 | 297 | 331 |
| 68 | 225 | 242 | 245 | 255 | 266 | 291 | 327 |
| 69 | 214 | 224 | 235 | 242 | 254 | 270 | 299 |
| 70 | 236 | 249 | 252 | 264 | 269 | 298 | 340 |
| Mean | 220.9 | 236.1 | 243.2 | 254.1 | 263.9 | 286.5 | 321.2 |
| SD | 9.7 | 11.4 | 8.9 | 12.1 | 12.8 | 15.2 | 17.4 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

###### Individual Body Weights: F0 Generation - Gestation 20334125

Sex: Female Bodyweight (g)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 | 4 | 7 | 11 | 14 | 17 | 20 |
| 71 | 238 | 256 | 257 | 273 | 277 | 302 | 333 |
| 72 | 198 | 212 | 218 | 217 | 223 | 249 | 280 |
| 73 | 215 | 228 | 232 | 248 | 260 | 282 | 314 |
| 74 | 237 | 252 | 252 | 269 | 272 | 297 | 334 |
| 75 | 223 | 242 | 249 | 259 | 267 | 291 | 322 |
| 76 | 236 | 263 | 264 | 278 | 285 | 308 | 340 |
| 77 NP | 220 E | 223 E | 220 E | 215 E | 225 E | 218 E | 223 E |
| 78 NP | 211 E | 231 E | 236 E | 230 E | 239 E | 245 E | 257 E |
| 79 | 205 | 218 | 217 | 230 | 240 | 256 | 281 |
| 80 | 208 | 216 | 226 | 234 | 242 | 258 | 285 |
| Mean | 220.0 | 235.9 | 239.4 | 251.0 | 258.3 | 280.4 | 311.1 |
| SD | 15.8 | 19.9 | 18.4 | 22.3 | 21.3 | 23.0 | 25.4 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

E = Exclude

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 | 4 | 7 | 10 | 13 |
| 41 | 264 | 279 | 301 | 308 | 311 |
| 42 | 258 ᵃ | 271 | 282 | 289 | 296 |
| 43 | 257 | 277 | 280 | 307 | 288 |
| 44 | 226 ᵃ | 239 | 246 | 258 | 264 |
| 45 | 251 | 269 | 291 | 289 | 295 |
| 46 | 266 ᵃ | 284 | 301 | 304 | 311 |
| 47 | 258 ᵃ | 272 | 293 | 287 | 307 |
| 49 | 249 ᵃ | 274 | 282 | 307 | 307 |
| 50 | 228 ᵃ | 243 | 257 | 268 | 275 |
| Mean | 250.8 | 267.6 | 281.4 | 290.8 | 294.9 |
| SD | 14.5 | 15.7 | 18.9 | 18.1 | 16.6 |
| N | 9 | 9 | 9 | 9 | 9 |

ᵃ [RC:Value Confirmed]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 | 4 | 7 | 10 | 13 |
| 51 | 259 ᵃ | 276 | 293 | 308 | 305 |
| 52 | 280 ᵃ | 296 | 304 | 317 | 324 |
| 53 | 242 ᵃ | 245 | 254 | 285 | 278 |
| 54 | 257 ᵃ | 257 | 281 | 288 | 305 |
| 55 | 272 ᵃ | 282 | 287 | 295 | 305 |
| 56 | 244 ᵃ | 260 | 278 | 278 | 287 |
| 57 | 272 | 287 | 299 | 311 | 320 |
| 58 | 241 ᵃ | 246 | 253 | 264 | 277 |
| 60 | 233 ᵃ | 251 | 265 | 260 | 277 |
| Mean | 255.6 | 266.7 | 279.3 | 289.6 | 297.6 |
| SD | 16.5 | 19.0 | 18.7 | 20.2 | 18.4 |
| N | 9 | 9 | 9 | 9 | 9 |

ᵃ [RC:Value Confirmed]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 | 4 | 7 | 10 | 13 |
| 61 | 242 ᵃ | 259 | 275 | 275 | 288 |
| 62 | 251 ᵃ | 262 | 283 | 285 | 283 |
| 63 | 242 ᵃ | 255 | 255 | 276 | 269 |
| 64 | 257 ᵃ | 277 | 281 | 286 | 294 |
| 65 | 214 | 226 | 241 | 255 | 245 |
| 66 | 240 ᵃ | 253 | 268 | 278 | 282 |
| 67 | 268 ᵃ | 263 | 286 | 289 | 295 |
| 68 | 249 | 265 | 288 | 278 | 287 |
| 69 | 242 ᵃ | 247 | 264 | 276 | 275 |
| 70 | 256 ᵃ | 269 | 280 | 292 | 277 |
| Mean | 246.1 | 257.6 | 272.1 | 279.0 | 279.5 |
| SD | 14.3 | 13.9 | 15.1 | 10.4 | 14.6 |
| N | 10 | 10 | 10 | 10 | 10 |

ᵃ [RC:Value Confirmed]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 | 4 | 7 | 10 | 13 |
| 71 | 260 ᵃ | 281 | 280 | 289 | 283 |
| 72 | 220 ᵃ | 227 | 230 | 231 | 224 |
| 73 | 248 | 248 | 260 | 262 | 254 |
| 74 | 266 ᵃ | 269 | 285 | 286 | 294 |
| 75 | 241 ᵃ | 258 | 271 | 279 | 272 |
| 76 | 267 ᵃ | 271 | 277 | 285 | 278 |
| 79 | 226 ᵃ | 231 | 235 | 240 | 235 |
| 80 | 223 ᵃ | 234 | 247 | 238 | 254 |
| Mean | 243.9 | 252.4 | 260.6 | 263.8 | 261.8 |
| SD | 19.4 | 20.5 | 21.1 | 24.3 | 24.3 |
| N | 8 | 8 | 8 | 8 | 8 |

ᵃ [RC:Value Confirmed]

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Day(s) Relative to Start Date | | | | | |
| 1 → 8 | 8 → 15 | 1 → 15 | 15 → 22 | 22 → 28 | 1 → 28 |
| 1 | 34 | 25 | 59 | 11 | 6 | 76 |
| 2 | 37 | 19 | 56 | 19 | 12 | 87 |
| 3 | 36 | 21 | 57 | 13 | 6 | 76 |
| 4 | 25 | 15 | 40 | 15 | 9 | 64 |
| 5 | 39 | 22 | 61 | 18 | 13 | 92 |
| 6 | 25 | 27 | 52 | 12 | 21 | 85 |
| 7 | 32 | 15 | 47 | 19 | 17 | 83 |
| 8 | 40 | 16 | 56 | 8 | 15 | 79 |
| 9 | 45 | 34 | 79 | 12 | 14 | 105 |
| 10 | 36 | 14 | 50 | 20 | 19 | 89 |
| Mean | 34.9 | 20.8 | 55.7 | 14.7 | 13.2 | 83.6 |
| SD | 6.3 | 6.4 | 10.3 | 4.1 | 5.1 | 11.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Day(s) Relative to Start Date | | | | | |
| 1 → 8 | 8 → 15 | 1 → 15 | 15 → 22 | 22 → 28 | 1 → 28 |
| 11 | 29 | 19 | 48 | 6 | 12 | 66 |
| 12 | 18 | 16 | 34 | 14 | 20 | 68 |
| 13 | 28 | 26 | 54 | 11 | 8 | 73 |
| 14 | 25 | 25 | 50 | 18 | 14 | 82 |
| 15 | 32 | 24 | 56 | 14 | 15 | 85 |
| 16 | 33 | 28 | 61 | 12 | 17 | 90 |
| 17 | 31 | 22 | 53 | 5 | 16 | 74 |
| 18 | 32 | 21 | 53 | 10 | 17 | 80 |
| 19 | 38 | 15 | 53 | 12 | 11 | 76 |
| 20 | 26 | 21 | 47 | 7 | 10 | 64 |
| Mean | 29.2 | 21.7 | 50.9 | 10.9 | 14.0 | 75.8 |
| SD | 5.4 | 4.2 | 7.2 | 4.0 | 3.7 | 8.5 |
| N | 10 | 10 | 10 | 10 | 10 | 10 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Day(s) Relative to Start Date | | | | | |
| 1 → 8 | 8 → 15 | 1 → 15 | 15 → 22 | 22 → 28 | 1 → 28 |
| 21 | 27 | 26 | 53 | 10 | 14 | 77 |
| 22 | 20 | 19 | 39 | 2 | 10 | 51 |
| 23 | 25 | 20 | 45 | 11 | 8 | 64 |
| 24 | 20 | 16 | 36 | 6 | 13 | 55 |
| 25 | 31 | 27 | 58 | 9 | 23 | 90 |
| 26 | 28 | 26 | 54 | 14 | 16 | 84 |
| 27 | 31 | 29 | 60 | 15 | 15 | 90 |
| 28 | 19 | 21 | 40 | 12 | 15 | 67 |
| 29 | 31 | 28 | 59 | 10 | 16 | 85 |
| 30 | 27 | 19 | 46 | 8 | 13 | 67 |
| Mean | 25.9 | 23.1 | 49.0 | 9.7 | 14.3 | 73.0 |
| SD | 4.7 | 4.6 | 8.9 | 3.8 | 4.0 | 14.2 |
| N | 10 | 10 | 10 | 10 | 10 | 10 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Day(s) Relative to Start Date | | | | | |
| 1 → 8 | 8 → 15 | 1 → 15 | 15 → 22 | 22 → 28 | 1 → 28 |
| 31 | 10 | 6 | 16 | 8 | 8 | 32 |
| 32 | 10 | 24 | 34 | 12 | 11 | 57 |
| 33 | -1 | 15 | 14 | 15 | 9 | 38 |
| 34 | 13 | 18 | 31 | 10 | 20 | 61 |
| 35 | 7 | 30 | 37 | 6 | 7 | 50 |
| 36 | 17 | 23 | 40 | 16 | 10 | 66 |
| 37 | 16 | 26 | 42 | 12 | 14 | 68 |
| 38 | 12 | 18 | 30 | 3 | 13 | 46 |
| 39 | 7 | 23 | 30 | 9 | 20 | 59 |
| 40 | 2 | 9 | 11 | 11 | 13 | 35 |
| Mean | 9.3 | 19.2 | 28.5 | 10.2 | 12.5 | 51.2 |
| SD | 5.7 | 7.6 | 11.1 | 3.9 | 4.6 | 13.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 |

|  |  |  |  |
| --- | --- | --- | --- |
| 0  ppm Group 1 | Day(s) Relative to Start Date | | |
| 1 → 8 | 8 → 15 | 1 → 15 |
| 41 | 12 | -6 | 6 |
| 42 | 1 | -1 | 0 |
| 43 | 6 | 5 | 11 |
| 44 | 6 | 9 | 15 |
| 45 | 5 | 1 | 6 |
| 46 | 22 | 4 | 26 |
| 47 | 12 | 3 | 15 |
| 48 | 13 | 3 | 16 |
| 49 | 9 | 8 | 17 |
| 50 | 5 | 7 | 12 |
| Mean | 9.1 | 3.3 | 12.4 |
| SD | 5.9 | 4.5 | 7.2 |
| N | 10 | 10 | 10 |

|  |  |  |  |
| --- | --- | --- | --- |
| 12500  ppm Group 2 | Day(s) Relative to Start Date | | |
| 1 → 8 | 8 → 15 | 1 → 15 |
| 51 | 9 | 6 | 15 |
| 52 | 6 | 3 | 9 |
| 53 | 2 | 11 | 13 |
| 54 | 4 | 1 | 5 |
| 55 | 14 | 5 | 19 |
| 56 | 4 | 12 | 16 |
| 57 | 6 | 2 | 8 |
| 58 | -8 | 15 | 7 |
| 59 | 12 | -2 | 10 |
| 60 | 16 | 8 | 24 |
| Mean | 6.5 | 6.1 | 12.6 |
| SD | 6.9 | 5.4 | 5.9 |
| N | 10 | 10 | 10 |

|  |  |  |  |
| --- | --- | --- | --- |
| 25000  ppm Group 3 | Day(s) Relative to Start Date | | |
| 1 → 8 | 8 → 15 | 1 → 15 |
| 61 | 7 | 7 | 14 |
| 62 | 6 | -2 | 4 |
| 63 | 5 | 11 | 16 |
| 64 | 16 | 12 | 28 |
| 65 | 9 | 4 | 13 |
| 66 | -4 | 12 | 8 |
| 67 | 11 | 5 | 16 |
| 68 | 5 | -1 | 4 |
| 69 | 2 | 4 | 6 |
| 70 | 8 | 6 | 14 |
| Mean | 6.5 | 5.8 | 12.3 |
| SD | 5.3 | 4.9 | 7.3 |
| N | 10 | 10 | 10 |

|  |  |  |  |
| --- | --- | --- | --- |
| 50000  ppm Group 4 | Day(s) Relative to Start Date | | |
| 1 → 8 | 8 → 15 | 1 → 15 |
| 71 | 6 | 5 | 11 |
| 72 | 4 | 3 | 7 |
| 73 | -4 | 4 | 0 |
| 74 | 9 | 4 | 13 |
| 75 | 8 | -3 | 5 |
| 76 | -6 | -2 | -8 |
| 77 | 0 | -1 | -1 |
| 78 | 1 | 0 | 1 |
| 79 | -4 | 5 | 1 |
| 80 | 5 | 1 | 6 |
| Mean | 1.9 | 1.6 | 3.5 |
| SD | 5.3 | 3.0 | 6.2 |
| N | 10 | 10 | 10 |

###### Individual Body Weight Gains (g): F0 Generation - Gestation 20334125

Sex: Female Bodyweight Gain (Interval)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | 0 → 20 |
| 41 | 19 | 10 | 13 | 10 | 29 | 31 | 112 |
| 42 | 9 | 5 | 9 | 11 | 24 | 30 | 88 |
| 43 | 6 | 3 | 16 | 6 | 21 | 37 | 89 |
| 44 | 19 | 11 | 11 | 10 | 25 | 34 | 110 |
| 45 | 21 | 9 | 10 | 19 | 24 | 36 | 119 |
| 46 | 18 | 7 | 12 | 15 | 17 | 37 | 106 |
| 47 | 14 | 12 | 5 | 11 | 25 | 39 | 106 |
| 49 | 16 | 7 | 14 | 8 | 21 | 42 | 108 |
| 50 | 5 | 11 | 8 | 3 | 21 | 24 | 72 |
| Mean | 14.1 | 8.3 | 10.9 | 10.3 | 23.0 | 34.4 | 101.1 |
| SD | 6.0 | 3.0 | 3.3 | 4.7 | 3.4 | 5.4 | 14.9 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

###### Individual Body Weight Gains (g): F0 Generation - Gestation 20334125

Sex: Female Bodyweight Gain (Interval)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | 0 → 20 |
| 51 | 21 | 8 | 16 | 6 | 24 | 42 | 117 |
| 52 | 15 | 21 | 10 | 6 | 21 | 23 | 96 |
| 53 | 20 | 5 | 9 | 7 | 19 | 24 | 84 |
| 54 | 9 | 9 | 10 | 17 | 28 | 34 | 107 |
| 55 | 11 | 9 | 5 | 15 | 20 | 36 | 96 |
| 56 | 14 | 10 | 17 | 5 | 23 | 35 | 104 |
| 57 | 21 | 5 | 12 | 15 | 17 | 32 | 102 |
| 58 | 13 | 7 | 11 | 6 | 32 | 22 | 91 |
| 59 NP | 16 E | 7 E | 1 E | -6 E | -3 E | 4 E | 19 E |
| 60 | 13 | 1 | 15 | 2 | 23 | 23 | 77 |
| Mean | 15.2 | 8.3 | 11.7 | 8.8 | 23.0 | 30.1 | 97.1 |
| SD | 4.4 | 5.5 | 3.8 | 5.4 | 4.6 | 7.3 | 12.1 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

E = Exclude

###### Individual Body Weight Gains (g): F0 Generation - Gestation 20334125

Sex: Female Bodyweight Gain (Interval)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | 0 → 20 |
| 61 | 23 | 4 | 14 | 7 | 27 | 41 | 116 |
| 62 | 17 | 8 | 11 | 15 | 22 | 33 | 106 |
| 63 | 17 | 9 | 7 | 10 | 26 | 36 | 105 |
| 64 | 17 | 3 | 17 | 10 | 24 | 35 | 106 |
| 65 | 6 | 12 | 5 | 7 | 17 | 34 | 81 |
| 66 | 14 | 7 | 11 | 11 | 17 | 27 | 87 |
| 67 | 18 | 11 | 15 | 10 | 23 | 34 | 111 |
| 68 | 17 | 3 | 10 | 11 | 25 | 36 | 102 |
| 69 | 10 | 11 | 7 | 12 | 16 | 29 | 85 |
| 70 | 13 | 3 | 12 | 5 | 29 | 42 | 104 |
| Mean | 15.2 | 7.1 | 10.9 | 9.8 | 22.6 | 34.7 | 100.3 |
| SD | 4.7 | 3.6 | 3.8 | 2.9 | 4.6 | 4.6 | 11.8 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

###### Individual Body Weight Gains (g): F0 Generation - Gestation 20334125

Sex: Female Bodyweight Gain (Interval)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | 0 → 20 |
| 71 | 18 | 1 | 16 | 4 | 25 | 31 | 95 |
| 72 | 14 | 6 | -1 | 6 | 26 | 31 | 82 |
| 73 | 13 | 4 | 16 | 12 | 22 | 32 | 99 |
| 74 | 15 | 0 | 17 | 3 | 25 | 37 | 97 |
| 75 | 19 | 7 | 10 | 8 | 24 | 31 | 99 |
| 76 | 27 | 1 | 14 | 7 | 23 | 32 | 104 |
| 77 NP | 3 E | -3 E | -5 E | 10 E | -7 E | 5 E | 3 E |
| 78 NP | 20 E | 5 E | -6 E | 9 E | 6 E | 12 E | 46 E |
| 79 | 13 | -1 | 13 | 10 | 16 | 25 | 76 |
| 80 | 8 | 10 | 8 | 8 | 16 | 27 | 77 |
| Mean | 15.9 | 3.5 | 11.6 | 7.3 | 22.1 | 30.8 | 91.1 |
| SD | 5.6 | 3.9 | 6.0 | 3.0 | 4.0 | 3.6 | 11.0 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

E = Exclude

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | 1 → 13 |
| 41 | 15 | 22 | 7 | 3 | 47 |
| 42 | 13 | 11 | 7 | 7 | 38 |
| 43 | 20 | 3 | 27 | -19 | 31 |
| 44 | 13 | 7 | 12 | 6 | 38 |
| 45 | 18 | 22 | -2 | 6 | 44 |
| 46 | 18 | 17 | 3 | 7 | 45 |
| 47 | 14 | 21 | -6 | 20 | 49 |
| 49 | 25 | 8 | 25 | 0 | 58 |
| 50 | 15 | 14 | 11 | 7 | 47 |
| Mean | 16.8 | 13.9 | 9.3 | 4.1 | 44.1 |
| SD | 3.9 | 7.1 | 11.1 | 10.2 | 7.8 |
| N | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | 1 → 13 |
| 51 | 17 | 17 | 15 | -3 | 46 |
| 52 | 16 | 8 | 13 | 7 | 44 |
| 53 | 3 | 9 | 31 | -7 | 36 |
| 54 | 0 | 24 | 7 | 17 | 48 |
| 55 | 10 | 5 | 8 | 10 | 33 |
| 56 | 16 | 18 | 0 | 9 | 43 |
| 57 | 15 | 12 | 12 | 9 | 48 |
| 58 | 5 | 7 | 11 | 13 | 36 |
| 60 | 18 | 14 | -5 | 17 | 44 |
| Mean | 11.1 | 12.7 | 10.2 | 8.0 | 42.0 |
| SD | 6.8 | 6.2 | 10.1 | 8.2 | 5.6 |
| N | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | 1 → 13 |
| 61 | 17 | 16 | 0 | 13 | 46 |
| 62 | 11 | 21 | 2 | -2 | 32 |
| 63 | 13 | 0 | 21 | -7 | 27 |
| 64 | 20 | 4 | 5 | 8 | 37 |
| 65 | 12 | 15 | 14 | -10 | 31 |
| 66 | 13 | 15 | 10 | 4 | 42 |
| 67 | -5 | 23 | 3 | 6 | 27 |
| 68 | 16 | 23 | -10 | 9 | 38 |
| 69 | 5 | 17 | 12 | -1 | 33 |
| 70 | 13 | 11 | 12 | -15 | 21 |
| Mean | 11.5 | 14.5 | 6.9 | 0.5 | 33.4 |
| SD | 7.0 | 7.7 | 8.7 | 9.1 | 7.5 |
| N | 10 | 10 | 10 | 10 | 10 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | 1 → 13 |
| 71 | 21 | -1 | 9 | -6 | 23 |
| 72 | 7 | 3 | 1 | -7 | 4 |
| 73 | 0 | 12 | 2 | -8 | 6 |
| 74 | 3 | 16 | 1 | 8 | 28 |
| 75 | 17 | 13 | 8 | -7 | 31 |
| 76 | 4 | 6 | 8 | -7 | 11 |
| 79 | 5 | 4 | 5 | -5 | 9 |
| 80 | 11 | 13 | -9 | 16 | 31 |
| Mean | 8.5 | 8.3 | 3.1 | -2.0 | 17.9 |
| SD | 7.3 | 6.0 | 5.9 | 8.9 | 11.5 |
| N | 8 | 8 | 8 | 8 | 8 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | No. in Cage | Day(s) Relative to Animal Start Date | | | |
| 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 |
| 1  2 | 5  5 | 24  25 | 25  26 | 27  26 | 24 n=4  24 n=4 |
| Mean | | 24.2 | 25.4 | 26.4 | 24.1 |
| SD | | 0.6 | 0.3 | 1.2 | 0.4 |
| N | | 2 | 2 | 2 | 2 |

n = Number of Animals in Cage

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | No. in Cage | Day(s) Relative to Animal Start Date | | | |
| 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 |
| 3  4 | 5  5 | 23  24 | 25  24 | 27  25 | 24  24 |
| Mean | | 23.7 | 24.7 | 25.8 | 24.1 |
| SD | | 0.3 | 0.4 | 1.2 | 0.1 |
| N | | 2 | 2 | 2 | 2 |
| %Diff | | -1.8 | -3.0 | -2.5 | -0.2 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | No. in Cage | Day(s) Relative to Animal Start Date | | | |
| 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 |
| 5  6 | 5  5 | 22  22 | 23  24 | 25  27 | 23  24 |
| Mean | | 21.8 | 23.6 | 26.3 | 23.4 |
| SD | | 0.3 | 0.7 | 1.6 | 0.9 |
| N | | 2 | 2 | 2 | 2 |
| %Diff | | -9.7 | -7.2 | -0.6 | -2.9 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | No. in Cage | Day(s) Relative to Animal Start Date | | | |
| 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 |
| 7  8 | 5  5 | 19  19 | 23  23 | 26  27 | 23  23 |
| Mean | | 18.9 | 23.2 | 26.4 | 23.4 |
| SD | | 0.1 | 0.3 | 0.4 | 0.0 |
| N | | 2 | 2 | 2 | 2 |
| %Diff | | -21.8 | -8.9 | -0.2 | -2.9 |

|  |  |  |  |
| --- | --- | --- | --- |
| 0  ppm Group 1 | No. in Cage | Day(s) Relative to Animal Start Date | |
| 1 → 8 | 8 → 15 |
| 9  10 | 5  5 | 15  15 | 16  16 |
| Mean | | 15.1 | 16.3 |
| SD | | 0.4 | 0.2 |
| N | | 2 | 2 |

|  |  |  |  |
| --- | --- | --- | --- |
| 12500  ppm Group 2 | No. in Cage | Day(s) Relative to Animal Start Date | |
| 1 → 8 | 8 → 15 |
| 11  12 | 5  5 | 15  14 | 17  16 |
| Mean | | 14.8 | 16.1 |
| SD | | 0.6 | 0.7 |
| N | | 2 | 2 |
| %Diff | | -2.1 | -0.9 |

|  |  |  |  |
| --- | --- | --- | --- |
| 25000  ppm Group 3 | No. in Cage | Day(s) Relative to Animal Start Date | |
| 1 → 8 | 8 → 15 |
| 13  14 | 5  5 | 15  15 | 17  16 |
| Mean | | 15.2 | 16.6 |
| SD | | 0.2 | 0.2 |
| N | | 2 | 2 |
| %Diff | | 0.6 | 2.4 |

|  |  |  |  |
| --- | --- | --- | --- |
| 50000  ppm Group 4 | No. in Cage | Day(s) Relative to Animal Start Date | |
| 1 → 8 | 8 → 15 |
| 15  16 | 5  5 | 14  15 | 16  15 |
| Mean | | 14.3 | 15.1 |
| SD | | 0.7 | 0.6 |
| N | | 2 | 2 |
| %Diff | | -5.1 | -7.2 |

###### Individual Food Consumption: F0 Generation - Gestation 20334125

Sex: Female Food Mean Daily Consumption (g/animal/day)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | 0 → 20 |
| 41 | 22 | 22 | 22 | 22 | 19 | 23 | 22 |
| 42 | 18 | 23 | 26 | 26 | 40 | 25 | 26 |
| 43 | 17 | 17 | 19 | 20 | 20 | 21 | 19 |
| 44 | 19 | 21 | 20 | 20 | 21 | 21 | 20 |
| 45 | 19 | 21 | 21 | 20 | 24 | 21 | 21 |
| 46 | 18 | 19 | 21 | 21 | 21 | 27 | 21 |
| 47 | 24 | 19 | 20 | 18 | 20 | 21 | 21 |
| 49 | 18 | 20 | 19 | 20 | 20 | 21 | 20 |
| 50 | 14 | 18 | 17 | 17 | 19 | 17 | 17 |
| Mean | 18.78 | 19.78 | 20.50 | 20.37 | 22.78 | 21.96 | 20.59 |
| SD | 2.80 | 1.90 | 2.54 | 2.64 | 6.78 | 2.98 | 2.49 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

###### Individual Food Consumption: F0 Generation - Gestation 20334125

Sex: Female Food Mean Daily Consumption (g/animal/day)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | 0 → 20 |
| 51 | 24 | 21 | 22 | 19 | 21 | 23 | 22 |
| 52 | 22 | 21 | 22 | 20 | 22 | 23 | 22 |
| 53 | 21 | 19 | 23 | 20 | 15 | 22 | 20 |
| 54 | 22 | 19 | 21 | 21 | 22 | 22 | 21 |
| 55 | 21 | 21 | 21 | 22 | 21 | 23 | 21 |
| 56 | 18 | 20 | 20 | 23 | 24 | 25 | 21 |
| 57 | 23 | 23 | 23 | 20 | 24 | 21 | 22 |
| 58 | 16 | 17 | 20 | 19 | 17 | 21 | 18 |
| 59 NP | 18 E | 19 E | 19 E | 12 E | 13 E | 15 E | 16 E |
| 60 | 17 | 18 | 19 | 19 | 19 | 21 | 19 |
| Mean | 20.28 | 19.96 | 21.11 | 20.33 | 20.63 | 22.26 | 20.76 |
| SD | 2.76 | 1.60 | 1.51 | 1.33 | 2.85 | 1.54 | 1.38 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

E = Exclude

###### Individual Food Consumption: F0 Generation - Gestation 20334125

Sex: Female Food Mean Daily Consumption (g/animal/day)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | 0 → 20 |
| 61 | 19 | 19 | 20 | 18 | 20 | 22 | 20 |
| 62 | 20 | 21 | 22 | 19 | 23 | 21 | 21 |
| 63 | 20 | 20 | 23 | 20 | 19 | 22 | 21 |
| 64 | 22 | 21 | 22 | 22 | 20 | 24 | 22 |
| 65 | 17 | 20 | 18 | 19 | 20 | 19 | 19 |
| 66 | 19 | 20 | 24 | 22 | 19 | 22 | 21 |
| 67 | 18 | 21 | 20 | 21 | 21 | 21 | 20 |
| 68 | 22 | 21 | 22 | 21 | 22 | 22 | 22 |
| 69 | 17 | 20 | 26 | 24 | 18 | 23 | 21 |
| 70 | 21 | 21 | 20 | 19 | 22 | 22 | 21 |
| Mean | 19.35 | 20.47 | 21.70 | 20.40 | 20.33 | 21.73 | 20.65 |
| SD | 1.92 | 0.67 | 2.39 | 1.89 | 1.50 | 1.30 | 1.00 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

###### Individual Food Consumption: F0 Generation - Gestation 20334125

Sex: Female Food Mean Daily Consumption (g/animal/day)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Day(s) Relative to Mating (Litter: A) | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | 0 → 20 |
| 71 | 21 | 21 | 22 | 18 | 25 | 21 | 21 |
| 72 | 20 | 19 | 18 | 15 | 20 | 20 | 19 |
| 73 | 19 | 19 | 20 | 19 | 23 | 20 | 20 |
| 74 | 23 | 20 | 22 | 20 | 21 | 21 | 21 |
| 75 | 20 | 22 | 21 | 16 | 23 | 20 | 21 |
| 76 | 26 | 23 | 24 | 21 | 23 | 23 | 23 |
| 77 NP | 19 E | 16 E | 16 E | 16 E | 16 E | 17 E | 17 E |
| 78 NP | 19 E | 20 E | 24 E | 18 E | 16 E | 19 E | 20 E |
| 79 | 20 | 16 | 19 | 17 | 18 | 18 | 18 |
| 80 | 17 | 19 | 19 | 19 | 19 | 18 | 18 |
| Mean | 20.53 | 19.92 | 20.47 | 18.29 | 21.46 | 20.29 | 20.19 |
| SD | 2.61 | 2.13 | 1.91 | 1.98 | 2.44 | 1.76 | 1.80 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

E = Exclude

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | 1 → 13 |
| 41 | 40 | 51 | 60 | 63 | 54 |
| 42 | 30 | 54 | 64 | 85 | 58 |
| 43 | 29 | 37 | 43 | 43 | 38 |
| 44 | 27 | 36 | 43 | 51 | 39 |
| 45 | 33 | 43 | 50 | 54 | 45 |
| 46 | 37 | 44 | 49 | 57 | 47 |
| 47 | 35 | 46 | 50 | 58 | 47 |
| 49 | 35 | 41 | 54 | 62 | 48 |
| 50 | 33 | 40 | 45 | 51 | 42 |
| Mean | 33.22 | 43.59 | 51.00 | 58.26 | 46.52 |
| SD | 4.12 | 5.96 | 7.30 | 11.74 | 6.47 |
| N | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | 1 → 13 |
| 51 | 39 | 49 | 57 | 53 | 49 |
| 52 | 29 | 40 | 49 | 58 | 44 |
| 53 | 33 | 38 | 49 | 56 | 44 |
| 54 | 30 | 40 | 49 | 62 | 45 |
| 55 | 29 | 39 | 50 | 52 | 43 |
| 56 | 33 | 43 | 47 | 56 | 45 |
| 57 | 32 | 43 | 55 | 56 | 47 |
| 58 | 30 | 39 | 43 | 55 | 42 |
| 60 | 30 | 38 | 40 | 51 | 40 |
| Mean | 31.74 | 41.04 | 48.67 | 55.56 | 44.25 |
| SD | 2.99 | 3.42 | 5.20 | 3.14 | 2.76 |
| N | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | 1 → 13 |
| 61 | 37 | 44 | 52 | 59 | 48 |
| 62 | 29 | 41 | 45 | 45 | 40 |
| 63 | 29 | 38 | 45 | 52 | 41 |
| 64 | 38 | 40 | 50 | 55 | 46 |
| 65 | 27 | 39 | 51 | 48 | 41 |
| 66 | 32 | 40 | 46 | 52 | 42 |
| 67 | 29 | 38 | 46 | 55 | 42 |
| 68 | 39 | 49 | 50 | 55 | 48 |
| 69 | 33 | 40 | 49 | 53 | 44 |
| 70 | 33 | 43 | 51 | 48 | 44 |
| Mean | 32.60 | 41.20 | 48.57 | 52.13 | 43.63 |
| SD | 4.27 | 3.18 | 2.81 | 4.26 | 2.85 |
| N | 10 | 10 | 10 | 10 | 10 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Day(s) Relative  to Littering (Litter: A) | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | 1 → 13 |
| 71 | 34 | 41 | 48 | 46 | 42 |
| 72 | 27 | 33 | 36 | 34 | 32 |
| 73 | 28 | 37 | 44 | 43 | 38 |
| 74 | 35 | 41 | 48 | 56 | 45 |
| 75 | 33 | 41 | 48 | 48 | 42 |
| 76 | 32 | 41 | 49 | 47 | 42 |
| 79 | 30 | 37 | 42 | 39 | 37 |
| 80 | 29 | 33 | 31 | 44 | 34 |
| Mean | 30.92 | 37.96 | 43.29 | 44.63 | 39.20 |
| SD | 3.00 | 3.62 | 6.60 | 6.55 | 4.48 |
| N | 8 | 8 | 8 | 8 | 8 |

###### Individual Test Material Intake: F0 Generation - Males

**20334125**

Sex: Male Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 0  ppm  Group: 1 | Cage | Day(s) Relative to Animal Start Date | | | | |
| 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 | Mean |
|  | 1 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 | 0 |
|  | N | 2 | 2 | 2 | 2 |  |

###### Individual Test Material Intake: F0 Generation - Males

**20334125**

Sex: Male Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm  Group: 2 | Cage | Day(s) Relative to Animal Start Date | | | | |
| 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 | Mean |
|  | 3 | 896 | 884 | 900 | 788 | 867 |
| 4 | 901 | 848 | 830 | 776 | 839 |
|  | N | 2 | 2 | 2 | 2 |  |

###### Individual Test Material Intake: F0 Generation - Males

**20334125**

Sex: Male Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm  Group: 3 | Cage | Day(s) Relative to Animal Start Date | | | | |
| 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 | Mean |
|  | 5 | 1709 | 1704 | 1782 | 1565 | 1690 |
| 6 | 1723 | 1739 | 1878 | 1593 | 1733 |
|  | N | 2 | 2 | 2 | 2 |  |

###### Individual Test Material Intake: F0 Generation - Males

**20334125**

Sex: Male Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm  Group: 4 | Cage | Day(s) Relative to Animal Start Date | | | | |
| 1 → 8 | 8 → 15 | 15 → 22 | 22 → 28 | Mean |
|  | 7 | 3003 | 3568 | 3812 | 3315 | 3424 |
| 8 | 2961 | 3438 | 3820 | 3236 | 3364 |
|  | N | 2 | 2 | 2 | 2 |  |

###### Individual Test Material Intake: F0 Generation - Premating

**20334125**

Sex: Female Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 0  ppm  Group: 1 | Cage | Day(s) Relative to Animal Start Date | | |
| 1 → 8 | 8 → 15 | Mean |
|  | 9 | 0 | 0 | 0 |
| 10 | 0 | 0 | 0 |
|  | N | 2 | 2 |  |

###### Individual Test Material Intake: F0 Generation - Premating

**20334125**

Sex: Female Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 12500  ppm  Group: 2 | Cage | Day(s) Relative to Animal Start Date | | |
| 1 → 8 | 8 → 15 | Mean |
|  | 11 | 863 | 917 | 890 |
| 12 | 842 | 892 | 867 |
|  | N | 2 | 2 |  |

###### Individual Test Material Intake: F0 Generation - Premating

**20334125**

Sex: Female Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 25000  ppm  Group: 3 | Cage | Day(s) Relative to Animal Start Date | | |
| 1 → 8 | 8 → 15 | Mean |
|  | 13 | 1819 | 1928 | 1874 |
| 14 | 1757 | 1890 | 1824 |
|  | N | 2 | 2 |  |

###### Individual Test Material Intake: F0 Generation - Premating

**20334125**

Sex: Female Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 50000  ppm  Group: 4 | Cage | Day(s) Relative to Animal Start Date | | |
| 1 → 8 | 8 → 15 | Mean |
|  | 15 | 3146 | 3477 | 3312 |
| 16 | 3477 | 3432 | 3454 |
|  | N | 2 | 2 |  |

###### Individual Test Material Intake: F0 Generation - Gestation

**20334125**

Sex: Female Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm  Group: 1 | Cage | Day(s) Relative to Animal Mating Date | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | Mean |
|  | 41 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 42 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 43 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 44 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 45 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 46 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 47 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 49 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  | N | 9 | 9 | 9 | 9 | 9 | 9 |  |

###### Individual Test Material Intake: F0 Generation - Gestation

**20334125**

Sex: Female Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm  Group: 2 | Cage | Day(s) Relative to Animal Mating Date | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | Mean |
|  | 51 | 1280 | 1048 | 1076 | 866 | 921 | 904 | 1016 |
| 52 | 1108 | 1022 | 996 | 893 | 912 | 888 | 970 |
| 53 | 1182 | 1038 | 1200 | 995 | 734 | 975 | 1021 |
| 54 | 1189 | 991 | 1028 | 999 | 952 | 859 | 1003 |
| 55 | 1015 | 986 | 988 | 970 | 896 | 896 | 958 |
| 56 | 1000 | 1055 | 973 | 1085 | 1089 | 1039 | 1040 |
| 57 | 1139 | 1069 | 1040 | 883 | 976 | 789 | 983 |
| 58 | 928 | 959 | 1039 | 993 | 825 | 895 | 940 |
| 59 NP | 991 E | 1012 E | 954 E | 625 E | 690 E | 794 E | 844 E |
| 60 | 927 | 980 | 983 | 950 | 919 | 906 | 944 |
|  | N | 9 | 9 | 9 | 9 | 9 | 9 |  |

E = Exclude

###### Individual Test Material Intake: F0 Generation - Gestation

**20334125**

Sex: Female Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm  Group: 3 | Cage | Day(s) Relative to Animal Mating Date | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | Mean |
|  | 61 | 2094 | 2027 | 2004 | 1748 | 1794 | 1783 | 1908 |
| 62 | 2114 | 2139 | 2079 | 1722 | 1983 | 1677 | 1952 |
| 63 | 2333 | 2202 | 2442 | 1994 | 1792 | 1833 | 2099 |
| 64 | 2299 | 2109 | 2124 | 1993 | 1732 | 1837 | 2016 |
| 65 | 1995 | 2218 | 1985 | 2008 | 1982 | 1734 | 1987 |
| 66 | 2037 | 2105 | 2434 | 2165 | 1750 | 1874 | 2061 |
| 67 | 1965 | 2125 | 1949 | 1980 | 1813 | 1648 | 1913 |
| 68 | 2334 | 2156 | 2200 | 1987 | 1975 | 1756 | 2068 |
| 69 | 1884 | 2211 | 2757 | 2389 | 1746 | 2047 | 2172 |
| 70 | 2113 | 2066 | 1919 | 1754 | 1914 | 1724 | 1915 |
|  | N | 10 | 10 | 10 | 10 | 10 | 10 |  |

###### Individual Test Material Intake: F0 Generation - Gestation

**20334125**

Sex: Female Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm  Group: 4 | Cage | Day(s) Relative to Animal Mating Date | | | | | | |
| 0 → 4 | 4 → 7 | 7 → 11 | 11 → 14 | 14 → 17 | 17 → 20 | Mean |
|  | 71 | 4150 | 4035 | 4208 | 3327 | 4266 | 3354 | 3890 |
| 72 | 4756 | 4488 | 4138 | 3477 | 4237 | 3837 | 4156 |
| 73 | 4289 | 4196 | 4125 | 3740 | 4188 | 3356 | 3982 |
| 74 | 4601 | 4028 | 4127 | 3697 | 3691 | 3328 | 3912 |
| 75 | 4301 | 4481 | 4134 | 3099 | 4176 | 3312 | 3917 |
| 76 | 5170 | 4307 | 4336 | 3783 | 3929 | 3596 | 4187 |
| 77 NP | 4176 E | 3679 E | 3747 E | 3705 E | 3612 E | 3855 E | 3796 E |
| 78 NP | 4186 E | 4218 E | 5215 E | 3838 E | 3368 E | 3845 E | 4112 E |
| 79 | 4728 | 3609 | 4206 | 3617 | 3569 | 3408 | 3856 |
| 80 | 4009 | 4367 | 4130 | 3992 | 3800 | 3260 | 3926 |
|  | N | 8 | 8 | 8 | 8 | 8 | 8 |  |

E = Exclude

###### Individual Test Material Intake: F0 Generation - Lactation

**20334125**

Sex: Female Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 0  ppm  Group: 1 | Cage | Day(s) Relative to Animal Littering Date | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | Mean |
|  | 41 | 0 | 0 | 0 | 0 | 0 |
| 42 | 0 | 0 | 0 | 0 | 0 |
| 43 | 0 | 0 | 0 | 0 | 0 |
| 44 | 0 | 0 | 0 | 0 | 0 |
| 45 | 0 | 0 | 0 | 0 | 0 |
| 46 | 0 | 0 | 0 | 0 | 0 |
| 47 | 0 | 0 | 0 | 0 | 0 |
| 49 | 0 | 0 | 0 | 0 | 0 |
| 50 | 0 | 0 | 0 | 0 | 0 |
|  | N | 9 | 9 | 9 | 9 |  |

###### Individual Test Material Intake: F0 Generation - Lactation

**20334125**

Sex: Female Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm  Group: 2 | Cage | Day(s) Relative to Animal Littering Date | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | Mean |
|  | 51 | 1808 | 2140 | 2359 | 2174 | 2120 |
| 52 | 1272 | 1667 | 1985 | 2250 | 1794 |
| 53 | 1679 | 1919 | 2273 | 2500 | 2093 |
| 54 | 1474 | 1873 | 2140 | 2601 | 2022 |
| 55 | 1322 | 1714 | 2148 | 2167 | 1838 |
| 56 | 1652 | 1984 | 2113 | 2491 | 2060 |
| 57 | 1431 | 1847 | 2242 | 2219 | 1935 |
| 58 | 1525 | 1969 | 2065 | 2555 | 2028 |
| 60 | 1565 | 1827 | 1905 | 2388 | 1921 |
|  | N | 9 | 9 | 9 | 9 |  |

###### Individual Test Material Intake: F0 Generation - Lactation

**20334125**

Sex: Female Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm  Group: 3 | Cage | Day(s) Relative to Animal Littering Date | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | Mean |
|  | 61 | 3723 | 4120 | 4755 | 5240 | 4460 |
| 62 | 2797 | 3761 | 3988 | 3935 | 3620 |
| 63 | 2948 | 3755 | 4237 | 4798 | 3934 |
| 64 | 3586 | 3557 | 4409 | 4767 | 4080 |
| 65 | 3068 | 4208 | 5171 | 4770 | 4304 |
| 66 | 3215 | 3810 | 4212 | 4670 | 3977 |
| 67 | 2731 | 3488 | 3974 | 4683 | 3719 |
| 68 | 3765 | 4403 | 4390 | 4841 | 4350 |
| 69 | 3405 | 3943 | 4537 | 4782 | 4167 |
| 70 | 3114 | 3889 | 4484 | 4218 | 3926 |
|  | N | 10 | 10 | 10 | 10 |  |

###### Individual Test Material Intake: F0 Generation - Lactation

**20334125**

Sex: Female Test Material Intake (mg substance/kg body weight/day)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm  Group: 4 | Cage | Day(s) Relative to Animal Littering Date | | | | |
| 1 → 4 | 4 → 7 | 7 → 10 | 10 → 13 | Mean |
|  | 71 | 6340 | 7308 | 8436 | 7990 | 7518 |
| 72 | 5973 | 7155 | 7809 | 7473 | 7102 |
| 73 | 5645 | 7283 | 8429 | 8333 | 7422 |
| 74 | 6486 | 7455 | 8459 | 9707 | 8027 |
| 75 | 6613 | 7694 | 8673 | 8657 | 7909 |
| 76 | 5948 | 7482 | 8719 | 8348 | 7624 |
| 79 | 6499 | 7940 | 8905 | 8211 | 7889 |
| 80 | 6346 | 6861 | 6392 | 9004 | 7151 |
|  | N | 8 | 8 | 8 | 8 |  |

###### 04-Oct-2022 00:08:37

**Individual Estrous Cycles: F0 Generation - Premating 20334125**

Sex: Female Day(s) Relative to Start Date

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Treatment: | | | | | | | | | | |
| Cycling  Status | Estrus Cycle  Summary | - | - | - | - | - | - | - | - | - |
| 1 → 15 | - | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| 41 | RC | 4 4 4 | D | D | /E | D | D | D | /E | D | D |
| 42 | RC | 4 4 4 | D | /E | D | D | P | /E | D | D | D |
| 43 | RC | 4 4 4 | D | D | /E | M | D | D | /E | D | D |
| 44 | RC | 4 4 | E | D | D | D | /E | D | D | D | /E |
| 45 | RC | 4 4 4 | D | D | /E | D | D | D | /E | D | D |
| 46 | RC | 4 4 | E | D | D | P | /E | D | D | D | /E |
| 47 | RC | 4 4 4 | P | /E | D | D | P | /E | D | D | D |
| 48 | RC | 4 4 4 | D | D | /E | D | D | D | /E | D | D |
| 49 | RC | 4 4 | E | D | D | D | /E | D | D | D | /E |
| 50 | RC | 4 4 | E | D | D | P | /E | D | D | D | /E |

###### 04-Oct-2022 00:08:37

**Individual Estrous Cycles: F0 Generation - Premating 20334125**

Sex: Female Day(s) Relative to Start Date

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Treatment: | | | | | |
| - | - | - | - | - | - |
| 10 | 11 | 12 | 13 | 14 | 15 |
| 41 | D | /E | D | D | D | E |
| 42 | /E | D | D | P | E | D |
| 43 | D | /E | M | D | D | E |
| 44 | D | D | D | E | D | D |
| 45 | D | /E | D | D | P | E |
| 46 | D | D | D | E | D | D |
| 47 | /E | D | D | D | E | D |
| 48 | D | /E | D | D | D | E |
| 49 | D | D | D | E | D | D |
| 50 | D | D | P | E | D | D |

###### 04-Oct-2022 00:08:37

**Individual Estrous Cycles: F0 Generation - Premating 20334125**

Sex: Female Day(s) Relative to Start Date

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Treatment: | | | | | | | | | | |
| Cycling  Status | Estrus Cycle  Summary | - | - | - | - | - | - | - | - | - |
| 1 → 15 | - | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| 51 | RC | 4 4 4 | P | /E | D | D | P | /E | D | D | P |
| 52 | RC | 4 4 4 | D | D | /E | D | D | D | /E | D | D |
| 53 | RC | 4 4 | D | D | D | /E | D | D | D | /E | D |
| 54 | RC | 4 4 | E | D | D | D | P | /E | D | D | P |
| 55 | RC | 4 4 4 | P | /E | D | D | P | /E | D | D | D |
| 56 | RC | 4 4 | E | D | D | P | /E | D | D | D | /E |
| 57 | RC | 4 4 4 | D | D | /E | D | D | D | /E | D | D |
| 58 | RC | 4 4 | D | D | D | /E | D | D | D | /E | D |
| 59 | RC | 4 4 4 | D | /E | D | D | D | /E | D | D | D |
| 60 | RC | 4 4 | E | D | D | D | /E | D | D | D | /E |

###### 04-Oct-2022 00:08:37

**Individual Estrous Cycles: F0 Generation - Premating 20334125**

Sex: Female Day(s) Relative to Start Date

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Treatment: | | | | | |
| - | - | - | - | - | - |
| 10 | 11 | 12 | 13 | 14 | 15 |
| 51 | /E | D | D | D | E | D |
| 52 | P | /E | D | D | D | E |
| 53 | D | D | E | D | D | D |
| 54 | /E | D | D | D | E | D |
| 55 | /E | D | D | D | E | D |
| 56 | D | D | P | E | D | D |
| 57 | D | /E | D | D | D | E |
| 58 | D | D | E | D | D | D |
| 59 | /E | D | D | D | E | D |
| 60 | D | D | D | E | D | D |

###### 04-Oct-2022 00:08:37

**Individual Estrous Cycles: F0 Generation - Premating 20334125**

Sex: Female Day(s) Relative to Start Date

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Treatment: | | | | | | | | | | |
| Cycling  Status | Estrus Cycle  Summary | - | - | - | - | - | - | - | - | - |
| 1 → 15 | - | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| 61 | RC | 4 4 | E | D | D | D | /E | D | D | D | /E |
| 62 | RC | 4 4 4 | D | D | /E | D | D | D | /E | D | D |
| 63 | RC | 4 4 | D | D | D | /E | M | D | D | /E | D |
| 64 | RC | 4 4 | E | D | D | P | /E | D | D | D | /E |
| 65 | RC | 4 4 4 | D | D | /E | D | D | P | /E | D | D |
| 66 | RC | 4 4 | M | D | P | /E | D | D | D | /E | D |
| 67 | RC | 4 4 | E | D | D | P | /E | D | D | P | /E |
| 68 | RC | 4 4 4 | D | P | /E | D | D | D | /E | D | D |
| 69 | RC | 4 4 | D | D | D | /E | D | D | D | /E | D |
| 70 | RC | 4 4 4 | D | D | /E | D | D | D | /E | D | D |

###### 04-Oct-2022 00:08:37

**Individual Estrous Cycles: F0 Generation - Premating 20334125**

Sex: Female Day(s) Relative to Start Date

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Treatment: | | | | | |
| - | - | - | - | - | - |
| 10 | 11 | 12 | 13 | 14 | 15 |
| 61 | D | D | D | E | D | D |
| 62 | D | /E | D | D | D | E |
| 63 | D | D | E | D | D | D |
| 64 | D | D | D | E | D | D |
| 65 | D | /E | D | D | D | E |
| 66 | D | D | E | D | D | D |
| 67 | D | D | D | E | D | D |
| 68 | D | /E | D | D | D | E |
| 69 | D | D | E | D | D | D |
| 70 | D | /E | D | D | D | E |

###### 04-Oct-2022 00:08:37

**Individual Estrous Cycles: F0 Generation - Premating 20334125**

Sex: Female Day(s) Relative to Start Date

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Treatment: | | | | | | | | | | |
| Cycling  Status | Estrus Cycle  Summary | - | - | - | - | - | - | - | - | - |
| 1 → 15 | - | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| 71 | IC | 4 2 2 4 | D | D | /E | D | D | D | /E | D | /P |
| 72 | RC | 4 4 | E | D | D | D | P | /E | D | D | D |
| 73 | RC | 4 4 4 | D | P | /E | D | D | D | /E | D | D |
| 74 | RC | 4 4 4 | D | /E | D | D | D | /E | D | D | D |
| 75 | RC | 4 4 4 | D | D | /E | D | D | D | /E | D | P |
| 76 | RC | 4 4 | D | D | D | D | D | /E | D | D | P |
| 77 | RC | 4 4 4 | D | D | /E | D | D | D | /E | D | D |
| 78 | RC | 4 4 4 | D | P | /E | D | D | D | /E | D | D |
| 79 | RC | 4 4 4 | D | /E | D | D | D | /E | D | D | D |
| 80 | RC | 4 4 | E | M | D | D | /E | D | D | P | /E |

###### 04-Oct-2022 00:08:37

**Individual Estrous Cycles: F0 Generation - Premating 20334125**

Sex: Female Day(s) Relative to Start Date

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Treatment: | | | | | |
| - | - | - | - | - | - |
| 10 | 11 | 12 | 13 | 14 | 15 |
| 71 | D | /E | D | D | D | E |
| 72 | /E | D | D | P | E | D |
| 73 | P | /E | D | D | D | E |
| 74 | /E | D | D | D | E | D |
| 75 | P | /E | D | D | P | E |
| 76 | /E | D | D | D | E | D |
| 77 | D | /E | D | D | D | E |
| 78 | P | /E | D | D | D | E |
| 79 | /E | D | D | D | E | D |
| 80 | D | D | D | E | D | D |

###### 04-Oct-2022 00:08:48

**Individual Estrous Cycles: F0 Generation - Cohabitation 20334125**

Sex: Female Day(s) Relative to Pairing (Litter: A)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Mating: | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 41 | D | D | D | E+ | - | - | - | - | - | - | - |
| 42 | D | P | D | D+ | - | - | - | - | - | - | - |
| 43 CD | D | D | D | D | D | D | D | D | D | D | D |
| 44 | D | E+ | - | - | - | - | - | - | - | - | - |
| 45 | D | D | D | E+ | - | - | - | - | - | - | - |
| 46 | D | E+ | - | - | - | - | - | - | - | - | - |
| 47 | D | D | E+ | - | - | - | - | - | - | - | - |
| 48 CD | D | D | D | D | D | D | D | D | D | D | D |
| 49 | D | E+ | - | - | - | - | - | - | - | - | - |
| 50 | D | E+ | - | - | - | - | - | - | - | - | - |

###### 04-Oct-2022 00:08:48

**Individual Estrous Cycles: F0 Generation - Cohabitation 20334125**

Sex: Female Day(s) Relative to Pairing (Litter: A)

|  |  |  |
| --- | --- | --- |
| 0  ppm Group 1 | Mating: | |
| - | - |
| 12 | 13 |
| 41 | - | - |
| 42 | - | - |
| 43 CD | D | D+ |
| 44 | - | - |
| 45 | - | - |
| 46 | - | - |
| 47 | - | - |
| 48 CD | D | D |
| 49 | - | - |
| 50 | - | - |

###### 04-Oct-2022 00:08:48

**Individual Estrous Cycles: F0 Generation - Cohabitation 20334125**

Sex: Female Day(s) Relative to Pairing (Litter: A)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Mating: | | | |
| - | - | - | - |
| 1 | 2 | 3 | 4 |
| 51 | D | D | E+ | - |
| 52 | D+ | - | - | - |
| 53 | E+ | - | - | - |
| 54 | D | P | E+ | - |
| 55 | D | D | E+ | - |
| 56 | D | E+ | - | - |
| 57 | D | D | D | E+ |
| 58 | E+ | - | - | - |
| 59 | D | D | E+ | - |
| 60 | D | E+ | - | - |

###### 04-Oct-2022 00:08:48

**Individual Estrous Cycles: F0 Generation - Cohabitation 20334125**

Sex: Female Day(s) Relative to Pairing (Litter: A)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Mating: | | | |
| - | - | - | - |
| 1 | 2 | 3 | 4 |
| 61 | D | E+ | - | - |
| 62 | D | D | D | E+ |
| 63 | D+ | - | - | - |
| 64 | D | 1 | - | - |
| 65 | D | D | P | E+ |
| 66 | E+ | - | - | - |
| 67 | P | E+ | - | - |
| 68 | D | D | D | E+ |
| 69 | E+ | - | - | - |
| 70 | D | D | D | E+ |

###### 04-Oct-2022 00:08:48

**Individual Estrous Cycles: F0 Generation - Cohabitation 20334125**

Sex: Female Day(s) Relative to Pairing (Litter: A)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Mating: | | | |
| - | - | - | - |
| 1 | 2 | 3 | 4 |
| 71 | D | D | D | E+ |
| 72 | D | P | E+ | - |
| 73 | D | D | D | E+ |
| 74 | D | P | E+ | - |
| 75 | D | D | P | E+ |
| 76 | D | P | E+ | - |
| 77 | D | D | D+ | - |
| 78 | M+ | - | - | - |
| 79 | D | D | E+ | - |
| 80 | D | E+ | - | - |

###### 05-Oct-2022 09:14:09

**Individual Estrous Cycles: Necropsy 20334125**

Sex: Female Stage of Estrous at Necropsy

|  |  |
| --- | --- |
| 0  ppm Group 1 | Day(s) Relative to Start Date |
| - |
| 41 | D |
| 42 | D |
| 43 | D |
| 44 | D |
| 45 | D |
| 46 | D |
| 47 | D |
| 48 | D |
| 49 | D |
| 50 | D |

###### 05-Oct-2022 09:14:09

**Individual Estrous Cycles: Necropsy 20334125**

Sex: Female Stage of Estrous at Necropsy

|  |  |
| --- | --- |
| 12500  ppm Group 2 | Day(s) Relative to Start Date |
| - |
| 51 | D |
| 52 | D |
| 53 | D |
| 54 | D |
| 55 | D |
| 56 | D |
| 57 | D |
| 58 | D |
| 59 | E |
| 60 | D |

###### 05-Oct-2022 09:14:09

**Individual Estrous Cycles: Necropsy 20334125**

Sex: Female Stage of Estrous at Necropsy

|  |  |
| --- | --- |
| 25000  ppm Group 3 | Day(s) Relative to Start Date |
| - |
| 61 | D |
| 62 | D |
| 63 | D |
| 64 | D |
| 65 | D |
| 66 | D |
| 67 | D |
| 68 | D |
| 69 | D |
| 70 | D |

###### 05-Oct-2022 09:14:09

**Individual Estrous Cycles: Necropsy 20334125**

Sex: Female Stage of Estrous at Necropsy

|  |  |
| --- | --- |
| 50000  ppm Group 4 | Day(s) Relative to Start Date |
| - |
| 71 | D |
| 72 | D |
| 73 | D |
| 74 | D |
| 75 | D |
| 76 | D |
| 77 | E |
| 78 | D |
| 79 | D |
| 80 | D |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Organ Weights | | | | |
| Terminal  Body Wt (g) | Epididymis  (g) | Epididymis  (%bw) | Testis  (g) | Testis  (%bw) |
| - | - | - | - | - |
| 1 | 396 | 1.175 | 0.2967 | 3.959 | 0.9997 |
| 2 | 378 ᵃ | 0.989 | 0.2616 | 3.040 | 0.8042 |
| 3 | 366 ᵃ | 1.086 | 0.2967 | 3.500 | 0.9563 |
| 4 | 357 ᵃ | 1.182 | 0.3311 | 3.672 | 1.0286 |
| 5 | 388 ᵃ | 1.137 | 0.2930 | 3.872 | 0.9979 |
| 6 | 343 ᵃ | 0.959 | 0.2796 | 3.350 | 0.9767 |
| 7 | 361 ᵃ | 1.092 | 0.3025 | 3.579 | 0.9914 |
| 8 | 369 ᵃ | 1.015 | 0.2751 | 3.704 | 1.0038 |
| 9 | 428 ᵃ | 1.348 | 0.3150 | 3.930 | 0.9182 |
| 10 | 364 ᵃ | 1.122 | 0.3082 | 4.066 | 1.1170 |
| Mean | 375.0 | 1.1105 | 0.29596 | 3.6672 | 0.97939 |
| SD | 24.1 | 0.1127 | 0.02022 | 0.3138 | 0.08016 |
| N | 10 | 10 | 10 | 10 | 10 |

ᵃ [RC:Value Confirmed]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Organ Weights | | | | |
| Terminal  Body Wt (g) | Epididymis  (g) | Epididymis  (%bw) | Testis  (g) | Testis  (%bw) |
| - | - | - | - | - |
| 11 | 354 ᵃ | 1.108 | 0.3130 | 3.531 | 0.9975 |
| 12 | 346 ᵃ | 0.936 | 0.2705 | 3.251 | 0.9396 |
| 13 | 381 | 1.029 | 0.2701 | 2.940 | 0.7717 |
| 14 | 379 ᵃ | 1.090 | 0.2876 | 3.725 | 0.9828 |
| 15 | 374 ᵃ | 0.951 | 0.2543 | 3.087 | 0.8254 |
| 16 | 380 ᵃ | 1.233 | 0.3245 | 4.089 | 1.0761 |
| 17 | 355 ᵃ | 1.084 | 0.3054 | 3.486 | 0.9820 |
| 18 | 386 ᵃ | 1.252 | 0.3244 | 3.890 | 1.0078 |
| 19 | 368 ᵃ | 1.092 | 0.2967 | 3.427 | 0.9313 |
| 20 | 373 ᵃ | 1.108 | 0.2971 | 3.731 | 1.0003 |
| Mean | 369.6 | 1.0883 | 0.29434 | 3.5157 | 0.95143 |
| SD | 13.5 | 0.1023 | 0.02380 | 0.3580 | 0.09060 |
| N | 10 | 10 | 10 | 10 | 10 |
| %Diff | -1.4 | -1.9991 | -0.54473 | -4.1312 | -2.85527 |

ᵃ [RC:Value Confirmed]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Organ Weights | | | | |
| Terminal  Body Wt (g) | Epididymis  (g) | Epididymis  (%bw) | Testis  (g) | Testis  (%bw) |
| - | - | - | - | - |
| 21 | 353 ᵃ | 1.182 | 0.3348 | 3.554 | 1.0068 |
| 22 | 326 ᵃ | 1.083 | 0.3322 | 3.550 | 1.0890 |
| 23 | 365 ᵃ | 0.997 | 0.2732 | 3.609 | 0.9888 |
| 24 | 330 ᵃ | 0.963 | 0.2918 | 3.518 | 1.0661 |
| 25 | 370 ᵃ | 0.963 | 0.2603 | 3.027 | 0.8181 |
| 26 | 374 ᵃ | 1.114 | 0.2979 | 3.541 | 0.9468 |
| 27 | 365 ᵃ | 1.053 | 0.2885 | 3.887 | 1.0649 |
| 28 | 362 ᵃ | 1.196 | 0.3304 | 3.626 | 1.0017 |
| 29 | 370 ᵃ | 1.059 | 0.2862 | 3.421 | 0.9246 |
| 30 | 339 ᵃ | 1.183 | 0.3490 | 3.622 | 1.0684 |
| Mean | 355.4 | 1.0793 | 0.30442 | 3.5355 | 0.99751 |
| SD | 17.6 | 0.0889 | 0.02995 | 0.2153 | 0.08359 |
| N | 10 | 10 | 10 | 10 | 10 |
| %Diff | -5.2 | -2.8095 | 2.86044 | -3.5913 | 1.85002 |

ᵃ [RC:Value Confirmed]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Organ Weights | | | | |
| Terminal  Body Wt (g) | Epididymis  (g) | Epididymis  (%bw) | Testis  (g) | Testis  (%bw) |
| - | - | - | - | - |
| 31 | 331 ᵃ | 1.150 | 0.3474 | 3.757 | 1.1350 |
| 32 | 341 ᵃ | 1.100 | 0.3226 | 3.865 | 1.1334 |
| 33 | 330 ᵃ | 1.098 | 0.3327 | 3.867 | 1.1718 |
| 34 | 350 ᵃ | 1.101 | 0.3146 | 3.824 | 1.0926 |
| 35 | 324 ᵃ | 1.030 | 0.3179 | 3.474 | 1.0722 |
| 36 | 351 ᵃ | 1.000 | 0.2849 | 3.157 | 0.8994 |
| 37 | 372 ᵃ | 1.150 | 0.3091 | 3.945 | 1.0605 |
| 38 | 333 ᵃ | 1.174 | 0.3526 | 3.722 | 1.1177 |
| 39 | 351 ᵃ | 1.170 | 0.3333 | 3.614 | 1.0296 |
| 40 | 327 ᵃ | 1.129 | 0.3453 | 3.680 | 1.1254 |
| Mean | 341.0 | 1.1102 | 0.32604 | 3.6905 | 1.08377 |
| SD | 15.0 | 0.0578 | 0.02059 | 0.2326 | 0.07703 |
| N | 10 | 10 | 10 | 10 | 10 |
| %Diff | -9.1 | -0.0270 | 10.16497 | 0.6354 | 10.65782 |

ᵃ [RC:Value Confirmed]

|  |  |
| --- | --- |
| 0  ppm Group 1 | Organ Weights |
| Terminal  Body Wt (g) |
| - |
| 41 | 310 |
| 42 | 301 |
| 43 | 287 |
| 44 | 255 |
| 45 | 295 |
| 46 | 325 |
| 47 | 314 |
| 49 | 300 |
| 50 | 278 |
| Mean | 296.1 |
| SD | 20.9 |
| N | 9 |

|  |  |
| --- | --- |
| 12500  ppm Group 2 | Organ Weights |
| Terminal  Body Wt (g) |
| - |
| 51 | 313 |
| 52 | 322 |
| 53 | 273 |
| 54 | 306 |
| 55 | 326 |
| 56 | 289 |
| 57 | 325 |
| 58 | 262 ᵃ |
| 60 | 270 |
| Mean | 298.4 |
| SD | 25.4 |
| N | 9 |
| %Diff | 0.8 |

ᵃ [RC:Value Confirmed]

|  |  |
| --- | --- |
| 25000  ppm Group 3 | Organ Weights |
| Terminal  Body Wt (g) |
| - |
| 61 | 289 |
| 62 | 283 |
| 63 | 274 |
| 64 | 282 |
| 65 | 258 |
| 66 | 268 ᵃ |
| 67 | 286 |
| 68 | 300 |
| 69 | 273 |
| 70 | 291 |
| Mean | 280.4 |
| SD | 12.3 |
| N | 10 |
| %Diff | -5.3 |

ᵃ [RC:Value Confirmed]

|  |  |
| --- | --- |
| 50000  ppm Group 4 | Organ Weights |
| Terminal  Body Wt (g) |
| - |
| 71 | 289 |
| 72 | 229 |
| 73 | 260 |
| 74 | 307 |
| 75 | 284 |
| 76 | 294 |
| 79 | 239 |
| 80 | 256 |
| Mean | 269.8 |
| SD | 27.9 |
| N | 8 |
| %Diff | -8.9 |

|  |  |
| --- | --- |
| 0  ppm Group 1 | Organ Weights |
| Terminal  Body Wt (g) |
| - |
| 48 | 251 |
| Mean SD N | 251.0  -  1 |

|  |  |
| --- | --- |
| 12500  ppm Group 2 | Organ Weights |
| Terminal  Body Wt (g) |
| - |
| 59 | 231 |
| Mean SD N  %Diff | 231.0  -  1  -8.0 |

|  |  |
| --- | --- |
| 50000  ppm Group 4 | Organ Weights |
| Terminal  Body Wt (g) |
| - |
| 77  78 | 224  260 |
| Mean SD N  %Diff | 242.0  25.5  2  -3.6 |

Animal: Species:

1

Rat

Group: Strain:

1

Han Wistar

Sex:

Male

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

2

Rat

Group: Strain:

1

Han Wistar

Sex:

Male

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

3

Rat

Group: Strain:

1

Han Wistar

Sex:

Male

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

4

Rat

Group: Strain:

1

Han Wistar

Sex:

Male

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

5

Rat

Group: Strain:

1

Han Wistar

Sex:

Male

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

6

Rat

Group: Strain:

1

Han Wistar

Sex:

Male

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

7

Rat

Group: Strain:

1

Han Wistar

Sex:

Male

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

8

Rat

Group: Strain:

1

Han Wistar

Sex:

Male

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

9

Rat

Group: Strain:

1

Han Wistar

Sex:

Male

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

10

Rat

Group: Strain:

1

Han Wistar

Sex:

Male

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

11

Rat

Group: Strain:

2

Han Wistar

Sex:

Male

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

12

Rat

Group: Strain:

2

Han Wistar

Sex:

Male

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

13

Rat

Group: Strain:

2

Han Wistar

Sex:

Male

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

14

Rat

Group: Strain:

2

Han Wistar

Sex:

Male

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

15

Rat

Group: Strain:

2

Han Wistar

Sex:

Male

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

16

Rat

Group: Strain:

2

Han Wistar

Sex:

Male

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

17

Rat

Group: Strain:

2

Han Wistar

Sex:

Male

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

18

Rat

Group: Strain:

2

Han Wistar

Sex:

Male

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

19

Rat

Group: Strain:

2

Han Wistar

Sex:

Male

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

20

Rat

Group: Strain:

2

Han Wistar

Sex:

Male

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

21

Rat

Group: Strain:

3

Han Wistar

Sex:

Male

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

22

Rat

Group: Strain:

3

Han Wistar

Sex:

Male

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

23

Rat

Group: Strain:

3

Han Wistar

Sex:

Male

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

24

Rat

Group: Strain:

3

Han Wistar

Sex:

Male

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

25

Rat

Group: Strain:

3

Han Wistar

Sex:

Male

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

26

Rat

Group: Strain:

3

Han Wistar

Sex:

Male

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

27

Rat

Group: Strain:

3

Han Wistar

Sex:

Male

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

28

Rat

Group: Strain:

3

Han Wistar

Sex:

Male

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

29

Rat

Group: Strain:

3

Han Wistar

Sex:

Male

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

30

Rat

Group: Strain:

3

Han Wistar

Sex:

Male

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

31

Rat

Group: Strain:

4

Han Wistar

Sex:

Male

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

32

Rat

Group: Strain:

4

Han Wistar

Sex:

Male

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

33

Rat

Group: Strain:

4

Han Wistar

Sex:

Male

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

34

Rat

Group: Strain:

4

Han Wistar

Sex:

Male

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

SPLEEN : Enlargement (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

SPLEEN : Congestion; diffuse, mild [SPLEEN : Enlargement (G)] SPLEEN : Hematopoietic cells, increased; mild

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

35

Rat

Group: Strain:

4

Han Wistar

Sex:

Male

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

36

Rat

Group: Strain:

4

Han Wistar

Sex:

Male

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

37

Rat

Group: Strain:

4

Han Wistar

Sex:

Male

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

38

Rat

Group: Strain:

4

Han Wistar

Sex:

Male

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

39

Rat

Group: Strain:

4

Han Wistar

Sex:

Male

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

40

Rat

Group: Strain:

4

Han Wistar

Sex:

Male

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

29 (5)

Animal Comment: Tissues submitted in 10% neutral buffered formalin, except testis and epididymis submitted in modified Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

EPIDIDYMIS; TESTIS

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

41

Rat

Group: Strain:

1

Han Wistar

Sex:

Female

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

42

Rat

Group: Strain:

1

Han Wistar

Sex:

Female

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

43

Rat

Group: Strain:

1

Han Wistar

Sex:

Female

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

63 (9)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

NO CORRELATE : No correlating lesion

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

44

Rat

Group: Strain:

1

Han Wistar

Sex:

Female

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

53 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

45

Rat

Group: Strain:

1

Han Wistar

Sex:

Female

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

46

Rat

Group: Strain:

1

Han Wistar

Sex:

Female

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

53 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

47

Rat

Group: Strain:

1

Han Wistar

Sex:

Female

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

48

Rat

Group: Strain:

1

Han Wistar

Sex:

Female

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

52 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

49

Rat

Group: Strain:

1

Han Wistar

Sex:

Female

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

52 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

50

Rat

Group: Strain:

1

Han Wistar

Sex:

Female

Dose: 0 ppm Group 1

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

53 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

51

Rat

Group: Strain:

2

Han Wistar

Sex:

Female

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

52

Rat

Group: Strain:

2

Han Wistar

Sex:

Female

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

51 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

53

Rat

Group: Strain:

2

Han Wistar

Sex:

Female

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

52 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

54

Rat

Group: Strain:

2

Han Wistar

Sex:

Female

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

53 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

55

Rat

Group: Strain:

2

Han Wistar

Sex:

Female

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

56

Rat

Group: Strain:

2

Han Wistar

Sex:

Female

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

53 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

57

Rat

Group: Strain:

2

Han Wistar

Sex:

Female

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

58

Rat

Group: Strain:

2

Han Wistar

Sex:

Female

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

52 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

59

Rat

Group: Strain:

2

Han Wistar

Sex:

Female

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

43 (7)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

60

Rat

Group: Strain:

2

Han Wistar

Sex:

Female

Dose: 12500 ppm Group 2

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

53 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

61

Rat

Group: Strain:

3

Han Wistar

Sex:

Female

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

53 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

62

Rat

Group: Strain:

3

Han Wistar

Sex:

Female

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

63

Rat

Group: Strain:

3

Han Wistar

Sex:

Female

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

51 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

64

Rat

Group: Strain:

3

Han Wistar

Sex:

Female

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

52 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

65

Rat

Group: Strain:

3

Han Wistar

Sex:

Female

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

66

Rat

Group: Strain:

3

Han Wistar

Sex:

Female

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

52 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

67

Rat

Group: Strain:

3

Han Wistar

Sex:

Female

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

52 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

68

Rat

Group: Strain:

3

Han Wistar

Sex:

Female

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

69

Rat

Group: Strain:

3

Han Wistar

Sex:

Female

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

52 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

70

Rat

Group: Strain:

3

Han Wistar

Sex:

Female

Dose: 25000 ppm Group 3

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

71

Rat

Group: Strain:

4

Han Wistar

Sex:

Female

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

72

Rat

Group: Strain:

4

Han Wistar

Sex:

Female

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

73

Rat

Group: Strain:

4

Han Wistar

Sex:

Female

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

74

Rat

Group: Strain:

4

Han Wistar

Sex:

Female

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

53 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

75

Rat

Group: Strain:

4

Han Wistar

Sex:

Female

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

76

Rat

Group: Strain:

4

Han Wistar

Sex:

Female

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

77

Rat

Group: Strain:

4

Han Wistar

Sex:

Female

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

43 (7)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

SKIN : Thin hair coat; forelimb, left (TGL) SKIN : Thin hair coat; forelimb, right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

78

Rat

Group: Strain:

4

Han Wistar

Sex:

Female

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

43 (7)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

CERVIX : Enlargement (TGL) CERVIX : Fluid accumulation, pale UTERUS : Enlargement (TGL) UTERUS : Fluid accumulation, pale

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

79

Rat

Group: Strain:

4

Han Wistar

Sex:

Female

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

56 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

Animal: Species:

80

Rat

Group: Strain:

4

Han Wistar

Sex:

Female

Dose: 50000 ppm Group 4

Removal Reason: Terminal Euthanasia

###### Gross Pathology Animal Details:

Study Day (Week) of Death:

53 (8)

Animal Comment: Tissues submitted in 10% neutral buffered formalin

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

###### Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

###### Gross Pathology - The following Tissues were Not Examined:

None

###### Histopathology Animal Details:

No animal details found

###### Histopathology Observations [Correlation]:

No observations found

###### Histopathology - The following Tissues were Within Normal Limits:

None

###### Histopathology - The following Tissues were Not Examined:

None

#### FINAL REPORT

**Study Phase: Pathology Test Facility Study No. 20334125**

#### TEST FACILITY:

Charles River Laboratories Den Bosch B.V. Hambakenwetering 7

5231 DD ‘s-Hertogenbosch The Netherlands

**Page 1 of 8**

#### TABLE OF CONTENTS

1. [SUMMARY 3](#_bookmark183)
2. [INTRODUCTION 4](#_bookmark184)
3. [STUDY DESIGN 4](#_bookmark185)
4. [METHODS 4](#_bookmark186)
   1. [Macroscopic Examination 4](#_bookmark187)
   2. [Organ Weights 5](#_bookmark188)
   3. [Microscopic Examination 5](#_bookmark189)
5. [RESULTS 6](#_bookmark190)
   1. [Mortality 6](#_bookmark191)
   2. [Macroscopic Findings 6](#_bookmark192)
   3. [Organ Weights 6](#_bookmark193)
   4. [Microscopic Findings 6](#_bookmark194)
6. [CONCLUSIONS 7](#_bookmark195)
7. [REPORT AUTHENTICATION 8](#_bookmark196)

Test Facility Study No. 20334125 Page 2

#### SUMMARY

Pathomorphologic examination was performed on 80 Wistar (Han) rats (40 males, 40 females) which had been subjected to a dose range finder for the extended one-generation reproductive toxicity Study with the test material **Code 10 (SF-002)** by dietary administration.

The rats were assigned to four dose groups, each containing 10 males and 10 females. The test material was administered daily by dietary administration at target doses of 12500, 25000 and 50000 ppm (dose Groups 2, 3 and 4 respectively). The test material was administered for at least 28 days from at least 14 days prior to mating, during mating and up to the day prior to necropsy. The rats of the control Group 1 received only standard powder rodent diet with propylene glycol without test material.

At the end of the Treatment Period all rats from all groups were sacrificed and subjected to complete necropsies. Histopathologic examination was performed on testes and epididymides from all control group and 50000 ppm treated animals and all organs with macroscopic findings from all rats.

There were no unscheduled deaths.

There were no test material-related macroscopic testes and epididymides findings. There were no test material-related testes and epididymides weight changes.

There were no test material-related microscopic testes and epididymides findings.

There were no test material-related morphologic alterations in the testes and epididymides following the dietary administration of Code 10 (SF-002) for at least 28 days to male rats treated up to 50000 ppm.

Stage aware evaluation of the testes did not show any indication for abnormal spermatogenesis.

Test Facility Study No. 20334125 Page 3

#### INTRODUCTION

The objective of this study was to provide information for the selection of dose levels for an extended one-generation reproductive toxicity study in rats.

This pathology report addresses the anatomical pathology endpoints of the study. It is based on the study plan and any study plan amendment.

#### STUDY DESIGN

Wistar (Han) rats, males approximately 10-12 weeks of age and females approximately 12-14 weeks of age (for exact details see Main study report) on Treatment Day 1, were administered test material via oral gavage daily from 2 weeks prior to mating, during mating, and up to the day prior to necropsy for at least 28 days as indicated in the following table.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Group No. | Dose level | | Number of Animals | | Animal Numbers | |
| mg/kg  bw/day | ppm | Males | Females | Males | Females |
| 1 | 0 a | 0 | 10 | 10 | 1-10 | 41-50 |
| 2 | 800 | 12500 | 10 | 10 | 11-20 | 51-60 |
| 3 | 1600 | 25000 | 10 | 10 | 21-30 | 61-70 |
| 4 | 3300 | 50000 | 10 | 10 | 31-40 | 71-80 |

a The control group received only standard powder rodent diet with propylene glycol without test material.

#### METHODS

##### Macroscopic Examination

Complete postmortem examinations were performed on all animals. Animals were anesthetized using isoflurane and subsequently exsanguinated. At the time of necropsy, the following tissues and organs were collected and placed in 10% neutral-buffered formalin fixative or Modified Davidson solution:

##### Tissue Weighing, Collection, Processing and Evaluation Table

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Tissue** | **Weigh** | **Collect** | **Histology** | **Microscopic Evaluation** |
| Animal identification | - | $ | - | - |
| Cervix | - | $ | - | - |
| Epididymis | $ (2) | $ (2) | $ (2) | $ (2) |
| Gland, mammary | - | $ | - | - |
| Gland, parathyroid | - | $ (2) | - | - |
| Gland, pituitary | - | $ | - | - |
| Gland, prostate | - | $ | - | - |
| Gland, seminal vesicle including coagulation gland and fluid | - | $ (2) | - | - |
| Gland, thyroid | - | $ (2) | - | - |
| Ovaries | - | $ (2) | - | - |
| Testes | $ (2) | $ (2) | $ (2) b | $ (2) b |
| Uterus | - | $ | - | - |
| Vagina | - | $ | - | - |

- = Not applicable; (1) = one side. (2) = both sides.

$ = Procedure was conducted for all animals;

Macroscopic abnormalities in the organs listed and in other organs were sampled at necropsy, processed for histology and examined microscopically.

Test Facility Study No. 20334125 Page 4

b For the testes of all males of Groups 1 and 4 detailed qualitative examination was made, taking into account the tubular stages of the spermatogenic cycle. The examination was conducted in order to identify treatment related effects such as missing germ cell layers or types, retained spermatids, multinucleate or apoptotic germ cells and sloughing of spermatogenic cells into the lumen. Any cell- or stage-specificity of testicular findings were noted.

##### Organ Weights

The organ weights (and terminal body weight) were recorded from all animals at the scheduled necropsy as indicated in the table above.

Paired organs were weighed together. Absolute organ weights were reported and organ weights as a percentage of terminal body weight were calculated and presented in the Main study report.

In the discussion of organ weights, statistical significance refers to the p ≤ 0.05 level. The discussion of organ weights refers to group mean values unless stated otherwise.

##### Microscopic Examination

Microscopic examination of routinely prepared hematoxylin-eosin stained paraffin sections was performed on testes and epididymides collected at necropsy from all control group and

50000 ppm treated males.

A detailed qualitative evaluation of the testis was conducted on H&E stained sections from all control and high dose animals. Testes were evaluated to assess the progression of stages of the spermatogenic cycle, cell associations, and proportions expected to be present during spermatogenesis along with assessment of interstitial and supporting cell types (Leydig cells, macrophages, vasculature, and rete testis). Any cell- or stage-specificity of testicular findings were noted.

Gross lesions were examined from all animals and correlated to microscopic findings if possible.

The animal data and macroscopic findings were electronically recorded in the Provantis® computer system. Stained histologic sections were examined by light microscopy on 27 July 2022 and the microscopic findings were recorded by the undersigned pathologist using on-line input.

Severity grades were assigned to non-neoplastic histopathologic diagnoses. Severity grades were assigned based on the severity of alterations in the examined histologic sections and may not reflect the overall severity of the pathologic process in the entire tissue, organ, or animal. The Provantis® histopathology tables contain all of the recorded data and serve as the basis for this narrative report.

In the separate pathology tables file, all macroscopic and microscopic findings are given for each animal in text form under "Individual Macroscopic and Microscopic Pathology". The incidence of microscopic findings is also presented in tabular form: “Summary of Microscopic Pathology”. Incidence tables were created by computer.

Histopathological changes were described according to distribution, severity (minimal, mild, moderate, marked, severe) and morphological character. The International Harmonization of Nomenclature and Diagnostic Criteria for Lesions (INHAND) was used as guidance for the description of histopathological changes.

Test Facility Study No. 20334125 Page 5

#### RESULTS

##### Mortality

There were no premature decedents in the study.

##### Macroscopic Findings

There were no test material-related gross observations.

All of the recorded macroscopic findings were within the range of background gross observations encountered in rats of this age and strain.

##### Organ Weights

There were no test material-related alterations in organ weights.

The testes and epididymides weights (relative to body weight) were statistically significant higher at 50000 ppm, when compared to the control group but were considered to be the result of a test material-related effect on the final body weight which was statistically significant lower.

##### Microscopic Findings

There were no test material-related microscopic observations.

All of the recorded microscopic findings were within the range of background pathology encountered in rats of this age and strain. There was no test material-related alteration in the prevalence, severity, or histologic character of those incidental tissue alterations.

Stage dependent qualitative evaluation of spermatogenesis in the testis was performed. The testis revealed normal progression of the spermatogenic cycle and the expected cell associations and proportions in the various stages of spermatogenesis were present.

Test Facility Study No. 20334125 Page 6

#### CONCLUSIONS

There were no test material-related morphologic alterations in the testes and epididymides following the dietary administration of Code 10 (SF-002) for at least 28 days to male rats treated up to 50000 ppm.

Stage aware evaluation of the testes did not show any indication for abnormal spermatogenesis.

Test Facility Study No. 20334125 Page 7

#### REPORT AUTHENTICATION

I, the undersigned, was responsible for the histopathology evaluation and reporting of the pathology data. The histopathology data in this report were compiled by me, and they reflect accurately the primary data records. Histopathology tables were created in Provantis® under number 20334125.

Project 20334125 Pathology Report Report Submitted By:

Joost Lensen, PhD

Dutch CRP/TP Certified Toxicologic Pathologist Study Pathologist

All electronic signatures appear at the end of this Phase Report upon finalization.

Test Facility Study No. 20334125 Page 8



**Individual Scientist:**

I approve this document.

Name:

**Lensen, Joost**

Lensen, Joost

Electronically Signed in

02-Mar-2023 08:56:44 (UTC+00:00)

Timestamp

**SIGNATURE(S) FOR DOCUMENT: 20334125 - 20334125 Histopathology Final Report**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 |  |  |  |  |  |
| Pairing  Male | 1st Pairing  Date | Confirmed  Mating Date | Pre-coital  Interval (Days) | Pregnancy  Type |
| - | - | - | - | - |
| 41 | 1 | 28-Jun-2022 | 02-Jul-2022 | 4 | - |
| 42 | 2 | 28-Jun-2022 | 02-Jul-2022 | 4 | - |
| 43 | 3 | 28-Jun-2022 | 11-Jul-2022 | 13 | - |
| 44 | 4 | 28-Jun-2022 | 30-Jun-2022 | 2 | - |
| 45 | 5 | 28-Jun-2022 | 02-Jul-2022 | 4 | - |
| 46 | 6 | 28-Jun-2022 | 30-Jun-2022 | 2 | - |
| 47 | 7 | 28-Jun-2022 | 01-Jul-2022 | 3 | - |
| 48 NM | 8 | 28-Jun-2022 | - | - | Not Pregnant |
| 49 | 9 | 28-Jun-2022 | 30-Jun-2022 | 2 | - |
| 50 | 10 | 28-Jun-2022 | 30-Jun-2022 | 2 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 |  |  |  |  |  |
| Pairing  Male | 1st Pairing  Date | Confirmed  Mating Date | Pre-coital  Interval (Days) | Pregnancy  Type |
| - | - | - | - | - |
| 51 | 11 | 28-Jun-2022 | 01-Jul-2022 | 3 | - |
| 52 | 12 | 28-Jun-2022 | 29-Jun-2022 | 1 | - |
| 53 | 13 | 28-Jun-2022 | 29-Jun-2022 | 1 | - |
| 54 | 14 | 28-Jun-2022 | 01-Jul-2022 | 3 | - |
| 55 | 15 | 28-Jun-2022 | 01-Jul-2022 | 3 | - |
| 56 | 16 | 28-Jun-2022 | 30-Jun-2022 | 2 | - |
| 57 | 17 | 28-Jun-2022 | 02-Jul-2022 | 4 | - |
| 58 | 18 | 28-Jun-2022 | 29-Jun-2022 | 1 | - |
| 59 | 19 | 28-Jun-2022 | 01-Jul-2022 | 3 | Not Pregnant |
| 60 | 20 | 28-Jun-2022 | 30-Jun-2022 | 2 | - |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 25000  ppm Group 3 |  |  |  |  |
| Pairing  Male | 1st Pairing  Date | Confirmed  Mating Date | Pre-coital  Interval (Days) |
| - | - | - | - |
| 61 | 21 | 28-Jun-2022 | 30-Jun-2022 | 2 |
| 62 | 22 | 28-Jun-2022 | 02-Jul-2022 | 4 |
| 63 | 23 | 28-Jun-2022 | 29-Jun-2022 | 1 |
| 64 | 24 | 28-Jun-2022 | 30-Jun-2022 | 2 |
| 65 | 25 | 28-Jun-2022 | 02-Jul-2022 | 4 |
| 66 | 26 | 28-Jun-2022 | 29-Jun-2022 | 1 |
| 67 | 27 | 28-Jun-2022 | 30-Jun-2022 | 2 |
| 68 | 28 | 28-Jun-2022 | 02-Jul-2022 | 4 |
| 69 | 29 | 28-Jun-2022 | 29-Jun-2022 | 1 |
| 70 | 30 | 28-Jun-2022 | 02-Jul-2022 | 4 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 |  |  |  |  |  |
| Pairing  Male | 1st Pairing  Date | Confirmed  Mating Date | Pre-coital  Interval (Days) | Pregnancy  Type |
| - | - | - | - | - |
| 71 | 31 | 28-Jun-2022 | 02-Jul-2022 | 4 | - |
| 72 | 32 | 28-Jun-2022 | 01-Jul-2022 | 3 | - |
| 73 | 33 | 28-Jun-2022 | 02-Jul-2022 | 4 | - |
| 74 | 34 | 28-Jun-2022 | 01-Jul-2022 | 3 | - |
| 75 | 35 | 28-Jun-2022 | 02-Jul-2022 | 4 | - |
| 76 | 36 | 28-Jun-2022 | 01-Jul-2022 | 3 | - |
| 77 | 37 | 28-Jun-2022 | 01-Jul-2022 | 3 | Not Pregnant |
| 78 | 38 | 28-Jun-2022 | 29-Jun-2022 | 1 | Not Pregnant |
| 79 | 39 | 28-Jun-2022 | 01-Jul-2022 | 3 | - |
| 80 | 40 | 28-Jun-2022 | 30-Jun-2022 | 2 | - |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 |  |  |  |  |  |  |  |
| Total Number  Newborn Pups | Number Live  Newborn Pups | Live Birth  Index (%) | Number Pups  Stillborn | Stillborn  Pups/Litter (%) | Post Implant  Loss/Litter (%) | Live Male  Pups/Litter (%) |
| Birth | Birth | Birth | Birth | Birth | - | Birth |
| 41 | 12 | 12 | 100.0 | 0 | 0.0 | 0.0 | 58.3 |
| 42 | 10 | 10 | 100.0 | 0 | 0.0 | 16.7 | 30.0 |
| 43 | 12 | 12 | 100.0 | 0 | 0.0 | 7.7 | 33.3 |
| 44 | 11 | 11 | 100.0 | 0 | 0.0 | 15.4 | 72.7 |
| 45 | 15 | 15 | 100.0 | 0 | 0.0 | 0.0 | 60.0 |
| 46 | 11 | 11 | 100.0 | 0 | 0.0 | 15.4 | 72.7 |
| 47 | 12 | 12 | 100.0 | 0 | 0.0 | 20.0 | 25.0 |
| 49 | 13 | 13 | 100.0 | 0 | 0.0 | 0.0 | 61.5 |
| 50 | 9 | 9 | 100.0 | 0 | 0.0 | 30.8 | 33.3 |
| Mean | 11.7 | 11.7 | 100.00 | 0.0 | 0.00 | 11.77 | 49.67 |
| SD | 1.7 | 1.7 | 0.00 | 0.0 | 0.00 | 10.67 | 19.09 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |
| --- | --- | --- | --- |
| 0  ppm Group 1 |  |  |  |
| Implants  -Total | Gestation  Length (Days) | Litter Date |
| - | - | - |
| 41 | 12 | 22 | 24-Jul-2022 |
| 42 | 12 | 21 | 23-Jul-2022 |
| 43 | 13 | 21 | 01-Aug-2022 |
| 44 | 13 | 22 | 22-Jul-2022 |
| 45 | 15 | 22 | 24-Jul-2022 |
| 46 | 13 | 22 | 22-Jul-2022 |
| 47 | 15 | 22 | 23-Jul-2022 |
| 49 | 13 | 21 | 21-Jul-2022 |
| 50 | 13 | 22 | 22-Jul-2022 |
| Mean | 13.2 | 21.7 | - |
| SD | 1.1 | 0.5 | - |
| N | 9 | 9 | - |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 |  |  |  |  |  |  |  |
| Total Number  Newborn Pups | Number Live  Newborn Pups | Live Birth  Index (%) | Number Pups  Stillborn | Stillborn  Pups/Litter (%) | Post Implant  Loss/Litter (%) | Live Male  Pups/Litter (%) |
| Birth | Birth | Birth | Birth | Birth | - | Birth |
| 51 | 13 | 13 | 100.0 | 0 | 0.0 | 0.0 | 53.8 |
| 52 | 7 | 7 | 100.0 | 0 | 0.0 | 12.5 | 42.9 |
| 53 | 10 | 10 | 100.0 | 0 | 0.0 | 0.0 | 70.0 |
| 54 | 11 | 11 | 100.0 | 0 | 0.0 | 26.7 | 54.5 |
| 55 | 9 | 9 | 100.0 | 0 | 0.0 | 10.0 | 44.4 |
| 56 | 10 | 10 | 100.0 | 0 | 0.0 | 16.7 | 70.0 |
| 57 | 11 | 11 | 100.0 | 0 | 0.0 | 21.4 | 72.7 |
| 58 | 10 | 10 | 100.0 | 0 | 0.0 | 9.1 | 20.0 |
| 60 | 8 | 8 | 100.0 | 0 | 0.0 | 11.1 | 75.0 |
| Mean | 9.9 | 9.9 | 100.00 | 0.0 | 0.00 | 11.94 | 55.94 |
| SD | 1.8 | 1.8 | 0.00 | 0.0 | 0.00 | 8.85 | 18.17 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |
| --- | --- | --- | --- |
| 12500  ppm Group 2 |  |  |  |
| Implants  -Total | Gestation  Length (Days) | Litter Date |
| - | - | - |
| 51 | 13 | 22 | 23-Jul-2022 |
| 52 | 8 | 21 | 20-Jul-2022 |
| 53 | 10 | 22 | 21-Jul-2022 |
| 54 | 15 | 21 | 22-Jul-2022 |
| 55 | 10 | 22 | 23-Jul-2022 |
| 56 | 12 | 22 | 22-Jul-2022 |
| 57 | 14 | 22 | 24-Jul-2022 |
| 58 | 11 | 22 | 21-Jul-2022 |
| 60 | 9 | 22 | 22-Jul-2022 |
| Mean | 11.3 | 21.8 | - |
| SD | 2.3 | 0.4 | - |
| N | 9 | 9 | - |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 |  |  |  |  |  |  |  |
| Total Number  Newborn Pups | Number Live  Newborn Pups | Live Birth  Index (%) | Number Pups  Stillborn | Stillborn  Pups/Litter (%) | Post Implant  Loss/Litter (%) | Live Male  Pups/Litter (%) |
| Birth | Birth | Birth | Birth | Birth | - | Birth |
| 61 | 13 | 13 | 100.0 | 0 | 0.0 | 13.3 | 15.4 |
| 62 | 13 | 13 | 100.0 | 0 | 0.0 | 0.0 | 53.8 |
| 63 | 14 | 14 | 100.0 | 0 | 0.0 | 0.0 | 50.0 |
| 64 | 13 | 13 | 100.0 | 0 | 0.0 | 0.0 | 38.5 |
| 65 | 11 | 11 | 100.0 | 0 | 0.0 | 15.4 | 72.7 |
| 66 | 9 | 9 | 100.0 | 0 | 0.0 | 10.0 | 55.6 |
| 67 | 10 | 9 | 90.0 | 1 | 10.0 | 23.1 | 44.4 |
| 68 | 14 | 14 | 100.0 | 0 | 0.0 | 12.5 | 42.9 |
| 69 | 9 | 9 | 100.0 | 0 | 0.0 | 10.0 | 22.2 |
| 70 | 14 | 14 | 100.0 | 0 | 0.0 | -7.7 | 78.6 |
| Mean | 12.0 | 11.9 | 99.00 | 0.1 | 1.00 | 7.66 | 47.41 |
| SD | 2.1 | 2.2 | 3.16 | 0.3 | 3.16 | 9.28 | 19.71 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

|  |  |  |  |
| --- | --- | --- | --- |
| 25000  ppm Group 3 |  |  |  |
| Implants  -Total | Gestation  Length (Days) | Litter Date |
| - | - | - |
| 61 | 15 | 22 | 22-Jul-2022 |
| 62 | 13 | 21 | 23-Jul-2022 |
| 63 | 14 | 21 | 20-Jul-2022 |
| 64 | 13 | 21 | 21-Jul-2022 |
| 65 | 13 | 22 | 24-Jul-2022 |
| 66 | 10 | 22 | 21-Jul-2022 |
| 67 | 13 | 21 | 21-Jul-2022 |
| 68 | 16 | 22 | 24-Jul-2022 |
| 69 | 10 | 22 | 21-Jul-2022 |
| 70 | 13 | 21 | 23-Jul-2022 |
| Mean | 13.0 | 21.5 | - |
| SD | 1.9 | 0.5 | - |
| N | 10 | 10 | - |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 |  |  |  |  |  |  |  |
| Total Number  Newborn Pups | Number Live  Newborn Pups | Live Birth  Index (%) | Number Pups  Stillborn | Stillborn  Pups/Litter (%) | Post Implant  Loss/Litter (%) | Live Male  Pups/Litter (%) |
| Birth | Birth | Birth | Birth | Birth | - | Birth |
| 71 | 12 | 12 | 100.0 | 0 | 0.0 | -9.1 | 41.7 |
| 72 | 10 | 10 | 100.0 | 0 | 0.0 | 9.1 | 50.0 |
| 73 | 10 | 10 | 100.0 | 0 | 0.0 | 16.7 | 60.0 |
| 74 | 14 | 14 | 100.0 | 0 | 0.0 | 6.7 | 71.4 |
| 75 | 12 | 12 | 100.0 | 0 | 0.0 | 7.7 | 58.3 |
| 76 | 13 | 13 | 100.0 | 0 | 0.0 | 0.0 | 46.2 |
| 79 | 10 | 10 | 100.0 | 0 | 0.0 | 9.1 | 40.0 |
| 80 | 9 | 9 | 100.0 | 0 | 0.0 | 18.2 | 55.6 |
| Mean | 11.3 | 11.3 | 100.00 | 0.0 | 0.00 | 7.29 | 52.89 |
| SD | 1.8 | 1.8 | 0.00 | 0.0 | 0.00 | 8.74 | 10.53 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

|  |  |  |  |
| --- | --- | --- | --- |
| 50000  ppm Group 4 |  |  |  |
| Implants  -Total | Gestation  Length (Days) | Litter Date |
| - | - | - |
| 71 | 11 | 21 | 23-Jul-2022 |
| 72 | 11 | 22 | 23-Jul-2022 |
| 73 | 12 | 22 | 24-Jul-2022 |
| 74 | 15 | 21 | 22-Jul-2022 |
| 75 | 13 | 21 | 23-Jul-2022 |
| 76 | 13 | 22 | 23-Jul-2022 |
| 79 | 11 | 22 | 23-Jul-2022 |
| 80 | 11 | 22 | 22-Jul-2022 |
| Mean | 12.1 | 21.6 | - |
| SD | 1.5 | 0.5 | - |
| N | 8 | 8 | - |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 |  |  |  |  |  |  |  |
| Live Pups  on Day 1 | Live Males  on Day 1 | Live Females  on Day 1 | Live Pups  on Day 4 | Live Males  on Day 4 | Live Females  on Day 4 | Live Pups  Postcull |
| - | - | - | - | - | - | 4 |
| 41 | 12 | 7 | 5 | 12 | 7 | 5 | 8 |
| 42 | 10 | 3 | 7 | 10 | 3 | 7 | 8 |
| 43 | 12 | 4 | 8 | 12 | 4 | 8 | 8 |
| 44 | 11 | 8 | 3 | 11 | 8 | 3 | 8 |
| 45 | 15 | 9 | 6 | 15 | 9 | 6 | 8 |
| 46 | 11 | 8 | 3 | 11 | 8 | 3 | 8 |
| 47 | 12 | 3 | 9 | 12 | 3 | 9 | 8 |
| 49 | 13 | 8 | 5 | 13 | 8 | 5 | 8 |
| 50 | 9 | 3 | 6 | 9 | 3 | 6 | 8 |
| Mean | 11.7 | 5.9 | 5.8 | 11.7 | 5.9 | 5.8 | 8.0 |
| SD | 1.7 | 2.6 | 2.0 | 1.7 | 2.6 | 2.0 | 0.0 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 |  |  |  |  |  |  |  |
| Postcull  Live Males | Postcull  Live Females | Live Pups  on Day 7 | Live Males  on Day 7 | Live Females  on Day 7 | Live Pups  on Day 10 | Live Males  on Day 10 |
| 4 | 4 | - | - | - | - | - |
| 41 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 42 | 3 | 5 | 8 | 3 | 5 | 8 | 3 |
| 43 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 44 | 5 | 3 | 8 | 5 | 3 | 8 | 5 |
| 45 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 46 | 5 | 3 | 8 | 5 | 3 | 8 | 5 |
| 47 | 3 | 5 | 8 | 3 | 5 | 8 | 3 |
| 49 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 50 | 3 | 5 | 8 | 3 | 5 | 8 | 3 |
| Mean | 3.9 | 4.1 | 8.0 | 3.9 | 4.1 | 8.0 | 3.9 |
| SD | 0.8 | 0.8 | 0.0 | 0.8 | 0.8 | 0.0 | 0.8 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 |  |  |  |  |  |  |  |
| Live Females  on Day 10 | Live Pups  on Day 13 | Live Males  on Day 13 | Live Females  on Day 13 | Viability  Index (%) | Survival  4Postcull-7 (%) | Survival  4Postcull-13 (%) |
| - | - | - | - | Birth-4 | - | - |
| 41 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 42 | 5 | 8 | 3 | 5 | 100.0 | 100.0 | 100.0 |
| 43 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 44 | 3 | 8 | 5 | 3 | 100.0 | 100.0 | 100.0 |
| 45 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 46 | 3 | 8 | 5 | 3 | 100.0 | 100.0 | 100.0 |
| 47 | 5 | 8 | 3 | 5 | 100.0 | 100.0 | 100.0 |
| 49 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 50 | 5 | 8 | 3 | 5 | 100.0 | 100.0 | 100.0 |
| Mean | 4.1 | 8.0 | 3.9 | 4.1 | 100.00 | 100.00 | 100.00 |
| SD | 0.8 | 0.0 | 0.8 | 0.8 | 0.00 | 0.00 | 0.00 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

|  |  |  |
| --- | --- | --- |
| 0  ppm Group 1 |  | |
| Live Male  Pups/Litter (%) | Live Male  Pups/Litter (%) |
| 1 | 13 |
| 41 | 58.3 | 50.0 |
| 42 | 30.0 | 37.5 |
| 43 | 33.3 | 50.0 |
| 44 | 72.7 | 62.5 |
| 45 | 60.0 | 50.0 |
| 46 | 72.7 | 62.5 |
| 47 | 25.0 | 37.5 |
| 49 | 61.5 | 50.0 |
| 50 | 33.3 | 37.5 |
| Mean | 49.67 | 48.61 |
| SD | 19.09 | 9.77 |
| N | 9 | 9 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 |  |  |  |  |  |  |  |
| Live Pups  on Day 1 | Live Males  on Day 1 | Live Females  on Day 1 | Live Pups  on Day 4 | Live Males  on Day 4 | Live Females  on Day 4 | Live Pups  Postcull |
| - | - | - | - | - | - | 4 |
| 51 | 13 | 7 | 6 | 13 | 7 | 6 | 8 |
| 52 | 7 | 3 | 4 | 7 | 3 | 4 | 7 |
| 53 | 10 | 7 | 3 | 10 | 7 | 3 | 8 |
| 54 | 11 | 6 | 5 | 11 | 6 | 5 | 8 |
| 55 | 9 | 4 | 5 | 9 | 4 | 5 | 8 |
| 56 | 10 | 7 | 3 | 10 | 7 | 3 | 8 |
| 57 | 11 | 8 | 3 | 10 | 7 | 3 | 8 |
| 58 | 10 | 2 | 8 | 10 | 2 | 8 | 8 |
| 60 | 8 | 6 | 2 | 8 | 6 | 2 | 8 |
| Mean | 9.9 | 5.6 | 4.3 | 9.8 | 5.4 | 4.3 | 7.9 |
| SD | 1.8 | 2.1 | 1.9 | 1.7 | 1.9 | 1.9 | 0.3 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 |  |  |  |  |  |  |  |
| Postcull  Live Males | Postcull  Live Females | Live Pups  on Day 7 | Live Males  on Day 7 | Live Females  on Day 7 | Live Pups  on Day 10 | Live Males  on Day 10 |
| 4 | 4 | - | - | - | - | - |
| 51 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 52 | 3 | 4 | 7 | 3 | 4 | 7 | 3 |
| 53 | 5 | 3 | 8 | 5 | 3 | 8 | 5 |
| 54 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 55 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 56 | 5 | 3 | 8 | 5 | 3 | 8 | 5 |
| 57 | 5 | 3 | 8 | 5 | 3 | 8 | 5 |
| 58 | 2 | 6 | 8 | 2 | 6 | 8 | 2 |
| 60 | 6 | 2 | 8 | 6 | 2 | 8 | 6 |
| Mean | 4.2 | 3.7 | 7.9 | 4.2 | 3.7 | 7.9 | 4.2 |
| SD | 1.2 | 1.1 | 0.3 | 1.2 | 1.1 | 0.3 | 1.2 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 |  |  |  |  |  |  |  |
| Live Females  on Day 10 | Live Pups  on Day 13 | Live Males  on Day 13 | Live Females  on Day 13 | Viability  Index (%) | Survival  4Postcull-7 (%) | Survival  4Postcull-13 (%) |
| - | - | - | - | Birth-4 | - | - |
| 51 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 52 | 4 | 7 | 3 | 4 | 100.0 | 100.0 | 100.0 |
| 53 | 3 | 8 | 5 | 3 | 100.0 | 100.0 | 100.0 |
| 54 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 55 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 56 | 3 | 8 | 5 | 3 | 100.0 | 100.0 | 100.0 |
| 57 | 3 | 8 | 5 | 3 | 90.9 | 100.0 | 100.0 |
| 58 | 6 | 8 | 2 | 6 | 100.0 | 100.0 | 100.0 |
| 60 | 2 | 8 | 6 | 2 | 100.0 | 100.0 | 100.0 |
| Mean | 3.7 | 7.9 | 4.2 | 3.7 | 98.99 | 100.00 | 100.00 |
| SD | 1.1 | 0.3 | 1.2 | 1.1 | 3.03 | 0.00 | 0.00 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

|  |  |  |
| --- | --- | --- |
| 12500  ppm Group 2 |  | |
| Live Male  Pups/Litter (%) | Live Male  Pups/Litter (%) |
| 1 | 13 |
| 51 | 53.8 | 50.0 |
| 52 | 42.9 | 42.9 |
| 53 | 70.0 | 62.5 |
| 54 | 54.5 | 50.0 |
| 55 | 44.4 | 50.0 |
| 56 | 70.0 | 62.5 |
| 57 | 72.7 | 62.5 |
| 58 | 20.0 | 25.0 |
| 60 | 75.0 | 75.0 |
| Mean | 55.94 | 53.37 |
| SD | 18.17 | 14.44 |
| N | 9 | 9 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 |  |  |  |  |  |  |  |
| Live Pups  on Day 1 | Live Males  on Day 1 | Live Females  on Day 1 | Live Pups  on Day 4 | Live Males  on Day 4 | Live Females  on Day 4 | Live Pups  Postcull |
| - | - | - | - | - | - | 4 |
| 61 | 13 | 2 | 11 | 13 | 2 | 11 | 8 |
| 62 | 13 | 7 | 6 | 13 | 7 | 6 | 8 |
| 63 | 14 | 7 | 7 | 14 | 7 | 7 | 8 |
| 64 | 13 | 5 | 8 | 13 | 5 | 8 | 8 |
| 65 | 11 | 8 | 3 | 11 | 8 | 3 | 8 |
| 66 | 9 | 5 | 4 | 9 | 5 | 4 | 8 |
| 67 | 9 | 4 | 5 | 9 | 4 | 5 | 8 |
| 68 | 14 | 6 | 8 | 14 | 6 | 8 | 8 |
| 69 | 9 | 2 | 7 | 9 | 2 | 7 | 8 |
| 70 | 14 | 11 | 3 | 14 | 11 | 3 | 8 |
| Mean | 11.9 | 5.7 | 6.2 | 11.9 | 5.7 | 6.2 | 8.0 |
| SD | 2.2 | 2.8 | 2.5 | 2.2 | 2.8 | 2.5 | 0.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 |  |  |  |  |  |  |  |
| Postcull  Live Males | Postcull  Live Females | Live Pups  on Day 7 | Live Males  on Day 7 | Live Females  on Day 7 | Live Pups  on Day 10 | Live Males  on Day 10 |
| 4 | 4 | - | - | - | - | - |
| 61 | 2 | 6 | 8 | 2 | 6 | 8 | 2 |
| 62 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 63 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 64 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 65 | 5 | 3 | 8 | 5 | 3 | 8 | 5 |
| 66 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 67 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 68 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 69 | 2 | 6 | 8 | 2 | 6 | 8 | 2 |
| 70 | 5 | 3 | 8 | 5 | 3 | 8 | 5 |
| Mean | 3.8 | 4.2 | 8.0 | 3.8 | 4.2 | 8.0 | 3.8 |
| SD | 1.0 | 1.0 | 0.0 | 1.0 | 1.0 | 0.0 | 1.0 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 |  |  |  |  |  |  |  |
| Live Females  on Day 10 | Live Pups  on Day 13 | Live Males  on Day 13 | Live Females  on Day 13 | Viability  Index (%) | Survival  4Postcull-7 (%) | Survival  4Postcull-13 (%) |
| - | - | - | - | Birth-4 | - | - |
| 61 | 6 | 8 | 2 | 6 | 100.0 | 100.0 | 100.0 |
| 62 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 63 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 64 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 65 | 3 | 8 | 5 | 3 | 100.0 | 100.0 | 100.0 |
| 66 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 67 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 68 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 69 | 6 | 8 | 2 | 6 | 100.0 | 100.0 | 100.0 |
| 70 | 3 | 8 | 5 | 3 | 100.0 | 100.0 | 100.0 |
| Mean | 4.2 | 8.0 | 3.8 | 4.2 | 100.00 | 100.00 | 100.00 |
| SD | 1.0 | 0.0 | 1.0 | 1.0 | 0.00 | 0.00 | 0.00 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

|  |  |  |
| --- | --- | --- |
| 25000  ppm Group 3 |  | |
| Live Male  Pups/Litter (%) | Live Male  Pups/Litter (%) |
| 1 | 13 |
| 61 | 15.4 | 25.0 |
| 62 | 53.8 | 50.0 |
| 63 | 50.0 | 50.0 |
| 64 | 38.5 | 50.0 |
| 65 | 72.7 | 62.5 |
| 66 | 55.6 | 50.0 |
| 67 | 44.4 | 50.0 |
| 68 | 42.9 | 50.0 |
| 69 | 22.2 | 25.0 |
| 70 | 78.6 | 62.5 |
| Mean | 47.41 | 47.50 |
| SD | 19.71 | 12.91 |
| N | 10 | 10 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 |  |  |  |  |  |  |  |
| Live Pups  on Day 1 | Live Males  on Day 1 | Live Females  on Day 1 | Live Pups  on Day 4 | Live Males  on Day 4 | Live Females  on Day 4 | Live Pups  Postcull |
| - | - | - | - | - | - | 4 |
| 71 | 12 | 5 | 7 | 12 | 5 | 7 | 8 |
| 72 | 10 | 5 | 5 | 10 | 5 | 5 | 8 |
| 73 | 10 | 6 | 4 | 10 | 6 | 4 | 8 |
| 74 | 14 | 10 | 4 | 14 | 10 | 4 | 8 |
| 75 | 12 | 7 | 5 | 12 | 7 | 5 | 8 |
| 76 | 13 | 6 | 7 | 13 | 6 | 7 | 8 |
| 79 | 10 | 4 | 6 | 10 | 4 | 6 | 8 |
| 80 | 9 | 5 | 4 | 9 | 5 | 4 | 8 |
| Mean | 11.3 | 6.0 | 5.3 | 11.3 | 6.0 | 5.3 | 8.0 |
| SD | 1.8 | 1.9 | 1.3 | 1.8 | 1.9 | 1.3 | 0.0 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 |  |  |  |  |  |  |  |
| Postcull  Live Males | Postcull  Live Females | Live Pups  on Day 7 | Live Males  on Day 7 | Live Females  on Day 7 | Live Pups  on Day 10 | Live Males  on Day 10 |
| 4 | 4 | - | - | - | - | - |
| 71 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 72 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 73 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 74 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 75 | 4 | 4 | 8 | 3 | 5 | 8 | 3 |
| 76 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 79 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| 80 | 4 | 4 | 8 | 4 | 4 | 8 | 4 |
| Mean | 4.0 | 4.0 | 8.0 | 3.9 | 4.1 | 8.0 | 3.9 |
| SD | 0.0 | 0.0 | 0.0 | 0.4 | 0.4 | 0.0 | 0.4 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 |  |  |  |  |  |  |  |
| Live Females  on Day 10 | Live Pups  on Day 13 | Live Males  on Day 13 | Live Females  on Day 13 | Viability  Index (%) | Survival  4Postcull-7 (%) | Survival  4Postcull-13 (%) |
| - | - | - | - | Birth-4 | - | - |
| 71 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 72 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 73 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 74 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 75 | 5 | 8 | 3 | 5 | 100.0 | 100.0 | 100.0 |
| 76 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 79 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| 80 | 4 | 8 | 4 | 4 | 100.0 | 100.0 | 100.0 |
| Mean | 4.1 | 8.0 | 3.9 | 4.1 | 100.00 | 100.00 | 100.00 |
| SD | 0.4 | 0.0 | 0.4 | 0.4 | 0.00 | 0.00 | 0.00 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

|  |  |  |
| --- | --- | --- |
| 50000  ppm Group 4 |  | |
| Live Male  Pups/Litter (%) | Live Male  Pups/Litter (%) |
| 1 | 13 |
| 71 | 41.7 | 50.0 |
| 72 | 50.0 | 50.0 |
| 73 | 60.0 | 50.0 |
| 74 | 71.4 | 50.0 |
| 75 | 58.3 | 37.5 |
| 76 | 46.2 | 50.0 |
| 79 | 40.0 | 50.0 |
| 80 | 55.6 | 50.0 |
| Mean | 52.89 | 48.44 |
| SD | 10.53 | 4.42 |
| N | 8 | 8 |

|  |  |  |  |
| --- | --- | --- | --- |
| 0  ppm Group 1 | Day(s) Relative to Littering (A) | Number of Pups | Observation Type: All Types |
| 49 | 1 | 1/13 | Skin, Lesion, Lower Lip, Slight |

|  |  |  |  |
| --- | --- | --- | --- |
| 12500  ppm Group 2 | Day(s) Relative to Littering (A) | Number of Pups | Observation Type: All Types |
| 57 | 1 | 1/11 | Skin, Pale, Dorsal Aspect Generalized |
|  |  | 1/11 | Skin, Pale, Ventral Aspect Generalized |

|  |  |  |  |
| --- | --- | --- | --- |
| 25000  ppm Group 3 | Day(s) Relative to Littering (A) | Number of Pups | Observation Type: All Types |
| 63 | 7 | 1/8 | Skin, Discolored, Tip of Tail, Black |
|  | 8 | 1/8 | Skin, Discolored, Tip of Tail, Black |
|  | 9 | 1/8 | Skin, Discolored, Tip of Tail, Black |
|  | 10 | 1/8 | Skin, Discolored, Tip of Tail, Black |
|  | 11 | 1/8 | Skin, Discolored, Tip of Tail, Black |
|  | 12 | 1/8 | Skin, Discolored, Tip of Tail, Black |
| 64 | 1 | 1/13 | Skin, Discolored, Tip of Tail, Purple |
| 67 | 1 | 1/9 | Skin, Discolored, Hindpaw, Right, Purple |
|  |  | 1/9 | Skin, Discolored, Interscapular, Black |

|  |  |  |  |
| --- | --- | --- | --- |
| 50000  ppm Group 4 | Day(s) Relative to Littering (A) | Number of Pups | Observation Type: All Types |
| 75 | 7 | 1/8 | Dehydrated Suspected, Slight |
|  | 8 | 1/8 | Dehydrated Suspected, Moderate |
|  | 9 | 1/8 | Dehydrated Suspected, Slight |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 |  | | | |  | | |
| Mean Pup BW  all | Mean Pup BW  all | Mean Pup BW  all | Mean Pup BW  all | Mean Pup BW  males | Mean Pup BW  males | Mean Pup BW  males |
| 1 | 4 | 7 | 13 | 1 | 4 | 7 |
| 41 | 6.7 | 10.5 | 18.6 | 34.6 | 6.9 | 10.7 | 18.9 |
| 42 | 7.1 | 11.4 | 18.6 | 33.8 | 7.2 | 11.4 | 18.8 |
| 43 | 5.9 | 8.1 | 14.8 | 27.7 | 6.0 | 8.3 | 15.2 |
| 44 | 6.9 | 10.3 | 16.5 | 30.5 | 7.0 | 10.3 | 16.6 |
| 45 | 6.5 | 9.5 | 18.3 | 33.4 | 6.5 | 9.3 | 18.2 |
| 46 | 7.2 | 10.9 | 17.7 | 32.8 | 7.4 | 11.0 | 18.0 |
| 47 | 6.5 | 9.9 | 17.0 | 32.3 | 6.8 | 10.3 | 17.6 |
| 49 | 5.9 | 8.7 | 15.3 | 31.3 | 6.0 | 8.7 | 15.4 |
| 50 | 7.1 | 10.9 | 16.7 | 30.0 | 7.2 | 11.0 | 16.9 |
| Mean | 6.64 | 10.01 | 17.05 | 31.80 | 6.77 | 10.11 | 17.29 |
| SD | 0.52 | 1.08 | 1.40 | 2.16 | 0.52 | 1.09 | 1.37 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 |  |  | | | |
| Mean Pup BW  males | Mean Pup BW  females | Mean Pup BW  females | Mean Pup BW  females | Mean Pup BW  females |
| 13 | 1 | 4 | 7 | 13 |
| 41 | 34.7 | 6.4 | 10.3 | 18.3 | 34.5 |
| 42 | 33.6 | 7.1 | 11.4 | 18.5 | 33.8 |
| 43 | 28.5 | 5.8 | 8.1 | 14.3 | 27.0 |
| 44 | 30.8 | 6.5 | 10.0 | 16.2 | 29.9 |
| 45 | 33.5 | 6.5 | 9.8 | 18.3 | 33.4 |
| 46 | 33.1 | 6.9 | 10.7 | 17.3 | 32.2 |
| 47 | 33.4 | 6.4 | 9.8 | 16.6 | 31.6 |
| 49 | 31.6 | 5.7 | 8.6 | 15.2 | 31.0 |
| 50 | 30.5 | 7.1 | 10.8 | 16.6 | 29.8 |
| Mean | 32.17 | 6.50 | 9.93 | 16.81 | 31.45 |
| SD | 1.99 | 0.51 | 1.06 | 1.46 | 2.36 |
| N | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 |  | | | |  | | |
| Mean Pup BW  all | Mean Pup BW  all | Mean Pup BW  all | Mean Pup BW  all | Mean Pup BW  males | Mean Pup BW  males | Mean Pup BW  males |
| 1 | 4 | 7 | 13 | 1 | 4 | 7 |
| 51 | 6.5 | 9.8 | 17.0 | 32.8 | 6.6 | 9.9 | 17.3 |
| 52 | 7.3 | 11.6 | 18.1 | 34.6 | 7.6 | 12.0 | 18.6 |
| 53 | 6.6 | 9.9 | 16.1 | 30.3 | 6.6 | 9.9 | 16.3 |
| 54 | 5.9 | 9.6 | 15.8 | 31.6 | 6.0 | 9.8 | 16.0 |
| 55 | 7.2 | 11.3 | 18.1 | 32.3 | 7.4 | 11.6 | 18.5 |
| 56 | 7.2 | 11.2 | 18.2 | 34.3 | 7.4 | 11.3 | 18.7 |
| 57 | 7.1 | 10.7 | 18.5 | 33.5 | 7.1 | 10.7 | 18.5 |
| 58 | 7.3 | 11.0 | 17.6 | 32.2 | 7.6 | 11.1 | 17.7 |
| 60 | 7.4 | 11.5 | 17.6 | 31.0 | 7.6 | 11.6 | 17.8 |
| Mean | 6.95 | 10.73 | 17.44 | 32.51 | 7.10 | 10.88 | 17.71 |
| SD | 0.51 | 0.77 | 0.96 | 1.46 | 0.57 | 0.83 | 1.02 |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 |  |  | | | |
| Mean Pup BW  males | Mean Pup BW  females | Mean Pup BW  females | Mean Pup BW  females | Mean Pup BW  females |
| 13 | 1 | 4 | 7 | 13 |
| 51 | 33.1 | 6.4 | 9.7 | 16.7 | 32.6 |
| 52 | 35.0 | 7.1 | 11.4 | 17.7 | 34.4 |
| 53 | 30.7 | 6.7 | 9.8 | 15.6 | 29.5 |
| 54 | 31.8 | 5.7 | 9.4 | 15.7 | 31.4 |
| 55 | 33.0 | 7.0 | 11.1 | 17.6 | 31.7 |
| 56 | 34.8 | 6.8 | 10.8 | 17.4 | 33.4 |
| 57 | 33.4 | 7.1 | 10.7 | 18.5 | 33.7 |
| 58 | 32.5 | 7.3 | 11.0 | 17.6 | 32.1 |
| 60 | 31.3 | 7.0 | 11.1 | 16.9 | 30.1 |
| Mean | 32.83 | 6.78 | 10.55 | 17.07 | 32.09 |
| SD | 1.46 | 0.47 | 0.72 | 0.95 | 1.64 |
| N | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 |  | | | |  | | |
| Mean Pup BW  all | Mean Pup BW  all | Mean Pup BW  all | Mean Pup BW  all | Mean Pup BW  males | Mean Pup BW  males | Mean Pup BW  males |
| 1 | 4 | 7 | 13 | 1 | 4 | 7 |
| 61 | 7.1 | 10.4 | 17.9 | 33.7 | 7.2 | 10.6 | 17.7 |
| 62 | 5.7 | 8.3 | 14.3 | 27.0 | 5.7 | 8.3 | 14.2 |
| 63 | 5.4 | 7.7 | 13.9 | 27.2 | 5.4 | 7.5 | 13.8 |
| 64 | 5.9 | 8.6 | 14.9 | 28.6 | 6.1 | 8.6 | 15.2 |
| 65 | 7.0 | 10.4 | 16.8 | 31.4 | 7.0 | 10.4 | 16.6 |
| 66 | 7.4 | 10.9 | 16.3 | 29.3 | 7.4 | 10.9 | 16.1 |
| 67 | 5.4 | 8.8 | 14.9 | 29.2 | 5.7 | 9.2 | 15.5 |
| 68 | 5.9 | 9.1 | 16.5 | 31.4 | 6.0 | 9.1 | 16.1 |
| 69 | 7.4 | 11.3 | 17.3 | 30.1 | 7.5 | 11.3 | 17.1 |
| 70 | 6.0 | 8.9 | 14.9 | 29.6 | 6.0 | 9.0 | 15.2 |
| Mean | 6.32 | 9.45 | 15.76 | 29.74 | 6.39 | 9.49 | 15.74 |
| SD | 0.81 | 1.24 | 1.35 | 2.05 | 0.77 | 1.22 | 1.23 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 |  |  | | | |
| Mean Pup BW  males | Mean Pup BW  females | Mean Pup BW  females | Mean Pup BW  females | Mean Pup BW  females |
| 13 | 1 | 4 | 7 | 13 |
| 61 | 33.5 | 7.0 | 10.4 | 17.9 | 33.8 |
| 62 | 26.9 | 5.7 | 8.3 | 14.4 | 27.1 |
| 63 | 27.0 | 5.4 | 7.8 | 14.1 | 27.4 |
| 64 | 29.1 | 5.8 | 8.6 | 14.5 | 28.1 |
| 65 | 31.1 | 7.1 | 10.5 | 17.0 | 31.9 |
| 66 | 29.1 | 7.4 | 11.0 | 16.5 | 29.6 |
| 67 | 29.8 | 5.2 | 8.5 | 14.3 | 28.5 |
| 68 | 30.8 | 5.8 | 9.0 | 16.9 | 32.1 |
| 69 | 30.5 | 7.4 | 11.4 | 17.4 | 29.9 |
| 70 | 29.9 | 5.7 | 8.5 | 14.5 | 29.2 |
| Mean | 29.75 | 6.26 | 9.40 | 15.74 | 29.75 |
| SD | 1.95 | 0.87 | 1.29 | 1.52 | 2.21 |
| N | 10 | 10 | 10 | 10 | 10 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 |  | | | |  | | |
| Mean Pup BW  all | Mean Pup BW  all | Mean Pup BW  all | Mean Pup BW  all | Mean Pup BW  males | Mean Pup BW  males | Mean Pup BW  males |
| 1 | 4 | 7 | 13 | 1 | 4 | 7 |
| 71 | 6.3 | 9.3 | 16.1 | 28.7 | 6.3 | 9.4 | 15.9 |
| 72 | 6.7 | 9.5 | 14.4 | 23.6 | 6.9 | 9.6 | 14.5 |
| 73 | 7.4 | 10.8 | 16.7 | 27.6 | 7.6 | 10.9 | 16.7 |
| 74 | 6.2 | 8.6 | 14.6 | 28.2 | 6.2 | 8.6 | 14.6 |
| 75 | 5.9 | 8.7 | 14.6 | 27.2 | 6.1 | 9.0 | 15.8 |
| 76 | 6.7 | 10.3 | 16.8 | 30.0 | 6.8 | 10.4 | 17.2 |
| 79 | 6.8 | 10.1 | 16.2 | 26.9 | 6.9 | 10.2 | 16.4 |
| 80 | 7.0 | 10.5 | 15.3 | 25.4 | 7.2 | 10.7 | 15.6 |
| Mean | 6.64 | 9.72 | 15.59 | 27.20 | 6.75 | 9.86 | 15.84 |
| SD | 0.48 | 0.81 | 0.98 | 2.00 | 0.51 | 0.82 | 0.96 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 |  |  | | | |
| Mean Pup BW  males | Mean Pup BW  females | Mean Pup BW  females | Mean Pup BW  females | Mean Pup BW  females |
| 13 | 1 | 4 | 7 | 13 |
| 71 | 28.4 | 6.2 | 9.2 | 16.2 | 29.0 |
| 72 | 23.7 | 6.6 | 9.4 | 14.4 | 23.4 |
| 73 | 27.5 | 7.2 | 10.6 | 16.7 | 27.8 |
| 74 | 28.0 | 6.1 | 8.6 | 14.7 | 28.5 |
| 75 | 29.5 | 5.7 | 8.3 | 13.9 | 25.8 |
| 76 | 30.2 | 6.7 | 10.1 | 16.5 | 29.8 |
| 79 | 27.0 | 6.7 | 10.0 | 16.0 | 26.8 |
| 80 | 25.6 | 6.7 | 10.1 | 14.9 | 25.1 |
| Mean | 27.48 | 6.49 | 9.56 | 15.40 | 27.03 |
| SD | 2.08 | 0.47 | 0.80 | 1.07 | 2.16 |
| N | 8 | 8 | 8 | 8 | 8 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 41 | Male | PBWT | 6.9 | 7.3 | 7.0 | 7.1 | 6.9 | 6.4 | 6.9 | 7.0 | - | - | - | - |
|  | Female | PBWT | 6.4 | 5.6 | 6.2 | 6.8 | 6.9 | 6.6 | - | - | - | - | - | - |
| 42 | Male | PBWT | 7.2 | 7.1 | 7.7 | 6.8 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 7.1 | 7.4 | 7.4 | 6.7 | 7.1 | 7.0 | 7.2 | 7.0 | - | - | - | - |
| 43 | Male | PBWT | 6.0 | 6.5 | 6.1 | 5.7 | 5.7 | - | - | - | - | - | - | - |
|  | Female | PBWT | 5.8 | 5.4 | 5.8 | 6.0 | 5.9 | 5.8 | 6.2 | 5.9 | 5.2 | - | - | - |
| 44 | Male | PBWT | 7.0 | 6.9 | 6.9 | 7.4 | 6.9 | 7.3 | 7.1 | 6.6 | 6.9 | - | - | - |
|  | Female | PBWT | 6.5 | 6.4 | 6.2 | 6.9 | - | - | - | - | - | - | - | - |
| 45 | Male | PBWT | 6.5 | 6.3 | 6.6 | 6.4 | 7.2 | 6.0 | 6.8 | 6.6 | 6.6 | 5.6 | - | - |
|  | Female | PBWT | 6.5 | 6.6 | 6.8 | 6.4 | 6.3 | 6.3 | 6.7 | - | - | - | - | - |
| 46 | Male | PBWT | 7.4 | 7.9 | 7.5 | 7.4 | 7.6 | 7.3 | 7.0 | 6.8 | 7.3 | - | - | - |
|  | Female | PBWT | 6.9 | 7.4 | 7.7 | 5.7 | - | - | - | - | - | - | - | - |
| 47 | Male | PBWT | 6.8 | 7.0 | 6.7 | 6.6 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 6.4 | 6.3 | 6.6 | 6.4 | 6.1 | 6.4 | 6.7 | 6.1 | 6.8 | 6.1 | - | - |
| 49 | Male | PBWT | 6.0 | 6.1 | 6.0 | 6.2 | 5.7 | 6.0 | 6.1 | 5.7 | 5.8 | - | - | - |
|  | Female | PBWT | 5.7 | 5.5 | 5.8 | 5.9 | 5.8 | 5.6 | - | - | - | - | - | - |
| 50 | Male | PBWT | 7.2 | 7.3 | 7.5 | 6.9 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 7.1 | 6.9 | 7.2 | 6.5 | 7.3 | 7.2 | 7.5 | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 51 | Male | PBWT | 6.6 | 6.1 | 6.6 | 6.5 | 6.5 | 7.2 | 7.0 | 6.5 | - | - | - | - |
|  | Female | PBWT | 6.4 | 6.7 | 5.9 | 6.6 | 6.3 | 6.6 | 6.4 | - | - | - | - | - |
| 52 | Male | PBWT | 7.6 | 7.6 | 7.8 | 7.4 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 7.1 | 7.5 | 6.7 | 6.8 | 7.2 | - | - | - | - | - | - | - |
| 53 | Male | PBWT | 6.6 | 6.7 | 7.4 | 6.8 | 5.7 | 7.0 | 5.4 | 7.2 | - | - | - | - |
|  | Female | PBWT | 6.7 | 6.4 | 7.2 | 6.4 | - | - | - | - | - | - | - | - |
| 54 | Male | PBWT | 6.0 | 6.2 | 6.2 | 5.1 | 5.9 | 6.2 | 6.3 | - | - | - | - | - |
|  | Female | PBWT | 5.7 | 5.4 | 6.3 | 6.1 | 5.2 | 5.7 | - | - | - | - | - | - |
| 55 | Male | PBWT | 7.4 | 7.8 | 7.0 | 7.5 | 7.3 | - | - | - | - | - | - | - |
|  | Female | PBWT | 7.0 | 7.4 | 7.1 | 6.9 | 6.7 | 7.0 | - | - | - | - | - | - |
| 56 | Male | PBWT | 7.4 | 8.0 | 6.7 | 7.4 | 7.1 | 7.8 | 7.6 | 7.5 | - | - | - | - |
|  | Female | PBWT | 6.8 | 7.4 | 6.9 | 6.0 | - | - | - | - | - | - | - | - |
| 57 | Male | PBWT | 7.1 | 7.1 | 7.0 | 6.6 | 7.0 | 6.6 | 8.0 | 7.3 | 7.3 | - | - | - |
|  | Female | PBWT | 7.1 | 7.0 | 7.1 | 7.3 | - | - | - | - | - | - | - | - |
| 58 | Male | PBWT | 7.6 | 7.7 | 7.5 | - | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 7.3 | 7.1 | 6.9 | 6.9 | 7.8 | 7.2 | 6.9 | 7.6 | 7.6 | - | - | - |
| 60 | Male | PBWT | 7.6 | 6.6 | 8.3 | 7.6 | 7.6 | 7.6 | 7.6 | - | - | - | - | - |
|  | Female | PBWT | 7.0 | 7.3 | 6.6 | - | - | - | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 61 | Male | PBWT | 7.2 | 6.9 | 7.4 | - | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 7.0 | 7.3 | 7.0 | 7.2 | 6.7 | 6.8 | 6.9 | 7.2 | 7.8 | 7.0 | 7.3 | 6.3 |
| 62 | Male | PBWT | 5.7 | 5.7 | 6.3 | 5.5 | 5.5 | 6.0 | 5.8 | 5.1 | - | - | - | - |
|  | Female | PBWT | 5.7 | 5.7 | 5.8 | 5.6 | 5.9 | 6.0 | 5.4 | - | - | - | - | - |
| 63 | Male | PBWT | 5.4 | 6.0 | 5.6 | 5.7 | 5.4 | 3.6 | 5.7 | 5.7 | - | - | - | - |
|  | Female | PBWT | 5.4 | 5.7 | 5.8 | 4.7 | 5.2 | 5.0 | 5.7 | 5.4 | - | - | - | - |
| 64 | Male | PBWT | 6.1 | 6.1 | 6.2 | 6.1 | 6.1 | 6.0 | - | - | - | - | - | - |
|  | Female | PBWT | 5.8 | 5.1 | 6.2 | 5.9 | 6.3 | 5.6 | 5.8 | 5.9 | 5.9 | - | - | - |
| 65 | Male | PBWT | 7.0 | 7.2 | 6.9 | 6.7 | 7.2 | 6.6 | 6.6 | 7.1 | 7.4 | - | - | - |
|  | Female | PBWT | 7.1 | 7.1 | 7.4 | 6.7 | - | - | - | - | - | - | - | - |
| 66 | Male | PBWT | 7.4 | 7.8 | 7.3 | 7.5 | 7.5 | 6.9 | - | - | - | - | - | - |
|  | Female | PBWT | 7.4 | 7.4 | 7.0 | 7.5 | 7.6 | - | - | - | - | - | - | - |
| 67 | Male | PBWT | 5.7 | 6.1 | 5.4 | 6.2 | 5.1 | - | - | - | - | - | - | - |
|  | Female | PBWT | 5.2 | 5.6 | 5.0 | 5.8 | 5.1 | 4.7 | - | - | - | - | - | - |
| 68 | Male | PBWT | 6.0 | 5.9 | 6.3 | 6.6 | 6.3 | 6.3 | 4.5 | - | - | - | - | - |
|  | Female | PBWT | 5.8 | 5.6 | 6.5 | 6.3 | 4.8 | 4.8 | 5.9 | 5.8 | 6.3 | - | - | - |
| 69 | Male | PBWT | 7.5 | 7.4 | 7.5 | - | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 7.4 | 7.7 | 7.4 | 7.2 | 7.2 | 7.8 | 7.5 | 7.3 | - | - | - | - |
| 70 | Male | PBWT | 6.0 | 5.9 | 5.5 | 6.5 | 6.1 | 6.0 | 5.9 | 6.2 | 6.1 | 6.4 | 5.9 | 5.8 |
|  | Female | PBWT | 5.7 | 5.9 | 5.6 | 5.7 | - | - | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 71 | Male | PBWT | 6.3 | 5.8 | 6.6 | 6.6 | 5.9 | 6.7 | - | - | - | - | - | - |
|  | Female | PBWT | 6.2 | 5.7 | 6.3 | 6.2 | 6.6 | 6.6 | 6.3 | 5.8 | - | - | - | - |
| 72 | Male | PBWT | 6.9 | 6.6 | 7.0 | 7.1 | 6.9 | 6.8 | - | - | - | - | - | - |
|  | Female | PBWT | 6.6 | 6.5 | 6.5 | 6.4 | 6.3 | 7.1 | - | - | - | - | - | - |
| 73 | Male | PBWT | 7.6 | 6.9 | 7.8 | 8.2 | 7.3 | 7.9 | 7.3 | - | - | - | - | - |
|  | Female | PBWT | 7.2 | 6.9 | 7.6 | 7.1 | 7.3 | - | - | - | - | - | - | - |
| 74 | Male | PBWT | 6.2 | 6.5 | 5.9 | 5.9 | 6.6 | 6.5 | 6.2 | 6.3 | 6.2 | 5.8 | 6.3 | - |
|  | Female | PBWT | 6.1 | 5.6 | 6.3 | 6.2 | 6.3 | - | - | - | - | - | - | - |
| 75 | Male | PBWT | 6.1 | 6.0 | 6.5 | 6.3 | 6.4 | 5.9 | 6.1 | 5.6 | - | - | - | - |
|  | Female | PBWT | 5.7 | 4.9 | 5.9 | 6.3 | 5.5 | 5.9 | - | - | - | - | - | - |
| 76 | Male | PBWT | 6.8 | 7.0 | 7.1 | 7.0 | 6.7 | 6.7 | 6.2 | - | - | - | - | - |
|  | Female | PBWT | 6.7 | 6.3 | 6.5 | 7.4 | 6.7 | 6.4 | 6.7 | 7.0 | - | - | - | - |
| 79 | Male | PBWT | 6.9 | 6.8 | 7.1 | 7.2 | 6.5 | - | - | - | - | - | - | - |
|  | Female | PBWT | 6.7 | 6.5 | 6.6 | 6.9 | 7.2 | 6.4 | 6.7 | - | - | - | - | - |
| 80 | Male | PBWT | 7.2 | 7.9 | 7.0 | 7.0 | 7.3 | 7.0 | - | - | - | - | - | - |
|  | Female | PBWT | 6.7 | 5.9 | 7.2 | 6.8 | 7.0 | - | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 41 | Male | PBWT | 10.7 | 11.1 | 10.7 | 11.0 | 10.6 | 9.8 | 10.9 | 10.7 | - | - | - | - |
|  | Female | PBWT | 10.3 | 9.5 | 9.9 | 10.8 | 10.7 | 10.5 | - | - | - | - | - | - |
| 42 | Male | PBWT | 11.4 | 11.4 | 11.7 | 11.0 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 11.4 | 11.6 | 11.9 | 11.1 | 11.1 | 11.2 | 11.6 | 11.3 | - | - | - | - |
| 43 | Male | PBWT | 8.3 | 9.0 | 8.7 | 7.6 | 8.0 | - | - | - | - | - | - | - |
|  | Female | PBWT | 8.1 | 7.8 | 8.0 | 8.2 | 8.2 | 8.1 | 8.5 | 8.4 | 7.2 | - | - | - |
| 44 | Male | PBWT | 10.3 | 10.2 | 10.2 | 10.9 | 10.5 | 10.8 | 10.5 | 9.7 | 9.9 | - | - | - |
|  | Female | PBWT | 10.0 | 9.9 | 9.7 | 10.5 | - | - | - | - | - | - | - | - |
| 45 | Male | PBWT | 9.3 | 8.4 | 9.3 | 9.5 | 10.5 | 9.0 | 10.3 | 9.8 | 8.9 | 7.6 | - | - |
|  | Female | PBWT | 9.8 | 9.9 | 10.0 | 10.3 | 8.8 | 10.0 | 10.0 | - | - | - | - | - |
| 46 | Male | PBWT | 11.0 | 11.4 | 11.2 | 11.0 | 11.1 | 11.0 | 10.9 | 10.3 | 10.7 | - | - | - |
|  | Female | PBWT | 10.7 | 11.4 | 11.7 | 8.9 | - | - | - | - | - | - | - | - |
| 47 | Male | PBWT | 10.3 | 10.6 | 10.3 | 10.1 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 9.8 | 9.6 | 10.1 | 10.2 | 9.5 | 9.9 | 10.0 | 9.4 | 9.8 | 9.3 | - | - |
| 49 | Male | PBWT | 8.7 | 9.1 | 9.1 | 8.9 | 8.4 | 8.7 | 8.5 | 8.5 | 8.5 | - | - | - |
|  | Female | PBWT | 8.6 | 8.2 | 8.7 | 9.1 | 8.5 | 8.3 | - | - | - | - | - | - |
| 50 | Male | PBWT | 11.0 | 11.1 | 11.4 | 10.6 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 10.8 | 10.4 | 11.1 | 9.7 | 11.2 | 10.9 | 11.4 | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 51 | Male | PBWT | 9.9 | 9.4 | 10.0 | 9.9 | 9.6 | 10.1 | 10.5 | 9.8 | - | - | - | - |
|  | Female | PBWT | 9.7 | 9.9 | 9.0 | 10.1 | 9.4 | 9.9 | 9.9 | - | - | - | - | - |
| 52 | Male | PBWT | 12.0 | 11.8 | 12.0 | 12.2 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 11.4 | 12.3 | 11.1 | 10.7 | 11.4 | - | - | - | - | - | - | - |
| 53 | Male | PBWT | 9.9 | 10.3 | 11.0 | 10.3 | 8.8 | 10.2 | 8.4 | 10.6 | - | - | - | - |
|  | Female | PBWT | 9.8 | 9.4 | 10.3 | 9.8 | - | - | - | - | - | - | - | - |
| 54 | Male | PBWT | 9.8 | 10.2 | 10.0 | 8.5 | 9.7 | 10.1 | 10.4 | - | - | - | - | - |
|  | Female | PBWT | 9.4 | 8.9 | 10.1 | 9.9 | 8.6 | 9.4 | - | - | - | - | - | - |
| 55 | Male | PBWT | 11.6 | 11.5 | 11.1 | 12.2 | 11.6 | - | - | - | - | - | - | - |
|  | Female | PBWT | 11.1 | 11.2 | 11.1 | 10.5 | 11.0 | 11.5 | - | - | - | - | - | - |
| 56 | Male | PBWT | 11.3 | 12.0 | 10.3 | 11.2 | 11.1 | 11.2 | 12.0 | 11.4 | - | - | - | - |
|  | Female | PBWT | 10.8 | 11.4 | 10.8 | 10.3 | - | - | - | - | - | - | - | - |
| 57 | Male | PBWT | 10.7 | 11.0 | 10.7 | 10.0 | 10.5 | 10.3 | 11.2 | 10.9 | - | - | - | - |
|  | Female | PBWT | 10.7 | 10.6 | 10.8 | 10.6 | - | - | - | - | - | - | - | - |
| 58 | Male | PBWT | 11.1 | 11.1 | 11.1 | - | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 11.0 | 10.8 | 11.0 | 10.6 | 11.2 | 10.8 | 11.0 | 10.9 | 11.4 | - | - | - |
| 60 | Male | PBWT | 11.6 | 10.6 | 12.5 | 11.4 | 11.6 | 11.9 | 11.7 | - | - | - | - | - |
|  | Female | PBWT | 11.1 | 11.3 | 10.9 | - | - | - | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 61 | Male | PBWT | 10.6 | 10.5 | 10.7 | - | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 10.4 | 10.8 | 10.6 | 10.2 | 10.0 | 10.5 | 10.1 | 10.8 | 11.4 | 10.2 | 10.6 | 9.4 |
| 62 | Male | PBWT | 8.3 | 8.4 | 8.6 | 8.1 | 8.3 | 8.6 | 8.4 | 7.8 | - | - | - | - |
|  | Female | PBWT | 8.3 | 8.4 | 8.3 | 7.9 | 8.4 | 8.8 | 7.8 | - | - | - | - | - |
| 63 | Male | PBWT | 7.5 | 8.1 | 7.9 | 7.6 | 8.0 | 4.9 | 8.2 | 7.9 | - | - | - | - |
|  | Female | PBWT | 7.8 | 8.2 | 8.2 | 7.1 | 7.6 | 7.0 | 8.4 | 8.2 | - | - | - | - |
| 64 | Male | PBWT | 8.6 | 8.6 | 8.7 | 8.7 | 8.9 | 8.2 | - | - | - | - | - | - |
|  | Female | PBWT | 8.6 | 7.6 | 9.0 | 8.9 | 9.1 | 8.5 | 8.4 | 8.7 | 8.6 | - | - | - |
| 65 | Male | PBWT | 10.4 | 10.7 | 10.3 | 10.1 | 10.6 | 9.9 | 10.0 | 10.6 | 10.8 | - | - | - |
|  | Female | PBWT | 10.5 | 10.4 | 10.8 | 10.4 | - | - | - | - | - | - | - | - |
| 66 | Male | PBWT | 10.9 | 11.2 | 10.8 | 10.9 | 11.5 | 10.0 | - | - | - | - | - | - |
|  | Female | PBWT | 11.0 | 11.1 | 10.8 | 10.9 | 11.2 | - | - | - | - | - | - | - |
| 67 | Male | PBWT | 9.2 | 9.6 | 8.8 | 9.8 | 8.6 | - | - | - | - | - | - | - |
|  | Female | PBWT | 8.5 | 9.2 | 8.1 | 9.5 | 8.1 | 7.8 | - | - | - | - | - | - |
| 68 | Male | PBWT | 9.1 | 9.1 | 9.4 | 10.7 | 9.5 | 9.6 | 6.5 | - | - | - | - | - |
|  | Female | PBWT | 9.0 | 8.6 | 10.0 | 9.9 | 7.6 | 7.3 | 9.6 | 9.3 | 9.8 | - | - | - |
| 69 | Male | PBWT | 11.3 | 11.2 | 11.3 | - | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 11.4 | 11.5 | 11.6 | 11.0 | 11.1 | 11.7 | 11.5 | 11.2 | - | - | - | - |
| 70 | Male | PBWT | 9.0 | 9.2 | 9.1 | 9.4 | 9.2 | 8.7 | 8.2 | 9.6 | 9.2 | 9.4 | 8.7 | 8.7 |
|  | Female | PBWT | 8.5 | 8.8 | 8.4 | 8.2 | - | - | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 71 | Male | PBWT | 9.4 | 9.0 | 9.9 | 9.6 | 8.9 | 9.8 | - | - | - | - | - | - |
|  | Female | PBWT | 9.2 | 8.7 | 9.5 | 9.1 | 9.6 | 9.6 | 9.2 | 8.7 | - | - | - | - |
| 72 | Male | PBWT | 9.6 | 9.2 | 9.6 | 9.6 | 9.9 | 9.9 | - | - | - | - | - | - |
|  | Female | PBWT | 9.4 | 9.6 | 9.4 | 9.2 | 9.0 | 9.9 | - | - | - | - | - | - |
| 73 | Male | PBWT | 10.9 | 10.0 | 11.5 | 11.5 | 10.7 | 11.1 | 10.6 | - | - | - | - | - |
|  | Female | PBWT | 10.6 | 10.2 | 11.1 | 10.4 | 10.8 | - | - | - | - | - | - | - |
| 74 | Male | PBWT | 8.6 | 9.1 | 7.8 | 8.1 | 9.2 | 8.7 | 8.5 | 8.9 | 9.1 | 8.2 | 8.8 | - |
|  | Female | PBWT | 8.6 | 7.8 | 8.9 | 8.9 | 8.9 | - | - | - | - | - | - | - |
| 75 | Male | PBWT | 9.0 | 8.9 | 9.0 | 9.2 | 9.4 | 8.8 | 9.1 | 8.4 | - | - | - | - |
|  | Female | PBWT | 8.3 | 6.4 | 8.9 | 9.1 | 8.4 | 8.8 | - | - | - | - | - | - |
| 76 | Male | PBWT | 10.4 | 11.1 | 10.4 | 10.3 | 10.5 | 10.8 | 9.4 | - | - | - | - | - |
|  | Female | PBWT | 10.1 | 10.0 | 9.6 | 10.5 | 9.8 | 10.0 | 10.4 | 10.6 | - | - | - | - |
| 79 | Male | PBWT | 10.2 | 10.2 | 10.8 | 10.4 | 9.2 | - | - | - | - | - | - | - |
|  | Female | PBWT | 10.0 | 9.6 | 9.8 | 10.5 | 10.8 | 9.7 | 9.8 | - | - | - | - | - |
| 80 | Male | PBWT | 10.7 | 11.5 | 10.2 | 10.4 | 11.0 | 10.6 | - | - | - | - | - | - |
|  | Female | PBWT | 10.1 | 9.0 | 10.8 | 10.1 | 10.5 | - | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 41 | Male | PBWT | 18.9 | 19.3 | 19.2 | 19.2 | 18.0 | - | - | - | - | - | - | - |
|  | Female | PBWT | 18.3 | 17.3 | 18.0 | 18.9 | 19.0 | - | - | - | - | - | - | - |
| 42 | Male | PBWT | 18.8 | 19.0 | 19.1 | 18.3 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 18.5 | 18.7 | 19.4 | 17.7 | 18.8 | 17.9 | - | - | - | - | - | - |
| 43 | Male | PBWT | 15.2 | 16.6 | 15.7 | 14.0 | 14.5 | - | - | - | - | - | - | - |
|  | Female | PBWT | 14.3 | 14.3 | 14.7 | 14.8 | 13.4 | - | - | - | - | - | - | - |
| 44 | Male | PBWT | 16.6 | 16.3 | 16.4 | 17.6 | 16.3 | 16.6 | - | - | - | - | - | - |
|  | Female | PBWT | 16.2 | 16.0 | 15.8 | 16.7 | - | - | - | - | - | - | - | - |
| 45 | Male | PBWT | 18.2 | 17.7 | 18.7 | 18.2 | 18.2 | - | - | - | - | - | - | - |
|  | Female | PBWT | 18.3 | 18.2 | 18.7 | 18.2 | 18.2 | - | - | - | - | - | - | - |
| 46 | Male | PBWT | 18.0 | 18.6 | 17.9 | 17.7 | 18.0 | 17.8 | - | - | - | - | - | - |
|  | Female | PBWT | 17.3 | 18.8 | 18.5 | 14.5 | - | - | - | - | - | - | - | - |
| 47 | Male | PBWT | 17.6 | 17.7 | 17.9 | 17.1 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 16.6 | 16.4 | 17.0 | 17.1 | 16.9 | 15.7 | - | - | - | - | - | - |
| 49 | Male | PBWT | 15.4 | 16.4 | 14.7 | 15.3 | 15.1 | - | - | - | - | - | - | - |
|  | Female | PBWT | 15.2 | 14.9 | 16.2 | 14.9 | 14.7 | - | - | - | - | - | - | - |
| 50 | Male | PBWT | 16.9 | 17.1 | 17.0 | 16.7 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 16.6 | 16.0 | 17.0 | 15.4 | 17.1 | 17.6 | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 51 | Male | PBWT | 17.3 | 17.4 | 16.6 | 18.4 | 16.7 | - | - | - | - | - | - | - |
|  | Female | PBWT | 16.7 | 17.4 | 15.4 | 17.2 | 16.9 | - | - | - | - | - | - | - |
| 52 | Male | PBWT | 18.6 | 18.4 | 18.4 | 19.0 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 17.7 | 18.7 | 17.0 | 17.0 | 17.9 | - | - | - | - | - | - | - |
| 53 | Male | PBWT | 16.3 | 17.0 | 17.7 | 16.4 | 13.6 | 16.8 | - | - | - | - | - | - |
|  | Female | PBWT | 15.6 | 14.7 | 16.3 | 15.9 | - | - | - | - | - | - | - | - |
| 54 | Male | PBWT | 16.0 | 16.7 | 13.8 | 16.6 | 16.8 | - | - | - | - | - | - | - |
|  | Female | PBWT | 15.7 | 14.5 | 15.8 | 16.7 | 15.7 | - | - | - | - | - | - | - |
| 55 | Male | PBWT | 18.5 | 18.7 | 17.5 | 19.3 | 18.5 | - | - | - | - | - | - | - |
|  | Female | PBWT | 17.6 | 17.5 | 17.3 | 17.6 | 18.1 | - | - | - | - | - | - | - |
| 56 | Male | PBWT | 18.7 | 19.4 | 18.1 | 18.5 | 18.3 | 19.3 | - | - | - | - | - | - |
|  | Female | PBWT | 17.4 | 18.3 | 17.5 | 16.5 | - | - | - | - | - | - | - | - |
| 57 | Male | PBWT | 18.5 | 19.3 | 18.2 | 17.4 | 19.2 | 18.6 | - | - | - | - | - | - |
|  | Female | PBWT | 18.5 | 18.8 | 18.7 | 17.9 | - | - | - | - | - | - | - | - |
| 58 | Male | PBWT | 17.7 | 17.8 | 17.5 | - | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 17.6 | 17.2 | 17.2 | 18.2 | 17.3 | 17.4 | 18.1 | - | - | - | - | - |
| 60 | Male | PBWT | 17.8 | 16.8 | 18.8 | 17.6 | 17.5 | 18.1 | 18.2 | - | - | - | - | - |
|  | Female | PBWT | 16.9 | 17.0 | 16.7 | - | - | - | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 61 | Male | PBWT | 17.7 | 17.5 | 17.9 | - | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 17.9 | 18.5 | 17.3 | 17.3 | 16.8 | 19.2 | 18.4 | - | - | - | - | - |
| 62 | Male | PBWT | 14.2 | 14.5 | 13.7 | 14.3 | 14.1 | - | - | - | - | - | - | - |
|  | Female | PBWT | 14.4 | 14.2 | 14.2 | 14.2 | 15.0 | - | - | - | - | - | - | - |
| 63 | Male | PBWT | 13.8 | 14.0 | 13.9 | 13.3 | 14.1 | - | - | - | - | - | - | - |
|  | Female | PBWT | 14.1 | 14.7 | 14.6 | 12.5 | 14.4 | - | - | - | - | - | - | - |
| 64 | Male | PBWT | 15.2 | 15.0 | 15.0 | 15.2 | 15.6 | - | - | - | - | - | - | - |
|  | Female | PBWT | 14.5 | 13.0 | 15.1 | 15.3 | 14.7 | - | - | - | - | - | - | - |
| 65 | Male | PBWT | 16.6 | 17.3 | 16.0 | 16.5 | 16.1 | 17.2 | - | - | - | - | - | - |
|  | Female | PBWT | 17.0 | 17.0 | 17.3 | 16.7 | - | - | - | - | - | - | - | - |
| 66 | Male | PBWT | 16.1 | 16.8 | 16.5 | 16.2 | 15.0 | - | - | - | - | - | - | - |
|  | Female | PBWT | 16.5 | 16.8 | 16.0 | 16.4 | 16.7 | - | - | - | - | - | - | - |
| 67 | Male | PBWT | 15.5 | 15.6 | 15.0 | 16.3 | 14.9 | - | - | - | - | - | - | - |
|  | Female | PBWT | 14.3 | 15.1 | 13.7 | 16.1 | 12.4 | - | - | - | - | - | - | - |
| 68 | Male | PBWT | 16.1 | 16.0 | 19.6 | 17.0 | 11.8 | - | - | - | - | - | - | - |
|  | Female | PBWT | 16.9 | 15.4 | 18.1 | 16.8 | 17.3 | - | - | - | - | - | - | - |
| 69 | Male | PBWT | 17.1 | 17.0 | 17.1 | - | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 17.4 | 17.7 | 17.8 | 16.5 | 17.1 | 18.1 | 17.1 | - | - | - | - | - |
| 70 | Male | PBWT | 15.2 | 15.4 | 14.3 | 16.2 | 14.8 | 15.1 | - | - | - | - | - | - |
|  | Female | PBWT | 14.5 | 15.1 | 14.2 | 14.1 | - | - | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 71 | Male | PBWT | 15.9 | 15.2 | 16.5 | 15.3 | 16.7 | - | - | - | - | - | - | - |
|  | Female | PBWT | 16.2 | 16.2 | 16.1 | 16.4 | 16.1 | - | - | - | - | - | - | - |
| 72 | Male | PBWT | 14.5 | 14.2 | 14.5 | 14.4 | 14.8 | - | - | - | - | - | - | - |
|  | Female | PBWT | 14.4 | 14.6 | 14.5 | 13.1 | 15.2 | - | - | - | - | - | - | - |
| 73 | Male | PBWT | 16.7 | 15.6 | 17.7 | 16.6 | 16.8 | - | - | - | - | - | - | - |
|  | Female | PBWT | 16.7 | 16.3 | 17.1 | 16.8 | 16.7 | - | - | - | - | - | - | - |
| 74 | Male | PBWT | 14.6 | 13.9 | 13.9 | 15.7 | 14.7 | - | - | - | - | - | - | - |
|  | Female | PBWT | 14.7 | 13.2 | 15.1 | 15.2 | 15.1 | - | - | - | - | - | - | - |
| 75 | Male | PBWT | 15.8 | 15.2 | 16.1 | 16.2 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 13.9 | 8.7 | 15.2 | 15.5 | 14.5 | 15.7 | - | - | - | - | - | - |
| 76 | Male | PBWT | 17.2 | 18.0 | 17.8 | 17.4 | 15.5 | - | - | - | - | - | - | - |
|  | Female | PBWT | 16.5 | 15.2 | 16.8 | 16.7 | 17.1 | - | - | - | - | - | - | - |
| 79 | Male | PBWT | 16.4 | 16.6 | 17.0 | 16.8 | 15.3 | - | - | - | - | - | - | - |
|  | Female | PBWT | 16.0 | 15.5 | 17.0 | 15.9 | 15.7 | - | - | - | - | - | - | - |
| 80 | Male | PBWT | 15.6 | 15.1 | 15.2 | 16.0 | 16.2 | - | - | - | - | - | - | - |
|  | Female | PBWT | 14.9 | 13.7 | 15.7 | 14.8 | 15.4 | - | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 41 | Male | PBWT | 34.7 | 35.9 | 33.3 | 35.6 | 33.9 | - | - | - | - | - | - | - |
|  | Female | PBWT | 34.5 | 31.9 | 35.6 | 34.7 | 35.7 | - | - | - | - | - | - | - |
| 42 | Male | PBWT | 33.6 | 33.1 | 35.1 | 32.7 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 33.8 | 34.4 | 34.6 | 32.7 | 34.0 | 33.4 | - | - | - | - | - | - |
| 43 | Male | PBWT | 28.5 | 29.9 | 29.0 | 27.5 | 27.4 | - | - | - | - | - | - | - |
|  | Female | PBWT | 27.0 | 26.7 | 26.7 | 27.4 | 27.0 | - | - | - | - | - | - | - |
| 44 | Male | PBWT | 30.8 | 30.3 | 30.7 | 31.5 | 30.6 | 30.8 | - | - | - | - | - | - |
|  | Female | PBWT | 29.9 | 29.7 | 29.5 | 30.6 | - | - | - | - | - | - | - | - |
| 45 | Male | PBWT | 33.5 | 32.8 | 34.3 | 33.4 | 33.3 | - | - | - | - | - | - | - |
|  | Female | PBWT | 33.4 | 33.6 | 33.4 | 33.0 | 33.4 | - | - | - | - | - | - | - |
| 46 | Male | PBWT | 33.1 | 34.4 | 32.7 | 32.7 | 33.1 | 32.6 | - | - | - | - | - | - |
|  | Female | PBWT | 32.2 | 34.0 | 33.4 | 29.1 | - | - | - | - | - | - | - | - |
| 47 | Male | PBWT | 33.4 | 34.0 | 33.8 | 32.5 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 31.6 | 30.8 | 32.4 | 31.4 | 32.1 | 31.3 | - | - | - | - | - | - |
| 49 | Male | PBWT | 31.6 | 33.6 | 29.5 | 31.1 | 32.0 | - | - | - | - | - | - | - |
|  | Female | PBWT | 31.0 | 30.1 | 32.7 | 30.7 | 30.4 | - | - | - | - | - | - | - |
| 50 | Male | PBWT | 30.5 | 30.7 | 30.3 | 30.4 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 29.8 | 29.6 | 30.1 | 28.4 | 30.3 | 30.5 | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 51 | Male | PBWT | 33.1 | 33.6 | 32.5 | 34.3 | 31.9 | - | - | - | - | - | - | - |
|  | Female | PBWT | 32.6 | 33.1 | 30.6 | 33.5 | 33.1 | - | - | - | - | - | - | - |
| 52 | Male | PBWT | 35.0 | 34.9 | 34.5 | 35.6 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 34.4 | 35.8 | 33.4 | 33.6 | 34.7 | - | - | - | - | - | - | - |
| 53 | Male | PBWT | 30.7 | 31.7 | 32.6 | 31.0 | 27.0 | 31.3 | - | - | - | - | - | - |
|  | Female | PBWT | 29.5 | 28.1 | 30.1 | 30.2 | - | - | - | - | - | - | - | - |
| 54 | Male | PBWT | 31.8 | 33.0 | 28.2 | 32.6 | 33.3 | - | - | - | - | - | - | - |
|  | Female | PBWT | 31.4 | 29.5 | 31.9 | 33.3 | 31.0 | - | - | - | - | - | - | - |
| 55 | Male | PBWT | 33.0 | 32.6 | 31.3 | 34.2 | 33.7 | - | - | - | - | - | - | - |
|  | Female | PBWT | 31.7 | 31.3 | 32.1 | 30.7 | 32.7 | - | - | - | - | - | - | - |
| 56 | Male | PBWT | 34.8 | 34.9 | 35.8 | 34.9 | 33.9 | 34.5 | - | - | - | - | - | - |
|  | Female | PBWT | 33.4 | 34.1 | 33.6 | 32.4 | - | - | - | - | - | - | - | - |
| 57 | Male | PBWT | 33.4 | 35.4 | 32.1 | 34.4 | 31.7 | 33.3 | - | - | - | - | - | - |
|  | Female | PBWT | 33.7 | 33.9 | 34.3 | 33.0 | - | - | - | - | - | - | - | - |
| 58 | Male | PBWT | 32.5 | 32.9 | 32.0 | - | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 32.1 | 31.6 | 32.3 | 32.5 | 32.1 | 31.5 | 32.5 | - | - | - | - | - |
| 60 | Male | PBWT | 31.3 | 30.1 | 31.9 | 31.9 | 30.8 | 31.4 | 31.7 | - | - | - | - | - |
|  | Female | PBWT | 30.1 | 30.2 | 29.9 | - | - | - | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 61 | Male | PBWT | 33.5 | 33.0 | 33.9 | - | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 33.8 | 34.2 | 33.2 | 33.0 | 32.5 | 35.1 | 34.9 | - | - | - | - | - |
| 62 | Male | PBWT | 26.9 | 27.1 | 26.1 | 27.3 | 26.9 | - | - | - | - | - | - | - |
|  | Female | PBWT | 27.1 | 27.2 | 26.5 | 26.8 | 27.8 | - | - | - | - | - | - | - |
| 63 | Male | PBWT | 27.0 | 27.4 | 26.0 | 27.2 | 27.2 | - | - | - | - | - | - | - |
|  | Female | PBWT | 27.4 | 28.5 | 28.2 | 25.3 | 27.4 | - | - | - | - | - | - | - |
| 64 | Male | PBWT | 29.1 | 28.5 | 28.5 | 29.4 | 29.8 | - | - | - | - | - | - | - |
|  | Female | PBWT | 28.1 | 26.3 | 29.2 | 27.9 | 28.9 | - | - | - | - | - | - | - |
| 65 | Male | PBWT | 31.1 | 31.2 | 30.6 | 30.9 | 30.9 | 31.9 | - | - | - | - | - | - |
|  | Female | PBWT | 31.9 | 32.3 | 31.8 | 31.5 | - | - | - | - | - | - | - | - |
| 66 | Male | PBWT | 29.1 | 30.2 | 29.7 | 28.9 | 27.6 | - | - | - | - | - | - | - |
|  | Female | PBWT | 29.6 | 30.8 | 28.4 | 29.1 | 29.9 | - | - | - | - | - | - | - |
| 67 | Male | PBWT | 29.8 | 29.8 | 29.2 | 30.5 | 29.8 | - | - | - | - | - | - | - |
|  | Female | PBWT | 28.5 | 29.7 | 27.9 | 30.4 | 26.1 | - | - | - | - | - | - | - |
| 68 | Male | PBWT | 30.8 | 30.9 | 34.7 | 32.3 | 25.3 | - | - | - | - | - | - | - |
|  | Female | PBWT | 32.1 | 31.3 | 33.0 | 31.9 | 32.1 | - | - | - | - | - | - | - |
| 69 | Male | PBWT | 30.5 | 30.0 | 30.9 | - | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 29.9 | 29.9 | 30.8 | 28.5 | 30.4 | 30.5 | 29.5 | - | - | - | - | - |
| 70 | Male | PBWT | 29.9 | 30.5 | 28.9 | 30.5 | 30.1 | 29.4 | - | - | - | - | - | - |
|  | Female | PBWT | 29.2 | 29.8 | 28.9 | 28.9 | - | - | - | - | - | - | - | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4  Dam Pup Sex | | Mean/ Meas. Count | |  | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 71 | Male | PBWT | 28.4 | 27.6 | 29.3 | 27.1 | 29.7 | - | - | - | - | - | - | - |
|  | Female | PBWT | 29.0 | 29.0 | 28.7 | 29.5 | 28.9 | - | - | - | - | - | - | - |
| 72 | Male | PBWT | 23.7 | 22.9 | 23.7 | 24.0 | 24.3 | - | - | - | - | - | - | - |
|  | Female | PBWT | 23.4 | 24.2 | 23.5 | 21.2 | 24.8 | - | - | - | - | - | - | - |
| 73 | Male | PBWT | 27.5 | 26.5 | 28.6 | 26.8 | 28.1 | - | - | - | - | - | - | - |
|  | Female | PBWT | 27.8 | 27.3 | 27.8 | 28.0 | 27.9 | - | - | - | - | - | - | - |
| 74 | Male | PBWT | 28.0 | 27.0 | 27.0 | 29.3 | 28.5 | - | - | - | - | - | - | - |
|  | Female | PBWT | 28.5 | 26.5 | 29.0 | 29.1 | 29.4 | - | - | - | - | - | - | - |
| 75 | Male | PBWT | 29.5 | 28.4 | 30.1 | 30.0 | - | - | - | - | - | - | - | - |
|  | Female | PBWT | 25.8 | 13.7 | 29.3 | 28.8 | 28.0 | 29.3 | - | - | - | - | - | - |
| 76 | Male | PBWT | 30.2 | 31.2 | 30.3 | 30.7 | 28.4 | - | - | - | - | - | - | - |
|  | Female | PBWT | 29.8 | 28.5 | 30.6 | 30.1 | 30.1 | - | - | - | - | - | - | - |
| 79 | Male | PBWT | 27.0 | 26.7 | 27.6 | 27.8 | 26.0 | - | - | - | - | - | - | - |
|  | Female | PBWT | 26.8 | 27.1 | 27.8 | 26.3 | 25.9 | - | - | - | - | - | - | - |
| 80 | Male | PBWT | 25.6 | 24.7 | 25.0 | 26.2 | 26.5 | - | - | - | - | - | - | - |
|  | Female | PBWT | 25.1 | 23.9 | 26.1 | 24.7 | 25.7 | - | - | - | - | - | - | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 |  |  |  |  |  |
| Mean Pup  AGD males (mm) | Mean Pup  AGD females (mm) | Mean Norm.  Pup AGD m | Mean Norm.  Pup AGD f | Mean Pup  A/N males |
| 1 | 1 | 1 | 1 | 13 |
| 41 | 2.9 | 1.0 | 1.53 | 0.54 | 0 |
| 42 | 2.4 | 1.1 | 1.24 | 0.56 | 0 |
| 43 | 2.8 | 1.0 | 1.54 | 0.54 | 0 |
| 44 | 2.9 | 1.2 | 1.52 | 0.63 | 0 |
| 45 | 3.0 | 1.0 | 1.59 | 0.55 | 0 |
| 46 | 3.0 | 1.2 | 1.53 | 0.63 | 0 |
| 47 | 2.3 | 1.2 | 1.22 | 0.67 | 0 |
| 49 | 2.4 | 1.2 | 1.32 | 0.69 | 0 |
| 50 | 3.4 | 1.3 | 1.74 | 0.68 | 0 |
| Mean | 2.78 | 1.14 | 1.470 | 0.611 | 0.0 |
| SD | 0.35 | 0.12 | 0.174 | 0.063 | 0.0 |
| N | 9 | 9 | 9 | 9 | 9 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 |  |  |  |  |  |
| Mean Pup  AGD males (mm) | Mean Pup  AGD females (mm) | Mean Norm.  Pup AGD m | Mean Norm.  Pup AGD f | Mean Pup  A/N males |
| 1 | 1 | 1 | 1 | 13 |
| 51 | 2.5 | 1.1 | 1.31 | 0.59 | 0 |
| 52 | 2.6 | 1.1 | 1.32 | 0.57 | 0 |
| 53 | 2.6 | 1.1 | 1.36 | 0.57 | 0 |
| 54 | 3.0 | 1.2 | 1.63 | 0.67 | 0 |
| 55 | 2.7 | 1.1 | 1.39 | 0.60 | 0 |
| 56 | 3.0 | 1.1 | 1.54 | 0.58 | 0 |
| 57 | 3.1 | 1.2 | 1.61 | 0.61 | 0 |
| 58 | 3.0 | 1.3 | 1.50 | 0.66 | 0 |
| 60 | 3.1 | 1.2 | 1.58 | 0.60 | 0 |
| Mean | 2.82 | 1.14 | 1.470 | 0.605 | 0.0 |
| SD | 0.24 | 0.06 | 0.126 | 0.036 | 0.0 |
| N | 9 | 9 | 9 | 9 | 9 |
| %Diff | 1.57 | 0.64 | 0.038 | -0.824 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 |  |  |  |  |  |
| Mean Pup  AGD males (mm) | Mean Pup  AGD females (mm) | Mean Norm.  Pup AGD m | Mean Norm.  Pup AGD f | Mean Pup  A/N males |
| 1 | 1 | 1 | 1 | 13 |
| 61 | 3.1 | 1.2 | 1.58 | 0.63 | 0 |
| 62 | 2.1 | 1.2 | 1.20 | 0.66 | 0 |
| 63 | 2.5 | 1.2 | 1.45 | 0.70 | 0 |
| 64 | 2.4 | 1.0 | 1.30 | 0.56 | 0 |
| 65 | 3.1 | 1.0 | 1.60 | 0.50 | 0 |
| 66 | 2.6 | 1.1 | 1.32 | 0.54 | 0 |
| 67 | 2.6 | 1.1 | 1.45 | 0.63 | 0 |
| 68 | 3.0 | 1.0 | 1.63 | 0.55 | 0 |
| 69 | 3.2 | 1.2 | 1.64 | 0.64 | 0 |
| 70 | 2.6 | 1.1 | 1.40 | 0.63 | 0 |
| Mean | 2.70 | 1.11 | 1.458 | 0.604 | 0.0 |
| SD | 0.34 | 0.10 | 0.152 | 0.061 | 0.0 |
| N | 10 | 10 | 10 | 10 | 10 |
| %Diff | -2.75 | -2.46 | -0.805 | -1.034 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 |  |  |  |  |  |
| Mean Pup  AGD males (mm) | Mean Pup  AGD females (mm) | Mean Norm.  Pup AGD m | Mean Norm.  Pup AGD f | Mean Pup  A/N males |
| 1 | 1 | 1 | 1 | 13 |
| 71 | 2.5 | 1.2 | 1.34 | 0.64 | 0 |
| 72 | 2.4 | 1.1 | 1.28 | 0.61 | 0 |
| 73 | 2.9 | 1.2 | 1.47 | 0.60 | 0 |
| 74 | 2.8 | 1.1 | 1.55 | 0.62 | 0 |
| 75 | 2.4 | 1.5 | 1.30 | 0.84 | 0 |
| 76 | 2.5 | 1.2 | 1.34 | 0.64 | 0 |
| 79 | 2.7 | 1.2 | 1.42 | 0.65 | 0 |
| 80 | 3.1 | 1.1 | 1.62 | 0.58 | 0 |
| Mean | 2.67 | 1.20 | 1.415 | 0.646 | 0.0 |
| SD | 0.27 | 0.12 | 0.123 | 0.081 | 0.0 |
| N | 8 | 8 | 8 | 8 | 8 |
| %Diff | -3.79 | 5.52 | -3.757 | 5.874 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 41 | Male | 41-1 | 3.0 | 1.55 | 0 |
|  |  | 41-2 | 2.8 | 1.46 | 0 |
|  |  | 41-3 | 2.9 | 1.51 | - |
|  |  | 41-4 | 3.0 | 1.58 | 0 |
|  |  | 41-5 | 3.1 | 1.67 | 0 |
|  |  | 41-6 | 2.9 | 1.52 | - |
|  |  | 41-7 | 2.7 | 1.41 | - |
|  | Female | 41-8 | 0.9 | 0.51 | - |
|  |  | 41-9 | 1.0 | 0.54 | - |
|  |  | 41-10 | 1.0 | 0.53 | - |
|  |  | 41-11 | 1.0 | 0.53 | - |
|  |  | 41-12 | 1.1 | 0.59 | - |
| 42 | Male | 42-1 | 2.4 | 1.25 | 0 |
|  |  | 42-2 | 2.6 | 1.32 | 0 |
|  |  | 42-3 | 2.2 | 1.16 | 0 |
|  | Female | 42-4 | 1.0 | 0.51 | - |
|  |  | 42-5 | 1.2 | 0.62 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 42 | Female | 42-6 | 1.1 | 0.58 | - |
|  |  | 42-7 | 1.1 | 0.57 | - |
|  |  | 42-8 | 1.0 | 0.52 | - |
|  |  | 42-9 | 1.1 | 0.57 | - |
|  |  | 42-10 | 1.1 | 0.58 | - |
| 43 | Male | 43-1 | 2.8 | 1.50 | 0 |
|  |  | 43-2 | 2.9 | 1.59 | 0 |
|  |  | 43-3 | 3.0 | 1.68 | 0 |
|  |  | 43-4 | 2.5 | 1.40 | 0 |
|  | Female | 43-5 | 0.9 | 0.51 | - |
|  |  | 43-6 | 1.1 | 0.61 | - |
|  |  | 43-7 | 1.0 | 0.55 | - |
|  |  | 43-8 | 1.1 | 0.61 | - |
|  |  | 43-9 | 0.9 | 0.50 | - |
|  |  | 43-10 | 1.0 | 0.54 | - |
|  |  | 43-11 | 0.8 | 0.44 | - |
|  |  | 43-12 | 0.9 | 0.52 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 44 | Male | 44-1 | 2.8 | 1.47 | 0 |
|  |  | 44-2 | 3.0 | 1.58 | 0 |
|  |  | 44-3 | 2.9 | 1.49 | 0 |
|  |  | 44-4 | 3.0 | 1.58 | 0 |
|  |  | 44-5 | 2.6 | 1.34 | - |
|  |  | 44-6 | 3.0 | 1.56 | 0 |
|  |  | 44-7 | 2.8 | 1.49 | - |
|  |  | 44-8 | 3.1 | 1.63 | - |
|  | Female | 44-9 | 1.3 | 0.70 | - |
|  |  | 44-10 | 1.1 | 0.60 | - |
|  |  | 44-11 | 1.1 | 0.58 | - |
| 45 | Male | 45-1 | 2.7 | 1.46 | - |
|  |  | 45-2 | 3.0 | 1.60 | - |
|  |  | 45-3 | 3.1 | 1.67 | 0 |
|  |  | 45-4 | 3.1 | 1.61 | 0 |
|  |  | 45-5 | 3.2 | 1.76 | - |
|  |  | 45-6 | 3.0 | 1.58 | 0 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 45 | Male | 45-7 | 3.0 | 1.60 | 0 |
|  |  | 45-8 | 2.9 | 1.55 | - |
|  |  | 45-9 | 2.7 | 1.52 | - |
|  | Female | 45-10 | 1.1 | 0.59 | - |
|  |  | 45-11 | 0.9 | 0.48 | - |
|  |  | 45-12 | 1.1 | 0.59 | - |
|  |  | 45-13 | 1.1 | 0.60 | - |
|  |  | 45-14 | 0.9 | 0.49 | - |
|  |  | 45-15 | 1.1 | 0.58 | - |
| 46 | Male | 46-1 | 3.1 | 1.56 | 0 |
|  |  | 46-2 | 2.8 | 1.43 | 0 |
|  |  | 46-3 | 3.2 | 1.64 | - |
|  |  | 46-4 | 3.0 | 1.53 | 0 |
|  |  | 46-5 | 3.1 | 1.60 | 0 |
|  |  | 46-6 | 2.9 | 1.52 | - |
|  |  | 46-7 | 2.9 | 1.53 | - |
|  |  | 46-8 | 2.8 | 1.44 | 0 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 46 | Female | 46-9 | 1.3 | 0.67 | - |
|  |  | 46-10 | 1.0 | 0.51 | - |
|  |  | 46-11 | 1.3 | 0.73 | - |
| 47 | Male | 47-1 | 2.2 | 1.15 | 0 |
|  |  | 47-2 | 2.5 | 1.33 | 0 |
|  |  | 47-3 | 2.2 | 1.17 | 0 |
|  | Female | 47-4 | 1.2 | 0.65 | - |
|  |  | 47-5 | 1.0 | 0.53 | - |
|  |  | 47-6 | 1.4 | 0.75 | - |
|  |  | 47-7 | 1.4 | 0.77 | - |
|  |  | 47-8 | 1.4 | 0.75 | - |
|  |  | 47-9 | 1.2 | 0.64 | - |
|  |  | 47-10 | 1.0 | 0.55 | - |
|  |  | 47-11 | 1.3 | 0.69 | - |
|  |  | 47-12 | 1.3 | 0.71 | - |
| 49 | Male | 49-1 | 2.5 | 1.37 | - |
|  |  | 49-2 | 2.2 | 1.21 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 49 | Male | 49-3 | 2.7 | 1.47 | 0 |
|  |  | 49-4 | 2.6 | 1.46 | 0 |
|  |  | 49-5 | 2.5 | 1.38 | - |
|  |  | 49-6 | 2.5 | 1.37 | - |
|  |  | 49-7 | 1.8 | 1.01 | 0 |
|  |  | 49-8 | 2.3 | 1.28 | 0 |
|  | Female | 49-9 | 1.0 | 0.57 | - |
|  |  | 49-10 | 0.9 | 0.50 | - |
|  |  | 49-11 | 1.0 | 0.55 | - |
|  |  | 49-12 | 1.7 | 0.95 | - |
|  |  | 49-13 | 1.6 | 0.90 | - |
| 50 | Male | 50-1 | 3.3 | 1.70 | 0 |
|  |  | 50-2 | 3.5 | 1.79 | 0 |
|  |  | 50-3 | 3.3 | 1.73 | 0 |
|  | Female | 50-4 | 1.8 | 0.95 | - |
|  |  | 50-5 | 1.3 | 0.67 | - |
|  |  | 50-6 | 1.4 | 0.75 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 0  ppm Group 1 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 50 | Female | 50-7 | 1.1 | 0.57 | - |
|  |  | 50-8 | 1.2 | 0.62 | - |
|  |  | 50-9 | 1.0 | 0.51 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 51 | Male | 51-1 | 2.0 | 1.09 | - |
|  |  | 51-2 | 2.4 | 1.28 | - |
|  |  | 51-3 | 2.6 | 1.39 | 0 |
|  |  | 51-4 | 2.6 | 1.39 | 0 |
|  |  | 51-5 | 2.7 | 1.40 | - |
|  |  | 51-6 | 2.6 | 1.36 | 0 |
|  |  | 51-7 | 2.3 | 1.23 | 0 |
|  | Female | 51-8 | 1.2 | 0.64 | - |
|  |  | 51-9 | 1.1 | 0.61 | - |
|  |  | 51-10 | 1.2 | 0.64 | - |
|  |  | 51-11 | 1.1 | 0.60 | - |
|  |  | 51-12 | 1.0 | 0.53 | - |
|  |  | 51-13 | 1.0 | 0.54 | - |
| 52 | Male | 52-1 | 2.6 | 1.32 | 0 |
|  |  | 52-2 | 2.7 | 1.36 | 0 |
|  |  | 52-3 | 2.5 | 1.28 | 0 |
|  | Female | 52-4 | 1.0 | 0.51 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 52 | Female | 52-5 | 1.2 | 0.64 | - |
|  |  | 52-6 | 1.1 | 0.58 | - |
|  |  | 52-7 | 1.1 | 0.57 | - |
| 53 | Male | 53-1 | 2.8 | 1.49 | 0 |
|  |  | 53-2 | 2.3 | 1.18 | 0 |
|  |  | 53-3 | 2.6 | 1.37 | 0 |
|  |  | 53-4 | 2.3 | 1.29 | - |
|  |  | 53-5 | 2.7 | 1.41 | - |
|  |  | 53-6 | 2.3 | 1.31 | 0 |
|  |  | 53-7 | 2.9 | 1.50 | 0 |
|  | Female | 53-8 | 1.1 | 0.59 | - |
|  |  | 53-9 | 1.2 | 0.62 | - |
|  |  | 53-10 | 0.9 | 0.48 | - |
| 54 | Male | 54-1 | 2.8 | 1.52 | - |
|  |  | 54-2 | 3.0 | 1.63 | 0 |
|  |  | 54-3 | 2.9 | 1.68 | 0 |
|  |  | 54-4 | 3.1 | 1.72 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 54 | Male | 54-5 | 3.0 | 1.63 | 0 |
|  |  | 54-6 | 2.9 | 1.57 | 0 |
|  | Female | 54-7 | 1.2 | 0.68 | - |
|  |  | 54-8 | 1.3 | 0.70 | - |
|  |  | 54-9 | 1.2 | 0.66 | - |
|  |  | 54-10 | 1.3 | 0.75 | - |
|  |  | 54-11 | 1.0 | 0.56 | - |
| 55 | Male | 55-1 | 2.2 | 1.11 | 0 |
|  |  | 55-2 | 2.9 | 1.52 | 0 |
|  |  | 55-3 | 2.8 | 1.43 | 0 |
|  |  | 55-4 | 2.9 | 1.49 | 0 |
|  | Female | 55-5 | 1.2 | 0.62 | - |
|  |  | 55-6 | 1.2 | 0.62 | - |
|  |  | 55-7 | 1.2 | 0.63 | - |
|  |  | 55-8 | 1.0 | 0.53 | - |
|  |  | 55-9 | 1.1 | 0.58 | - |
| 56 | Male | 56-1 | 3.1 | 1.55 | 0 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 56 | Male | 56-2 | 2.8 | 1.49 | - |
|  |  | 56-3 | 3.0 | 1.54 | 0 |
|  |  | 56-4 | 2.8 | 1.46 | 0 |
|  |  | 56-5 | 3.1 | 1.56 | 0 |
|  |  | 56-6 | 3.2 | 1.63 | 0 |
|  |  | 56-7 | 3.0 | 1.53 | - |
|  | Female | 56-8 | 1.2 | 0.62 | - |
|  |  | 56-9 | 1.0 | 0.53 | - |
|  |  | 56-10 | 1.1 | 0.61 | - |
| 57 | Male | 57-1 | 3.1 | 1.61 | 0 |
|  |  | 57-2 | 3.2 | 1.67 | 0 |
|  |  | 57-3 | 3.1 | 1.65 | 0 |
|  |  | 57-4 | 3.2 | 1.67 | - |
|  |  | 57-5 | 3.1 | 1.65 | - |
|  |  | 57-6 | 3.2 | 1.60 | - |
|  |  | 57-7 | 2.8 | 1.44 | 0 |
|  |  | 57-8 | 3.0 | 1.55 | 0 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 57 | Female | 57-9 | 1.2 | 0.63 | - |
|  |  | 57-10 | 1.1 | 0.57 | - |
|  |  | 57-11 | 1.2 | 0.62 | - |
| 58 | Male | 58-1 | 3.0 | 1.52 | 0 |
|  |  | 58-2 | 2.9 | 1.48 | 0 |
|  | Female | 58-3 | 1.5 | 0.78 | - |
|  |  | 58-4 | 1.2 | 0.63 | - |
|  |  | 58-5 | 1.4 | 0.74 | - |
|  |  | 58-6 | 1.3 | 0.66 | - |
|  |  | 58-7 | 1.2 | 0.62 | - |
|  |  | 58-8 | 1.4 | 0.74 | - |
|  |  | 58-9 | 1.1 | 0.56 | - |
|  |  | 58-10 | 1.1 | 0.56 | - |
| 60 | Male | 60-1 | 2.9 | 1.55 | 0 |
|  |  | 60-2 | 3.1 | 1.53 | 0 |
|  |  | 60-3 | 3.1 | 1.58 | 0 |
|  |  | 60-4 | 3.1 | 1.58 | 0 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 12500  ppm Group 2 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 60 | Male | 60-5 | 3.3 | 1.68 | 0 |
|  |  | 60-6 | 3.1 | 1.58 | 0 |
|  | Female | 60-7 | 1.2 | 0.62 | - |
|  |  | 60-8 | 1.1 | 0.59 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 61 | Male | 61-1 | 2.9 | 1.52 | 0 |
|  |  | 61-2 | 3.2 | 1.64 | 0 |
|  | Female | 61-3 | 1.4 | 0.72 | - |
|  |  | 61-4 | 1.2 | 0.63 | - |
|  |  | 61-5 | 1.3 | 0.67 | - |
|  |  | 61-6 | 1.1 | 0.58 | - |
|  |  | 61-7 | 1.0 | 0.53 | - |
|  |  | 61-8 | 1.2 | 0.63 | - |
|  |  | 61-9 | 1.4 | 0.73 | - |
|  |  | 61-10 | 1.4 | 0.71 | - |
|  |  | 61-11 | 1.2 | 0.63 | - |
|  |  | 61-12 | 1.1 | 0.57 | - |
|  |  | 61-13 | 0.9 | 0.49 | - |
| 62 | Male | 62-1 | 2.1 | 1.18 | 0 |
|  |  | 62-2 | 2.3 | 1.25 | - |
|  |  | 62-3 | 1.7 | 0.96 | 0 |
|  |  | 62-4 | 2.2 | 1.25 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 62 | Male | 62-5 | 2.4 | 1.32 | 0 |
|  |  | 62-6 | 2.0 | 1.11 | 0 |
|  |  | 62-7 | 2.3 | 1.34 | - |
|  | Female | 62-8 | 1.3 | 0.73 | - |
|  |  | 62-9 | 1.3 | 0.72 | - |
|  |  | 62-10 | 1.3 | 0.73 | - |
|  |  | 62-11 | 1.0 | 0.55 | - |
|  |  | 62-12 | 1.1 | 0.61 | - |
|  |  | 62-13 | 1.1 | 0.63 | - |
| 63 | Male | 63-1 | 2.5 | 1.38 | 0 |
|  |  | 63-2 | 2.9 | 1.63 | 0 |
|  |  | 63-3 | 2.3 | 1.29 | 0 |
|  |  | 63-4 | 2.6 | 1.48 | - |
|  |  | 63-5 | 2.1 | 1.37 | - |
|  |  | 63-6 | 2.5 | 1.40 | - |
|  |  | 63-7 | 2.9 | 1.62 | 0 |
|  | Female | 63-8 | 1.3 | 0.73 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 63 | Female | 63-9 | 1.1 | 0.61 | - |
|  |  | 63-10 | 1.3 | 0.78 | - |
|  |  | 63-11 | 1.3 | 0.75 | - |
|  |  | 63-12 | 1.2 | 0.70 | - |
|  |  | 63-13 | 1.2 | 0.67 | - |
|  |  | 63-14 | 1.1 | 0.63 | - |
| 64 | Male | 64-1 | 2.3 | 1.26 | 0 |
|  |  | 64-2 | 2.4 | 1.31 | 0 |
|  |  | 64-3 | 2.6 | 1.42 | 0 |
|  |  | 64-4 | 2.4 | 1.31 | 0 |
|  |  | 64-5 | 2.2 | 1.21 | - |
|  | Female | 64-6 | 0.8 | 0.46 | - |
|  |  | 64-7 | 0.9 | 0.49 | - |
|  |  | 64-8 | 1.2 | 0.66 | - |
|  |  | 64-9 | 0.7 | 0.38 | - |
|  |  | 64-10 | 0.9 | 0.51 | - |
|  |  | 64-11 | 1.1 | 0.61 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 64 | Female | 64-12 | 1.1 | 0.61 | - |
|  |  | 64-13 | 1.4 | 0.77 | - |
| 65 | Male | 65-1 | 3.1 | 1.61 | - |
|  |  | 65-2 | 3.2 | 1.68 | 0 |
|  |  | 65-3 | 2.9 | 1.54 | 0 |
|  |  | 65-4 | 3.2 | 1.66 | - |
|  |  | 65-5 | 3.2 | 1.71 | 0 |
|  |  | 65-6 | 2.9 | 1.55 | 0 |
|  |  | 65-7 | 3.0 | 1.56 | - |
|  |  | 65-8 | 2.9 | 1.49 | 0 |
|  | Female | 65-9 | 1.0 | 0.52 | - |
|  |  | 65-10 | 1.0 | 0.51 | - |
|  |  | 65-11 | 0.9 | 0.48 | - |
| 66 | Male | 66-1 | 2.7 | 1.36 | 0 |
|  |  | 66-2 | 2.3 | 1.19 | 0 |
|  |  | 66-3 | 2.4 | 1.23 | 0 |
|  |  | 66-4 | 2.7 | 1.38 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 66 | Male | 66-5 | 2.8 | 1.47 | 0 |
|  | Female | 66-6 | 1.1 | 0.56 | - |
|  |  | 66-7 | 1.0 | 0.52 | - |
|  |  | 66-8 | 1.0 | 0.51 | - |
|  |  | 66-9 | 1.1 | 0.56 | - |
| 67 | Male | 67-1 | 2.1 | 1.15 | 0 |
|  |  | 67-2 | 2.7 | 1.54 | 0 |
|  |  | 67-3 | 2.5 | 1.36 | 0 |
|  |  | 67-4 | 3.0 | 1.74 | 0 |
|  | Female | 67-5 | 1.2 | 0.68 | - |
|  |  | 67-6 | 0.7 | 0.41 | - |
|  |  | 67-7 | 1.1 | 0.61 | - |
|  |  | 67-8 | 1.2 | 0.70 | - |
|  |  | 67-9 | 1.3 | 0.78 | - |
|  |  | 67-10 | NSCH | - | - |
| 68 | Male | 68-1 | 2.9 | 1.60 | 0 |
|  |  | 68-2 | 3.1 | 1.68 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 68 | Male | 68-3 | 2.9 | 1.55 | 0 |
|  |  | 68-4 | 3.1 | 1.68 | 0 |
|  |  | 68-5 | 2.9 | 1.57 | - |
|  |  | 68-6 | 2.8 | 1.70 | 0 |
|  | Female | 68-7 | 1.0 | 0.56 | - |
|  |  | 68-8 | 1.0 | 0.54 | - |
|  |  | 68-9 | 1.1 | 0.60 | - |
|  |  | 68-10 | 0.8 | 0.47 | - |
|  |  | 68-11 | 0.8 | 0.47 | - |
|  |  | 68-12 | 0.9 | 0.50 | - |
|  |  | 68-13 | 1.1 | 0.61 | - |
|  |  | 68-14 | 1.2 | 0.65 | - |
| 69 | Male | 69-1 | 3.1 | 1.59 | 0 |
|  |  | 69-2 | 3.3 | 1.69 | 0 |
|  | Female | 69-3 | 1.6 | 0.81 | - |
|  |  | 69-4 | 1.5 | 0.77 | - |
|  |  | 69-5 | 1.1 | 0.57 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 69 | Female | 69-6 | 1.2 | 0.62 | - |
|  |  | 69-7 | 1.0 | 0.50 | - |
|  |  | 69-8 | 1.0 | 0.51 | - |
|  |  | 69-9 | 1.3 | 0.67 | - |
| 70 | Male | 70-1 | 2.2 | 1.22 | 0 |
|  |  | 70-2 | 2.0 | 1.13 | - |
|  |  | 70-3 | 2.8 | 1.50 | - |
|  |  | 70-4 | 2.5 | 1.37 | - |
|  |  | 70-5 | 2.7 | 1.49 | - |
|  |  | 70-6 | 2.7 | 1.49 | 0 |
|  |  | 70-7 | 2.5 | 1.36 | - |
|  |  | 70-8 | 2.8 | 1.53 | - |
|  |  | 70-9 | 2.8 | 1.51 | 0 |
|  |  | 70-10 | 2.8 | 1.55 | 0 |
|  |  | 70-11 | 2.3 | 1.28 | 0 |
|  | Female | 70-12 | 1.1 | 0.61 | - |
|  |  | 70-13 | 1.1 | 0.62 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 25000  ppm Group 3 | | |  |  |  |
| Anogenital Distance (mm) | Normalized AGD Pup | Areola/ Nipple Count |
| Dam Pup Sex Pup | | |  |  |  |
| 1 | 1 | 13 |
| 70 | Female | 70-14 | 1.2 | 0.67 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 71 | Male | 71-1 | 2.4 | 1.34 | 0 |
|  |  | 71-2 | 2.3 | 1.23 | - |
|  |  | 71-3 | 2.7 | 1.44 | 0 |
|  |  | 71-4 | 2.6 | 1.44 | 0 |
|  |  | 71-5 | 2.4 | 1.27 | 0 |
|  | Female | 71-6 | 1.0 | 0.56 | - |
|  |  | 71-7 | 1.2 | 0.65 | - |
|  |  | 71-8 | 1.3 | 0.71 | - |
|  |  | 71-9 | 1.2 | 0.64 | - |
|  |  | 71-10 | 1.0 | 0.53 | - |
|  |  | 71-11 | 1.2 | 0.65 | - |
|  |  | 71-12 | 1.3 | 0.72 | - |
| 72 | Male | 72-1 | 2.1 | 1.12 | 0 |
|  |  | 72-2 | 2.1 | 1.10 | 0 |
|  |  | 72-3 | 2.7 | 1.40 | 0 |
|  |  | 72-4 | 2.7 | 1.42 | - |
|  |  | 72-5 | 2.6 | 1.37 | 0 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 72 | Female | 72-6 | 1.1 | 0.59 | - |
|  |  | 72-7 | 1.1 | 0.59 | - |
|  |  | 72-8 | 1.2 | 0.65 | - |
|  |  | 72-9 | 1.1 | 0.60 | - |
|  |  | 72-10 | 1.2 | 0.62 | - |
| 73 | Male | 73-1 | 2.6 | 1.37 | 0 |
|  |  | 73-2 | 2.9 | 1.46 | - |
|  |  | 73-3 | 3.1 | 1.54 | 0 |
|  |  | 73-4 | 3.2 | 1.65 | 0 |
|  |  | 73-5 | 2.7 | 1.36 | - |
|  |  | 73-6 | 2.8 | 1.44 | 0 |
|  | Female | 73-7 | 1.5 | 0.79 | - |
|  |  | 73-8 | 1.0 | 0.51 | - |
|  |  | 73-9 | 1.0 | 0.52 | - |
|  |  | 73-10 | 1.1 | 0.57 | - |
| 74 | Male | 74-1 | 2.9 | 1.55 | - |
|  |  | 74-2 | 3.2 | 1.77 | 0 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 74 | Male | 74-3 | 2.8 | 1.55 | 0 |
|  |  | 74-4 | 2.7 | 1.44 | 0 |
|  |  | 74-5 | 2.7 | 1.45 | 0 |
|  |  | 74-6 | 2.9 | 1.58 | - |
|  |  | 74-7 | 2.8 | 1.52 | - |
|  |  | 74-8 | 3.0 | 1.63 | - |
|  |  | 74-9 | 2.7 | 1.50 | - |
|  |  | 74-10 | 2.7 | 1.46 | - |
|  | Female | 74-11 | 1.4 | 0.79 | - |
|  |  | 74-12 | 1.1 | 0.60 | - |
|  |  | 74-13 | 0.9 | 0.49 | - |
|  |  | 74-14 | 1.1 | 0.60 | - |
| 75 | Male | 75-1 | 2.8 | 1.54 | 0 |
|  |  | 75-2 | 2.4 | 1.29 | - |
|  |  | 75-3 | 2.5 | 1.35 | 0 |
|  |  | 75-4 | 2.5 | 1.35 | 0 |
|  |  | 75-6 | 2.5 | 1.38 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 75 | Male | 75-7 | 2.3 | 1.26 | - |
|  |  | 75-12 | 1.6 | 0.90 | - |
|  | Female | 75-5 | 2.7 | 1.59 | - |
|  |  | 75-8 | 1.1 | 0.61 | - |
|  |  | 75-9 | 1.2 | 0.65 | - |
|  |  | 75-10 | 1.0 | 0.57 | - |
|  |  | 75-11 | 1.4 | 0.77 | - |
| 76 | Male | 76-1 | 2.7 | 1.41 | 0 |
|  |  | 76-2 | 2.6 | 1.35 | 0 |
|  |  | 76-3 | 2.3 | 1.20 | 0 |
|  |  | 76-4 | 2.6 | 1.38 | - |
|  |  | 76-5 | 2.5 | 1.33 | - |
|  |  | 76-6 | 2.5 | 1.36 | 0 |
|  | Female | 76-7 | 1.1 | 0.60 | - |
|  |  | 76-8 | 1.2 | 0.64 | - |
|  |  | 76-9 | 1.2 | 0.62 | - |
|  |  | 76-10 | 1.1 | 0.58 | - |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 76 | Female | 76-11 | 1.3 | 0.70 | - |
|  |  | 76-12 | 1.3 | 0.69 | - |
|  |  | 76-13 | 1.3 | 0.68 | - |
| 79 | Male | 79-1 | 3.0 | 1.58 | 0 |
|  |  | 79-2 | 2.7 | 1.40 | 0 |
|  |  | 79-3 | 2.6 | 1.35 | 0 |
|  |  | 79-4 | 2.5 | 1.34 | 0 |
|  | Female | 79-5 | 1.3 | 0.70 | - |
|  |  | 79-6 | 1.2 | 0.64 | - |
|  |  | 79-7 | 1.3 | 0.68 | - |
|  |  | 79-8 | 1.1 | 0.57 | - |
|  |  | 79-9 | 1.1 | 0.59 | - |
|  |  | 79-10 | 1.3 | 0.69 | - |
| 80 | Male | 80-1 | 3.2 | 1.61 | - |
|  |  | 80-2 | 2.9 | 1.52 | 0 |
|  |  | 80-3 | 3.3 | 1.73 | 0 |
|  |  | 80-4 | 3.3 | 1.70 | 0 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 50000  ppm Group 4 | Pup Sex | Pup |  |  |  |
| Anogenital  Distance (mm) | Normalized  AGD Pup | Areola/  Nipple Count |
| Dam |  |  |  |
| 1 | 1 | 13 |
| 80 | Male | 80-5 | 3.0 | 1.57 | 0 |
|  | Female | 80-6 | 1.2 | 0.66 | - |
|  |  | 80-7 | 1.2 | 0.62 | - |
|  |  | 80-8 | 1.0 | 0.53 | - |
|  |  | 80-9 | 1.0 | 0.52 | - |

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 0  ppm Group 1 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 41 | | | |
| 41-1 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 41-2 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 41-3 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 41-4 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 41-5 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 41-6 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 41-7 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 41-8 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 41-9 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 41-10 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 41-11 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 41-12 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| Dam: 42 | | | |
| 42-1 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 42-2 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 42-3 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 42-4 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 42-5 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 42-6 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 42-7 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 42-8 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 42-9 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 42-10 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| Dam: 43 | | | |
| 43-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 43-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 43-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 43-4 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 43-5 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 43-6 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 43-7 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 43-8 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 43-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 43-10 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 43-11 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 43-12 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| Dam: 44 | | | |
| 44-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 44-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 44-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 0  ppm Group 1 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 44 | (Continued...) | | |
| 44-4 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 44-5 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 44-6 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 44-7 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 44-8 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 44-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 44-10 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 44-11 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| Dam: 45 | | | |
| 45-1 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 45-2 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 45-3 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 45-4 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 45-5 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 45-6 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 45-7 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 45-8 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 45-9 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 45-10 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 45-11 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 45-12 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 45-13 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 45-14 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 45-15 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| Dam: 46 | | | |
| 46-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 46-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 46-3 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 46-4 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 46-5 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 46-6 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 46-7 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 46-8 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 46-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 46-10 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 46-11 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| Dam: 47 | | | |
| 47-1 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 47-2 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 47-3 | MT | 16 | . Pup Necropsy, No abnormalities detected |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 0  ppm Group 1 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 47 | (Continued...) | | |
| 47-4 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 47-5 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 47-6 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 47-7 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 47-8 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 47-9 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 47-10 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 47-11 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 47-12 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| Dam: 49 | | | |
| 49-1 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 49-2 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 49-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 49-4 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 49-5 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 49-6 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 49-7 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 49-8 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 49-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 49-10 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 49-11 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 49-12 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 49-13 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| Dam: 50 | | | |
| 50-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 50-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 50-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 50-4 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 50-5 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 50-6 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 50-7 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 50-8 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 50-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 12500  ppm Group 2 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 51 | | | |
| 51-1 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 51-2 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 51-3 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 51-4 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 51-5 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 51-6 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 51-7 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 51-8 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 51-9 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 51-10 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 51-11 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 51-12 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 51-13 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| Dam: 52 | | | |
| 52-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 52-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 52-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 52-4 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 52-5 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 52-6 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 52-7 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| Dam: 53 | | | |
| 53-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 53-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 53-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 53-4 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 53-5 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 53-6 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 53-7 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 53-8 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 53-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 53-10 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| Dam: 54 | | | |
| 54-1 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 54-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 54-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 54-4 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 54-5 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 54-6 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 54-7 | FT | 14 | . Pup Necropsy, No abnormalities detected |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 12500  ppm Group 2 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 54 | (Continued...) | | |
| 54-8 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 54-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 54-10 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 54-11 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| Dam: 55 | | | |
| 55-1 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 55-2 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 55-3 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 55-4 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 55-5 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 55-6 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 55-7 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 55-8 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 55-9 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| Dam: 56 | | | |
| 56-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 56-2 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 56-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 56-4 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 56-5 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 56-6 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 56-7 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 56-8 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 56-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 56-10 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| Dam: 57 | | | |
| 57-1 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 57-2 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 57-3 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 57-4 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 57-5 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 57-6 | MD | 4 | . Pup Necropsy, General |
|  |  |  | General, Cannibalization No More Ob - Incidental |
| 57-7 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 57-8 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 57-9 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 57-10 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 57-11 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| Dam: 58 | | | |
| 58-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 12500  ppm Group 2 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 58 | (Continued...) | | |
| 58-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 58-3 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 58-4 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 58-5 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 58-6 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 58-7 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 58-8 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 58-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 58-10 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| Dam: 60 | | | |
| 60-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 60-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 60-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 60-4 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 60-5 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 60-6 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 60-7 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 60-8 | FT | 14 | . Pup Necropsy, No abnormalities detected |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 25000  ppm Group 3 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 61 | | | |
| 61-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 61-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 61-3 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 61-4 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 61-5 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 61-6 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 61-7 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 61-8 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 61-9 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 61-10 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 61-11 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 61-12 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 61-13 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| Dam: 62 | | | |
| 62-1 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 62-2 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 62-3 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 62-4 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 62-5 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 62-6 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 62-7 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 62-8 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 62-9 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 62-10 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 62-11 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 62-12 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 62-13 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| Dam: 63 | | | |
| 63-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 63-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 63-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 63-4 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 63-5 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 63-6 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 63-7 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 63-8 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 63-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 63-10 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 63-11 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 63-12 | FC | 4 | . Pup Necropsy, No abnormalities detected |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 25000  ppm Group 3 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 63 | (Continued...) | | |
| 63-13  63-14 | FC  FT | 4  14 | . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected |
| Dam: 64 | | | |
| 64-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 64-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 64-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 64-4 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 64-5 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 64-6 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 64-7 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 64-8 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 64-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 64-10 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 64-11 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 64-12 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 64-13 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| Dam: 65 | | | |
| 65-1 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 65-2 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 65-3 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 65-4 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 65-5 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 65-6 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 65-7 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 65-8 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 65-9 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 65-10 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 65-11 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| Dam: 66 | | | |
| 66-1 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 66-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 66-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 66-4 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 66-5 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 66-6 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 66-7 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 66-8 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 66-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| Dam: 67 | | | |
|  | | | |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 25000  ppm Group 3 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 67 (Continued...) | | | |
| 67-1  67-2  67-3  67-4  67-5  67-6  67-7  67-8  67-9  67-10 | MT MT MT MT FT FT FT FC FT FS | 14  14  14  14  14  14  14  4  14  1 | . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy - Unscheduled, General  General, Autolysis precludes evaluation |
| Dam: 68 | | | |
| 68-1  68-2  68-3  68-4  68-5  68-6  68-7  68-8  68-9  68-10  68-11  68-12  68-13  68-14 | MT MC MT MT MC MT FT FT FT FC FC FC FC FT | 15  4  15  15  4  15  15  15  15  4  4  4  4  15 | . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected |
| Dam: 69 | | | |
| 69-1  69-2  69-3  69-4  69-5  69-6  69-7  69-8  69-9 | MT MT FT FT FT FT FT FC FT | 14  14  14  14  14  14  14  4  14 | . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected |
| Dam: 70 | | | |
| 70-1  70-2  70-3 | MT MC MC | 16  4  4 | . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected  . Pup Necropsy, No abnormalities detected |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 25000  ppm Group 3 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 70 | (Continued...) | | |
| 70-4 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 70-5 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 70-6 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 70-7 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 70-8 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 70-9 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 70-10 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 70-11 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 70-12 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 70-13 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 70-14 | FT | 16 | . Pup Necropsy, No abnormalities detected |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 50000  ppm Group 4 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 71 | | | |
| 71-1 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 71-2 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 71-3 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 71-4 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 71-5 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 71-6 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 71-7 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 71-8 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 71-9 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 71-10 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 71-11 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 71-12 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| Dam: 72 | | | |
| 72-1 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 72-2 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 72-3 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 72-4 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 72-5 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 72-6 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 72-7 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 72-8 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 72-9 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 72-10 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| Dam: 73 | | | |
| 73-1 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 73-2 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 73-3 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 73-4 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 73-5 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 73-6 | MT | 15 | . Pup Necropsy, No abnormalities detected |
| 73-7 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 73-8 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 73-9 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| 73-10 | FT | 15 | . Pup Necropsy, No abnormalities detected |
| Dam: 74 | | | |
| 74-1 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 74-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 74-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 74-4 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 74-5 | MT | 14 | . Pup Necropsy, No abnormalities detected |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 50000  ppm Group 4 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 74 | (Continued...) | | |
| 74-6 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 74-7 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 74-8 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 74-9 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 74-10 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 74-11 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 74-12 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 74-13 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 74-14 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| Dam: 75 | | | |
| 75-1 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 75-2 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 75-3 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 75-4 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 75-5 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 75-6 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 75-7 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 75-8 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 75-9 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 75-10 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 75-11 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 75-12 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| Dam: 76 | | | |
| 76-1 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 76-2 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 76-3 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 76-4 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 76-5 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 76-6 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 76-7 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 76-8 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 76-9 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 76-10 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 76-11 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 76-12 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 76-13 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| Dam: 79 | | | |
| 79-1 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 79-2 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 79-3 | MT | 16 | . Pup Necropsy, No abnormalities detected |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

###### 14-Oct-2022 09:09:21

**Individual Pup Gross Pathology: F1 Generation 20334125**

Litter: A

|  |  |  |  |
| --- | --- | --- | --- |
| 50000  ppm Group 4 | Pup Sex and Status | Pup Day of Death | Findings |
| Dam: 79 | (Continued...) | | |
| 79-4 | MT | 16 | . Pup Necropsy, No abnormalities detected |
| 79-5 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 79-6 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 79-7 | FC | 4 | . Pup Necropsy, No abnormalities detected |
| 79-8 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 79-9 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| 79-10 | FT | 16 | . Pup Necropsy, No abnormalities detected |
| Dam: 80 | | | |
| 80-1 | MC | 4 | . Pup Necropsy, No abnormalities detected |
| 80-2 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 80-3 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 80-4 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 80-5 | MT | 14 | . Pup Necropsy, No abnormalities detected |
| 80-6 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 80-7 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 80-8 | FT | 14 | . Pup Necropsy, No abnormalities detected |
| 80-9 | FT | 14 | . Pup Necropsy, No abnormalities detected |

A=Alive T=Terminal C=Culled D=Found Dead S=Stillborn N=Unscheduled X=Transferred Y= Euthanized Maternal Death K=Missing; Presumed Cannibalized G=Missing Z=Accidental

* 1. **DEVELOPMENTAL DATA**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **MEASUREMENT** | **Mean** | **St.dev** | **N** | **P5** | **P95** | **Min** | **Max** |
| **Total number of offspring born** | 105 | 15 | 110 | 76 | 128 | 60 | 135 |
| **Total number of uterine implantation sites** | 114 | 15 | 108 | 83 | 137 | 62 | 144 |
| **Number of live offspring on Day 1 after littering** | 103 | 15 | 110 | 76 | 125 | 60 | 135 |
| **Number of live offspring on Day 4 (before culling)** | 102 | 15 | 110 | 75 | 125 | 59 | 135 |
| **Number of live offspring on Day 4 (after culling)** | 70 | 8 | 108 | 56 | 80 | 51 | 80 |
| **Number of live offspring on Day 13 after littering** | 70 | 8 | 105 | 56 | 80 | 51 | 80 |
| **Post-implantation survival index (%)** | 91 | 5 | 111 | 83 | 97 | 77 | 99 |
| **Live birth index (%)** | 99 | 2 | 114 | 94 | 100 | 89 | 100 |
| **Viability index (%)** | 99 | 2 | 114 | 97 | 100 | 87 | 100 |
| **Lactation index (%)** | 99 | 1 | 112 | 97 | 100 | 88 | 100 |

**HISTORICAL** **DATA** **FEMALES**

* 1. **DEVELOPMENTAL** **DATA**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Females** | **MEAN** | **STD.DEV.** | **N** | **P5** | **P95** |
| **F0-GENERATION** **LACTATION** |  |  |  |  |  |
| Duration of gestation | 21.4 | 0.55 | 1011 | 21.00 | 22.00 |
| Dead pups at first litter check | 0.1 | 0.68 | 1011 | 0.00 | 1.00 |
| Living pups at first litter check | 11.3 | 2.89 | 1011 | 5.00 | 15.00 |
| Postnatal loss | 0.1 | 0.66 | 1011 | 0.00 | 1.00 |
| Culled pups | 3.4 | 2.20 | 1011 | 0.00 | 7.00 |
| Living pups on culling day | 7.6 | 1.46 | 1011 | 4.00 | 8.00 |
| Breeding loss culling day - rearing day | 0.0 | 0.41 | 1011 | 0.00 | 0.00 |
| Living pups on rearing day | 7.5 | 1.67 | 1011 | 4.00 | 8.00 |

 **24Mar22** **11h08**

**HISTORICAL** **DATA** **FEMALES**

* 1. **DEVELOPMENTAL** **DATA** **SUBSET**

**Parameter** **Value**

**F0-GENERATION** **LACTATION**

Litters total 1011

Dead pups at first litter check 125

Number of litters affected 64

Living pups at first litter check 11382

Live males 5664

% of living pups at first litter check 49.8

Live females 5718

% of living pups at first litter check 50.2

Postnatal loss 125

% of living pups at first litter check 1.1

Number of litters affected 89

Culled pups 3482

Living pups on culling day 7691

Breeding loss culling day - rearing day 41

% of living pups on culling day 0.5

Number of litters affected 22

Living pups on rearing day 7550

Live males 3756

% of living pups on rearing day 49.7

Live females 3794

% of living pups on rearing day 50.3

 **24Mar22** **11h08**

* 1. **REPRODUCTION DATA**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MEASUREMENT** | **Mean** | **St.dev** | **N** | **P5** | **P95** | **Min** | **Max** | |
| **Mating index** | 99 | 3.2 | 114 | 90 | 100 | 90 | | 100 |
| **Fertility index** | 95 | 6.9 | 114 | 80 | 100 | 70 | | 100 |
| **Gestation index** | 98 | 4.1 | 114 | 89 | 100 | 78 | | 100 |

**HISTORICAL** **DATA** **FEMALES**

* 1. **PRECOITAL** **TIME**

**Day** **of** **the** **pairing** **period**

**Number** **of** **females** **mated**

|  |  |
| --- | --- |
| **F0-GENERATION** **POST** **COITUM;** **PAIRING** **PERIOD** **1** | |
| 1 | 358 |
| 2 | 253 |
| 3 | 239 |
| 4 | 179 |
| 5 | 2 |
| 6 | 4 |
| 7 | 1 |
| 9 | 1 |
| 12 | 2 |
| 13 | 17 |
| 14 | 15 |
| 15 | 1 |
| N | 1072 |
| MEAN PRECOITAL TIME | 2.6 |
| MEDIAN PRECOITAL TIME | 2.0 |
| **F0-GENERATION** **POST** **COITUM;** **PAIRING** **PERIOD** **2** | |
| -1 | 1 |
| 1 | 3 |
| 2 | 2 |
| 3 | 1 |
| N | 7 |
| MEAN PRECOITAL TIME | 1.3 |
| MEDIAN PRECOITAL TIME | 1.0 |

 **24Mar22** **11h08**

**HISTORICAL** **DATA** **FEMALES**

* 1. **IMPLANTATION** **SITES**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **'** | **UNITS** | **MEAN** | **STD.DEV.** | **N** | **P5** | **P95** |
| **AT** **NECROPSY**  Implantations |  | 12.3 | 2.79 | 991 | 7.00 | 16.00 |

 **23Mar22** **16h16**

**HISTORICAL** **DATA** **MALES**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **1.7 BODY** **WEIGHTS** **OF** **PUPS** **(GRAM)** | | | | | |
| **DAYS** | **MEAN** | **STD.DEV.** | **N** | **P5** | **P95** |
| **F0-GENERATION** **LACTATION** | | | | | |
| DAY 1 | 6.4 | 0.68 | 5648 | 5.40 | 7.50 |
| DAY 4 | 9.5 | 1.23 | 5601 | 7.80 | 11.70 |
| DAY 7 | 16.0 | 1.80 | 3778 | 13.20 | 19.00 |
| DAY 10 | 23.8 | 2.01 | 41 | 21.10 | 27.60 |
| DAY 13 | 30.7 | 2.83 | 3736 | 26.00 | 35.20 |
| DAY 17 | 41.6 | 2.05 | 41 | 38.90 | 45.00 |
| DAY 21 | 52.6 | 4.44 | 124 | 47.00 | 60.50 |
| DAY 28 | 92.8 | 5.96 | 41 | 85.00 | 102.00 |
| **FEMALES** |  |  |  |  |  |
| **1.7** **BODY** **WEIGHTS** **OF** **PUPS** **(GRAM)** | | | | | |
| **DAYS** | **MEAN** | **STD.DEV.** | **N** | **P5** | **P95** |
| **F0-GENERATION** **LACTATION** | | | | | |
| DAY 1 | 6.1 | 0.67 | 5706 | 5.10 | 7.20 |
| DAY 4 | 9.2 | 1.22 | 5657 | 7.40 | 11.20 |
| DAY 7 | 15.5 | 1.82 | 3822 | 12.60 | 18.50 |
| DAY 10 | 22.4 | 2.13 | 38 | 18.70 | 26.80 |
| DAY 13 | 29.9 | 2.88 | 3778 | 25.00 | 34.60 |
| DAY 17 | 40.3 | 1.90 | 37 | 38.00 | 44.00 |
| DAY 21 | 50.3 | 4.21 | 117 | 44.00 | 58.00 |
| DAY 28 | 85.5 | 4.75 | 37 | 79.00 | 94.00 |

 **24Mar22** **11h08**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **1.8 ESTROUS CYCLE TREATMENT PERIOD** |  | | | | | | | |
| **PARAMETER** | **Mean** | **St.dev** | **N** | **P5** | **P95** | **Min** | **Max** | |
| **Regular estrous cycle (%)** | 97.2 | 7.2 | 111 | 80 | 100 | 60.0 | 100 | |
| **PARAMETER Total Regular Irregular Extended di-estrous Acyclic Extended estrous** | | | | | | | | |
| **Cycle classification (%)** | 100 | 95.8 | 1.8 | 0.6 | 0.3 |  | 0.3 |  |
| **Cycle classification (count)** | 1097 | 1051 | 20 | 7 | 3 |  | 3 |  |
| **ESTROUS CYCLE PRETEST PERIOD** |  |  |  |  |  |  |  |  |
| **PARAMETER** | **Mean** | **St.dev** | **N** | **P5** | **P95** | **Min** |  | **Max** |
| **Regular estrous cycle (%)** | 99.7 | 1.7 | 107 | 100 | 100 | 88.9 |  | 100 |
| **PARAMETER** | **Total** | **Regular** | **Irregular** | **Extended di-estrous** | **Acyclic** | **Extended estrous** | | |
| **Cycle classification (%)** | 100 | 99.6 | 0.1 | 0.0 | 0.0 | 0.0 | | |
| **Cycle classification (count)** | 1065 | 1061 | 1 | 0 | 0 | 0 | | |

**HISTORICAL** **DATA**

* 1. **Anogenital** **Distance**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **MEAN** | **STD.DEV.** | **N** | **P5** | **P95** |
| **F0-GENERATION** **LACTATION**  anogenital dist M mm | 2.70 | 0.295 | 912 | 2.265 | 3.266 |
| anogenital dist F mm | 1.03 | 0.187 | 914 | 0.725 | 1.376 |

 **24Mar22** **11h36**

**HISTORICAL** **DATA** **MALES**

* 1. **Nipple** **Retention**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **MEAN** | **STD.DEV.** | **N** | **P5** | **P95** |
| **F0-GENERATION** **LACTATION**  Number of nipples | 0 | 0.3 | 178 | 0.0 | 0.0 |

 **28Mar22** **08h58**

**HISTORICAL** **DATA**

* 1. **Normalized Anogenital** **Distance**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **'** | **UNITS** | **MEAN** | **STD.DEV.** | **N** | **P5** | **P95** |
| **PND** **1**  norm anog dist F | mm | 0.57 | 0.103 | 892 | 0.400 | 0.750 |
| norm anog dist M | mm | 1.45 | 0.148 | 890 | 1.230 | 1.730 |

 **24Mar22** **09h41**

**MALES**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **1.12 MOTOR ACTIVITY AND MOVEMENTS** | | | | | |
| **MEASUREMENT** | **Mean** | **St.dev** | **N** | **P5** | **P95** |
| **Total movements** | 3472 | 1078 | 470 | 1848 | 5344 |
| **Ambulations** | 718 | 272 | 470 | 309 | 1249 |
| **FEMALES** |  |  |  |  |  |
| **1.12 MOTOR ACTIVITY AND MOVEMENTS** | | | | | |
| **MEASUREMENT** | **Mean** | **St.dev** | **N** | **P5** | **P95** |
| **Total movements** | 3524 | 1244 | 416 | 1763 | 5751 |
| **Ambulations** | 835 | 340 | 416 | 379 | 1472 |



**QA Approval:**

I approve the Quality Assurance Statement for this report.

Name:

**van Dooren, Maaike**

van Dooren, Maaike

Electronically Signed in

21-Mar-2023 12:27:09 (UTC+00:00)

Timestamp



**Study Director Approval:**

I approve this Report.

Name:

**van den Oetelaar, Daphne**

van den Oetelaar, Daphne

Electronically Signed in

23-Mar-2023 13:55:33 (UTC+00:00)

Timestamp

**SIGNATURE(S) FOR DOCUMENT: 20334125 Reproductive Toxicology Final Report**