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FINAL REPORT

Test Facility Study No. 20172120

Combined 28-Day Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test of DiHEP Aqueous Solution by Oral Gavage in Rats

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QUALITY ASSURANCE STATEMENT

Study title: Combined 28-Day Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test of DiHEP Aqueous Solution by Oral Gavage in Rats.

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. 20172120

Type of Inspections	Phase/Process	Start Inspection date	End Inspection date	Reporting date to TFM and SD*
Study	Final Study Plan	16-Jan-2019	16-Jan-2019	16-Jan-2019
	Littering/Culling	18-Mar-2019	18-Mar-2019	18-Mar-2019
	Study Plan Amendment 01	21-May-2019	21-May-2019	21-May-2019
	Data Review - Formulations	20-Aug-2019	20-Aug-2019	04-Sep-2019
	Report - Materials and Methods	04-Sep-2019	06-Sep-2019	09-Sep-2019
	Data Review - Technical Operations	05-Sep-2019	06-Sep-2019	09-Sep-2019
	Data Review - Necropsy	05-Sep-2019	06-Sep-2019	09-Sep-2019
	Report - Results	05-Sep-2019	09-Sep-2019	09-Sep-2019
	Data Review - Clinical Pathology	05-Sep-2019	06-Sep-2019	09-Sep-2019
	Data Review - Fetal Pathology	06-Sep-2019	06-Sep-2019	09-Sep-2019
	Data Review - Histology/Pathology Working Group	06-Sep-2019	06-Sep-2019	09-Sep-2019
	Phase Report - Pathology	06-Sep-2019	06-Sep-2019	09-Sep-2019
	Statistics	09-Sep-2019	09-Sep-2019	09-Sep-2019
	Final Report	16-Sep-2019	16-Sep-2019	16-Sep-2019
Process	**Animal Facilities** Test Item Handling Exposure Observations/Measurements Specimen Handling	21-Jan-2019	31-Jan-2019	04-Feb-2019
	Clinical pathology Observations/Measurements Specimen Handling	13-Feb-2019	22-Feb-2019	22-Feb-2019

Test Item Formulation Test Item Handling	19-Feb-2019	28-Feb-2019	07-Mar-2019
Fetal Pathology Observations/Measurements Specimen Handling	26-Feb-2019	08-Mar-2019	08-Mar-2019
Test Item Receipt Test Item Handling	04-Mar-2019	15-Mar-2019	15-Mar-2019
Necropsy Observations/Measurements Specimen Handling	12-Mar-2019	21-Mar-2019	22-Mar-2019
Histology Specimen Handling	26-Mar-2019	29-Mar-2019	29-Mar-2019

*TFM=Test Facility Management SD = Study Director

DocuSigned by:
Roland Dassen
Signer Name: Roland Dassen
Signing Reason: I approve this document
Signing Time: 17-Sep-2019 | 12:34:42 CEST
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R. Dassen
Quality Assurance Auditor

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.

D. van den Oetelaar, MSc
Study Director

1. RESPONSIBLE PERSONNEL

1.1. Test Facility

Study Director	D. van den Oetelaar, MSc
Test Facility Management	H.H. Emmen, MSc

1.2. Individual Scientists (IS) at Test Facility

Histopathology	E.J.M. Lambregts, DVM

1.3. Sponsor

Sponsor Representative	M. Rooseboom, PhD, ERT

2. SUMMARY

The objectives of this study were to determine the potential toxic effects of Dihydroxyethylpiperazine (DiHEP) Aqueous Solution when given orally by gavage for a minimum of 28 days to Wistar Han rats, and to evaluate the potential to affect male and female reproductive performance such as gonadal function, mating behaviour, conception, parturition and early postnatal development.

In addition, parental, reproduction (up to and including implantation) and developmental (from implantation onwards) No Observed Adverse Effect Levels (NOAELs) were evaluated.

The dose levels in this study were selected to be 0, 100, 300 and 1000 mg/kg/day, based on information provided by the sponsor (see section 4.7.2). The tolerability of 1000 mg/kg/day was confirmed in a dose range finder (Test Facility Study No. 521627, see Appendix 5).

The study design was as follows:

Text Table 1
Experimental Design

Group No.	Test Item Id.	Dose Level (mg/kg)	Dose Volume (mL/kg)[a]	Corrected Test Item Concentration (mg/mL)[b]	Number of Animals	
					Males	Females
1	-	0 (Control)[c]	2.07	-	10	10
2	DiHEP Aqueous Solution	100	0.21	482.9	10	10
3		300	0.62		10	10
4		1000	2.07		10	10

Id.= identification.
[a] Dose volume was calculated as dose level (mg/kg) / corrected test item concentration (mg/ml).
[b] The test item consisted of 43.9% DiHEP, test item concentration was corrected for % DiHEP and specific gravity (factor: 1.1). See section 4.5.1 for details.
[c] Test-item treated animals received undiluted test item and consequently, no vehicle was used. Control animals were dosed with water (Elix) at the same dose volume as Group 4.

The following parameters and end points were evaluated in this study: mortality/ moribundity, clinical signs, functional observations, body weight and food consumption, estrous cycle determination, clinical pathology, measurement of thyroid hormone T4 (F_0-males), gross necropsy findings, organ weights and histopathologic examinations.

In addition, the following reproduction/developmental parameters were determined: mating and fertility indices, precoital time, number of implantation sites, gestation index and duration, parturition, maternal care, sex ratio and early postnatal pup development (mortality, clinical signs, body weights, sex, anogenital distance, areola/nipple retention and macroscopy, measurement of thyroid hormone T4 (PND 4 and PND 14-16 pups)).

No parental toxicity was observed up to 1000 mg/kg, test item-related findings were limited to non-adverse changes as described below:

Clinical signs included slight salivation directly after dosing in animals at 1000 mg/kg, which was regarded as a physiological response to the taste of the test item rather than a sign of systemic toxicity. In addition, piloerection and hunched posture were noted on multiple consecutive days for a few animals at 1000 mg/kg/day. At the incidence observed, and since the findings were transient, these were considered not toxicologically significant.

The slight, not statistically significant, changes in mean grip strength (females at 1000 mg/kg/day), total movements (males and females at 100 and 1000 mg/kg/day) and ambulations (males at 100 and 1000 mg/kg/day and females at all dose levels) were not supported by clinical observations or other functional observation tests, were slight in nature (within the normal range for rats of this age and strain), and had no supportive morphological

correlates in examined neuronal tissues. These effects were therefore considered not to represent an adverse effect on neurobehaviour.

Thymus weight (absolute and relative) was decreased in all treated males in a dose-related manner. No statistical significance was achieved, all values remained within the historical control range and this decrease was not accompanied by any anatomic pathology alterations. As such, this finding was considered non-adverse.

Microscopic test item-related findings were present in the stomach of males at 1000 mg/kg/day, consisting of (multi) focal erosions of the glandular mucosa. Based on the low degrees (up to slight) and absence of concomitant test item-related microscopic changes, these findings were regarded as non-adverse.

No reproduction or developmental toxicity was observed up to the highest dose level tested (1000 mg/kg/day).

In conclusion, based on the results of this combined 28-day repeated dose toxicity study with the reproduction/developmental toxicity screening test, the Parental, Reproduction and Developmental No Observed Adverse Effect Levels (NOAEL) for DiHEP Aqueous Solution were established to be at least 1000 mg/kg/day.

3. INTRODUCTION

The objectives of this study were to determine the potential toxic effects of DiHEP Aqueous Solution when given orally by gavage for a minimum of 28 days to Wistar Han rats, and to evaluate the potential to affect male and female reproductive performance such as gonadal function, mating behaviour, conception, parturition and early postnatal development.

In addition, parental, reproduction (up to and including implantation) and developmental (from implantation onwards) No Observed Adverse Effect Levels (NOAELs) were evaluated.

The design of this study was based on the following study guidelines:

- OECD 422, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, 2016.
- EPA OPPTS 870.3650, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, 2000.

In addition, the procedures described in this study plan essentially conform to the following guidelines:

- OECD 421, Reproduction/Developmental Toxicity Screening Test, 2016.
- EPA OPPTS 870.3550, Reproduction/Developmental Toxicity Screening Test, 2000.
- EC No 440/2008, B.7 Repeated Dose (28 days) Toxicity (oral), 2008.
- OECD 407, Repeated Dose 28-day Oral Toxicity Study in Rodents, 2008.
- EPA OPPTS 870.3050, Repeated Dose 28-day Oral Toxicity Study in Rodents, 2000.

The Study Director signed the study plan on 16 Jan 2019, and dosing of the main study was initiated on 05 Feb 2019. The in-life phase of the main study was completed on 02 Apr 2019. The experimental start date was 18 Jan 2019, and the experimental completion date was 11 Jun 2019. The study plan, last amended study plan and deviations are presented in Appendix 7.

For data collection in the dose range finder, an additional Test Facility Study No. was generated (No. 521627). For a complete overview of all used study numbers, see Appendix 6. The entire study is reported under Test Facility Study No. 20172120.

4. MATERIALS AND METHODS

4.1. Test Item

Identification:	DiHEP Aqueous Solution[1]
Batch (Lot) Number:	D2921BF000
Expiry date:	31 August 2020 (expiry date)
Physical Description:	Yellow aqueous liquid
Purity/Composition:	See Certificate of Analysis[2]
Storage Conditions:	At room temperature protected from light

Additional information

Test Facility Test Item Number:	209813/A
Purity/Composition correction factor:	Correct for percentage solid matter and additionally for percentage DiHEP.
Test item handling:	No specific handling conditions required
Chemical name (IUPAC, synonym or trade name):	1,4-Bis(2-hydroxyethyl)piperazine Dihydroxyethylpiperazine
CAS number:	122-96-3
Molecular formula:	$C_8H_{18}N_2O_2$
Molecular weight:	174.24
Irritant or corrosive:	Yes
pH:	13
Specific gravity / density:	1.1 kg/m^3 at 20°C

4.2. Test Item Characterization

The Sponsor provided to the Test Facility documentation of the identity, purity, composition, and stability for the test item. The characterization of the test item was conducted in a GLP quality environment. A Certificate of Analysis was provided to the Test Facility and is presented in Appendix 3.

4.3. Reserve Samples

For the used batch (lot) of test item, a reserve sample (about 0.5 gram) was collected and maintained under the appropriate storage conditions by the Test Facility. The sample will be destroyed after the expiry date.

4.4. Test Item Inventory and Disposition

Records of the receipt, distribution, and storage of test item were maintained. With the exception of reserve samples, all unused Sponsor-supplied test item was discarded after completion of the scheduled program of work. Records of the decisions made will be kept at the Test Facility.

[1] DiHEP stands for Dihydroxyethylpiperazine.
[2] For Certificate of Analysis see Appendix 3.

4.5. Dose Formulation and Analysis

4.5.1. Preparation of Test Item

The test item, DiHEP Aqueous Solution was administered as received. An adequate amount of the test item was dispensed into daily aliquots, which were stored in a controlled temperature area set to maintain 21°C until use.

Test item dosing formulations were kept at room temperature until dosing.

Adjustment was made for specific gravity of the test item. A factor of 43.9 was used to correct for the purity/composition of the test item (based on the 48.9% solid matter of which 89.7% is DiHEP).

Any residual volumes were discarded.

4.5.2. Sample Collection and Analysis

The test item was used as received from the Sponsor; therefore, samples for dose formulation analysis were not collected by the Test Facility.

4.6. Test System

4.6.1. Receipt

On 16 Jan 2019, female Crl: WI(Han) rats were received and on 30 Jan 2019, male Crl:WI(Han) rats were received from Charles River Deutschland, Sulzfeld, Germany. At initiation of dosing, males were 10-11 weeks old and weighed between 268 and 331 g and females were 13-14 weeks old and weighed between 201 and 246 g.

A health inspection was performed before the initiation of dosing.

4.6.2. Justification for Test System and Number of Animals

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.

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

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 which do not use live animals currently do not exist.

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 approved by the Central Authority for Scientific Procedures on Animals (CCD) as required by the Dutch Act on Animal Experimentation (December 2014).

4.6.3. Animal Identification

Prior to start of the pretest period (females) or treatment period (males), each animal was identified using earmark and tattoo. Prior to the pretest period, reserve females were numbered R1 through R8 at random by indelible marker. Any reserve female replacing an allocated female prior to treatment received identification by earmark and tattoo.

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

4.6.4. Environmental Acclimation

The animals were allowed to acclimate to the Test Facility toxicology accommodation for 6 days prior to start of the pretest period (females) or 6 days before the commencement of dosing (males).

4.6.5. Selection, Assignment, Replacement, and Disposition of Animals

A total of 40 females was selected at randomization before initiation of the pretest phase. Any selected female classified as not having regular estrous cycles during the pretest phase was replaced before initiation of dosing by one of the 8 additional females having regular estrous cycles. A total of 40 females with regular estrous cycles continued in the study. The supernumerary females were removed from the study, and their estrous cycle results were kept in the raw data but not reported.

Animals were assigned to groups by a computer-generated random algorithm according to body weights, with all animals within ± 20% of the sex mean. Males and females were randomized separately.

4.6.6. Husbandry

4.6.6.1. Housing

On arrival and following the pretest (females only) and pre-mating period, animals were group housed (up to 5 animals of the same sex and same dosing group together) in polycarbonate cages (Macrolon, MIV type, height 18 cm).

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

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

During the lactation phase, females were housed in Macrolon plastic cages (MIII type, height 18 cm). Pups were housed with the dam, except during locomotor activity monitoring of the dams, when the pups were kept warm in their home cage using bottles filled with warm water. In order to avoid hypothermia of pups, pups were not left without their dam or a bottle filled with warm water for longer than 30-40 minutes.

During locomotor activity monitoring, animals were housed individually in a Hi-temp polycarbonate cage (Ancare corp., USA; dimensions: 48.3 x 26.7 x 20.3 cm) without cage-enrichment, bedding material, food and water.

The cages contained appropriate bedding (Lignocel S 8-15, JRS - J.Rettenmaier & Söhne GmbH + CO. KG, Rosenberg, Germany) and were equipped with water bottles. The rooms in which the animals were kept were documented in the study records.

Animals were separated during designated procedures/activities.

Each cage was clearly labeled with a color-coded cage card indicating Test Facility Study No., group, animal number(s), and sex.

4.6.6.2. Environmental Conditions

Target temperatures of 18 to 24°C with a relative target humidity of 40 to 70% were maintained. The actual daily mean temperature during the study period was 20 to 21°C with an actual daily mean relative humidity of 45to 51%. A 12-hour light/12-hour dark cycle was maintained. Ten or greater air changes per hour with 100% fresh air (no air recirculation) were maintained in the animal rooms.

4.6.6.3. Food

Pelleted rodent diet (SM R/M-Z from SSNIFF® Spezialdiäten GmbH, Soest, Germany) was provided *ad libitum* throughout the study, except during designated procedures. During motor activity measurements, animals had no access to food for a maximum of 2 hours.

The feed was analyzed by the supplier for nutritional components and environmental contaminants. Results of the analysis were provided by the supplier and are on file at the Test Facility.

It is considered that there were no known contaminants in the feed that would interfere with the objectives of the study.

4.6.6.4. Water

Municipal tap water was freely available to each animal via water bottles. During motor activity measurements, animals had no access to water for a maximum of 2 hours.

Periodic analysis of the water was performed, and results of these analyses are on file at the Test Facility.

It is considered that there were no known contaminants in the water that would interfere with the objectives of the study.

4.6.6.5. Animal Enrichment

For psychological/environmental enrichment and nesting material, animals were provided with paper (Enviro-dri, Wm. Lilico & Son (Wonham Mill Ltd), Surrey, United Kingdom).

4.6.6.6. Veterinary Care

Veterinary care was available throughout the course of the study; however, no examinations or treatments were required.

4.7. Experimental Design

Text Table 2
Experimental Design

Group No.	Test Item Id.	Dose Level (mg/kg)	Dose Volume (mL/kg)[a]	Corrected Test Item Concentration (mg/mL)[b]	Number of Animals		Animal Numbers	
					Males	Females	Males	Females
1	-	0 (Control)[c]	2.07	-	10	10	01-10	41-50
2	DiHEP Aqueous Solution	100	0.21	482.9	10	10	11-20	51-60
3		300	0.62		10	10	21-30	61-70
4		1000	2.07		10	10	31-40	71-80

Id.= identification.

[a] Dose volume was calculated as dose level (mg/kg) / corrected test item concentration (mg/ml).

[b] The test item consisted of 43.9% DiHEP, test item concentration was corrected for % DiHEP and specific gravity (factor: 1.1). See section 4.5.1 for details.

[c] Test-item treated animals received undiluted test item and consequently, no vehicle was used. Control animals were dosed with water (Elix) at the same dose volume as Group 4.

The following 5 animals/sex/group were selected for functional tests, clinical pathology, collection of full list of organs/tissues at macroscopic examination, organ weights (full list) and histopathology (full list), see also respective paragraphs:

Group No.	Animal numbers	
	Males	Females[a]
1	01-05	41, 44, 45, 47, 50
2	11-15	52, 54, 56, 57, 58
3	21-25	62, 64, 66, 68, 70
4	31-35	71, 73, 74, 79, 80

[a] Females with living pups.

4.7.1. Administration of Test Materials

The test item or water (Elix) were administered to the appropriate animals by once daily oral gavage 7 days a week for a minimum of 28 days. Males were treated for 29 days, i.e. 14 days prior to mating, during mating and up to and including the day before scheduled necropsy. Females that delivered were treated for 51-56 days, i.e. 14 days prior to mating (with the objective to cover at least two complete estrous cycles), the variable time to conception, the duration of pregnancy and at least 14 days after delivery, up to and including the day before scheduled necropsy. Females which failed to deliver were treated for 42-52 days.

The first day of dosing was designated as Day 1.

On Day 2 of dosing, the males of Group 2 received a dose volume corresponding with a dose level of 1000 mg/kg instead of 100 mg/kg. Based on the available results, the single dose at the same level as Group 4 animals did not impact the study outcome.

Female Nos. 43 (control), 55, 59 (100 mg/kg/day), 61, 62, 67 (300 mg/kg/day), 77, 78 (1000 mg/kg/day), were not dosed on one occasion as these females were littering at the moment of dosing. The omission of one day of dosing over a period of several weeks was considered not to affect the toxicological evaluation.

The dose volume for each animal was based on the most recent body weight measurement. The doses were given using a plastic feeding tube.

A dose control system (DCS) was used as additional check to verify the dosing procedure according to Standard Operating Procedures.

Pups were not treated directly but were potentially exposed to the test item in utero, via maternal milk, or from exposure to maternal urine/feces.

4.7.2. Justification of Route and Dose Levels

The oral route of administration was selected because this is the recommended route by OECD TG 422, REACH regulation and ECHA guidelines. In addition, the test material is a non-volatile aqueous solution.

The dose levels were selected based on information provided by the Sponsor (data on file at Sponsor site), and in an attempt to produce graded responses to the test item.

A previously performed acute toxicity study with DiHEP Aqueous Solution via oral gavage in Sprague Dawley (SD) rats indicated a low acute toxicity ($LD50_{males}$ was 20,093 mg/kg and $LD50_{females}$ was 18,738 mg/kg).

In addition, multiple studies were performed with several structural analogs:

- A dietary 7-day toxicity study was performed with a hydroxypiperazine solution (containing 12-20% piperazine, 38-47% hydroxypiperazine, 16-25%

dihydroxypiperazine, 17-26% water). During this study Wistar han rats received 590, 1420, and 3720 mg/kg for males and 680, 1610 and 3970 mg/kg for female rats. A slight body weight decrease was observed in females fed 3970 mg/kg/day but was not observed in females fed lower doses or in males. This body weight decrease was statistically significant after days 1 and 4 but not day 7. Remaining parameters were considered unaffected by treatment.

- A dietary 90-day toxicity study was performed with analog piperazine. During this study, SD rats received 400, 1200 and 2394 mg/kg by dietary administration. A dose related decrease in body-weight gain (a decrease of 10% in high dose animals when compared with concurrent control) was noted. Remaining parameters were considered unaffected by treatment.
- A dietary 90-day toxicity study was performed with analog anhydrous piperazine. Rats received 1000, 3000 and 10000 ppm (corresponding to 50, 150 and 500 mg/kg/day piperazine base). At 10000 ppm histopathological degenerative changes were noted in the liver and kidney, at 3000 ppm similar changes were noted to a lesser extent and at 1000 ppm no adverse effects were noted. In addition, at 10000 ppm a decrease in body weight gain was noted (statistically significant in females only). Remaining parameters were considered unaffected by treatment.
- A developmental toxicity study was performed, in which pregnant SD females received 0, 105, 420 and 2100 mg/kg piperazine base during days 6-15 by oral gavage. In high-dose females, excessive salivation, lethargy and a reduction in body weight gain and food consumption were noted. Remaining parameters, including pre- and post-implantation loss, litter size and sex ratio, were considered unaffected by treatment.
- In a dietary two generation study with piperazine dihydrochloride, SD rats received 0, 5000, 12000 and 25000 ppm (corresponding to 0, 125, 300 and 625 mg/kg piperazine base). The mid-dose was considered as LOAEL, with effects mainly on fertility (i.e. reduced pregnancy index and decreased number of implantation sites). These effects were not observed in the developmental toxicity study, which is be considered to support that the effect on fertility are the main effect of piperazine on reproduction.

Based on the observed low acute toxicity of DiHEP Aqueous Solution and the effects noted in the studies performed with structural analogs, 0, 100, 300 and 1000 mg/kg were selected as dose levels for this study.

The high-dose level should produce some toxic effects, but not death nor obvious suffering. The mid-dose level is expected to produce minimal to moderate toxic effects. The low-dose level should produce no observable indications of toxicity.

4.8. In-life Procedures, Observations, and Measurements – F_0-Generation

4.8.1. Mortality/Moribundity Checks – F_0-Generation

Throughout the study, animals were observed for general health/mortality and moribundity twice daily, in the morning and at the end of the working day. Animals were not removed from the cage during observation, unless necessary for identification or confirmation of possible findings.

4.8.2. Clinical Observations – F_0-Generation

Clinical observations were performed once daily, beginning during the first administration of the test item and lasting throughout the dosing periods up to the day prior to necropsy.

During the dosing period, these observations were performed after dosing at no specific time point, but within a similar time period after dosing for the respective animals (no peak effect of occurrence of clinical signs was observed in the dose range finder (Test Facility Study No. 521627, see Appendix 5)).

The time of onset, grade and duration of any observed sign was recorded. Signs were graded for severity and the maximum grade was predefined at 3 or 4. Grades were coded as slight (grade 1), moderate (grade 2), severe (grade 3) and very severe (grade 4). For certain signs, only its presence (grade 1) or absence (grade 0) was scored. In the data tables, the scored grades were reported, as well as the percentage of animals affected in summary tables.

4.8.2.1. Arena Observations – F_0-Generation

Clinical observations were conducted in a standard arena beginning before the first administration of the test item and then once weekly throughout treatment.

4.8.3. Body Weights – F_0-Generation

Animals were weighed individually on the first day of treatment (prior to dosing), and weekly thereafter. Mated females were weighed on Days 0, 4, 7, 11, 14, 17, and 20 post-coitum and during lactation on PND 1, 4, 7, and 13.

A terminal weight was recorded on the day of scheduled necropsy (fasted for males and non-fasted for females).

4.8.4. Food Consumption – F_0-Generation

Food consumption was quantitatively measured weekly, except for males and females which were housed together for mating and for females without evidence of mating. Food consumption of mated females was measured on Days 0, 4, 7, 11, 14, 17, and 20 post-coitum and during lactation on PND 1, 4, 7, and 13.

4.8.5. Water Consumption – F_0-Generation

Subjective appraisal was maintained during the study, but no quantitative investigation was introduced as no effect was expected or noted at visual inspection of the water bottles.

4.8.6. Functional Tests – F_0-Generation

Functional tests were performed on the selected 5 males during Week 4 of treatment and the selected 5 females during the last week of lactation (i.e. PND 10-13). These tests were performed after completion of clinical observations (including arena observation, if applicable).

The following tests were performed (abbreviations mentioned in the respective tables are indicated between brackets):

- Hearing ability (HEARING) (Score 0 = normal/present, score 1 = abnormal/absent).
- Pupillary reflex (PUPIL L/R) (Score 0 = normal/present, score 1 = abnormal/absent).
- Static righting reflex (STATIC R) (Score 0 = normal/present, score 1 = abnormal/absent).
- Fore- and hind-limb grip strength, recorded as the mean of three measurements per animal (Series M4-10, Mark-10 Corporation, J.J. Bos, Gouda, The Netherlands).
- Locomotor activity (recording period: 1-hour under normal laboratory light conditions, using a computerized monitoring system, Kinder Scientific LLC, Poway, USA). Total movements and ambulations were reported. Ambulations represent

movements characterized by a relocation of the entire body position like walking, whereas total movements represent all movements made by the animals, including ambulations but also smaller or more fine movements like grooming, weaving or movements of the head.

4.8.7. Estrous cycle determination – F_0-Generation

Estrous cycles were evaluated by examining the vaginal cytology of samples obtained by vaginal lavage.

Daily vaginal lavage was performed for all females beginning 14 days prior to treatment (pretest period), the first 14 days of treatment and during mating until evidence of copulation was observed. Vaginal lavage was continued for those females with no evidence of copulation until termination of the mating period.

On the day of necropsy, a vaginal lavage was also taken to determine the stage of estrous.

4.8.8. Cohabitation/Mating Procedure – F_0-Generation

After 14 days of treatment, animals were cohabitated on a 1:1 basis within the same treatment group, avoiding sibling mating. Detection of mating was confirmed by evidence of sperm in the vaginal lavage or by the appearance of an intravaginal copulatory plug. This day was designated Day 0 post-coitum. Once mating had occurred, the males and females were separated.

Detection of mating was not confirmed in first instance for female no. 78. Evidence of mating was obtained by palpation and indirectly by delivery of a litter. Apparently, mating was overlooked in the assessment of the vaginal lavage, which explains the continued estrous during the mating in this female. The mating date of this animal was estimated at 21 days prior to the actual delivery date. This day was designated Day 0 post-coitum.

4.8.9. General Reproduction Data – F_0-Generation

From the mating period onwards, the following parameters were recorded for each female: male number paired with, mating date, confirmation of pregnancy and delivery day.

Females were allowed to litter normally. 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 were littering were left undisturbed.

Cage debris of pregnant females was examined for evidence of premature delivery and pregnant females were examined to detect signs of difficult or prolonged parturition or deficiencies in maternal care.

4.9. In-life Procedures, Observations, and Measurements – F_1-Generation

4.9.1. Mortality/Moribundity Checks – F_1-Generation

Pups were observed daily for general health/mortality. The number of live and dead pups was determined on PND 1 and daily thereafter. Pups were not removed from the cage during observation, unless necessary for identification or confirmation of possible findings.

4.9.2. Clinical Observations – F_1-Generation

Clinical observations were performed at least once daily for all pups. Only days on which clinical signs were present between the first and last litter check were given in the respective report tables.

4.9.3. Body Weights – F_1-Generation

Live pups were weighed individually on PND 1, 4, 7 and 13.

4.9.4. Sex – F_1-Generation

Sex was externally determined for all pups on PND 1 and 4.

4.9.5. Anogenital Distance – F_1-Generation

Anogenital distance (AGD) was measured for all live pups on PND 1. The AGD was normalized to the cube root of body weight.

4.9.6. Areola/Nipple Retention – F_1-Generation

All male pups in each litter were examined for the number of areola/nipples on PND 13.

4.9.7. Culling – F_1-Generation

To reduce variability among the litters, on PND 4 eight pups from each litter of equal sex distribution (if possible) were selected. Blood samples were collected from two of the surplus pups (if possible from one male and one female pup). Selective elimination of pups, e.g. based upon body weight or AGD, was not done.

4.10. Laboratory Evaluations

4.10.1. Clinical Pathology

4.10.1.1. Sample Collection

Blood of F_0-animals was collected on the day of scheduled necropsy. Samples were collected, between 7.00 and 10.30 a.m., from the retro-orbital sinus under anesthesia using isoflurane in the animal facility. Due to clotting of non-serum samples of individual animals, additional blood samples were obtained in necropsy room. After collection all samples were transferred to the appropriate laboratory for analysis.

F_0-males were fasted overnight with a maximum of 24 hours before blood sampling, but water was available. F_0-females were not fasted overnight.

Blood of F_1-animals was collected on PND 4 and PND 14-16, if possible. This was performed in the necropsy room.

On PND 4 at culling, blood was collected from two surplus pups per litter (if possible) by decapitation, between 7.00 and 10.30 a.m., and samples were pooled to one sample per litter. If available, blood was collected from one male and one female pup. If only one surplus pup per litter was available at culling, as much blood as possible was collected from this single pup.

On PND 14-16, separate blood samples were collected from two pups per litter (from one male and one female). Blood was drawn, between 7.00 and 10.30 a.m., by aorta puncture under anaesthesia using isoflurane as part of the necropsy procedure.

Samples were collected according to the following table.

Text Table 3
Samples for Clinical Pathology Evaluation

Animals	Time Point	Hematology	Coagulation	Clinical Chemistry	Thyroid Hormone
Selected F_0-animals (5/sex/group)[a]	On the day of scheduled necropsy	X	X	X	X
Non-selected F_0-animals ($\leq$ 5/sex/group)[a,]	On the day of scheduled necropsy	-	-	-	X
2 pups/litter	PND 4	-	-	-	X
2 pups/litter	PND 14-16	-	-	-	X

X = Collected sample; - = Not applicable.
[a] See section 4.7 for details of the selected F_0-animals.

4.10.1.2. Hematology

Blood samples at a target volume of 0.5 mL were collected into tubes containing K_3-EDTA as anticoagulant. Samples were analyzed for the parameters specified in the following table.

Text Table 4
Hematology Parameters

White blood cells (WBC)	Red Blood Cell Distribution Width (RDW)
Neutrophils (absolute)	Haemoglobin
Lymphocytes (absolute)	Haematocrit
Monocytes (absolute)	Mean corpuscular volume (MCV)
Eosinophils (absolute)	Mean corpuscular haemoglobin (MCH)
Basophils (absolute)	Mean corpuscular haemoglobin concentration (MCHC)
Red blood cells	Platelets
Reticulocytes (absolute)	

A blood smear was prepared from each hematology sample. Blood smears were labeled, stained, and stored. In case additional examination of blood smears was deemed necessary, the smears were subsequently evaluated.

4.10.1.3. Coagulation

Blood samples at a target volume of 0.45 mL were collected into tubes containing Citrate as anticoagulant. Samples were processed for plasma, and plasma was analyzed for the parameters listed in the following table.

Text Table 5
Coagulation Parameters

Prothrombin Time (PT)	Activated Partial Thromboplastin Time (APTT)

4.10.1.4. Clinical Chemistry

Blood samples at a target volume of 0.5 mL (plasma) were collected into tubes containing Li-Heparin as anticoagulant. Serum samples at a target volume of 0.25 mL for males and 1.0 mL for females were collected in tubes without anticoagulant. Blood samples were processed for plasma or serum (bile acids), which was analyzed for the parameters specified in the following table.

Text Table 6
Clinical Chemistry Parameters

Alanine aminotransferase (ALAT)	Creatinine
Aspartate aminotransferase (ASAT)	Glucose
Alkaline Phosphatase (ALP)	Cholesterol
Total protein	Sodium
Albumin	Potassium
Total Bilirubin	Chloride
Bile Acids	Calcium
Urea	Inorganic Phosphate (Inorg. Phos)

4.10.1.5. Thyroid hormone

Blood samples at a target volume of 1.0 mL (F_0-animals), 0.5 mL (pooled PND 4 pups) and 1.0 mL (PND 14-16 pups) were collected into tubes without anticoagulant. Blood samples were processed for serum, and serum was analyzed for total Thyroxine (T4).

Measurement of total T4 was conducted for F_0-males and PND 14-16 pups PND 4 pups.

For the F_0-generation, assessment of T4 (females) and Thyroid Stimulating Hormone (TSH; both sexes) was considered not relevant because no treatment-related changes in T4 were noted in F_0-males, no adverse effects on thyroid histopathology were noted and no treatment related changes in thyroid weight were recorded (see section 9.1.8 for more details).

Assessment of T4 for PND 4 pups and TSH for PND 14-16 pups was considered not relevant because no treatment-related changes in T4 were noted in pups at PND 14-16 (see section 9.3.13 for more details).

Serum samples retained for possible future analysis were maintained by the Test Facility in the freezer (≤-75°C). Under these storage conditions, samples are stable for 6 months. Any remaining sample will be discarded.

4.11. Terminal Procedures – F_0-Generation

Terminal procedures are summarized in the following table.

Text Table 7
Terminal Procedures

Group No.	(Non) Selected Animals	No. of Animals		Scheduled Euthanasia	Necropsy Procedures			Histology and histopathology
		M	F		Necropsy	Tissue Collection	Organ Weights	
1	Selected	5	5	**Males:** after a minimum of 28 days of administration **Females:** PND 14-16	X	X[a]	X[b]	Full list
	Non-selected	5	5					Gross lesions Reproductive tissues[c]
2	Selected	5	5					Gross lesions Target tissues[d] Reproductive tissues[c]
	Non-selected	5	5					Gross lesions Reproductive tissues[c]
3	Selected	5	5					Gross lesions Target tissues[d] Reproductive tissues[c]
	Non-selected	5	5					Gross lesions Reproductive tissues[c]
4	Selected	5	5					Full list
	Non-selected	5	5					Gross lesions Reproductive tissues[c]

X = Conducted procedure.

[a] See Tissue Collection and Preservation table for listing of tissues (section 4.11.5).

[b] See Organ Weights table for listing of tissues (section 4.11.4).

[c] Reproductive tissues were applicable for males that failed to sire and females that failed to deliver pups (i.e. non-pregnant females). See Tissue Collection and Preservation table for listing of tissues (section 4.11.5).

[d] Adrenal glands and Stomach of selected males of Group 2 and 3, based on possible treatment-related changes in these tissues..

4.11.1. Unscheduled Deaths

No animals died during the course of the study.

4.11.2. Scheduled Euthanasia

Animals surviving until scheduled euthanasia were weighed, and deeply anaesthetized using isoflurane and subsequently exsanguinated and subjected to a full *post mortem* examination.

Scheduled necropsies were conducted on the following days:

Males:	Following completion of the mating period (a minimum of 28 days of administration).
Females which delivered:	PND 14-16.
Females which failed to deliver (Nos. 42, 46, 51, 53, 63 and 72):	With evidence of mating: Post-coitum Days 25-27.

All males surviving to scheduled necropsy were fasted overnight with a maximum of 24 hours before necropsy. Water was available. F_0- females were not fasted.

4.11.3. Necropsy – F_0-Generation

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

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

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

In case no macroscopically visible implantation sites were present, non-gravid uteri were stained using the Salewski technique in order to detect any former implantation sites and the number of corpora lutea was recorded in addition (for exceptions, see Appendix 7).

4.11.4. Organ Weights – F_0-Generation

The organs identified in the table below were weighed at necropsy for all scheduled euthanasia animals. Paired organs were weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of the aberrant organ was taken and recorded in the raw data. Organ to body weight ratios (using the terminal body weight) were calculated.

Text Table 8
Organs Weighed at Necropsy for all selected animals

Brain	Heart
Cervix[a]	Kidney[b]
Epididymis[b]	Liver
Gland, adrenal[b]	Ovaries[b]
Gland, coagulation[b, c]	Spleen
Gland, parathyroid[d]	Testes[b]
Gland, prostate	Thymus
Gland, seminal vesicle[b]	Uterus
Gland, thyroid	

[a] Weighed together with the uterus.
[b] Paired organ weight.
[c] Weighed together with the seminal vesicles.
[d] Weighed together with the thyroid.

Text Table 9
Organs Weighed at Necropsy for all remaining animals (incl. males that failed to sire and females that failed to deliver pups).

Epididymis[a]	Gland, seminal vesicle[a]
Gland, coagulation[a, b]	Gland, thyroid
Gland, parathyroid[c]	Testes[a]
Gland, prostate	

[a] Paired organ weight.
[b] Weighed together with the seminal vesicles.
[c] Weighed together with the thyroid.

4.11.5. Tissue Collection and Preservation – F_0-Generation

Representative samples of the tissues identified in the table below were collected from all animals and preserved in 10% neutral buffered formalin (neutral phosphate buffered 4% formaldehyde solution, Klinipath, Duiven, The Netherlands), unless otherwise indicated.

Text Table 10
Tissue Collection and Preservation for all selected animals

Animal identification	Large intestine, cecum
Artery, aorta	Large intestine, colon
Body cavity, nasopharynx	Large intestine, rectum
Bone marrow	Larynx
Bone, femur	Liver
Bone, sternum	Lung
Brain (eight levels)	Lymph node (mandibular and mesenteric site)
Cervix	Muscle, skeletal
Epididymides[a]	Nerve, optic[a, b]
Esophagus	Nerve, sciatic
Eye[a]	Ovaries
Gland, adrenal	Pancreas
Gland, coagulation	Skin
Gland, Harderian[a, b]	Small intestine, duodenum
Gland, lacrimal	Small intestine, ileum
Gland, mammary	Small intestine, jejunum
Gland, parathyroid[c]	Spinal cord
Gland, pituitary	Spleen
Gland, prostate	Stomach
Gland, salivary	Testes[a]
Gland, seminal vesicle	Thymus
Gland, thyroid	Tongue
Gross lesions/masses	Trachea
Gut-associated lymphoid tissue	Urinary bladder
Heart	Uterus
Kidney	Vagina

[a] Preserved in modified Davidson's fixative and transferred to formalin after fixation for at least 24 hours.
[b] Only collected if present in the routine section of the eye.
[c] Only collected if present in the routine section of the thyroid.

Text Table 11
Tissue Collection and Preservation for all remaining animals (incl. males that failed to sire and females that failed to deliver pups).

Animal identification	Gland, seminal vesicle
Cervix	Gland, thyroid
Epididymis[a]	Gross lesions/masses
Gland, coagulation	Ovaries
Gland, mammary	Testes[a]
Gland, parathyroid[b]	Uterus
Gland, pituitary	Vagina
Gland, prostate	

[a] Preserved in modified Davidson's fixative and transferred to formalin after fixation for at least 24 hours.
[b] Only collected if present in the routine section of the thyroid.

4.11.6. Histology – F_0-Generation

The following tissues were embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin:

Selected animals:	Tissues identified in Text Table 10 (except animal identification, aorta, nasopharynx, esophagus, harderian gland, lacrimal gland, salivary gland, larynx, optic nerve, pancreas, skin and tongue).
Males that failed to sire (except for males which were selected) and females that failed to deliver pups:	Cervix, epididymis, coagulation gland, prostate gland, seminal vesicles, ovaries, testes, uterus and vagina.
Remaining animals:	Gross lesions/masses.

4.11.7. Histopathology – F_0-Generation

All tissues as defined under Histology – F_0-Generation (section 4.11.6) were examined by a board-certified toxicological pathologist with training and experience in laboratory animal pathology. Target tissues identified by the study pathologist during microscopic evaluation were communicated to the Study Director; tissues were evaluated and reported.

For the testes of all selected males of Groups 1 and 4 and all males that failed to sire, a detailed qualitative examination was made, taking into account the tubular stages of the spermatogenic cycle.

A peer review on the histopathology data was performed by a second pathologist.

4.12. Terminal Procedures – F_1-Generation

4.12.1. Method of Euthanasia - F_1-Generation

Pups, younger than 7 days were euthanized by decapitation.

All remaining pups (PND 14-16), except for the two pups per litter selected for blood collection were euthanized by an intraperitoneal injection of sodium pentobarbital (Euthasol® 20%).

The pups selected for blood collection on PND 14-16 were anesthetized using isoflurane followed by exsanguination.

4.12.2. Unscheduled Deaths - F_1-Generation

Pup that died before scheduled termination were examined externally and sexed (both externally and internally). The stomach of pups not surviving to the scheduled necropsy date was examined for the presence of milk, if possible. If possible, defects or cause of death were evaluated.

4.12.3. Scheduled Euthanasia - F_1-Generation

On PND 4, the surplus pups (> 8 pups per litter) were euthanized by decapitation. From two surplus pups per litter, blood was collected, if possible. For details see also section 4.10.1.

All remaining pups were euthanized on PND 14-16. Sex was determined both externally and internally. Descriptions of all external abnormalities were recorded. Particular attention was paid to the external reproductive genitals to examine signs of altered development.

In addition, blood was collected from two pups per litter (see also section 4.10.1), and the thyroid from two pups per litter (one male and one female pup) was preserved in 10%

buffered formalin. The pups selected for (complete) blood sampling were the same pups as selected for thyroid preservation.

5. CONSTRUCTED VARIABLES

All results presented in the tables of the report were calculated using values as per the raw data rounding procedure and may not be exactly reproduced from the individual data presented.

5.1. Parental Variables

Body Weight Gains:	Calculated against the body weight on Day 1 (pre-mating, mating and lactation periods) or Day 0 (post-coitum period).
Relative Food Consumption	Calculated against the body weight for scheduled intervals.
Organ Weight Relative to Body Weight:	Calculated against the terminal body weight.

5.2. Reproduction and Developmental Variables

For each group, the following calculations were performed. Group mean values of precoital time and duration of gestation were calculated from individual values of F_0-females, the remaining group values were calculated from the total number in each group.

Mating index (%):
$$\frac{\text{Number of females mated}}{\text{Number of females paired}} \times 100$$

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

Fertility index (%):
$$\frac{\text{Number of pregnant females}}{\text{Number of females mated}} \times 100$$

Gestation index (%):
$$\frac{\text{Number of females with living pups on Day 1}}{\text{Number of pregnant females}} \times 100$$

Duration of gestation: Number of days between confirmation of mating and the beginning of parturition

Post-implantation survival index (%):
$$\frac{\text{Total number of offspring born}}{\text{Total number of uterine implantation sites}} \times 100$$

Live birth index (%):
$$\frac{\text{Number of live offspring on Day 1 after littering}}{\text{Total number of offspring born}} \times 100$$

Percentage live males at First Litter Check (%):
$$\frac{\text{Number of live male pups at First Litter Check}}{\text{Number of live pups at First Litter Check}} \times 100$$

Percentage live females at First Litter Check (%):
$$\frac{\text{Number of live female pups at First Litter Check}}{\text{Number of live pups at First Litter Check}} \times 100$$

$$\text{Viability index (\%):} \quad \frac{\text{Number of live offspring on Day 4 before culling}}{\text{Number live offspring on Day 1 after littering}} \times 100$$

$$\text{Lactation index (\%):} \quad \frac{\text{Number of live offspring on Day 13 after littering}}{\text{Number live offspring on Day 4 (after culling)}} \times 100$$

6. STATISTICAL ANALYSIS

All statistical tests were conducted at the 5% significance level. All pairwise comparisons were conducted using two sided tests and were reported at the 1% or 5% levels.

Numerical data collected on scheduled occasions for the listed variables were analyzed as indicated according to sex and occasion. Descriptive statistics number, mean and standard deviation (or %CV or SE when deemed appropriate) were reported whenever possible. Inferential statistics were performed according to the comparison matrix below when possible, but excluded semi-quantitative data, and any group with less than 3 observations.

The following pairwise comparisons were made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

6.1. Parametric

Datasets with at least 3 groups (the designated control group and at least 2 other groups) were compared using Dunnett-test (many-to-one-t-test).

For the motor activity data set (at least 3 groups) parametric (ANOVA) tests on group means were applied with Bonferroni correction for multiple testing. Mixed modelling techniques, comparing six different covariance structures, were used in order to select the best fitting statistical model (for deviation, see Appendix 7).

6.2. Non-Parametric

Datasets with at least 3 groups was compared using a Steel-test (many-to-one rank test).

6.3. Incidence

An overall Fisher's exact test was used to compare all groups at the 5% significance level. The above pairwise comparisons were conducted using Fisher's exact test whenever the overall test is significant.

7. COMPUTERIZED SYSTEMS

Critical computerized systems used in the study are listed below and/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. The Study Numbers used to collect online data are presented in Appendix 6.

Text Table 12
Critical Computerized Systems

System name	Version No.	Description of Data Collected and/or Analyzed
ToxData [a]	8.0	In-life phase (Mortality; Clinical signs; Body weights; Food consumption; Functional tests, Organ weights; Reproduction parameters; Observations pups[b]) data collection
REES Centron	SQL 2.0	Temperature and humidity (animal and laboratory facilities) data collection
Deviation Information Library	2.1.61	Deviations
ADVIA® 2120i	6.3.2-MS	Haematology data collection
STA Compact®	107.07	Clotting Parameters data collection
AU400	9.1	Clinical biochemistry data collection
MotorMonitor II	16224-11GLP	Motor activity measurement data collection
Pathdata	6.2e2	Histopathology data collection
IMMULITE® 1000	5.22	Thyroid hormone data collection

[a] For logistic reasons, data was captured under separate Study numbers, see Appendix 6.
[b] Only at first and last litter check, and in case of clinical pup findings also on the respective days in between.

8. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, samples, specimens, and final report(s) from this study were archived at the Test Facility by no later than the date of final report issue.

After two years of archiving, all study-specific raw data, electronic data, documentation, study plan and final reports will be transferred to Iron Mountain Germany, Harpener Hellweg 31, D-44805 Bochum, Germany. They shall be indexed by using the Test Facility Project No. allowing unequivocal identification and providing the necessary information (e.g. test system, test item, date of Toxicology and Ecology for the time period set by the GLP regulations). In order to index and before the actual transfer to Iron Mountain Germany the test facility will connect with the sponsor. Records of transfer will be retained by test facility. The Sponsor will be informed about the transfer and will receive a digital copy of the record of transfer. The sponsor will ensure that all study material is expediently returned to Charles River Den Bosch if requested by GLP monitoring authorities for audit.

9. RESULTS

9.1. Parental Data

9.1.1. Mortality

(Appendix 2)

No mortality occurred during the study period.

9.1.2. Clinical Observations

(Appendix 1 and Appendix 2)

No test item-related clinical signs were noted during the observation period up to 300 mg/kg/day and no findings were noted during the weekly arena observations up to 1000 mg/kg/day.

At 1000 mg/kg/day, one male showed piloerection on 4 consecutive days and one female showed hunched posture for 6 consecutive days, on 4 occasions combined with piloerection. At the incidence observed, and since the findings were transient, these were considered not toxicologically significant.

Salivation seen after dosing among most males and few females of the 1000 mg/kg/day dose group during week 4 and/or 5 of the treatment period was considered not toxicologically relevant, taking into account the nature and minor severity of the effect and its time of occurrence (i.e. after dosing). This sign was considered to be a physiological response related to taste of the test item rather than a sign of systemic toxicity.

Note to clinical signs tables: For males, "Repro period" represents the mating phase. For females, "Repro period" represents the mating, post coitum and lactation phase.

9.1.3. Body Weights and Body Weight Gains

(Appendix 1 and Appendix 2)

Body weights and body weight gain were considered to have been unaffected by treatment with the test item up to 1000 mg/kg/day.

Body weight gain of control females was slightly lower when compared with historical control data[3] on Day 8 and Day 15 of treatment (Day 1 of the mating period), resulting in the statistical significance noted for mean body weight gain of females at 300 and 1000 mg/kg/day on Day 1 of the mating period. The body weight development of females up to 1000 mg/kg/day remained within normal limits and was therefore considered unaffected by the test item.

The statistical significant higher mean body weight of females at 300 mg/kg/day on Day 17 post coitum was considered unrelated to treatment with the test item, as no trend was apparent regarding dose and duration of treatment.

[3] Historical control data for body weight gain for female Wistar Han rats (period 2017 - wk 4 2019).
Mean body weight gain Day 8 (%) = 2, P5 – P95 = -2 – 6 (n=474).
Mean body weight gain Day 15 (%) = 4, P5 – P95 = -1 – 6 (n=474).

9.1.4. Food Consumption

(Appendix 1 and Appendix 2)

Food consumption before or after correction for body weight considered to be unaffected by treatment with the test item up to 1000 mg/kg/day.

The statistically significant changes in relative food consumption over Days 7-11 and 14-20 for females at 100 mg/kg/day and over Days 17-20 for females at 300 mg/kg/day were considered to be unrelated to treatment with the test item, as no trend was apparent regarding dose and duration of treatment.

9.1.5. Functional Tests

(Appendix 1 and Appendix 2)

Hearing ability, pupillary reflex and static righting reflex were normal in all examined animals. Forelimb and hind limb grip strength of males were unaffected by treatment with the test item up to 1000 mg/kg/day.

In females at 1000 mg/kg/day, mean grip strength of the fore legs appeared higher than concurrent controls (18%). No statistical significance was achieved and values remained well within historical control range[4].

Total movements were slightly decreased in males and females at 100 and 1000 mg/kg/day as compared with concurrent control (up to 35%). Ambulations were slightly decreased in males at 100 and 1000 mg/kg/day and females at all dose levels compared with concurrent controls (up to 41%). For males, no dose-related trend was apparent, but for females, a dose-related trend was observed for the decreased ambulations. No statistical significance was achieved and values remained within the historical control range[5]. All groups showed a similar habituation profile with very high activity in the first interval that decreased over the duration of the test period.

9.1.6. Haematology

(Appendix 1 and Appendix 2)

Haematological parameters of treated rats were considered not to have been affected by treatment with the test item up to 1000 mg/kg/day.

The statistically significant change in the mean neutrophil level of males at 100 mg/kg/day was considered to be unrelated to treatment with the test item in the absence of a dose-related trend.

9.1.7. Coagulation

(Appendix 1 and Appendix 2)

Coagulation parameters of treated females were considered not to have been affected by treatment with the test item up to 1000 mg/kg/day.

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[4] Historical control data of female Wistar Han rats (period 2015-2018):
Grip strength fore leg (gram): Mean = 1009; P5 - P95 = 551 – 1458 (n=400).

[5] Historical control data of Wistar Han rats (period 2015 - 2018):

Total movements:	Males:	Mean = 3592; P5 - P95 = 1798 – 5617 (n=445).
	Females:	Mean = 3372; P5 - P95 = 1529 – 5618 (n=400).
Ambulations:	Males:	Mean = 806; P5 - P95 = 302 – 1295 (n=445).
	Females:	Mean = 817; P5 - P95 = 317 – 1440 (n=400).

Prothrombin time (PT) of males at 100, 300 and 1000 mg/kg/day was decreased with statistical significance when compared with controls (all 0.94x of control). As there was no dose response and mean values remained within normal limits[6], this was considered to be of no toxicological relevance.

9.1.8. Clinical Chemistry

(Appendix 1 and Appendix 2)

The following (not statistically significant) changes distinguished treated from control animals. Relative changes in mean values as compared to the concurrent control group are indicated between parentheses:

- Mean urea levels were dose-dependently increased in treated animals (up to 1.1x of control for both sexes). Values generally remained within the historical control range[7].
- Mean glucose levels in males at 1000 mg/kg were decreased (0.8x of control). Values generally remained within the historical control range[8].

As no statistical significance was achieved for any of the differences, mean values remained within normal limits and differences were minimal, the above mentioned changes were considered not toxicologically relevant.

Thyroid hormone analyses:

Serum T4 levels in F_0-males were considered not to be affected by treatment with the test item.

Mean serum T4 levels were decreased with statistical significance for males at 300 mg/kg/day (0.8x of control). Since values generally remained within the historical control range[9] and no dose-related trend was observed, this was considered unrelated to treatment with the test item.

9.1.9. Gross Pathology

(Appendix 1 and Appendix 2)

Macroscopic observations at necropsy did not reveal any alterations that were considered to have arisen as a result of treatment with the test item.

A macroscopic finding of note was recorded in two females of the 100 mg/kg/day group (Nos. 52 and 57) and one female of the 300 mg/kg/day group (No. 70). This finding consisted of watery clear fluid of the thoracic cavity. Since this finding was absent in the high dose group, and since there were no other macroscopic findings of organs of the thoracic cavity, or related clinical findings, this finding was considered to be unrelated to the test item.

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

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[6] Historical control data of male Wistar Han rats (period 2017 - wk 4 2019):
PT (s): Mean = 18.2; P5 - P95 = 16.2 – 21.2 (n=252).

[7] Historical control data of urea (mmol/L) in Wistar Han rats (period 2017 - wk 4 2019):
Males: mean = 6.7, P5 – P95 = 4.8 – 9.2 (n=270).
Females: mean = 10.1, P5 – P95 = 8.4 – 12.0 (n=210).

[8] Historical control data of glucose (mmol/L) in Wistar Han rats (period 2017 - wk 4 2019):
Males: mean = 9.05, P5 – P95 = 6.40 – 12.22 (n=270).

[9] Historical control data of male Wistar Han rats (period 2017 - 2019):
Total T4 (ug/dL): Mean = 4.51; P5 - P95 = 2.85 – 6.37 (n=557).

9.1.10. Organ Weights

(Appendix 1 and Appendix 2)

Thymus weights of test item-treated males were lower in a dose-related manner. This organ weight change was not statistically significantly different from the concurrent controls and group mean values remained within background ranges. However, individual organ weight values of 1/5 males of the 300 mg/kg/day group and 2/5 males of the 1000 mg/kg/day group were at the lower range[10]. Therefore a possible test item relationship at these dose levels could not be excluded.

The apparent dose-related decrease noted for absolute and relative spleen weight of treated males was attributed to a relatively high concurrent control value[11]. This change was therefore considered a chance finding, unrelated to the test item.

Any other differences, including those that reached statistical significance (i.e. absolute weight of adrenal glands in males at 300 mg/kg/day and relative weight of the heart in males at 100 mg/kg/day, absolute weight of kidneys in females at 1000 mg/kg/day and relative weight of thymus in females at 100 mg/kg/day) were considered not to be test item-related due to the direction of the change, lack of a dose-related pattern, and/or general overlap and variability in individual values.

9.1.11. Histopathology

(Appendix 4)

Test item-related microscopic findings after treatment with DiHEP Aqueous Solution were noted in the stomach of males at 1000 mg/kg/day and are summarized in Text Table 13.

Text Table 13
Summary Test Item-Related Microscopic Findings – Scheduled Euthanasia Animals (Day 29)

	Males			
Dose level (mg/kg/day):	0	100	300	1000
STOMACH [a]	5	5	5	5
Erosion glandular mucosa, focal				
Minimal	-	-	-	2
Slight	-	-	-	1

[a] = Number of tissues examined from each group.

(Multi) focal erosions of the glandular mucosa of the stomach were noted in 1000 mg/kg/day males (up to slight degree). These erosions were all located at the pyloric area.

The remainder of the recorded microscopic findings, including the low degrees of vacuolation of the zona fasciculate of the adrenal glands of males, were within the range of background pathology encountered in rats of this age and strain. There was no test item-related alteration in the prevalence, severity, or histologic character of those incidental tissue alterations.

[10] Historical control data for thymus weight in male Wistar Han rats (period 2017 – wk 4 2019):
Absolute mean = 0.364, P5 – P95 = 0.243 – 0.503 (n=255).
Relative mean = 0.107, P5 – P95 = 0.071 – 0.144 (n=255).
[11] Historical control data for spleen weight in male Wistar Han rats (period 2017 – wk 2019):
Absolute mean = 0.578, P5 – P95 = 0.464 – 0.721 (n=245).
Relative mean = 0.170, P5 – P95 = 0.141 – 0.204 (n=245).

Reproductive performance

Text Table 14
Correlation of Histopathology Findings with In-Life Reason for Males that Failed to Sire and Females that Failed to Deliver Healthy Pups.

Group	Dose level mg/kg bw/day	Female/Male Nos.	In-Life Reason	Histopathology
1	0	42 / 2	Not pregnant	Implantation site and necrosis of placenta of the uterus (observed as nodule)
		46 / 6	Not pregnant	-
2	100	51 / 11	Not pregnant	-
		53 / 13	Not pregnant	-
3	300	63 / 23	Not pregnant	-
4	1000	72 / 32	Not pregnant	-

There were 2/10 couples of the control group, 2/10 couples of 100 mg/kg/day group, 1/10 couples of the 300 mg/kg/day group and 1/10 couples of the 1000 mg/kg/day group with no offspring. Female No. 42 showed evidence of a former pregnancy, in the form of the presence of a necrotic placenta. For the other couples, no abnormalities which could account for the lack of offspring were seen in the reproductive organs.

There were no morphological findings in the reproductive organs of either sex which could be attributed to the test item. Stage aware evaluation of the testes did not show any indication for abnormal spermatogenesis. The testis revealed normal progression of the spermatogenic cycle and the expected cell associations and proportions in the various stages of spermatogenesis were present.

9.2. Reproduction Data

Note: For one female of the control group (No. 42), no implantation sites were noted at necropsy. As no Salewski staining was performed (see Appendix 7), the total number of implantation sites could not be determined and was not included in the tables. During the microscopic evaluation one implantation site was noted, providing evidence that this female was in fact pregnant.

9.2.1. Estrous Cycle

(Appendix 2)

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

All females had regular cycles of 4 days, with exception of one female at 1000 mg/kg/day (No. 79; with normal litter) for which the estrous stage could not be determined during the premating phase. Given the incidental nature and absence of an apparent correlation to pregnancy status, this finding did not indicate a relation with the test item.

9.2.2. Mating Index

(Appendix 1 and Appendix 2)

Mating index was not affected by treatment with the test item. All females showed evidence of mating, the mating index was therefore 100% for all groups.

9.2.3. Precoital Time

(Appendix 1 and Appendix 2)

Precoital time was not affected by treatment with the test item. Most females showed evidence of mating within 4 days, except for one control female, for which mating took 13 days.

9.2.4. Number of Implantation Sites

(Appendix 1 and Appendix 2)

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

9.2.5. Fertility Index

(Appendix 1 and Appendix 2)

The fertility index was considered not to be affected by treatment. The fertility indices were 90% for the control, 300 and 1000 mg/kg/day groups and 80% for the100 mg/kg/day group.

A total of 1/10 control females, 2/10 females at 100 mg/kg/day and 1/10 females at 300 and 1000 mg/kg/day each were not pregnant. In the absence of a dose-related incidence and based on the occurrence within the control group, these non-pregnancies were considered unrelated to the test item.

9.3. Developmental Data

Note: For one female of the control group (No. 42), no implantation sites were noted at necropsy. As no Salewski staining was performed (see Appendix 7), the total number of implantation sites could not be determined and was not included in the tables. During the microscopic evaluation one implantation site was noted, providing evidence that this female was in fact pregnant. This female was excluded from the calculation of the post-implantation survival index.

9.3.1. Gestation Index and Duration

(Appendix 1 and Appendix 2)

Gestation index and duration of gestation were considered not to be affected by treatment with the test item up to 1000 mg/kg/day.

Except for one control female, all pregnant females had live offspring. The gestation indices were 89% for the control group and 100% for all treated groups.

During microscopic evaluation, an implantation site and necrosis of placenta of the uterus were noted for control Female No. 42. As this occurred in a single female of the control group, the failed pregnancy was considered a chance finding.

9.3.2. 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.

9.3.3. Post-Implantation Survival Index

(Appendix 1 and Appendix 2)

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 item.

Post-implantation survival index (total number of offspring born as percentage of total number of uterine implantation sites) was 95, 97, 94 and 89% for the control, 100, 300 and 1000 mg/kg groups, respectively. The survival index at 1000 mg/kg/day was slightly lower than concurrent controls, however as this occasionally occurs in controls and the survival index remained within historical control range[12] this was considered a change finding.

For Female No. 61 (300 mg/kg/day), 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 16 days of) lactation. No toxicological relevance was attached to this finding in the current study.

9.3.4. Litter Size

(Appendix 1 and Appendix 2)

Litter size was considered not affected by treatment with the test item up to 1000 mg/kg/day.

Live litter sizes were 11.1, 14.1, 12.0 and 12.9 living pups/litter for the control, 100, 300 and 1000 mg/kg/day groups, respectively.

9.3.5. Live Birth Index

(Appendix 1 and Appendix 2)

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

Live birth indices (number of live offspring on PND 1 as percentage of total number of offspring born) were 100% for the control, 100 and 1000 mg/kg/day groups and 99% for the 300 mg/kg/day group.

One pup of the 300 mg/kg/day group (Litter No. 65) was found dead at first litter check. No toxicological relevance was attributed to this dead pup since the mortality incidence did not show a dose-related trend and remained within the range considered normal for pups of this age.

9.3.6. Viability Index

(Appendix 1 and Appendix 2)

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

Viability indices (number of live offspring on PND 4 before culling as percentage of number of live offspring on PND 1) were 99% for the control group and 100% for the 100, 300 and 1000 mg/kg/day groups.

One pup of the control group (Litter No. 48) went missing on PND 4, which was most likely cannibalised. The incidence remained within the range considered normal for pups of this age and given the occurrence in control group only this mortality was not attributed to the test item.

[12] Historical control data for post-implantation survival index for Wistar Han rats (period 2015 – wk 4 2019): Mean = 92, P5 – P95 = 83 – 98 (n=118).

9.3.7. Lactation Index

(Appendix 1 and Appendix 2)

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 item up to 1000 mg/kg/day. The lactation indices were 98% for the control for the control group and 100% for the 100, 300 and 1000 mg/kg/day groups.

One pup of the control group (Female No. 48) went missing on PND 6, which was most likely cannibalised. The incidence remained within the range considered normal for pups of this age and given the occurrence in control group only this mortality was not attributed to the test item.

One pup at 300 mg/kg/day (Litter No. 61) died spontaneously on PND 16. No toxicological relevance was attributed to this since the mortality incidence did not show a dose-related trend and remained within the range considered normal for pups of this age. Note: as this pup died on PND 16 it was not included in the tables as breeding loss.

9.3.8. Clinical Signs

(Appendix 2)

No clinical signs occurred among pups that were considered to be related to treatment with the test item.

The nature and incidence of observed clinical signs remained within the range considered normal for pups of this age, and were therefore considered not to be toxicologically relevant.

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

9.3.9. Body Weights

(Appendix 1 and Appendix 2)

Mean body weights of male and female pups at 1000 mg/kg/day were slightly lower when compared with concurrent controls (up to 0.91x of control). As all values were within normal limits and body weights of these pups were similar to concurrent control on Day 13 of lactation, this slight decrease at the beginning of the lactation period was considered not toxicologically relevant.

9.3.10. Sex Ratio

(Appendix 1 and Appendix 2)

Sex ratio was unaffected by treatment with the test item.

9.3.11. Anogenital Distance

(Appendix 1 and Appendix 2)

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

9.3.12. Areola/Nipple Retention

(Appendix 1 and Appendix 2)

Treatment up to 1000 mg/kg/day had no effect on areola/nipple retention. For none of the examined male pups nipples were observed at PND 13.

9.3.13. Clinical Biochemistry (T4 levels)

(Appendix 1 and Appendix 2)

Serum T4 levels in male and female pups at PND 14-16 were considered not to be affected by treatment with the test item. All values remained within the historical control range[13].

9.3.14. Macroscopy

(Appendix 2)

No macroscopic findings were noted among pups that were considered to be related to treatment with the test item.

The nature and incidence of macroscopic findings remained within the range considered normal for pups of this age, and were therefore considered not to be related to treatment.

[13] Historical control data for total T4 in PND 14-16 pups of Wistar Han rats (period 2017 – wk4 2019):
Males mean = 5.93, P5 – P95 = 4.28 – 8.03 (n=499)
Females mean = 5.57, P5 – P95 = 4.04 – 7.50 (n=499)

10. DISCUSSION

Wistar Han rats were treated with undiluted DiHEP Aqueous Solution by daily oral gavage at dose levels of 100, 300 and 1000 mg/kg. Concurrent controls (10 rats/sex) received Elix water.

Males were treated for 2 weeks prior to mating, during mating, and up to termination (for a total of 29 days). Females that delivered offspring were treated for 2 weeks prior to mating, during mating, during post-coitum, and at least 13-15 days of lactation (for a total of 51-56 days). Females that failed to deliver pups were treated for 42-52 days.

Parental results

No parental toxicity was observed up to the highest dose level tested (1000 mg/kg/day) and no mortality occurred. Test item-related findings were limited to non-adverse changes as described below:

Test item-related clinical signs included slight salivation directly after dosing among most males and few females of the 1000 mg/kg/day dose group during week 4 and/or 5 of treatment. This was regarded as a physiological response to the taste of the test item rather than a sign of systemic toxicity. In addition, one male showed piloerection on 4 consecutive days and one female showed hunched posture for 6 consecutive days, on 4 occasions combined with piloerection. At the incidence observed, and since the findings were transient, these were considered not toxicologically significant.

The slight, not statistically significant, changes in mean grip strength (females at 1000 mg/kg/day), total movements (males and females at 100 and 1000 mg/kg/day) and ambulations (males at 100 and 1000 mg/kg/day and females at all dose levels) were not supported by clinical observations or other functional observation tests, were slight in nature (within the normal range for rats of this age and strain), and had no supportive morphological correlates in examined neuronal tissues. These effects were therefore considered not to represent an adverse effect on neurobehaviour.

Thymus weight (absolute and relative) was decreased in all treated males in a dose-related manner. No statistical significance was achieved, all values remained within the historical control range and this decrease was not accompanied by any anatomic pathology alterations. As such, this finding was considered non-adverse.

Microscopic test item-related findings were present in the stomach of males at 1000 mg/kg/day, consisting of (multi) focal erosions of the glandular mucosa. Based on the low degrees (up to slight) and absence of concomitant test item-related microscopic changes, these findings were regarded as non-adverse.

No toxicologically significant changes were noted in any of the remaining parameters investigated in this study (i.e. body weight, food consumption, clinical laboratory investigations (including male T4 thyroid hormone levels) and macroscopic examination).

Reproductive results

No reproduction toxicity was observed up to the highest dose level tested (1000 mg/kg/day).

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

Developmental results

No developmental toxicity was observed up to the highest dose level tested (1000 mg/kg/day).

No toxicologically relevant changes were noted in any of the developmental parameters investigated in this study (i.e. gestation, viability and lactation indices, duration of gestation, parturition, sex ratio, maternal care and early postnatal pup development consisting of mortality, clinical signs, body weight, anogenital distance, areola/nipple retention, T4 thyroid hormone levels and macroscopic examination.

11. CONCLUSION

Based on the results of this combined 28-day repeated dose toxicity study with the reproduction/developmental toxicity screening test, the Parental, Reproduction and Developmental No Observed Adverse Effect Levels (NOAEL) for DiHEP Aqueous Solution were established to be at least 1000 mg/kg/day.

Appendix 1
Summary Tables

DIHEP AQUEOUS SOLUTION
APPENDIX 1

1.1 CLINICAL SIGNS SUMMARY
MALES

SIGN (MAX. GRADE) / (LOCATION)		PRE MATING	REPRO PERIOD
	WEEK:	1.	1. . . . .
	DAY:	12345671234567	123456712345671
GROUP 1 (CONTROL)			
No clinical signs noted			
GROUP 2 (100 MG/KG)			
Various			
Broken (1)	G:	. . . . .	 1111
(Tail apex)	%:	. . . . .	 1111
GROUP 3 (300 MG/KG)			
No clinical signs noted			
GROUP 4 (1000 MG/KG)			
Skin / fur			
Piloerection (1)	G:	. . . . .	. . . . . 1111. .
	%:	. . . . .	. . . . . 1111. .
Secretion / excretion			
Salivation (3)	G:	. . . . .	 11111
	%:	. . . . .	 45689

G: Median value of the highest individual daily grades
%: Percent of affected animals (0=less than 5%, 1=between 5% and 15%,..., A=more than 95%)
.: Observation performed, sign not present

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DIHEP AQUEOUS SOLUTION
APPENDIX 1

1.1 CLINICAL SIGNS SUMMARY
FEMALES

SIGN (MAX. GRADE)		PRE MATING	REPRO PERIOD
	WEEK:	1	1 4
(LOCATION)	DAY:	12345671234567	12345671234567123456712345671234567123456712345671234567
GROUP 1 (CONTROL)			
No clinical signs noted			
GROUP 2 (100 MG/KG)			
No clinical signs noted			
GROUP 3 (300 MG/KG)			
Skin / fur			
Scabs (3)	G:	1	11
(Cheek left)	%:	1	11
Scabs (3)	G:	1	11
(Cheek right)	%:	1	11
GROUP 4 (1000 MG/KG)			
Posture			
Hunched posture (1)	G:		1111111
	%:		1111111
Skin / fur			
Piloerection (1)	G:		11111
	%:		11111
Secretion / excretion			
Salivation (3)	G:		1111111 1
	%:		1111121 1

G: Median value of the highest individual daily grades
%: Percent of affected animals (0=less than 5%, 1=between 5% and 15%,..., A=more than 95%)
.: Observation performed, sign not present

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DIHEP AQUEOUS SOLUTION
APPENDIX 1

Project 20172120

1.2 BODY WEIGHTS (GRAM) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
PRE MATING					
DAY 1	MEAN	294	295	294	295
WEEK 1	ST.DEV	13.4	14.9	18.5	12.7
	N	10	10	10	10
DAY 8	MEAN	316	318	312	312
WEEK 2	ST.DEV	15.9	17.5	19.9	19.5
	N	10	10	10	10
MATING PERIOD					
DAY 1	MEAN	333	334	330	330
WEEK 1	ST.DEV	18.9	21.1	20.5	24.8
	N	10	10	10	10
DAY 8	MEAN	342	348	344	342
WEEK 2	ST.DEV	20.4	23.2	22.4	25.3
	N	10	10	10	10
DAY 15	MEAN	358	365	361	358
WEEK 3	ST.DEV	21.2	27.6	25.5	29.0
	N	10	10	10	10

FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
PRE MATING					
DAY 1	MEAN	225	222	226	223
WEEK 1	ST.DEV	10.7	11.7	15.1	9.8
	N	10	10	10	10
DAY 8	MEAN	225	225	228	228
WEEK 2	ST.DEV	13.3	11.0	15.7	7.9
	N	10	10	10	10
MATING PERIOD					
DAY 1	MEAN	230	233	239	237
WEEK 1	ST.DEV	11.9	12.2	14.6	6.4
	N	10	10	10	10
DAY 8	MEAN	271			271
WEEK 2	ST.DEV	---			---
	N	1			1
DAY 15	MEAN				294
WEEK 3	ST.DEV				---
	N				1
DAY 22	MEAN				330
WEEK 4	ST.DEV				---
	N				1

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

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DIHEP AQUEOUS SOLUTION
APPENDIX 1

1.2 BODY WEIGHTS (GRAM) SUMMARY
FEMALES

F0-GENERATION

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
POST COITUM					
DAY 0	MEAN	229	231	240	237
	ST.DEV.	11.4	10.8	15.5	5.0
	N	9	8	9	8
DAY 4	MEAN	243	246	254	248
	ST.DEV.	12.0	11.9	15.4	8.1
	N	9	8	9	8
DAY 7	MEAN	251	252	261	255
	ST.DEV.	12.5	13.4	17.8	8.2
	N	9	8	9	8
DAY 11	MEAN	264	265	276	272
	ST.DEV.	10.9	13.1	17.6	11.9
	N	9	8	9	8
DAY 14	MEAN	273	276	288	281
	ST.DEV.	11.2	13.3	18.5	13.0
	N	9	8	9	8
DAY 17	MEAN	292	300	318 *	306
	ST.DEV.	16.5	14.4	26.6	13.0
	N	9	8	9	8
DAY 20	MEAN	325	342	350	345
	ST.DEV.	24.2	15.5	26.5	19.5
	N	9	8	9	8
LACTATION					
DAY 1	MEAN	255	252	267	266
	ST.DEV.	11.8	18.5	19.0	12.2
	N	8	8	9	9
DAY 4	MEAN	268	269	285	283
	ST.DEV.	7.9	18.8	20.0	12.8
	N	8	8	9	9
DAY 7	MEAN	277	276	293	291
	ST.DEV.	12.3	15.6	22.4	13.7
	N	8	8	9	9
DAY 13	MEAN	290	294	306	300
	ST.DEV.	13.2	15.9	18.3	11.4
	N	8	8	9	9

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level
Explanations for excluded data are listed in the tables of the individual values

1.3 BODY WEIGHT GAIN (%) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
PRE MATING					
DAY 1	MEAN	0	0	0	0
WEEK 1	ST.DEV	0.0	0.0	0.0	0.0
	N	10	10	10	10
DAY 8	MEAN	7	8	6	6
WEEK 2	ST.DEV	1.7	2.4	1.3	3.1
	N	10	10	10	10
MATING PERIOD					
DAY 1	MEAN	13	13	12	12
WEEK 1	ST.DEV	2.8	4.3	2.7	4.3
	N	10	10	10	10
DAY 8	MEAN	16	18	17	16
WEEK 2	ST.DEV	3.3	5.4	3.1	4.6
	N	10	10	10	10
DAY 15	MEAN	22	23	23	21
WEEK 3	ST.DEV	4.3	7.3	4.1	5.7
	N	10	10	10	10

FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
PRE MATING					
DAY 1	MEAN	0	0	0	0
WEEK 1	ST.DEV	0.0	0.0	0.0	0.0
	N	10	10	10	10
DAY 8	MEAN	0	1	1	2
WEEK 2	ST.DEV	1.9	2.7	2.1	1.9
	N	10	10	10	10
MATING PERIOD					
DAY 1	MEAN	2	5	6 *	6 *
WEEK 1	ST.DEV	2.7	4.2	2.5	2.3
	N	10	10	10	10
DAY 8	MEAN	12			13
WEEK 2	ST.DEV	---			---
	N	1			1
DAY 15	MEAN				23
WEEK 3	ST.DEV				---
	N				1
DAY 22	MEAN				38
WEEK 4	ST.DEV				---
	N				1

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

1.3 BODY WEIGHT GAIN (%) SUMMARY
FEMALES

F0-GENERATION

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
POST COITUM					
DAY 0	MEAN	0	0	0	0
	ST.DEV.	0.0	0.0	0.0	0.0
	N	9	8	9	8
DAY 4	MEAN	6	6	6	5
	ST.DEV.	1.5	1.9	1.9	2.3
	N	9	8	9	8
DAY 7	MEAN	10	9	9	7
	ST.DEV.	1.8	2.5	2.6	2.4
	N	9	8	9	8
DAY 11	MEAN	16	15	15	15
	ST.DEV.	2.7	3.0	2.9	3.4
	N	9	8	9	8
DAY 14	MEAN	20	20	20	18
	ST.DEV.	3.8	3.1	3.4	3.9
	N	9	8	9	8
DAY 17	MEAN	28	30	33	29
	ST.DEV.	7.0	2.5	7.0	3.8
	N	9	8	9	8
DAY 20	MEAN	42	48	46	45
	ST.DEV.	11.3	3.9	5.5	6.3
	N	9	8	9	8
LACTATION					
DAY 1	MEAN	0	0	0	0
	ST.DEV.	0.0	0.0	0.0	0.0
	N	8	8	9	9
DAY 4	MEAN	5	7	7	6
	ST.DEV.	3.4	2.0	2.0	3.3
	N	8	8	9	9
DAY 7	MEAN	9	10	10	9
	ST.DEV.	1.3	2.6	2.3	3.4
	N	8	8	9	9
DAY 13	MEAN	14	17	15	13
	ST.DEV.	3.6	3.2	3.7	5.1
	N	8	8	9	9

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level
Explanations for excluded data are listed in the tables of the individual values

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

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
PRE MATING					
DAYS 1-8	MEAN	24	25	24	24
WEEKS 1-2	ST.DEV	0.0	0.8	0.5	1.6
	N (CAGE)	2	2	2	2
DAYS 8-15	MEAN	24	25	24	24
WEEKS 2-3	ST.DEV	0.1	1.1	0.0	1.3
	N (CAGE)	2	2	2	2
MEAN OF MEANS					
OVER PRE MATI...	MEAN	24	25	24	24
MATING PERIOD					
DAYS 1-8	MEAN	25	26	26	25
WEEKS 1-2	ST.DEV	0.5	0.7	0.7	0.2
	N (CAGE)	2	2	2	2
DAYS 8-15	MEAN	25	25	25	24
WEEKS 2-3	ST.DEV	0.4	0.7	0.5	0.0
	N (CAGE)	2	2	2	2
MEAN OF MEANS					
OVER MATING P...	MEAN	25	25	25	25

FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
PRE MATING					
DAYS 1-8	MEAN	18	18	18	18
WEEKS 1-2	ST.DEV	0.5	0.2	0.7	0.8
	N (CAGE)	2	2	2	2
DAYS 8-15	MEAN	18	17	18	18
WEEKS 2-3	ST.DEV	0.3	0.4	0.8	0.4
	N (CAGE)	2	2	2	2
MEAN OF MEANS					
OVER PRE MATI...	MEAN	18	18	18	18

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

F0-GENERATION

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
POST COITUM					
DAYS 0-4	MEAN	21	21	21	21
	ST.DEV.	1.0	1.6	1.3	2.5
	N	9	8	9	8
DAYS 4-7	MEAN	22	21	22	21
	ST.DEV.	1.2	1.8	2.4	2.1
	N	9	8	9	8
DAYS 7-11	MEAN	22	20	23	21
	ST.DEV.	1.2	1.2	2.1	1.7
	N	9	8	9	7
DAYS 11-14	MEAN	23	22	24	22
	ST.DEV.	1.6	1.2	1.8	3.2
	N	9	8	9	8
DAYS 14-17	MEAN	23	22	24	23
	ST.DEV.	2.3	1.0	1.9	2.0
	N	9	8	9	8
DAYS 17-20	MEAN	28	25	28	27
	ST.DEV.	2.6	2.2	3.8	2.9
	N	9	8	9	8
MEAN OF MEANS		23	22	24	23
LACTATION					
DAYS 1-4	MEAN	35	37	38	36
	ST.DEV.	5.4	9.2	6.5	4.3
	N	8	8	9	9
DAYS 4-7	MEAN	42	44	45	46
	ST.DEV.	5.8	3.1	3.7	4.8
	N	8	8	9	9
DAYS 7-13	MEAN	53	57	56	57
	ST.DEV.	6.1	1.7	3.1	1.9
	N	8	8	9	9
MEAN OF MEANS		43	46	46	46

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level
Explanations for excluded data are listed in the tables of the individual values

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

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
PRE MATING					
DAYS 1-8	MEAN	77	79	77	77
WEEKS 1-2	ST.DEV	0.7	3.0	0.3	0.9
	N (CAGE)	2	2	2	2
DAYS 8-15	MEAN	76	79	77	78
WEEKS 2-3	ST.DEV	0.2	3.8	1.8	0.1
	N (CAGE)	2	2	2	2
MEAN OF MEANS					
OVER PRE MATI...	MEAN	76	79	77	77
MATING PERIOD					
DAYS 1-8	MEAN	73	74	75	74
WEEKS 1-2	ST.DEV	0.3	2.0	0.5	5.7
	N (CAGE)	2	2	2	2
DAYS 8-15	MEAN	69	69	69	68
WEEKS 2-3	ST.DEV	0.1	1.8	0.2	5.3
	N (CAGE)	2	2	2	2
MEAN OF MEANS					
OVER MATING P...	MEAN	71	72	72	71

FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
PRE MATING					
DAYS 1-8	MEAN	80	80	80	80
WEEKS 1-2	ST.DEV	1.3	0.4	0.6	3.0
	N (CAGE)	2	2	2	2
DAYS 8-15	MEAN	79	77	80	79
WEEKS 2-3	ST.DEV	0.5	3.0	0.0	1.6
	N (CAGE)	2	2	2	2
MEAN OF MEANS					
OVER PRE MATI...	MEAN	80	79	80	80

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

F0-GENERATION

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
POST COITUM					
DAYS 0-4	MEAN	87	84	85	84
	ST.DEV.	3.7	6.0	4.2	9.2
	N	9	8	9	8
DAYS 4-7	MEAN	87	83	86	82
	ST.DEV.	3.1	6.8	6.0	6.9
	N	9	8	9	8
DAYS 7-11	MEAN	83	77 *	84	79
	ST.DEV.	4.7	3.6	5.4	5.6
	N	9	8	9	7
DAYS 11-14	MEAN	84	79	84	79
	ST.DEV.	4.8	3.1	4.4	12.5
	N	9	8	9	8
DAYS 14-17	MEAN	79	73 *	76	76
	ST.DEV.	5.1	2.5	4.4	4.7
	N	9	8	9	8
DAYS 17-20	MEAN	86	73 **	78 *	79
	ST.DEV.	4.9	4.0	7.1	6.0
	N	9	8	9	8
MEAN OF MEANS		84	78	82	80
LACTATION					
DAYS 1-4	MEAN	132	135	135	128
	ST.DEV.	19.9	31.1	24.3	14.4
	N	8	8	9	9
DAYS 4-7	MEAN	152	160	152	158
	ST.DEV.	19.2	12.6	10.7	16.6
	N	8	8	9	9
DAYS 7-13	MEAN	182	195	183	189
	ST.DEV.	20.0	7.3	11.4	4.5
	N	8	8	9	9
MEAN OF MEANS		155	164	157	159

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level
Explanations for excluded data are listed in the tables of the individual values

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1.6 FUNCTIONAL OBSERVATIONS SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
HEARING	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5
PUPIL L	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5
PUPIL R	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5
STATIC R	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5
GRIP FORE	MEAN	1313	1474	1268	1395
GRAM	ST.DEV	155	47	130	216
	N	5	5	5	5
GRIP HIND	MEAN	720	789	790	769
GRAM	ST.DEV	87	83	138	130
	N	5	5	5	5

FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
HEARING	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5
PUPIL L	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5
PUPIL R	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5
STATIC R	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5
GRIP FORE	MEAN	940	1029	1070	1108
GRAM	ST.DEV	282	257	157	220
	N	5	5	5	5
GRIP HIND	MEAN	582	647	620	570
GRAM	ST.DEV	88	41	106	85
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level
+/++ Steel-test significant at 5% (+) or 1% (++) level

03Jun19 12h49

1.7 MOTOR ACTIVITY TEST SUMMARY
MALES

Total Movements	CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
MEAN	4006	3366	3812	3068
N	5	5	5	5
STDEV	379	936	499	544

* indicates a p-value <0.05, ** indicates a p-value <0.01
MEAN and STDEV values are calculated per group, from each animal's total Total Movements over all intervals

29May19 12h06

1.7 MOTOR ACTIVITY TEST SUMMARY
MALES

Ambulations	CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
MEAN	910	775	909	867
N	5	5	5	5
STDEV	170	247	237	139

* indicates a p-value <0.05, ** indicates a p-value <0.01
MEAN and STDEV values are calculated per group, from each animal's total Ambulations over all intervals

29May19 12h06

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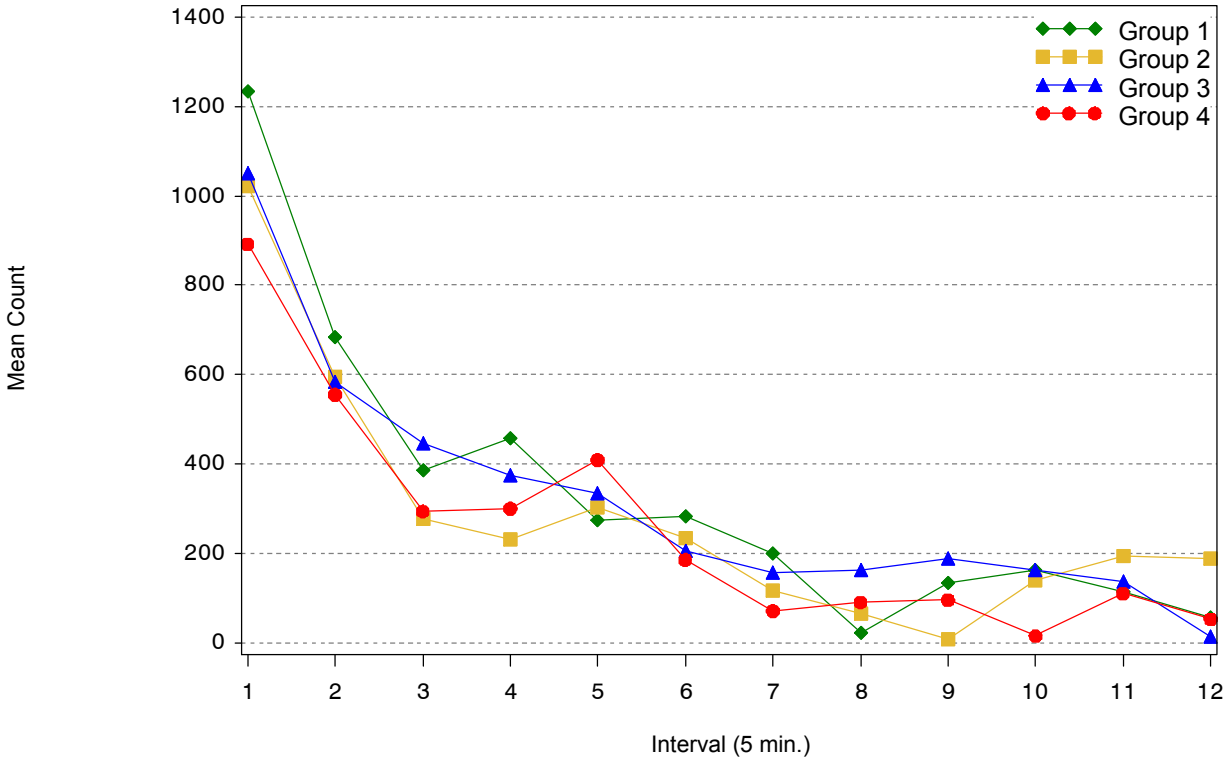
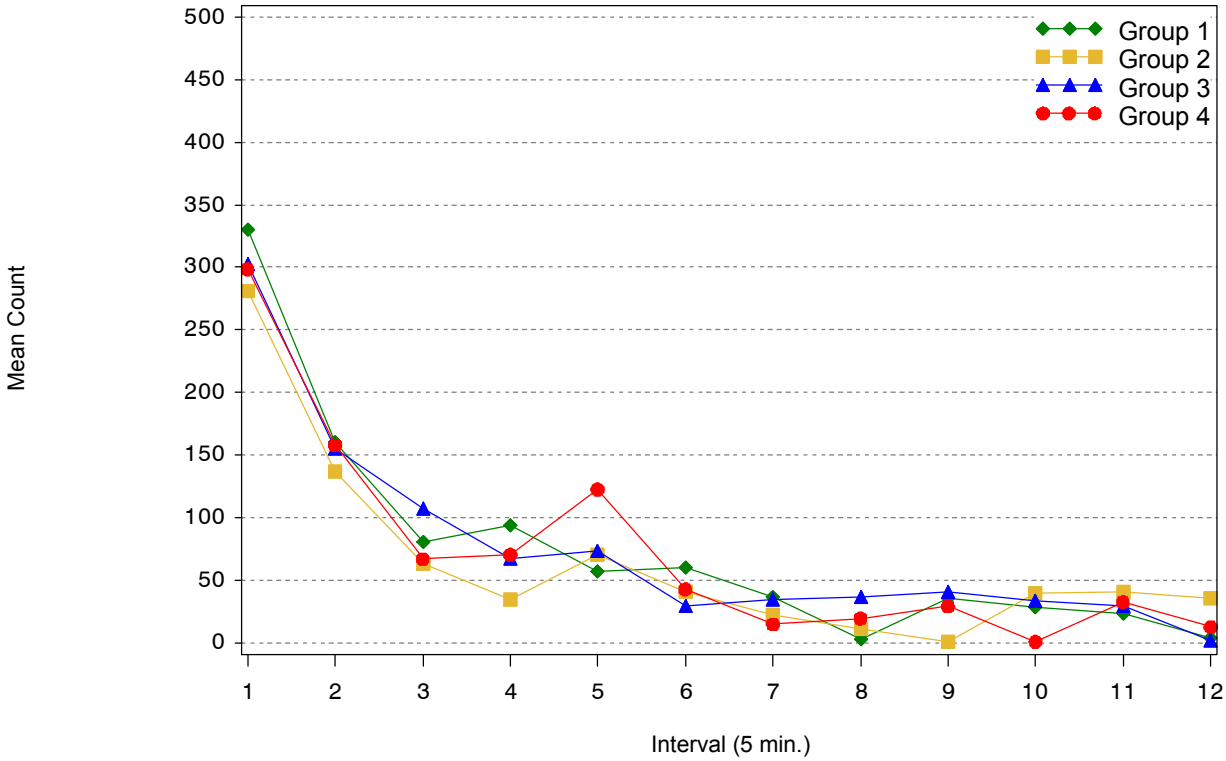
Project 20172120

1.7 MOTOR ACTIVITY: TOTAL MOVEMENTS
MALES



29May19 12h06

1.7 MOTOR ACTIVITY: AMBULATIONS
MALES



29May19 12h07

1.7 MOTOR ACTIVITY TEST SUMMARY
FEMALES

Total Movements	CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
MEAN	4626	3802	4663	3016
N	5	5	5	5
STDEV	1179	707	1255	1715

* indicates a p-value <0.05, ** indicates a p-value <0.01
MEAN and STDEV values are calculated per group, from each animal's total Total Movements over all intervals

29May19 12h07

1.7 MOTOR ACTIVITY TEST SUMMARY
FEMALES

Ambulations	CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
MEAN	1229	1040	1000	728
N	5	5	5	5
STDEV	311	275	218	518

* indicates a p-value <0.05, ** indicates a p-value <0.01
MEAN and STDEV values are calculated per group, from each animal's total Ambulations over all intervals

29May19 12h07

DIHEP AQUEOUS SOLUTION
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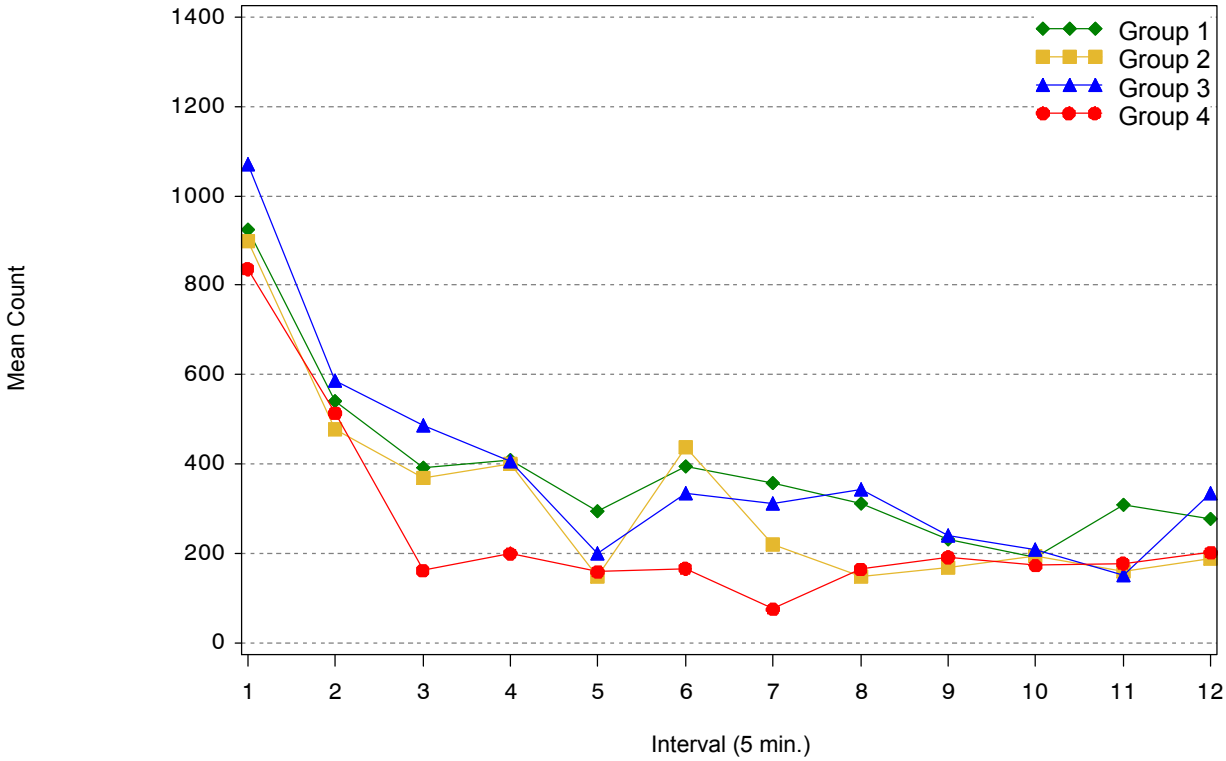
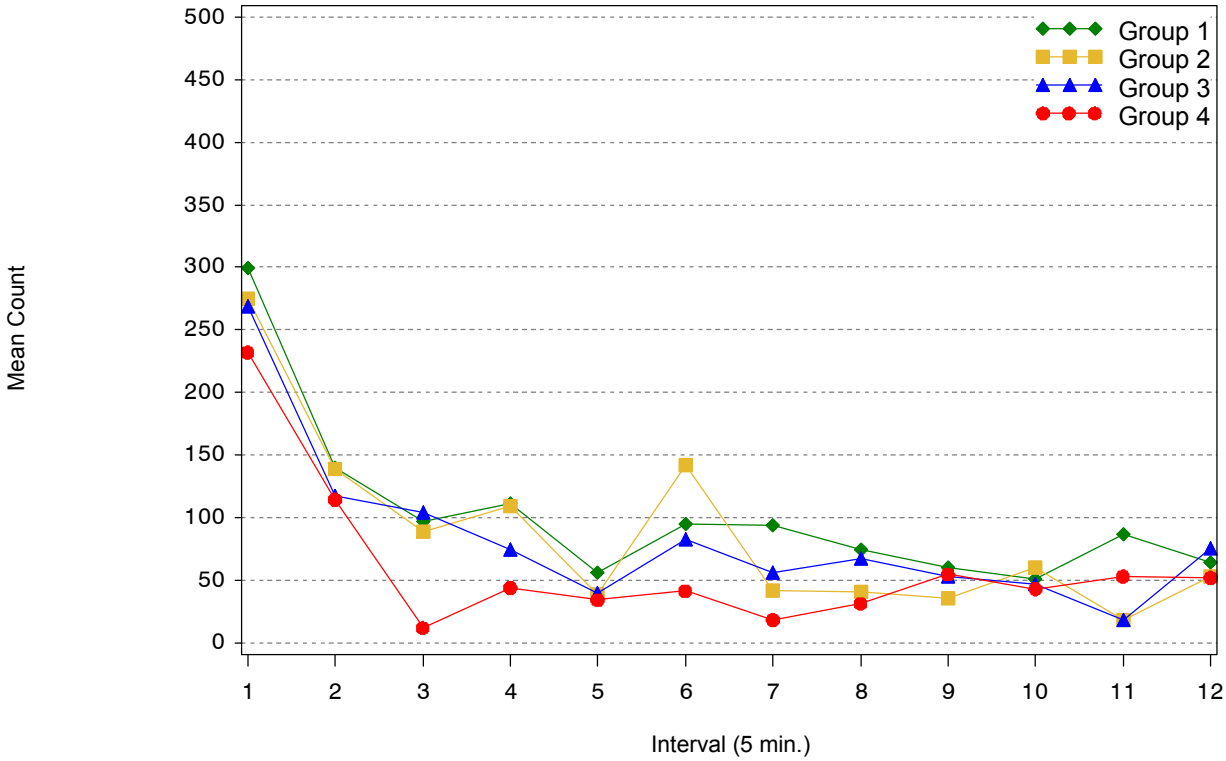
Project 20172120

1.7 MOTOR ACTIVITY: TOTAL MOVEMENTS
FEMALES



29May19 12h07

1.7 MOTOR ACTIVITY: AMBULATIONS
FEMALES



29May19 12h07

1.8 HAEMATOLOGY SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
WBC	MEAN	9.0	6.6	6.0	7.8
10E9/L	ST.DEV	1.4	1.7	2.1	2.1
	N	5	5	5	5
Neutrophils	MEAN	1.4	0.9 +	1.1	1.2
10E9/L	ST.DEV	0.3	0.1	0.3	0.2
	N	5	5	5	5
Lymphocytes	MEAN	7.4	5.4	4.7	6.5
10E9/L	ST.DEV	1.4	1.6	1.9	2.2
	N	4	5	5	4
Monocytes	MEAN	0.2	0.1	0.1	0.1
10E9/L	ST.DEV	0.1	0.1	0.0	0.0
	N	5	5	5	5
Eosinophils	MEAN	0.1	0.1	0.1	0.1
10E9/L	ST.DEV	0.1	0.0	0.0	0.1
	N	5	5	5	5
Basophils	MEAN	0.0	0.0	0.0	0.0
10E9/L	ST.DEV	0.0	0.0	0.0	0.0
	N	5	5	5	5
Red blood cells	MEAN	8.93	8.45	8.44	8.94
10E12/L	ST.DEV	0.29	0.49	0.68	0.23
	N	5	5	5	5
Reticulocytes	MEAN	210.0	202.5	247.8	219.2
10E9/L	ST.DEV	24.1	13.7	23.9	24.0
	N	5	5	5	5
RDW	MEAN	11.8	12.2	12.1	12.2
%	ST.DEV	0.3	0.9	0.3	0.5
	N	5	5	5	5
Haemoglobin	MEAN	10.1	9.7	9.3	10.0
mmol/L	ST.DEV	0.5	0.7	0.6	0.3
	N	5	5	5	5
Haematocrit	MEAN	0.476	0.450	0.446	0.478
L/L	ST.DEV	0.026	0.035	0.025	0.015
	N	5	5	5	5
MCV	MEAN	53.3	53.2	52.9	53.4
fL	ST.DEV	1.8	1.5	2.1	1.4
	N	5	5	5	5
MCH	MEAN	1.13	1.14	1.10	1.11
fmol	ST.DEV	0.03	0.04	0.04	0.04
	N	5	5	5	5
MCHC	MEAN	21.18	21.43	20.78	20.85
mmol/L	ST.DEV	0.37	0.67	0.34	0.36
	N	5	5	5	5
Platelets	MEAN	675	690	763	681
10E9/L	ST.DEV	31	133	64	75
	N	5	5	5	5

+/++ Steel-test significant at 5% (+) or 1% (++) level
*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

1.8 HAEMATOLOGY SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
PT	MEAN	18.9	17.7 *	17.8 *	17.7 *
s	ST.DEV	0.7	0.9	0.8	0.4
	N	5	4	5	5
APTT	MEAN	16.1	15.0	13.9	16.7
s	ST.DEV	3.2	2.6	2.7	2.0
	N	5	5	5	5

+/++ Steel-test significant at 5% (+) or 1% (++) level
*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

19Jun19 15h26

1.8 HAEMATOLOGY SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
WBC	MEAN	5.9	5.0	6.2	4.9
10E9/L	ST.DEV	2.1	1.1	1.6	1.4
	N	5	5	5	5
Neutrophils	MEAN	1.6	1.3	1.8	1.3
10E9/L	ST.DEV	0.4	0.4	0.9	0.3
	N	5	5	5	5
Lymphocytes	MEAN	4.0	3.5	4.1	3.4
10E9/L	ST.DEV	1.7	1.0	1.0	1.1
	N	5	5	5	5
Monocytes	MEAN	0.1	0.1	0.1	0.1
10E9/L	ST.DEV	0.1	0.0	0.0	0.0
	N	5	5	5	5
Eosinophils	MEAN	0.2	0.1	0.1	0.1
10E9/L	ST.DEV	0.1	0.0	0.0	0.0
	N	5	5	5	5
Basophils	MEAN	0.0	0.0	0.0	0.0
10E9/L	ST.DEV	0.0	0.0	0.0	0.0
	N	5	5	5	5
Red blood cells	MEAN	7.33	7.22	7.02	7.17
10E12/L	ST.DEV	0.72	0.38	0.29	0.61
	N	5	5	5	5
Reticulocytes	MEAN	223.3	233.4	204.9	215.7
10E9/L	ST.DEV	47.7	31.1	22.0	26.5
	N	5	5	5	5
RDW	MEAN	12.6	12.9	12.4	12.3
%	ST.DEV	1.3	0.8	1.1	0.8
	N	5	5	5	5
Haemoglobin	MEAN	8.8	8.8	8.8	8.6
mmol/L	ST.DEV	0.5	0.5	0.2	0.6
	N	5	5	5	5
Haematocrit	MEAN	0.431	0.434	0.433	0.423
L/L	ST.DEV	0.032	0.019	0.014	0.029
	N	5	5	5	5
MCV	MEAN	59.0	60.0	61.7	59.1
fL	ST.DEV	2.2	1.2	2.2	1.7
	N	5	5	5	5
MCH	MEAN	1.20	1.22	1.25	1.20
fmol	ST.DEV	0.07	0.02	0.05	0.03
	N	5	5	5	5
MCHC	MEAN	20.35	20.26	20.23	20.37
mmol/L	ST.DEV	0.53	0.42	0.26	0.37
	N	5	5	5	5
Platelets	MEAN	717	775	652	705
10E9/L	ST.DEV	20	114	80	117
	N	5	5	5	5

+/++ Steel-test significant at 5% (+) or 1% (++) level
*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

19Jun19 15h26

1.8 HAEMATOLOGY SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
PT	MEAN	17.2	17.3	17.6	16.9
s	ST.DEV	0.8	1.2	0.3	1.0
	N	4	5	4	5
APTT	MEAN	19.2	20.7	21.3	19.1
s	ST.DEV	1.1	1.9	3.0	0.9
	N	4	5	5	5

+/++ Steel-test significant at 5% (+) or 1% (++) level
*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

1.9 CLINICAL BIOCHEMISTRY SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
ALAT	MEAN	49.2	46.4	45.1	50.5
U/L	ST.DEV	8.1	11.4	10.3	5.4
	N	5	5	5	5
ASAT	MEAN	86.4	82.3	81.0	90.5
U/L	ST.DEV	7.8	4.6	12.9	9.3
	N	5	5	5	5
ALP	MEAN	151	135	123	160
U/L	ST.DEV	40	23	23	26
	N	5	5	5	5
Total protein	MEAN	62.4	62.8	62.2	61.4
g/L	ST.DEV	1.7	2.0	1.0	3.5
	N	5	5	5	5
Albumin	MEAN	31.7	31.9	31.7	31.2
g/L	ST.DEV	0.5	0.3	0.2	1.3
	N	5	5	5	5
Total bilirubin	MEAN	2.3	2.2	2.1	2.4
umol/L	ST.DEV	0.6	0.2	0.2	0.2
	N	5	5	5	5
Urea	MEAN	6.4	6.8	7.0	7.2
mmol/L	ST.DEV	1.0	1.5	1.3	1.3
	N	5	5	5	5
Creatinine	MEAN	36.8	39.4	37.6	35.6
umol/L	ST.DEV	2.6	2.3	2.5	1.6
	N	5	5	5	5
Glucose	MEAN	9.67	8.23	8.69	7.92
mmol/L	ST.DEV	1.94	1.21	1.67	1.70
	N	5	5	5	5
Cholesterol	MEAN	1.77	1.90	1.59	1.66
mmol/L	ST.DEV	0.18	0.26	0.20	0.43
	N	5	5	5	5
Bile Acids	MEAN	24.1	16.9	22.3	32.1
umol/L	ST.DEV	10.4	5.8	6.9	13.6
	N	5	5	5	5
Sodium	MEAN	140.4	140.5	139.9	141.2
mmol/L	ST.DEV	0.9	0.8	1.1	1.0
	N	5	5	5	5
Potassium	MEAN	4.06	3.96	3.89	3.92
mmol/L	ST.DEV	0.18	0.09	0.14	0.34
	N	5	5	5	5
Chloride	MEAN	104	105	104	104
mmol/L	ST.DEV	1	1	2	1
	N	5	5	5	5
Calcium	MEAN	2.54	2.55	2.53	2.54
mmol/L	ST.DEV	0.03	0.04	0.08	0.04
	N	5	5	5	5

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

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1.9 CLINICAL BIOCHEMISTRY SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
Inorg.Phos	MEAN	1.85	1.78	1.78	1.94
mmol/L	ST.DEV	0.13	0.28	0.10	0.10
	N	5	5	5	5
Total T4	MEAN	5.11	4.73	4.03 *	4.49
ug/dL	ST.DEV	1.05	0.95	0.46	1.07
	N	10	10	10	10

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

1.9 CLINICAL BIOCHEMISTRY SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
ALAT	MEAN	99.3	108.4	111.0	100.1
U/L	ST.DEV	8.0	8.8	14.6	13.0
	N	5	5	5	5
ASAT	MEAN	104.1	134.5	113.5	113.6
U/L	ST.DEV	16.1	57.9	22.1	22.2
	N	5	5	5	5
ALP	MEAN	364	461	360	333
U/L	ST.DEV	187	57	152	144
	N	5	5	5	5
Total protein	MEAN	56.6	56.7	56.9	56.0
g/L	ST.DEV	3.5	2.9	2.2	1.8
	N	5	5	5	5
Albumin	MEAN	30.5	29.6	30.0	29.5
g/L	ST.DEV	1.4	1.2	1.0	1.0
	N	5	5	5	5
Total bilirubin	MEAN	2.4	2.0	2.4	1.9
umol/L	ST.DEV	0.5	0.4	0.5	0.3
	N	5	5	5	5
Urea	MEAN	10.1	10.2	10.9	11.0
mmol/L	ST.DEV	1.0	0.6	0.9	2.3
	N	5	5	5	5
Creatinine	MEAN	36.2	37.5	34.9	35.9
umol/L	ST.DEV	2.2	1.5	1.9	2.7
	N	5	5	5	5
Glucose	MEAN	7.33	6.80	6.54	7.44
mmol/L	ST.DEV	0.80	0.69	0.71	0.66
	N	5	5	5	5
Cholesterol	MEAN	2.25	2.04	2.17	2.13
mmol/L	ST.DEV	0.22	0.17	0.28	0.16
	N	5	5	5	5
Bile Acids	MEAN	25.5	27.2	26.3	20.2
umol/L	ST.DEV	11.4	13.4	11.6	6.1
	N	5	5	5	5
Sodium	MEAN	139.8	140.3	139.7	139.5
mmol/L	ST.DEV	2.2	1.8	0.6	2.2
	N	5	5	5	5
Potassium	MEAN	4.43	4.43	4.85	4.79
mmol/L	ST.DEV	0.27	0.26	0.21	0.37
	N	5	5	5	5
Chloride	MEAN	102	103	103	102
mmol/L	ST.DEV	2	1	1	2
	N	5	5	5	5
Calcium	MEAN	2.50	2.45	2.51	2.51
mmol/L	ST.DEV	0.05	0.08	0.08	0.07
	N	5	5	5	5

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

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1.9 CLINICAL BIOCHEMISTRY SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
Inorg.Phos	MEAN	0.70	0.81	0.99	0.89
mmol/L	ST.DEV	0.24	0.50	0.41	0.62
	N	5	5	5	5

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

1.10 MACROSCOPIC FINDINGS SUMMARY
MALES

	GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT				
Animals examined	10	10	10	10
Animals without findings	10	9	10	7
Animals affected	0	1	0	3
Liver				
Discolouration	0	0	0	1
Kidneys				
Irregular surface	0	0	0	1
Epididymides				
Nodule(s)	0	0	0	1
Bone				
Tail bent	0	1	0	0

FEMALES

	GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT				
Animals examined	10	10	10	10
Animals without findings	9	8	4	8
Animals affected	1	2	6	2
Jejunum				
Focus/foci	0	0	1	0
Uterus				
Nodule(s)	1	0	0	0
Contains fluid	0	0	1	1
Contents:	1	0	0	0
Clitoral glands				
Focus/foci	0	1	0	0
Thyroid gland				
Discolouration	0	0	1	1
Thymus				
Focus/foci	1	0	1	0
Mandibular lymph n				
Focus/foci	1	0	0	1
Eyes				
Exophthalmus	1	0	1	1
Body cavities				
Nodule(s)	0	0	1	0
Contains fluid	0	2	1	0

/ ## Fisher's Exact test significant at 5% (#) or 1% (##) level

1.11 ORGAN WEIGHTS (GRAM) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
BODY W.	MEAN	335	340	335	332
(GRAM)	ST.DEV	20	25	22	28
	N	10	10	10	10
BRAIN	MEAN	2.00	2.02	2.02	1.98
(GRAM)	ST.DEV	0.07	0.11	0.10	0.07
	N	5	5	5	5
HEART	MEAN	0.962	0.894	0.938	0.869
(GRAM)	ST.DEV	0.073	0.063	0.102	0.048
	N	5	5	5	5
LIVER	MEAN	8.06	7.88	8.15	7.29
(GRAM)	ST.DEV	0.56	0.67	0.70	0.63
	N	5	5	5	5
THYROIDS	MEAN	0.016	0.016	0.016	0.018
(GRAM)	ST.DEV	0.002	0.003	0.003	0.003
	N	10	10	10	10
THYMUS	MEAN	0.385	0.367	0.346	0.300
(GRAM)	ST.DEV	0.064	0.068	0.089	0.089
	N	5	5	5	5
KIDNEYS	MEAN	2.27	2.19	2.32	2.29
(GRAM)	ST.DEV	0.09	0.11	0.30	0.19
	N	5	5	5	5
ADRENALS	MEAN	0.060	0.053	0.070 *	0.058
(GRAM)	ST.DEV	0.008	0.003	0.005	0.004
	N	5	5	5	5
SPLEEN	MEAN	0.652	0.617	0.587	0.525
(GRAM)	ST.DEV	0.122	0.056	0.085	0.044
	N	5	5	5	5
TESTES	MEAN	3.39	3.29	3.39	3.32
(GRAM)	ST.DEV	0.27	0.16	0.24	0.22
	N	10	10	10	10
PROSTATE GLAND	MEAN	0.863	0.836	0.841	0.785
(GRAM)	ST.DEV	0.110	0.126	0.141	0.147
	N	10	10	10	10
EPIDIDYMIDES	MEAN	1.060	1.059	1.075	1.066
(GRAM)	ST.DEV	0.087	0.058	0.074	0.078
	N	10	10	10	10
SEMINAL VESICLES	MEAN	1.339	1.276	1.305	1.172
(GRAM)	ST.DEV	0.140	0.190	0.243	0.214
	N	10	10	10	10

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

1.11 ORGAN/BODY WEIGHT RATIOS (%) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
BODY W.	MEAN	335	340	335	332
(GRAM)	ST.DEV	20	25	22	28
	N	10	10	10	10
BRAIN	MEAN	0.60	0.60	0.59	0.63
(%)	ST.DEV	0.04	0.04	0.04	0.04
	N	5	5	5	5
HEART	MEAN	0.289	0.263 **	0.274	0.277
(%)	ST.DEV	0.010	0.006	0.010	0.013
	N	5	5	5	5
LIVER	MEAN	2.42	2.32	2.39	2.33
(%)	ST.DEV	0.09	0.06	0.06	0.17
	N	5	5	5	5
THYROIDS	MEAN	0.005	0.005	0.005	0.005
(%)	ST.DEV	0.001	0.001	0.001	0.001
	N	10	10	10	10
THYMUS	MEAN	0.117	0.108	0.101	0.095
(%)	ST.DEV	0.025	0.017	0.020	0.025
	N	5	5	5	5
KIDNEYS	MEAN	0.68	0.65	0.68	0.73
(%)	ST.DEV	0.03	0.05	0.05	0.08
	N	5	5	5	5
ADRENALS	MEAN	0.018	0.016	0.021	0.019
(%)	ST.DEV	0.003	0.001	0.001	0.001
	N	5	5	5	5
SPLEEN	MEAN	0.195	0.182	0.172	0.168
(%)	ST.DEV	0.031	0.018	0.022	0.010
	N	5	5	5	5
TESTES	MEAN	1.01	0.97	1.01	1.00
(%)	ST.DEV	0.05	0.05	0.09	0.07
	N	10	10	10	10
PROSTATE GLAND	MEAN	0.258	0.246	0.251	0.237
(%)	ST.DEV	0.028	0.038	0.036	0.043
	N	10	10	10	10
EPIDIDYMIDES	MEAN	0.317	0.312	0.322	0.324
(%)	ST.DEV	0.023	0.019	0.026	0.042
	N	10	10	10	10
SEMINAL VESICLES	MEAN	0.400	0.377	0.391	0.356
(%)	ST.DEV	0.039	0.061	0.076	0.075
	N	10	10	10	10

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

1.11 ORGAN WEIGHTS (GRAM) SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
BODY W.	MEAN	276	279	290	290
(GRAM)	ST.DEV	15	21	30	25
	N	10	10	10	10
BRAIN	MEAN	1.89	1.90	1.91	1.94
(GRAM)	ST.DEV	0.09	0.05	0.05	0.09
	N	5	5	4	5
HEART	MEAN	0.828	0.830	0.861	0.861
(GRAM)	ST.DEV	0.063	0.059	0.087	0.041
	N	5	5	5	5
LIVER	MEAN	11.84	12.12	11.90	13.20
(GRAM)	ST.DEV	1.28	0.65	0.74	0.58
	N	5	5	5	5
THYROIDS	MEAN	0.017	0.019	0.018	0.018
(GRAM)	ST.DEV	0.004	0.004	0.004	0.004
	N	10	10	10	10
THYMUS	MEAN	0.237	0.187	0.225	0.200
(GRAM)	ST.DEV	0.054	0.022	0.017	0.044
	N	5	5	5	5
KIDNEYS	MEAN	1.87	2.05	2.01	2.09 *
(GRAM)	ST.DEV	0.14	0.17	0.08	0.06
	N	5	5	5	5
ADRENALS	MEAN	0.076	0.081	0.078	0.078
(GRAM)	ST.DEV	0.008	0.007	0.008	0.008
	N	5	5	5	5
SPLEEN	MEAN	0.500	0.507	0.510	0.551
(GRAM)	ST.DEV	0.052	0.037	0.090	0.134
	N	5	5	5	5
OVARIES	MEAN	0.113	0.115	0.117	0.115
(GRAM)	ST.DEV	0.010	0.008	0.013	0.018
	N	5	5	5	5
UTERUS	MEAN	0.360	0.360	0.356	0.345
(GRAM)	ST.DEV	0.038	0.068	0.055	0.031
	N	5	5	5	5

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

1.11 ORGAN/BODY WEIGHT RATIOS (%) SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
BODY W.	MEAN	276	279	290	290
(GRAM)	ST.DEV	15	21	30	25
	N	10	10	10	10
BRAIN	MEAN	0.69	0.65	0.66	0.67
(%)	ST.DEV	0.04	0.02	0.04	0.04
	N	5	5	4	5
HEART	MEAN	0.301	0.286	0.296	0.298
(%)	ST.DEV	0.024	0.018	0.020	0.011
	N	5	5	5	5
LIVER	MEAN	4.30	4.18	4.09	4.57
(%)	ST.DEV	0.37	0.18	0.07	0.12
	N	5	5	5	5
THYROIDS	MEAN	0.006	0.007	0.006	0.006
(%)	ST.DEV	0.001	0.002	0.002	0.001
	N	10	10	10	10
THYMUS	MEAN	0.086	0.065 *	0.077	0.069
(%)	ST.DEV	0.020	0.007	0.005	0.015
	N	5	5	5	5
KIDNEYS	MEAN	0.68	0.71	0.69	0.73
(%)	ST.DEV	0.05	0.05	0.04	0.03
	N	5	5	5	5
ADRENALS	MEAN	0.027	0.028	0.027	0.027
(%)	ST.DEV	0.002	0.003	0.003	0.003
	N	5	5	5	5
SPLEEN	MEAN	0.182	0.175	0.175	0.190
(%)	ST.DEV	0.019	0.012	0.025	0.043
	N	5	5	5	5
OVARIES	MEAN	0.041	0.040	0.040	0.040
(%)	ST.DEV	0.003	0.003	0.003	0.007
	N	5	5	5	5
UTERUS	MEAN	0.131	0.124	0.122	0.120
(%)	ST.DEV	0.014	0.022	0.017	0.012
	N	5	5	5	5

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

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1.12 REPRODUCTION DATA SUMMARY

	GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
Females paired	10	10	10	10
Females mated	10	10	10	10
Pregnant females	9	8	9	9
Females with living pups on Day 1	8	8	9	9
Mating index (%) (Females mated / Females paired) * 100	100	100	100	100
Fertility index (%) (Pregnant females / Females mated) * 100	90	80	90	90
Gestation index (%) (Females with living pups on Day 1 / Pregnant females) * 100	89	100	100	100

1.13 PRECOITAL TIME

F0-GENERATION - POST COITUM

DAY OF THE PAIRING PERIOD	**GROUP 1 CONTROL**	**GROUP 2 100 MG/KG**	**GROUP 3 300 MG/KG**	**GROUP 4 1000 MG/KG**
NUMBER OF FEMALES MATED				
1	2	2	3	3
2	-	4	1	1
3	6	3	4	4
4	1	1	2	2
13	1	-	-	-
MEDIAN PRECOITAL TIME	3	2	3	3
MEAN PRECOITAL TIME	3.7	2.3	2.5	2.5
N	10	10	10	10

+/++ Steel-test significant at 5% (+) or 1% (++) level

1.14 IMPLANTATION SITES SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
AT NECROPSY					
Implantations	MEAN	11.8	14.6	12.9	14.4
	ST.DEV	3.2	2.2	1.6	2.0
	N	8	8	9	9

+/++ Steel-test significant at 5% (+) or 1% (++) level

1.15 DEVELOPMENTAL DATA

F0-GENERATION - LACTATION

	GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
LITTERS				
TOTAL	8	8	9	9
DURATION OF GESTATION				
MEAN (+)	21.4	21.3	21.7	21.0
ST.DEV.	0.5	0.5	0.5	0.0
N	8	8	9	9
DEAD PUPS AT FIRST LITTER CHECK				
LITTERS AFFECTED (#)	0	0	1	0
TOTAL	0	0	1	0
MEAN (+)	0.0	0.0	0.1	0.0
ST.DEV.	0.0	0.0	0.3	0.0
N	8	8	9	9
LIVING PUPS AT FIRST LITTER CHECK				
% OF MALES / FEMALES (#)	49 / 51	50 / 50	48 / 52	48 / 52
TOTAL	89	113	108	116
MEAN (+)	11.1	14.1	12.0	12.9
ST.DEV.	3.3	1.9	1.7	1.9
N	8	8	9	9
POSTNATAL LOSS				
% OF LIVING PUPS	1.1	0.0	0.0	0.0
LITTERS AFFECTED (#)	1	0	0	0
TOTAL (#)	1	0	0	0
MEAN (+)	0.1	0.0	0.0	0.0
ST.DEV.	0.4	0.0	0.0	0.0
N	8	8	9	9
CULLED PUPS				
TOTAL	26	49	36	44
LIVING PUPS DAY 4 P.P.				
TOTAL	62	64	72	72
MEAN (+)	7.8	8.0	8.0	8.0
ST.DEV.	0.7	0.0	0.0	0.0
N	8	8	9	9
BREEDING LOSS DAYS 5 - 13 P.P.				
% OF LIVING PUPS AT DAY 4 P.P.	1.6	0.0	0.0	0.0
LITTERS AFFECTED (#)	1	0	0	0
TOTAL (#)	1	0	0	0
MEAN (+)	0.1	0.0	0.0	0.0
ST.DEV.	0.4	0.0	0.0	0.0
N	8	8	9	9
LIVING PUPS DAY 13 P.P.				
% OF MALES / FEMALES (#)	51 / 49	50 / 50	48 / 52	50 / 50
TOTAL	61	64	71	72
MEAN (+)	7.6	8.0	7.9	8.0
ST.DEV.	0.7	0.0	0.3	0.0
N	8	8	9	9

+/++ Steel-test significant at 5% (+) or 1% (++) level
/ ## Fisher's Exact test significant at 5% (#) or 1% (##) level

DIHEP AQUEOUS SOLUTION
APPENDIX 1

Project 20172120

1.15 DEVELOPMENTAL DATA

	GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
Total number of offspring born	89	113	109	116
Total number of uterine implantation sites	94	117	116	130
Number of live offspring on Day 1 after littering	89	113	108	116
Number of live offspring on Day 4 (before culling)	88	113	108	116
Number of live offspring on Day 4 (after culling)	62	64	72	72
Number of live offspring on Day 13 after littering	61	64	72	72
Post-implantation survival index (%) (Total number of offspring born/Total number of uterine implantation sites) * 100	95	97	94	89
Live birth index (%) (Number of live offspring on Day 1 after littering/Total number of offspring born) * 100	100	100	99	100
Viability index (%) (Number of live offspring on Day 4 (before culling)/Number of live offspring on Day 1 after littering)*100	99	100	100	100
Lactation index (%) (Number of live offspring on Day 13 after littering/Number of live offspring on Day 4 (after culling)) * 100	98	100	100	100

1.16 BODY WEIGHTS OF PUPS (GRAM)

F0-GENERATION - LACTATION

DAY	SEX		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
1	M	MEAN	6.6	6.1	6.7	6.1
		ST.DEV.	0.8	0.4	0.7	0.3
		N	8	8	9	9
	F	MEAN	6.4	5.8	6.4	5.8
		ST.DEV.	0.8	0.4	0.7	0.4
		N	8	8	9	9
	M+F	MEAN	6.5	5.9	6.6	6.0
		ST.DEV.	0.8	0.4	0.6	0.3
		N	8	8	9	9
4	M	MEAN	9.8	8.7	10.2	9.1
		ST.DEV.	1.6	0.5	1.2	0.4
		N	8	8	9	9
	F	MEAN	9.5	8.4	9.8	8.7
		ST.DEV.	1.5	0.5	1.1	0.5
		N	8	8	9	9
	M+F	MEAN	9.6	8.6	10.0	8.9
		ST.DEV.	1.5	0.5	1.2	0.5
		N	8	8	9	9
7	M	MEAN	16.1	15.2	17.3	15.9
		ST.DEV.	2.1	0.8	1.8	0.6
		N	8	8	9	9
	F	MEAN	15.8	14.6	16.4	15.1
		ST.DEV.	2.0	0.6	1.7	0.9
		N	8	8	9	9
	M+F	MEAN	16.0	14.9	16.9	15.5
		ST.DEV.	2.0	0.6	1.8	0.7
		N	8	8	9	9
13	M	MEAN	31.3	30.7	32.7	31.6
		ST.DEV.	2.6	1.3	2.8	1.1
		N	8	8	9	9
	F	MEAN	30.7	29.6	31.7	30.4
		ST.DEV.	2.5	0.8	2.7	1.0
		N	8	8	9	9
	M+F	MEAN	31.0	30.1	32.2	31.0
		ST.DEV.	2.5	1.0	2.8	0.8
		N	8	8	9	9

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

1.17 ANOGENITAL DISTANCE AND NIPPLE RETENTION PER GROUP

F0-GENERATION - LACTATION

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
anogenital dist M mm	MEAN	2.61	2.59	2.66	2.65
	ST.DEV.	0.11	0.09	0.14	0.08
	N	8	8	9	9
anogenital dist F mm	MEAN	0.95	1.04	1.00	1.01
	ST.DEV.	0.08	0.20	0.14	0.18
	N	8	8	9	9
Number of nipples	MEAN	0.00	0.00	0.00	0.00
	MEDIAN (+)	0.00	0.00	0.00	0.00
	N	8	8	9	8

/ ## Fisher's Exact test significant at 5% (#) or 1% (##) level
+/++ Steel-test significant at 5% (+) or 1% (++) level

03Jun19 14h19

1.18 CORRECTED ANOGENITAL DISTANCE SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
PND 1					
norm anog dist M	MEAN	1.40	1.42	1.41	1.45
mm	ST.DEV	0.05	0.03	0.07	0.05
	N	8	8	9	9
norm anog dist F	MEAN	0.51	0.58	0.54	0.56
mm	ST.DEV	0.05	0.10	0.08	0.10
	N	8	8	9	9

+/++ Steel-test significant at 5% (+) or 1% (++) level

03Jun19 13h42

1.19 CLINICAL BIOCHEMISTRY SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
PUPS (PND 14-16)					
Total T4	MEAN	6.58	6.19	6.11	6.03
ug/dL	ST.DEV	1.35	0.92	0.79	0.69
	N	8	8	9	9

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

DIHEP AQUEOUS SOLUTION
APPENDIX 1

Project 20172120

1.19 CLINICAL BIOCHEMISTRY SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
PUPS (PND 14-16)					
Total T4	MEAN	5.98	5.93	5.74	5.28
ug/dL	ST.DEV	0.98	0.75	0.61	0.89
	N	8	8	9	9

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

03Jun19 14h12

Appendix 2
Individual Tables

DIHEP AQUEOUS SOLUTION
APPENDIX 2

Project 20172120

2.1 MORTALITY DATA
MALES

ANIMAL	SCHEDULED SACRIFICE	TREATMENT FROM	TO
GROUP 1 (CONTROL)			
1	06MAR19	05FEB19	05MAR19
2	06MAR19	05FEB19	05MAR19
3	06MAR19	05FEB19	05MAR19
4	06MAR19	05FEB19	05MAR19
5	06MAR19	05FEB19	05MAR19
6	06MAR19	05FEB19	05MAR19
7	06MAR19	05FEB19	05MAR19
8	06MAR19	05FEB19	05MAR19
9	06MAR19	05FEB19	05MAR19
10	06MAR19	05FEB19	05MAR19
GROUP 2 (100 MG/KG)			
11	06MAR19	05FEB19	05MAR19
12	06MAR19	05FEB19	05MAR19
13	06MAR19	05FEB19	05MAR19
14	06MAR19	05FEB19	05MAR19
15	06MAR19	05FEB19	05MAR19
16	06MAR19	05FEB19	05MAR19
17	06MAR19	05FEB19	05MAR19
18	06MAR19	05FEB19	05MAR19
19	06MAR19	05FEB19	05MAR19
20	06MAR19	05FEB19	05MAR19
GROUP 3 (300 MG/KG)			
21	06MAR19	05FEB19	05MAR19
22	06MAR19	05FEB19	05MAR19
23	06MAR19	05FEB19	05MAR19
24	06MAR19	05FEB19	05MAR19
25	06MAR19	05FEB19	05MAR19
26	06MAR19	05FEB19	05MAR19
27	06MAR19	05FEB19	05MAR19
28	06MAR19	05FEB19	05MAR19
29	06MAR19	05FEB19	05MAR19
30	06MAR19	05FEB19	05MAR19
GROUP 4 (1000 MG/KG)			
31	06MAR19	05FEB19	05MAR19
32	06MAR19	05FEB19	05MAR19
33	06MAR19	05FEB19	05MAR19
34	06MAR19	05FEB19	05MAR19
35	06MAR19	05FEB19	05MAR19
36	06MAR19	05FEB19	05MAR19
37	06MAR19	05FEB19	05MAR19
38	06MAR19	05FEB19	05MAR19
39	06MAR19	05FEB19	05MAR19
40	06MAR19	05FEB19	05MAR19

FEMALES

ANIMAL	SCHEDULED SACRIFICE	TREATMENT FROM	TO
GROUP 1 (CONTROL)			
41	29MAR19	05FEB19	28MAR19
42	19MAR19	05FEB19	18MAR19
43	01APR19	05FEB19	31MAR19
44	29MAR19	05FEB19	28MAR19
45	29MAR19	05FEB19	28MAR19
46	29MAR19	05FEB19	28MAR19
47	28MAR19	05FEB19	27MAR19

DIHEP AQUEOUS SOLUTION
APPENDIX 2

2.1 MORTALITY DATA
FEMALES

ANIMAL	SCHEDULED SACRIFICE	TREATMENT FROM	TO
GROUP 1 (CONTROL)			
48	01APR19	05FEB19	31MAR19
49	01APR19	05FEB19	31MAR19
50	29MAR19	05FEB19	28MAR19
GROUP 2 (100 MG/KG)			
51	19MAR19	05FEB19	18MAR19
52	29MAR19	05FEB19	28MAR19
53	19MAR19	05FEB19	18MAR19
54	28MAR19	05FEB19	27MAR19
55	02APR19	05FEB19	01APR19
56	29MAR19	05FEB19	28MAR19
57	29MAR19	05FEB19	28MAR19
58	29MAR19	05FEB19	28MAR19
59	01APR19	05FEB19	31MAR19
60	29MAR19	05FEB19	28MAR19
GROUP 3 (300 MG/KG)			
61	02APR19	05FEB19	01APR19
62	01APR19	05FEB19	31MAR19
63	19MAR19	05FEB19	18MAR19
64	29MAR19	05FEB19	28MAR19
65	01APR19	05FEB19	31MAR19
66	29MAR19	05FEB19	28MAR19
67	01APR19	05FEB19	31MAR19
68	29MAR19	05FEB19	28MAR19
69	01APR19	05FEB19	31MAR19
70	29MAR19	05FEB19	28MAR19
GROUP 4 (1000 MG/KG)			
71	28MAR19	05FEB19	27MAR19
72	19MAR19	05FEB19	18MAR19
73	28MAR19	05FEB19	27MAR19
74	29MAR19	05FEB19	28MAR19
75	29MAR19	05FEB19	28MAR19
76	29MAR19	05FEB19	28MAR19
77	01APR19	05FEB19	31MAR19
78	01APR19	05FEB19	31MAR19
79	28MAR19	05FEB19	27MAR19
80	29MAR19	05FEB19	28MAR19

2.2 CLINICAL SIGNS
MALES

SIGN (MAX. GRADE) / (LOCATION)		PRE MATING	REPRO PERIOD
	WEEK:	1.	1. . . . .
	DAY:	12345671234567	123456712345671
GROUP 1 (CONTROL)			
ANIMAL 1			
No clinical signs noted			
ANIMAL 2			
No clinical signs noted			
ANIMAL 3			
No clinical signs noted			
ANIMAL 4			
No clinical signs noted			
ANIMAL 5			
No clinical signs noted			
ANIMAL 6			
No clinical signs noted			
ANIMAL 7			
No clinical signs noted			
ANIMAL 8			
No clinical signs noted			
ANIMAL 9			
No clinical signs noted			
ANIMAL 10			
No clinical signs noted			
GROUP 2 (100 MG/KG)			
ANIMAL 11			
No clinical signs noted			
ANIMAL 12			
No clinical signs noted			
ANIMAL 13			
No clinical signs noted			
ANIMAL 14			
Various			
Broken (1) (Tail apex)	G:	. . . . .	 1111
ANIMAL 15			
No clinical signs noted			
ANIMAL 16			
No clinical signs noted			
ANIMAL 17			
No clinical signs noted			
ANIMAL 18			
No clinical signs noted			
ANIMAL 19			
No clinical signs noted			
ANIMAL 20			
No clinical signs noted			
GROUP 3 (300 MG/KG)			
ANIMAL 21			
No clinical signs noted			
ANIMAL 22			
No clinical signs noted			
ANIMAL 23			
No clinical signs noted			
ANIMAL 24			
No clinical signs noted			
ANIMAL 25			
No clinical signs noted			
ANIMAL 26			
No clinical signs noted			
ANIMAL 27			
No clinical signs noted			

G: Highest daily grades
.: Observation performed, sign not present

03Jun19 13h46

2.2 CLINICAL SIGNS
MALES

SIGN (MAX. GRADE) / (LOCATION)		PRE MATING WEEK: 1 DAY: 12345671234567	REPRO PERIOD WEEK: 1 DAY: 123456712345671
GROUP 3 (300 MG/KG)			
ANIMAL 28			
No clinical signs noted			
ANIMAL 29			
No clinical signs noted			
ANIMAL 30			
No clinical signs noted			
GROUP 4 (1000 MG/KG)			
ANIMAL 31			
Secretion / excretion			
Salivation (3)	G:	. . . . .	 111
ANIMAL 32			
Secretion / excretion			
Salivation (3)	G:	. . . . .	 11
ANIMAL 33			
Secretion / excretion			
Salivation (3)	G:	. . . . .	. . . . . 1. . 11
ANIMAL 34			
Secretion / excretion			
Salivation (3)	G:	. . . . .	 11111
ANIMAL 35			
Secretion / excretion			
Salivation (3)	G:	. . . . .	 11111
ANIMAL 36			
Skin / fur			
Piloerection (1)	G:	. . . . .	. . . . . 1111. .
Secretion / excretion			
Salivation (3)	G:	. . . . .	 1
ANIMAL 37			
Secretion / excretion			
Salivation (3)	G:	. . . . .	 11111
ANIMAL 38			
Secretion / excretion			
Salivation (3)	G:	. . . . .	 1111
ANIMAL 39			
Secretion / excretion			
Salivation (3)	G:	. . . . .	 1111
ANIMAL 40			
No clinical signs noted			

G: Highest daily grades
.: Observation performed, sign not present

2.2 CLINICAL SIGNS
FEMALES

SIGN (MAX. GRADE) / (LOCATION)		PRE MATING WEEK: 1 / DAY: 12345671234567	REPRO PERIOD WEEK: 1 / DAY: 1234567123456712345671234567	4 / 12345671234567
GROUP 1 (CONTROL)				
ANIMAL 41				
No clinical signs noted				
ANIMAL 42				
No clinical signs noted				
ANIMAL 43				
No clinical signs noted				
ANIMAL 44				
No clinical signs noted				
ANIMAL 45				
No clinical signs noted				
ANIMAL 46				
No clinical signs noted				
ANIMAL 47				
No clinical signs noted				
ANIMAL 48				
No clinical signs noted				
ANIMAL 49				
No clinical signs noted				
ANIMAL 50				
No clinical signs noted				
GROUP 2 (100 MG/KG)				
ANIMAL 51				
No clinical signs noted				
ANIMAL 52				
No clinical signs noted				
ANIMAL 53				
No clinical signs noted				
ANIMAL 54				
No clinical signs noted				
ANIMAL 55				
No clinical signs noted				
ANIMAL 56				
No clinical signs noted				
ANIMAL 57				
No clinical signs noted				
ANIMAL 58				
No clinical signs noted				
ANIMAL 59				
No clinical signs noted				
ANIMAL 60				
No clinical signs noted				
GROUP 3 (300 MG/KG)				
ANIMAL 61				
No clinical signs noted				
ANIMAL 62				
No clinical signs noted				
ANIMAL 63				
No clinical signs noted				
ANIMAL 64				
No clinical signs noted				
ANIMAL 65				
Skin / fur				
Scabs (3) (Cheek left)	G:	 1	11.	. . . . .
Scabs (3) (Cheek right)	G:	 1	11.	. . . . .
ANIMAL 66				
No clinical signs noted				

G: Highest daily grades
.: Observation performed, sign not present

2.2 CLINICAL SIGNS
FEMALES

SIGN (MAX. GRADE) / (LOCATION)		PRE MATING WEEK: 1 / DAY: 12345671234567	REPRO PERIOD WEEK: 1 / DAY: 1234567123456712345671234567	REPRO PERIOD WEEK: 4 / DAY: 12345671234567
GROUP 3 (300 MG/KG)				
ANIMAL 67				
No clinical signs noted				
ANIMAL 68				
No clinical signs noted				
ANIMAL 69				
No clinical signs noted				
ANIMAL 70				
No clinical signs noted				
GROUP 4 (1000 MG/KG)				
ANIMAL 71				
No clinical signs noted				
ANIMAL 72				
Posture				
Hunched posture (1)	G:	.....	.....	1111111..
Skin / fur				
Piloerection (1)	G:	.....	.....	11111....
ANIMAL 73				
Secretion / excretion				
Salivation (3)	G:	.....	.....	11..1.....
ANIMAL 74				
No clinical signs noted				
ANIMAL 75				
No clinical signs noted				
ANIMAL 76				
Secretion / excretion				
Salivation (3)	G:	.....	.....	11111.....
ANIMAL 77				
No clinical signs noted				
ANIMAL 78				
No clinical signs noted				
ANIMAL 79				
Secretion / excretion				
Salivation (3)	G:	.....	.....	1.....
ANIMAL 80				
No clinical signs noted				

G: Highest daily grades
.: Observation performed, sign not present

03Jun19 13h46

2.3 BODY WEIGHTS (GRAM)
MALES

	PRE MATING		MATING PERIOD		
DAYS	1	8	1	8	15
WEEKS	1	2	1	2	3
ANIMAL					
GROUP 1 (CONTROL)					
1	285	304	311	321	339
2	268	284	298	304	327
3	317	337	353	362	374
4	295	324	340	350	364
5	296	321	343	354	368
6	287	306	325	330	331
7	291	311	327	340	361
8	302	334	359	372	395
9	308	326	345	354	371
10	294	312	328	335	351
GROUP 2 (100 MG/KG)					
11	285	315	337	354	377
12	315	343	360	371	391
13	280	307	328	345	366
14	301	322	334	351	363
15	295	308	311	317	323
16	305	337	363	378	403
17	270	282	294	302	314
18	285	310	327	340	360
19	305	323	339	356	371
20	313	330	349	361	378
GROUP 3 (300 MG/KG)					
21	331	357	378	391	415
22	283	296	313	330	342
23	311	328	341	360	372
24	280	300	314	325	342
25	282	307	331	341	361
26	284	301	329	346	362
27	311	326	340	361	381
28	280	299	318	337	357
29	298	315	330	337	353
30	275	293	306	311	321
GROUP 4 (1000 MG/KG)					
31	280	295	309	320	326
32	280	282	294	307	317
33	300	300	323	340	364
34	297	312	331	339	356
35	291	308	319	319	328
36	290	310	326	346	361
37	296	315	324	341	360
38	321	349	384	395	414
39	308	338	356	368	384
40	286	308	330	345	367

2.3 BODY WEIGHTS (GRAM)
FEMALES

	PRE MATING		MATING PERIOD			
DAYS	1	8	1	8	15	22
WEEKS	1	2	1	2	3	4
ANIMAL						
GROUP 1 (CONTROL)						
41	213	214	215	---		
42	222	223	229	---		
43	239	247	254	---		
44	218	220	225	---		
45	220	215	234	---		
46	243	246	240	271		
47	216	212	224	---		
48	228	222	225	---		
49	234	238	239	---		
50	214	217	216	---		
GROUP 2 (100 MG/KG)						
51	224	227	232			
52	201	214	226			
53	237	238	240			
54	224	217	230			
55	213	215	215			
56	220	220	227			
57	215	222	232			
58	223	232	249			
59	218	215	222			
60	242	246	255			
GROUP 3 (300 MG/KG)						
61	246	244	255			
62	243	247	255			
63	220	219	228			
64	207	217	227			
65	243	250	263			
66	217	215	236			
67	233	236	243			
68	226	225	236			
69	221	229	228			
70	203	202	219			
GROUP 4 (1000 MG/KG)						
71	224	224	236	---	---	---
72	214	224	230	---	---	---
73	220	223	235	---	---	---
74	236	240	245	---	---	---
75	222	230	236	---	---	---
76	217	224	238	---	---	---
77	219	226	233	---	---	---
78	240	242	245	271	294	330
79	229	226	245	---	---	---
80	208	216	227	---	---	---

2.3 BODY WEIGHTS (GRAM)
FEMALES

F0-GENERATION

	POST COITUM							LACTATION			
DAYS	0	4	7	11	14	17	20	1	4	7	13
ANIMAL											
GROUP 1 (CONTROL)											
41	212	231	239	258	266	287	316	250	262	274	283
42 <IO>	230	247	256	265	260	258	269	---	---	---	---
43	251	269	274	284	292	310	339	273	276	298	318
44	227	237	248	261	270	301	339	246	272	271	290
45	229	243	248	263	272	288	312	262	266	281	280
46 <NP>	261	264	270	271	268	262	259	---	---	---	---
47	225	240	246	264	280	298	330	267	274	285	296
48	233	243	261	271	280	306	351	250	272	275	290
49	235	250	255	268	281	305	339	257	271	277	292
50	215	228	231	243	257	279	327	237	252	255	274
GROUP 2 (100 MG/KG)											
51 <NP>	237	239	241	246	244	243	246	---	---	---	---
52	224	240	239	252	261	286	325	234	261	264	279
53 <NP>	246	255	266	275	262	262	260	---	---	---	---
54	226	241	244	258	271	289	330	245	259	272	285
55	223	238	248	266	276	292	328	234	250	268	283
56	225	243	256	265	279	304	349	244	261	266	296
57	230	247	250	267	276	299	337	262	274	281	297
58	242	260	265	278	289	317	366	273	291	294	312
59	225	230	238	247	259	288	336	238	254	260	276
60	253	266	277	287	299	325	361	282	303	304	320
GROUP 3 (300 MG/KG)											
61	258	264	269	282	297	317	354	276	294	309	314
62	253	273	279	293	308	336	375	278	303	310	317
63 <NP>	225	244	246	245	244	236	235	---	---	---	---
64	227	242	243	261	278	298	336	263	275	275	288
65	258	277	289	305	320	355	403	304	323	332	338
66	230	246	250	263	278	295	337	249	269	278	303
67	241	252	264	278	285	356	356	259	283	287	308
68	240	256	267	285	295	319	348	279	289	305	319
69	238	250	252	269	274	305	332	250	262	272	286
70	211	228	233	248	260	280	312	245	264	265	282
GROUP 4 (1000 MG/KG)											
71	236	244	250	271	274	299	326	269	276	286	291
72 <NP>	230	244	251	257	243	241	245	---	---	---	---
73	236	251	252	279	286	314	353	274	290	296	302
74	242	247	254	267	276	301	345	246	262	273	282
75	236	257	263	274	289	312	357	265	277	292	305
76	232	242	254	259	266	290	321	249	277	280	301
77	244	257	265	291	302	325	380	285	303	312	303
78	---	---	---	---	---	---	---	268	300	310	322
79	240	254	259	282	289	316	348	273	280	290	302
80	229	234	239	255	264	289	328	263	280	277	290

<IO> Implantation site only
<NP> Non-pregnant

2.4 BODY WEIGHT GAIN (%)
MALES

	PRE MATING		MATING PERIOD		
DAYS	1	8	1	8	15
WEEKS	1	2	1	2	3
ANIMAL					
GROUP 1 (CONTROL)					
1	0	7	9	13	19
2	0	6	11	13	22
3	0	6	11	14	18
4	0	10	15	19	23
5	0	8	16	20	24
6	0	7	13	15	15
7	0	7	12	17	24
8	0	11	19	23	31
9	0	6	12	15	20
10	0	6	12	14	19
GROUP 2 (100 MG/KG)					
11	0	11	18	24	32
12	0	9	14	18	24
13	0	10	17	23	31
14	0	7	11	17	21
15	0	4	5	7	9
16	0	10	19	24	32
17	0	4	9	12	16
18	0	9	15	19	26
19	0	6	11	17	22
20	0	5	12	15	21
GROUP 3 (300 MG/KG)					
21	0	8	14	18	25
22	0	5	11	17	21
23	0	5	10	16	20
24	0	7	12	16	22
25	0	9	17	21	28
26	0	6	16	22	27
27	0	5	9	16	23
28	0	7	14	20	28
29	0	6	11	13	18
30	0	7	11	13	17
GROUP 4 (1000 MG/KG)					
31	0	5	10	14	16
32	0	1	5	10	13
33	0	0	8	13	21
34	0	5	11	14	20
35	0	6	10	10	13
36	0	7	12	19	24
37	0	6	9	15	22
38	0	9	20	23	29
39	0	10	16	19	25
40	0	8	15	21	28

2.4 BODY WEIGHT GAIN (%)
FEMALES

	PRE MATING		MATING PERIOD			
DAYS	1	8	1	8	15	22
WEEKS	1	2	1	2	3	4
ANIMAL						
GROUP 1 (CONTROL)						
41	0	0	1	---		
42	0	0	3	---		
43	0	3	6	---		
44	0	1	3	---		
45	0	-2	6	---		
46	0	1	-1	12		
47	0	-2	4	---		
48	0	-3	-1	---		
49	0	2	2	---		
50	0	1	1	---		
GROUP 2 (100 MG/KG)						
51	0	1	4			
52	0	6	12			
53	0	0	1			
54	0	-3	3			
55	0	1	1			
56	0	0	3			
57	0	3	8			
58	0	4	12			
59	0	-1	2			
60	0	2	5			
GROUP 3 (300 MG/KG)						
61	0	-1	4			
62	0	2	5			
63	0	0	4			
64	0	5	10			
65	0	3	8			
66	0	-1	9			
67	0	1	4			
68	0	0	4			
69	0	4	3			
70	0	0	8			
GROUP 4 (1000 MG/KG)						
71	0	0	5	---	---	---
72	0	5	7	---	---	---
73	0	1	7	---	---	---
74	0	2	4	---	---	---
75	0	4	6	---	---	---
76	0	3	10	---	---	---
77	0	3	6	---	---	---
78	0	1	2	13	23	38
79	0	-1	7	---	---	---
80	0	4	9	---	---	---

DIHEP AQUEOUS SOLUTION
APPENDIX 2

2.4 BODY WEIGHT GAIN (%)
FEMALES

F0-GENERATION

	POST COITUM							LACTATION			
DAYS	0	4	7	11	14	17	20	1	4	7	13
ANIMAL											
GROUP 1 (CONTROL)											
41	0	9	13	22	25	35	49	0	5	10	13
42 <IO>	0	7	11	15	13	12	17	---	---	---	---
43	0	7	9	13	16	24	35	0	1	9	16
44	0	4	9	15	19	33	49	0	11	10	18
45	0	6	8	15	19	26	36	0	2	7	7
46 <NP>	0	1	3	4	3	0	-1	---	---	---	---
47	0	7	9	17	24	32	47	0	3	7	11
48	0	4	12	16	20	31	51	0	9	10	16
49	0	6	9	14	20	30	44	0	5	8	14
50	0	6	7	13	20	30	52	0	6	8	16
GROUP 2 (100 MG/KG)											
51 <NP>	0	1	2	4	3	3	4	---	---	---	---
52	0	7	7	13	17	28	45	0	12	13	19
53 <NP>	0	4	8	12	7	7	6	---	---	---	---
54	0	7	8	14	20	28	46	0	6	11	16
55	0	7	11	19	24	31	47	0	7	15	21
56	0	8	14	18	24	35	55	0	7	9	21
57	0	7	9	16	20	30	47	0	5	7	13
58	0	7	10	15	19	31	51	0	7	8	14
59	0	2	6	10	15	28	49	0	7	9	16
60	0	5	9	13	18	28	43	0	7	8	13
GROUP 3 (300 MG/KG)											
61	0	2	4	9	15	23	37	0	7	12	14
62	0	8	10	16	22	33	48	0	9	12	14
63 <NP>	0	8	9	9	8	5	4	---	---	---	---
64	0	7	7	15	22	31	48	0	5	5	10
65	0	7	12	18	24	38	56	0	6	9	11
66	0	7	9	14	21	28	47	0	8	12	22
67	0	5	10	15	18	48	48	0	9	11	19
68	0	7	11	19	23	33	45	0	4	9	14
69	0	5	6	13	15	28	39	0	5	9	14
70	0	8	10	18	23	33	48	0	8	8	15
GROUP 4 (1000 MG/KG)											
71	0	3	6	15	16	27	38	0	3	6	8
72 <NP>	0	6	9	12	6	5	7	---	---	---	---
73	0	6	7	18	21	33	50	0	6	8	10
74	0	2	5	10	14	24	43	0	7	11	15
75	0	9	11	16	22	32	51	0	5	10	15
76	0	4	9	12	15	25	38	0	11	12	21
77	0	5	9	19	24	33	56	0	6	9	6
78	---	---	---	---	---	---	---	0	12	16	20
79	0	6	8	18	20	32	45	0	3	6	11
80	0	2	4	11	15	26	43	0	6	5	10

<IO> Implantation site only
<NP> Non-pregnant

28Jun19 09h03

2.5 FOOD CONSUMPTION (G/ANIMAL/DAY)
MALES

	PRE MATING		MATING PERIOD	
DAYS	1-8	8-15	1-8	8-15
WEEKS	1-2	2-3	1-2	2-3
CAGE				
GROUP 1 (CONTROL)				
1	24	24	25	24
2	24	24	25	25
GROUP 2 (100 MG/KG)				
3	24	24	25	25
4	26	26	26	26
GROUP 3 (300 MG/KG)				
5	24	24	26	25
6	24	24	25	25
GROUP 4 (1000 MG/KG)				
7	23	23	26	24
8	25	25	25	24

FEMALES

	PRE MATING	
DAYS	1-8	8-15
WEEKS	1-2	2-3
CAGE		
GROUP 1 (CONTROL)		
9	18	18
10	18	18
GROUP 2 (100 MG/KG)		
11	18	18
12	18	17
GROUP 3 (300 MG/KG)		
13	19	19
14	18	18
GROUP 4 (1000 MG/KG)		
15	19	18
16	18	18

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2.5 FOOD CONSUMPTION (G/ANIMAL/DAY)
FEMALES

F0-GENERATION

	POST COITUM						LACTATION		
DAYS	0-4	4-7	7-11	11-14	14-17	17-20	1-4	4-7	7-13
ANIMAL									
GROUP 1 (CONTROL)									
41	20	22	22	21	22	27	42	39	50
42 <IO>	21	23	22	21	17	23	---	---	---
43	22	23	21	23	23	30	33	47	58
44	22	22	23	24	24	30	43	43	59
45	21	20	21	23	23	27	32	36	45
46 <NP>	18	21	25	29	18	17	---	---	---
47	21	21	23	26	24	26	31	53	54
48	22	23	23	23	25	29	40	35	44
49	22	22	23	23	24	28	33	43	57
50	20	20	20	23	24	31	29	41	57
GROUP 2 (100 MG/KG)									
51 <NP>	19	18	20	18	18	18	---	---	---
52	21	20	20	21	21	22	50	43	58
53 <NP>	24	24	24	22	20	17	---	---	---
54	20	19	19	22	21	23	34	51	55
55	20	21	22	21	22	23	27	44	57
56	23	25	22	23	21	26	30	40	57
57	21	19	20	21	22	25	33	43	58
58	23	21	21	24	24	27	51	43	59
59	18	20	19	20	21	27	30	42	56
60	20	22	21	22	22	28	36	46	60
GROUP 3 (300 MG/KG)									
61	21	21	22	22	24	24	36	50	56
62	24	25	26	26	26	31	46	42	55
63 <NP>	25	21	19	16	15	17	---	---	---
64	21	23	24	25	23	25	48	40	55
65	22	26	26	26	27	33	38	50	58
66	22	20	20	23	21	26	36	46	59
67	23	24	24	24	24	30	37	47	60
68	22	24	24	26	25	30	28	43	55
69	22	20	22	22	23	23	42	41	50
70	19	19	21	22	23	25	32	43	55
GROUP 4 (1000 MG/KG)									
71	24	18	21	24	22	23	36	56	55
72 <NP>	23	24	23	22	20	21	---	---	---
73	23	20	24	25	25	28	38	46	59
74	18	19	19	21	20	27	30	42	53
75	23	23	23	24	24	30	44	40	57
76	19	21	20	22	23	28	30	45	58
77	20	24	41 (8)	15	26	32	37	50	57
78	---	---	---	---	---	---	37	45	59
79	23	22	22	24	25	27	35	44	57
80	18	21	22	22	21	24	37	46	57

(8) Accidental food loss
<IO> Implantation site only
<NP> Non-pregnant

28Jun19 08h28

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

	PRE MATING		MATING PERIOD	
DAYS	1-8	8-15	1-8	8-15
WEEKS	1-2	2-3	1-2	2-3
CAGE				
GROUP 1 (CONTROL)				
1	77	76	73	69
2	76	76	73	69
GROUP 2 (100 MG/KG)				
3	76	77	73	67
4	81	82	76	70
GROUP 3 (300 MG/KG)				
5	77	76	75	69
6	77	78	75	69
GROUP 4 (1000 MG/KG)				
7	77	78	79	72
8	78	78	70	65

FEMALES

	PRE MATING	
DAYS	1-8	8-15
WEEKS	1-2	2-3
CAGE		
GROUP 1 (CONTROL)		
9	79	79
10	81	80
GROUP 2 (100 MG/KG)		
11	80	80
12	80	75
GROUP 3 (300 MG/KG)		
13	80	80
14	81	80
GROUP 4 (1000 MG/KG)		
15	83	80
16	78	78

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

F0-GENERATION

	POST COITUM						LACTATION		
DAYS	0-4	4-7	7-11	11-14	14-17	17-20	1-4	4-7	7-13
ANIMAL									
GROUP 1 (CONTROL)									
41	84	92	83	80	78	85	162	142	175
42 <IO>	85	89	84	79	67	86	---	---	---
43	81	85	73	80	75	89	121	157	183
44	94	90	87	88	81	88	158	159	204
45	87	82	79	83	80	85	120	128	161
46 <NP>	66	79	93	109	69	64	---	---	---
47	88	84	88	94	79	78	114	185	184
48	91	87	84	83	83	83	146	126	150
49	87	88	87	83	79	82	122	156	196
50	87	85	83	88	85	95	114	161	206
GROUP 2 (100 MG/KG)									
51 <NP>	78	75	79	72	74	75	---	---	---
52	85	85	80	79	75	68	193	164	207
53 <NP>	95	91	85	83	75	64	---	---	---
54	83	78	75	81	72	70	133	186	191
55	82	86	83	76	76	71	109	163	201
56	94	96	81	81	70	74	114	152	191
57	86	76	75	77	72	74	120	152	194
58	87	78	75	83	75	75	175	146	188
59	78	85	75	79	73	80	119	163	202
60	73	78	74	74	69	77	120	152	188
GROUP 3 (300 MG/KG)									
61	79	77	78	75	76	67	122	161	179
62	86	91	90	84	78	84	153	135	174
63 <NP>	100	87	79	66	62	74	---	---	---
64	85	93	93	91	77	74	175	145	192
65	78	89	84	82	77	83	119	151	171
66	88	80	75	83	71	76	134	164	196
67	90	91	86	85	67	85	132	164	196
68	86	89	82	88	79	87	96	140	171
69	86	79	83	82	75	69	162	151	174
70	83	83	85	83	82	80	122	161	196
GROUP 4 (1000 MG/KG)									
71	97	71	78	88	72	70	130	196	190
72 <NP>	94	97	89	89	84	87	---	---	---
73	93	81	84	89	81	79	132	154	194
74	73	75	69	77	68	78	116	153	187
75	90	89	82	83	76	83	160	136	186
76	77	81	77	81	80	88	108	162	193
77	76	91	141 (8)	50	79	84	123	161	186
78	---	---	---	---	---	---	123	146	182
79	90	84	79	83	80	77	126	152	190
80	78	88	86	85	74	74	133	165	196

(8) Accidental food loss
<IO> implantation site only
<NP> Non-pregnant

2.7 FUNCTIONAL OBSERVATIONS
MALES

END OF TREATMENT

ANIMAL	HEARING SCORE 0/1	PUPIL L SCORE 0/1	PUPIL R SCORE 0/1	STATIC R SCORE 0/1	GRIP FORE GRAM	GRIP HIND GRAM
GROUP 1 (CONTROL)						
1	0	0	0	0	1379	627
2	0	0	0	0	1325	723
3	0	0	0	0	1322	853
4	0	0	0	0	1480	737
5	0	0	0	0	1060	658
GROUP 2 (100 MG/KG)						
11	0	0	0	0	1475	769
12	0	0	0	0	1535	927
13	0	0	0	0	1496	753
14	0	0	0	0	1452	787
15	0	0	0	0	1410	707
GROUP 3 (300 MG/KG)						
21	0	0	0	0	1253	773
22	0	0	0	0	1070	683
23	0	0	0	0	1280	909
24	0	0	0	0	1305	633
25	0	0	0	0	1431	951
GROUP 4 (1000 MG/KG)						
31	0	0	0	0	1391	771
32	0	0	0	0	1063	601
33	0	0	0	0	1663	940
34	0	0	0	0	1401	838
35	0	0	0	0	1458	695

FEMALES

END OF TREATMENT

ANIMAL	HEARING SCORE 0/1	PUPIL L SCORE 0/1	PUPIL R SCORE 0/1	STATIC R SCORE 0/1	GRIP FORE GRAM	GRIP HIND GRAM
GROUP 1 (CONTROL)						
41	0	0	0	0	761	651
44	0	0	0	0	1407	638
45	0	0	0	0	679	540
47	0	0	0	0	920	635
50	0	0	0	0	931	447
GROUP 2 (100 MG/KG)						
52	0	0	0	0	819	674
54	0	0	0	0	1111	663
56	0	0	0	0	719	599
57	0	0	0	0	1146	690
58	0	0	0	0	1351	607
GROUP 3 (300 MG/KG)						
62	0	0	0	0	883	531
64	0	0	0	0	1116	687
66	0	0	0	0	1103	764
68	0	0	0	0	1289	605
70	0	0	0	0	960	513
GROUP 4 (1000 MG/KG)						
71	0	0	0	0	1016	617
73	0	0	0	0	993	595
74	0	0	0	0	1220	651
79	0	0	0	0	1434	555

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2.7 FUNCTIONAL OBSERVATIONS
FEMALES

END OF TREATMENT

ANIMAL	HEARING SCORE 0/1	PUPIL L SCORE 0/1	PUPIL R SCORE 0/1	STATIC R SCORE 0/1	GRIP FORE GRAM	GRIP HIND GRAM
GROUP 4 (1000 MG/KG)						
80	0	0	0	0	877	431

2.8 MOTOR ACTIVITY TEST - TOTAL MOVEMENTS
MALES

	INTERVAL (5 min.)												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total**
ANIMAL													
Group 1 (CONTROL)													
1	1096	484	274	341	270	288	303	38	356	187	344	153	4134
2	1221	910	419	325	96	33	13	2	41	348	89	31	3528
3	1336	661	405	442	532	439	203	64	0	263	102	95	4542
4	1313	578	295	664	131	374	359	6	274	18	5	6	4023
5	1204	792	538	508	344	275	121	0	0	0	22	0	3804
Group 2 (100 MG/KG)													
11	977	583	346	308	545	439	67	1	0	196	331	137	3930
12	1042	554	141	14	0	48	14	112	3	274	125	2	2329
13	751	608	391	156	372	297	288	149	13	209	499	428	4161
14	1327	680	217	622	589	369	170	58	0	10	2	7	4051
15	1005	548	295	49	3	12	41	0	18	13	7	369	2360
Group 3 (300 MG/KG)													
21	885	566	492	498	411	148	265	8	78	3	2	31	3387
22	1203	521	451	413	187	2	4	12	12	48	459	9	3321
23	769	478	400	424	333	214	304	369	238	44	165	1	3739
24	976	630	452	82	502	129	61	416	613	238	0	5	4104
25	1425	718	434	460	231	538	141	7	4	484	51	14	4507
Group 4 (1000 MG/KG)													
31	1153	676	253	175	398	311	0	0	4	25	19	119	3133
32	729	385	324	244	179	1	91	291	173	28	0	3	2448
33	729	468	283	45	590	65	18	3	22	20	507	116	2866
34	703	446	381	358	91	321	242	153	263	0	1	4	2963
35	1145	801	228	678	785	228	2	4	14	0	24	22	3931

2.8 MOTOR ACTIVITY TEST - AMBULATIONS
MALES

	INTERVAL (5 min.)												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total**
ANIMAL													
Group 1 (CONTROL)													
1	327	117	58	111	60	87	109	2	126	34	112	15	1158
2	276	216	67	72	5	0	0	0	6	70	1	1	714
3	340	148	88	25	139	92	1	11	0	37	0	4	885
4	339	84	43	147	7	72	74	0	44	0	0	0	810
5	369	234	144	114	71	50	0	0	0	0	0	0	982
Group 2 (100 MG/KG)													
11	309	110	58	17	137	86	14	0	0	36	67	17	851
12	319	124	30	0	0	5	1	32	0	88	10	0	609
13	212	185	128	7	109	37	90	15	2	74	125	95	1079
14	345	182	25	146	104	73	3	6	0	0	0	0	884
15	220	84	76	2	0	0	1	0	1	0	1	65	450
Group 3 (300 MG/KG)													
21	321	159	102	95	100	2	23	1	0	0	0	1	804
22	270	118	79	59	3	0	0	1	0	8	76	1	615
23	281	193	159	89	138	27	138	102	43	21	69	0	1260
24	264	136	118	1	113	0	0	76	158	28	0	0	894
25	375	167	78	92	14	115	12	0	0	112	1	5	971
Group 4 (1000 MG/KG)													
31	396	166	64	19	108	80	0	0	0	2	0	29	864
32	240	88	129	47	54	0	0	66	65	1	0	1	691
33	258	139	5	2	205	5	3	0	0	0	161	32	810
34	255	148	101	98	34	81	71	31	79	0	0	0	898
35	344	249	36	185	211	47	0	0	0	0	1	0	1073

2.8 MOTOR ACTIVITY TEST - TOTAL MOVEMENTS
FEMALES

	INTERVAL (5 min.)												
	1	2	3	4	5	6	7	8	9	10	11	12	Total
ANIMAL													
Group 1 (CONTROL)													
41	876	592	316	125	62	251	136	283	28	6	45	34	2754
44	1054	608	448	370	470	587	386	135	406	291	422	419	5596
45	912	386	413	451	239	465	374	366	213	285	504	454	5062
47	908	471	410	462	415	574	483	473	334	312	356	299	5497
50	871	642	364	634	278	97	406	304	167	65	212	182	4222
Group 2 (100 MG/KG)													
52	958	627	361	391	32	554	201	16	41	5	10	369	3565
54	718	344	311	253	19	576	331	26	7	480	338	238	3641
56	921	649	620	472	466	303	238	294	171	297	232	81	4744
57	1058	406	259	375	30	308	53	192	133	9	44	0	2867
58	838	364	284	505	196	450	280	204	484	172	168	248	4193
Group 3 (300 MG/KG)													
62	749	564	406	246	47	447	324	306	235	451	54	266	4095
64	1370	689	544	532	192	478	452	553	343	228	1	649	6031
66	1097	654	708	500	363	667	410	254	303	344	292	226	5818
68	997	615	401	557	242	70	348	163	38	4	381	523	4339
70	1141	411	371	191	146	5	18	430	280	13	24	1	3031
Group 4 (1000 MG/KG)													
71	950	704	173	48	96	8	8	27	24	2	0	22	2062
73	863	437	95	36	51	49	12	274	7	0	0	145	1969
74	467	178	76	3	4	138	82	115	25	37	33	198	1356
79	764	660	79	595	180	615	0	0	378	423	499	273	4466
80	1138	592	384	314	459	19	272	406	520	399	355	371	5229

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2.8 MOTOR ACTIVITY TEST - AMBULATIONS
FEMALES

	INTERVAL (5 min.)												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total**
ANIMAL													
Group 1 (CONTROL)													
41	253	169	73	29	22	75	18	65	1	0	0	0	705
44	331	119	116	67	90	178	91	1	127	63	129	93	1405
45	285	88	113	111	42	60	94	87	9	62	137	117	1205
47	306	134	92	160	40	135	105	165	104	103	83	58	1485
50	324	190	92	189	85	28	158	54	61	28	86	52	1347
Group 2 (100 MG/KG)													
52	298	191	63	147	2	204	44	0	0	0	0	123	1072
54	174	88	65	58	0	174	59	0	0	135	51	60	864
56	337	245	210	125	134	108	30	91	43	109	14	13	1459
57	333	104	70	93	2	64	1	61	2	3	1	0	734
58	230	64	37	124	55	161	76	52	131	51	22	68	1071
Group 3 (300 MG/KG)													
62	263	112	97	36	0	140	54	83	60	146	13	74	1078
64	300	135	132	110	45	116	76	136	58	49	0	150	1307
66	224	138	111	91	46	155	75	22	62	37	0	6	967
68	228	114	91	136	70	0	74	0	1	0	79	145	938
70	326	86	87	0	35	0	0	92	82	0	0	0	708
Group 4 (1000 MG/KG)													
71	291	165	0	0	5	0	0	0	0	0	0	0	461
73	227	85	0	3	1	0	0	29	0	0	0	34	379
74	111	51	0	0	0	36	19	0	0	0	0	45	262
79	197	121	3	139	52	170	0	0	108	63	141	84	1078
80	334	150	56	77	112	1	71	127	164	151	123	96	1462

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2.9 HAEMATOLOGY
MALES
END OF TREATMENT

ANIMAL	WBC 10E9/L	Neutrophils 10E9/L	Lymphocytes 10E9/L	Monocytes 10E9/L	Eosinophils 10E9/L
GROUP 1 (CONTROL)					
1	8.2	1.5	---	0.2	0.0
2	7.8	1.2	6.4	0.1	0.1
3	10.1	1.1	8.6	0.2	0.2
4	8.0	1.6	6.1	0.2	0.1
5	10.8	1.8	8.6	0.2	0.2
GROUP 2 (100 MG/KG)					
11	8.7	1.0	7.4	0.2	0.1
12	6.2	0.9	5.2	0.1	0.1
13	7.1	0.8	6.1	0.1	0.1
14	3.9	0.9	2.9	0.1	0.1
15	6.8	1.1	5.4	0.2	0.1
GROUP 3 (300 MG/KG)					
21	7.8	1.4	6.2	0.1	0.1
22	2.7	0.8	1.9	0.0	0.0
23	5.7	1.0	4.5	0.1	0.1
24	6.2	1.5	4.5	0.1	0.1
25	7.8	1.0	6.5	0.1	0.1
GROUP 4 (1000 MG/KG)					
31	11.5	1.4	9.8	0.2	0.1
32	6.6	1.2	5.2	0.1	0.1
33	6.8	1.2	5.4	0.1	0.1
34	7.2	1.4	---	0.1	0.0
35	7.1	1.0	5.8	0.1	0.2

MALES
END OF TREATMENT

ANIMAL	Basophils 10E9/L	Red blood cells 10E12/L	Reticulocytes 10E9/L	RDW %	Haemoglobin mmol/L
GROUP 1 (CONTROL)					
1	0.0	9.29	218.7	11.6	10.5
2	0.0	8.56	232.3	12.3	9.3
3	0.0	9.14	224.1	11.6	10.6
4	0.0	8.75	203.8	12.0	10.0
5	0.0	8.89	171.2	11.7	10.1
GROUP 2 (100 MG/KG)					
11	0.0	8.49	212.9	12.3	9.5
12	0.0	8.93	193.2	11.4	9.9
13	0.0	8.50	202.8	11.2	9.8
14	0.0	7.64	185.2	13.2	8.6
15	0.0	8.71	218.6	13.1	10.5
GROUP 3 (300 MG/KG)					
21	0.0	8.03	256.2	12.2	9.1
22	0.0	8.69	205.5	12.0	9.2
23	0.0	8.99	262.7	11.7	10.1
24	0.0	7.47	254.0	12.6	8.4
25	0.0	9.04	260.6	12.1	9.6
GROUP 4 (1000 MG/KG)					
31	0.0	9.08	237.4	11.6	10.5
32	0.0	9.21	192.1	12.7	9.8
33	0.0	8.64	243.8	12.7	9.8
34	0.0	8.96	227.1	12.3	10.0

2.9 HAEMATOLOGY
MALES
END OF TREATMENT

ANIMAL	Basophils 10E9/L	Red blood cells 10E12/L	Reticulocytes 10E9/L	RDW %	Haemoglobin mmol/L
GROUP 4 (1000 MG/KG)					
35	0.0	8.79	195.4	11.7	9.7

MALES
END OF TREATMENT

ANIMAL	Haematocrit L/L	MCV fL	MCH fmol	MCHC mmol/L	Platelets 10E9/L
GROUP 1 (CONTROL)					
1	0.484	52.1	1.13	21.67	651
2	0.440	51.3	1.09	21.14	695
3	0.512	56.0	1.16	20.63	656
4	0.469	53.6	1.14	21.30	655
5	0.475	53.4	1.13	21.18	720
GROUP 2 (100 MG/KG)					
11	0.455	53.6	1.12	20.83	707
12	0.470	52.6	1.11	21.01	621
13	0.467	54.9	1.15	20.98	507
14	0.389	51.0	1.13	22.12	760
15	0.471	54.0	1.20	22.20	855
GROUP 3 (300 MG/KG)					
21	0.436	54.3	1.14	20.96	814
22	0.438	50.5	1.06	20.92	833
23	0.480	53.4	1.13	21.09	697
24	0.414	55.4	1.12	20.21	697
25	0.461	51.0	1.06	20.74	776
GROUP 4 (1000 MG/KG)					
31	0.499	54.9	1.16	21.06	810
32	0.482	52.3	1.06	20.29	673
33	0.473	54.8	1.13	20.71	662
34	0.477	53.2	1.12	21.06	629
35	0.457	52.0	1.10	21.14	630

MALES
END OF TREATMENT

ANIMAL	PT s	APTT s
GROUP 1 (CONTROL)		
1	18.9	12.9
2	18.0	14.0
3	19.7	20.6
4	19.4	18.4
5	18.6	14.8
GROUP 2 (100 MG/KG)		
11	18.8	18.9
12	17.9	16.2
13	17.2	12.5
14	16.8	13.6
15	---	13.7

2.9 HAEMATOLOGY
MALES
END OF TREATMENT

ANIMAL	PT s	APTT s
GROUP 3 (300 MG/KG)		
21	16.8	10.6
22	18.4	17.2
23	17.2	12.7
24	18.7	16.1
25	17.7	13.1
GROUP 4 (1000 MG/KG)		
31	17.3	17.8
32	17.8	19.4
33	17.8	16.8
34	17.3	15.3
35	18.1	14.4

FEMALES
END OF TREATMENT

ANIMAL	WBC 10E9/L	Neutrophils 10E9/L	Lymphocytes 10E9/L	Monocytes 10E9/L	Eosinophils 10E9/L
GROUP 1 (CONTROL)					
41	8.5	1.7	6.5	0.1	0.1
44	7.4	2.0	5.0	0.2	0.3
45	5.4	1.8	3.2	0.2	0.2
47	4.3	1.1	2.9	0.1	0.2
50	3.7	1.1	2.4	0.1	0.1
GROUP 2 (100 MG/KG)					
52	6.9	1.3	5.3	0.1	0.1
54	4.4	1.2	3.1	0.1	0.1
56	5.3	2.0	3.2	0.1	0.1
57	4.5	1.3	3.1	0.1	0.0
58	4.1	0.9	3.0	0.1	0.1
GROUP 3 (300 MG/KG)					
62	5.9	0.9	4.9	0.1	0.0
64	6.9	2.4	4.3	0.1	0.1
66	3.8	1.1	2.5	0.1	0.1
68	8.1	3.0	4.8	0.2	0.1
70	6.1	1.8	4.1	0.1	0.1
GROUP 4 (1000 MG/KG)					
71	5.1	1.3	3.6	0.1	0.1
73	6.9	1.6	5.1	0.1	0.1
74	3.3	1.1	2.1	0.1	0.0
79	4.1	0.9	3.0	0.1	0.1
80	5.1	1.6	3.3	0.1	0.1

FEMALES
END OF TREATMENT

ANIMAL	Basophils 10E9/L	Red blood cells 10E12/L	Reticulocytes 10E9/L	RDW %	Haemoglobin mmol/L
GROUP 1 (CONTROL)					
41	0.0	8.26	285.5	13.2	9.5
44	0.0	7.31	246.5	13.7	9.1

2.9 HAEMATOLOGY
FEMALES
END OF TREATMENT

ANIMAL	Basophils 10E9/L	Red blood cells 10E12/L	Reticulocytes 10E9/L	RDW %	Haemoglobin mmol/L
GROUP 1 (CONTROL)					
45	0.0	7.41	156.4	10.3	8.5
47	0.0	7.43	208.5	12.9	8.6
50	0.0	6.25	219.5	12.9	8.2
GROUP 2 (100 MG/KG)					
52	0.0	7.80	215.2	12.4	9.4
54	0.0	7.22	208.3	11.8	8.8
56	0.0	7.15	245.5	13.2	8.5
57	0.0	6.73	282.8	12.9	8.2
58	0.0	7.22	215.3	14.0	8.9
GROUP 3 (300 MG/KG)					
62	0.0	7.18	189.3	11.7	8.7
64	0.0	7.02	184.0	12.4	8.7
66	0.0	6.69	195.6	14.2	9.0
68	0.0	6.81	220.3	11.5	8.5
70	0.0	7.41	235.3	12.3	8.9
GROUP 4 (1000 MG/KG)					
71	0.0	7.47	238.8	11.5	9.0
73	0.0	7.45	243.2	11.8	8.8
74	0.0	6.09	199.2	13.6	7.6
79	0.0	7.29	180.3	12.3	8.8
80	0.0	7.57	217.0	12.3	8.9

FEMALES
END OF TREATMENT

ANIMAL	Haematocrit L/L	MCV fL	MCH fmol	MCHC mmol/L	Platelets 10E9/L
GROUP 1 (CONTROL)					
41	0.471	57.0	1.15	20.11	708
44	0.448	61.3	1.25	20.32	696
45	0.423	57.1	1.14	20.02	722
47	0.431	58.0	1.16	20.02	748
50	0.384	61.4	1.31	21.28	712
GROUP 2 (100 MG/KG)					
52	0.458	58.7	1.21	20.62	929
54	0.425	58.8	1.22	20.72	639
56	0.433	60.6	1.19	19.69	845
57	0.408	60.6	1.22	20.15	715
58	0.444	61.5	1.24	20.14	745
GROUP 3 (300 MG/KG)					
62	0.437	60.8	1.21	19.95	741
64	0.427	60.8	1.24	20.38	565
66	0.439	65.6	1.34	20.41	622
68	0.413	60.7	1.24	20.47	732
70	0.449	60.5	1.21	19.93	602
GROUP 4 (1000 MG/KG)					
71	0.432	57.9	1.21	20.87	669
73	0.427	57.3	1.18	20.60	828
74	0.373	61.2	1.25	20.34	703
79	0.442	60.6	1.21	19.96	531
80	0.441	58.3	1.17	20.08	796

2.9 HAEMATOLOGY
FEMALES
END OF TREATMENT

ANIMAL	PT s	APTT s
GROUP 1 (CONTROL)		
41	17.9	20.0
44	16.3	17.5
45	17.8	19.7
47	16.7	19.5
50	---	---
GROUP 2 (100 MG/KG)		
52	16.9	22.8
54	15.4	17.7
56	18.1	21.2
57	18.6	21.0
58	17.4	20.9
GROUP 3 (300 MG/KG)		
62	17.5	20.5
64	17.9	21.6
66	---	26.0
68	17.5	20.6
70	17.3	17.9
GROUP 4 (1000 MG/KG)		
71	15.8	18.4
73	18.1	19.5
74	17.7	18.7
79	16.1	18.6
80	16.8	20.5

2.10 CLINICAL BIOCHEMISTRY
MALES
END OF TREATMENT

ANIMAL	ALAT U/L	ASAT U/L	ALP U/L	Total protein g/L	Albumin g/L
GROUP 1 (CONTROL)					
1	49.2	97.2	157	62.0	31.2
2	55.3	89.9	132	64.8	31.9
3	48.6	87.2	150	62.9	32.5
4	36.2	79.8	103	60.1	31.2
5	56.7	78.0	211	62.0	31.6
6	---	---	---	---	---
7	---	---	---	---	---
8	---	---	---	---	---
9	---	---	---	---	---
10	---	---	---	---	---
GROUP 2 (100 MG/KG)					
11	57.5	81.5	171	65.7	32.4
12	41.4	90.1	117	63.9	31.9
13	58.6	77.7	141	62.3	32.0
14	32.2	81.6	114	61.0	31.7
15	42.1	80.6	133	61.2	31.6
16	---	---	---	---	---
17	---	---	---	---	---
18	---	---	---	---	---
19	---	---	---	---	---
20	---	---	---	---	---
GROUP 3 (300 MG/KG)					
21	31.4	65.0	116	63.1	31.8
22	50.6	81.8	92	62.7	31.9
23	54.6	100.7	132	62.6	31.7
24	36.9	80.9	120	60.5	31.3
25	51.8	76.5	155	62.2	31.8
26	---	---	---	---	---
27	---	---	---	---	---
28	---	---	---	---	---
29	---	---	---	---	---
30	---	---	---	---	---
GROUP 4 (1000 MG/KG)					
31	59.5	95.2	126	65.2	33.0
32	51.2	87.5	158	59.8	31.3
33	45.7	104.2	200	58.8	29.8
34	48.4	85.3	161	65.0	31.9
35	47.6	80.4	154	58.0	30.2
36	---	---	---	---	---
37	---	---	---	---	---
38	---	---	---	---	---
39	---	---	---	---	---
40	---	---	---	---	---

MALES
END OF TREATMENT

ANIMAL	Total bilirubin umol/L	Urea mmol/L	Creatinine umol/L	Glucose mmol/L	Cholesterol mmol/L
GROUP 1 (CONTROL)					
1	3.1	4.8	36.3	6.52	1.48
2	2.1	7.5	32.7	11.02	1.85
3	2.7	6.4	37.5	11.03	1.73
4	1.9	6.6	39.9	9.07	1.97
5	1.8	6.7	37.5	10.73	1.82

2.10 CLINICAL BIOCHEMISTRY
MALES
END OF TREATMENT

ANIMAL	Total bilirubin umol/L	Urea mmol/L	Creatinine umol/L	Glucose mmol/L	Cholesterol mmol/L
GROUP 1 (CONTROL)					
6	---	---	---	---	---
7	---	---	---	---	---
8	---	---	---	---	---
9	---	---	---	---	---
10	---	---	---	---	---
GROUP 2 (100 MG/KG)					
11	2.4	6.9	38.1	7.07	1.78
12	2.0	5.7	39.3	8.65	2.31
13	2.0	9.3	43.5	8.75	2.01
14	2.1	5.8	38.1	6.93	1.69
15	2.4	6.1	38.1	9.77	1.72
16	---	---	---	---	---
17	---	---	---	---	---
18	---	---	---	---	---
19	---	---	---	---	---
20	---	---	---	---	---
GROUP 3 (300 MG/KG)					
21	2.0	6.4	36.3	9.61	1.53
22	1.9	8.1	39.9	8.68	1.71
23	2.1	6.0	34.5	7.57	1.51
24	2.0	5.8	36.9	6.67	1.33
25	2.3	8.8	40.5	10.92	1.86
26	---	---	---	---	---
27	---	---	---	---	---
28	---	---	---	---	---
29	---	---	---	---	---
30	---	---	---	---	---
GROUP 4 (1000 MG/KG)					
31	2.4	7.6	34.5	6.91	2.28
32	2.6	7.4	33.9	9.89	1.37
33	2.6	8.8	37.5	5.57	1.64
34	2.3	5.1	35.1	8.29	1.85
35	2.1	7.3	36.9	8.92	1.16
36	---	---	---	---	---
37	---	---	---	---	---
38	---	---	---	---	---
39	---	---	---	---	---
40	---	---	---	---	---

MALES
END OF TREATMENT

ANIMAL	Bile Acids umol/L	Sodium mmol/L	Potassium mmol/L	Chloride mmol/L	Calcium mmol/L
GROUP 1 (CONTROL)					
1	14.8	141.0	3.77	105	2.49
2	30.5	140.9	4.09	104	2.56
3	33.3	139.2	4.28	105	2.56
4	10.9	141.2	4.05	105	2.52
5	30.8	139.8	4.10	102	2.57
6	---	---	---	---	---
7	---	---	---	---	---
8	---	---	---	---	---
9	---	---	---	---	---
10	---	---	---	---	---

2.10 CLINICAL BIOCHEMISTRY
MALES
END OF TREATMENT

ANIMAL	Bile Acids umol/L	Sodium mmol/L	Potassium mmol/L	Chloride mmol/L	Calcium mmol/L
GROUP 2 (100 MG/KG)					
11	22.7	141.0	3.95	104	2.60
12	12.0	141.5	3.86	106	2.55
13	22.4	140.7	4.07	104	2.57
14	10.0	139.8	3.89	104	2.53
15	17.6	139.5	4.02	105	2.49
16	---	---	---	---	---
17	---	---	---	---	---
18	---	---	---	---	---
19	---	---	---	---	---
20	---	---	---	---	---
GROUP 3 (300 MG/KG)					
21	13.1	140.6	3.97	105	2.64
22	22.9	138.1	4.09	102	2.45
23	18.0	140.5	3.83	106	2.54
24	27.4	140.7	3.81	105	2.47
25	30.1	139.5	3.75	104	2.57
26	---	---	---	---	---
27	---	---	---	---	---
28	---	---	---	---	---
29	---	---	---	---	---
30	---	---	---	---	---
GROUP 4 (1000 MG/KG)					
31	34.6	140.3	3.88	104	2.59
32	43.9	141.6	3.87	103	2.53
33	42.3	142.7	3.73	105	2.50
34	10.2	140.5	4.51	105	2.57
35	29.3	141.0	3.63	105	2.50
36	---	---	---	---	---
37	---	---	---	---	---
38	---	---	---	---	---
39	---	---	---	---	---
40	---	---	---	---	---

MALES
END OF TREATMENT

ANIMAL	Inorg.Phos mmol/L	Total T4 ug/dL
GROUP 1 (CONTROL)		
1	1.96	6.06
2	1.92	4.67
3	1.63	4.04
4	1.89	5.26
5	1.86	6.73
6	---	4.10
7	---	3.64
8	---	6.35
9	---	4.71
10	---	5.51
GROUP 2 (100 MG/KG)		
11	2.09	6.39
12	1.76	3.65
13	2.01	5.07
14	1.67	3.71
15	1.39	3.45

2.10 CLINICAL BIOCHEMISTRY
MALES
END OF TREATMENT

ANIMAL	Inorg.Phos mmol/L	Total T4 ug/dL
GROUP 2 (100 MG/KG)		
16	---	5.69
17	---	4.63
18	---	5.39
19	---	4.86
20	---	4.45
GROUP 3 (300 MG/KG)		
21	1.93	4.31
22	1.78	3.35
23	1.69	3.74
24	1.83	3.74
25	1.69	4.17
26	---	4.73
27	---	3.83
28	---	4.44
29	---	4.48
30	---	3.52
GROUP 4 (1000 MG/KG)		
31	1.96	4.50
32	1.89	2.73
33	2.08	5.50
34	1.96	4.81
35	1.80	3.54
36	---	4.69
37	---	6.23
38	---	5.41
39	---	3.50
40	---	3.99

FEMALES
END OF TREATMENT

ANIMAL	ALAT U/L	ASAT U/L	ALP U/L	Total protein g/L	Albumin g/L
GROUP 1 (CONTROL)					
41	108.9	116.9	385	58.7	31.3
44	90.5	89.0	185	56.4	30.3
45	98.0	93.6	158	60.6	32.0
47	92.9	95.4	543	55.7	30.5
50	106.0	125.6	547	51.4	28.2
GROUP 2 (100 MG/KG)					
52	118.2	99.6	434	61.1	31.2
54	94.6	97.7	556	53.5	28.0
56	106.7	111.2	466	57.2	30.0
57	110.2	128.5	440	54.6	29.0
58	112.1	235.7	410	57.1	29.8
GROUP 3 (300 MG/KG)					
62	100.4	90.9	399	59.0	30.8
64	118.5	105.7	429	54.9	29.4
66	118.6	111.2	278	56.5	29.4
68	91.2	109.2	149	59.5	31.3
70	126.2	150.4	547	54.7	29.0
GROUP 4 (1000 MG/KG)					
71	117.6	95.9	512	53.8	28.1

2.10 CLINICAL BIOCHEMISTRY
FEMALES
END OF TREATMENT

ANIMAL	ALAT U/L	ASAT U/L	ALP U/L	Total protein g/L	Albumin g/L
GROUP 4 (1000 MG/KG)					
73	81.2	110.9	218	55.3	29.0
74	100.9	151.2	236	56.8	30.0
79	98.4	98.3	230	55.5	29.7
80	102.6	111.9	468	58.6	30.6

FEMALES
END OF TREATMENT

ANIMAL	Total bilirubin umol/L	Urea mmol/L	Creatinine umol/L	Glucose mmol/L	Cholesterol mmol/L
GROUP 1 (CONTROL)					
41	2.3	9.1	35.9	7.50	2.26
44	2.3	10.2	35.9	7.64	2.37
45	3.3	9.1	38.8	7.74	2.11
47	2.0	10.6	37.5	7.86	2.53
50	2.3	11.4	32.9	5.91	1.97
GROUP 2 (100 MG/KG)					
52	2.4	9.8	35.9	6.70	2.19
54	2.0	10.9	38.2	7.28	1.99
56	2.0	9.6	38.8	7.53	1.82
57	2.2	10.8	35.9	5.73	1.95
58	1.4	10.1	38.8	6.78	2.24
GROUP 3 (300 MG/KG)					
62	1.9	10.9	36.9	7.65	2.41
64	2.4	11.1	32.9	5.98	1.76
66	2.1	12.2	35.9	6.01	2.00
68	3.2	10.2	32.9	6.82	2.38
70	2.2	9.9	35.9	6.23	2.29
GROUP 4 (1000 MG/KG)					
71	2.0	11.5	32.7	6.43	2.16
73	2.3	9.5	35.5	8.22	2.09
74	1.7	8.6	37.3	7.73	2.31
79	2.0	14.5	39.6	7.54	2.23
80	1.7	10.9	34.4	7.26	1.88

FEMALES
END OF TREATMENT

ANIMAL	Bile Acids umol/L	Sodium mmol/L	Potassium mmol/L	Chloride mmol/L	Calcium mmol/L
GROUP 1 (CONTROL)					
41	45.7	141.6	4.89	103	2.55
44	19.9	138.5	4.44	100	2.51
45	19.0	140.9	4.37	104	2.50
47	21.8	136.6	4.17	99	2.53
50	20.9	141.5	4.30	104	2.41
GROUP 2 (100 MG/KG)					
52	27.0	142.2	4.09	101	2.58
54	14.4	137.5	4.55	103	2.43
56	18.6	139.8	4.78	104	2.45

2.10 CLINICAL BIOCHEMISTRY
FEMALES
END OF TREATMENT

ANIMAL	Bile Acids umol/L	Sodium mmol/L	Potassium mmol/L	Chloride mmol/L	Calcium mmol/L
GROUP 2 (100 MG/KG)					
57	49.0	140.6	4.34	104	2.38
58	27.1	141.3	4.37	104	2.40
GROUP 3 (300 MG/KG)					
62	45.7	139.7	5.07	101	2.56
64	17.0	139.8	4.70	103	2.59
66	20.0	140.3	4.63	104	2.38
68	28.1	140.1	4.76	104	2.52
70	20.9	138.7	5.07	104	2.52
GROUP 4 (1000 MG/KG)					
71	21.7	138.2	4.57	100	2.55
73	20.1	136.3	5.39	100	2.56
74	13.3	139.9	4.83	103	2.40
79	29.5	141.6	4.43	104	2.55
80	16.4	141.3	4.74	104	2.50

FEMALES
END OF TREATMENT

ANIMAL	Inorg.Phos mmol/L
GROUP 1 (CONTROL)	
41	0.79
44	1.07
45	0.43
47	0.64
50	0.57
GROUP 2 (100 MG/KG)	
52	1.64
54	0.36
56	0.76
57	0.79
58	0.50
GROUP 3 (300 MG/KG)	
62	1.24
64	1.20
66	0.47
68	1.42
70	0.64
GROUP 4 (1000 MG/KG)	
71	1.59
73	1.54
74	0.32
79	0.54
80	0.46

2.11 MACROSCOPIC FINDINGS
MALES

ALL NECROPSIES

ANIMAL	ORGAN	FINDING	DAY OF DEATH
GROUP 1 (CONTROL)			
1		No findings noted	Scheduled sacrifice, 06Mar2019
2		No findings noted	Scheduled sacrifice, 06Mar2019
3		No findings noted	Scheduled sacrifice, 06Mar2019
4		No findings noted	Scheduled sacrifice, 06Mar2019
5		No findings noted	Scheduled sacrifice, 06Mar2019
6		No findings noted	Scheduled sacrifice, 06Mar2019
7		No findings noted	Scheduled sacrifice, 06Mar2019
8		No findings noted	Scheduled sacrifice, 06Mar2019
9		No findings noted	Scheduled sacrifice, 06Mar2019
10		No findings noted	Scheduled sacrifice, 06Mar2019
GROUP 2 (100 MG/KG)			
11		No findings noted	Scheduled sacrifice, 06Mar2019
12		No findings noted	Scheduled sacrifice, 06Mar2019
13		No findings noted	Scheduled sacrifice, 06Mar2019
14	Bone	Tail, tail apex: tail bent.	Scheduled sacrifice, 06Mar2019
15		No findings noted	Scheduled sacrifice, 06Mar2019
16		No findings noted	Scheduled sacrifice, 06Mar2019
17		No findings noted	Scheduled sacrifice, 06Mar2019
18		No findings noted	Scheduled sacrifice, 06Mar2019
19		No findings noted	Scheduled sacrifice, 06Mar2019
20		No findings noted	Scheduled sacrifice, 06Mar2019
GROUP 3 (300 MG/KG)			
21		No findings noted	Scheduled sacrifice, 06Mar2019
22		No findings noted	Scheduled sacrifice, 06Mar2019
23		No findings noted	Scheduled sacrifice, 06Mar2019
24		No findings noted	Scheduled sacrifice, 06Mar2019
25		No findings noted	Scheduled sacrifice, 06Mar2019
26		No findings noted	Scheduled sacrifice, 06Mar2019
27		No findings noted	Scheduled sacrifice, 06Mar2019
28		No findings noted	Scheduled sacrifice, 06Mar2019
29		No findings noted	Scheduled sacrifice, 06Mar2019
30		No findings noted	Scheduled sacrifice, 06Mar2019
GROUP 4 (1000 MG/KG)			
31	Liver	Discolouration, red-brown.	Scheduled sacrifice, 06Mar2019
32	Kidneys	Cranial pole, right side middle part irregular surface.	Scheduled sacrifice, 06Mar2019
33		No findings noted	Scheduled sacrifice, 06Mar2019
34		No findings noted	Scheduled sacrifice, 06Mar2019
35	Epididymides	Left side, tail: nodule(s), d=10x6 mm, yellowish, soft.	Scheduled sacrifice, 06Mar2019
36		No findings noted	Scheduled sacrifice, 06Mar2019
37		No findings noted	Scheduled sacrifice, 06Mar2019
38		No findings noted	Scheduled sacrifice, 06Mar2019
39		No findings noted	Scheduled sacrifice, 06Mar2019
40		No findings noted	Scheduled sacrifice, 06Mar2019

FEMALES

ALL NECROPSIES

ANIMAL	ORGAN	FINDING	DAY OF DEATH
GROUP 1 (CONTROL)			
41		No findings noted	Scheduled sacrifice, 29Mar2019
42	Uterus	Right horn: nodule(s), d=8x7 mm, tan, reddish, hard. Right horn: contents: greenish, gelatinous.	Scheduled sacrifice, 19Mar2019

2.11 MACROSCOPIC FINDINGS
FEMALES

ALL NECROPSIES

ANIMAL	ORGAN	FINDING	DAY OF DEATH
GROUP 1 (CONTROL)			
	Thymus	Right side: focus/foci, isolated, reddish.	
	Mandibular lymph n	Both sides: focus/foci, isolated, dark red.	
	Eyes	Left side: exophthalmus.	
43		No findings noted	Scheduled sacrifice, 01Apr2019
44		No findings noted	Scheduled sacrifice, 29Mar2019
45		No findings noted	Scheduled sacrifice, 29Mar2019
46		No findings noted	Scheduled sacrifice, 29Mar2019
47		No findings noted	Scheduled sacrifice, 28Mar2019
48		No findings noted	Scheduled sacrifice, 01Apr2019
49		No findings noted	Scheduled sacrifice, 01Apr2019
50		No findings noted	Scheduled sacrifice, 29Mar2019
GROUP 2 (100 MG/KG)			
51		No findings noted	Scheduled sacrifice, 19Mar2019
52	Body cavities	Thoracic cavity: contains fluid, watery-clear.	Scheduled sacrifice, 29Mar2019
53		No findings noted	Scheduled sacrifice, 19Mar2019
54		No findings noted	Scheduled sacrifice, 28Mar2019
55		No findings noted	Scheduled sacrifice, 02Apr2019
56		No findings noted	Scheduled sacrifice, 29Mar2019
57	Clitoral glands	Left side: focus/foci, d=6x2 mm, tan.	Scheduled sacrifice, 29Mar2019
	Body cavities	Thoracic cavity: contains fluid, watery-clear.	
58		No findings noted	Scheduled sacrifice, 29Mar2019
59		No findings noted	Scheduled sacrifice, 01Apr2019
60		No findings noted	Scheduled sacrifice, 29Mar2019
GROUP 3 (300 MG/KG)			
61		No findings noted	Scheduled sacrifice, 02Apr2019
62		No findings noted	Scheduled sacrifice, 01Apr2019
63	Uterus	Contains fluid.	Scheduled sacrifice, 19Mar2019
64	Jejunum	Focus/foci, d=2x1 mm, reddish.	Scheduled sacrifice, 29Mar2019
65	Body cavities	Abdominal cavity, uterine adipose tissue, right side: nodule(s), d=5x2 mm, tan, hard.	Scheduled sacrifice, 01Apr2019
66	Thyroid gland	Both sides: discolouration, pale.	Scheduled sacrifice, 29Mar2019
	Eyes	Right side: exophthalmus.	
67	Thymus	Right side: focus/foci, many, reddish.	Scheduled sacrifice, 01Apr2019
68		No findings noted	Scheduled sacrifice, 29Mar2019
69		No findings noted	Scheduled sacrifice, 01Apr2019
70	Body cavities	Thoracic cavity: contains fluid, watery-clear.	Scheduled sacrifice, 29Mar2019
GROUP 4 (1000 MG/KG)			
71		No findings noted	Scheduled sacrifice, 28Mar2019
72	Uterus	Contains fluid.	Scheduled sacrifice, 19Mar2019
	Mandibular lymph n	Both sides: focus/foci, isolated, dark red.	
	Eyes	Left side: exophthalmus.	
73		No findings noted	Scheduled sacrifice, 28Mar2019
74	Thyroid gland	Both sides: discolouration, pale.	Scheduled sacrifice, 29Mar2019
75		No findings noted	Scheduled sacrifice, 29Mar2019
76		No findings noted	Scheduled sacrifice, 29Mar2019
77		No findings noted	Scheduled sacrifice, 01Apr2019
78		No findings noted	Scheduled sacrifice, 01Apr2019
79		No findings noted	Scheduled sacrifice, 28Mar2019
80		No findings noted	Scheduled sacrifice, 29Mar2019

2.12 ORGAN WEIGHTS (GRAM)
MALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (GRAM)	HEART (GRAM)	LIVER (GRAM)
GROUP 1 (CONTROL)				
1	317	1.94	0.963	7.64
2	304	2.00	0.837	7.44
3	351	2.10	1.024	8.42
4	347	2.03	0.993	7.99
5	345	1.92	0.993	8.81
6	310	---	---	---
7	335	---	---	---
8	368	---	---	---
9	348	---	---	---
10	326	---	---	---
GROUP 2 (100 MG/KG)				
11	353	2.15	0.898	8.51
12	364	2.07	0.982	8.42
13	341	1.86	0.887	7.88
14	337	2.05	0.898	7.78
15	306	1.99	0.803	6.83
16	374	---	---	---
17	292	---	---	---
18	335	---	---	---
19	345	---	---	---
20	357	---	---	---
GROUP 3 (300 MG/KG)				
21	383	2.08	1.105	9.05
22	320	1.95	0.863	7.59
23	344	2.13	0.914	8.38
24	318	2.05	0.852	7.31
25	341	1.88	0.956	8.40
26	337	---	---	---
27	351	---	---	---
28	330	---	---	---
29	331	---	---	---
30	299	---	---	---
GROUP 4 (1000 MG/KG)				
31	303	2.04	0.838	7.48
32	291	1.87	0.865	6.97
33	338	1.94	0.945	7.08
34	334	2.03	0.874	8.29
35	302	2.02	0.821	6.63
36	330	---	---	---
37	335	---	---	---
38	383	---	---	---
39	359	---	---	---
40	346	---	---	---

MALES
END OF TREATMENT

ANIMAL	THYROIDS (GRAM)	THYMUS (GRAM)	KIDNEYS (GRAM)	ADRENALS (GRAM)
GROUP 1 (CONTROL)				
1	0.021	0.484	2.24	0.071
2	0.018	0.397	2.18	0.048
3	0.016	0.383	2.39	0.059
4	0.016	0.317	2.31	0.062
5	0.016	0.343	2.21	0.058

2.12 ORGAN WEIGHTS (GRAM)
MALES
END OF TREATMENT

ANIMAL	THYROIDS (GRAM)	THYMUS (GRAM)	KIDNEYS (GRAM)	ADRENALS (GRAM)
GROUP 1 (CONTROL)				
6	0.016	---	---	---
7	0.017	---	---	---
8	0.015	---	---	---
9	0.016	---	---	---
10	0.014	---	---	---
GROUP 2 (100 MG/KG)				
11	0.017	0.463	2.18	0.056
12	0.015	0.348	2.35	0.054
13	0.013	0.407	2.16	0.054
14	0.015	0.298	2.06	0.048
15	0.013	0.317	2.23	0.054
16	0.014	---	---	---
17	0.015	---	---	---
18	0.014	---	---	---
19	0.023	---	---	---
20	0.018	---	---	---
GROUP 3 (300 MG/KG)				
21	0.019	0.469	2.73	0.076
22	0.015	0.230	2.10	0.067
23	0.016	0.307	2.54	0.076
24	0.013	0.339	2.01	0.068
25	0.017	0.385	2.22	0.064
26	0.013	---	---	---
27	0.019	---	---	---
28	0.021	---	---	---
29	0.015	---	---	---
30	0.011	---	---	---
GROUP 4 (1000 MG/KG)				
31	0.014	0.359	2.54	0.061
32	0.016	0.204	2.30	0.053
33	0.015	0.310	2.18	0.060
34	0.019	0.411	2.40	0.061
35	0.015	0.218	2.05	0.055
36	0.023	---	---	---
37	0.018	---	---	---
38	0.019	---	---	---
39	0.016	---	---	---
40	0.022	---	---	---

MALES
END OF TREATMENT

ANIMAL	SPLEEN (GRAM)	TESTES (GRAM)	PROSTATE GLAND (GRAM)	EPIDIDYMIDES (GRAM)
GROUP 1 (CONTROL)				
1	0.689	3.40	0.945	1.141
2	0.502	2.84	0.623	0.968
3	0.833	3.90	0.767	1.212
4	0.606	3.40	0.858	1.001
5	0.630	3.46	0.908	1.041
6	---	3.22	0.828	0.988
7	---	3.26	0.863	1.083
8	---	3.54	0.965	1.132
9	---	3.57	1.007	1.098
10	---	3.28	0.870	0.940

2.12 ORGAN WEIGHTS (GRAM)
MALES
END OF TREATMENT

ANIMAL	SPLEEN (GRAM)	TESTES (GRAM)	PROSTATE GLAND (GRAM)	EPIDIDYMIDES (GRAM)
GROUP 2 (100 MG/KG)				
11	0.624	3.44	0.792	1.071
12	0.617	3.42	0.837	1.160
13	0.561	3.25	1.018	1.007
14	0.704	3.09	0.724	1.107
15	0.577	3.06	0.675	1.022
16	---	3.47	0.939	1.068
17	---	3.17	0.865	0.999
18	---	3.17	0.816	0.972
19	---	3.44	1.016	1.096
20	---	3.35	0.677	1.089
GROUP 3 (300 MG/KG)				
21	0.665	3.51	1.090	1.145
22	0.461	3.03	0.867	1.032
23	0.632	3.28	0.922	1.176
24	0.638	3.79	0.899	1.095
25	0.538	3.29	0.567	1.028
26	---	3.44	0.931	0.960
27	---	3.21	0.861	1.066
28	---	3.59	0.809	1.185
29	---	3.59	0.737	1.012
30	---	3.13	0.731	1.054
GROUP 4 (1000 MG/KG)				
31	0.557	3.37	0.625	1.048
32	0.476	3.12	0.614	1.025
33	0.564	3.19	0.919	1.014
34	0.551	3.17	0.852	1.092
35	0.478	3.23	0.766	1.214
36	---	3.34	0.876	1.173
37	---	3.24	0.884	1.006
38	---	3.72	0.718	0.992
39	---	3.72	0.582	0.994
40	---	3.12	1.017	1.100

MALES
END OF TREATMENT

ANIMAL	SEMINAL VESICLES (GRAM)
GROUP 1 (CONTROL)	
1	1.479
2	1.200
3	1.279
4	1.218
5	1.510
6	1.269
7	1.450
8	1.496
9	1.365
10	1.119
GROUP 2 (100 MG/KG)	
11	1.263
12	1.086
13	0.974
14	1.379
15	1.330

2.12 ORGAN WEIGHTS (GRAM)
MALES
END OF TREATMENT

ANIMAL	SEMINAL VESICLES (GRAM)
GROUP 2 (100 MG/KG)	
16	1.332
17	1.236
18	1.098
19	1.621
20	1.440
GROUP 3 (300 MG/KG)	
21	1.029
22	1.337
23	1.743
24	1.434
25	1.233
26	1.312
27	1.209
28	1.621
29	1.152
30	0.976
GROUP 4 (1000 MG/KG)	
31	1.248
32	0.905
33	1.115
34	1.281
35	1.374
36	1.584
37	1.160
38	1.176
39	0.942
40	0.933

2.12 ORGAN/BODY WEIGHT RATIOS (%)
MALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)
GROUP 1 (CONTROL)				
1	317	0.61	0.304	2.41
2	304	0.66	0.275	2.45
3	351	0.60	0.292	2.40
4	347	0.59	0.286	2.30
5	345	0.56	0.288	2.55
6	310	---	---	---
7	335	---	---	---
8	368	---	---	---
9	348	---	---	---
10	326	---	---	---
GROUP 2 (100 MG/KG)				
11	353	0.61	0.254	2.41
12	364	0.57	0.270	2.31
13	341	0.55	0.260	2.31
14	337	0.61	0.266	2.31
15	306	0.65	0.262	2.23
16	374	---	---	---
17	292	---	---	---
18	335	---	---	---
19	345	---	---	---
20	357	---	---	---
GROUP 3 (300 MG/KG)				
21	383	0.54	0.289	2.36
22	320	0.61	0.270	2.37
23	344	0.62	0.266	2.44
24	318	0.64	0.268	2.30
25	341	0.55	0.280	2.46
26	337	---	---	---
27	351	---	---	---
28	330	---	---	---
29	331	---	---	---
30	299	---	---	---
GROUP 4 (1000 MG/KG)				
31	303	0.67	0.277	2.47
32	291	0.64	0.297	2.39
33	338	0.57	0.280	2.10
34	334	0.61	0.262	2.48
35	302	0.67	0.272	2.20
36	330	---	---	---
37	335	---	---	---
38	383	---	---	---
39	359	---	---	---
40	346	---	---	---

MALES
END OF TREATMENT

ANIMAL	THYROIDS (%)	THYMUS (%)	KIDNEYS (%)	ADRENALS (%)
GROUP 1 (CONTROL)				
1	0.007	0.153	0.71	0.022
2	0.006	0.131	0.72	0.016
3	0.005	0.109	0.68	0.017
4	0.005	0.091	0.67	0.018
5	0.005	0.099	0.64	0.017

2.12 ORGAN/BODY WEIGHT RATIOS (%)
MALES
END OF TREATMENT

ANIMAL	THYROIDS (%)	THYMUS (%)	KIDNEYS (%)	ADRENALS (%)
GROUP 1 (CONTROL)				
6	0.005	---	---	---
7	0.005	---	---	---
8	0.004	---	---	---
9	0.005	---	---	---
10	0.004	---	---	---
GROUP 2 (100 MG/KG)				
11	0.005	0.131	0.62	0.016
12	0.004	0.096	0.65	0.015
13	0.004	0.119	0.63	0.016
14	0.004	0.088	0.61	0.014
15	0.004	0.104	0.73	0.018
16	0.004	---	---	---
17	0.005	---	---	---
18	0.004	---	---	---
19	0.007	---	---	---
20	0.005	---	---	---
GROUP 3 (300 MG/KG)				
21	0.005	0.122	0.71	0.020
22	0.005	0.072	0.66	0.021
23	0.005	0.089	0.74	0.022
24	0.004	0.107	0.63	0.021
25	0.005	0.113	0.65	0.019
26	0.004	---	---	---
27	0.005	---	---	---
28	0.006	---	---	---
29	0.005	---	---	---
30	0.004	---	---	---
GROUP 4 (1000 MG/KG)				
31	0.005	0.118	0.84	0.020
32	0.005	0.070	0.79	0.018
33	0.004	0.092	0.65	0.018
34	0.006	0.123	0.72	0.018
35	0.005	0.072	0.68	0.018
36	0.007	---	---	---
37	0.005	---	---	---
38	0.005	---	---	---
39	0.004	---	---	---
40	0.006	---	---	---

MALES
END OF TREATMENT

ANIMAL	SPLEEN (%)	TESTES (%)	PROSTATE GLAND (%)	EPIDIDYMIDES (%)
GROUP 1 (CONTROL)				
1	0.217	1.07	0.298	0.360
2	0.165	0.93	0.205	0.318
3	0.237	1.11	0.219	0.345
4	0.175	0.98	0.247	0.288
5	0.183	1.00	0.263	0.302
6	---	1.04	0.267	0.319
7	---	0.97	0.258	0.323
8	---	0.96	0.262	0.308
9	---	1.03	0.289	0.316
10	---	1.01	0.267	0.288

2.12 ORGAN/BODY WEIGHT RATIOS (%)
MALES
END OF TREATMENT

ANIMAL	SPLEEN (%)	TESTES (%)	PROSTATE GLAND (%)	EPIDIDYMIDES (%)
GROUP 2 (100 MG/KG)				
11	0.177	0.97	0.224	0.303
12	0.170	0.94	0.230	0.319
13	0.165	0.95	0.299	0.295
14	0.209	0.92	0.215	0.328
15	0.189	1.00	0.221	0.334
16	---	0.93	0.251	0.286
17	---	1.09	0.296	0.342
18	---	0.94	0.244	0.290
19	---	1.00	0.294	0.318
20	---	0.94	0.190	0.305
GROUP 3 (300 MG/KG)				
21	0.174	0.92	0.285	0.299
22	0.144	0.95	0.271	0.323
23	0.184	0.95	0.268	0.342
24	0.201	1.19	0.283	0.344
25	0.158	0.97	0.166	0.301
26	---	1.02	0.276	0.285
27	---	0.91	0.245	0.304
28	---	1.09	0.245	0.359
29	---	1.08	0.223	0.306
30	---	1.05	0.244	0.353
GROUP 4 (1000 MG/KG)				
31	0.184	1.11	0.206	0.346
32	0.164	1.07	0.211	0.352
33	0.167	0.94	0.272	0.300
34	0.165	0.95	0.255	0.327
35	0.158	1.07	0.254	0.402
36	---	1.01	0.265	0.355
37	---	0.97	0.264	0.300
38	---	0.97	0.187	0.259
39	---	1.04	0.162	0.277
40	---	0.90	0.294	0.318

MALES
END OF TREATMENT

ANIMAL	SEMINAL VESICLES (%)
GROUP 1 (CONTROL)	
1	0.467
2	0.395
3	0.364
4	0.351
5	0.438
6	0.409
7	0.433
8	0.407
9	0.392
10	0.343
GROUP 2 (100 MG/KG)	
11	0.358
12	0.298
13	0.286
14	0.409
15	0.435

2.12 ORGAN/BODY WEIGHT RATIOS (%)
MALES
END OF TREATMENT

ANIMAL	SEMINAL VESICLES (%)
GROUP 2 (100 MG/KG)	
16	0.356
17	0.423
18	0.328
19	0.470
20	0.403
GROUP 3 (300 MG/KG)	
21	0.269
22	0.418
23	0.507
24	0.451
25	0.362
26	0.389
27	0.344
28	0.491
29	0.348
30	0.326
GROUP 4 (1000 MG/KG)	
31	0.412
32	0.311
33	0.330
34	0.384
35	0.455
36	0.480
37	0.346
38	0.307
39	0.262
40	0.270

2.12 ORGAN WEIGHTS (GRAM)
FEMALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (GRAM)	HEART (GRAM)	LIVER (GRAM)
GROUP 1 (CONTROL)				
41	258	1.87	0.854	10.75
42	260	---	---	---
43	296	---	---	---
44	292	1.86	0.873	13.53
45	276	2.02	0.730	10.37
46	258	---	---	---
47	288	1.94	0.883	12.36
48	284	---	---	---
49	282	---	---	---
50	262	1.77	0.802	12.19
GROUP 2 (100 MG/KG)				
51	233	---	---	---
52	283	1.94	0.743	11.01
53	253	---	---	---
54	287	1.87	0.874	12.34
55	286	---	---	---
56	291	1.84	0.794	12.58
57	293	1.86	0.865	12.09
58	296	1.96	0.875	12.57
59	271	---	---	---
60	301	---	---	---
GROUP 3 (300 MG/KG)				
61	309	---	---	---
62	309	1.94	0.910	12.83
63	229	---	---	---
64	289	1.84	0.809	11.97
65	342	---	---	---
66	274	1.91	0.793	10.94
67	291	---	---	---
68	301	---	0.992	12.33
69	272	---	---	---
70	281	1.94	0.803	11.43
GROUP 4 (1000 MG/KG)				
71	285	1.83	0.814	12.76
72	231	---	---	---
73	303	1.87	0.891	13.52
74	276	1.97	0.864	12.84
75	302	---	---	---
76	297	---	---	---
77	305	---	---	---
78	323	---	---	---
79	297	2.05	0.911	14.08
80	284	1.98	0.827	12.79

FEMALES
END OF TREATMENT

ANIMAL	THYROIDS (GRAM)	THYMUS (GRAM)	KIDNEYS (GRAM)	ADRENALS (GRAM)
GROUP 1 (CONTROL)				
41	0.019	0.196	1.78	0.072
42	0.014	---	---	---
43	0.020	---	---	---
44	0.013	0.253	2.11	0.085
45	0.016	0.310	1.77	0.079

2.12 ORGAN WEIGHTS (GRAM)
FEMALES
END OF TREATMENT

ANIMAL	THYROIDS (GRAM)	THYMUS (GRAM)	KIDNEYS (GRAM)	ADRENALS (GRAM)
GROUP 1 (CONTROL)				
46	0.013	---	---	---
47	0.018	0.172	1.79	0.079
48	0.018	---	---	---
49	0.024	---	---	---
50	0.010	0.252	1.91	0.064
GROUP 2 (100 MG/KG)				
51	0.024	---	---	---
52	0.015	0.158	1.96	0.081
53	0.023	---	---	---
54	0.020	0.201	1.83	0.091
55	0.016	---	---	---
56	0.016	0.203	2.02	0.072
57	0.016	0.169	2.21	0.079
58	0.022	0.206	2.24	0.080
59	0.015	---	---	---
60	0.020	---	---	---
GROUP 3 (300 MG/KG)				
61	0.011	---	---	---
62	0.012	0.249	1.93	0.073
63	0.024	---	---	---
64	0.024	0.229	2.12	0.077
65	0.015	---	---	---
66	0.018	0.227	1.96	0.083
67	0.017	---	---	---
68	0.022	0.208	2.05	0.089
69	0.017	---	---	---
70	0.021	0.210	2.00	0.069
GROUP 4 (1000 MG/KG)				
71	0.021	0.175	2.03	0.068
72	0.014	---	---	---
73	0.021	0.208	2.06	0.085
74	0.024	0.139	2.07	0.087
75	0.018	---	---	---
76	0.018	---	---	---
77	0.021	---	---	---
78	0.015	---	---	---
79	0.020	0.224	2.18	0.076
80	0.012	0.252	2.14	0.075

FEMALES
END OF TREATMENT

ANIMAL	SPLEEN (GRAM)	OVARIES (GRAM)	UTERUS (GRAM)
GROUP 1 (CONTROL)			
41	0.517	0.098	0.380
42	---	---	---
43	---	---	---
44	0.581	0.114	0.384
45	0.452	0.123	0.389
46	---	---	---
47	0.461	0.120	0.345
48	---	---	---
49	---	---	---
50	0.487	0.112	0.300

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2.12 ORGAN WEIGHTS (GRAM)
FEMALES
END OF TREATMENT

ANIMAL	SPLEEN (GRAM)	OVARIES (GRAM)	UTERUS (GRAM)
GROUP 2 (100 MG/KG)			
51	---	---	---
52	0.474	0.112	0.341
53	---	---	---
54	0.523	0.115	0.316
55	---	---	---
56	0.529	0.128	0.319
57	0.461	0.108	0.346
58	0.547	0.114	0.479
59	---	---	---
60	---	---	---
GROUP 3 (300 MG/KG)			
61	---	---	---
62	0.577	0.129	0.339
63	---	---	---
64	0.438	0.124	0.319
65	---	---	---
66	0.479	0.100	0.320
67	---	---	---
68	0.632	0.125	0.451
69	---	---	---
70	0.426	0.105	0.352
GROUP 4 (1000 MG/KG)			
71	0.484	0.123	0.313
72	---	---	---
73	0.510	0.106	0.346
74	0.530	0.089	0.332
75	---	---	---
76	---	---	---
77	---	---	---
78	---	---	---
79	0.784	0.119	0.339
80	0.445	0.138	0.396

2.12 ORGAN/BODY WEIGHT RATIOS (%)
FEMALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)
GROUP 1 (CONTROL)				
41	258	0.72	0.331	4.17
42	260	---	---	---
43	296	---	---	---
44	292	0.64	0.299	4.63
45	276	0.73	0.264	3.76
46	258	---	---	---
47	288	0.67	0.307	4.29
48	284	---	---	---
49	282	---	---	---
50	262	0.67	0.307	4.66
GROUP 2 (100 MG/KG)				
51	233	---	---	---
52	283	0.69	0.263	3.90
53	253	---	---	---
54	287	0.65	0.305	4.30
55	286	---	---	---
56	291	0.63	0.273	4.32
57	293	0.63	0.295	4.12
58	296	0.66	0.296	4.25
59	271	---	---	---
60	301	---	---	---
GROUP 3 (300 MG/KG)				
61	309	---	---	---
62	309	0.63	0.294	4.15
63	229	---	---	---
64	289	0.64	0.280	4.14
65	342	---	---	---
66	274	0.70	0.289	3.99
67	291	---	---	---
68	301	---	0.330	4.10
69	272	---	---	---
70	281	0.69	0.286	4.07
GROUP 4 (1000 MG/KG)				
71	285	0.64	0.286	4.48
72	231	---	---	---
73	303	0.62	0.294	4.46
74	276	0.71	0.313	4.65
75	302	---	---	---
76	297	---	---	---
77	305	---	---	---
78	323	---	---	---
79	297	0.69	0.307	4.74
80	284	0.70	0.292	4.51

FEMALES
END OF TREATMENT

ANIMAL	THYROIDS (%)	THYMUS (%)	KIDNEYS (%)	ADRENALS (%)
GROUP 1 (CONTROL)				
41	0.008	0.076	0.69	0.028
42	0.005	---	---	---
43	0.007	---	---	---
44	0.004	0.087	0.72	0.029
45	0.006	0.112	0.64	0.029

2.12 ORGAN/BODY WEIGHT RATIOS (%)
FEMALES
END OF TREATMENT

ANIMAL	THYROIDS (%)	THYMUS (%)	KIDNEYS (%)	ADRENALS (%)
GROUP 1 (CONTROL)				
46	0.005	---	---	---
47	0.006	0.060	0.62	0.027
48	0.006	---	---	---
49	0.008	---	---	---
50	0.004	0.096	0.73	0.024
GROUP 2 (100 MG/KG)				
51	0.010	---	---	---
52	0.005	0.056	0.69	0.029
53	0.009	---	---	---
54	0.007	0.070	0.64	0.032
55	0.006	---	---	---
56	0.005	0.070	0.69	0.025
57	0.005	0.058	0.75	0.027
58	0.007	0.070	0.76	0.027
59	0.005	---	---	---
60	0.007	---	---	---
GROUP 3 (300 MG/KG)				
61	0.004	---	---	---
62	0.004	0.081	0.62	0.024
63	0.011	---	---	---
64	0.008	0.079	0.73	0.027
65	0.004	---	---	---
66	0.006	0.083	0.72	0.030
67	0.006	---	---	---
68	0.007	0.069	0.68	0.030
69	0.006	---	---	---
70	0.007	0.075	0.71	0.025
GROUP 4 (1000 MG/KG)				
71	0.007	0.061	0.71	0.024
72	0.006	---	---	---
73	0.007	0.069	0.68	0.028
74	0.009	0.050	0.75	0.031
75	0.006	---	---	---
76	0.006	---	---	---
77	0.007	---	---	---
78	0.005	---	---	---
79	0.007	0.075	0.73	0.026
80	0.004	0.089	0.75	0.026

FEMALES
END OF TREATMENT

ANIMAL	SPLEEN (%)	OVARIES (%)	UTERUS (%)
GROUP 1 (CONTROL)			
41	0.200	0.038	0.147
42	---	---	---
43	---	---	---
44	0.199	0.039	0.131
45	0.164	0.045	0.141
46	---	---	---
47	0.160	0.042	0.120
48	---	---	---
49	---	---	---
50	0.186	0.043	0.115

2.12 ORGAN/BODY WEIGHT RATIOS (%)
FEMALES
END OF TREATMENT

ANIMAL	SPLEEN (%)	OVARIES (%)	UTERUS (%)
GROUP 2 (100 MG/KG)			
51	---	---	---
52	0.168	0.040	0.121
53	---	---	---
54	0.182	0.040	0.110
55	---	---	---
56	0.182	0.044	0.109
57	0.157	0.037	0.118
58	0.185	0.039	0.162
59	---	---	---
60	---	---	---
GROUP 3 (300 MG/KG)			
61	---	---	---
62	0.187	0.042	0.110
63	---	---	---
64	0.152	0.043	0.110
65	---	---	---
66	0.175	0.036	0.117
67	---	---	---
68	0.210	0.042	0.150
69	---	---	---
70	0.152	0.037	0.125
GROUP 4 (1000 MG/KG)			
71	0.170	0.043	0.110
72	---	---	---
73	0.168	0.035	0.114
74	0.192	0.032	0.120
75	---	---	---
76	---	---	---
77	---	---	---
78	---	---	---
79	0.264	0.040	0.114
80	0.157	0.049	0.140

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2.13 ESTROUS CYCLE DETERMINATION
FEMALES

ANIMAL	PRETEST DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14	PREMATING DAY 15 16 17 18 19 20 21 22 23 24 25 26 27 28	MATING DAY 29 30 31 32 33 34 35 36 37 38 39 40 41 42	N	CYCLE LENGTH PT	CYCLE LENGTH PM	CYCLE CODE PT	CYCLE CODE PM
GROUP 1 (CONTROL)								
41	d d d e **d** d d e **d** d d e **d** d	d e **d** d d e **d** d d e **d** d d e	**d** d p e^{s}	d	4,4	4,4,4	R	R
42	d d d e **d** d d e **m** d d e **d** d	d e **m** d d e **m** d d e **d** d d e	**d** d d e^{s}	d	4,4	4,4,4	R	R
43	d d d e **d** d p e **d** d p e **d** d	p e **d** d d e **d** d d e **d** d d e	**d** d p e^{s}	d	4,4	4,4,4	R	R
44	d d d e **d** d d e **d** d d e **d** d	d e **d** d d e **d** d d e **d** d d e	**d** d d	d	4,4	4,4,4	R	R
45	d e **d** d d e **d** d d e **d** d d e	d d d e **d** d d e **d** d d e **d** d	d	d	4,4	4,4	R	R
46	e **d** d d e **d** d d e **m** d d e **d**	d p e **d** d d e **d** d p e **d** d d	e d d d d d d d d d d d m	d	4,4,4	4,4	R	R
47	p e **d** d p e **d** d p e **d** d p e	d d p e **d** d p e **d** d p e **d** d	p	d	4,4	4,4	R	R
48	e **d** d d e **d** d d e **d** d d e **d**	d d e **d** d d e **d** d d e **d** d d	e d d d e^{s}	d	4,4,4	4,4	R	R
49	d d d e **d** d d e **d** d d e **d** d	d e **d** d d e **d** d d e **d** d d e	**d** d p	d	4,4	4,4,4	R	R
50	d d p e **d** d p e **d** d p e **d** d	d e **d** d d e **d** d d e **d** d d e	**d** d p e^{s}	d	4,4	4,4,4	R	R
GROUP 2 (100 mg/kg)					4,4	4,4,4	R	R
51	d d p e **d** d d e **d** d d e **d** d	d e **d** d d e **d** d d e **d** d d e	**d** d d	d	4,4	4,4,4	R	R
52	d p e **d** d d e **d** d d e **d** d d	e **d** d p e **d** d d e **d** d d e **d**	d d e^{s}	d	4,4	4,4,4	R	R
53	e **d** d d e **d** d d e **d** d d e **d**	d d e **d** d d e **d** d d e **d** d d	e	d	4,4,4	4,4	R	R
54	d e **d** d d e **d** d d e **d** d e e	d d p e **d** d d e **d** d d e **d** d	d e^{s}	d	4,4	4,4	R	R
55	e **d** d d e **d** d d e **d** d d d d	d d e **d** d d e **d** d d e **d** d d	e d d d	d	4,4	4,4	R	R
56	d d d e **d** d d e **d** d p e **d** d	d e **d** d d e **d** d d e **d** d d e	**d** d p	d	4,4	4,4,4	R	R
57	d d e **d** d d e **d** d d e **d** d d	e **d** d d e **d** d d e **d** d d e **d**	d d e^{s}	d	4,4	4,4,4	R	R
58	d p e **d** d d e **d** d d e **d** d p	e **d** d d e **d** d d e **d** d d e **d**	d d e^{s}	d	4,4	4,4,4	R	R
59	d d d e **d** d d e **d** d p e **d** d	d e **d** d d e **d** d p e **d** d d e	**d** d p e^{s}	d	4,4	4,4,4	R	R
60	d d p e **d** d d e **d** d d e **d** d	d e **d** d d e **d** d d e **d** d d e	**d** d d e^{s}	d	4,4	4,4,4	R	R

N = DAY OF NECROPSY: PT = PRETEST: PM = PREMATING
ESTROUS STAGE CODE: e = ESTRUS, d = DI-ESTRUS, m = MET-ESTRUS, p = PRO-ESTRUS, u = UNABLE TO DETERMINE ESTROUS STAGE,
s = SMEARED POSITIVE FOR SPERM. Estrous cycle length is determined by counting the number of days from the first M or D in a cycle (indicated in bold) to the first M or D in a subsequent cycle.

CYCLE CLASSIFICATION CODE: R = REGULAR (all cycles either 4 or 5 days); IR = IRREGULAR (at least one cycle of 2, 3 or 6-10 days, irrespective of the number of 4-5 day cycles); A = ACYCLIC (at least 10 days without estrus irrespective of the number of 4-5 day cycles); EE = EXTENDED ESTRUS (at least 4 consecutive days of estrus; U = UNABLE TO DETERMINE.

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2.13 ESTROUS CYCLE DETERMINATION
FEMALES

ANIMAL	PRETEST DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14	PREMATING DAY 15 16 17 18 19 20 21 22 23 24 25 26 27 28	MATING DAY 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43	N	CYCLE LENGTH PT	CYCLE LENGTH PM	CYCLE CODE PT	CYCLE CODE PM
GROUP 3 (300 mg/kg)								
61	e **d** d d e **d** d d e **d** d d e **d**	d d e **d** d d e **d** d d e **d** d p	e m d d e^s	d	4,4,4	4,4	R	R
62	d d d e **d** d d e **d** d d e **d** d	d e **d** d d e **d** d d e **d** d d e	**d** d d e^s	d	4,4	4,4,4	R	R
63	e **d** d d e **d** d p e **d** d d e **d**	d p e **d** d d e **d** d d e **d** d p	e m	e	4,4,4	4,4	R	R
64	d d e **d** d d e **d** d d e **d** d d	e **d** d d e **d** d d e **d** d d e **d**	d d e^s	d	4,4	4,4,4	R	R
65	d d d e **d** d d e **d** d d e **d** d	d e **d** d d e **d** d d e **d** d d e	**d** d p e^s	d	4,4	4,4,4	R	R
66	d e **d** d d e **d** d d e **d** d d e	d d p e **d** d d e **d** d d e **d** d	d e^s	d	4,4	4,4	R	R
67	d d d e **d** d d e **d** d d e **d** d	d e **m** d d e **d** d d e **d** d d e	**d** d p e^s	d	4,4	4,4,4	R	R
68	d d d e **d** d p e **d** d p e **d** d	p e **d** d p e **d** d p e **d** d p e	**d** d p e^s	d	4,4	4,4,4	R	R
69	e **d** d d e **d** d p e **d** d d e **d**	d p e **d** d d e **d** d d e **d** d d	e d d d	d	4,4,4	4,4	R	R
70	d e **d** d d e **d** d d e **d** d d e	d d d e **d** d d e **d** d d e **d** d	d e^s	d	4,4	4,4	R	R
GROUP 4 (1000 mg/kg)								
71	d e **d** d d e **d** d d e **d** d d e	d d d e **d** d d e **d** d d e **d** d	d e^s	d	4,4	4,4	R	R
72	d d d e **d** d d e **d** d p e **d** d	p e **d** d p e **d** d d e **d** d p e	**d** d d e^s	d	4,4	4,4,4	R	R
73	d e **d** d d e **d** d d e **d** d d e	d d p e **d** d d e **d** d d e **d** d	d e^s	d	4,4	4,4	R	R
74	d d d e **d** d p e **d** d p e **d** d	d e **d** d d e **d** d d e **d** d p e	**d** d d	d	4,4	4,4,4	R	R
75	d d d e **d** d d e **d** d p e **d** d	d e **d** d d e **d** d d e **d** d d e	**d** d d e^s	d	4,4	4,4,4	R	R
76	d d d e **d** d d e **d** d p e **d** d	d e **d** d d e **d** d d e **d** d d e	**d** d p	d	4,4	4,4,4	R	R
77	e **d** d d e **d** d d e **d** d p e **d**	d d e **d** d d e **d** d d e **d** d d	e d d p e^s	d	4,4,4	4,4	R	R
78	e **d** d d e **d** d d e **d** d d e **d**	d p e **d** d d e **d** d d e **d** d d	e d d d d d d d d d d d d d	d	4,4,4	4,4	R	R
79	d e **d** d d e **d** d p e **d** d d e	d d p e **d** d d e **d** d d d d d	d e^s	d	4,4	4	R	U
80	d d e **d** d p e **d** d p e **d** d p	e **d** d d e **d** d p e **d** d e e **d**	d d	d	4,4	4,4,4	R	R

N = DAY OF NECROPSY: PT = PRETEST: PM = PREMATING
ESTROUS STAGE CODE: e = ESTRUS, d = DI-ESTRUS, m = MET-ESTRUS, p = PRO-ESTRUS, u = UNABLE TO DETERMINE ESTROUS STAGE,
s = SMEARED POSITIVE FOR SPERM. Estrous cycle length is determined by counting the number of days from the first M or D in a cycle (indicated in bold) to the first M or D in a subsequent cycle.

CYCLE CLASSIFICATION CODE: R = REGULAR (all cycles either 4 or 5 days); IR = IRREGULAR (at least one cycle of 2, 3 or 6-10 days, irrespective of the number of 4-5 day cycles); A = ACYCLIC (at least 10 days without estrus irrespective of the number of 4-5 day cycles); EE = EXTENDED ESTRUS (at least 4 consecutive days of estrus; U = UNABLE TO DETERMINE.

2.14 GENERAL REPRODUCTION DATA

F0-GENERATION - POST COITUM

FEMALE NUMBER	MALE NUMBER	MATING DATE	PREGNANT	SCHEDULE	DELIVERY RECORDED	NECROPSY DATE
GROUP 1 (CONTROL)						
41	1	22FEB2019	YES	BREEDING	15MAR2019	29MAR2019
42 <IO>	2	22FEB2019	YES	---	---	19MAR2019
43	3	22FEB2019	YES	BREEDING	16MAR2019	01APR2019
44	4	22FEB2019	YES	BREEDING	15MAR2019	29MAR2019
45	5	20FEB2019	YES	BREEDING	14MAR2019	29MAR2019
46 <NP>	6	04MAR2019	NO	---	---	29MAR2019
47	7	20FEB2019	YES	BREEDING	13MAR2019	28MAR2019
48	8	23FEB2019	YES	BREEDING	16MAR2019	01APR2019
49	9	22FEB2019	YES	BREEDING	16MAR2019	01APR2019
50	10	22FEB2019	YES	BREEDING	15MAR2019	29MAR2019
GROUP 2 (100 MG/KG)						
51 <NP>	11	21FEB2019	NO	---	---	19MAR2019
52	12	21FEB2019	YES	BREEDING	14MAR2019	29MAR2019
53 <NP>	13	20FEB2019	NO	---	---	19MAR2019
54	14	20FEB2019	YES	BREEDING	13MAR2019	28MAR2019
55	15	23FEB2019	YES	BREEDING	17MAR2019	02APR2019
56	16	22FEB2019	YES	BREEDING	15MAR2019	29MAR2019
57	17	21FEB2019	YES	BREEDING	14MAR2019	29MAR2019
58	18	21FEB2019	YES	BREEDING	14MAR2019	29MAR2019
59	19	22FEB2019	YES	BREEDING	16MAR2019	01APR2019
60	20	22FEB2019	YES	BREEDING	15MAR2019	29MAR2019
GROUP 3 (300 MG/KG)						
61	21	23FEB2019	YES	BREEDING	17MAR2019	02APR2019
62	22	22FEB2019	YES	BREEDING	16MAR2019	01APR2019
63 <NP>	23	20FEB2019	NO	---	---	19MAR2019
64	24	21FEB2019	YES	BREEDING	14MAR2019	29MAR2019
65	25	22FEB2019	YES	BREEDING	16MAR2019	01APR2019
66	26	20FEB2019	YES	BREEDING	14MAR2019	29MAR2019
67	27	22FEB2019	YES	BREEDING	16MAR2019	01APR2019
68	28	22FEB2019	YES	BREEDING	15MAR2019	29MAR2019
69	29	23FEB2019	YES	BREEDING	16MAR2019	01APR2019
70	30	20FEB2019	YES	BREEDING	14MAR2019	29MAR2019
GROUP 4 (1000 MG/KG)						
71	31	20FEB2019	YES	BREEDING	13MAR2019	28MAR2019
72 <NP>	32	22FEB2019	NO	---	---	19MAR2019
73	33	20FEB2019	YES	BREEDING	13MAR2019	28MAR2019
74	34	22FEB2019	YES	BREEDING	15MAR2019	29MAR2019
75	35	22FEB2019	YES	BREEDING	15MAR2019	29MAR2019
76	36	22FEB2019	YES	BREEDING	15MAR2019	29MAR2019
77	37	23FEB2019	YES	BREEDING	16MAR2019	01APR2019
78	38	23FEB2019	YES	BREEDING	16MAR2019	01APR2019
79	39	20FEB2019	YES	BREEDING	13MAR2019	28MAR2019
80	40	21FEB2019	YES	BREEDING	14MAR2019	29MAR2019

<IO> Implantations only
<NP> Non-pregnant

2.15 IMPLANTATION SITES
FEMALES

AT NECROPSY

ANIMAL	Implantations
GROUP 1 (CONTROL)	
41	11.0
42	---
43	9.0
44	15.0
45	7.0
46	---
47	9.0
48	14.0
49	13.0
50	16.0
GROUP 2 (100 MG/KG)	
51	---
52	14.0
53	---
54	13.0
55	14.0
56	17.0
57	11.0
58	14.0
59	17.0
60	17.0
GROUP 3 (300 MG/KG)	
61	12.0
62	13.0
63	---
64	14.0
65	14.0
66	13.0
67	15.0
68	10.0
69	14.0
70	11.0
GROUP 4 (1000 MG/KG)	
71	11.0
72	---
73	14.0
74	16.0
75	14.0
76	14.0
77	16.0
78	17.0
79	12.0
80	16.0

Female No. 42: implantations only

03Jun19 13h46

2.16 DEVELOPMENTAL DATA PER LITTER
FEMALES

F0-GENERATION - LACTATION

		FIRST LITTER CHECK					P.NATAL LOSS			LIVING PUPS		
LITTER	DURATION OF GESTATION	DEAD PUPS M	F	LIVING PUPS M	F	TOT.	DAYS 0 - 4 M	F	CULLED PUPS TOT.	DAY 4 P.P. M	F	TOT.
GROUP 1 (CONTROL)												
41	21	0	0	3	7	10	0	0	2	3	5	8
43	22	0	0	5	3	8	0	0	0	5	3	8
44	21	0	0	9	6	15	0	0	7	4	4	8
45	22	0	0	3	3	6	0	0	0	3	3	6
47	21	0	0	5	4	9	0	0	1	4	4	8
48	21	0	0	5	9	14	0	1	5	4	4	8
49	22	0	0	5	8	13	0	0	5	4	4	8
50	21	0	0	9	5	14	0	0	6	4	4	8
TOTAL		0	0	44	45	89	0	1	26	31	31	62
N	8	8	8	8	8	8	8	8	8	8	8	8
MEAN	21.4	0.0	0.0	5.5	5.6	11.1	0.0	0.1	3.3	3.9	3.9	7.8
ST.DEV.	0.5	0.0	0.0	2.3	2.3	3.3	0.0	0.4	2.8	0.6	0.6	0.7

2.16 DEVELOPMENTAL DATA PER LITTER
FEMALES

F0-GENERATION - LACTATION

		FIRST LITTER CHECK					P.NATAL LOSS			LIVING PUPS		
LITTER	DURATION OF GESTATION	DEAD M	PUPS F	LIVING M	PUPS F	TOT.	DAYS M	0 - 4 F	CULLED PUPS TOT.	DAY 4 M	P.P. F	TOT.
GROUP 2 (100 MG/KG)												
52	21	0	0	5	9	14	0	0	6	4	4	8
54	21	0	0	6	7	13	0	0	5	4	4	8
55	22	0	0	9	4	13	0	0	5	4	4	8
56	21	0	0	9	8	17	0	0	9	4	4	8
57	21	0	0	6	5	11	0	0	3	4	4	8
58	21	0	0	6	8	14	0	0	6	4	4	8
59	22	0	0	7	9	16	0	0	8	4	4	8
60	21	0	0	8	7	15	0	0	7	4	4	8
TOTAL		0	0	56	57	113	0	0	49	32	32	64
N	8	8	8	8	8	8	8	8	8	8	8	8
MEAN	21.3	0.0	0.0	7.0	7.1	14.1	0.0	0.0	6.1	4.0	4.0	8.0
ST.DEV.	0.5	0.0	0.0	1.5	1.8	1.9	0.0	0.0	1.9	0.0	0.0	0.0

2.16 DEVELOPMENTAL DATA PER LITTER
FEMALES

F0-GENERATION - LACTATION

		FIRST LITTER CHECK					P.NATAL LOSS			LIVING PUPS		
LITTER	DURATION OF GESTATION	DEAD PUPS M	DEAD PUPS F	LIVING PUPS M	LIVING PUPS F	TOT.	DAYS 0 - 4 M	DAYS 0 - 4 F	CULLED PUPS TOT.	DAY 4 P.P. M	DAY 4 P.P. F	TOT.
GROUP 3 (300 MG/KG)												
61	22	0	0	4	9	13	0	0	5	4	4	8
62	22	0	0	6	7	13	0	0	5	4	4	8
64	21	0	0	7	6	13	0	0	5	4	4	8
65	22	1	0	6	6	12	0	0	4	4	4	8
66	22	0	0	7	4	11	0	0	3	4	4	8
67	22	0	0	8	6	14	0	0	6	4	4	8
68	21	0	0	6	4	10	0	0	2	4	4	8
69	21	0	0	3	10	13	0	0	5	3	5	8
70	22	0	0	5	4	9	0	0	1	4	4	8
TOTAL		1	0	52	56	108	0	0	36	35	37	72
N	9	9	9	9	9	9	9	9	9	9	9	9
MEAN	21.7	0.1	0.0	5.8	6.2	12.0	0.0	0.0	4.0	3.9	4.1	8.0
ST.DEV.	0.5	0.3	0.0	1.6	2.2	1.7	0.0	0.0	1.7	0.3	0.3	0.0

2.16 DEVELOPMENTAL DATA PER LITTER
FEMALES

F0-GENERATION - LACTATION

		FIRST LITTER CHECK					P.NATAL LOSS			LIVING PUPS		
LITTER	DURATION OF GESTATION	DEAD PUPS M	F	LIVING PUPS M	F	TOT.	DAYS 0 - 4 M	F	CULLED PUPS TOT.	DAY 4 P.P. M	F	TOT.
GROUP 4 (1000 MG/KG)												
71	21	0	0	7	4	11	0	0	3	4	4	8
73	21	0	0	5	9	14	0	0	6	4	4	8
74	21	0	0	7	6	13	0	0	5	4	4	8
75	21	0	0	6	7	13	0	0	5	4	4	8
76	21	0	0	4	6	10	0	0	2	4	4	8
77	21	0	0	8	7	15	0	0	7	4	4	8
78	21	0	0	7	9	16	0	0	8	4	4	8
79	21	0	0	4	8	12	0	0	4	4	4	8
80	21	0	0	8	4	12	0	0	4	4	4	8
TOTAL		0	0	56	60	116	0	0	44	36	36	72
N	9	9	9	9	9	9	9	9	9	9	9	9
MEAN	21.0	0.0	0.0	6.2	6.7	12.9	0.0	0.0	4.9	4.0	4.0	8.0
ST.DEV.	0.0	0.0	0.0	1.6	1.9	1.9	0.0	0.0	1.9	0.0	0.0	0.0

2.16 DEVELOPMENTAL DATA PER LITTER
FEMALES

F0-GENERATION - LACTATION

	BREEDING LOSS		LIVING PUPS		
LITTER	DAYS 5 - 13		DAY 13	P.P.	
	M	F	M	F	TOT.
GROUP 1 (CONTROL)					
41	0	0	3	5	8
43	0	0	5	3	8
44	0	0	4	4	8
45	0	0	3	3	6
47	0	0	4	4	8
48	0	1	4	3	7
49	0	0	4	4	8
50	0	0	4	4	8
TOTAL	0	1	31	30	61
N	8	8	8	8	8
MEAN	0.0	0.1	3.9	3.8	7.6
ST.DEV.	0.0	0.4	0.6	0.7	0.7

2.16 DEVELOPMENTAL DATA PER LITTER
FEMALES

F0-GENERATION - LACTATION

	BREEDING LOSS		LIVING PUPS		
LITTER	DAYS 5 - 13		DAY 13 P.P.		
	M	F	M	F	TOT.
GROUP 2 (100 MG/KG)					
52	0	0	4	4	8
54	0	0	4	4	8
55	0	0	4	4	8
56	0	0	4	4	8
57	0	0	4	4	8
58	0	0	4	4	8
59	0	0	4	4	8
60	0	0	4	4	8
TOTAL	0	0	32	32	64
N	8	8	8	8	8
MEAN	0.0	0.0	4.0	4.0	8.0
ST.DEV.	0.0	0.0	0.0	0.0	0.0

2.16 DEVELOPMENTAL DATA PER LITTER
FEMALES

F0-GENERATION - LACTATION

	BREEDING LOSS		LIVING PUPS		
LITTER	DAYS 5 - 13		DAY 13 P.P.		
	M	F	M	F	TOT.
GROUP 3 (300 MG/KG)					
61	0	0	3	4	7
62	0	0	4	4	8
64	0	0	4	4	8
65	0	0	4	4	8
66	0	0	4	4	8
67	0	0	4	4	8
68	0	0	4	4	8
69	0	0	3	5	8
70	0	0	4	4	8
TOTAL	0	0	34	37	71
N	9	9	9	9	9
MEAN	0.0	0.0	3.8	4.1	7.9
ST.DEV.	0.0	0.0	0.4	0.3	0.3

2.16 DEVELOPMENTAL DATA PER LITTER
FEMALES

F0-GENERATION - LACTATION

	BREEDING LOSS		LIVING PUPS		
LITTER	DAYS 5 - 13		DAY 13 P.P.		
	M	F	M	F	TOT.
GROUP 4 (1000 MG/KG)					
71	0	0	4	4	8
73	0	0	4	4	8
74	0	0	4	4	8
75	0	0	4	4	8
76	0	0	4	4	8
77	0	0	4	4	8
78	0	0	4	4	8
79	0	0	4	4	8
80	0	0	4	4	8
TOTAL	0	0	36	36	72
N	9	9	9	9	9
MEAN	0.0	0.0	4.0	4.0	8.0
ST.DEV.	0.0	0.0	0.0	0.0	0.0

2.17 BODY WEIGHTS OF PUPS PER LITTER (GRAM)

F0-GENERATION - LACTATION

LITTER	SEX	DAY 1	DAY 4	DAY 7	DAY 13
GROUP 1 (CONTROL)					
41	M	6.4	9.1	14.3	27.1
	F	6.1	8.7	14.0	26.7
	M+F	6.2	8.8	14.1	26.9
43	M	7.6	11.3	17.5	32.3
	F	7.7	11.4	18.2	33.0
	M+F	7.6	11.3	17.8	32.6
44	M	6.1	8.4	14.1	29.8
	F	5.6	8.0	13.0	27.7
	M+F	5.9	8.3	13.6	28.7
45	M	7.8	12.6	19.7	35.6
	F	7.2	11.5	18.4	34.1
	M+F	7.5	12.1	19.1	34.9
47	M	6.6	10.5	18.1	33.4
	F	6.6	10.2	17.4	32.2
	M+F	6.6	10.4	17.8	32.8
48	M	5.7	8.3	14.5	30.1
	F	5.4	8.0	14.5	29.7
	M+F	5.5	8.1	14.5	29.9
49	M	6.5	10.0	16.5	31.8
	F	6.4	9.5	15.9	31.2
	M+F	6.4	9.7	16.2	31.5
50	M	5.8	8.1	14.5	30.1
	F	6.1	8.3	15.2	30.9
	M+F	5.9	8.2	14.8	30.5
GROUP 2 (100 MG/KG)					
52	M	5.8	8.3	14.5	30.5
	F	5.6	8.0	14.0	29.3
	M+F	5.7	8.1	14.2	29.9
54	M	6.6	9.1	15.6	30.9
	F	5.9	8.6	14.8	29.3
	M+F	6.2	8.8	15.2	30.1
55	M	6.8	9.5	16.4	32.0
	F	6.5	8.9	15.3	30.0
	M+F	6.7	9.3	15.8	31.0
56	M	5.4	7.9	14.6	30.5
	F	5.2	7.6	13.7	28.6
	M+F	5.3	7.7	14.1	29.5
57	M	6.0	8.9	15.4	30.4
	F	5.9	8.9	15.6	30.7
	M+F	6.0	8.9	15.5	30.5
58	M	6.0	8.7	15.1	30.5
	F	5.5	8.3	14.6	29.6
	M+F	5.7	8.5	14.8	30.1
59	M	6.1	8.6	14.1	28.2
	F	6.3	8.9	14.7	28.5
	M+F	6.2	8.8	14.4	28.3

2.17 BODY WEIGHTS OF PUPS PER LITTER (GRAM)

F0-GENERATION - LACTATION

LITTER	SEX	DAY 1	DAY 4	DAY 7	DAY 13
GROUP 2 (100 MG/KG)					
60	M	6.0	8.9	16.1	32.9
	F	5.4	8.3	14.5	30.5
	M+F	5.7	8.6	15.3	31.7
GROUP 3 (300 MG/KG)					
61	M	7.2	10.9	19.2	35.4
	F	6.8	10.3	17.8	34.3
	M+F	6.9	10.5	18.5	34.8
62	M	7.2	10.6	18.1	33.1
	F	6.6	10.0	16.3	31.5
	M+F	6.9	10.3	17.2	32.3
64	M	6.0	8.8	15.9	30.7
	F	5.5	8.5	14.9	29.4
	M+F	5.8	8.7	15.4	30.1
65	M	6.8	11.5	19.4	36.8
	F	6.4	10.8	18.0	35.0
	M+F	6.6	11.1	18.7	35.9
66	M	7.3	11.1	18.1	33.6
	F	7.2	10.9	18.3	33.8
	M+F	7.3	11.0	18.2	33.7
67	M	6.9	10.4	17.4	33.7
	F	6.8	10.2	16.9	33.0
	M+F	6.8	10.3	17.2	33.3
68	M	5.9	8.4	14.1	27.0
	F	5.5	8.0	13.6	26.5
	M+F	5.7	8.2	13.8	26.8
69	M	5.8	8.9	15.3	31.3
	F	5.7	8.8	14.5	30.2
	M+F	5.7	8.8	14.8	30.6
70	M	7.5	11.4	18.2	33.1
	F	7.1	11.0	17.7	32.1
	M+F	7.3	11.2	17.9	32.6
GROUP 4 (1000 MG/KG)					
71	M	5.9	9.1	15.8	31.0
	F	5.6	8.8	15.8	30.7
	M+F	5.8	9.0	15.8	30.8
73	M	6.2	8.9	15.8	31.1
	F	5.6	8.2	14.7	29.7
	M+F	5.8	8.4	15.3	30.4
74	M	6.2	9.1	15.1	29.9
	F	5.9	8.7	14.8	29.5
	M+F	6.0	8.9	15.0	29.7
75	M	6.2	8.7	15.2	31.5
	F	6.1	8.7	14.8	30.6
	M+F	6.1	8.7	15.0	31.0

2.17 BODY WEIGHTS OF PUPS PER LITTER (GRAM)

F0-GENERATION - LACTATION

LITTER	SEX	DAY 1	DAY 4	DAY 7	DAY 13
GROUP 4 (1000 MG/KG)					
76	M	6.5	9.8	16.7	33.0
	F	6.0	9.1	15.2	31.1
	M+F	6.2	9.4	16.0	32.1
77	M	6.2	9.2	16.8	33.4
	F	5.7	8.4	15.2	30.8
	M+F	5.9	8.8	16.0	32.1
78	M	6.1	8.9	15.6	31.8
	F	5.3	8.0	13.3	28.6
	M+F	5.6	8.4	14.4	30.2
79	M	6.5	9.7	16.3	31.1
	F	6.6	9.9	16.8	31.8
	M+F	6.6	9.8	16.5	31.4
80	M	5.6	8.8	16.2	31.5
	F	5.7	8.6	15.3	31.0
	M+F	5.6	8.7	15.7	31.2

2.18 BODY WEIGHTS OF PUPS (GRAM)

F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4	DAY 7	DAY 13
GROUP 1 (CONTROL)						
41	1	M	6.4	9.1	14.0	26.9
	2	M	6.5	9.2	14.7	27.1
	3	M	6.4	8.9	14.1	27.3
	4	F	6.1	8.8	14.1	26.7
	5	F	6.4	8.8	13.7	26.9
	6	F	6.1	8.8	14.1	26.7
	7	F	5.9	8.7	14.5	27.3
	8	F	5.8	8.2	13.6	26.0
	9	F	6.2	8.9	--	--
	10	F	6.0	8.8	--	--
43	1	M	5.9	8.1	11.7	22.6
	2	M	8.2	12.7	19.9	35.6
	3	M	7.6	11.5	18.3	34.4
	4	M	8.1	12.3	19.0	34.2
	5	M	8.0	11.9	18.7	34.7
	6	F	7.9	11.1	17.5	32.1
	7	F	7.8	11.8	19.0	34.0
	8	F	7.4	11.3	18.0	32.9
44	1	M	6.2	8.4	13.9	29.7
	2	M	6.4	9.0	14.5	29.9
	3	M	6.5	8.9	15.0	31.6
	4	M	5.6	7.8	13.1	28.0
	5	M	5.9	7.9	--	--
	6	M	6.2	8.6	--	--
	7	M	5.5	7.4	--	--
	8	M	6.4	9.3	--	--
	9	M	6.0	8.5	--	--
	10	F	6.2	8.8	14.6	30.2
	11	F	4.8	7.3	12.6	27.2
	12	F	5.3	8.0	13.4	28.1
	13	F	5.1	7.1	11.5	25.1
	14	F	6.3	9.0	--	--
	15	F	5.6	7.9	--	--
45	1	M	7.7	12.3	19.4	35.8
	2	M	8.0	12.9	20.1	35.9
	3	M	7.6	12.7	19.7	35.2
	4	F	7.4	11.8	18.6	34.8
	5	F	7.3	11.7	18.8	34.4
	6	F	6.9	11.1	17.9	33.0
47	1	M	7.0	11.1	19.3	35.0
	2	M	6.4	9.8	17.4	31.9
	3	M	6.6	11.1	18.1	33.5
	4	M	6.9	10.6	17.7	33.0
	5	M	6.2	10.1	--	--
	6	F	6.6	10.8	18.3	32.8
	7	F	6.9	10.8	17.8	32.7
	8	F	6.3	8.5	15.6	30.2
	9	F	6.5	10.7	18.0	32.9
48	1	M	6.1	9.1	15.5	31.6
	2	M	5.8	8.4	14.5	30.4
	3	M	5.3	7.5	13.5	28.3
	4	M	5.5	8.4	14.3	30.1
	5	M	5.8	8.3	--	--
	6	F	5.9	8.6	14.8	30.3
	7	F	5.8	8.8	14.6	29.5
	8	F	5.6	8.4	--	--
	9	F	5.6	7.9	14.1	29.3

2.18 BODY WEIGHTS OF PUPS (GRAM)

F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4	DAY 7	DAY 13
GROUP 1 (CONTROL)						
	10	F	5.5	7.9	--	--
	11	F	5.4	7.9	--	--
	12	F	5.4	--	--	--
	13	F	5.4	7.9	--	--
	14	F	4.4	6.3	--	--
49	1	M	6.8	9.9	16.8	31.6
	2	M	6.6	10.3	17.0	32.8
	3	M	6.3	10.0	16.1	32.0
	4	M	6.3	9.6	16.2	30.9
	5	M	6.7	10.3	--	--
	6	F	6.4	10.0	16.8	32.2
	7	F	6.3	9.2	15.8	31.3
	8	F	6.2	9.4	16.0	31.4
	9	F	6.3	8.9	14.9	29.9
	10	F	6.6	9.6	--	--
	11	F	6.1	9.2	--	--
	12	F	6.4	9.5	--	--
	13	F	6.7	9.9	--	--
50	1	M	4.9	6.6	11.5	26.2
	2	M	6.3	9.0	15.7	31.8
	3	M	6.4	9.0	16.2	32.6
	4	M	5.9	8.2	14.4	29.8
	5	M	5.5	7.2	--	--
	6	M	6.3	8.5	--	--
	7	M	6.4	8.9	--	--
	8	M	5.1	7.1	--	--
	9	M	5.8	8.1	--	--
	10	F	6.3	8.7	15.9	31.8
	11	F	5.9	7.9	14.7	30.2
	12	F	6.0	8.5	15.4	31.5
	13	F	5.9	8.1	14.8	30.2
	14	F	6.3	8.5	--	--
GROUP 2 (100 MG/KG)						
52	1	M	6.2	8.8	15.6	31.8
	2	M	5.4	7.9	13.8	29.8
	3	M	5.9	8.2	14.2	29.9
	4	M	5.9	8.3	14.4	30.6
	5	M	5.8	8.3	--	--
	6	F	5.8	8.2	14.0	30.0
	7	F	5.1	7.0	12.2	26.3
	8	F	5.6	8.2	14.5	30.2
	9	F	6.0	8.4	15.1	30.6
	10	F	5.7	8.0	--	--
	11	F	5.2	7.3	--	--
	12	F	5.3	8.3	--	--
	13	F	5.6	8.4	--	--
	14	F	5.8	8.2	--	--
54	1	M	6.6	9.3	15.8	31.4
	2	M	6.4	8.6	15.3	31.0
	3	M	6.7	9.1	15.3	29.9
	4	M	6.8	9.5	15.8	31.3
	5	M	6.4	9.0	--	--
	6	M	6.5	9.0	--	--
	7	F	5.7	8.0	14.0	28.3
	8	F	6.3	8.8	15.0	29.7
	9	F	6.2	8.8	15.3	29.5
	10	F	5.9	9.0	14.8	29.7

2.18 BODY WEIGHTS OF PUPS (GRAM)

F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4	DAY 7	DAY 13
GROUP 2 (100 MG/KG)						
	11	F	5.5	8.1	--	--
	12	F	5.9	8.7	--	--
	13	F	6.1	8.7	--	--
55	1	M	7.0	9.7	17.0	33.2
	2	M	7.0	9.6	16.7	32.0
	3	M	6.6	9.2	16.2	31.9
	4	M	6.7	9.1	15.7	30.7
	5	M	7.1	9.5	--	--
	6	M	6.3	9.3	--	--
	7	M	6.9	9.7	--	--
	8	M	7.1	9.7	--	--
	9	M	6.9	9.7	--	--
	10	F	6.7	9.1	15.3	30.1
	11	F	6.7	9.3	15.9	31.0
	12	F	6.9	9.5	16.2	31.0
	13	F	5.5	7.5	13.6	27.9
56	1	M	5.5	7.7	14.1	30.2
	2	M	5.8	8.5	15.0	31.8
	3	M	5.5	8.4	14.9	31.0
	4	M	5.4	7.7	14.2	28.8
	5	M	5.3	7.9	--	--
	6	M	4.9	7.0	--	--
	7	M	5.3	7.5	--	--
	8	M	5.8	8.5	--	--
	9	F	5.5	8.2	13.8	29.3
	10	F	4.9	7.3	12.9	28.2
	11	F	4.8	6.5	12.2	26.5
	12	F	5.9	8.6	15.7	30.3
	13	F	4.9	7.1	--	--
	14	F	5.4	7.8	--	--
	15	F	5.6	7.8	--	--
	16	M	5.4	8.0	--	--
	17	F	4.7	7.1	--	--
57	1	M	6.1	9.0	15.0	30.0
	2	M	6.2	9.0	15.7	31.1
	3	M	5.9	8.7	15.2	30.7
	4	M	6.0	9.0	15.7	29.8
	5	M	6.1	9.1	--	--
	6	M	5.8	8.4	--	--
	7	F	5.9	8.8	15.5	30.4
	8	F	5.8	8.9	15.1	30.1
	9	F	5.9	9.2	16.0	31.3
	10	F	5.9	8.8	15.6	30.8
	11	F	5.9	8.8	--	--
58	1	M	5.8	7.9	14.0	28.8
	2	M	5.8	8.9	15.4	31.1
	3	M	6.1	9.1	15.3	30.4
	4	M	6.3	9.5	15.7	31.8
	5	M	6.4	8.8	--	--
	6	M	5.6	8.1	--	--
	7	F	6.0	8.6	15.7	30.4
	8	F	5.5	8.1	14.5	29.6
	9	F	5.5	8.3	14.5	29.8
	10	F	4.9	7.5	13.6	28.7
	11	F	5.6	8.1	--	--
	12	F	5.7	8.0	--	--
	13	F	5.3	8.3	--	--
	14	F	5.5	9.1	--	--

2.18 BODY WEIGHTS OF PUPS (GRAM)

F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4	DAY 7	DAY 13
GROUP 2 (100 MG/KG)						
59	1	M	5.9	7.8	13.4	26.5
	2	M	5.9	8.6	14.8	29.2
	3	M	5.6	7.8	13.1	28.1
	4	M	6.2	8.9	14.9	29.0
	5	M	6.1	8.7	--	--
	6	M	6.5	9.0	--	--
	7	M	6.5	9.7	--	--
	8	F	6.7	9.4	15.0	29.5
	9	F	6.7	9.3	16.3	29.7
	10	F	5.9	8.6	13.8	27.3
	11	F	6.4	8.5	13.7	27.3
	12	F	6.1	8.3	--	--
	13	F	6.4	9.5	--	--
	14	F	6.7	9.4	--	--
	15	F	7.0	9.9	--	--
	16	F	5.1	7.1	--	--
60	1	M	5.9	9.5	16.4	33.3
	2	M	6.0	9.0	16.1	33.0
	3	M	6.0	9.0	15.9	32.8
	4	M	6.0	9.0	15.8	32.3
	5	M	5.3	7.1	--	--
	6	M	6.2	9.1	--	--
	7	M	6.3	9.5	--	--
	8	M	6.3	9.3	--	--
	9	F	6.3	9.2	16.1	33.8
	10	F	5.5	8.4	15.1	30.6
	11	F	5.0	7.4	13.3	28.8
	12	F	4.6	7.7	13.5	28.9
	13	F	5.6	8.4	--	--
	14	F	5.6	8.4	--	--
	15	F	5.3	8.3	--	--
GROUP 3 (300 MG/KG)						
61	1	M	7.6	11.4	19.9	35.6
	2	M	7.0	10.5	18.4	34.7
	3	M	6.5	10.4	18.7	35.0
	4	M	7.5	11.4	19.7	36.2
	5	F	7.1	10.6	18.3	34.8
	6	F	6.4	9.9	17.4	33.3
	7	F	7.0	10.6	18.1	34.5
	8	F	6.5	9.8	17.5	34.4
	9	F	6.6	10.4	--	--
	10	F	7.4	10.8	--	--
	11	F	6.7	10.3	--	--
	12	F	6.3	9.6	--	--
	13	F	7.0	10.7	--	--
62	1	M	7.4	11.0	18.4	33.3
	2	M	7.3	11.1	18.5	34.2
	3	M	7.5	10.6	18.0	33.6
	4	M	7.3	10.4	17.3	31.3
	5	M	6.7	10.3	--	--
	6	M	7.1	10.3	--	--
	7	F	5.4	8.6	14.5	29.2
	8	F	6.9	10.2	17.1	32.4
	9	F	6.8	10.5	17.5	33.4
	10	F	6.6	9.4	16.1	30.9
	11	F	6.8	10.2	--	--
	12	F	6.8	10.2	--	--

2.18 BODY WEIGHTS OF PUPS (GRAM)

F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4	DAY 7	DAY 13
GROUP 3 (300 MG/KG)						
	13	F	7.2	10.7	--	--
64	1	M	6.1	8.7	16.1	30.7
	2	M	5.4	8.0	14.9	29.9
	3	M	5.9	8.9	16.0	30.9
	4	M	6.1	9.2	16.4	31.4
	5	M	5.9	8.7	--	--
	6	M	5.9	8.6	--	--
	7	M	6.7	9.7	--	--
	8	F	5.4	8.1	14.5	29.0
	9	F	5.7	8.9	15.6	30.4
	10	F	5.7	8.8	15.4	29.8
	11	F	5.2	7.9	14.1	28.3
	12	F	5.8	8.7	--	--
	13	F	5.4	8.4	--	--
65	1	M	6.6	11.6	19.4	36.9
	2	M	6.8	11.2	18.6	35.2
	3	M	6.7	11.8	19.0	36.4
	4	M	7.7	12.1	20.5	38.7
	5	M	--	--	--	--
	6	M	7.2	12.8	--	--
	7	M	5.7	9.6	--	--
	8	F	6.4	11.2	18.1	35.0
	9	F	6.1	10.7	17.9	34.9
	10	F	7.1	11.6	19.3	36.5
	11	F	5.9	9.9	16.6	33.6
	12	F	6.8	11.0	--	--
	13	F	6.3	10.2	--	--
66	1	M	7.0	10.8	17.5	32.9
	2	M	7.4	11.2	18.4	34.1
	3	M	7.6	11.2	18.8	33.2
	4	M	6.6	10.3	17.7	34.0
	5	M	7.8	11.4	--	--
	6	M	7.5	11.3	--	--
	7	M	7.4	11.3	--	--
	8	F	7.0	10.6	17.9	33.2
	9	F	7.5	11.4	18.8	33.8
	10	F	6.9	10.8	18.2	34.0
	11	F	7.2	10.8	18.3	34.2
67	1	M	7.0	10.3	17.4	33.8
	2	M	7.1	10.8	18.1	34.6
	3	M	6.6	9.8	16.5	32.6
	4	M	6.8	10.3	17.7	33.7
	5	M	6.6	10.3	--	--
	6	F	6.9	10.5	16.9	32.9
	7	M	6.5	10.1	--	--
	8	M	7.2	10.8	--	--
	9	M	7.1	10.4	--	--
	10	F	6.7	10.5	16.7	32.5
	11	F	6.8	10.3	17.2	33.3
	12	F	6.3	10.0	16.8	33.1
	13	F	6.9	9.9	--	--
	14	F	6.9	10.0	--	--
68	1	M	5.9	9.0	15.6	27.8
	2	M	5.9	8.2	13.4	26.6
	3	M	5.5	7.8	12.9	25.7
	4	M	5.9	8.6	14.5	27.8
	5	M	5.7	8.0	--	--

2.18 BODY WEIGHTS OF PUPS (GRAM)

F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4	DAY 7	DAY 13
GROUP 3 (300 MG/KG)						
	6	M	6.2	8.7	--	--
	7	F	5.8	7.9	13.7	26.9
	8	F	6.0	9.3	15.1	28.4
	9	F	5.4	8.2	14.0	26.9
	10	F	4.9	6.7	11.4	23.9
69	1	M	5.9	8.8	14.9	30.8
	2	M	5.6	8.7	15.2	30.9
	3	M	6.0	9.2	15.9	32.1
	4	F	5.4	8.7	14.4	30.2
	5	F	5.5	7.9	13.9	29.2
	6	F	5.8	9.0	13.9	31.1
	7	F	5.6	8.6	15.5	30.0
	8	F	5.4	8.7	14.8	30.3
	9	F	6.0	9.3	--	--
	10	F	6.0	9.1	--	--
	11	F	6.1	9.1	--	--
	12	F	5.3	8.2	--	--
	13	F	6.0	9.1	--	--
70	1	M	7.3	11.0	17.7	33.2
	2	M	7.4	11.5	18.7	33.4
	3	M	7.3	11.0	17.6	32.4
	4	M	7.5	11.5	18.7	33.4
	5	M	8.0	12.2	--	--
	6	F	7.2	11.4	18.2	32.5
	7	F	7.4	11.2	18.0	33.0
	8	F	6.8	10.8	17.2	31.6
	9	F	7.1	10.6	17.3	31.4
GROUP 4 (1000 MG/KG)						
71	1	M	6.1	9.3	16.4	31.7
	2	M	6.5	9.6	16.6	32.5
	3	M	5.6	8.8	16.0	30.7
	4	M	5.6	8.2	14.1	28.9
	5	M	5.9	9.6	--	--
	6	M	5.8	9.0	--	--
	7	M	5.8	8.9	--	--
	8	F	5.8	9.1	16.3	31.5
	9	F	5.2	8.4	15.4	30.5
	10	F	5.5	8.6	15.7	30.4
	11	F	6.0	9.1	15.8	30.5
73	1	M	6.0	8.4	14.7	29.2
	2	M	6.9	9.4	17.2	32.9
	3	M	5.7	8.1	14.7	30.7
	4	M	6.1	9.4	16.7	31.6
	5	M	6.1	9.1	--	--
	6	F	5.4	8.4	15.2	30.4
	7	F	6.0	8.7	15.8	31.7
	8	F	5.7	7.9	14.4	29.3
	9	F	5.3	7.6	13.5	27.5
	10	F	5.5	8.4	--	--
	11	F	5.5	8.2	--	--
	12	F	5.4	7.8	--	--
	13	F	5.6	8.3	--	--
	14	F	5.7	8.1	--	--
74	1	M	6.1	9.0	15.0	28.9
	2	M	5.6	8.5	14.5	29.2
	3	M	6.1	9.2	15.5	30.7

2.18 BODY WEIGHTS OF PUPS (GRAM)

F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4	DAY 7	DAY 13
GROUP 4 (1000 MG/KG)						
	4	M	6.5	9.3	15.4	30.6
	5	M	6.7	9.9	--	--
	6	F	5.6	8.8	14.3	29.3
	7	M	6.3	9.4	--	--
	8	M	5.8	8.6	--	--
	9	F	6.1	8.6	14.9	29.1
	10	F	6.2	9.3	15.4	30.3
	11	F	5.9	8.6	14.7	29.2
	12	F	5.8	8.5	--	--
	13	F	5.5	8.6	--	--
75	1	M	6.5	9.1	15.1	31.0
	2	M	6.1	8.6	14.6	30.6
	3	M	6.4	8.9	14.8	31.3
	4	M	6.7	9.5	16.1	33.1
	5	M	5.8	8.4	--	--
	6	M	5.5	7.6	--	--
	7	F	5.4	7.8	13.5	28.5
	8	F	6.4	9.2	15.6	31.8
	9	F	6.3	9.2	15.5	31.9
	10	F	6.0	8.4	14.5	30.1
	11	F	5.8	7.9	--	--
	12	F	6.1	9.3	--	--
	13	F	6.6	9.1	--	--
76	1	M	6.7	10.0	17.4	34.3
	2	M	6.6	10.1	16.6	33.1
	3	M	7.0	10.3	17.6	34.0
	4	M	5.8	8.8	15.2	30.7
	5	F	6.3	9.7	16.1	32.1
	6	F	6.0	8.5	14.7	31.0
	7	F	6.5	9.9	17.1	33.4
	8	F	4.9	7.4	13.0	27.9
	9	F	6.7	10.0	--	--
	10	F	5.6	8.9	--	--
77	1	M	6.5	10.2	18.1	35.3
	2	M	6.1	9.7	17.4	34.6
	3	M	5.8	8.8	15.7	31.5
	4	M	6.1	8.4	15.8	32.3
	5	M	6.3	9.3	--	--
	6	M	5.6	7.7	--	--
	7	M	6.3	9.5	--	--
	8	M	6.5	9.7	--	--
	9	F	5.6	8.4	15.2	30.4
	10	F	5.7	8.3	14.8	30.3
	11	F	5.9	8.7	16.2	32.0
	12	F	5.1	7.9	14.7	30.4
	13	F	6.2	8.5	--	--
	14	F	6.2	9.2	--	--
	15	F	5.2	7.5	--	--
78	1	M	6.2	9.2	15.4	32.8
	2	M	6.1	8.3	14.5	30.6
	3	M	6.4	9.3	15.3	31.2
	4	M	6.4	9.6	17.0	32.4
	5	M	6.2	9.1	--	--
	6	M	6.3	9.2	--	--
	7	M	4.9	7.6	--	--
	8	F	4.0	5.4	9.4	23.1
	9	F	5.5	8.2	14.7	30.6
	10	F	5.5	8.4	14.3	30.1

2.18 BODY WEIGHTS OF PUPS (GRAM)

F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4	DAY 7	DAY 13
GROUP 4 (1000 MG/KG)						
	11	F	5.5	8.5	14.8	30.6
	12	F	5.8	9.1	--	--
	13	F	4.8	7.5	--	--
	14	F	5.7	8.7	--	--
	15	F	5.1	7.9	--	--
	16	F	5.6	8.4	--	--
79	1	M	6.4	9.7	16.8	31.8
	2	M	7.3	10.6	17.6	32.5
	3	M	5.4	8.5	14.2	28.6
	4	M	6.9	10.0	16.4	31.4
	5	F	7.1	10.3	17.2	32.4
	6	F	6.3	9.2	15.8	30.0
	7	F	6.5	9.9	16.9	32.1
	8	F	6.8	10.2	17.4	32.7
	9	F	6.7	10.3	--	--
	10	F	6.3	9.6	--	--
	11	F	6.5	9.0	--	--
	12	F	6.9	10.4	--	--
80	1	M	5.8	9.2	16.4	31.7
	2	M	5.7	8.9	15.7	30.9
	3	M	5.6	8.9	16.2	31.0
	4	M	6.0	9.3	16.3	32.3
	5	M	5.3	8.2	--	--
	6	M	5.8	9.3	--	--
	7	M	4.7	7.5	--	--
	8	M	5.7	8.8	--	--
	9	F	6.1	9.1	15.9	32.1
	10	F	5.3	8.2	14.7	30.7
	11	F	5.3	8.1	14.5	29.3
	12	F	6.0	9.0	16.1	31.8

2.19 ANOGENITAL DISTANCE AND NIPPLE RETENTION PER LITTER
FEMALES

F0-GENERATION - LACTATION

LITTER	anogenital dist M mm	anogenital dist F mm	Number of nipples
GROUP 1 (CONTROL)			
41	2.51	1.00	0.00
42	--	--	--
43	2.64	0.94	0.00
44	2.48	0.91	0.00
45	2.74	0.92	0.00
46 <NP>	--	--	--
47	2.68	0.78	0.00
48	2.62	0.96	0.00
49	2.72	1.01	0.00
50	2.47	1.06	0.00
MEAN	2.61	0.95	0.00
N	8	8	8
GROUP 2 (100 MG/KG)			
51 <NP>	--	--	--
52	2.52	1.01	0.00
53 <NP>	--	--	--
54	2.70	0.80	0.00
55	2.66	1.49	0.00
56	2.48	0.99	0.00
57	2.59	1.01	0.00
58	2.63	0.89	0.00
59	2.63	1.07	0.00
60	2.47	1.02	0.00
MEAN	2.59	1.04	0.00
N	8	8	8
GROUP 3 (300 MG/KG)			
61	2.86	1.36	0.00
62	2.88	1.02	0.00
63 <NP>	--	--	--
64	2.65	0.93	0.00
65	2.45	0.91	0.00
66	2.63	0.91	0.00
67	2.67	0.94	0.00
68	2.63	1.03	0.00
69	2.50	0.93	0.00
70	2.67	0.94	0.00
MEAN	2.66	1.00	0.00
N	9	9	9
GROUP 4 (1000 MG/KG)			
71	2.71	0.78	0.00
72 <NP>	--	--	--
73	2.56	1.32	0.00
74	2.55	1.03	0.00
75	2.65	1.05	0.00
76	2.67	0.99	--
77	2.81	0.85	0.00
78	2.66	0.91	0.00
79	2.68	1.27	0.00
80	2.60	0.90	0.00
MEAN	2.65	1.01	0.00
N	9	9	8

<NP> Non-pregnant

2.20 ANOGENITAL DISTANCE AND NIPPLE RETENTION

F0-GENERATION - LACTATION

LITTER	PUP	SEX	anogenital dist M mm	anogenital dist F mm	Number of nipples
GROUP 1 (CONTROL)					
41	1	M	2.52	--	0.00
	2	M	2.45	--	0.00
	3	M	2.57	--	0.00
	4	F	--	1.02	--
	5	F	--	0.90	--
	6	F	--	0.96	--
	7	F	--	0.95	--
	8	F	--	1.12	--
	9	F	--	0.99	--
	10	F	--	1.08	--
43	1	M	2.53	--	0.00
	2	M	2.83	--	0.00
	3	M	2.73	--	0.00
	4	M	2.52	--	0.00
	5	M	2.59	--	0.00
	6	F	--	0.81	--
	7	F	--	1.05	--
	8	F	--	0.96	--
44	1	M	2.43	--	0.00
	2	M	2.92	--	0.00
	3	M	2.47	--	0.00
	4	M	2.25	--	0.00
	5	M	2.60	--	--
	6	M	2.54	--	--
	7	M	2.30	--	--
	8	M	2.57	--	--
	9	M	2.23	--	--
	10	F	--	0.90	--
	11	F	--	0.80	--
	12	F	--	0.87	--
	13	F	--	1.00	--
	14	F	--	1.00	--
	15	F	--	0.89	--
45	1	M	2.84	--	0.00
	2	M	2.53	--	0.00
	3	M	2.85	--	0.00
	4	F	--	0.98	--
	5	F	--	1.00	--
	6	F	--	0.77	--
47	1	M	2.80	--	0.00
	2	M	2.60	--	0.00
	3	M	2.65	--	0.00
	4	M	2.61	--	0.00
	5	M	2.73	--	--
	6	F	--	0.84	--
	7	F	--	0.72	--
	8	F	--	0.77	--
	9	F	--	0.78	--
48	1	M	2.53	--	0.00
	2	M	2.57	--	0.00
	3	M	2.61	--	0.00
	4	M	2.76	--	0.00
	5	M	2.62	--	--
	6	F	--	0.96	--
	7	F	--	0.94	--
	8	F	--	1.11	--
	9	F	--	0.92	--
	10	F	--	0.98	--

2.20 ANOGENITAL DISTANCE AND NIPPLE RETENTION

F0-GENERATION - LACTATION

LITTER	PUP	SEX	anogenital dist M mm	anogenital dist F mm	Number of nipples
GROUP 1 (CONTROL)					
	11	F	--	1.03	--
	12	F	--	1.00	--
	13	F	--	0.76	--
	14	F	--	0.93	--
49	1	M	2.77	--	0.00
	2	M	2.75	--	0.00
	3	M	2.79	--	0.00
	4	M	2.67	--	0.00
	5	M	2.63	--	--
	6	F	--	1.07	--
	7	F	--	0.95	--
	8	F	--	1.05	--
	9	F	--	0.98	--
	10	F	--	1.13	--
	11	F	--	1.10	--
	12	F	--	0.88	--
	13	F	--	0.93	--
50	1	M	2.60	--	0.00
	2	M	2.66	--	0.00
	3	M	2.47	--	0.00
	4	M	2.69	--	0.00
	5	M	2.29	--	--
	6	M	2.34	--	--
	7	M	2.35	--	--
	8	M	2.40	--	--
	9	M	2.42	--	--
	10	F	--	0.82	--
	11	F	--	1.34	--
	12	F	--	1.01	--
	13	F	--	1.06	--
	14	F	--	1.09	--
GROUP 2 (100 MG/KG)					
52	1	M	2.63	--	0.00
	2	M	2.35	--	0.00
	3	M	2.36	--	0.00
	4	M	2.70	--	0.00
	5	M	2.56	--	--
	6	F	--	1.19	--
	7	F	--	0.88	--
	8	F	--	1.21	--
	9	F	--	1.07	--
	10	F	--	1.05	--
	11	F	--	1.06	--
	12	F	--	0.98	--
	13	F	--	0.87	--
	14	F	--	0.75	--
54	1	M	2.67	--	0.00
	2	M	2.65	--	0.00
	3	M	2.73	--	0.00
	4	M	2.76	--	0.00
	5	M	2.74	--	--
	6	M	2.67	--	--
	7	F	--	0.82	--
	8	F	--	0.90	--
	9	F	--	0.86	--
	10	F	--	0.71	--
	11	F	--	0.77	--
	12	F	--	0.69	--

2.20 ANOGENITAL DISTANCE AND NIPPLE RETENTION

F0-GENERATION - LACTATION

LITTER	PUP	SEX	anogenital dist M mm	anogenital dist F mm	Number of nipples
GROUP 2 (100 MG/KG)					
	13	F	--	0.84	--
55	1	M	2.79	--	0.00
	2	M	3.29	--	0.00
	3	M	2.48	--	0.00
	4	M	2.66	--	0.00
	5	M	2.81	--	--
	6	M	2.46	--	--
	7	M	2.85	--	--
	8	M	2.45	--	--
	9	M	2.19	--	--
	10	F	--	1.51	--
	11	F	--	1.78	--
	12	F	--	1.50	--
	13	F	--	1.17	--
56	1	M	2.60	--	0.00
	2	M	2.59	--	0.00
	3	M	2.33	--	0.00
	4	M	2.58	--	0.00
	5	M	2.50	--	--
	6	M	2.47	--	--
	7	M	2.44	--	--
	8	M	2.45	--	--
	9	F	--	1.01	--
	10	F	--	0.98	--
	11	F	--	0.85	--
	12	F	--	0.87	--
	13	F	--	0.92	--
	14	F	--	0.92	--
	15	F	--	1.12	--
	16	M	2.40	--	--
	17	F	--	1.26	--
57	1	M	2.50	--	0.00
	2	M	2.67	--	0.00
	3	M	2.53	--	0.00
	4	M	2.55	--	0.00
	5	M	2.65	--	--
	6	M	2.64	--	--
	7	F	--	1.18	--
	8	F	--	1.04	--
	9	F	--	0.79	--
	10	F	--	1.08	--
	11	F	--	0.96	--
58	1	M	2.65	--	0.00
	2	M	2.55	--	0.00
	3	M	2.69	--	0.00
	4	M	2.62	--	0.00
	5	M	2.63	--	--
	6	M	2.65	--	--
	7	F	--	0.95	--
	8	F	--	0.89	--
	9	F	--	0.90	--
	10	F	--	0.86	--
	11	F	--	0.83	--
	12	F	--	0.91	--
	13	F	--	0.83	--
	14	F	--	0.93	--
59	1	M	2.46	--	0.00
	2	M	2.58	--	0.00

2.20 ANOGENITAL DISTANCE AND NIPPLE RETENTION

F0-GENERATION - LACTATION

LITTER	PUP	SEX	anogenital dist M mm	anogenital dist F mm	Number of nipples
GROUP 2 (100 MG/KG)					
	3	M	2.67	--	0.00
	4	M	2.67	--	0.00
	5	M	2.69	--	--
	6	M	2.57	--	--
	7	M	2.79	--	--
	8	F	--	1.23	--
	9	F	--	1.14	--
	10	F	--	1.14	--
	11	F	--	1.07	--
	12	F	--	1.06	--
	13	F	--	0.98	--
	14	F	--	1.07	--
	15	F	--	0.99	--
	16	F	--	0.98	--
60	1	M	2.42	--	0.00
	2	M	2.63	--	0.00
	3	M	2.68	--	0.00
	4	M	2.44	--	0.00
	5	M	2.23	--	--
	6	M	2.35	--	--
	7	M	2.50	--	--
	8	M	2.48	--	--
	9	F	--	0.97	--
	10	F	--	1.05	--
	11	F	--	0.97	--
	12	F	--	0.98	--
	13	F	--	1.08	--
	14	F	--	1.11	--
	15	F	--	1.00	--
GROUP 3 (300 MG/KG)					
61	1	M	3.21	--	0.00
	2	M	2.91	--	0.00
	3	M	2.62	--	0.00
	4	M	2.71	--	0.00
	5	F	--	1.26	--
	6	F	--	1.73	--
	7	F	--	1.39	--
	8	F	--	1.11	--
	9	F	--	1.49	--
	10	F	--	1.06	--
	11	F	--	1.18	--
	12	F	--	1.72	--
	13	F	--	1.27	--
62	1	M	2.91	--	0.00
	2	M	2.80	--	0.00
	3	M	2.95	--	0.00
	4	M	2.83	--	0.00
	5	M	2.99	--	--
	6	M	2.78	--	--
	7	F	--	1.12	--
	8	F	--	1.05	--
	9	F	--	1.05	--
	10	F	--	1.09	--
	11	F	--	0.91	--
	12	F	--	0.93	--
	13	F	--	0.99	--
64	1	M	2.64	--	0.00
	2	M	2.53	--	0.00

2.20 ANOGENITAL DISTANCE AND NIPPLE RETENTION

F0-GENERATION - LACTATION

LITTER	PUP	SEX	anogenital dist M mm	anogenital dist F mm	Number of nipples
GROUP 3 (300 MG/KG)					
	3	M	2.70	--	0.00
	4	M	2.64	--	0.00
	5	M	2.71	--	--
	6	M	2.68	--	--
	7	M	2.66	--	--
	8	F	--	1.00	--
	9	F	--	0.82	--
	10	F	--	0.96	--
	11	F	--	0.94	--
	12	F	--	0.89	--
	13	F	--	0.98	--
65	1	M	2.54	--	0.00
	2	M	2.36	--	0.00
	3	M	2.47	--	0.00
	4	M	2.43	--	0.00
	5	M	--	--	--
	6	M	2.30	--	--
	7	M	2.60	--	--
	8	F	--	0.98	--
	9	F	--	0.81	--
	10	F	--	1.00	--
	11	F	--	0.77	--
	12	F	--	1.01	--
	13	F	--	0.87	--
66	1	M	2.70	--	0.00
	2	M	2.68	--	0.00
	3	M	2.69	--	0.00
	4	M	2.54	--	0.00
	5	M	2.57	--	--
	6	M	2.57	--	--
	7	M	2.69	--	--
	8	F	--	0.84	--
	9	F	--	1.02	--
	10	F	--	0.88	--
	11	F	--	0.89	--
67	1	M	2.62	--	0.00
	2	M	2.50	--	0.00
	3	M	2.49	--	0.00
	4	M	2.84	--	0.00
	5	M	2.90	--	--
	6	F	--	1.01	--
	7	M	2.51	--	--
	8	M	2.85	--	--
	9	M	2.63	--	--
	10	F	--	0.86	--
	11	F	--	1.01	--
	12	F	--	0.99	--
	13	F	--	0.96	--
	14	F	--	0.82	--
68	1	M	2.45	--	0.00
	2	M	2.56	--	0.00
	3	M	2.76	--	0.00
	4	M	2.68	--	0.00
	5	M	2.51	--	--
	6	M	2.79	--	--
	7	F	--	1.06	--
	8	F	--	1.10	--
	9	F	--	1.00	--
	10	F	--	0.96	--

2.20 ANOGENITAL DISTANCE AND NIPPLE RETENTION

F0-GENERATION - LACTATION

LITTER	PUP	SEX	anogenital dist M mm	anogenital dist F mm	Number of nipples
GROUP 3 (300 MG/KG)					
69	1	M	2.53	--	0.00
	2	M	2.51	--	0.00
	3	M	2.45	--	0.00
	4	F	--	0.74	--
	5	F	--	0.98	--
	6	F	--	1.01	--
	7	F	--	1.11	--
	8	F	--	0.99	--
	9	F	--	0.89	--
	10	F	--	1.00	--
	11	F	--	0.98	--
	12	F	--	0.80	--
	13	F	--	0.78	--
70	1	M	2.63	--	0.00
	2	M	2.78	--	0.00
	3	M	2.54	--	0.00
	4	M	2.73	--	0.00
	5	M	2.68	--	--
	6	F	--	0.82	--
	7	F	--	1.01	--
	8	F	--	0.98	--
	9	F	--	0.93	--
GROUP 4 (1000 MG/KG)					
71	1	M	2.67	--	0.00
	2	M	2.80	--	0.00
	3	M	2.72	--	0.00
	4	M	2.66	--	0.00
	5	M	2.73	--	--
	6	M	2.74	--	--
	7	M	2.63	--	--
	8	F	--	0.84	--
	9	F	--	0.63	--
	10	F	--	0.85	--
	11	F	--	0.81	--
73	1	M	2.87	--	0.00
	2	M	1.92	--	0.00
	3	M	2.67	--	0.00
	4	M	2.61	--	0.00
	5	M	2.73	--	--
	6	F	--	1.41	--
	7	F	--	1.39	--
	8	F	--	1.16	--
	9	F	--	1.06	--
	10	F	--	1.22	--
	11	F	--	1.34	--
	12	F	--	1.33	--
	13	F	--	1.66	--
	14	F	--	1.30	--
74	1	M	2.67	--	0.00
	2	M	2.37	--	0.00
	3	M	2.48	--	0.00
	4	M	2.70	--	0.00
	5	M	2.60	--	--
	6	F	--	1.15	--
	7	M	2.51	--	--
	8	M	2.52	--	--
	9	F	--	1.15	--

2.20 ANOGENITAL DISTANCE AND NIPPLE RETENTION

F0-GENERATION - LACTATION

LITTER	PUP	SEX	anogenital dist M mm	anogenital dist F mm	Number of nipples
GROUP 4 (1000 MG/KG)					
	10	F	--	1.06	--
	11	F	--	0.98	--
	12	F	--	0.99	--
	13	F	--	0.84	--
75	1	M	2.77	--	0.00
	2	M	2.68	--	0.00
	3	M	2.50	--	0.00
	4	M	2.56	--	0.00
	5	M	2.63	--	--
	6	M	2.74	--	--
	7	F	--	1.09	--
	8	F	--	0.90	--
	9	F	--	1.11	--
	10	F	--	1.04	--
	11	F	--	0.98	--
	12	F	--	1.14	--
	13	F	--	1.12	--
76	1	M	2.68	--	
	2	M	2.58	--	
	3	M	2.95	--	
	4	M	2.47	--	
	5	F	--	1.12	
	6	F	--	0.97	
	7	F	--	1.02	
	8	F	--	0.93	
	9	F	--	1.01	
	10	F	--	0.89	
77	1	M	2.97	--	0.00
	2	M	2.84	--	0.00
	3	M	2.86	--	0.00
	4	M	2.86	--	0.00
	5	M	2.67	--	--
	6	M	2.77	--	--
	7	M	2.80	--	--
	8	M	2.68	--	--
	9	F	--	0.89	--
	10	F	--	0.80	--
	11	F	--	0.79	--
	12	F	--	0.80	--
	13	F	--	0.98	--
	14	F	--	0.74	--
	15	F	--	0.94	--
78	1	M	2.84	--	0.00
	2	M	2.66	--	0.00
	3	M	2.64	--	0.00
	4	M	2.62	--	0.00
	5	M	2.59	--	--
	6	M	2.74	--	--
	7	M	2.54	--	--
	8	F	--	0.69	--
	9	F	--	0.85	--
	10	F	--	1.00	--
	11	F	--	1.01	--
	12	F	--	0.92	--
	13	F	--	0.84	--
	14	F	--	1.07	--
	15	F	--	0.94	--
	16	F	--	0.90	--

2.20 ANOGENITAL DISTANCE AND NIPPLE RETENTION

F0-GENERATION - LACTATION

LITTER	PUP	SEX	anogenital dist M mm	anogenital dist F mm	Number of nipples
GROUP 4 (1000 MG/KG)					
79	1	M	2.82	--	0.00
	2	M	2.64	--	0.00
	3	M	2.16	--	0.00
	4	M	3.08	--	0.00
	5	F	--	1.51	--
	6	F	--	1.23	--
	7	F	--	1.39	--
	8	F	--	1.12	--
	9	F	--	1.14	--
	10	F	--	0.89	--
	11	F	--	1.18	--
	12	F	--	1.72	--
80	1	M	2.71	--	0.00
	2	M	2.53	--	0.00
	3	M	2.54	--	0.00
	4	M	2.61	--	0.00
	5	M	2.61	--	--
	6	M	2.57	--	--
	7	M	2.64	--	--
	8	M	2.62	--	--
	9	F	--	1.00	--
	10	F	--	0.91	--
	11	F	--	0.86	--
	12	F	--	0.84	--

2.21 CORRECTED ANOGENITAL DISTANCE

PND 1

LITTER	norm anog dist M mm	norm anog dist F mm
GROUP 1 (CONTROL)		
41	1.35	0.55
43	1.34	0.48
44	1.36	0.51
45	1.38	0.48
47	1.43	0.42
48	1.47	0.55
49	1.46	0.54
50	1.37	0.58
GROUP 2 (100 MG/KG)		
52	1.40	0.57
54	1.44	0.44
55	1.40	0.80
56	1.41	0.57
57	1.43	0.56
58	1.45	0.50
59	1.44	0.58
60	1.36	0.58
GROUP 3 (300 MG/KG)		
61	1.48	0.72
62	1.49	0.54
64	1.46	0.53
65	1.29	0.49
66	1.36	0.47
67	1.40	0.50
68	1.46	0.58
69	1.39	0.52
70	1.36	0.49
GROUP 4 (1000 MG/KG)		
71	1.50	0.44
73	1.39	0.74
74	1.39	0.57
75	1.44	0.57
76	1.43	0.54
77	1.53	0.48
78	1.46	0.52
79	1.44	0.68
80	1.46	0.50

DIHEP AQUEOUS SOLUTION
APPENDIX 2

2.22 CLINICAL BIOCHEMISTRY
MALES
PUPS (PND 14-16)

LITTER	Total T4 ug/dL
GROUP 1 (CONTROL)	
41	8.59
43	7.88
44	5.62
45	7.08
47	7.36
48	6.02
49	5.19
50	4.87
GROUP 2 (100 MG/KG)	
52	6.23
54	6.61
55	7.16
56	5.87
57	6.10
58	7.45
59	5.60
60	4.52
GROUP 3 (300 MG/KG)	
61	5.83
62	5.10
64	6.29
65	5.82
66	5.94
67	5.89
68	6.61
69	5.58
70	7.89
GROUP 4 (1000 MG/KG)	
71	6.12
73	6.58
74	5.84
75	5.27
76	5.40
77	7.04
78	6.10
79	6.79
80	5.11

FEMALES
PUPS (PND 14-16)

LITTER	Total T4 ug/dL
GROUP 1 (CONTROL)	
41	5.32
43	7.11
44	5.39
45	5.42
47	7.41
48	5.94
49	6.65
50	4.62

DIHEP AQUEOUS SOLUTION
APPENDIX 2

2.22 CLINICAL BIOCHEMISTRY
FEMALES
PUPS (PND 14-16)

LITTER	Total T4 ug/dL
GROUP 2 (100 MG/KG)	
52	6.35
54	6.57
55	5.25
56	5.15
57	5.86
58	6.54
59	6.85
60	4.88
GROUP 3 (300 MG/KG)	
61	5.94
62	6.32
64	4.77
65	4.93
66	6.08
67	5.18
68	6.06
69	6.21
70	6.21
GROUP 4 (1000 MG/KG)	
71	5.99
73	5.04
74	4.56
75	3.64
76	4.58
77	5.93
78	5.46
79	6.12
80	6.22

DIHEP AQUEOUS SOLUTION
APPENDIX 2

Project 20172120

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 1 (CONTROL)					
LITTER 41	1	M	DAY 14 Planned Necropsy	FLC	Wound nose
15MAR2019				DAY 2	Scabs snout
				DAY 3	Scab snout
				DAY 4	Scab snout
				LLC	No findings
				MACRO	No findings
	2	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	9	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 43	1	M	DAY 16 Planned Necropsy	FLC	No findings
16MAR2019				LLC	No findings
				MACRO	No findings
	2	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 44	1	M	DAY 14 Planned Necropsy	FLC	No findings
15MAR2019				LLC	No findings
				MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

03Jun19 14h50

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 1 (CONTROL)						
	2	M	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	14	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	15	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 45 14MAR2019	1	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 1 (CONTROL)					
LITTER 47	1	M	DAY 15 Planned Necropsy	FLC	No findings
13MAR2019				LLC	No findings
				MACRO	No findings
	2	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	9	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 48	1	M	DAY 16 Planned Necropsy	FLC	No findings
16MAR2019				LLC	No findings
				MACRO	No findings
	2	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	F	DAY 6 Missing	FLC	No findings
	9	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	11	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	12	F	DAY 4 Missing	FLC	No findings
	13	F	DAY 4 Culling	FLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 1 (CONTROL)					
				LLC	No findings
				MACRO	No findings
	14	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 49 16MAR2019	1	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	9	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	11	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	12	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	13	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 50 15MAR2019	1	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	M	DAY 4 Culling	FLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 1 (CONTROL)						
					LLC	No findings
					MACRO	No findings
	7	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 14	Planned Necropsy	FLC	Wound nose
					LLC	No findings
					MACRO	No findings
	12	F	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	14	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
GROUP 2 (100 MG/KG)						
LITTER 52 14MAR2019	1	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 4	Culling	FLC	No findings
					LLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 2 (100 MG/KG)					
	12	F	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	13	F	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	14	F	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
LITTER 54 13MAR2019	1	M	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	2	M	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	3	M	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	4	M	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	5	M	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	6	M	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	7	F	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	8	F	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	9	F	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	10	F	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	11	F	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	12	F	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	13	F	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
LITTER 55 17MAR2019	1	M	DAY 16 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	2	M	DAY 16 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	3	M	DAY 16 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	4	M	DAY 16 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 2 (100 MG/KG)						
					MACRO	No findings
	5	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 56 15MAR2019	1	M	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 4	Culling	FLC	Wound leg
					LLC	No findings
					MACRO	No findings
	7	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 14	Planned Necropsy	FLC	No findings
					LLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

DIHEP AQUEOUS SOLUTION
APPENDIX 2

Project 20172120

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 2 (100 MG/KG)					
				MACRO	No findings
	12	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	13	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	14	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	15	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	16	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	17	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 57 14MAR2019	1	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	9	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	11	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 58 14MAR2019	1	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

03Jun19 14h50

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 2 (100 MG/KG)					
	4	M	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	5	M	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	6	M	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	7	F	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	8	F	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	9	F	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	10	F	DAY 15 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	11	F	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	12	F	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	13	F	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	14	F	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
LITTER 59 16MAR2019	1	M	DAY 16 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	2	M	DAY 16 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	3	M	DAY 16 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	4	M	DAY 16 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	5	M	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	6	M	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	7	M	DAY 4 Culling	MACRO	No findings
				FLC	No findings
				LLC	No findings
	8	F	DAY 16 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings
	9	F	DAY 16 Planned Necropsy	MACRO	No findings
				FLC	No findings
				LLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 2 (100 MG/KG)					
				MACRO	No findings
	10	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	11	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	12	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	13	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	14	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	15	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	16	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 60 15MAR2019	1	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	9	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	11	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	12	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	13	F	DAY 4 Culling	FLC	No findings
				LLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 2 (100 MG/KG)						
					MACRO	No findings
	14	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	15	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
GROUP 3 (300 MG/KG)						
LITTER 61 17MAR2019	1	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 16	Spontaneous death	FLC	No findings
					LLC	Dead
					MACRO	No findings
	3	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 62 16MAR2019	1	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 3 (300 MG/KG)						
	5	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 64 14MAR2019	1	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

03Jun19 14h50

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 3 (300 MG/KG)						
	12	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 65 16MAR2019	1	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 1	Dead at FLC	FLC	Dead
					LLC	Dead
					MACRO	Beginning autolysis
	6	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 66 14MAR2019	1	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 3 (300 MG/KG)						
	6	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 67 16MAR2019	1	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	14	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

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DIHEP AQUEOUS SOLUTION
APPENDIX 2

Project 20172120

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 3 (300 MG/KG)					
LITTER 68 15MAR2019	1	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	9	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 69 16MAR2019	1	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	F	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	9	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

03Jun19 14h50

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 3 (300 MG/KG)						
	11	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 70 14MAR2019	1	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
GROUP 4 (1000 MG/KG)						
LITTER 71 13MAR2019	1	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 15	Planned Necropsy	FLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 4 (1000 MG/KG)					
				LLC	No findings
				MACRO	No findings
	9	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	11	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 73 13MAR2019	1	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	M	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	9	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	11	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	12	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	13	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	14	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 74 15MAR2019	1	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 14 Planned Necropsy	FLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 4 (1000 MG/KG)					
				LLC	No findings
				MACRO	No findings
	4	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	9	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	11	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	12	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	13	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 75 15MAR2019	1	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	9	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 14 Planned Necropsy	FLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 4 (1000 MG/KG)					
				LLC	No findings
				MACRO	No findings
	11	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	12	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	13	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 76 15MAR2019	1	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	M	DAY 14 Planned Necropsy	FLC	No findings
				LLC	Left hind leg bend at the hight of the knee
				MACRO	Left hind leg bend at the hight of the knee
	5	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	F	DAY 14 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	9	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
LITTER 77 16MAR2019	1	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	3	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	4	M	DAY 16 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	M	DAY 4 Culling	FLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 4 (1000 MG/KG)						
					LLC	No findings
					MACRO	No findings
	8	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	14	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	15	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 78 16MAR2019	1	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	M	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 16	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 4	Culling	FLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 4 (1000 MG/KG)						
					LLC	No findings
					MACRO	No findings
	13	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	14	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	15	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	16	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 79 13MAR2019	1	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 4	Culling	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 80 14MAR2019	1	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 15	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 15	Planned Necropsy	FLC	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.23 MORTALITY, CLINICAL SIGNS AND MACROSCOPY OF PUPS
FEMALES

F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 4 (1000 MG/KG)					
				LLC	No findings
				MACRO	No findings
	5	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	M	DAY 4 Culling	FLC	No findings
				LLC	No findings
				MACRO	No findings
	9	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	11	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	12	F	DAY 15 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

2.24 KEY TO MISSING VALUES/REMARKS

Necropsy

Organ Weights:

Animal(s):	Organ	Weight (g)	Weight (g) aberrant side	Reason
35	Epididymis	---	0.736	Left side: Macroscopic finding
68	Brain	2.245	--	The brain was not weighed at necropsy but after fixation.

End of Treatment

Haematology:

Animal(s):		
41, 44, 45, 50, 52, 56, 57, 58, 64, 66, 68, 70, 74, 80		Samples were stored at ≤ -75ºC prior to analysis on the STA Compact
50	---	= Citrate sample clotted
15, 66	---	= Value for PT could not be reproduced
1, 34		Differential leucocyte count was also performed manually because of an abnormal plot in the automated count and these results are reported
1, 34		Manual differential leucocyte count revealed that 5.6% and 5% of neutrophils were band cells, respectively.

Clinical Biochemistry:

Animal(s):		
All animals		Samples were stored at ≤ -75ºC prior to (possible) analysis on the Immulite1000
62		Samples were stored at ≤ -75ºC prior to analysis on the AU400

PND4

Clinical Biochemistry:

Animal(s):		
All animals		Samples were stored at ≤ -75ºC prior to analysis on the IMMULITE 1000
41, 43-45, 48-50, 52, 54-62, 64-70, 74-80		Lipemic serum sample; common occurrence during lactation
52, 57, 58, 61, 64, 66, 80		Hemolytic sample
47, 71, 73		Not Lipemic sample

PND14-16

Clinical Biochemistry:

Animal(s):		
All animals		Samples were stored at ≤ -75ºC prior to analysis on the IMMULITE 1000
41, 43-45, 47-50, 52, 54-62, 64-68, 70-71, 73-76, 78-80 male + female & 77 female		Lipemic serum sample; common occurrence during lactation
47 male		Hemolytic serum sample
69 male + female, 77 male		Not lipemic serum sample

Appendix 3
Test Item Characterization

Page 1 of 1

Certificate of analysis

THE DOW CHEMICAL COMPANY

Certificate of analysis		Quality order	
Product name	CANSOLV ABSORBANT DS	Customer Batch number	D2921BF000
Reference number		Batch number	
		Reference lot	

Test	Unit	Test result	Min	Max
% Water	%	51.14	51	54
Appearance		Pass	-	-
Gardner Color	Color	3	-	6
Foam Height	ml	75	-	100
Foam Break Time	Seconds	7.7	-	15
Gas Chromatography, HEP	%	9.01	-	14
Gas Chromatography, DIHEP	%	89.69	80	100
Gas Chromatograph Heavies GT DHEP	%	0.4	-	5
Gas Chromatography, Piperazine	%	0	-	2
Gas Chromatograph EG & DEG	%	0.2	-	0.6
Cansolv DS Alkalinity	meq/g	5.76	-	-

Notes: Tank 105

APPROVED BY: **KENDRICK JUNIUS**

Appendix 4
Histopathology Report

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APPENDIX 1 HISTOPATHOLOGY TABLES

1. SUMMARY

Pathomorphologic examination was performed on 80 Wistar (Han) rats (40 males, 40 females) which had been subjected to a combined 28-Day oral (gavage) toxicity study with the reproduction/developmental toxicity screening test with the test item **DiHEP Aqueous Solution**.

The rats were assigned to four dose groups, each containing 10 males and 10 females. The test item was administered undiluted once daily by gavage at doses of 100, 300 and 1000 mg/kg/day (dose groups 2, 3 and 4 respectively) for a minimum of 28 days. The rats of the control group 1 received water (Elix), alone.

At the end of the treatment period all rats from all groups were killed and subjected to complete necropsies. Histopathologic examination was performed on an extensive list of organs and tissues from five selected group 1 and 4 animals as well as the adrenal glands and stomach from selected group 2 and 3 males and all organs with macroscopic findings from all rats. The reproductive organs were examined from all males that failed to sire and all females that failed to deliver healthy pups.

There were no unscheduled deaths.

There were no test item-related macroscopic findings.

A possible test item-related non-adverse lower thymus weight was observed in 300 and 1000 mg/kg/day males.

Test item-related microscopic findings were present in the **stomach** of 1000 mg/kg/day males, consisting of (multi)focal erosions of the mucosal layer of the glandular stomach. Based on the low degrees (up to slight) and absence of concomitant test item-related changes, this finding was regarded as non-adverse.

There were 2/10 couples of the Control group, 2/10 couples treated at 100 mg/kg/day, 1/10 couples treated at 300 mg/kg/day and 1/10 couples treated at 1000 mg/kg/day that failed to deliver healthy pups. Histopathology did not reveal any changes in the reproductive organs that could explain this, besides a necrotic placenta in control female no. 42.

In conclusion, non-adverse test item-related morphologic alterations following the oral (gavage) administration of DiHEP Aqueous Solution for at least 28 days to Wistar (Han) rats at doses up to 1000 mg/kg/day, were present in the stomach of 1000 mg/kg/day group males Furthermore, possible test-item related lower thymus weights were present in 300 and 1000 mg/kg/day group males.
There were no morphologic alterations in males treated up to 300 mg/kg/day and in females up to 1000 mg/kg/day.

There were no morphological findings in the reproductive organs of either sex which could be attributed to the test item and stage aware evaluation of the testes did not show any indication for abnormal spermatogenesis.

2. INTRODUCTION

The objectives of this study were to determine the potential toxic effects of DiHEP Aqueous Solution when given orally by gavage for a minimum of 28 days to Wistar Han rats, and to evaluate the potential to affect male and female reproductive performance such as gonadal function, mating behavior, conception, parturition and early postnatal development. This pathology report addresses the anatomical pathology endpoints of the study. It is based on the study plan and any study plan amendment.

3. 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 undiluted DiHEP Aqueous Solution 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 Number	Dose level mg/kg bw /day	Number of animals		Animal numbers		Selected animals	
		Males	Females	Males	Females	Males	Females
1	0[a]	10	10	01-10	41-50	01-05	41,44,45,47,50
2	100	10	10	11-20	51-60	11-15	52,54,56,57,58
3	300	10	10	21-30	61-70	21-25	62,64,66,68,70
4	1000	10	10	31-40	71-80	31-35	71,73,74,79,80

[a] The control group received only water (Elix).

4. METHODS

4.1. 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 unless otherwise noted:

Table 1: All selected animals:

Tissue	**Weigh**	**Collect**	**Histology[a]**	**Microscopic Evaluation[a]**	**Comment**
Animal identification	-	X	-	-	Location: ear and foot
Artery, aorta	-	X	-	-	-
Body cavity, nasopharynx	-	X	-	-	-.
Bone marrow	-	X	X	X	Collected as part of the femur and sternum.
Bone, femur	-	X	X	X	Including joint.
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Eight brain levels were examined including cerebellum, midbrain and cortex.
Cervix	X	X	X	X	Collected and weighed together with the uterus.
Epididymis	X	X	X	X	Paired examination. Initially preserved in modified Davidson's fixative.
Esophagus	-	X	-	-	-

Eye	-	X	X	X	Paired examination. Initially preserved in modified Davidson's fixative.
Gland, adrenal	X	X	X	X	Paired examination.
Gland, coagulation	X	X	X	X	Collected and weighed together with the seminal vesicles.
Gland, harderian	-	X	-	-	-
Gland, lacrimal	-	X	-	-	Collected exorbital.
Gland, mammary	-	X	X	X	Collected: inguinal region with skin. Examined for both males and females.
Gland, parathyroid	X	X	-	-	Examined only if present in the routine section of thyroid. Collected and weighed together with thyroid.
Gland, pituitary	-	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	-	-	Collected at mandibular, sublingual and parotid site.
Gland, seminal vesicle	X	X	X	X	Paired examination. Collected and weighed together with the coagulation gland.
Gland, thyroid	X	X	X	X	Paired examination. Collected and weighed together with the parathyroid.
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	Examined only if present in routine section of intestine.
Heart	X	X	X	X	-
Kidney	X	X	X	X	Paired examination.
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	-	X	X	X	Infused with formalin.
Lymph node	-	X	X	X	Collected at mandibular and mesenteric site. Only 1 mandibular required for microscopic examination
Muscle, skeletal	-	X	X	X	-
Nerve, optic	-	X	-	-	Examined only if present in the routine section of the eye. Initially preserved in modified Davidson's fixative.
Nerve, sciatic	-	X	X	X	Only 1 required for microscopic examination
Ovaries	X	X	X	X	Paired examination.
Pancreas	-	X	-	-	-
Skin	-	X	-	-	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-

Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	Examined one transverse and one longitudinal section from each of the following areas: cervical, mid-thoracic, lumbar.
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testes	X	X	X	X	Paired examination. Initially preserved in modified Davidson's fixative.
Thymus	X	X	X	X	-
Tongue	-	X	-	-	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

X = Procedure conducted; - = Not applicable.

[a] Procedure conducted for selected group 1 and 4 animals, targets organs/tissues from group 2 and 3 animals and all gross lesions from all animals.

Table 2: All remaining animals (incl. males that failed to sire[a] and females that failed to deliver healthy pups):

Tissue	**Weigh**	**Collect**	**Histology**	**Microscopic Evaluation**	**Comment**
Animal identification	-	X	-	-	Location: ear and foot
Cervix	-	X	@	@	-
Epididymis	X	X	@	@	Paired examination. Initially preserved in modified Davidson's fixative.
Gland, coagulation	X	X	@	@	Collected and weighed together with the seminal vesicles.
Gland, mammary	-	X	-	-	Collected inguinal region with skin. Collected for both males and females.
Gland, parathyroid	X	X	-	-	Examined only if present in the routine section of thyroid. Collected and weighed together with thyroid.
Gland, pituitary	-	X	-	-	-
Gland, prostate	X	X	@	@	-
Gland, seminal vesicle	X	X	@	@	Paired examination. Collected and weighed together with the coagulation gland.
Gland, thyroid	X	X	-	-	Paired examination. Collected and weighed together with the parathyroid.
Gross lesions/masses	-	X	X	X	-
Ovaries	-	X	@	@	Paired examination.
Testes	X	X	@	@	Paired examination. Initially preserved in modified Davidson's fixative.
Uterus	-	X	@	@	-
Vagina	-	X	@	@	-

X = Procedure conducted for all remaining animals; - = Not applicable;

@ = Procedure conducted for males that failed to sire[a] and females that failed to deliver healthy pups only.

[a] Except for males that failed to sire which were also selected. These males were processed as noted in table 1.

4.2. Organ Weights

The organ weights (and terminal body weight) were recorded from all animals at the scheduled necropsy as indicated in the tables above.

Paired organs were weighed together. Absolute organ weights were reported and organ to terminal body weights were calculated and presented in the main study report.

4.3. Microscopic Examination

Microscopic examination of routinely prepared hematoxylin-eosin stained paraffin sections was performed:

Group	Dose level mg/kg bw/day	Selected animals		Non-Selected animals	
		Males	Females	Males	Females
1	0	All tissues*	All tissues*	Reproductive organs[#]: no. 6.	Reproductive organs[#]: nos. 42 and 46.
2	100	Stomach, Adrenals	Not applicable	Reproductive organs[#]: nos. 11 and 13.	Reproductive organs[#]: nos. 51 and 53.
3	300	Stomach, Adrenals	Not applicable	Reproductive organs[#]: no. 23.	Reproductive organs[#]: no. 63.
4	1000	All tissues*	All tissues*	Not applicable.	Reproductive organs[#]: no. 72.

* All collected tissues, as indicated on the tissue list above.
[#] Selected reproductive organs, as indicated on the tissue list above.

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).

Gross lesions were examined from all animals and correlated to microscopic findings if possible.

The animal data and macroscopic findings were electronically transferred from the necropsy raw data files of ToxData system® into the computer system PathData®. Stained histologic sections were examined by light microscopy in the period 07 May – 07 June 2019 and the microscopic findings were recorded by the undersigned pathologist using on-line input under pathology number 31906 LAA.

Severity grades were assigned to non-neoplastic histopathologic diagnoses, as presented in the following table. 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 PathData® 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 "Text of Gross and Microscopic Findings". The incidence of microscopic findings is also presented in tabular form: “Incidence table – Selected findings with grades” and “Incidence table - all microscopic findings”. Incidence tables were created by computer.

Histopathological changes were described according to distribution, severity and morphological character. The International Harmonization of Nomenclature and Diagnostic Criteria for Lesions (INHAND) was used as guidance for the description of histopathological changes.

Severity scores were assigned as follows:

Present	Finding present, grading not scored.
Grade 1	Minimal/very few/very small.
Grade 2	Slight/few/small.
Grade 3	Moderate/moderate number/moderate size.
Grade 4	Marked/many/large.
Grade 5	Massive/extensive number/extensive size.
N.A.D.	No Abnormality Detected

4.4. Internal Peer Review

Pathology findings were subjected to an internal review conducted by Hetty van den Brink-Knol (Dutch CRP/TP Certified Toxicologic Pathologist). Following the peer review, a consensus was reached between the study pathologist and the peer review pathologist with regard to diagnoses and interpretation. Histopathology data entries in PathData® and pathology data presented in the pathology report reflect this consensus.

5. RESULTS

5.1. Mortality

There were no premature decedents in the study.

5.2. Clinical Pathology

Clinical pathology data were evaluated and discussed by the study pathologist and the study director. Clinical pathology results are presented in the main toxicology report.

5.3. Macroscopic Findings

There were no test item-related gross observations.

A macroscopic finding of note was recorded in two females of the 100 mg/kg/day group (nos. 52 and 57) and one female of the 300 mg/kg/day group (no. 70). This finding consisted of watery clear fluid of the thoracic cavity. Since this finding was absent in the high dose group, and since there were no other macroscopic findings of organs of the thoracic cavity, or related clinical findings, this finding was considered to be unrelated to the test item.

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

5.4. Organ Weights

Thymus weights of test item-treated males were lower in a dose-related manner. This organ weight change was not statistically significantly different from the concurrent controls and group mean values remained within background ranges. However, individual organ weight values of 1/5 males of the 300 mg/kg/day group and 2/5 males of the 1000 mg/kg/day group were at the lower range. Therefore a possible test item relationship at these dose levels could not be excluded.

Any other differences, including those that reached statistical significance (i.e. the absolute weight of adrenal glands and relative to body weight of the heart of 100 mg/kg/day males, and absolute weights of kidneys of 1000 mg/kg/day females and relative to body weight of thymus of 100 mg/kg/day females) were considered not to be DiHEP Aqueous Solution - related due to the direction of the change, lack of a dose-related pattern, and/or general overlap and variability in individual values.

5.5. Microscopic Findings

Test item-related microscopic findings after treatment with DiHEP Aqueous Solution were noted in the **stomach** of the 1000 mg/kg/day group males and are summarized in text table 1.

Text Table 1.
Summary Test Item-Related Microscopic Findings – Scheduled Euthanasia Animals (Day 29)

	Males			
Dose level (mg/kg/day):	0	100	300	1000
STOMACH [a]	5	5	5	5
Erosion glandular mucosa, focal				
Minimal	-	-	-	2
Slight	-	-	-	1

[a] = Number of tissues examined from each group.

(Multi) focal erosions of the glandular mucosa of the **stomach** were noted in 1000 mg/kg/day males (up to slight degree). These erosions were all located at the pyloric area.

The remainder of the recorded microscopic findings, including the low degrees of vacuolation of the zona fasciculate of the adrenal glands of males, were within the range of background pathology encountered in rats of this age and strain. There was no test item-related alteration in the prevalence, severity, or histologic character of those incidental tissue alterations.

5.6. Reproductive Performance

Text Table 2.
Correlation of Histopathology Findings with In-Life Reason for Males that Failed to Sire and Females that Failed to Deliver Healthy Pups.

Group	Dose level mg/kg bw/day	Female/Male nos.	In-Life Reason	Histopathology
1	0	42 / 2	Not pregnant	Implantation site and necrosis of placenta of the uterus (observed as nodule)
		46 / 6	Not pregnant	
2	100	51 / 11	Not pregnant	
		53 / 13	Not pregnant	
3	300	63 / 23	Not pregnant	
4	1000	72 / 32	Not pregnant	

There were 2/10 couples of the Control group (male no. 2 and female no. 42; male no. 6 and female no. 46), 2/10 couples of 100 mg/kg/day group (male no.11 and female no. 51; male no. 13 and female no. 53), 1/10 couples of the 300 mg/kg/day group (male no. 23 and female no. 63) and 1/10 couples) of the 1000 mg/kg/day group (male no. 32 and female no. 72) with no offspring. Female no. 42 showed evidence of a former pregnancy, in the form of the presence of a necrotic placenta. For the other couples, no abnormalities were seen in the reproductive organs, which could account for their lack of offspring.

There were no morphological findings in the reproductive organs of either sex which could be attributed to the test item and stage aware evaluation of the testes did not show any indication for abnormal spermatogenesis. The testis revealed normal progression of the spermatogenic cycle and the expected cell associations and proportions in the various stages of spermatogenesis were present.

6. DISCUSSION

Test item-related findings were present in the 1000 mg/kg/day group, consisting of (multi) focal erosions of the glandular mucosa of the **stomach** of males. Based on the low degrees (up to slight) and absence of concomitant test item-related microscopic changes, these findings were regarded as non-adverse.
The possible test item related lower thymus weights observed in 300 and 1000 mg/kg/day group males, was in absence of correlating microscopy or clinical pathology considered as non-adverse.

7. CONCLUSIONS

Non- adverse test item-related morphologic alterations following the oral (gavage) administration of **DiHEP Aqueous Solution** for at least 28 days to Wistar (Han) rats at doses up to 1000 mg/kg/day, were present in the stomach of 1000 mg/kg/day group males.
Furthermore, possible test-item related lower thymus weights were present in 300 and 1000 mg/kg/day group males.
There were no morphologic alterations in males treated up to 300 mg/kg/day and in females up to 1000 mg/kg/day.

There were no morphological findings in the reproductive organs of either sex which could be attributed to the test item and stage aware evaluation of the testes did not show any indication for abnormal spermatogenesis.

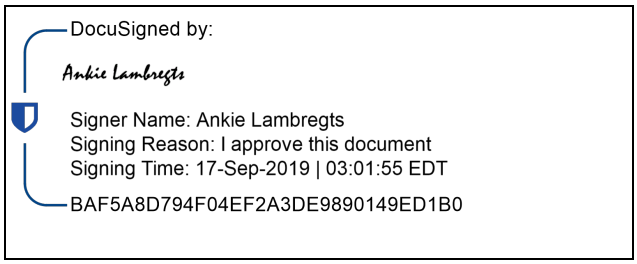
8. REPORT AUTHENTICATION

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 PathData® under number 31906 LAA.

Final histopathology tables generated 11 September 2019

Project 20172120 Pathology Report

Report and Histopathology Tables Submitted By:



Ankie Lambregts, DVM

Dutch CRP/TP Certified Toxicologic Pathologist

Study Pathologist

APPENDIX 1
HISTOPATHOLOGY TABLES

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

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TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
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EXPLANATION OF CODES AND SYMBOLS

CODES AND SYMBOLS USED AT ANIMAL LEVEL:

M = Male animal
F = Female animal
K0 = Terminal sacrifice group

CODES AND SYMBOLS USED AT ORGAN LEVEL:

G = Gross observation checked off histologically
! = Gross observat.not checked off histologically
* = Comment in text of individual animal data
' = Histologic examination not required
+ = Organ examined, findings present
- = Organ examined, no pathologic findings noted (AOFT only)
(= Only one of paired organs examined/present

CODES AND SYMBOLS USED AT FINDING LEVEL:

GRADE 1 = Minimal / very few / very small
GRADE 2 = Slight / few / small
GRADE 3 = Moderate / moderate number / moderate size
GRADE 4 = Marked / many / large
P = Finding present, severity not scored
(= Finding unilateral in paired organs

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
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SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (K0)
Incidence table - Selected findings with grades

Sex		Males			
Dose Group		01	02	03	04
No. Animals per Dose Group		10	10	10	10
STOMACH	No.Examined	5	5	5	5
- Erosion glandular stomach	GRADE 1	-	-	-	2
	GRADE 2	-	-	-	1
	TOTAL AFFECTED	-	-	-	3
	MEAN GRADE/TISS.AFFECTED	-	-	-	1.3

Group 01, CONTROL, males: DiHEP Aqueous Solution (0 MG/KG)
Group 02, 100 MG/KG, males: DiHEP Aqueous Solution (100 MG/KG)
Group 03, 300 MG/KG, males: DiHEP Aqueous Solution (300 MG/KG)
Group 04, 1000 MG/KG, males: DiHEP Aqueous Solution (1000 MG/KG)

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
Incidence table - All microscopic findings

SEX :					MALE
DOSE GROUP:	01	02	03	04	
NO.ANIMALS:	10	10	10	10	
BRAIN :	5	-	-	5	
N.A.D. :	5	-	-	5	
SPINAL CORD, CERVIC. :	5	-	-	5	
N.A.D. :	5	-	-	5	
SPINAL CORD, THORAC. :	5	-	-	5	
N.A.D. :	5	-	-	5	
SPINAL CORD, LUMBAR :	5	-	-	5	
N.A.D. :	5	-	-	5	
PITUITARY GLAND :	5	-	-	5	
N.A.D. :	5	-	-	5	
SCIATIC NERVE,RIGHT :	5	-	-	5	
N.A.D. :	5	-	-	5	
EYES :	5	-	-	5	
N.A.D. :	5	-	-	5	
THYMUS :	5	-	-	5	
N.A.D. :	4	-	-	5	
- Cyst(s) :	1	-	-	-	
Grade 1:	1	-	-	-	
MANDIB.LYMPH NODE :	5	-	-	5	
N.A.D. :	5	-	-	4	
- Erythrocytes, sinus :	-	-	-	1	
Grade 1:	-	-	-	1	
Grade 2:	-	-	-	-	
Grade 3:	-	-	-	-	

Group 01, CONTROL, males: DiHEP Aqueous Solution (0 MG/KG)
Group 02, 100 MG/KG, males: DiHEP Aqueous Solution (100 MG/KG)
Group 03, 300 MG/KG, males: DiHEP Aqueous Solution (300 MG/KG)
Group 04, 1000 MG/KG, males: DiHEP Aqueous Solution (1000 MG/KG)

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
Incidence table - All microscopic findings

SEX :					MALE
DOSE GROUP:	01	02	03	04	
NO.ANIMALS:	10	10	10	10	
ADRENAL GLANDS :	5	5	5	5	
N.A.D. :	4	2	3	3	
- Vacuol. fasciculata :	1	3	2	2	
Grade 1:	1	3	2	2	
THYROID GLAND :	5	-	-	5	
N.A.D. :	4	-	-	4	
- Hypertrophy foll. c.:	1	-	-	1	
Grade 1:	1	-	-	1	
MAMMARY GLAND :	5	-	-	5	
N.A.D. :	5	-	-	5	
LUNG :	5	-	-	5	
N.A.D. :	1	-	-	3	
- Inflamm. alv. acute :	2	-	-	-	
Grade 1:	2	-	-	-	
- Alveolar macrophages:	-	-	-	1	
Grade 1:	-	-	-	1	
- Inflamm. peribronch.:	3	-	-	2	
Grade 1:	2	-	-	2	
Grade 2:	1	-	-	-	
TRACHEA :	5	-	-	5	
N.A.D. :	5	-	-	5	
SKELETAL MUSCLE :	5	-	-	5	
N.A.D. :	3	-	-	3	
- Infiltrate inflamm. :	2	-	-	2	
Grade 1:	2	-	-	2	

Group 01, CONTROL, males: DiHEP Aqueous Solution (0 MG/KG)
Group 02, 100 MG/KG, males: DiHEP Aqueous Solution (100 MG/KG)
Group 03, 300 MG/KG, males: DiHEP Aqueous Solution (300 MG/KG)
Group 04, 1000 MG/KG, males: DiHEP Aqueous Solution (1000 MG/KG)

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
Incidence table - All microscopic findings

SEX :				MALE
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
HEART :	5	-	-	5
N.A.D. :	5	-	-	4
- Infiltrate inflamm. :	-	-	-	1
Grade 1:	-	-	-	1
SPLEEN :	5	-	-	5
- Hematopoiesis, :	5	-	-	4
Grade 1:	4	-	-	4
Grade 2:	1	-	-	-
- Pigmentation, hemos.:	3	-	-	5
Grade 1:	3	-	-	5
Grade 2:	-	-	-	-
LIVER :	5	-	-	5
N.A.D. :	1	-	-	3
- Infiltrate inflamm. :	4	-	-	2
Grade 1:	4	-	-	2
URINARY BLADDER :	5	-	-	5
N.A.D. :	5	-	-	5
KIDNEYS :	5	-	-	5
N.A.D. :	1	-	-	2
- Infiltrate inflamm. :	1	-	-	2
Grade 1:	1	-	-	2
- Hyaline droplet acc.:	1	-	-	-
Grade 1:	1	-	-	-
- Basophilia, tubule :	2	-	-	3
Grade 1:	2	-	-	3
- Cyst :	1	-	-	-
Grade 1:	1	-	-	-

Group 01, CONTROL, males: DiHEP Aqueous Solution (0 MG/KG)
Group 02, 100 MG/KG, males: DiHEP Aqueous Solution (100 MG/KG)
Group 03, 300 MG/KG, males: DiHEP Aqueous Solution (300 MG/KG)
Group 04, 1000 MG/KG, males: DiHEP Aqueous Solution (1000 MG/KG)

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
Incidence table - All microscopic findings

SEX :					MALE
DOSE GROUP:	01	02	03	04	
NO.ANIMALS:	10	10	10	10	
STOMACH :	5	5	5	5	
N.A.D. :	4	2	5	1	
- Inflammation, gland.:	1	2	-	-	
Grade 1:	1	2	-	-	
- Erosion glandular :	-	-	-	3	
Grade 1:	-	-	-	2	
Grade 2:	-	-	-	1	
- Hemorrhage :	-	1	-	-	
Grade 1:	-	1	-	-	
- Cyst(s) :	1	-	-	-	
Grade 1:	1	-	-	-	
- Vacuolation, lim. r.:	1	-	-	1	
Grade 1:	1	-	-	1	
DUODENUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
JEJUNUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
ILEUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
GALT :	5	-	-	5	
N.A.D. :	4	-	-	5	
- Increas. vacuolation:	1	-	-	-	
Grade 1:	1	-	-	-	
CECUM :	5	-	-	5	
N.A.D. :	5	-	-	5	

Group 01, CONTROL, males: DiHEP Aqueous Solution (0 MG/KG)
Group 02, 100 MG/KG, males: DiHEP Aqueous Solution (100 MG/KG)
Group 03, 300 MG/KG, males: DiHEP Aqueous Solution (300 MG/KG)
Group 04, 1000 MG/KG, males: DiHEP Aqueous Solution (1000 MG/KG)

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
Incidence table - All microscopic findings

SEX :				MALE
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
COLON :	5	-	-	5
N.A.D. :	5	-	-	5
RECTUM :	5	-	-	5
N.A.D. :	5	-	-	5
MESENT. LYMPH NODE :	5	-	-	5
N.A.D. :	5	-	-	5
SEMINAL VESICLES :	6	2	1	5
N.A.D. :	6	2	1	5
COAGULATING GLANDS :	6	2	1	5
N.A.D. :	6	2	1	5
PROSTATE GLAND :	6	2	1	5
N.A.D. :	4	2	1	5
- Infiltrate inflamm. :	2	-	-	-
Grade 1:	1	-	-	-
Grade 2:	1	-	-	-
TESTES :	6	2	1	5
N.A.D. :	6	2	1	4
- Atrophy, tubular :	-	-	-	1
Grade 1:	-	-	-	1
EPIDIDYMIDES :	6	2	1	5
N.A.D. :	6	2	1	4
- Sperm granuloma :	-	-	-	1
Grade 3:	-	-	-	1

Group 01, CONTROL, males: DiHEP Aqueous Solution (0 MG/KG)
Group 02, 100 MG/KG, males: DiHEP Aqueous Solution (100 MG/KG)
Group 03, 300 MG/KG, males: DiHEP Aqueous Solution (300 MG/KG)
Group 04, 1000 MG/KG, males: DiHEP Aqueous Solution (1000 MG/KG)

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
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SPONSOR : Shell International B.V. PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
Incidence table - All microscopic findings

SEX :				MALE
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
BONE, STERNUM :	5	-	-	5
N.A.D. :	5	-	-	5
BONE MARROW, STERNUM :	5	-	-	5
N.A.D. :	5	-	-	5
BONE, FEMUR :	5	-	-	5
N.A.D. :	5	-	-	5
BONE MARROW, FEMUR :	5	-	-	5
N.A.D. :	5	-	-	5
JOINT,KNEE,LEFT :	5	-	-	5
N.A.D. :	5	-	-	5

Group 01, CONTROL, males: DiHEP Aqueous Solution (0 MG/KG)
Group 02, 100 MG/KG, males: DiHEP Aqueous Solution (100 MG/KG)
Group 03, 300 MG/KG, males: DiHEP Aqueous Solution (300 MG/KG)
Group 04, 1000 MG/KG, males: DiHEP Aqueous Solution (1000 MG/KG)

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
Incidence table - All microscopic findings

SEX :				FEMALE
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
BRAIN :	5	-	-	5
N.A.D. :	5	-	-	5
SPINAL CORD, CERVIC. :	5	-	-	5
N.A.D. :	5	-	-	5
SPINAL CORD, THORAC. :	5	-	-	5
N.A.D. :	5	-	-	5
SPINAL CORD, LUMBAR :	5	-	-	5
N.A.D. :	5	-	-	5
PITUITARY GLAND :	5	-	-	5
N.A.D. :	5	-	-	5
SCIATIC NERVE,RIGHT :	5	-	-	5
N.A.D. :	5	-	-	5
EYES :	6	-	1	6
N.A.D. :	5	-	1	4
- Retinal dysplasia :	-	-	-	1
Grade 1:	-	-	-	1
- Hemorrhage :	1	-	-	1
Grade 3:	-	-	-	1
Grade 4:	1	-	-	-

Group 01, CONTROL, females: DiHEP Aqueous Solution (0 MG/KG)
Group 02, 100 MG/KG, females: DiHEP Aqueous Solution (100 MG/KG)
Group 03, 300 MG/KG, females: DiHEP Aqueous Solution (300 MG/KG)
Group 04, 1000 MG/KG, females: DiHEP Aqueous Solution (1000 MG/KG)

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
Incidence table - All microscopic findings

SEX :					FEMALE
DOSE GROUP:	01	02	03	04	
NO.ANIMALS:	10	10	10	10	
THYMUS :	6	-	1	5	
N.A.D. :	3	-	-	2	
- Congestion :	1	-	1	-	
- Lymphoid atrophy, :	1	-	-	2	
Grade 1:	1	-	-	2	
- Hyperplasia, epith. :	2	-	-	1	
Grade 1:	2	-	-	1	
MANDIB.LYMPH NODE :	6	-	-	6	
N.A.D. :	5	-	-	4	
- Plasmacytosis :	-	-	-	1	
Grade 2:	-	-	-	1	
- Erythrocytes, sinus :	1	-	-	1	
Grade 1:	-	-	-	-	
Grade 2:	-	-	-	1	
Grade 3:	1	-	-	-	
ADRENAL GLANDS :	5	-	-	5	
N.A.D. :	5	-	-	5	
THYROID GLAND :	5	-	1	5	
N.A.D. :	3	-	1	4	
- Thymus, ectopic :	1	-	-	-	
- Hypertrophy foll. c.:	1	-	-	1	
Grade 1:	1	-	-	1	
MAMMARY GLAND :	5	-	-	5	
N.A.D. :	-	-	-	-	
- Lobuloalveolar dev. :	5	-	-	5	

Group 01, CONTROL, females: DiHEP Aqueous Solution (0 MG/KG)
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Group 04, 1000 MG/KG, females: DiHEP Aqueous Solution (1000 MG/KG)

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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
Incidence table - All microscopic findings

SEX :				FEMALE
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
LUNG :	5	-	-	5
N.A.D. :	4	-	-	2
- Alveolar macrophages:	1	-	-	2
Grade 1:	1	-	-	2
- Inflamm. peribronch.:	1	-	-	1
Grade 1:	1	-	-	1
Grade 2:	-	-	-	-
TRACHEA :	5	-	-	5
N.A.D. :	5	-	-	5
SKELETAL MUSCLE :	5	-	-	5
N.A.D. :	5	-	-	4
- Infiltrate inflamm. :	-	-	-	1
Grade 1:	-	-	-	1
HEART :	5	-	-	5
N.A.D. :	5	-	-	5
SPLEEN :	5	-	-	5
- Hematopoiesis, :	5	-	-	4
Grade 1:	5	-	-	4
Grade 2:	-	-	-	-
- Pigmentation, hemos.:	5	-	-	5
Grade 1:	3	-	-	2
Grade 2:	2	-	-	3
LIVER :	5	-	-	5
N.A.D. :	4	-	-	4
- Infiltrate inflamm. :	1	-	-	1
Grade 1:	1	-	-	1

Group 01, CONTROL, females: DiHEP Aqueous Solution (0 MG/KG)
Group 02, 100 MG/KG, females: DiHEP Aqueous Solution (100 MG/KG)
Group 03, 300 MG/KG, females: DiHEP Aqueous Solution (300 MG/KG)
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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
Incidence table - All microscopic findings

SEX :				FEMALE
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
URINARY BLADDER :	5	-	-	5
N.A.D. :	5	-	-	5
KIDNEYS :	5	-	-	5
N.A.D. :	4	-	-	3
- Basophilia, tubule :	1	-	-	2
Grade 1:	1	-	-	2
- Hyaline casts :	-	-	-	1
Grade 1:	-	-	-	1
STOMACH :	5	-	-	5
N.A.D. :	4	-	-	3
- Inflammation, gland.:	-	-	-	1
Grade 1:	-	-	-	1
- Glandular dilation, :	1	-	-	1
Grade 1:	-	-	-	1
Grade 2:	1	-	-	-
DUODENUM :	5	-	-	5
N.A.D. :	5	-	-	5
JEJUNUM :	5	-	1	5
N.A.D. :	5	-	-	5
- Congestion, :	-	-	1	-
Grade 1:	-	-	1	-
ILEUM :	5	-	-	5
N.A.D. :	5	-	-	5

Group 01, CONTROL, females: DiHEP Aqueous Solution (0 MG/KG)
Group 02, 100 MG/KG, females: DiHEP Aqueous Solution (100 MG/KG)
Group 03, 300 MG/KG, females: DiHEP Aqueous Solution (300 MG/KG)
Group 04, 1000 MG/KG, females: DiHEP Aqueous Solution (1000 MG/KG)

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
Incidence table - All microscopic findings

SEX :				FEMALE
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
GALT :	5	-	-	5
N.A.D. :	5	-	-	5
CECUM :	5	-	-	5
N.A.D. :	5	-	-	5
COLON :	5	-	-	5
N.A.D. :	5	-	-	5
RECTUM :	5	-	-	5
N.A.D. :	5	-	-	5
MESENT. LYMPH NODE :	5	-	-	5
N.A.D. :	5	-	-	5
OVARIES :	7	2	1	6
N.A.D. :	7	2	1	6
UTERUS :	7	2	1	6
N.A.D. :	2	2	-	-
- Cyclic dilation :	-	-	1	1
- Implantation site(s):	5	-	-	5
- Placenta necrosis :	1	-	-	-
Grade 3:	1	-	-	-
CERVIX :	7	2	1	6
N.A.D. :	7	2	1	6

Group 01, CONTROL, females: DiHEP Aqueous Solution (0 MG/KG)
Group 02, 100 MG/KG, females: DiHEP Aqueous Solution (100 MG/KG)
Group 03, 300 MG/KG, females: DiHEP Aqueous Solution (300 MG/KG)
Group 04, 1000 MG/KG, females: DiHEP Aqueous Solution (1000 MG/KG)

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K0
Incidence table - All microscopic findings

SEX :					FEMALE
DOSE GROUP:	01	02	03	04	
NO.ANIMALS:	10	10	10	10	
VAGINA :	7	2	1	6	
N.A.D. :	5	-	-	5	
- Cycle: Proestrus :	-	-	1	1	
- Cycle: Metestrus :	1	1	-	-	
- Cycle: Diestrus :	-	1	-	-	
- Incr. mucification :	1	-	-	-	
Grade 3:	1	-	-	-	
BONE, STERNUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
BONE MARROW, STERNUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
BONE, FEMUR :	5	-	-	5	
N.A.D. :	5	-	-	5	
BONE MARROW, FEMUR :	5	-	-	5	
N.A.D. :	5	-	-	5	
JOINT,KNEE,LEFT :	5	-	-	5	
N.A.D. :	5	-	-	5	
BODY CAVITIES :	-	-	1	-	
- Fat necrosis, :	-	-	1	-	
Grade 1:	-	-	1	-	
CLITORAL GLANDS :	-	1	-	-	
- Dilation, :	-	1	-	-	
Grade 2:	-	1	-	-	

Group 01, CONTROL, females: DiHEP Aqueous Solution (0 MG/KG)
Group 02, 100 MG/KG, females: DiHEP Aqueous Solution (100 MG/KG)
Group 03, 300 MG/KG, females: DiHEP Aqueous Solution (300 MG/KG)
Group 04, 1000 MG/KG, females: DiHEP Aqueous Solution (1000 MG/KG)

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER :	1	2	3	4	5	6	7	8	9	10
	MK0	MK0	MK0	MK0	MK0	MK0	MK0	MK0	MK0	MK0
BRAIN	-	-	-	-	-	'	'	'	'	'
SPINAL CORD, CERVIC.	-	-	-	-	-	'	'	'	'	'
SPINAL CORD, THORAC.	-	-	-	-	-	'	'	'	'	'
SPINAL CORD, LUMBAR	-	-	-	-	-	'	'	'	'	'
PITUITARY GLAND	-	-	-	-	-	'	'	'	'	'
SCIATIC NERVE,RIGHT	-	-	-	-	-	'	'	'	'	'
EYES	-	-	-	-	-	'	'	'	'	'
THYMUS	+	-	-	-	-	'	'	'	'	'
- Cyst(s)	1.	.	.	.	.					
MANDIB.LYMPH NODE	-	-	-	-	-	'	'	'	'	'
ADRENAL GLANDS	-	-	-	+	-	'	'	'	'	'
- Vacuol. fasciculata	.	.	.	1.	.					
THYROID GLAND	-	-	-	-	+	'	'	'	'	'
- Hypertrophy foll. c.	.	.	.	.	1.					
MAMMARY GLAND	-	-	-	-	-	'	'	'	'	'
LUNG	+	-	+	+	+	'	'	'	'	'
- Inflamm. alv. acute	1.	.	.	1.	.					
- Inflamm. peribronch.	.	.	1.	1.	2.					
TRACHEA	-	-	-	-	-	'	'	'	'	'
SKELETAL MUSCLE	-	-	-	+	+	'	'	'	'	'
- Infiltrate inflamm.	.	.	.	1.	1.					
HEART	-	-	-	-	-	'	'	'	'	'

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER :	1	2	3	4	5	6	7	8	9	10
	MK0	MK0	MK0	MK0	MK0	MK0	MK0	MK0	MK0	MK0
SPLEEN	+	+	+	+	+	'	'	'	'	'
- Hematopoiesis,	1.	1.	2.	1.	1.					
- Pigmentation, hemos.	1.	.	1.	.	1.					
LIVER	+	+	+	+	-	'	'	'	'	'
- Infiltrate inflamm.	1.	1.	1.	1.	.					
URINARY BLADDER	-	-	-	-	-	'	'	'	'	'
KIDNEYS	+	+	-	+	+	'	'	'	'	'
- Infiltrate inflamm.	.	.	.	(1.	.					
- Hyaline droplet acc.	1.	.	.	.	.					
- Basophilia, tubule	.	(1.	.	.	(1.					
- Cyst	.	(1.	.	.	.					
STOMACH	-	-	-	-	+	'	'	'	'	'
- Inflammation, gland.	.	.	.	.	1.					
- Cyst(s)	.	.	.	.	1.					
- Vacuolation, lim. r.	.	.	.	.	1.					
DUODENUM	-	-	-	-	-	'	'	'	'	'
JEJUNUM	-	-	-	-	-	'	'	'	'	'
ILEUM	-	-	-	-	-	'	'	'	'	'
GALT	-	-	-	+	-	'	'	'	'	'
- Increas. vacuolation	.	.	.	1.	.					
CECUM	-	-	-	-	-	'	'	'	'	'
COLON	-	-	-	-	-	'	'	'	'	'
RECTUM	-	-	-	-	-	'	'	'	'	'
MESENT. LYMPH NODE	-	-	-	-	-	'	'	'	'	'
SEMINAL VESICLES	-	-	-	-	-	-	'	'	'	'

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER :	1 MK0	2 MK0	3 MK0	4 MK0	5 MK0	6 MK0	7 MK0	8 MK0	9 MK0	10 MK0
COAGULATING GLANDS	-	-	-	-	-	-	'	'	'	'
PROSTATE GLAND	-	-	-	-	+	+	'	'	'	'
- Infiltrate inflamm.	.	.	.	.	2.	1.				
TESTES	-	-	-	-	-	-	'	'	'	'
EPIDIDYMIDES	-	-	-	-	-	-	'	'	'	'
BONE, STERNUM	-	-	-	-	-	'	'	'	'	'
BONE MARROW, STERNUM	-	-	-	-	-	'	'	'	'	'
BONE, FEMUR	-	-	-	-	-	'	'	'	'	'
BONE MARROW, FEMUR	-	-	-	-	-	'	'	'	'	'
JOINT,KNEE,LEFT	-	-	-	-	-	'	'	'	'	'

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER :	41 FK0	42 FK0	43 FK0	44 FK0	45 FK0	46 FK0	47 FK0	48 FK0	49 FK0	50 FK0
BRAIN	-	'	'	-	-	'	-	'	'	-
SPINAL CORD, CERVIC.	-	'	'	-	-	'	-	'	'	-
SPINAL CORD, THORAC.	-	'	'	-	-	'	-	'	'	-
SPINAL CORD, LUMBAR	-	'	'	-	-	'	-	'	'	-
PITUITARY GLAND	-	'	'	-	-	'	-	'	'	-
SCIATIC NERVE,RIGHT	-	'	'	-	-	'	-	'	'	-
EYES	-	(+G	'	-	-	'	-	'	'	-
- Hemorrhage	.	(4.		.	.		.			.
THYMUS	+	+G	'	-	-	'	+	'	'	-
- Congestion	.	P.		.	.		.			.
- Lymphoid atrophy,	1.	.		.	.		.			.
- Hyperplasia, epith.	1.	.		.	.		1.			.
MANDIB.LYMPH NODE	-	+G	'	-	-	'	-	'	'	-
- Erythrocytes, sinus	.	3.		.	.		.			.
ADRENAL GLANDS	-	'	'	-	-	'	-	'	'	-
THYROID GLAND	-	'	'	-	+	'	+	'	'	-
- Thymus, ectopic	.			.	(P.		.			.
- Hypertrophy foll. c.	.			.	.		1.			.
MAMMARY GLAND	+	'	'	+	+	'	+	'	'	+
- Lobuloalveolar dev.	P.			P.	P.		P.			P.
LUNG	+	'	'	-	-	'	-	'	'	-
- Alveolar macrophages	1.			.	.		.			.
- Inflamm. peribronch.	1.			.	.		.			.
TRACHEA	-	'	'	-	-	'	-	'	'	-
SKELETAL MUSCLE	-	'	'	-	-	'	-	'	'	-

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER :	41 FK0	42 FK0	43 FK0	44 FK0	45 FK0	46 FK0	47 FK0	48 FK0	49 FK0	50 FK0
HEART	-	'	'	-	-	'	-	'	'	-
SPLEEN	+	'	'	+	+	'	+	'	'	+
- Hematopoiesis,	1.			1.	1.		1.			1.
- Pigmentation, hemos.	1.			1.	2.		2.			1.
LIVER	-	'	'	-	-	'	+	'	'	-
- Infiltrate inflamm.	.			.	.		1.			.
URINARY BLADDER	-	'	'	-	-	'	-	'	'	-
KIDNEYS	-	'	'	-	-	'	-	'	'	+
- Basophilia, tubule	.			.	.		.			(1.
STOMACH	-	'	'	-	+	'	-	'	'	-
- Glandular dilation,	.			.	2.		.			.
DUODENUM	-	'	'	-	-	'	-	'	'	-
JEJUNUM	-	'	'	-	-	'	-	'	'	-
ILEUM	-	'	'	-	-	'	-	'	'	-
GALT	-	'	'	-	-	'	-	'	'	-
CECUM	-	'	'	-	-	'	-	'	'	-
COLON	-	'	'	-	-	'	-	'	'	-
RECTUM	-	'	'	-	-	'	-	'	'	-
MESENT. LYMPH NODE	-	'	'	-	-	'	-	'	'	-
OVARIES	-	-	'	-	-	-	-	'	'	-
UTERUS	+	+G	'	-	+	-*	+	'	'	+
- Implantation site(s)	P.	P.		.	P.	.	P.			P.
- Placenta necrosis	.	3.		.	.	.	.			.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER :	41 FK0	42 FK0	43 FK0	44 FK0	45 FK0	46 FK0	47 FK0	48 FK0	49 FK0	50 FK0
CERVIX	-	-	'	-	-	-	-	'	'	-
VAGINA	-	+	'	-	-	+	-	'	'	-
- Cycle: Metestrus	.	.		.	.	P.	.			.
- Incr. mucification	.	3.		.	.	.	.			.
BONE, STERNUM	-	'	'	-	-	'	-	'	'	-
BONE MARROW, STERNUM	-	'	'	-	-	'	-	'	'	-
BONE, FEMUR	-	'	'	-	-	'	-	'	'	-
BONE MARROW, FEMUR	-	'	'	-	-	'	-	'	'	-
JOINT,KNEE,LEFT	-	'	'	-	-	'	-	'	'	-

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 02, 100 MG/KG

ANIMAL NUMBER :	11 MK0	12 MK0	13 MK0	14 MK0	15 MK0	16 MK0	17 MK0	18 MK0	19 MK0	20 MK0
ADRENAL GLANDS	+	-	-	+	+	'	'	'	'	'
- Vacuol. fasciculata	1.	.	.	1.	1.					
STOMACH	+	+	-	+	-	'	'	'	'	'
- Inflammation, gland.	.	1.	.	1.	.					
- Hemorrhage	1.	.	.	.	.					
SEMINAL VESICLES	-	'	-	'	'	'	'	'	'	'
COAGULATING GLANDS	-	'	-	'	'	'	'	'	'	'
PROSTATE GLAND	-	'	-	'	'	'	'	'	'	'
TESTES	-	'	-	'	'	'	'	'	'	'
EPIDIDYMIDES	-	'	-	'	'	'	'	'	'	'
BONE	'	'	'	'!	'	'	'	'	'	'

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 02, 100 MG/KG

ANIMAL NUMBER :	51 FK0	52 FK0	53 FK0	54 FK0	55 FK0	56 FK0	57 FK0	58 FK0	59 FK0	60 FK0
OVARIES	-	'	-	'	'	'	'	'	'	'
UTERUS	-*	'	-*	'	'	'	'	'	'	'
CERVIX	-	'	-	'	'	'	'	'	'	'
VAGINA	+	'	+	'	'	'	'	'	'	'
- Cycle: Metestrus	P.		.							
- Cycle: Diestrus	.		P.							
BODY CAVITIES	'	'!	'	'	'	'	'!	'	'	'
CLITORAL GLANDS	'	'	'	'	'	'	+G	'	'	'
- Dilation,							(2.			

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 03, 300 MG/KG

ANIMAL NUMBER :	21 MK0	22 MK0	23 MK0	24 MK0	25 MK0	26 MK0	27 MK0	28 MK0	29 MK0	30 MK0
ADRENAL GLANDS	-	+	+	-	-	'	'	'	'	'
- Vacuol. fasciculata	.	1.	1.	.	.					
STOMACH	-	-	-	-	-	'	'	'	'	'
SEMINAL VESICLES	'	'	-	'	'	'	'	'	'	'
COAGULATING GLANDS	'	'	-	'	'	'	'	'	'	'
PROSTATE GLAND	'	'	-	'	'	'	'	'	'	'
TESTES	'	'	-	'	'	'	'	'	'	'
EPIDIDYMIDES	'	'	-	'	'	'	'	'	'	'

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 03, 300 MG/KG

ANIMAL NUMBER :	61 FK0	62 FK0	63 FK0	64 FK0	65 FK0	66 FK0	67 FK0	68 FK0	69 FK0	70 FK0
EYES						(-G				
THYMUS							+G			
- Congestion							P.			
THYROID GLAND						-G				
JEJUNUM				+G						
- Congestion,				1.						
OVARIES			-							
UTERUS			+G							
- Cyclic dilation			P.							
CERVIX			-							
VAGINA			+							
- Cycle: Proestrus			P.							
BODY CAVITIES					+G					!
- Fat necrosis,					1.					

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 04, 1000 MG/KG

ANIMAL NUMBER :	31 MK0	32 MK0	33 MK0	34 MK0	35 MK0	36 MK0	37 MK0	38 MK0	39 MK0	40 MK0
BRAIN	-	-	-	-	-	'	'	'	'	'
SPINAL CORD, CERVIC.	-	-	-	-	-	'	'	'	'	'
SPINAL CORD, THORAC.	-	-	-	-	-	'	'	'	'	'
SPINAL CORD, LUMBAR	-	-	-	-	-	'	'	'	'	'
PITUITARY GLAND	-	-	-	-	-	'	'	'	'	'
SCIATIC NERVE,RIGHT	-	-	-	-	-	'	'	'	'	'
EYES	-	-	-	-	-	'	'	'	'	'
THYMUS	-	-	-	-	-	'	'	'	'	'
MANDIB.LYMPH NODE	-	-	-	+	-	'	'	'	'	'
- Erythrocytes, sinus	.	.	.	1.	.					
ADRENAL GLANDS	-	+	-	-	+	'	'	'	'	'
- Vacuol. fasciculata	.	1.	.	.	1.					
THYROID GLAND	-	-	-	-	+	'	'	'	'	'
- Hypertrophy foll. c.	.	.	.	.	1.					
MAMMARY GLAND	-	-	-	-	-	'	'	'	'	'
LUNG	+	-	+	-	-	'	'	'	'	'
- Alveolar macrophages	.	.	1.	.	.					
- Inflamm. peribronch.	1.	.	1.	.	.					
TRACHEA	-	-	-	-	-	'	'	'	'	'
SKELETAL MUSCLE	+	-	+	-	-	'	'	'	'	'
- Infiltrate inflamm.	1.	.	1.	.	.					
HEART	-	-	+	-	-	'	'	'	'	'
- Infiltrate inflamm.	.	.	1.	.	.					

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 04, 1000 MG/KG

ANIMAL NUMBER :	31 MK0	32 MK0	33 MK0	34 MK0	35 MK0	36 MK0	37 MK0	38 MK0	39 MK0	40 MK0
SPLEEN	+	+	+	+	+	'	'	'	'	'
- Hematopoiesis,	1.	1.	1.	1.	.					
- Pigmentation, hemos.	1.	1.	1.	1.	1.					
LIVER	+G	-	+	-	-	'	'	'	'	'
- Infiltrate inflamm.	1.	.	1.	.	.					
URINARY BLADDER	-	-	-	-	-	'	'	'	'	'
KIDNEYS	+	+G	-	-	+	'	'	'	'	'
- Infiltrate inflamm.	.	(1.	.	.	(1.					
- Basophilia, tubule	1.	1.	.	.	(1.					
STOMACH	-	+	+	+	+	'	'	'	'	'
- Erosion glandular	.	2.	1.	1.	.					
- Vacuolation, lim. r.	.	.	.	.	1.					
DUODENUM	-	-	-	-	-	'	'	'	'	'
JEJUNUM	-	-	-	-	-	'	'	'	'	'
ILEUM	-	-	-	-	-	'	'	'	'	'
GALT	-	-	-	-	-	'	'	'	'	'
CECUM	-	-	-	-	-	'	'	'	'	'
COLON	-	-	-	-	-	'	'	'	'	'
RECTUM	-	-	-	-	-	'	'	'	'	'
MESENT. LYMPH NODE	-	-	-	-	-	'	'	'	'	'
SEMINAL VESICLES	-	-	-	-	-	'	'	'	'	'
COAGULATING GLANDS	-	-	-	-	-	'	'	'	'	'
PROSTATE GLAND	-	-	-	-	-	'	'	'	'	'

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 04, 1000 MG/KG

ANIMAL NUMBER :	31 MK0	32 MK0	33 MK0	34 MK0	35 MK0	36 MK0	37 MK0	38 MK0	39 MK0	40 MK0
TESTES	-	+	-	-	-	'	'	'	'	'
- Atrophy, tubular	.	(1.	.	.	.					
EPIDIDYMIDES	-	-	-	-	+G	'	'	'	'	'
- Sperm granuloma	.	.	.	.	(3.					
BONE, STERNUM	-	-	-	-	-	'	'	'	'	'
BONE MARROW, STERNUM	-	-	-	-	-	'	'	'	'	'
BONE, FEMUR	-	-	-	-	-	'	'	'	'	'
BONE MARROW, FEMUR	-	-	-	-	-	'	'	'	'	'
JOINT,KNEE,LEFT	-	-	-	-	-	'	'	'	'	'

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 04, 1000 MG/KG

ANIMAL NUMBER :	71 FK0	72 FK0	73 FK0	74 FK0	75 FK0	76 FK0	77 FK0	78 FK0	79 FK0	80 FK0
BRAIN	-	'	-	-	'	'	'	'	-	-
SPINAL CORD, CERVIC.	-	'	-	-	'	'	'	'	-	-
SPINAL CORD, THORAC.	-	'	-	-	'	'	'	'	-	-
SPINAL CORD, LUMBAR	-	'	-	-	'	'	'	'	-	-
PITUITARY GLAND	-	'	-	-	'	'	'	'	-	-
SCIATIC NERVE,RIGHT	-	'	-	-	'	'	'	'	-	-
EYES	-	(+G	-	+	'	'	'	'	-	-
- Retinal dysplasia	.	.	.	(1.					.	.
- Hemorrhage	.	(3.	.	.					.	.
THYMUS	+	'	-	+	'	'	'	'	-	+
- Lymphoid atrophy,	1.		.	1.					.	.
- Hyperplasia, epith.	.		.	.					.	1.
MANDIB.LYMPH NODE	-	+G	-	-	'	'	'	'	+	-
- Plasmacytosis	.	.	.	.					2.	.
- Erythrocytes, sinus	.	2.	.	.					.	.
ADRENAL GLANDS	-	'	-	-	'	'	'	'	-	-
THYROID GLAND	-	'	-	-G	'	'	'	'	+	-
- Hypertrophy foll. c.	.		.	.					1.	.
MAMMARY GLAND	+	'	+	+	'	'	'	'	+	+
- Lobuloalveolar dev.	P.		P.	P.					P.	P.
LUNG	-	'	-	+	'	'	'	'	+	+
- Alveolar macrophages	.		.	1.					.	1.
- Inflamm. peribronch.	.		.	.					1.	.
TRACHEA	-	'	-	-	'	'	'	'	-	-

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 04, 1000 MG/KG

ANIMAL NUMBER :	71 FK0	72 FK0	73 FK0	74 FK0	75 FK0	76 FK0	77 FK0	78 FK0	79 FK0	80 FK0
SKELETAL MUSCLE	-	'	-	-	'	'	'	'	+	-
- Infiltrate inflamm.	.		.	.					1.	.
HEART	-	'	-	-	'	'	'	'	-	-
SPLEEN	+	'	+	+	'	'	'	'	+	+
- Hematopoiesis,	1.		1.	1.					1.	.
- Pigmentation, hemos.	2.		2.	1.					1.	2.
LIVER	-	'	-	-	'	'	'	'	-	+
- Infiltrate inflamm.	.		.	.					.	1.
URINARY BLADDER	-	'	-	-	'	'	'	'	-	-
KIDNEYS	-	'	-	-	'	'	'	'	+	+
- Basophilia, tubule	.		.	.					(1.	(1.
- Hyaline casts	.		.	.					.	(1.
STOMACH	-	'	+	-	'	'	'	'	-	+
- Inflammation, gland.	.		1.	.					.	.
- Glandular dilation,	.		.	.					.	1.
DUODENUM	-	'	-	-	'	'	'	'	-	-
JEJUNUM	-	'	-	-	'	'	'	'	-	-
ILEUM	-	'	-	-	'	'	'	'	-	-
GALT	-	'	-	-	'	'	'	'	-	-
CECUM	-	'	-	-	'	'	'	'	-	-
COLON	-	'	-	-	'	'	'	'	-	-
RECTUM	-	'	-	-	'	'	'	'	-	-
MESENT. LYMPH NODE	-	'	-	-	'	'	'	'	-	-
OVARIES	-	-	-	-	'	'	'	'	-	-

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 04, 1000 MG/KG

ANIMAL NUMBER :	71 FK0	72 FK0	73 FK0	74 FK0	75 FK0	76 FK0	77 FK0	78 FK0	79 FK0	80 FK0
UTERUS	+	+G	+	+	'	'	'	'	+	+
- Cyclic dilation	.	P.	.	.					.	.
- Implantation site(s)	P.	.	P.	P.					P.	P.
CERVIX	-	-	-	-	'	'	'	'	-	-
VAGINA	-	+	-	-	'	'	'	'	-	-
- Cycle: Proestrus	.	P.	.	.					.	.
BONE, STERNUM	-	'	-	-	'	'	'	'	-	-
BONE MARROW, STERNUM	-	'	-	-	'	'	'	'	-	-
BONE, FEMUR	-	'	-	-	'	'	'	'	-	-
BONE MARROW, FEMUR	-	'	-	-	'	'	'	'	-	-
JOINT,KNEE,LEFT	-	'	-	-	'	'	'	'	-	-

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

ANIMAL HEADING DATA
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER	SEX M/F	DEFINED STATE OF NECROPSY	AND FINAL STATE OF NECROPSY	TEST DAYS	FIRST DAY UNDER TEST	AND LAST DAY UNDER TEST	DATE OF NECROPSY
1	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
2	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
3	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
4	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
5	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
6	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
7	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
8	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
9	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
10	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
41	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
42	F	K0	K0	42	05-FEB-19	18-MAR-19	19-MAR-19
43	F	K0	K0	55	05-FEB-19	31-MAR-19	01-APR-19
44	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
45	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
46	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
47	F	K0	K0	51	05-FEB-19	27-MAR-19	28-MAR-19
48	F	K0	K0	55	05-FEB-19	31-MAR-19	01-APR-19
49	F	K0	K0	55	05-FEB-19	31-MAR-19	01-APR-19
50	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 1

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

THYMUS:
-Cyst(s), grade 1
LUNG:
-Inflammation bronchioalveolar, acute, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 1
LIVER:
-Infiltrate inflammatory cell, mononuclear, grade 1
KIDNEYS:
-Hyaline droplet accumulation, bilateral, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), MAMMARY GLAND, TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, STOMACH, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 2

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
-Hematopoiesis, extramedullary, grade 1
LIVER:
-Infiltrate inflammatory cell, mononuclear, grade 1
KIDNEYS:
-Basophilia, tubule, unilateral, grade 1
-Cyst, single, unilateral, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), MAMMARY GLAND, LUNG, TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, STOMACH, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 3

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LUNG:
-Inflammation peribronchial/perivascular, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 2
-Pigmentation, hemosiderin, grade 1
LIVER:
-Infiltrate inflammatory cell, mononuclear, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), MAMMARY GLAND, TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 4

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:
-Vacuolation zona fasciculata, bilateral, grade 1
LUNG:
-Inflammation bronchioalveolar, acute, grade 1
-Inflammation peribronchial/perivascular, grade 1
SKELETAL MUSCLE:
-Infiltrate inflammatory cell, mononuclear, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
LIVER:
-Infiltrate inflammatory cell, mononuclear, grade 1
KIDNEYS:
-Infiltrate inflammatory cell, lymphocytic, unilateral, grade 1
GUT-ASSOCIATED LYMPHOID TISSUE:
-Increased vacuolation, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL MALE

CONT./FF. ANIMAL NO. : 4

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, MANDIBULAR LYMPH NODE, THYROID GLAND (BOTH LOBES), MAMMARY GLAND, TRACHEA, HEART, URINARY BLADDER, STOMACH, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

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* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 5

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):
-Hypertrophy follicular cell, bilateral, grade 1
LUNG:
-Inflammation peribronchial/perivascular, grade 2
SKELETAL MUSCLE:
-Infiltrate inflammatory cell, mononuclear, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 1
KIDNEYS:
-Basophilia, tubule, unilateral, grade 1

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL MALE

CONT./FF. ANIMAL NO. : 5

STOMACH:
-Inflammation, glandular stomach, lymphogranulocytic, grade 1
-Cyst(s), squamous cell, grade 1
-Vacuolation, limiting ridge, grade 1
PROSTATE GLAND:
-Infiltrate inflammatory cell, mononuclear, grade 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, MAMMARY GLAND, TRACHEA, HEART, LIVER, URINARY BLADDER, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), TESTES, EPIDIDYMIDES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 6

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL MALE

CONT./FF. ANIMAL NO. : 6

* MICROSCOPIC FINDINGS

PROSTATE GLAND:
-Infiltrate inflammatory cell, mononuclear, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), TESTES, EPIDIDYMIDES.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 7

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 8

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 9

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 10

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 41

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

THYMUS:
-Lymphoid atrophy, grade 1
-Hyperplasia, epithelial tubules and cords, grade 1
MAMMARY GLAND:
-Lobuloalveolar development
LUNG:
-Alveolar macrophage aggregation, grade 1
-Inflammation peribronchial/perivascular, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 1
UTERUS:
-Implantation site(s)
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), TRACHEA, SKELETAL MUSCLE, HEART, LIVER, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, CERVIX, VAGINA, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 42 * ANIMAL NO. : 42

* NECROPSY FINDINGS

EYES:
01: LEFT SIDE: EXOPHTHALMUS.
THYMUS:
01: RIGHT SIDE: FOCUS/FOCI, ISOLATED, REDDISH.
MANDIBULAR LYMPH NODE:
01: BOTH SIDES: FOCUS/FOCI, ISOLATED, DARK RED.
UTERUS:
01: RIGHT HORN: CONTENTS: GREENISH, GELATINOUS.
02: RIGHT HORN: NODULE(S), D=8X7 MM, TAN, REDDISH, HARD.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

EYES:
Only one of paired organs examined/present
-Hemorrhage, peribulbar and intraocular, unilateral, grade 4
This finding corresponds to necropsy observation no: 01.
THYMUS:
-Congestion
This finding corresponds to necropsy observation no: 01.
MANDIBULAR LYMPH NODE:
One of the mandibular lymph nodes is not present/recognizable on the slide. Instead there is large hemmorhaghe, with an area containing plant material.
-Erythrocytes, intrasinusoidal, grade 3
This finding corresponds to necropsy observation no: 01.
UTERUS:
Draining lymphnode without abnormalities.
-Implantation site(s)
This finding corresponds to necropsy observation no: 02.
-Placenta necrosis, grade 3
This finding corresponds to necropsy observations nos: 01,02.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO. : 42

VAGINA:
-Increased mucification, grade 3
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- OVARIES, CERVIX.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 55 * ANIMAL NO. : 43

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 44

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

MAMMARY GLAND:
-Lobuloalveolar development
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), LUNG, TRACHEA, SKELETAL MUSCLE, HEART, LIVER, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, UTERUS, CERVIX, VAGINA, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 45

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):
-Thymus, ectopic, unilateral
MAMMARY GLAND:
-Lobuloalveolar development
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 2
STOMACH:
-Glandular dilation, grade 2
UTERUS:
-Implantation site(s)
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, LUNG, TRACHEA, SKELETAL MUSCLE, HEART, LIVER, URINARY BLADDER, KIDNEYS, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, CERVIX, VAGINA, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 46

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

UTERUS:
Autolytic endometrium due to Salewski staining.
VAGINA:
-Cycle: metestrus
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- OVARIES, UTERUS, CERVIX.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 51 * ANIMAL NO. : 47

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

THYMUS:
-Hyperplasia, epithelial tubules and cords, grade 1
THYROID GLAND (BOTH LOBES):
-Hypertrophy follicular cell, bilateral, grade 1

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO. : 47

MAMMARY GLAND:
-Lobuloalveolar development
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 2
LIVER:
-Infiltrate inflammatory cell, mononuclear, grade 1
UTERUS:
-Implantation site(s)
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, LUNG, TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, CERVIX, VAGINA, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

* STATE AT NECROPSY: K0
DAYS ON TEST : 55 * ANIMAL NO. : 48

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO. : 48

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 55 * ANIMAL NO. : 49

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 50

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO. : 50

* MICROSCOPIC FINDINGS

MAMMARY GLAND:
-Lobuloalveolar development
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 1
KIDNEYS:
-Basophilia, tubule, unilateral, grade 1
UTERUS:
-Implantation site(s)
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), LUNG, TRACHEA, SKELETAL MUSCLE, HEART, LIVER, URINARY BLADDER, STOMACH, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, CERVIX, VAGINA, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

ANIMAL HEADING DATA
DOSE GROUP : 02, 100 MG/KG

ANIMAL NUMBER	SEX M/F	DEFINED AND FINAL STATE OF NECROPSY		TEST DAYS	FIRST AND LAST DAY UNDER TEST		DATE OF NECROPSY
11	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
12	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
13	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
14	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
15	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
16	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
17	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
18	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
19	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
20	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
51	F	K0	K0	42	05-FEB-19	18-MAR-19	19-MAR-19
52	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
53	F	K0	K0	42	05-FEB-19	18-MAR-19	19-MAR-19
54	F	K0	K0	51	05-FEB-19	27-MAR-19	28-MAR-19
55	F	K0	K0	56	05-FEB-19	01-APR-19	02-APR-19
56	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
57	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
58	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
59	F	K0	K0	55	05-FEB-19	31-MAR-19	01-APR-19
60	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 11

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:
-Vacuolation zona fasciculata, bilateral, grade 1
STOMACH:
-Hemorrhage, focal, glandular mucosa pylorus, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES.

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 12

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG MALE

CONT./FF. ANIMAL NO. : 12

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:
Organ examined, no pathologic findings noted
STOMACH:
-Inflammation, glandular stomach, lymphogranulocytic, grade 1

* ORGANS WITHOUT ABNORMALITIES

- ADRENAL GLANDS.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 13

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

* ORGANS WITHOUT ABNORMALITIES

- ADRENAL GLANDS, STOMACH, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 14

* NECROPSY FINDINGS

BONE:
01: TAIL, TAIL APEX: TAIL BENT.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:
-Vacuolation zona fasciculata, bilateral, grade 1
STOMACH:
-Inflammation, glandular stomach, lymphogranulocytic, grade 1

---

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 15

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:
-Vacuolation zona fasciculata, bilateral, grade 1
STOMACH:
Organ examined, no pathologic findings noted

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG MALE

CONT./FF. ANIMAL NO. : 15

* ORGANS WITHOUT ABNORMALITIES

- STOMACH.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 16

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 17

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG MALE

CONT./FF. ANIMAL NO. : 17

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

---

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 18

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 19

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG MALE

CONT./FF. ANIMAL NO. : 19

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

---

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 20

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 42 * ANIMAL NO. : 51

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

UTERUS:
Autolytic endometrium due to Salewski staining.
VAGINA:
-Cycle: metestrus
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- OVARIES, UTERUS, CERVIX.

---

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 52

* NECROPSY FINDINGS

BODY CAVITIES:
01: THORACIC CAVITY: CONTAINS FLUID, WATERY-CLEAR.
NO OTHER NECROPSY OBSERVATIONS NOTED

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG FEMALE

CONT./FF. ANIMAL NO. : 52

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

---

* STATE AT NECROPSY: K0
DAYS ON TEST : 42 * ANIMAL NO. : 53

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

UTERUS:
Autolytic endometrium due to Salewski staining.
VAGINA:
-Cycle: diestrus
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- OVARIES, UTERUS, CERVIX.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 51 * ANIMAL NO. : 54

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 56 * ANIMAL NO. : 55

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 56

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

---

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 57

* NECROPSY FINDINGS

BODY CAVITIES:
01: THORACIC CAVITY: CONTAINS FLUID, WATERY-CLEAR.
CLITORAL GLANDS:
01: LEFT SIDE: FOCUS/FOCI, D=6X2 MM, TAN.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

CLITORAL GLANDS:
-Dilation, unilateral, grade 2
This finding corresponds to necropsy observation no: 01.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 58

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 55 * ANIMAL NO. : 59

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 60

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

ANIMAL HEADING DATA
DOSE GROUP : 03, 300 MG/KG

ANIMAL NUMBER	SEX M/F	DEFINED AND FINAL STATE OF NECROPSY		TEST DAYS	FIRST AND LAST DAY UNDER TEST		DATE OF NECROPSY
21	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
22	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
23	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
24	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
25	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
26	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
27	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
28	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
29	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
30	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
61	F	K0	K0	56	05-FEB-19	01-APR-19	02-APR-19
62	F	K0	K0	55	05-FEB-19	31-MAR-19	01-APR-19
63	F	K0	K0	42	05-FEB-19	18-MAR-19	19-MAR-19
64	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
65	F	K0	K0	55	05-FEB-19	31-MAR-19	01-APR-19
66	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
67	F	K0	K0	55	05-FEB-19	31-MAR-19	01-APR-19
68	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
69	F	K0	K0	55	05-FEB-19	31-MAR-19	01-APR-19
70	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 21

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

* ORGANS WITHOUT ABNORMALITIES

- ADRENAL GLANDS, STOMACH.

---

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 22

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:
-Vacuolation zona fasciculata, bilateral, grade 1
STOMACH:
Organ examined, no pathologic findings noted

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG MALE

CONT./FF. ANIMAL NO. : 22

* ORGANS WITHOUT ABNORMALITIES

- STOMACH.

---

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 23

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:
-Vacuolation zona fasciculata, bilateral, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- STOMACH, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 24

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

* ORGANS WITHOUT ABNORMALITIES

- ADRENAL GLANDS, STOMACH.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 25

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

* ORGANS WITHOUT ABNORMALITIES

- ADRENAL GLANDS, STOMACH.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 26

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 27

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 29

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 30

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 56 * ANIMAL NO. : 61

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 55 * ANIMAL NO. : 62

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 42 * ANIMAL NO. : 63

* NECROPSY FINDINGS

UTERUS:
01: CONTAINS FLUID.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

UTERUS:
Autolytic endometrium due to Salewski staining.
For diagnosis of necropsy observation no. 01 see under: VAGINA.
-Cyclic dilation
This finding corresponds to necropsy observation no: 01.
VAGINA:
-Cycle: proestrus
This finding corresponds to necropsy observation no.: 01
in the UTERUS.
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- OVARIES, CERVIX.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 64

* NECROPSY FINDINGS

JEJUNUM:
01: FOCUS/FOCI, D=2X1 MM, REDDISH.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

JEJUNUM:
-Congestion, grade 1
This finding corresponds to necropsy observation no: 01.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 55 * ANIMAL NO. : 65

* NECROPSY FINDINGS

BODY CAVITIES:
01: ABDOMINAL CAVITY, UTERINE ADIPOSE TISSUE, RIGHT SIDE:
NODULE(S), D=5X2 MM, TAN, HARD.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

BODY CAVITIES:
Draining lymph nodes without abnormality.
-Fat necrosis, grade 1
This finding corresponds to necropsy observation no: 01.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 66

* NECROPSY FINDINGS

EYES:
01: RIGHT SIDE: EXOPHTHALMUS.
THYROID GLAND (BOTH LOBES):
01: BOTH SIDES: DISCOLOURATION, PALE.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

EYES:
Only one of paired organs examined/present
No microscopic finding corresponding to necropsy observation no. 01.
THYROID GLAND (BOTH LOBES):
No microscopic finding corresponding to necropsy observation no. 01.
NO MICROSCOPIC FINDINGS NOTED.

* ORGANS WITHOUT ABNORMALITIES

- EYES, THYROID GLAND (BOTH LOBES).

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* STATE AT NECROPSY: K0
DAYS ON TEST : 55 * ANIMAL NO. : 67

* NECROPSY FINDINGS

THYMUS:
01: RIGHT SIDE: FOCUS/FOCI, MANY, REDDISH.
NO OTHER NECROPSY OBSERVATIONS NOTED

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG FEMALE

CONT./FF. ANIMAL NO. : 67

* MICROSCOPIC FINDINGS

THYMUS:
-Congestion
This finding corresponds to necropsy observation no: 01.

---

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 68

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 55 * ANIMAL NO. : 69

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG FEMALE

CONT./FF. ANIMAL NO. : 69

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 70

* NECROPSY FINDINGS

BODY CAVITIES:
01: THORACIC CAVITY: CONTAINS FLUID, WATERY-CLEAR.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

ANIMAL HEADING DATA
DOSE GROUP : 04, 1000 MG/KG

ANIMAL NUMBER	SEX M/F	DEFINED AND FINAL STATE OF NECROPSY		TEST DAYS	FIRST AND LAST DAY UNDER TEST		DATE OF NECROPSY
31	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
32	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
33	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
34	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
35	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
36	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
37	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
38	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
39	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
40	M	K0	K0	29	05-FEB-19	05-MAR-19	06-MAR-19
71	F	K0	K0	51	05-FEB-19	27-MAR-19	28-MAR-19
72	F	K0	K0	42	05-FEB-19	18-MAR-19	19-MAR-19
73	F	K0	K0	51	05-FEB-19	27-MAR-19	28-MAR-19
74	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
75	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
76	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19
77	F	K0	K0	55	05-FEB-19	31-MAR-19	01-APR-19
78	F	K0	K0	55	05-FEB-19	31-MAR-19	01-APR-19
79	F	K0	K0	51	05-FEB-19	27-MAR-19	28-MAR-19
80	F	K0	K0	52	05-FEB-19	28-MAR-19	29-MAR-19

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 31

* NECROPSY FINDINGS

LIVER:
01: DISCOLOURATION, RED-BROWN.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

LUNG:
-Inflammation peribronchial/perivascular, grade 1
SKELETAL MUSCLE:
-Infiltrate inflammatory cell, mononuclear, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 1
LIVER:
No microscopic finding corresponding to necropsy observation no. 01.
-Infiltrate inflammatory cell, mononuclear, grade 1
KIDNEYS:
-Basophilia, tubule, bilateral, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG MALE

CONT./FF. ANIMAL NO. : 31

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), MAMMARY GLAND, TRACHEA, HEART, URINARY BLADDER, STOMACH, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

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* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 32

* NECROPSY FINDINGS

KIDNEYS:
01: CRANIAL POLE, RIGHT SIDE MIDDLE PART IRREGULAR SURFACE.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:
-Vacuolation zona fasciculata, bilateral, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 1
KIDNEYS:
No microscopic finding corresponding to necropsy observation no. 01.
-Infiltrate inflammatory cell, lymphocytic, unilateral, grade 1
-Basophilia, tubule, bilateral, grade 1

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG MALE

CONT./FF. ANIMAL NO. : 32

STOMACH:
-Erosion glandular stomach, multifocal, pylorus, grade 2
TESTES:
-Atrophy, tubular, unilateral, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, MANDIBULAR LYMPH NODE, THYROID GLAND (BOTH LOBES), MAMMARY GLAND, LUNG, TRACHEA, SKELETAL MUSCLE, HEART, LIVER, URINARY BLADDER, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, EPIDIDYMIDES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 33

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG MALE

CONT./FF. ANIMAL NO. : 33

* MICROSCOPIC FINDINGS

LUNG:
-Alveolar macrophage aggregation, grade 1
-Inflammation peribronchial/perivascular, grade 1
SKELETAL MUSCLE:
-Infiltrate inflammatory cell, mononuclear, grade 1
HEART:
-Infiltrate inflammatory cell, mononuclear, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 1
LIVER:
-Infiltrate inflammatory cell, mononuclear, grade 1
STOMACH:
-Erosion glandular stomach, multifocal, pylorus, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), MAMMARY GLAND, TRACHEA, URINARY BLADDER, KIDNEYS, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 34

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

MANDIBULAR LYMPH NODE:
-Erythrocytes, intrasinusoidal, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 1
STOMACH:
-Erosion glandular stomach, focal, pylorus, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), MAMMARY GLAND, LUNG, TRACHEA, SKELETAL MUSCLE, HEART, LIVER, URINARY BLADDER, KIDNEYS, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 35

* NECROPSY FINDINGS

EPIDIDYMIDES:
01: LEFT SIDE, TAIL: NODULE(S), D=10X6 MM, YELLOWISH, SOFT.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:
-Vacuolation zona fasciculata, bilateral, grade 1
THYROID GLAND (BOTH LOBES):
-Hypertrophy follicular cell, bilateral, grade 1
SPLEEN:
-Pigmentation, hemosiderin, grade 1
KIDNEYS:
-Infiltrate inflammatory cell, mononuclear, unilateral, grade 1
-Basophilia, tubule, unilateral, grade 1
STOMACH:
-Vacuolation, limiting ridge, grade 1
EPIDIDYMIDES:
-Sperm granuloma, unilateral, grade 3
This finding corresponds to necropsy observation no: 01.
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG MALE

CONT./FF. ANIMAL NO. : 35

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, MANDIBULAR LYMPH NODE, MAMMARY GLAND, LUNG, TRACHEA, SKELETAL MUSCLE, HEART, LIVER, URINARY BLADDER, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 36

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 37

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 38

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 39

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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* STATE AT NECROPSY: K0
DAYS ON TEST : 29 * ANIMAL NO. : 40

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 51 * ANIMAL NO. : 71

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

THYMUS:
-Lymphoid atrophy, grade 1
MAMMARY GLAND:
-Lobuloalveolar development
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 2
UTERUS:
-Implantation site(s)
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), LUNG, TRACHEA, SKELETAL MUSCLE, HEART, LIVER, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, CERVIX, VAGINA, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 42 * ANIMAL NO. : 72

* NECROPSY FINDINGS

EYES:
01: LEFT SIDE: EXOPHTHALMUS.
MANDIBULAR LYMPH NODE:
01: BOTH SIDES: FOCUS/FOCI, ISOLATED, DARK RED.
UTERUS:
01: CONTAINS FLUID.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

EYES:
Only one of paired organs examined/present
-Hemorrhage, peribulbar, unilateral, grade 3
This finding corresponds to necropsy observation no: 01.
MANDIBULAR LYMPH NODE:
-Erythrocytes, intrasinusoidal, bilateral, grade 2
This finding corresponds to necropsy observation no: 01.
UTERUS:
For diagnosis of necropsy observation no. 01 see under: VAGINA.
-Cyclic dilation
This finding corresponds to necropsy observation no: 01.
VAGINA:
-Cycle: proestrus
This finding corresponds to necropsy observation no.: 01
in the UTERUS.
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- OVARIES, CERVIX.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 51 * ANIMAL NO. : 73

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

MAMMARY GLAND:
-Lobuloalveolar development
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 2
STOMACH:
-Inflammation, glandular stomach, lymphogranulocytic, grade 1
UTERUS:
-Implantation site(s)
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), LUNG, TRACHEA, SKELETAL MUSCLE, HEART, LIVER, URINARY BLADDER, KIDNEYS, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, CERVIX, VAGINA, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 74

* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):
01: BOTH SIDES: DISCOLOURATION, PALE.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

EYES:
-Retinal dysplasia (rosettes), unilateral, grade 1
THYMUS:
-Lymphoid atrophy, grade 1
THYROID GLAND (BOTH LOBES):
No microscopic finding corresponding to necropsy observation no. 01.
MAMMARY GLAND:
-Lobuloalveolar development
LUNG:
-Alveolar macrophage aggregation, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 1
UTERUS:
-Implantation site(s)
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG FEMALE

CONT./FF. ANIMAL NO. : 74

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), MANDIBULAR LYMPH NODE, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), TRACHEA, SKELETAL MUSCLE, HEART, LIVER, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, CERVIX, VAGINA, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 75

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 76

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

---

* STATE AT NECROPSY: K0
DAYS ON TEST : 55 * ANIMAL NO. : 77

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 55 * ANIMAL NO. : 78

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

---

* STATE AT NECROPSY: K0
DAYS ON TEST : 51 * ANIMAL NO. : 79

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

MANDIBULAR LYMPH NODE:
-Plasmacytosis, grade 2
THYROID GLAND (BOTH LOBES):
-Hypertrophy follicular cell, bilateral, grade 1
MAMMARY GLAND:
-Lobuloalveolar development
LUNG:
-Inflammation peribronchial/perivascular, grade 1
SKELETAL MUSCLE:
-Infiltrate inflammatory cell, mononuclear, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 1

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG FEMALE

CONT./FF. ANIMAL NO. : 79

KIDNEYS:
-Basophilia, tubule, unilateral, grade 1
UTERUS:
-Implantation site(s)
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, THYMUS, ADRENAL GLANDS, TRACHEA, HEART, LIVER, URINARY BLADDER, STOMACH, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, CERVIX, VAGINA, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

* STATE AT NECROPSY: K0
DAYS ON TEST : 52 * ANIMAL NO. : 80

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

THYMUS:
-Hyperplasia, epithelial tubules and cords, grade 1
MAMMARY GLAND:
-Lobuloalveolar development
LUNG:
-Alveolar macrophage aggregation, grade 1

TEST ITEM : DiHEP Aqueous Solution PATHOL. NO.: 31906 LAA
TEST SYSTEM : RAT, Combined 28-Day, Oral FINALIZED : 11-SEP-19
SPONSOR : Shell International B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG FEMALE

CONT./FF. ANIMAL NO. : 80

SPLEEN:
-Pigmentation, hemosiderin, grade 2
LIVER:
-Infiltrate inflammatory cell, lymphocytic, grade 1
KIDNEYS:
-Basophilia, tubule, unilateral, grade 1
-Hyalin casts, unilateral, grade 1
STOMACH:
-Glandular dilation, grade 1
UTERUS:
-Implantation site(s)
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), PITUITARY GLAND, SCIATIC NERVE (RIGHT), EYES, MANDIBULAR LYMPH NODE, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, DUODENUM, JEJUNUM, ILEUM, GUT-ASSOCIATED LYMPHOID TISSUE, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, CERVIX, VAGINA, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), BONE MARROW (FEMUR), JOINT (KNEE, LEFT).

Appendix 5
Summary of the Dose Range Finder

Summary of the Dose Range Finder (DRF)

A dose range finder (Test Facility Study No. 521627) was conducted to determine the tolerability of the test item when administered as received. No guidelines were applicable as this study was intended for dose level selection purposes only.

If not mentioned otherwise, test system, procedures and techniques were identical to those used during the main study.

For the DRF, all animal activities were performed at the 's-Hertogenbosch location.

Dosing of the DRF was initiated on 18 Jan 2019. The in-life phase of the DRF was completed on 23 Jan 2019.

Dose Formulations

As the test item was used as received from the Sponsor, samples for dose formulation analysis were not collected by the Test Facility.

Test System

On 12 Dec 2018, female Crl: WI(Han) rats were received from Charles River Deutschland, Sulzfeld, Germany. Females were 10 weeks old and weighed between 223 and 228 g at initiation of dosing.

On arrival, animals were group housed (up to 3 animals of the same dosing group together) in polycarbonate cages (Macrolon, MIV type, height 18 cm). At study assignment, each animal was identified using earmark and tailmark.

The actual daily mean temperature during the study period was 20-21°C with an actual daily mean relative humidity of 38 to 52% (see deviation in Appendix 7).

Experimental Design

Text Table 15
Experimental Design DRF

Group No.	Test Item Id.	Dose Level (mg/kg/day)[a]	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Females	Animal Numbers
1	DiHEP Aqueous Solution	1000	2.07	482.9	3	1-3

The test item was administered to the appropriate animals by once daily oral gavage for 5 consecutive days.

To determine the tolerability of the test item when administered as received, animals were dosed at the highest dose of the main study (1000 mg/kg) as the dose volume was the largest at this dose level.

In-life procedures

Mortality:	Twice daily throughout the study.
Clinical Observations:	At least daily from Days 1-10, at 0-15 minutes, 1 hour (±15 minutes) and 3 hours (± 30 minutes) after dosing.
Body Weights:	On Day 1 prior to dosing and on Days 3 and 5.
Food Consumption	Over Days 1-3 and 3-5.

Terminal Procedures

All animals were subjected to an external, thoracic and abdominal examination on Day 6 (scheduled necropsy). Based on the high pH of the test item, special attention was paid to the esophagus and stomach at necropsy. Animals were not deprived of food prior to necropsy. No organs were fixed and histopathological examination was not performed.

RESULTS

No signs of toxicity were noted at 1000 mg/kg/day.

Parameter	1000 mg/kg/day
Mortality	No mortality.
Clinical appearance	No findings.
Body weight	Normal.
Food consumption	Normal.
Macroscopic examination	No abnormalities noted.

CONCLUSION

Based on the results of the dose range finder, 1000 mg/kg/day was considered tolerable and appropriate as high dose for the main study.

Since no clinical signs were observed in the dose range finder, clinical observations were conducted and functional observations were started in the main study after dosing at no specific time point, but within a similar time period after dosing for the respective animals.

Appendix 6
Study Numbers used for Data Collection

Study Numbers which were used to collect online data are presented in the table below. All data was reported under Test Facility Study No. 20172120.

Text Table 16
Data Collection Study Numbers

Test Facility Study No.	**Study Number Online Data**	
521627 (DRF)	521627	ToxData; all data of the Dose Range Finder (DRF)
20172120 (Main)	521417	ToxData Parental animals: Mortality Clinical signs (except arena observations) Functional tests (except motor activity) Body weights and food consumption pre-mating Body weights mating period Food consumption mating period (males only) Clinical laboratory investigations Macroscopic findings and organ weights Implantation sites
20172120 (Main)	521418	ToxData: Arena observations (F_0- animals)
20172120 (Main)	521419	ToxData: Clinical pathology PND 14-16 pups
20172120 (Main)	521416	ToxData: All other data of the main study

Appendix 7
Study plan, Last Amended Study Plan, and Deviations

FINAL STUDY PLAN

Test Facility Study No. 20172120

Combined 28-Day Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test of DiHEP Aqueous Solution by Oral Gavage in Rats

SPONSOR:
Shell International B.V.
Carel van Bylandtlaan 16
2596 HR The Hague
The Netherlands

TEST FACILITY:
Charles River Laboratories Den Bosch B.V.
Hambakenwetering 7
5231 DD 's-Hertogenbosch
The Netherlands

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxic effects of DiHEP Aqueous Solution when given orally by gavage for a minimum of 28 days to Wistar Han rats, and to evaluate the potential to affect male and female reproductive performance such as gonadal function, mating behavior, conception, parturition and early postnatal development.

In addition, parental, reproduction (up to and including implantation) and developmental (from implantation onwards) No Observed Adverse Effect Levels (NOAELs) will be evaluated.

2. PROPOSED STUDY SCHEDULE

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

Experimental Start Date:	18 Jan 2019 (First date of study-specific data collection; randomization dose range finder)
Experimental Completion Date:	27 Jun 2019 (Last date data are collected from the study)
Animal Arrival:	Males: 30 Jan 2019 Females: 16 Jan 2019
Initiation of Estrous Cycle Determination (Pretest Period):	22 Jan 2019
Initiation of Dosing:	05 Feb 2019
Initiation of Mating:	19 Feb 2019
Necropsy Males incl. Blood Sampling:	06 Mar 2019[a]
Delivery of Litters (PND 1):	≥ 13 Mar 2019
Measurement Anogenital Distance (PND 1):	≥ 13 Mar 2019
Culling of F_1-pups incl. Blood Sampling (PND 4):	≥ 16 Mar 2019
Determination Areola/Nipple Retention (PND 13):	≥ 25 Mar 2019
Necropsy Females and Pups incl. Blood Sampling (PND 14-16):	≥ 26 Mar 2019
Completion of In-life:	12 Apr 2019 (Last date of necropsy)
Unaudited Draft Report:	28 Jun 2019

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.

3. GUIDELINES FOR STUDY DESIGN

The design of this study was based on the study objective(s), the overall product development strategy for the test item, and the following study design guidelines:

- OECD Guideline 422. *Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test*, July 2016.
- EPA Health Effects Test Guideline OPPTS 870.3650: *Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test,* July 2000.

In addition, the procedures described in this study plan essentially conform to the following guidelines.

- OECD Guideline 421. *Reproduction/Developmental Toxicity Screening Test*, July 2016.
- EPA Health Effects Test Guideline OPPTS 870.3550: *Reproduction/Developmental Toxicity Screening Test*, July 2000.
- Council Regulation (EC) No 440/2008 Part B: *Methods for the Determination of Toxicity and other Health Effects; B.7: "Repeated Dose (28 days) Toxicity (oral)"*. Official Journal of the European Union No. L142, May 2008.
- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*, October 2008.
- EPA Health Effects Test Guideline OPPTS 870.3050: *Repeated dose 28-day oral toxicity study in rodents*, July 2000.

4. 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.

5. QUALITY ASSURANCE

5.1 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 study and/or process 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.

The Test Facility QAU contact is indicated below:

C.J. Mitchell, BSc.
Address as cited for Test Facility
Tel: +31 73 640 6700
E-mail: QADenBosch@crl.com

6. SPONSOR

Sponsor Representative

M. Rooseboom, PhD, ERT
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E-mail: Martijn.Rooseboom@shell.com

7. RESPONSIBLE PERSONNEL

Study Director

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Management Contact

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Individual Scientist (IS) at the Test Facility

Histopathology	E.J.M. Lambregts, DVM address as cited for Test Facility Tel: +31 73 640 6700 E-mail: ankie.lambregts@crl.com

Each IS is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. 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 phase report will include the following:

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

8. Dose range finder (DRF)

A dose range finder (Test Facility Study No. 521627) will be conducted to determine the tolerability of the test item when administered as received. No testing guidelines are applicable as this dose range finder is intended for confirmation of tolerability only.

8.1 Proposed Study Schedule (DRF)

Initiation of Dosing:	Group 1	18 Jan 2019
Necropsy:	Group 1	23 Jan 2019

8.2 Test Item (DRF)

The information, procedures and safety instructions will be identical to those used during the main study. See sections 9 and 10 for details.

8.3 Dose Formulations and Analysis (DRF)

The preparation of test item will be identical as for the main study. See section 11 for details.

The test item will be used as received from the Sponsor; therefore, samples for dose formulation analysis will not be collected by the Test Facility.

8.4 Test System (DRF)

Species:	Rat.
Strain:	Crl: WI(Han).
Condition:	Outbred, SPF-Quality.
Source:	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 Females	3 (nulliparous and non-pregnant).
Target Age at the Initiation of Dosing:	10-12 weeks.
Target Weight at the Initiation of Dosing:	200 to 250 g.

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

At study assignment, each animal will be identified using earmark and tailmark.

Animals will be assigned at random at the discretion of the biotechnician.

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 maintained under the same environmental conditions.

The justification of test system and environmental acclimation will be identical as for the main study. See section 12 for details.

8.5 Husbandry (DRF)

On arrival and following randomization, animals will be group housed (up to 3 animals of the same dosing group together) in polycarbonate cages (Macrolon, MIV type, height 18 cm).

Other conditions will be identical as for the main study. See section 13 for details.

8.6 Experimental design (DRF)

Group No.	Test Item Id.	Dose Level (mg/kg)	Dose Volume (mL/kg)[a]	Dose Concentration (mg/mL)[b]	Number of Females	Animal Numbers
1	DiHEP Aqueous Solution	1000	2.07	482.9	3	1-3

Id.= identification.

[a] Dose volume will be calculated as dose level (mg/kg) / corrected test item concentration (mg/ml).

[b] The test item consists of 43.9% DiHEP, test item concentration will be corrected for % DiHEP and specific gravity (factor: 1.1). See section 11.1 for details.

The test item and vehicle will be administered to the appropriate animals by once daily oral gavage for a minimum of 5 days.

A dose control system (DCS) will be used as additional check to verify the dosing procedure according to Standard Operating Procedures (Study No. 521627 will be used for DCS).

The justification of the route of administration is identical as for the main study. See section 14.2 for details. To determine the tolerability of the test item when administered as received, animals will be dosed at the highest dose of the main study (1000 mg/kg) as the dose volume is the largest at this dose level.

8.7 In-life Procedures, Observations, and Measurements (DRF)

Only the following observations and measurements will be performed.

Mortality: Twice daily throughout the study.

Clinical Observations: At least once daily up to the day prior to necropsy, during the following observation intervals:

Actual time after dosing	Reported as hours after dosing	Nominal time[a]
0-15 min	0 hour	07:00
1 hr ± 15 min	1 hour	08:00
3 hr ± 30 min	3 hours	10:00

[a] Nominal times will be used for computer registration only.

Body Weights: On Day 1 prior to dosing and on Days 3 and 5.

In order to monitor the health status animals may be weighed more often. This will be documented in the study raw data.

Food Consumption Over Days 1-3 and 3-5.

8.8 Terminal Procedures (DRF)

All animals will be subjected to an external, thoracic and abdominal examination on Day 6 (scheduled necropsy) or sooner (decedents). Based on the high pH of the test item (see section 9.1), special attention will be paid to the esophagus and stomach at necropsy. Animals will not be deprived of food prior to necropsy. Gross lesions will be recorded but will not be retained, no organs will be fixed and histopathological examination will not be performed.

8.9 Reporting (DRF)

The procedures of statistical analysis, computerized systems, amendments and deviations, and retention of records will be identical as for the main study, if applicable. See sections 22, 23, 24, and 25 for details.

A summary of results of the dose range finder will be included in report 20172120 as an appendix.

9. TEST ITEM

9.1 Test Item

Identification:	DiHEP Aqueous Solution[1]
Batch (Lot) Number:	D2921BF000
Expiry date:	31 August 2020 (expiry date)
Physical Description:	Yellow aqueous liquid
Purity/Composition:	See Certificate of Analysis[2]
Storage Conditions:	At room temperature protected from light

Additional information

Test Facility Test Item Number:	209813/A
Purity/Composition correction factor:	Correct for percentage solid matter and additionally for percentage DiHEP.
Test item handling:	No specific handling conditions required
Chemical name (IUPAC, synonym or trade name):	1,4-Bis(2-hydroxyethyl)piperazine Dihydroxyethylpiperazine
CAS number:	122-96-3
Molecular formula:	$C_8H_{18}N_2O_2$
Molecular weight:	174.24
Irritant or corrosive:	Yes
pH:	13
Specific gravity / density:	1.1 kg/m^3 at 20°C

9.2 Test Item Characterization

The Sponsor will provide to the Test Facility documentation of the identity, purity, composition, and stability for the test item. If available, a Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report. The Sponsor

[1] DiHEP stands for Dihydroxyethylpiperazine.
[2] For Certificate of Analysis see ATTACHMENT D.

will also provide information concerning the regulatory standard that was followed for these evaluations.

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

9.3 Analysis of Test Item

The stability of the bulk test item will not be determined during the course of this study. Information to support the stability of each lot of the bulk test item will be provided by the Sponsor.

9.4 Reserve Samples

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

9.5 Test Item and Vehicle Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of test item will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk test item will be discarded.

10. SAFETY

The following safety instructions apply to this study:

Standard safety precautions specified in Charles River Den Bosch procedures.

11. DOSE FORMULATION AND ANALYSIS

11.1 Preparation of Test Item

The test item, DiHEP Aqueous Solution will be administered as received. An adequate amount of the test item will be dispensed into daily aliquots, which will be stored in a controlled temperature area set to maintain 21°C until use.

Test item for dosing will be kept at room temperature until dosing. Adjustment will be made for specific gravity of the test item. A factor of 43.9 will be used to correct for the purity/composition of the test item (based on the 48.9% solid matter of which 89.7% is DiHEP.

Any residual volumes will be discarded.

11.2 Sample Collection and Analysis

The test item will be used as received from the Sponsor; therefore, samples for dose formulation analysis will not be collected by the Test Facility.

12. TEST SYSTEM

Species:	Rat.
Strain:	Crl: WI(Han).
Condition:	Outbred, SPF-Quality.
Source:	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:	48 (nulliparous and non-pregnant).
Number of Pups Expected:	Approximately 480 pups (40 litters x 12 pups).
Target Age at the Initiation of the Pretest Period:	Females: approximately 10-12 weeks.
Target Age at the Initiation of Dosing:	Males: approximately 10-12 weeks. Females: approximately 12-14 weeks.
Target Weight at the Initiation of Dosing:	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.

12.1 Justification of Test System and Number of Animals

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.

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 item. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

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 which do not use live animals currently do not exist.

12.2 Animal Identification

Prior to start of the pretest period (females) or treatment period (males), each allocated animal will be identified using earmark and tattoo. Prior to start of the pretest period, reserve females will be numbered R1 through R8 at random by indelible marker. Any reserve female replacing an allocated female prior to treatment will receive identification by earmark and tattoo.

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.

12.3 Environmental Acclimation

The animals will be allowed to acclimate to the Test Facility toxicology accommodation for at least 5 days prior to start of the pretest period (females) or at least 5 days before the commencement of dosing (males).

12.4 Selection, Assignment, Replacement, and Disposition of Animals

A total of 40 females will be selected at randomization before initiation of the pretest phase. Each selected female classified as not having regular estrous cycles during the pretest phase will be replaced before initiation of dosing by one of the 8 additional females having regular estrous cycles, if feasible. A total of 40 females with regular estrous cycles will continue in the study. The supernumerary females will then be removed from the study, and their estrous cycle results will be kept in the raw data but will not be reported.

Animals will be assigned to groups by a computer-generated random algorithm according to body weights, with all animals within ± 20% of the sex mean. Males and females will be randomized separately. Animals in poor health or at extremes of body weight range 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 dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-test item-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.

13. HUSBANDRY

13.1 Housing

On arrival and following the pretest (females only) and pre-mating period, animals will be group housed (up to 5 animals of the same sex and same dosing group together) in polycarbonate cages (Macrolon, MIV type, height 18 cm).

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

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

During the lactation phase, females will be housed in Macrolon plastic cages (MIII type, height 18 cm). Pups will be housed with the dam, except during locomotor activity monitoring of the dams, when the pups will be kept warm in their home cage using bottles filled with warm water. In order to avoid hypothermia of pups, pups should not be left without their dam or a bottle filled with warm water for longer than 30-40 minutes.

During locomotor activity monitoring, F_0-animals will be housed individually in a Hi-temp polycarbonate cage (Ancare corp., USA; dimensions: 48.3 x 26.7 x 20.3 cm) without cage-enrichment, bedding material, food and water.

The cages will contain appropriate bedding (Lignocel S 8-15, JRS - J.Rettenmaier & Söhne GmbH + CO. KG, Rosenberg, Germany) and will be equipped with water bottles. The 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. Each cage will be clearly labeled with a color-coded cage card indicating Test Facility Study No., group, animal number(s), and sex.

13.2 Environmental Conditions

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

Temperature:	18 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.

13.3 Food

Pelleted rodent diet (SM R/M-Z from SSNIFF® Spezialdiäten GmbH, Soest, Germany) will be provided *ad libitum* throughout the study, except during designated procedures. During motor activity measurements, animals will not have access to food for a maximum of 2 hours.

The feed is analyzed by the supplier for nutritional components and environmental contaminants. Results of the analysis 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.

13.4 Water

Municipal tap water will be freely available to each animal via water bottles. During motor activity measurements, animals will not have access to water for a maximum of 2 hours.

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 would interfere with the objectives of the study.

13.5 Animal Enrichment

For psychological/environmental enrichment and nesting material, animals will be provided with paper (Enviro-dri, Wm. Lilico & Son (Wonham Mill Ltd), Surrey, United Kingdom), except when interrupted by study procedures/activities.

13.6 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 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 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 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 representative will be fully informed of any such events.

14. EXPERIMENTAL DESIGN

Group No.	Test Item Id.	Dose Level (mg/kg)	Dose Volume (mL/kg)[a]	Corrected Test Item Concentration (mg/mL)[b]	Number of Animals		Animal Numbers	
					Males	Females	Males	Females
1	-	0 (Control)[c]	2.07	-	10	10	01-10	41-50
2	DiHEP Aqueous Solution	100	0.21	482.9	10	10	11-20	51-60
3		300	0.62		10	10	21-30	61-70
4		1000	2.07		10	10	31-40	71-80

TBD. = To be determined. Id.= identification.

[a] Dose volume will be calculated as dose level (mg/kg) / corrected test item concentration (mg/ml).

[b] The test item consists of 43.9% DiHEP, test item concentration will be corrected for % DiHEP and specific gravity (factor: 1.1). See section 11.1 for details.

[c] Test-item treated animals will receive undiluted test item and consequently, no vehicle will be used. Control animals will be dosed with water (Elix) in the same dose volume as Group 4.

The following 5 animals/sex/group are selected for functional tests, clinical pathology, collection of full list of organs/tissues at macroscopic examination, organ weights (full list) and histopathology (full list), see also respective paragraphs:

Group No.	Animal numbers	
	Males	Females[a]
1	01-05	To be selected
2	11-15	To be selected
3	21-25	To be selected
4	31-35	To be selected

[a] Females with live pups, if feasible. These animals will be selected and approved by the Study Director in the study files. The selected female animal numbers will be specified in the report.

14.1 Administration of Test item

The test item and vehicle will be administered to the appropriate animals by once daily oral gavage 7 days a week for a minimum of 28 days. Males will be treated for a minimum of 28 days, up to and including the day before scheduled necropsy. This includes a minimum of two weeks prior to mating and during the mating period. Females will be treated 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 before scheduled necropsy. Females will not be dosed during littering.

The dose volume for each animal will be based on the most recent body weight measurement. Dose volumes ≤ 50 µL will be administered using a plastic feeding tube which is connected to a digital syringe and dose volumes > 50 µL will be given with a plastic feeding tube connected to an appropriately graded syringe. The accuracy of the digital syringe will be determined prior to start dosing at relevant dose levels for this study.

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

A dose control system (DCS) will be used as additional check to verify the dosing procedure according to Standard Operating Procedures (Study No. 521417 will be used for DCS).

Pups will not be treated directly but could potentially be exposed to the test item in utero, via maternal milk, or from exposure to maternal urine/feces.

14.2 Justification of Route and Dose Levels

The oral route of administration was selected because this is the recommended route by OECD TG 422, REACH regulation and ECHA guidelines. In addition, the test material is a non-volatile aqueous solution.

The dose levels were selected based on information provided by the Sponsor (data on file at Sponsor site), and in an attempt to produce graded responses to the test item.

A previously performed acute toxicity study with DiHEP Aqueous Solution via oral gavage in Sprague Dawley (SD) rats indicated a low acute toxicity ($LD50_{males}$ was 20,093 mg/kg and $LD50_{females}$ was 18,738 mg/kg).

In addition, multiple studies were performed with several structural analogs:

- A dietary 7-day toxicity study was performed with a hydroxypiperazine solution (containing 12-20% piperazine, 38-47% hydroxypiperazine, 16-25% dihydroxypiperazine, 17-26% water). During this study Wistar han rats received 590, 1420, and 3720 mg/kg for males and 680, 1610 and 3970 mg/kg for female rats. A slight body weight decrease was observed in females fed 3970 mg/kg/day but was not observed in females fed lower doses or in males. This body weight decrease was statistically significant after days 1 and 4 but not day 7. Remaining parameters were considered unaffected by treatment.
- A dietary 90-day toxicity study was performed with analog piperazine. During this study, SD rats received 400, 1200 and 2394 mg/kg by dietary administration. A dose related decrease in body-weight gain (a decrease of 10% in high dose animals when compared with concurrent control) was noted. Remaining parameters were considered unaffected by treatment.
- A dietary 90-day toxicity study was performed with analog anhydrous piperazine. Rats received 1000, 3000 and 10000 ppm (corresponding to 50, 150 and 500 mg/kg/day piperazine base). At 10000 ppm histopathological degenerative changes were noted in the liver and kidney, at 3000 ppm similar changes were noted to a lesser extent and at 1000 ppm no adverse effects were noted. In addition, at 10000 ppm a decrease in body weight gain was noted (statistically significant in females only). Remaining parameters were considered unaffected by treatment.
- A developmental toxicity study was performed, in which pregnant SD females received 0, 105, 420 and 2100 mg/kg piperazine base during days 6-15 by oral gavage. In high-dose females, excessive salivation, lethargy and a reduction in body weight gain and food consumption were noted. Remaining parameters, including pre- and post-implantation loss, litter size and sex ratio, were considered unaffected by treatment.
- In a dietary two generation study with piperazine dihydrochloride, SD rats received 0, 5000, 12000 and 25000 ppm (corresponding to 0, 125, 300 and 625 mg/kg piperazine base). The mid-dose was considered as LOAEL, with effects mainly on fertility (i.e. reduced pregnancy index and decreased number of implantation sites). These effects were not observed in the developmental toxicity study, which is be considered to support that the effect on fertility are the main effect of piperazine on reproduction.

Based on the observed low acute toxicity of DiHEP Aqueous Solution and the effects noted in the studies performed with structural analogs, 0, 100, 300 and 1000 mg/kg were selected as dose levels for this study.

The high-dose level should produce some toxic effects, but not death nor obvious suffering. The mid-dose level is expected to produce minimal to moderate toxic effects. The low-dose level should produce no observable indications of toxicity.

15. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS – F_0-GENERATION

The in-life procedures, observations, and measurements listed below will be performed for parental animals.

15.1 Mortality/Moribundity Checks – F_0-Generation

Frequency:	At least twice daily throughout the study.
Procedure:	Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

15.2 Clinical Observations – F_0-Generation

Frequency:	During treatment, animals will be observed at least once daily, up to the day prior to necropsy. These clinical observations will at least be conducted after dosing at no specific time point, but within a similar time period after dosing for the respective animals.
Procedure:	Animals will be observed for specific clinical signs. The time of onset, grade and duration of any observed signs will be recorded. Signs will be graded for severity and the maximum grade will be predefined at 3 or 4. Grades will be coded as slight (grade 1), moderate (grade 2), severe (grade 3) and very severe (grade 4). For certain signs, only its presence (grade 1) or absence (grade 0) will be scored. In the data tables, the scored grades will be reported, as well as the percentage of animals affected in summary tables.

15.2.1 Arena Observations – F_0-Generation

Frequency:	Once before the first administration of the test item and at weekly intervals during the treatment period.
Procedure:	Animals will be observed for specific clinical signs in a standard arena. The time of onset, grade and duration of any observed signs will be recorded.

15.3 Body Weights – F_0-Generation

Frequency: Males and females will be weighed on the first day of treatment (prior to dosing), and weekly thereafter. Mated females will be weighed on Days 0, 4, 7, 11, 14, 17, and 20 post-coitum 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.

Procedure: Animals will be individually weighed.

15.4 Food Consumption – F_0-Generation

Frequency: Weekly, except for males and females which are housed together for mating and for females without evidence of mating. Food consumption of mated females will be measured on Days 0, 4, 7, 11, 14, 17, and 20 post-coitum and during lactation on PND 1, 4, 7, and 13.

Procedure: Food consumption will be quantitatively measured.

15.4.1 Water Consumption – F_0-Generation

Frequency: Regular basis throughout the study.

Procedure: Water consumption will be monitored by visual inspection of the water bottles. If inter group differences are noted, consumption may be assessed by weight.

15.5 Functional Tests – F_0-Generation

Frequency: Once during the treatment period. The selected 5 males will be tested once during Week 4 of treatment and the selected 5 females will be tested once during the last week of lactation (i.e. PND 6-13). These tests will be performed after clinical observations and arena observation, if applicable.

Procedure: The following tests will be performed :

- hearing ability, pupillary reflex and static righting reflex (score 0 = normal/present, score 1 = abnormal/absent).
- fore- and hind-limb grip strength will be recorded as the mean of three measurements , using a grip strength meter.
- locomotor activity (recording period: 1 hour under normal laboratory light conditions) will be tested using the Kinder Scientific Motor Monitor System. Total movements and ambulations will be reported. Ambulations represent movements characterized by a relocation of the entire body position like walking, whereas total movements represent all movements made by the animals, including ambulations but also smaller or finer movements like grooming, weaving or movements of the head.

15.6 Estrous Cycle Evaluations – F_0-Generation

Frequency: Daily vaginal lavage will be performed beginning 14 days prior to treatment (pretest period), 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.

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.

15.7 Cohabitation/Mating Procedure – F_0-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 post-coitum. 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 14) will be used for re-mating.

15.8 General Reproduction Data – F_0-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 normally. 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.

16. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS – F_1-GENERATION

The in-life procedures, observations, and measurements listed below will be performed for the pups.

16.1 Mortality/Moribundity Checks – F_1-Generation

Frequency: The number of live and dead pups will be determined on PND 1 and daily thereafter.

Procedure: Pups will be observed for general health/mortality and moribundity. If possible, defects or cause of death will be evaluated. Pups will not be removed from the cage during observation, unless necessary for identification or confirmation of possible findings.

16.2 Clinical Observations – F_1-Generation

Frequency: At least once daily.

Procedure: Detailed clinical observations will be made for all pups. Only days on which clinical signs are present between the first and last litter check will be given in the respective report tables.

16.3 Body Weights – F_1-Generation

Frequency: On PND 1, 4, 7, and 13.

Procedure: Live pups will be individually weighed.

16.4 Sex – F_1-Generation

Frequency: On PND 1 and 4.

Procedure: Sex will be externally determined for all pups.

16.5 Anogenital Distance – F_1-Generation

Frequency: On PND 1.

Procedure: Anogenital distance (AGD) will be measured for all live pups. The AGD will be normalized to the cube root of body weight.

16.6 Areola/Nipple Retention – F_1-Generation

Frequency: On PND 13.

Procedure: All males in each litter will be examined for the number of areola/nipples.

16.7 Culling – F_1-Generation

Frequency:	On PND 4.
Procedure:	To reduce variability among the litters, eight pups from each litter of equal sex distribution (if possible) will be selected. Blood samples will be collected from two of the surplus pups (if possible from one male and one female pup). 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 sections 17.1.1 and 20.3.

17. LABORATORY EVALUATIONS

17.1 Clinical Pathology

17.1.1 Sample Collection

Blood of F_0-animals (except for animals which were sacrificed *in extremis* or found dead and females with total litter loss) will be collected on the day of scheduled necropsy. Samples will be collected, between 7.00 and 10.30 a.m., from the retro-orbital sinus under anesthesia using isoflurane in the animal facility. Additional blood samples may be obtained (e.g. due to clotting of non-serum samples) in both the animal facility and in the necropsy room if permissible sampling frequency and blood volume are not exceeded. After collection, samples will be transferred to the appropriate laboratory for processing.

F_0-males (except for animals which were sacrificed *in extremis* or found dead) will be fasted overnight with a maximum of 24 hours before blood sampling, but water will be available. F_0-females will not be fasted overnight.

Blood of F_1-animals will be collected on PND 4 and PND 14-16, if possible. This will be performed in the necropsy room.
On PND 4 at culling, blood will be collected from two surplus pups per litter (if possible) by decapitation, between 7.00 and 10.30 a.m., and will be pooled to one sample per litter. If available, blood will be collected from one male and one female pup. If only one surplus pup per litter is available at culling, as much as possible blood will be collected from this single pup. If the target volume of 0.5 mL cannot be reached by pooling from two pups, blood from a third surplus pup of the same litter should be added, if available.

On PND 14-16, separate blood samples will be collected from two pups per litter (from one male and one female, if possible). If the target volume of 1.0 mL/pup cannot be reached, a separate blood sample should be collected from another pup of the same litter and sex (if possible). Any incomplete blood sample will be discarded. Blood will be drawn, between 7.00 and 10.30 a.m., by aorta puncture under anesthesia using isoflurane as part of the necropsy procedure.

Samples will be collected according to the table below.

Samples for Clinical Pathology Evaluation

Animals	Time Point	Hematology	Coagulation	Clinical Chemistry	Thyroid Hormone
Selected F_0-animals (5/sex/group)[a, b,]	On the day of scheduled necropsy	X	X	X	X
Non-selected F_0-animals (≤ 5/sex/group)[a, b,]	On the day of scheduled necropsy	-	-	-	X
2 pups/litter	PND 4	-	-	-	X
2 pups/litter	PND 14-16	-	-	-	X

X = Sample to be collected; - = Not applicable.
[a] See section 14 for details of the selected F_0-animals.
[b] Except for animals which were sacrificed *in extremis* or found dead, and females with total litter loss.

17.1.2 Hematology

Target Volume: 0.5 mL.

Anticoagulant: K_3-EDTA (tubes; Greiner Bio-One GmbH, Kremsmünster, Austria).

Hematology Parameters

White blood cells (WBC)	Red Blood Cell Distribution Width (RDW)
Neutrophils (absolute)	Haemoglobin
Lymphocytes (absolute)	Haematocrit
Monocytes (absolute)	Mean corpuscular volume (MCV)
Eosinophils (absolute)	Mean corpuscular haemoglobin (MCH)
Basophils (absolute)	Mean corpuscular haemoglobin concentration (MCHC)
Red blood cells	Platelets
Reticulocyte (absolute)	

A blood smear will be prepared from each hematology sample. Blood smears will be labeled, stained, and stored. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a study plan amendment.

17.1.3 Coagulation

Target Volume: 0.45 mL.

Anticoagulant: Citrate (tubes; Greiner Bio-One GmbH, Kremsmünster, Austria).

Coagulation Parameters

Prothrombin Time (PT)	Activated Partial Thromboplastin Time (APTT)

17.1.4 Clinical Chemistry

Target Volume: 0.5 mL.

For bile acid measurement: 1.0 mL (same sample as for thyroid hormone measurement).

Anticoagulant: Li-Heparin (tubes; Greiner Bio-One GmbH, Kremsmünster, Austria).

Not applicable for serum tubes.

Processing: To serum (bile acids) or to plasma

Clinical Chemistry Parameters

Alanine aminotransferase (ALAT)	Creatinine
Aspartate aminotransferase (ASAT)	Glucose
Alkaline Phosphatase (ALP)	Cholesterol
Total protein	Sodium
Albumin	Potassium
Total Bilirubin	Chloride
Bile Acids	Calcium
Urea	Inorganic Phosphate (Inorg. Phos)

17.1.5 Thyroid Hormone

Target Volume: F_0-animals: 1.0 mL (same sample as for bile acid measurement).

PND 4 pups: 0.5 mL in total (pooled).

PND 14-16 pups: 1.0 mL per pup.

Anticoagulant: Not applicable for serum. (tubes; Greiner Bio-One GmbH, Kremsmünster, Austria).

Thyroid Hormone Parameters

Thyroxine (T4)	Thyroid-Stimulating Hormone (TSH; only if required)

After clotting and centrifugation, serum will be used as listed below.

F_0-Males: Serum from each sample will be divided into 2 aliquots: 150 µL serum for measurement of total T4 and the remaining volume of serum for possible future measurement of TSH (added by study plan amendment if applicable).

F_0-Females: The serum will be used for possible future measurement of total T4 and/or thyroid-stimulating hormone TSH (added by study plan amendment if applicable).

PND 4 Pups The pooled serum will be used for possible future measurement of total T4 (added by study plan amendment if applicable).

PND 14-16 Pups Serum from each sample will be divided into 2 aliquots: 150 µL serum for measurement of total T4, and the remaining volume of serum for possible future measurement of TSH (added by study plan amendment if applicable).

Serum samples retained for possible future analysis will be maintained by the Test Facility in the freezer (≤-75°C). Under these storage conditions, samples will be stable for 6 months. Any remaining sample will be discarded prior to finalization of the report

18. TERMINAL PROCEDURES – F_0-GENERATION

Terminal procedures are summarized in the following table:

Terminal Procedures

Group No.	(Non) Selected Animals	No. of Animals M	No. of Animals F	Scheduled Euthanasia	Necropsy Procedures: Necropsy	Necropsy Procedures: Tissue Collection	Necropsy Procedures: Organ Weights	Histology and histopathology
1	Selected	5	5	**Males:** after a minimum of 28 days of administration **Females:** PND 14-16	X	X[a]	X[a]	Full list
	Non-selected	≤ 5	≤ 5					Gross lesions Reproductive tissues[b]
2	Selected	5	5					Gross lesions Target tissues[c] Reproductive tissues[b]
	Non-selected	≤ 5	≤ 5					Gross lesions Reproductive tissues[b]
3	Selected	5	5					Gross lesions Target tissues[c] Reproductive tissues[b]
	Non-selected	≤ 5	≤ 5					Gross lesions Reproductive tissues[b]
4	Selected	5	5					Full list
	Non-selected	≤ 5	≤ 5					Gross lesions Reproductive tissues[b]
Unscheduled Deaths (sacrificed *in extremis* or found dead)					X	X	-	Full list

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

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

[b] Reproductive tissues are applicable for males that fail to sire and females that fail to deliver pups (i.e. non-pregnant females, implantation sites only or no offspring) and females with total litter loss. See ATTACHMENT C for listing of tissues.

[c] Target tissues are applicable in case of possible treatment-related changes in any of the tissues of any animal in the high dose group. Then, histological examination will be extended to that particular tissue of the selected 5 animals of Groups 2 and 3.

18.1 Unscheduled Deaths – F_0-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 anaesthetized using isoflurane and subsequently exsanguinated. They will undergo necropsy, and specified tissues will be retained, but not weighed.

The specified tissues which will be retained are mentioned in ATTACHMENT C.

18.2 Scheduled Euthanasia – F_0-Generation

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

Scheduled necropsies are summarized below:

Males (which sire and 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: Post-coitum Days 25-27.
	Without evidence of mating: Approximately 24-26 days after the last day of the mating period.
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.

All males surviving to scheduled necropsy will be fasted overnight with a maximum of 24 hours before necropsy. Water will be available. F_0- females will not be fasted overnight.

The specified tissues which will be retained are mentioned in ATTACHMENT C.

18.3 Necropsy – F_0-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.

In case no macroscopically visible implantation sites are present, nongravid uteri will be stained using the Salewski technique in order to detect any former implantation sites and the number of corpora lutea will be recorded in addition.

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.

18.4 Organ weights – F_0-Generation

The organs identified for weighing in the Tissue Collection and Preservation table in ATTACHMENT C will be weighed at necropsy for all scheduled euthanasia animals. 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.

18.5 Tissue Collection and Preservation – F_0-Generation

Representative samples of the tissues identified in the Tissue Collection and Preservation table in ATTACHMENT C will be collected from all animals and preserved in 10% buffered formalin (neutral phosphate buffered 4% formaldehyde solution), unless otherwise indicated. 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.

19. HISTOLOGY AND HISTOPATHOLOGY

19.1 Histology

Tissues in the Tissue Collection and Preservation table in ATTACHMENT C from F_0-animals identified in the Terminal Procedures table will be embedded in paraffin, sectioned at a thickness of 2-4 micrometers, mounted on glass slides, and stained with hematoxylin and eosin.

19.2 Histopathology

All tissues as defined under Histology (section 19.1) will be examined 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.

Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by study plan amendment following discussion with the Study Director and in consultation with the Sponsor.

At the discretion of the study pathologist and after acknowledgement by the Study Director, images may be captured for consultation purposes.

A peer review on the histopathology data will be performed by a second pathologist.

20. TERMINAL PROCEDURES – F_1-GENERATION

20.1 Method of Euthanasia – F_1-Generation

Pups, younger than 7 days will be euthanized by decapitation.

All remaining pups (PND 7-16), except the pups selected for blood collection, will be euthanized by an intraperitoneal injection of sodium pentobarbital (Euthasol® 20%).

The pups selected for blood collection on PND 14-16 will be anesthetized using isoflurane followed by exsanguination.

20.2 Unscheduled Deaths – F_1-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 necropsied 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.

20.3 Scheduled Euthanasia – F_1-Generation

On PND 4, the surplus pups (> 8 pups per litter) will be euthanized by decapitation. Sex will be determined both externally and internally. From two surplus pups per litter, blood will be collected, if possible. For details see also sections 16.7 and 17.1.1.

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. External abnormalities may be collected and fixed in 10% buffered formalin at discretion of the Study Director. In addition, the thyroid will be collected from two pups per litter (if possible, from one male and one female pup and preferably from the same pups as selected for (complete) blood collection, see also section 17.1.1), and will be preserved in 10% buffered formalin.

21. CONSTRUCTED VARIABLES

21.1 Parental Variables

Body Weight Gains:	Calculated against the body weight on Day 1 (pre-mating, mating and lactation periods) or Day 0 (post-coitum period).
Relative Food Consumption:	Calculated against the body weight for scheduled intervals.
Organ Weight Relative to Body Weight:	Calculated against the terminal body weight.

21.2 Reproduction and Developmental Variables

For each group, the following calculations will be performed. Group mean values of precoital time and duration of gestation will be calculated from individual values of F_0-females, the remaining group values will be calculated from the total number in each group. Additional calculations may be used, the methods and results will be described in the report.

Mating index (%): $\frac{\text{Number of females mated}}{\text{Number of females paired}} \times 100$

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

Fertility index (%): $\frac{\text{Number of pregnant females}}{\text{Number of females mated}} \times 100$

Gestation index (%): $\frac{\text{Number of females with living pups on Day 1}}{\text{Number of pregnant females}} \times 100$

Duration of gestation: Number of days between confirmation of mating and the beginning of parturition

Post-implantation survival index (%): $\frac{\text{Total number of offspring born}}{\text{Total number of uterine implantation sites}} \times 100$

Post-implantation survival index will be expressed as 100% when the number of offspring exceeds the number of implantation sites recorded.

Live birth index (%): $\frac{\text{Number of live offspring on Day 1 after littering}}{\text{Total number of offspring born}} \times 100$

Percentage live males at First Litter Check (%): $\frac{\text{Number of live male pups at First Litter Check}}{\text{Number of live pups at First Litter Check}} \times 100$

Percentage live females at First Litter Check (%): $\frac{\text{Number of live female pups at First Litter Check}}{\text{Number of live pups at First Litter Check}} \times 100$

Viability index (%): $\frac{\text{Number of live offspring on Day 4 before culling}}{\text{Number live offspring on Day 1 after littering}} \times 100$

Lactation index (%): $\frac{\text{Number of live offspring on Day 13 after littering}}{\text{Number live offspring on Day 4 (after culling)}} \times 100$

22. STATISTICAL ANALYSIS

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.

Numerical data collected on scheduled occasions will be analyzed according to sex and occasion. Descriptive statistics number, mean and standard deviation will be reported whenever possible. Values may also be expressed as a percentage of predose or control values when deemed appropriate. Inferential statistics will be performed according to the comparison matrix below when possible, but will exclude semi-quantitative data, and any group with less than 3 observations.

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

22.1 Parametric

Datasets with at least 3 groups (the designated control group and 2 other groups) will be compared using Dunnett-test (many-to-one-t-test).

22.2 Non-Parametric

Datasets with at least 3 groups will be compared using a Steel-test (many-to-one rank test).

The motor activity data set (at least 3 groups) will be compared using an overall Kruskal-Wallis. Whenever, the overall test is significant, the Wilcoxon Rank-Sum test will be applied to compare the treated groups to the control group.

22.3 Incidence

An overall Fisher's exact test will be used to compare all groups. The above pairwise comparisons will be conducted using Fisher's exact test whenever the overall test is significant.

Additional methods of statistical analysis may be used at the discretion of the Study Director. The methods and the results will be described in the report.

23. COMPUTERIZED SYSTEMS

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

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.

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
ToxData [a]	In-life phase (Mortality; Clinical signs; Body weights; Food consumption; Functional tests; Organ weights; Reproduction parameters; Observations pups[b]) data collection
REES Centron	Temperature and humidity (animal and laboratory facilities) data collection
MotorMonitor II	Motor activity measurement data collection
ADVIA® 2120i	Hematology data collection
STA Compact®	Clotting parameters data collection
AU400	Clinical biochemistry data collection
IMMULITE® 1000	Thyroid hormone data collection
Pathdata	Histopathology data collection

[a] For logistic reasons, data will be captured under separate Study numbers, see ATTACHMENT B.
[b] Only at first and last litter check, and in case of clinical pup findings also on the respective days in between.

24. 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.

All study plan and SOP deviations will be documented in the study records. Deviations from the study plan and/or SOP related to the phase(s) of the study conducted at a Test Site shall be documented, acknowledged by the PI/IS, and reported to the Study Director for

authorization/acknowledgement. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

25. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River from this study will be transferred to a Charles River archive.

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 item receipt, identification and preparation
- In-life measurements and observations
- Clinical pathology sample collection and evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

After two years of archiving, all study-specific raw data, electronic data, documentation, study plan and final reports will be transferred to Iron Mountain Germany, Harpener Hellweg 31, D-44805 Bochum, Germany. They shall be indexed by using the Test Facility Project No. allowing unequivocal identification and providing the necessary information (e.g. test system, test item, date of Toxicology and Ecology for the time period set by the GLP regulations). Records of transfer will be retained by test facility. The Sponsor will be informed about the transfer and will receive a digital copy of the record of transfer. The sponsor will ensure that all study material is expediently returned to Charles River Den Bosch if requested by GLP monitoring authorities for audit.

26. REPORTING

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. An original copy of the report with the Test Facility's signatures will be retained.

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.

27. 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).

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 APPROVAL

The signature below acknowledges Test Facility Management's responsibility to the study as defined by the relevant GLP regulations.

Date: 16 January 2019

K.C.G. Hartman-Van Dycke, PhD
Test Facility Management

The signature below indicates that the Study Director approves the study plan.

Date: 16 January 2019

D. van den Oetelaar, MSc.
Study Director

SPONSOR APPROVAL

The signature of the Sponsor Representative below indicates approval of this study plan.

Date: 26 Jan 2015

M. Rooseboom, PhD, ERT
Sponsor Representative

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	Formulations	Tsfher;
1 Copy	Estrous Cycle Determination	Daoud, M; Hungs, S;
1 Copy	Clinical Pathology	Her/clinical pathology;
1 Copy	Necropsy	Her/necropsy;
1 Copy	Histotechnology	Her/histology
1 Copy	Study Assistants	Sagit;
1 Copy	Individual Scientist Histopathology	Lambregts, A;
1 Paper Copy	Coordinating Biotechnician DRF	Coppes, M;
1 Paper Copy	Coordinating Biotechnician Main	Van Beek, B;

ATTACHMENT B

Separate Study Numbers for online data collection will be used as indicated below. All data will be reported under Test Facility Study No. 20172120.

Test Facility Study No.	Study Number Online Data	
521627 (DRF)	521627	ToxData; all data of the Dose Range Finder (DRF)
20172120 (Main)	521417	ToxData Parental animals : Mortality Clinical signs (except arena observations) Functional tests (except motor activity) Body weights and food consumption pre-mating Body weights mating period Food consumption mating period (males only) Clinical laboratory investigations Macroscopic findings and organ weights Implantation sites
20172120 (Main)	521418	ToxData: Arena observations (F_0- animals)
20172120 (Main)	521419	ToxData: Clinical pathology PND 14-16 pups
20172120 (Main)	521416	ToxData: All other data of the main study

ATTACHMENT C

Tissue Collection and Preservation

This attachment contains two tables describing the procedures of tissue weighing, collection, histology and microscopic evaluation. The first table is applicable for all selected animals and all animals that die spontaneously or are sacrificed *in extremis*. The second table is applicable for all remaining animals, including the males that fail to sire and females that fail to deliver pups (i.e. non-pregnant, implantation sites only or no offspring) and females with total litter loss.

Table 1: All selected animals and all animals that die spontaneously or are sacrificed *in extremis*:

Tissue	Weigh[a]	Collect	Histology	Microscopic Evaluation[c]	Comment
Animal identification	-	X	-	-	Location: ear and foot
Artery, aorta	-	X	-	-	Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Body cavity, nasopharynx	-	X	-	-	Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Bone marrow	-	X	X	X	Collect as part of the femur and sternum.
Bone, femur	-	X	X	X	Including joint.
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Eight brain levels to be examined including cerebellum, midbrain and cortex.
Cervix	X	X	X	X	Collect and weigh together with the uterus.
Epididymis	X	X	X	X	Paired examination. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours.
Esophagus	-	X	-	-	-
Eye	-	X	X	X	Paired examination. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours.
Gland, adrenal	X	X	X	X	Paired examination.
Gland, coagulation	X	X	X	X	Collect and weigh together with the seminal vesicles.
Gland, harderian	-	X	-	-	Examine only if present in the routine section of the eye. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours. Only 1 required for microscopic examination.
Gland, lacrimal	-	X	-	-	Collect exorbital. Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Gland, mammary	-	X	X	X	Collect inguinal region with skin. Examine for both males and females.

Gland, parathyroid	X	X	-	-	Examine only if present in the routine section of thyroid. Collect and weigh together with thyroid.
Gland, pituitary	-	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	-	-	Collect at mandibular, sublingual and parotid site. Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Gland, seminal vesicle	X	X	X	X	Paired examination. Collect and weigh together with the coagulation gland.
Gland, thyroid	X	X	X	X	Paired examination. Collect and weigh together with the parathyroid.
Gross lesions/masses	-	X	X	X	Only at the discretion of the Study Director, this can be omitted.
Gut-associated lymphoid tissue	-	X	X	X	Examine only if present in routine section of intestine.
Heart	X	X	X	X	-
Kidney	X	X	X	X	Paired examination.
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Liver	X	X	X	X	-
Lung	-	X	X	X	Infused with formalin.
Lymph node	-	X	X	X	Collected at mandibular and mesentric site. Only 1 mandibular required for microscopic examination
Muscle, skeletal	-	X	X	X	-
Nerve, optic	-	X	-	-	Examine only if present in the routine section of the eye. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours.
Nerve, sciatic	-	X	X	X	Only 1 required for microscopic examination
Ovaries	X	X	X	X	Paired examination.
Pancreas	-	X	-	-	Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Skin	-	X	-	-	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-

Spinal cord	-	X	X	X	Examine one transverse and one longitudinal section from each of the following areas: cervical, mid-thoracic, lumbar.
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testes	X	X	X[b]	X[b]	Paired examination. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours.
Thymus	X	X	X	X	-
Tongue	-	X	-	-	Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

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

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

[b] For the testes of all selected males of Groups 1 and 4, and all males that fail to sire or died before mating 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.

[c] Efforts will be made to evaluate all protocol-required tissues microscopically; however, it is not always feasible for every protocol-required tissue to be present on every slide. Protocol-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.

Table 2: All remaining animals (incl. males that fail to sire[a], females that fail to deliver pups and females with total litter loss):

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[c]	Comment
Animal identification	-	X	-	-	Location: ear and foot
Cervix	-	X	@	@	-
Epididymis	X	X	@	@	Paired examination. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours.
Gland, coagulation	X	X	@	@	Collect and weigh together with the seminal vesicles.
Gland, mammary	-	X	#	#	Collect inguinal region with skin. Collect for both males and females.
Gland, parathyroid	X	X	-	-	Examine only if present in the routine section of thyroid. Collect and weigh together with thyroid.
Gland, pituitary	-	X	-	-	-
Gland, prostate	X	X	@	@	-
Gland, seminal vesicle	X	X	@	@	Paired examination. Collect and weigh together with the coagulation gland.
Gland, thyroid	X	X	-	-	Paired examination. Collect and weigh together with the parathyroid.
Gross lesions/masses	-	X	X	X	-
Ovaries	-	X	@	@	Paired examination.
Testes	X	X	@[b]	@[b]	Paired examination. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours.
Uterus	-	X	@	@	-
Vagina	-	X	@	@	-

X = Procedure to be conducted for all remaining animals;
- = Not applicable;
@ = Procedure to be conducted only for males that fail to sire[a], females that fail to deliver pups and females with total litter loss.
# = Procedure to be conducted for females with total litter loss only.

[a] Except for males that fail to sire which are also selected. These males will be processed as noted in table 1 of ATTACHMENT C.

[b] For the testes of all males that fail to sire or died before mating 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.

[c] Efforts will be made to evaluate all protocol-required tissues microscopically; however, it is not always feasible for every protocol-required tissue to be present on every slide. Protocol-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.

ATTACHMENT D

Certificate of Analysis

Certificate of analysis

THE DOW CHEMICAL COMPANY

Certificate of analysis		Quality order	
Product name	CANSOLV ABSORBANT DS	Customer Batch number	D2921BF000
Reference number		Batch number	
		Reference lot	

Test	Unit	Test result	Min	Max
% Water	%	51.14	51	54
Appearance		Pass	-	-
Gardner Color	Color	3	-	6
Foam Height	ml	75	-	100
Foam Break Time	Seconds	7.7	-	15
Gas Chromatography, HEP	%	9.01	-	14
Gas Chromatography, DIHEP	%	89.69	80	100
Gas Chromatograph Heavies GT DHEP	%	0.4	-	5
Gas Chromatography, Piperazine	%	0	-	2
Gas Chromatograph EG & DEG	%	0.2	-	0.6
Cansolv DS Alkalinity	meq/g	5.76	-	-

Notes: Tank 105

APPROVED BY: **KENDRICK JUNIUS**

STUDY PLAN AMENDMENT NO. 1

Test Facility Study No. 20172120

Combined 28-Day Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test of DiHEP Aqueous Solution by Oral Gavage in Rats

SPONSOR:
Shell International B.V.
Carel van Bylandtlaan 16
2596 HR The Hague
The Netherlands

TEST FACILITY:
Charles River Laboratories Den Bosch B.V.
Hambakenwetering 7
5231 DD 's-Hertogenbosch
The Netherlands

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SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Plan effective date: 16 Jan 2018

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: 20 May 2019**
18. Terminal Procedures – F_0-Generation	At request of the histopathologist. A treatment-related microscopic finding is suspected in these organs.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxic effects of DiHEP Aqueous Solution when given orally by gavage for a minimum of 28 days to Wistar Han rats, and to evaluate the potential to affect male and female reproductive performance such as gonadal function, mating behavior, conception, parturition and early postnatal development.

In addition, parental, reproduction (up to and including implantation) and developmental (from implantation onwards) No Observed Adverse Effect Levels (NOAELs) will be evaluated.

2. PROPOSED STUDY SCHEDULE

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

Experimental Start Date:	18 Jan 2019 (First date of study-specific data collection; randomization dose range finder)
Experimental Completion Date:	27 Jun 2019 (Last date data are collected from the study)
Animal Arrival:	Males: 30 Jan 2019 Females: 16 Jan 2019
Initiation of Estrous Cycle Determination (Pretest Period):	22 Jan 2019
Initiation of Dosing:	05 Feb 2019
Initiation of Mating:	19 Feb 2019
Necropsy Males incl. Blood Sampling:	06 Mar 2019[a]
Delivery of Litters (PND 1):	≥ 13 Mar 2019
Measurement Anogenital Distance (PND 1):	≥ 13 Mar 2019
Culling of F_1-pups incl. Blood Sampling (PND 4):	≥ 16 Mar 2019
Determination Areola/Nipple Retention (PND 13):	≥ 25 Mar 2019
Necropsy Females and Pups incl. Blood Sampling (PND 14-16):	≥ 26 Mar 2019
Completion of In-life:	12 Apr 2019 (Last date of necropsy)
Unaudited Draft Report:	28 Jun 2019

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.

3. GUIDELINES FOR STUDY DESIGN

The design of this study was based on the study objective(s), the overall product development strategy for the test item, and the following study design guidelines:

- OECD Guideline 422. *Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test*, July 2016.
- EPA Health Effects Test Guideline OPPTS 870.3650: *Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test,* July 2000.

In addition, the procedures described in this study plan essentially conform to the following guidelines.

- OECD Guideline 421. *Reproduction/Developmental Toxicity Screening Test*, July 2016.
- EPA Health Effects Test Guideline OPPTS 870.3550: *Reproduction/Developmental Toxicity Screening Test*, July 2000.
- Council Regulation (EC) No 440/2008 Part B: *Methods for the Determination of Toxicity and other Health Effects; B.7: "Repeated Dose (28 days) Toxicity (oral)"*. Official Journal of the European Union No. L142, May 2008.
- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*, October 2008.
- EPA Health Effects Test Guideline OPPTS 870.3050: *Repeated dose 28-day oral toxicity study in rodents*, July 2000.

4. 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.

5. QUALITY ASSURANCE

5.1 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 study and/or process 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.

The Test Facility QAU contact is indicated below:

C.J. Mitchell, BSc.
Address as cited for Test Facility
Tel: +31 73 640 6700
E-mail: QADenBosch@crl.com

6. SPONSOR

Sponsor Representative

M. Rooseboom, PhD, ERT
Tel: +31.70.377.3463
E-mail: Martijn.Rooseboom@shell.com

7. RESPONSIBLE PERSONNEL

Study Director

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Management Contact

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Individual Scientist (IS) at the Test Facility

Histopathology	E.J.M. Lambregts, DVM address as cited for Test Facility Tel: +31 73 640 6700 E-mail: ankie.lambregts@crl.com

Each IS is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. 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 phase report will include the following:

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

8. Dose range finder (DRF)

A dose range finder (Test Facility Study No. 521627) will be conducted to determine the tolerability of the test item when administered as received. No testing guidelines are applicable as this dose range finder is intended for confirmation of tolerability only.

8.1 Proposed Study Schedule (DRF)

Initiation of Dosing:	Group 1	18 Jan 2019
Necropsy:	Group 1	23 Jan 2019

8.2 Test Item (DRF)

The information, procedures and safety instructions will be identical to those used during the main study. See sections 9 and 10 for details.

8.3 Dose Formulations and Analysis (DRF)

The preparation of test item will be identical as for the main study. See section 11 for details.

The test item will be used as received from the Sponsor; therefore, samples for dose formulation analysis will not be collected by the Test Facility.

8.4 Test System (DRF)

Species:	Rat.
Strain:	Crl: WI(Han).
Condition:	Outbred, SPF-Quality.
Source:	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 Females	3 (nulliparous and non-pregnant).
Target Age at the Initiation of Dosing:	10-12 weeks.
Target Weight at the Initiation of Dosing:	200 to 250 g.

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

At study assignment, each animal will be identified using earmark and tailmark.

Animals will be assigned at random at the discretion of the biotechnician.

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 maintained under the same environmental conditions.

The justification of test system and environmental acclimation will be identical as for the main study. See section 12 for details.

8.5 Husbandry (DRF)

On arrival and following randomization, animals will be group housed (up to 3 animals of the same dosing group together) in polycarbonate cages (Macrolon, MIV type, height 18 cm).

Other conditions will be identical as for the main study. See section 13 for details.

8.6 Experimental design (DRF)

Group No.	Test Item Id.	Dose Level (mg/kg)	Dose Volume (mL/kg)[a]	Dose Concentration (mg/mL)[b]	Number of Females	Animal Numbers
1	DiHEP Aqueous Solution	1000	2.07	482.9	3	1-3

Id.= identification.

[a] Dose volume will be calculated as dose level (mg/kg) / corrected test item concentration (mg/ml).

[b] The test item consists of 43.9% DiHEP, test item concentration will be corrected for % DiHEP and specific gravity (factor: 1.1). See section 11.1 for details.

The test item and vehicle will be administered to the appropriate animals by once daily oral gavage for a minimum of 5 days.

A dose control system (DCS) will be used as additional check to verify the dosing procedure according to Standard Operating Procedures (Study No. 521627 will be used for DCS).

The justification of the route of administration is identical as for the main study. See section 14.2 for details. To determine the tolerability of the test item when administered as received, animals will be dosed at the highest dose of the main study (1000 mg/kg) as the dose volume is the largest at this dose level.

8.7 In-life Procedures, Observations, and Measurements (DRF)

Only the following observations and measurements will be performed.

Mortality: Twice daily throughout the study.

Clinical Observations: At least once daily up to the day prior to necropsy, during the following observation intervals:

Actual time after dosing	Reported as hours after dosing	Nominal time[a]
0-15 min	0 hour	07:00
1 hr ± 15 min	1 hour	08:00
3 hr ± 30 min	3 hours	10:00

[a] Nominal times will be used for computer registration only.

Body Weights: On Day 1 prior to dosing and on Days 3 and 5.

In order to monitor the health status animals may be weighed more often. This will be documented in the study raw data.

Food Consumption Over Days 1-3 and 3-5.

8.8 Terminal Procedures (DRF)

All animals will be subjected to an external, thoracic and abdominal examination on Day 6 (scheduled necropsy) or sooner (decedents). Based on the high pH of the test item (see section 9.1), special attention will be paid to the esophagus and stomach at necropsy. Animals will not be deprived of food prior to necropsy. Gross lesions will be recorded but will not be retained, no organs will be fixed and histopathological examination will not be performed.

8.9 Reporting (DRF)

The procedures of statistical analysis, computerized systems, amendments and deviations, and retention of records will be identical as for the main study, if applicable. See sections 22, 23, 24, and 25 for details.

A summary of results of the dose range finder will be included in report 20172120 as an appendix.

9. TEST ITEM

9.1 Test Item

Identification:	DiHEP Aqueous Solution[1]
Batch (Lot) Number:	D2921BF000
Expiry date:	31 August 2020 (expiry date)
Physical Description:	Yellow aqueous liquid
Purity/Composition:	See Certificate of Analysis[2]
Storage Conditions:	At room temperature protected from light

Additional information

Test Facility Test Item Number:	209813/A
Purity/Composition correction factor:	Correct for percentage solid matter and additionally for percentage DiHEP.
Test item handling:	No specific handling conditions required
Chemical name (IUPAC, synonym or trade name):	1,4-Bis(2-hydroxyethyl)piperazine Dihydroxyethylpiperazine
CAS number:	122-96-3
Molecular formula:	$C_8H_{18}N_2O_2$
Molecular weight:	174.24
Irritant or corrosive:	Yes
pH:	13
Specific gravity / density:	1.1 kg/m^3 at 20°C

9.2 Test Item Characterization

The Sponsor will provide to the Test Facility documentation of the identity, purity, composition, and stability for the test item. If available, a Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report. The Sponsor

[1] DiHEP stands for Dihydroxyethylpiperazine.
[2] For Certificate of Analysis see ATTACHMENT D.

will also provide information concerning the regulatory standard that was followed for these evaluations.

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

9.3 Analysis of Test Item

The stability of the bulk test item will not be determined during the course of this study. Information to support the stability of each lot of the bulk test item will be provided by the Sponsor.

9.4 Reserve Samples

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

9.5 Test Item and Vehicle Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of test item will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk test item will be discarded.

10. SAFETY

The following safety instructions apply to this study:

Standard safety precautions specified in Charles River Den Bosch procedures.

11. DOSE FORMULATION AND ANALYSIS

11.1 Preparation of Test Item

The test item, DiHEP Aqueous Solution will be administered as received. An adequate amount of the test item will be dispensed into daily aliquots, which will be stored in a controlled temperature area set to maintain 21°C until use.

Test item for dosing will be kept at room temperature until dosing. Adjustment will be made for specific gravity of the test item. A factor of 43.9 will be used to correct for the purity/composition of the test item (based on the 48.9% solid matter of which 89.7% is DiHEP.

Any residual volumes will be discarded.

11.2 Sample Collection and Analysis

The test item will be used as received from the Sponsor; therefore, samples for dose formulation analysis will not be collected by the Test Facility.

12. TEST SYSTEM

Species:	Rat.
Strain:	Crl: WI(Han).
Condition:	Outbred, SPF-Quality.
Source:	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:	48 (nulliparous and non-pregnant).
Number of Pups Expected:	Approximately 480 pups (40 litters x 12 pups).
Target Age at the Initiation of the Pretest Period:	Females: approximately 10-12 weeks.
Target Age at the Initiation of Dosing:	Males: approximately 10-12 weeks. Females: approximately 12-14 weeks.
Target Weight at the Initiation of Dosing:	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.

12.1 Justification of Test System and Number of Animals

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.

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 item. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

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 which do not use live animals currently do not exist.

12.2 Animal Identification

Prior to start of the pretest period (females) or treatment period (males), each allocated animal will be identified using earmark and tattoo. Prior to start of the pretest period, reserve females will be numbered R1 through R8 at random by indelible marker. Any reserve female replacing an allocated female prior to treatment will receive identification by earmark and tattoo.

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.

12.3 Environmental Acclimation

The animals will be allowed to acclimate to the Test Facility toxicology accommodation for at least 5 days prior to start of the pretest period (females) or at least 5 days before the commencement of dosing (males).

12.4 Selection, Assignment, Replacement, and Disposition of Animals

A total of 40 females will be selected at randomization before initiation of the pretest phase. Each selected female classified as not having regular estrous cycles during the pretest phase will be replaced before initiation of dosing by one of the 8 additional females having regular estrous cycles, if feasible. A total of 40 females with regular estrous cycles will continue in the study. The supernumerary females will then be removed from the study, and their estrous cycle results will be kept in the raw data but will not be reported.

Animals will be assigned to groups by a computer-generated random algorithm according to body weights, with all animals within ± 20% of the sex mean. Males and females will be randomized separately. Animals in poor health or at extremes of body weight range 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 dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-test item-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.

13. HUSBANDRY

13.1 Housing

On arrival and following the pretest (females only) and pre-mating period, animals will be group housed (up to 5 animals of the same sex and same dosing group together) in polycarbonate cages (Macrolon, MIV type, height 18 cm).

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

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

During the lactation phase, females will be housed in Macrolon plastic cages (MIII type, height 18 cm). Pups will be housed with the dam, except during locomotor activity monitoring of the dams, when the pups will be kept warm in their home cage using bottles filled with warm water. In order to avoid hypothermia of pups, pups should not be left without their dam or a bottle filled with warm water for longer than 30-40 minutes.

During locomotor activity monitoring, F_0-animals will be housed individually in a Hi-temp polycarbonate cage (Ancare corp., USA; dimensions: 48.3 x 26.7 x 20.3 cm) without cage-enrichment, bedding material, food and water.

The cages will contain appropriate bedding (Lignocel S 8-15, JRS - J.Rettenmaier & Söhne GmbH + CO. KG, Rosenberg, Germany) and will be equipped with water bottles. The 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. Each cage will be clearly labeled with a color-coded cage card indicating Test Facility Study No., group, animal number(s), and sex.

13.2 Environmental Conditions

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

Temperature:	18 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.

13.3 Food

Pelleted rodent diet (SM R/M-Z from SSNIFF® Spezialdiäten GmbH, Soest, Germany) will be provided *ad libitum* throughout the study, except during designated procedures. During motor activity measurements, animals will not have access to food for a maximum of 2 hours.

The feed is analyzed by the supplier for nutritional components and environmental contaminants. Results of the analysis 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.

13.4 Water

Municipal tap water will be freely available to each animal via water bottles. During motor activity measurements, animals will not have access to water for a maximum of 2 hours.

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 would interfere with the objectives of the study.

13.5 Animal Enrichment

For psychological/environmental enrichment and nesting material, animals will be provided with paper (Enviro-dri, Wm. Lilico & Son (Wonham Mill Ltd), Surrey, United Kingdom), except when interrupted by study procedures/activities.

13.6 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 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 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 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 representative will be fully informed of any such events.

14. EXPERIMENTAL DESIGN

Group No.	Test Item Id.	Dose Level (mg/kg)	Dose Volume (mL/kg)[a]	Corrected Test Item Concentration (mg/mL)[b]	Number of Animals		Animal Numbers	
					Males	Females	Males	Females
1	-	0 (Control)[c]	2.07	-	10	10	01-10	41-50
2	DiHEP Aqueous Solution	100	0.21	482.9	10	10	11-20	51-60
3		300	0.62		10	10	21-30	61-70
4		1000	2.07		10	10	31-40	71-80

TBD. = To be determined. Id.= identification.

[a] Dose volume will be calculated as dose level (mg/kg) / corrected test item concentration (mg/ml).

[b] The test item consists of 43.9% DiHEP, test item concentration will be corrected for % DiHEP and specific gravity (factor: 1.1). See section 11.1 for details.

[c] Test-item treated animals will receive undiluted test item and consequently, no vehicle will be used. Control animals will be dosed with water (Elix) in the same dose volume as Group 4.

The following 5 animals/sex/group are selected for functional tests, clinical pathology, collection of full list of organs/tissues at macroscopic examination, organ weights (full list) and histopathology (full list), see also respective paragraphs:

Group No.	Animal numbers	
	Males	Females[a]
1	01-05	To be selected
2	11-15	To be selected
3	21-25	To be selected
4	31-35	To be selected

[a] Females with live pups, if feasible. These animals will be selected and approved by the Study Director in the study files. The selected female animal numbers will be specified in the report.

14.1 Administration of Test item

The test item and vehicle will be administered to the appropriate animals by once daily oral gavage 7 days a week for a minimum of 28 days. Males will be treated for a minimum of 28 days, up to and including the day before scheduled necropsy. This includes a minimum of two weeks prior to mating and during the mating period. Females will be treated 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 before scheduled necropsy. Females will not be dosed during littering.

The dose volume for each animal will be based on the most recent body weight measurement. Dose volumes ≤ 50 µL will be administered using a plastic feeding tube which is connected to a digital syringe and dose volumes > 50 µL will be given with a plastic feeding tube connected to an appropriately graded syringe. The accuracy of the digital syringe will be determined prior to start dosing at relevant dose levels for this study.

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

A dose control system (DCS) will be used as additional check to verify the dosing procedure according to Standard Operating Procedures (Study No. 521417 will be used for DCS).

Pups will not be treated directly but could potentially be exposed to the test item in utero, via maternal milk, or from exposure to maternal urine/feces.

14.2 Justification of Route and Dose Levels

The oral route of administration was selected because this is the recommended route by OECD TG 422, REACH regulation and ECHA guidelines. In addition, the test material is a non-volatile aqueous solution.

The dose levels were selected based on information provided by the Sponsor (data on file at Sponsor site), and in an attempt to produce graded responses to the test item.

A previously performed acute toxicity study with DiHEP Aqueous Solution via oral gavage in Sprague Dawley (SD) rats indicated a low acute toxicity ($LD50_{males}$ was 20,093 mg/kg and $LD50_{females}$ was 18,738 mg/kg).

In addition, multiple studies were performed with several structural analogs:

- A dietary 7-day toxicity study was performed with a hydroxypiperazine solution (containing 12-20% piperazine, 38-47% hydroxypiperazine, 16-25% dihydroxypiperazine, 17-26% water). During this study Wistar han rats received 590, 1420, and 3720 mg/kg for males and 680, 1610 and 3970 mg/kg for female rats. A slight body weight decrease was observed in females fed 3970 mg/kg/day but was not observed in females fed lower doses or in males. This body weight decrease was statistically significant after days 1 and 4 but not day 7. Remaining parameters were considered unaffected by treatment.
- A dietary 90-day toxicity study was performed with analog piperazine. During this study, SD rats received 400, 1200 and 2394 mg/kg by dietary administration. A dose related decrease in body-weight gain (a decrease of 10% in high dose animals when compared with concurrent control) was noted. Remaining parameters were considered unaffected by treatment.
- A dietary 90-day toxicity study was performed with analog anhydrous piperazine. Rats received 1000, 3000 and 10000 ppm (corresponding to 50, 150 and 500 mg/kg/day piperazine base). At 10000 ppm histopathological degenerative changes were noted in the liver and kidney, at 3000 ppm similar changes were noted to a lesser extent and at 1000 ppm no adverse effects were noted. In addition, at 10000 ppm a decrease in body weight gain was noted (statistically significant in females only). Remaining parameters were considered unaffected by treatment.
- A developmental toxicity study was performed, in which pregnant SD females received 0, 105, 420 and 2100 mg/kg piperazine base during days 6-15 by oral gavage. In high-dose females, excessive salivation, lethargy and a reduction in body weight gain and food consumption were noted. Remaining parameters, including pre- and post-implantation loss, litter size and sex ratio, were considered unaffected by treatment.
- In a dietary two generation study with piperazine dihydrochloride, SD rats received 0, 5000, 12000 and 25000 ppm (corresponding to 0, 125, 300 and 625 mg/kg piperazine base). The mid-dose was considered as LOAEL, with effects mainly on fertility (i.e. reduced pregnancy index and decreased number of implantation sites). These effects were not observed in the developmental toxicity study, which is be considered to support that the effect on fertility are the main effect of piperazine on reproduction.

Based on the observed low acute toxicity of DiHEP Aqueous Solution and the effects noted in the studies performed with structural analogs, 0, 100, 300 and 1000 mg/kg were selected as dose levels for this study.

The high-dose level should produce some toxic effects, but not death nor obvious suffering. The mid-dose level is expected to produce minimal to moderate toxic effects. The low-dose level should produce no observable indications of toxicity.

15. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS – F_0-GENERATION

The in-life procedures, observations, and measurements listed below will be performed for parental animals.

15.1 Mortality/Moribundity Checks – F_0-Generation

Frequency:	At least twice daily throughout the study.
Procedure:	Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

15.2 Clinical Observations – F_0-Generation

Frequency:	During treatment, animals will be observed at least once daily, up to the day prior to necropsy. These clinical observations will at least be conducted after dosing at no specific time point, but within a similar time period after dosing for the respective animals.
Procedure:	Animals will be observed for specific clinical signs. The time of onset, grade and duration of any observed signs will be recorded. Signs will be graded for severity and the maximum grade will be predefined at 3 or 4. Grades will be coded as slight (grade 1), moderate (grade 2), severe (grade 3) and very severe (grade 4). For certain signs, only its presence (grade 1) or absence (grade 0) will be scored. In the data tables, the scored grades will be reported, as well as the percentage of animals affected in summary tables.

15.2.1 Arena Observations – F_0-Generation

Frequency:	Once before the first administration of the test item and at weekly intervals during the treatment period.
Procedure:	Animals will be observed for specific clinical signs in a standard arena. The time of onset, grade and duration of any observed signs will be recorded.

15.3 Body Weights – F_0-Generation

Frequency: Males and females will be weighed on the first day of treatment (prior to dosing), and weekly thereafter. Mated females will be weighed on Days 0, 4, 7, 11, 14, 17, and 20 post-coitum 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.

Procedure: Animals will be individually weighed.

15.4 Food Consumption – F_0-Generation

Frequency: Weekly, except for males and females which are housed together for mating and for females without evidence of mating. Food consumption of mated females will be measured on Days 0, 4, 7, 11, 14, 17, and 20 post-coitum and during lactation on PND 1, 4, 7, and 13.

Procedure: Food consumption will be quantitatively measured.

15.4.1 Water Consumption – F_0-Generation

Frequency: Regular basis throughout the study.

Procedure: Water consumption will be monitored by visual inspection of the water bottles. If inter group differences are noted, consumption may be assessed by weight.

15.5 Functional Tests – F_0-Generation

Frequency: Once during the treatment period. The selected 5 males will be tested once during Week 4 of treatment and the selected 5 females will be tested once during the last week of lactation (i.e. PND 6-13). These tests will be performed after clinical observations and arena observation, if applicable.

Procedure: The following tests will be performed :

- hearing ability, pupillary reflex and static righting reflex (score 0 = normal/present, score 1 = abnormal/absent).
- fore- and hind-limb grip strength will be recorded as the mean of three measurements , using a grip strength meter.
- locomotor activity (recording period: 1 hour under normal laboratory light conditions) will be tested using the Kinder Scientific Motor Monitor System. Total movements and ambulations will be reported. Ambulations represent movements characterized by a relocation of the entire body position like walking, whereas total movements represent all movements made by the animals, including ambulations but also smaller or finer movements like grooming, weaving or movements of the head.

15.6 Estrous Cycle Evaluations – F_0-Generation

Frequency: Daily vaginal lavage will be performed beginning 14 days prior to treatment (pretest period), 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.

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.

15.7 Cohabitation/Mating Procedure – F_0-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 post-coitum. 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 14) will be used for re-mating.

15.8 General Reproduction Data – F_0-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 normally. 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.

16. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS – F_1-GENERATION

The in-life procedures, observations, and measurements listed below will be performed for the pups.

16.1 Mortality/Moribundity Checks – F_1-Generation

Frequency: The number of live and dead pups will be determined on PND 1 and daily thereafter.

Procedure: Pups will be observed for general health/mortality and moribundity. If possible, defects or cause of death will be evaluated. Pups will not be removed from the cage during observation, unless necessary for identification or confirmation of possible findings.

16.2 Clinical Observations – F_1-Generation

Frequency: At least once daily.

Procedure: Detailed clinical observations will be made for all pups. Only days on which clinical signs are present between the first and last litter check will be given in the respective report tables.

16.3 Body Weights – F_1-Generation

Frequency: On PND 1, 4, 7, and 13.

Procedure: Live pups will be individually weighed.

16.4 Sex – F_1-Generation

Frequency: On PND 1 and 4.

Procedure: Sex will be externally determined for all pups.

16.5 Anogenital Distance – F_1-Generation

Frequency: On PND 1.

Procedure: Anogenital distance (AGD) will be measured for all live pups. The AGD will be normalized to the cube root of body weight.

16.6 Areola/Nipple Retention – F_1-Generation

Frequency: On PND 13.

Procedure: All males in each litter will be examined for the number of areola/nipples.

16.7 Culling – F_1-Generation

Frequency:	On PND 4.
Procedure:	To reduce variability among the litters, eight pups from each litter of equal sex distribution (if possible) will be selected. Blood samples will be collected from two of the surplus pups (if possible from one male and one female pup). 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 sections 17.1.1 and 20.3.

17. LABORATORY EVALUATIONS

17.1 Clinical Pathology

17.1.1 Sample Collection

Blood of F_0-animals (except for animals which were sacrificed *in extremis* or found dead and females with total litter loss) will be collected on the day of scheduled necropsy. Samples will be collected, between 7.00 and 10.30 a.m., from the retro-orbital sinus under anesthesia using isoflurane in the animal facility. Additional blood samples may be obtained (e.g. due to clotting of non-serum samples) in both the animal facility and in the necropsy room if permissible sampling frequency and blood volume are not exceeded. After collection, samples will be transferred to the appropriate laboratory for processing.

F_0-males (except for animals which were sacrificed *in extremis* or found dead) will be fasted overnight with a maximum of 24 hours before blood sampling, but water will be available. F_0-females will not be fasted overnight.

Blood of F_1-animals will be collected on PND 4 and PND 14-16, if possible. This will be performed in the necropsy room.
On PND 4 at culling, blood will be collected from two surplus pups per litter (if possible) by decapitation, between 7.00 and 10.30 a.m., and will be pooled to one sample per litter. If available, blood will be collected from one male and one female pup. If only one surplus pup per litter is available at culling, as much as possible blood will be collected from this single pup. If the target volume of 0.5 mL cannot be reached by pooling from two pups, blood from a third surplus pup of the same litter should be added, if available.

On PND 14-16, separate blood samples will be collected from two pups per litter (from one male and one female, if possible). If the target volume of 1.0 mL/pup cannot be reached, a separate blood sample should be collected from another pup of the same litter and sex (if possible). Any incomplete blood sample will be discarded. Blood will be drawn, between 7.00 and 10.30 a.m., by aorta puncture under anesthesia using isoflurane as part of the necropsy procedure.

Samples will be collected according to the table below.

Samples for Clinical Pathology Evaluation

Animals	Time Point	Hematology	Coagulation	Clinical Chemistry	Thyroid Hormone
Selected F_0-animals (5/sex/group)[a, b,]	On the day of scheduled necropsy	X	X	X	X
Non-selected F_0-animals (≤ 5/sex/group)[a, b,]	On the day of scheduled necropsy	-	-	-	X
2 pups/litter	PND 4	-	-	-	X
2 pups/litter	PND 14-16	-	-	-	X

X = Sample to be collected; - = Not applicable.
[a] See section 14 for details of the selected F_0-animals.
[b] Except for animals which were sacrificed *in extremis* or found dead, and females with total litter loss.

17.1.2 Hematology

Target Volume: 0.5 mL.

Anticoagulant: K_3-EDTA (tubes; Greiner Bio-One GmbH, Kremsmünster, Austria).

Hematology Parameters

White blood cells (WBC)	Red Blood Cell Distribution Width (RDW)
Neutrophils (absolute)	Haemoglobin
Lymphocytes (absolute)	Haematocrit
Monocytes (absolute)	Mean corpuscular volume (MCV)
Eosinophils (absolute)	Mean corpuscular haemoglobin (MCH)
Basophils (absolute)	Mean corpuscular haemoglobin concentration (MCHC)
Red blood cells	Platelets
Reticulocyte (absolute)	

A blood smear will be prepared from each hematology sample. Blood smears will be labeled, stained, and stored. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a study plan amendment.

17.1.3 Coagulation

Target Volume: 0.45 mL.

Anticoagulant: Citrate (tubes; Greiner Bio-One GmbH, Kremsmünster, Austria).

Coagulation Parameters

Prothrombin Time (PT)	Activated Partial Thromboplastin Time (APTT)

17.1.4 Clinical Chemistry

Target Volume: 0.5 mL.

For bile acid measurement: 1.0 mL (same sample as for thyroid hormone measurement).

Anticoagulant: Li-Heparin (tubes; Greiner Bio-One GmbH, Kremsmünster, Austria).

Not applicable for serum tubes.

Processing: To serum (bile acids) or to plasma

Clinical Chemistry Parameters

Alanine aminotransferase (ALAT)	Creatinine
Aspartate aminotransferase (ASAT)	Glucose
Alkaline Phosphatase (ALP)	Cholesterol
Total protein	Sodium
Albumin	Potassium
Total Bilirubin	Chloride
Bile Acids	Calcium
Urea	Inorganic Phosphate (Inorg. Phos)

17.1.5 Thyroid Hormone

Target Volume: F_0-animals: 1.0 mL (same sample as for bile acid measurement).

PND 4 pups: 0.5 mL in total (pooled).

PND 14-16 pups: 1.0 mL per pup.

Anticoagulant: Not applicable for serum. (tubes; Greiner Bio-One GmbH, Kremsmünster, Austria).

Thyroid Hormone Parameters

Thyroxine (T4)	Thyroid-Stimulating Hormone (TSH; only if required)

After clotting and centrifugation, serum will be used as listed below.

F_0-Males: Serum from each sample will be divided into 2 aliquots: 150 µL serum for measurement of total T4 and the remaining volume of serum for possible future measurement of TSH (added by study plan amendment if applicable).

F_0-Females: The serum will be used for possible future measurement of total T4 and/or thyroid-stimulating hormone TSH (added by study plan amendment if applicable).

PND 4 Pups The pooled serum will be used for possible future measurement of total T4 (added by study plan amendment if applicable).

PND 14-16 Pups Serum from each sample will be divided into 2 aliquots: 150 µL serum for measurement of total T4, and the remaining volume of serum for possible future measurement of TSH (added by study plan amendment if applicable).

Serum samples retained for possible future analysis will be maintained by the Test Facility in the freezer (≤-75°C). Under these storage conditions, samples will be stable for 6 months. Any remaining sample will be discarded prior to finalization of the report

18. TERMINAL PROCEDURES – F_0-GENERATION

Terminal procedures are summarized in the following table:

Terminal Procedures

Group No.	(Non) Selected Animals	No. of Animals M	No. of Animals F	Scheduled Euthanasia	Necropsy Procedures: Necropsy	Necropsy Procedures: Tissue Collection	Necropsy Procedures: Organ Weights	Histology and histopathology
1	Selected	5	5	**Males:** after a minimum of 28 days of administration **Females:** PND 14-16	X	X[a]	X[a]	Full list
	Non-selected	≤ 5	≤ 5					Gross lesions Reproductive tissues[b]
2	Selected	5	5					Gross lesions Target tissues[c] Reproductive tissues[b]
	Non-selected	≤ 5	≤ 5					Gross lesions Reproductive tissues[b]
3	Selected	5	5					Gross lesions Target tissues[c] Reproductive tissues[b]
	Non-selected	≤ 5	≤ 5					Gross lesions Reproductive tissues[b]
4	Selected	5	5					Full list
	Non-selected	≤ 5	≤ 5					Gross lesions Reproductive tissues[b]
Unscheduled Deaths (sacrificed *in extremis* or found dead)					X	X	-	Full list

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

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

[b] Reproductive tissues are applicable for males that fail to sire and females that fail to deliver pups (i.e. non-pregnant females, implantation sites only or no offspring) and females with total litter loss. See ATTACHMENT C for listing of tissues.

[c] **Target tissue: Adrenal glands and Stomach of selected males of Group 2 and 3, based on possible treatment-related changes in these tissues.** ~~**Target tissues are applicable in case of possible treatment-related changes in any of the tissues of any animal in the high dose group. Then, histological examination will be extended to that particular tissue of the selected 5 animals of Groups 2 and 3.**~~

18.1 Unscheduled Deaths – F_0-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 anaesthetized using isoflurane and subsequently exsanguinated. They will undergo necropsy, and specified tissues will be retained, but not weighed.

The specified tissues which will be retained are mentioned in ATTACHMENT C.

18.2 Scheduled Euthanasia – F_0-Generation

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

Scheduled necropsies are summarized below:

Males (which sire and 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: Post-coitum Days 25-27.
	Without evidence of mating: Approximately 24-26 days after the last day of the mating period.
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.

All males surviving to scheduled necropsy will be fasted overnight with a maximum of 24 hours before necropsy. Water will be available. F_0- females will not be fasted overnight.

The specified tissues which will be retained are mentioned in ATTACHMENT C.

18.3 Necropsy – F_0-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.

In case no macroscopically visible implantation sites are present, nongravid uteri will be stained using the Salewski technique in order to detect any former implantation sites and the number of corpora lutea will be recorded in addition.

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.

18.4 Organ weights – F_0-Generation

The organs identified for weighing in the Tissue Collection and Preservation table in ATTACHMENT C will be weighed at necropsy for all scheduled euthanasia animals. 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.

18.5 Tissue Collection and Preservation – F_0-Generation

Representative samples of the tissues identified in the Tissue Collection and Preservation table in ATTACHMENT C will be collected from all animals and preserved in 10% buffered formalin (neutral phosphate buffered 4% formaldehyde solution), unless otherwise indicated. 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.

19. HISTOLOGY AND HISTOPATHOLOGY

19.1 Histology

Tissues in the Tissue Collection and Preservation table in ATTACHMENT C from F_0-animals identified in the Terminal Procedures table will be embedded in paraffin, sectioned at a thickness of 2-4 micrometers, mounted on glass slides, and stained with hematoxylin and eosin.

19.2 Histopathology

All tissues as defined under Histology (section 19.1) will be examined 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.

Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by study plan amendment following discussion with the Study Director and in consultation with the Sponsor.

At the discretion of the study pathologist and after acknowledgement by the Study Director, images may be captured for consultation purposes.

A peer review on the histopathology data will be performed by a second pathologist.

20. TERMINAL PROCEDURES – F_1-GENERATION

20.1 Method of Euthanasia – F_1-Generation

Pups, younger than 7 days will be euthanized by decapitation.

All remaining pups (PND 7-16), except the pups selected for blood collection, will be euthanized by an intraperitoneal injection of sodium pentobarbital (Euthasol® 20%).

The pups selected for blood collection on PND 14-16 will be anesthetized using isoflurane followed by exsanguination.

20.2 Unscheduled Deaths – F_1-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 necropsied 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.

20.3 Scheduled Euthanasia – F_1-Generation

On PND 4, the surplus pups (> 8 pups per litter) will be euthanized by decapitation. Sex will be determined both externally and internally. From two surplus pups per litter, blood will be collected, if possible. For details see also sections 16.7 and 17.1.1.

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. External abnormalities may be collected and fixed in 10% buffered formalin at discretion of the Study Director. In addition, the thyroid will be collected from two pups per litter (if possible, from one male and one female pup and preferably from the same pups as selected for (complete) blood collection, see also section 17.1.1), and will be preserved in 10% buffered formalin.

21. CONSTRUCTED VARIABLES

21.1 Parental Variables

Body Weight Gains:	Calculated against the body weight on Day 1 (pre-mating, mating and lactation periods) or Day 0 (post-coitum period).
Relative Food Consumption:	Calculated against the body weight for scheduled intervals.
Organ Weight Relative to Body Weight:	Calculated against the terminal body weight.

21.2 Reproduction and Developmental Variables

For each group, the following calculations will be performed. Group mean values of precoital time and duration of gestation will be calculated from individual values of F_0-females, the remaining group values will be calculated from the total number in each group. Additional calculations may be used, the methods and results will be described in the report.

Mating index (%):
$$\frac{\text{Number of females mated}}{\text{Number of females paired}} \times 100$$

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

Fertility index (%):
$$\frac{\text{Number of pregnant females}}{\text{Number of females mated}} \times 100$$

Gestation index (%):
$$\frac{\text{Number of females with living pups on Day 1}}{\text{Number of pregnant females}} \times 100$$

Duration of gestation: Number of days between confirmation of mating and the beginning of parturition

Post-implantation survival index (%): $\frac{\text{Total number of offspring born}}{\text{Total number of uterine implantation sites}} \times 100$

Post-implantation survival index will be expressed as 100% when the number of offspring exceeds the number of implantation sites recorded.

Live birth index (%): $\frac{\text{Number of live offspring on Day 1 after littering}}{\text{Total number of offspring born}} \times 100$

Percentage live males at First Litter Check (%): $\frac{\text{Number of live male pups at First Litter Check}}{\text{Number of live pups at First Litter Check}} \times 100$

Percentage live females at First Litter Check (%): $\frac{\text{Number of live female pups at First Litter Check}}{\text{Number of live pups at First Litter Check}} \times 100$

Viability index (%): $\frac{\text{Number of live offspring on Day 4 before culling}}{\text{Number live offspring on Day 1 after littering}} \times 100$

Lactation index (%): $\frac{\text{Number of live offspring on Day 13 after littering}}{\text{Number live offspring on Day 4 (after culling)}} \times 100$

22. STATISTICAL ANALYSIS

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.

Numerical data collected on scheduled occasions will be analyzed according to sex and occasion. Descriptive statistics number, mean and standard deviation will be reported whenever possible. Values may also be expressed as a percentage of predose or control values when deemed appropriate. Inferential statistics will be performed according to the comparison matrix below when possible, but will exclude semi-quantitative data, and any group with less than 3 observations.

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

22.1 Parametric

Datasets with at least 3 groups (the designated control group and 2 other groups) will be compared using Dunnett-test (many-to-one-t-test).

22.2 Non-Parametric

Datasets with at least 3 groups will be compared using a Steel-test (many-to-one rank test).

The motor activity data set (at least 3 groups) will be compared using an overall Kruskal-Wallis. Whenever, the overall test is significant, the Wilcoxon Rank-Sum test will be applied to compare the treated groups to the control group.

22.3 Incidence

An overall Fisher's exact test will be used to compare all groups. The above pairwise comparisons will be conducted using Fisher's exact test whenever the overall test is significant.

Additional methods of statistical analysis may be used at the discretion of the Study Director. The methods and the results will be described in the report.

23. COMPUTERIZED SYSTEMS

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

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.

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
ToxData [a]	In-life phase (Mortality; Clinical signs; Body weights; Food consumption; Functional tests; Organ weights; Reproduction parameters; Observations pups[b]) data collection
REES Centron	Temperature and humidity (animal and laboratory facilities) data collection
MotorMonitor II	Motor activity measurement data collection
ADVIA® 2120i	Hematology data collection
STA Compact®	Clotting parameters data collection
AU400	Clinical biochemistry data collection
IMMULITE® 1000	Thyroid hormone data collection
Pathdata	Histopathology data collection

[a] For logistic reasons, data will be captured under separate Study numbers, see ATTACHMENT B.
[b] Only at first and last litter check, and in case of clinical pup findings also on the respective days in between.

24. 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.

All study plan and SOP deviations will be documented in the study records. Deviations from the study plan and/or SOP related to the phase(s) of the study conducted at a Test Site shall be documented, acknowledged by the PI/IS, and reported to the Study Director for

authorization/acknowledgement. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

25. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River from this study will be transferred to a Charles River archive.

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 item receipt, identification and preparation
- In-life measurements and observations
- Clinical pathology sample collection and evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

After two years of archiving, all study-specific raw data, electronic data, documentation, study plan and final reports will be transferred to Iron Mountain Germany, Harpener Hellweg 31, D-44805 Bochum, Germany. They shall be indexed by using the Test Facility Project No. allowing unequivocal identification and providing the necessary information (e.g. test system, test item, date of Toxicology and Ecology for the time period set by the GLP regulations). Records of transfer will be retained by test facility. The Sponsor will be informed about the transfer and will receive a digital copy of the record of transfer. The sponsor will ensure that all study material is expediently returned to Charles River Den Bosch if requested by GLP monitoring authorities for audit.

26. REPORTING

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. An original copy of the report with the Test Facility's signatures will be retained.

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.

27. 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).

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.

AMENDMENT APPROVAL

D. van den Oetelaar, MSc
Study Director

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	Formulations	Tsfher;
1 Copy	Estrous Cycle Determination	Daoud, M; Hungs, S;
1 Copy	Clinical Pathology	Her/clinical pathology;
1 Copy	Necropsy	Her/necropsy;
1 Copy	Histotechnology	Her/histology
1 Copy	Study Assistants	Sagit;
1 Copy	Individual Scientist Histopathology	Lambregts, A;
1 Paper Copy	Coordinating Biotechnician DRF	Coppes, M;
1 Paper Copy	Coordinating Biotechnician Main	Van Beek, B;

ATTACHMENT B

Separate Study Numbers for online data collection will be used as indicated below. All data will be reported under Test Facility Study No. 20172120.

Test Facility Study No.	Study Number Online Data	
521627 (DRF)	521627	ToxData; all data of the Dose Range Finder (DRF)
20172120 (Main)	521417	ToxData Parental animals : Mortality Clinical signs (except arena observations) Functional tests (except motor activity) Body weights and food consumption pre-mating Body weights mating period Food consumption mating period (males only) Clinical laboratory investigations Macroscopic findings and organ weights Implantation sites
20172120 (Main)	521418	ToxData: Arena observations (F_0- animals)
20172120 (Main)	521419	ToxData: Clinical pathology PND 14-16 pups
20172120 (Main)	521416	ToxData: All other data of the main study

ATTACHMENT C

Tissue Collection and Preservation

This attachment contains two tables describing the procedures of tissue weighing, collection, histology and microscopic evaluation. The first table is applicable for all selected animals and all animals that die spontaneously or are sacrificed *in extremis*. The second table is applicable for all remaining animals, including the males that fail to sire and females that fail to deliver pups (i.e. non-pregnant, implantation sites only or no offspring) and females with total litter loss.

Table 1: All selected animals and all animals that die spontaneously or are sacrificed *in extremis*:

Tissue	Weigh[a]	Collect	Histology	Microscopic Evaluation[c]	Comment
Animal identification	-	X	-	-	Location: ear and foot
Artery, aorta	-	X	-	-	Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Body cavity, nasopharynx	-	X	-	-	Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Bone marrow	-	X	X	X	Collect as part of the femur and sternum.
Bone, femur	-	X	X	X	Including joint.
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Eight brain levels to be examined including cerebellum, midbrain and cortex.
Cervix	X	X	X	X	Collect and weigh together with the uterus.
Epididymis	X	X	X	X	Paired examination. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours.
Esophagus	-	X	-	-	-
Eye	-	X	X	X	Paired examination. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours.
Gland, adrenal	X	X	X	X	Paired examination.
Gland, coagulation	X	X	X	X	Collect and weigh together with the seminal vesicles.
Gland, harderian	-	X	-	-	Examine only if present in the routine section of the eye. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours. Only 1 required for microscopic examination.
Gland, lacrimal	-	X	-	-	Collect exorbital. Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Gland, mammary	-	X	X	X	Collect inguinal region with skin. Examine for both males and females.

Gland, parathyroid	X	X	-	-	Examine only if present in the routine section of thyroid. Collect and weigh together with thyroid.
Gland, pituitary	-	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	-	-	Collect at mandibular, sublingual and parotid site. Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Gland, seminal vesicle	X	X	X	X	Paired examination. Collect and weigh together with the coagulation gland.
Gland, thyroid	X	X	X	X	Paired examination. Collect and weigh together with the parathyroid.
Gross lesions/masses	-	X	X	X	Only at the discretion of the Study Director, this can be omitted.
Gut-associated lymphoid tissue	-	X	X	X	Examine only if present in routine section of intestine.
Heart	X	X	X	X	-
Kidney	X	X	X	X	Paired examination.
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Liver	X	X	X	X	-
Lung	-	X	X	X	Infused with formalin.
Lymph node	-	X	X	X	Collected at mandibular and mesentric site. Only 1 mandibular required for microscopic examination
Muscle, skeletal	-	X	X	X	-
Nerve, optic	-	X	-	-	Examine only if present in the routine section of the eye. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours.
Nerve, sciatic	-	X	X	X	Only 1 required for microscopic examination
Ovaries	X	X	X	X	Paired examination.
Pancreas	-	X	-	-	Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Skin	-	X	-	-	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-

Spinal cord	-	X	X	X	Examine one transverse and one longitudinal section from each of the following areas: cervical, mid-thoracic, lumbar.
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testes	X	X	X[b]	X[b]	Paired examination. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours.
Thymus	X	X	X	X	-
Tongue	-	X	-	-	Examine only if changes in macroscopic appearance are indicative of potential toxicity.
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

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

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

[b] For the testes of all selected males of Groups 1 and 4, and all males that fail to sire or died before mating 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.

[c] Efforts will be made to evaluate all protocol-required tissues microscopically; however, it is not always feasible for every protocol-required tissue to be present on every slide. Protocol-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.

Table 2: All remaining animals (incl. males that fail to sire[a], females that fail to deliver pups and females with total litter loss):

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[c]	Comment
Animal identification	-	X	-	-	Location: ear and foot
Cervix	-	X	@	@	-
Epididymis	X	X	@	@	Paired examination. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours.
Gland, coagulation	X	X	@	@	Collect and weigh together with the seminal vesicles.
Gland, mammary	-	X	#	#	Collect inguinal region with skin. Collect for both males and females.
Gland, parathyroid	X	X	-	-	Examine only if present in the routine section of thyroid. Collect and weigh together with thyroid.
Gland, pituitary	-	X	-	-	-
Gland, prostate	X	X	@	@	-
Gland, seminal vesicle	X	X	@	@	Paired examination. Collect and weigh together with the coagulation gland.
Gland, thyroid	X	X	-	-	Paired examination. Collect and weigh together with the parathyroid.
Gross lesions/masses	-	X	X	X	-
Ovaries	-	X	@	@	Paired examination.
Testes	X	X	@[b]	@[b]	Paired examination. Preserve in modified Davidson's fixative. Tissues will be transferred to formalin after fixation for at least 24 hours.
Uterus	-	X	@	@	-
Vagina	-	X	@	@	-

X = Procedure to be conducted for all remaining animals;
- = Not applicable;
@ = Procedure to be conducted only for males that fail to sire[a], females that fail to deliver pups and females with total litter loss.
# = Procedure to be conducted for females with total litter loss only.

[a] Except for males that fail to sire which are also selected. These males will be processed as noted in table 1 of ATTACHMENT C.

[b] For the testes of all males that fail to sire or died before mating 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.

[c] Efforts will be made to evaluate all protocol-required tissues microscopically; however, it is not always feasible for every protocol-required tissue to be present on every slide. Protocol-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.

ATTACHMENT D

Certificate of Analysis

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Certificate of analysis

THE DOW CHEMICAL COMPANY

Certificate of analysis		Quality order	
Product name	CANSOLV ABSORBANT DS	Customer Batch number	D2921BF000
Reference number		Batch number	
		Reference lot	

Test	Unit	Test result	Min	Max
% Water	%	51.14	51	54
Appearance		Pass	-	-
Gardner Color	Color	3	-	6
Foam Height	ml	75	-	100
Foam Break Time	Seconds	7.7	-	15
Gas Chromatography, HEP	%	9.01	-	14
Gas Chromatography, DIHEP	%	89.69	80	100
Gas Chromatograph Heavies GT DHEP	%	0.4	-	5
Gas Chromatography, Piperazine	%	0	-	2
Gas Chromatograph EG & DEG	%	0.2	-	0.6
Cansolv DS Alkalinity	meq/g	5.76	-	-

Notes: Tank 105

APPROVED BY: **KENDRICK JUNIUS**

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.

Formulations and Dosing

- On Day 2 of treatment, all males of Group 2 received a dose volume corresponding with a dose level of 1000 mg/kg instead of 100 mg/kg.
  Evaluation: Based on the available results, a single dose at the same level as Group 4 animals did not impact the study outcome.

In-life phase

- For the males of Litter No. 76 (1000 mg/kg/day), the nipple retention was not determined on PND 13.
  Evaluation: sufficient information from other litters at the same dose level was available for evaluation.

Terminal procedures

- The brain from Female No. 68 (300 mg/kg/day) was not weighed on the day of necropsy.
  Evaluation: Brain weight of this female was determined after fixation but was considered affected by fixation and therefore excluded from the tables. Sufficient information was available from remaining Group 3 females for evaluation.
- For Female No. 42 (control), no visible implantation sites were noted in the uterus during necropsy. Due to a macroscopic finding (i.e. a nodule) and in consultation with the pathologist, the Salewski staining was not performed.
  Evaluation: As the Salewski staining could interfere with the evaluation of the uterus tissue, preservation of the gross finding for histopathological evaluation was preferred to the staining. This deviation was considered not to have a negative impact on the study outcome, as sufficient information was available for evaluation.

Other

- Inadvertently, the new standard analysis method for the motor activity data set (i.e. parametric (ANOVA) tests on group means with Bonferroni correction for multiple testing) was used while this method was not included in the Study Plan.
  Evaluation: The new method (mixed model) is an extension of standard regression (or ANOVA) model for repeated data. The repeated measure (mixed models) is considered statistically the best approach for this type of dataset as multiple measurements are performed over an interval of one hour. Hence, the study outcome was not affected.

Dose Range Finding Study

- Temporary deviations from the minimum level of target humidity occurred on two consecutive days.
  Evaluation: This study plan deviation is considered not to have affected the integrity of the study because it did not noticeably affect the clinical condition of the animals or the outcome of the study.
- Dosing formulations were placed on a magnetic stirrer during dosing.
  Evaluation: As the dosing formulations consisted of water (control) or undiluted test item (Groups 2, 3 and 4) it was not required to place them on a magnetic stirrer. This deviation had no impact on the study outcome.